YIM OP-1

APOPTOSIS OF REGULATORY T CELLS (TREG): HOMEOSTATIC CONTROL OF TREG AND LOSS OF TREG IN DERMAL LESIONS OF LUPUS PATIENTS (CLE)

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$CD4^+CD25^+FOXP3^+$ regulatory T cells (T_{reg}) are potent immunosuppressive T cells. Reduced peripheral blood T_{reg} numbers have been reported to be associated with pediatric autoimmune disease. Mechanisms of T_{reg}-reduction during autoimmune disease are not clear. We have recently reported high sensitivity of T_{reg} towards CD95L-mediated apoptosis[1]. However, a T_{reg} subpopulation remains consistently apoptosis-resistant. Gene micro array and 6-color flow cytometry analysis including FOXP3 revealed that naïve T_{reg} with an apoptosis-resistant phenotype constitute this so far neglected T_{reg} population. We demonstrate the importance of naïve T_{reg} for the homeostasis of T_{reg} and translate our findings into cutaneous lupus erythematosus (CLE). Analysis of CLE-patients revealed a significant loss of T_{reg} in the skin compared to other inflammatory skin diseases and peripheral blood. To elucidate the underlying mechanism, we tested for alterations in migratory and cell death properties of CLE-derived T_{reg}. Based on the high apoptosis sensitivity of memory T_{reg} compared to apoptosis-resistant naïve T_{reg}, we present a new hypothesis for paucity of T_{reg} in the dermal lesion during autoimmune disease.

[1] Fritzsching et al., Cutting Edge, Journal of Immunology l. 2005 Jul 1; 175(1):32-6.

YIM OP-2

INTERLEUKIN-6 AND INNATE IMMUNITY: HYPER-RESPONSIVENESS TO A TOLL-LIKE RECEPTOR LIGAND IN INTERLEUKIN-6 TRANSGENIC MICE

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High levels of interleukin (IL)-6 are present in patients with systemic juvenile idiopathic arthritis (JIA). Little information is available on the effects of IL-6 on the innate immune response. The purpose of this study was to evaluate if chronic overexpression of IL-6 affects responses to toll-like receptor (TLR) ligands. We used IL-6 transgenic (TG) mice and wild-type (WT) control mice. Spleen cells were used to evaluate cytokine production ex vivo. Mice were injected i.p. with LPS at different doses and serum was obtained at different times for cytokine measurement in vitro following LPS treatment. Spleen cells of TG mice produced higher levels of IL-1β and tumor necrosis factor (TNF)-α than WT mice. After LPS in vivo, serum IL-1β, IL-18, TNF-α, and MIP-2 were significantly higher in TG mice than in WT mice. After LPS, survival was significantly reduced in TG compared to WT mice: number dead/number treated was 2/10 in the WT vs 9/10 in the TG groups in response to 20 mcg/g ($p<0.001$), and 2/18 in the WT vs 5/5 in the TG groups in response to 10 mcg/g ($p<0.001$). Cotreatment with cyclosporin-A improved survival and delayed death in TG mice, while it did not affect survival in WT mice following a dose of LPS lethal for WT mice. Our results show that chronic overexpression of IL-6 in vivo induces hyper-responsiveness to an innate immune stimulus such as LPS; the increased mortality is delayed and partially reverted by treatment with cyclosporin-A. This animal model may help understanding mechanisms leading to exaggerated response to infections in patients with chronic inflammation.

YIM OP-3

MUTATIONS IN THE PERFORIN GENE MAY BE LINKED TO MACROPHAGE ACTIVATION SYNDROME IN PATIENTS WITH SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: Macrophage activation syndrome (MAS) is a life-threatening complication of systemic onset juvenile idiopathic arthritis (SoJIA) and is considered to be an acquired form of hemophagocytic lymphohistiocytosis (HLH). Familial HLH is an autosomal recessive disorder caused by mutations in the perforin gene PRF1 in 20-50% of affected patients. Here we analyzed the PRF1 gene and its putative promoter in SoJIA patients with or without MAS.

Methods: DNA of 62 SoJIA patients (47 Italian, 15 Dutch) was isolated. 34% (21/62) of our patients had a confirmed history of MAS. All exons, flanking splice sites and 1.2 kb of the 5'-upstream region were sequenced. Mutations were screened in Italian (98) and Dutch (48) healthy controls. DNA sequence variations in the 5'-upstream region were functionally tested in transfection experiments using a human NK cell line.

Results: 11 out of 62 SoJIA patients and 7 out of 21 patients with a history of MAS were heterozygous for a missense mutation in PRF1. Four different mutations were identified: formerly described Arg4His (1x), Ala91Val (7x) and Asn252Ser (3x) and a novel Arg28Cys (1x) change. In particular, the Ala91Val had a significantly higher incidence in SoJIA patients with MAS (5/21; 23.8%) compared to SoJIA patients without MAS (2/41; 4.9%). In addition, we detected two novel sequence variations in the putative promoter. Both were present at polymorphic frequencies in healthy controls and were found to be nonfunctional in a human NK cell line.

Conclusions: This study shows a correlation between the Ala91Val variant in PRF1 and the occurrence of MAS in patients with SoJIA.

YIM OP-4

VALIDATION OF A DIAGNOSTIC SCORE FOR MOLECULAR ANALYSIS OF HEREDITARY AUTOINFLAMMATORY SYNDROMES WITH PERIODIC FEVER

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Objective: To validate a set of clinical parameters to predict gene mutations in hereditary autoinflammatory diseases associated with periodic fever.

Patients & Methods: 234 consecutive patients with a clinical history of periodic fever were screened for mutations of MVK, TNFRSF1A and MEFV genes, and detailed clinical information was collected. A diagnostic score was formulated on the basis of univariate and multivariate analyses in genetically positive and negative patients (training set). The score was validated using an independent set of 76 patients (validation set).

Results: Age at onset (OR=0.94, p=0.003), positive familial history (OR=4.1, p=0.039), thoracic (OR=4.6, p=0.05) and abdominal pain (OR=33.1, p<0.001), diarrhea (OR=3.3, p=0.028) and oral aphthosis (OR=0.2, p=0.007) were the variables independently correlated with positivity on genetic testing. These variables were combined in a linear score, the ability of which to predict the probability of positive results on genetic testing was validated on an independent data set. The diagnostic score in the validation set revealed high sensitivity (82%) and specificity (72%) in discriminating positive and negative patients. A regression tree analysis was able to provide, for patients with a high probability of positivity on the genetic test, the most reasonable order of the genes to be screened.

Conclusions: The proposed approach in patients with periodic fever will increase the probability in obtaining a positive result in genetic testing with good specificity and sensitivity. Our results further suggest the order of the genes to be screened.

YIM OP-5

PREDICTION OF DIFFERENT CLINICAL SUBSETS IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS BY CLUSTERING ANALYSIS OF AUTOANTIBODIES

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Objective: To analyze autoantibody clusters and their associations with clinical features and cumulative organ damage in patients with juvenile systemic lupus erythematosus (JSLE).

Methods: A multi-national, cross-sectional study of 134 patients with JSLE (according to American College of Rheumatology [ACR] criteria and with disease onset before 18 years) was conducted. The group included 86.5% females with a mean ± SD age of onset of 11.6 ± 3.0 years; 49% were Caucasian, 36% Asian, 10% African-American and 7% were Hispanic. Seven autoantibodies (anti–double stranded DNA [anti-dsDNA], anti-Sm, anti-Ro, anti-La, anti-RNP, lupus anticoagulant (LAC), and anticardiolipin antibody [aCL]) were selected for cluster analysis using the K-means cluster analysis procedure.

Results: Two autoantibody clusters were identified: cluster 1 (anti-Sm, anti-RNP, anti-Ro / anti-La) and cluster 2 (LAC and aCL). Compared to cluster 2, cluster 1 included a greater proportion of African-American patients ($p<0.000$) and of patients with estimated or measured glomerular filtration rate <50% ($p<0.05$). Patients in cluster 1 had a lower frequency of oral ulcers ($p=0.021$), hematological abnormalities at disease onset ($p=0.004$), and of nephrotic range proteinuria along the disease course ($p=0.038$). Patients in cluster 2 had a greater proportion of thrombotic events ($p=0.050$), particularly venous thrombosis ($p=0.036$), but had less frequent cutaneous manifestations ($p=0.036$) and visceral and lympho-reticular organ involvement at disease onset ($p=0.048$).

Conclusion: Autoantibody clustering is a valuable tool to distinguish among different clinical subsets of JSLE and enables prediction of diverse types of disease onset and clinical course.

YIM OP-6

ULTRASOUND AND MRI MEASUREMENTS OFJOINT CARTILAGE: A VALIDATION STUDY

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Introduction: Ultrasound (US) is a promising imaging tool in pediatric rheumatology. Loss of joint cartilage is among one of the parameters judging the severity of disease progress. However, US still needs validation before it can be used as a diagnostic bedside tool in a pediatric setting.

Purpose: This study aims to validate US measurements of cartilage thickness (CTh) in the joints of healthy children by comparing it with magnetic resonance imaging (MRI) measurements (gold standard).

Materials & Methods: The study included 26 healthy children (17 boys/9 girls), aged 11.4. The right knee, ankle, wrist, 2nd metacarpophalangeal (MCP) and 2nd proximal interphalangeal (PIP) joints were examined with MRI and US on the same day. MRI was performed on a 1.5 T MR system (Sigma Twin Speed; G.E. Systems) using a dedicated coil. Fat suppressed T1-weighted three dimensional (3D) spoiled gradient echo sequences were used. US standard scans (EULAR) were performed with B-mode using a linear transducer (10 MHz) (Hitachi EUB-6500 CFM). Prior to the study, the investigators reached consensus on the anatomical landmarks for measurement of CTh in the five joints.

Results: Table 1.

Conclusions: We found good agreement (SD 95% CI and CV) between the two methods in assessment of CTh in juvenile idiopathic arthritis (JIA) target joints in healthy children. US is equally as good an imaging modality as MRI when considering measurements of CTh and can be used in a pediatric setting when monitoring JIA disease progress.

Table I.

	Mean Cartilage Thickness (mm) ± Standard Deviation	95% Confidence Interval (CI)	Coefficient of Variation (CV)
Knee			
MRI	3.7 ± 0.44	3.5-3.9	0.12
US	3.7 ± 0.62	3.5-4.0	0.16
Ankle			
	1.5 ± 0.19[1]	1.4-1.5[1]	
MRI	1.4 ± 0.25[2]	1.2-1.6[2]	0.13
	1.1 ± 0.17[1]	1.06-1.2[1]	
US	0.9 ± 0.13[2]	0.80-1.02[2]	0.15
Wrist			
MRI	1.4 ± 0.28[3]	1.3-1.5[3]	0.20[3]
US	1.5 ± 0.40[3]	1.4-1.7[3]	0.26[3]
MCP			
MRI	1.2 ± 0.21	1.1-1.3	0.15
US	1.2 ± 0.18	1.1-1.2	0.17
PIP			
MRI	0.7 ± 0.11	0.7-0.8	0.16
US	0.8 ± 0.14	0.8-0.9	0.15

[1] Scan A Longitudinal scan (n=26) Talus [2] Scan B 1. Transverse scan on Talus and ½ of the width than a 2. longitudinal scan on talus (n=8) [3] Scan C= Os Scaphoideum.

YIM OP-7

CREM ALPHA IS A NEGATIVE REGULATOR OF ANTIGEN PRESENTATION

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The cAMP responsive element modulator (CREM) is a transcriptional repressor and important in T cell pathophysiology of systemic lupus erythematosus (SLE). Since patients with SLE also display defects in antigen presentation, we identified binding sites of CREM in antigen-presenting cells by chromatin-immunoprecipitation based promoter array technology (ChIP on Chip).

We used the U937 monocytic cell line and chose 0, 6 and 24 hours after LPS stimulation for immunoprecipitation, since CREM is induced in U937 by treatment with LPS.

ChIP on Chip identified about 1400 target genes of CREM in U937 cells. Of those, 10 genes involved in antigen presentation including MHC II, CD80 and CD86 are bound by CREM and were confirmed by real time polymerase chain reaction (PCR) with promoter specific primers. Binding of CREM to these promoters negatively correlated with transcription, and transfection of anti-sense CREM enhanced the activity of these promoters in U937 cells.

To investigate the physiological significance of this finding, we crossed CREM knockout and wild-type mice into an ova-T cell receptor (DO11.10) transgenic background. We generated dendritic cells (DCs) from those mice and primed them with ova-peptide. We cocultivated the DCs with fluorescence-labeled isogenic wild-type T cells. While we found no difference in the basal proliferation of T cells cocultivated with knockout or wild-type DCs in the absence of specific antigen, there is a significantly higher ova- antigen- specific proliferation of T cells that have been cocultivated with knockout CREM DCs.

Therefore, CREM is a negative regulator of antigen presentation.

YIM OP-8

SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS IS UNIQUELY CHARACTERIZED BY A FUNCTIONAL IL18 MEDIATED CELL-SIGNALLING DEFECT IN NK CELLS

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Systemic onset juvenile idiopathic arthritis (JIA) is an auto-inflammatory disease with unknown immunopathogenesis. To investigate if there is a relation between high interleukin (IL)18 levels and depressed NK cell function, we studied cells and plasma of 20 JIA patients (10 polyarticular and 10 systemic JIA) as well as 10 healthy controls.

All cell culture experiments were performed with both PBMC and NK cells with several concentrations of IL18 in the presence or absence of IL12. Cells and supernatants were analyzed by flow cytometry and Luminex. NK cell function was assessed by chromium release assays.

IL18BP and perforin levels were similar in all subjects whereas significant higher (free) IL18 levels were present in plasma of systemic JIA patients compared to polyarticular JIA patients and healthy controls. When NK cells of healthy subjects were cultured with plasma of systemic patients, an increase of NK cell activity was observed whereas NK cells of systemic JIA patients did not respond. In addition, NK cell function was not boosted by IL18 in systemic patients whereas polyarticular JIA and healthy controls showed an increased NK cell function. Furthermore, cells of systemic JIA did not show any change in perforin levels, interferon (IFN)γ production or CD107a expression after stimulation with IL18.

These results clearly indicate a function defect in systemic JIA in either the IL18 receptor or in the downstream signalling pathway.

YIM OP-9

IS THERE A DEFECT IN THE NEUROENDOCRINE IMMUNE SYSTEM IN FAMILIAL MEDITERRANEAN FEVER?

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The aim was to determine the interactions between the neuroendocrine and immune system in patients with familial Mediterranean fever (FMF) and investigate the role of the neuroendocrine system in the acute inflammation process. Demographic characteristics, disease activity, mutation analysis and duration of the disease were defined in 15 FMF patients (7 female, 8 male; mean age ± SD 9.1 ± 4.2 years). The diagnosis was based on Tel-Hashomer criteria. Ten healthy volunteers and 21 active juvenile idiopathic arthritis (JIA) patients comprised the control groups. Furthermore, 10 of these 15 patients with FMF were also studied during the attack- free period. Erythrocyte sedimentation rate, C-reactive protein (CRP), fibrinogen, ACTH, cortisol, insulinlike growth factor (IGF)-1, IGF binding protein (BP)3, urine cortisol levels, interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α were evaluated in FMF patients with attack and in the attack-free period. The median levels of ACTH (12.7 pg/ml) and cortisol (12 ug/dl) at 08.00 a.m. were lower in FMF patients with attack than in the attack-free period, but this did not reach statistical significance. On the other hand, the median levels of ACTH and cortisol were significantly lower in attack than in the healthy control group ($p<0.05$). The median level of IGF-1 (118.5 ng/ml) was significantly lower in FMF attack than in the attack-free period ($p<0.05$). There was a negative correlation between IGF-1 and CRP ($r=-0.69$). The median level of IL-6 was 18.1 pg/dl in FMF attack and significantly higher than in the attack-free period and healthy control groups ($p<0.05$). There was a negative correlation between cortisol levels at 08.00 a.m. and IL-6 ($r = -0.55$).

When we compared JIA with FMF patients in attack, inappropriately low secretion of adrenal cortisol and ACTH and impaired diurnal rhythm of cortisol were more pronounced in JIA than FMF. Although it is more prominent in chronic inflammation, the neuroendocrine immune system is impaired in relation to acute inflammation in FMF.

YIM OP-10

SINGLE INJECTION OF MESENCHYMAL STEM CELLS DECREASES PROGRESSION OF PROTEOGLYCAN-INDUCED ARTHRITIS

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Background: Mesenchymal stem cells (MSC) are adult stem cells that are mainly present in bone marrow and fat. The cell is a fine candidate for treatment of juvenile idiopathic arthritis since it has strong suppressive activities in vitro as well as in vivo. Moreover it has the tendency to migrate to damaged areas and has good regenerative qualities since it can differentiate into bone, fat, muscle or cartilage tissues.

Objectives: A single injection of MSC will reduce the arthritis score of established proteoglycan-induced arthritis in Balb/c mice. MSC are visible in vivo for a longer period by bioluminscence imaging (BLI).

Methods: We performed a study with 83 Balb/c mice with 25 as donors of MSC. The 52 (95%) mice that developed arthritis were randomly assigned to a positive control group and three treatment groups (intravenous [iv] 1 million, intraarticular [ia] in the right knee 0.3 million, and intraperitoneal [ip] 5 million MSC). Treatment was given 10 days after manifest arthritis. MSC used were syngeneic, characteristic in form, phenotype and differentiation potential. Suppression of proliferation of 0.2 million splenocytes was already substantial with 300 MSC. Transduced MSC contained a vector with GFP and luciferase with 65% transduction.

Results: The median arthritis score after six weeks was 10 (max 16) in the control group. BLI signal was strong after one week and still visible after five weeks when MSC were injected ia or ip. Homing to areas outside injection region was not seen. MSC injected iv were never visualized and the procedure was hazardous. High-dose MSC ip had the best immunosuppressive action on progression of arthritis.

Differences in arthritis score after five weeks per group and relative to control group:

Groups	Posttreatment per group relative to pretreatment	Posttreatment relative to control group
Control	667%	100%
IV	360%	46%
IA	300%	35%
IP	200%	18%

YIM OP-11

CIRCULATING ENDOTHELIAL CELLS AND ENDOTHELIAL PROGENITOR CELLS IN PRIMARY SYSTEMIC VASCULITIS OF THE YOUNG

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Introduction: Circulating endothelial cells (CECs) are increasingly described as biomarkers for tracking vascular injury in adults. Additionally, endothelial progenitor cells (EPCs) are important in endothelial repair, but neither has yet been studied in primary systemic vasculitis (PSV) of children. This study describes the relationship between CECs, EPCs, and disease activity in children with PSV.

Methods: 25 children (median age 9.7 years (0.1-15.8); 13 males) with PSV at various stages of disease activity were studied. PSV was classified as: polyarteritis nodosa (n=10); Wegener's granulomatosis (n=5); Kawasaki syndrome (n=3); Takayasu disease (n=3); and unclassified (n=4). Peripheral blood CECs were counted using immunomagnetic beads coated with CD146, then stained with FITC-conjugated ULEX. EPCs were detected using flow cytometry and were defined as mononuclear cells triple-positive for CD34, CD133, and VEGFR2.

Results: Median CEC count was higher in 19 children with active PSV (BVAS>0) compared with 14 children with inactive PSV (BVAS=0), and 23 control children [active PSV CECs 168/ml (8-1136/ml); inactive PSV CECs 32/ml (4-320); child control CECs 32/ml (0-112/ml); $p<0.005$]. CECs showed significant correlation with disease activity as measured using a modified childhood BVAS score ($R=0.42$; $p=0.0036$), although CECs did not correlate significantly with ESR or CRP. Peripheral blood EPCs (CD34+CD133+VEGFR2+) were higher in 12 children with active PSV prior to treatment compared to 20 child controls. In particular, the proportion of CD133+ cells within the CD34 population was significantly higher in children with untreated PSV than in controls ($p=0.001$). Following a median 3-months treatment, EPCs fell to within the healthy child control range.

Conclusion: Our data suggest that CECs can be used in children to non-invasively track endothelial injury due to PSV, and also to monitor therapeutic responses. Our preliminary observations suggest mobilization of EPCs at the time of maximal endothelial injury, perhaps indicative of a compensatory reparative vasculogenic response.

YIM OP-12

MECHANISMS OF MUSCLE DAMAGE IN A TRANSGENIC MODEL OF MYOSITIS: ACCELERATED PATHOLOGICAL RESPONSE IN YOUNG MUSCLE

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Objective: Juvenile dermatomyositis (JDM) is the most common idiopathic inflammatory myopathy of childhood. As yet, the pathogenic mechanisms of JDM are unclear. A growing body of evidence suggests a critical role for MHC class I, endoplasmic reticulum (ER) stress and subsequent inflammatory activation in the pathogenesis. Using a muscle specific mouse MHC I (H-2Kb) upregulation model, we aimed to characterize early pathogenic events in juvenile myositis muscle.

Methods: A myositis model, in which self-MHC class l was specifically upregulated in muscle at 21 (HT-E) and 35 (HT-L) days of age, was used to assess effects of myopathic insult on juvenile and adult mice. Gene expression profiling and immunohistochemical analysis were used to characterize the early pathogenic mechanisms.

Results: Early upregulation of H-2Kb in muscle produced an accelerated, lethal myopathic phenotype. Genes encoding proteins involved in ER transit, vesicle budding and protein degradation were upregulated early in the HT-E model, compared to HT-L and control mice. Classical inflammatory genes were not elevated two weeks post MHC upregulation in HT-E or HT-L models. The regenerative capacity differed between the HT-E and HT-L models, with early upregulation of myoblast specific transcription factors seen at RNA and protein level. Inflammatory cell infiltration occurred relatively late in disease, suggesting inflammation may be secondary to ER stress.

Conclusions: MHC class I upregulation is an early event in JDM. These results suggest an inability of young mouse muscle to cope with aberrant protein load, which results in an exaggerated ER stress-like response and accelerated myopathic phenotype.

YIM OP-13

FUNCTIONAL COMPARISON BETWEEN IN VITRO TRANSFECTED CELLS WITH DIFFERENT MUTANT FORMS OF TNF RECEPTOR I AND MONOCYTES ISOLATED FROM TRAPS PATIENTS: TWO SIDES OF THE SAME COIN?

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Aim: To analyze in the same experimental setting the expression and internalization of tumor necrosis factor receptor 1 (TNFRI) in monocytes of patients carrying different *TNFRSF1A* mutations and in 293T cells transfected with the equivalent mutant forms of TNFRI.

Patients and methods: Monocytes from 9 TNF receptor-associated periodic syndrome (TRAPS) patients, 6 healthy controls and 293T transfected cells were stimulated with and without 30 ng/ml recombinant TNF-α and analyzed by flow cytometry. 293T cells were transiently transfected with 500 ng of pcDNA3.1/CT-GFP-TOPO carrying in frame cDNA of wild-type TNFRSF1A and of its following mutant forms: del27, C29Y, C55Y R92Q, C43R and Y207A. Transfections were performed using Fugene6 Transfection Reagent and cells were harvested after 48h.

Results: Monocytes from TRAPS patients displayed a normal surface expression of TNFRI and an impaired internalization after binding with TNF-α (62%, range 40-73% vs 32%, 27-42% in healthy controls). 293T cells transfected with wild-type TNFR1 and the R92Q mutant form displayed an equivalent expression and internalization of TNFRI receptor. No surface expression of TNFRI was observed in cells transfected with cysteine mutations. Conversely, cells transfected with del27 mutation were able to normally express TNFR1 on the cellular surface and displayed the same impaired internalization observed in 293T cells transfected with a mutant form of TNFR1 carrying an amino acid substitution affecting the internalization consensus motif (Y207A).

Conclusion: An impaired internalization of TNFR1 may represent a relevant pathogenetic mechanism related to the impaired apoptosis observed in TRAPS patients. Discrepancies among data obtained from ex vivo and in vitro transfected cells will be discussed.

YIM OP-14

IL-17 PRODUCING CELLS ARE ENRICHED IN JUVENILE IDIOPATHIC ARTHRITIS (JIA) SYNOVIAL FLUID BUT ARE RECIPROCAL TO REGULATORY T CELL (TREG) NUMBERS

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Introduction: The prevailing model of autoimmune pathology in JIA has had a central role for interferon gamma (IFNγ) secreting T cells within the joint. However, recent data have demonstrated a new subset of T cells, Th17, that are critical to produce arthritis in animal models, but their role in humans is unclear.

Methods: Peripheral blood (PBMC) and synovial fluid mononuclear cells (SFMC) samples from 18 JIA patients (3 polyarthritis, 2 systemic, 13 oligoarthritis JIA) and 5 healthy controls (PBMC) were analyzed for interleukin (IL)-17 and Foxp3 expression. SFMC samples were depleted of CD25+ cells, and proliferation to anti-CD3 and PHA was assessed using CFSE, with intracellular cytokine staining for IL-17 also performed.

Results: IL-17+ T cells are enriched in SFMC (1.9% of CD4+ T cells vs 0.57% and 0.48% in JIA and adult healthy control PBMC, respectively). The frequency of IL-17 cells in the joint showed subtype-specific associations. Foxp3+ cells were inversely related to the frequency of IL-17+ T cells but not IFNγ+ cells ($r = -0.737$, $p = 0.01$). Depletion of CD25+ cells led to increased proliferation of IL-17+ cells in response to mitogens, and this was reversed by addition of CD25+ cells.

Conclusions: We have demonstrated that Th17 cells are enriched within the joints of children with JIA. Remarkably, Th17 numbers are inversely related to Treg, but only within synovial fluid. We are investigating the possibility that the link between enhanced Treg numbers and a milder form of JIA may be a result of Treg suppression of Th17 cells.

YIM OP-15

NASAL CO-ADMINISTRATION OF CPG INCREASES THE ARTHRITIS-PROTECTIVE EFFECT OF HSP60 PEPTIDE P1

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Peptide-based immune therapy is a promising way to treat autoimmune diseases. Nasal administration of a PanDR-binding HSP60 epitope (p1) prevented adjuvant arthritis in the majority of rats. To further enhance this arthritis-protective effect, we tested CpG as an adjuvant for p1. CpG binds TLR9 on dendritic cells (DCs) and B cells, leading to their activation and enhanced peptide presentation.

Rats were treated with three nasal doses of p1, CpG or a combination of p1 and CpG. Two days after the last treatment, mandibular lymph node (MLN) cells were harvested. We determined phenotype and activation status of antigen-presenting cells (pDC, CD4+DC and CD4-DC) and proliferative responses of T cells. Five days after the last treatment, arthritis was induced with CFA. Spleens were harvested sixty days after arthritis induction. Interferon (IFN)γ production of in vitro p1 restimulated spleen cells was measured by ELISA.

Nasal co-administration of CpG enhanced the arthritis-protective effect of p1. CpG treatment alone could not prevent arthritis. After p1+CpG co-treatment, an increase in number and activation status of DCs and B cells was observed in MLN cells. The increased p1 specific proliferation of T cells in the MLN was accompanied by enhanced p1 specific production of IFNγ systemically, which could be detected after treatment of arthritis.

Clinical and immunological data imply that CpG may be a suitable adjuvant for peptide-specific immune therapy in arthritis. Future plans include adoptive transfer of p1+CpG treated spleen cells and a further analysis of the regulatory capacity of the induced p1 specific T cells.

YIM OP-16

INADEQUATE PPD RESPONSE IN POLYARTICULAR AND SYSTEMIC JIA

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Background: The tuberculin skin test is the only widely used method that detects latent tuberculosis infection and is dependent on a normal T cell function. In juvenile idiopathic arthritis (JIA), the T cell function is altered, which may result in an inability to develop an adequate PPD reaction.

Objective: To evaluate the response of JIA patients to PPD in different subgroups at the time of diagnosis prior to immunosuppressive therapy.

Methods: 80 patients with JIA were studied. PPD 5 U was applied using the Mantoux method, and skin reaction was measured at 72 hours. The reaction was considered negative for PPD<5mm. All patients were evaluated with a chest X-ray.

Results: Thirty-eight patients had 1 BCG vaccination, 41 had 2 BCG vaccinations and 1 had 3 BCG vaccinations. The mean age and number of BCG vaccinations was higher in enthesitis-related arthritis, whereas there were no differences in these parameters between polyarticular, oligoarticular, and systemic arthritis. Erythrocyte sedimentation rate (ESR) was significantly lower in oligoarthritis than in the other groups. PPD reaction was significantly lower in polyarticular and systemic JIA. 46 patients (58%) had a negative PPD reaction. 27 of 30 (90%) patients with polyarticular and systemic JIA had a negative PPD reaction. The chest X-rays of all patients were normal. Nine patients had a PPD reaction ≥15 mm, and they were put on isoniazid prophylaxis.

	Polyarticular (n=20)	Oligoarticular (n=29)	Systemic-onset (n=10)	Enthesitis-related (n=21)
Age (month)*	97±45	84±39	71±43	148±41†
Duration of the disease (week)*	50±52	45±69	6±7†	38±49
Number of joints*	17±12†	1.5±1	3.5±8	3.5±3
PPD reaction (mm)*	1.5±3.1†	6.8±6.2	0±0†	9.5±6.6
Number of BCG vaccinations*	1.35±0.7	1.38±0.5	1.30±0.5	1.8±0.4†
ESR (mm/h)*	52±35	30±25†	85±41	55±33

*mean±SD
† p<0.01

Conclusion: A tuberculin skin test may have difficulty in detecting latent tuberculosis infection in patients with polyarticular and systemic onset JIA. However, it may reflect the true reaction in patients with oligoarticular and enthesitis-related JIA.

YIM OP-17

MEFV MUTATIONS: AN IMPORTANT GENETIC PREDISPOSING FACTOR IN HENOCH-SCHONLEIN PURPURA (PRELIMINARY RESULTS)

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Objectives: Henoch-Schönlein purpura (HSP) is one of the most common vasculitides of childhood. Although the overall estimated annual incidence of HSP was 20.4/100,000 in children, it occurs in 5% of patients with familial Mediterranean fever (FMF). The aim of this study was to investigate the prevalence of MEFV mutations in patients with HSP.

Study design: Forty-eight (28 M, 20 F) pediatric patients with HSP were enrolled in this study. A questionnaire that encompassed the clinical characteristics of the patients was completed by the physicians. Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the MEFV gene were studied.

Results: The mean age at the diagnosis of HSP was 8.2 ± 3.4 years (range 2 to 15 years). Twenty-three (48.0%) patients were found to carry MEFV mutations. Six (12.5%) of them had homozygous and compound heterozygous mutations. Seventeen out of 48 patients (35.4%) were observed to be heterozygous for one of the screened MEFV mutations: p.M694V in 10, p.E148Q in two, p.M680I in two and p.V726A in three patients. Fourteen patients had clinical findings compatible with FMF. Eleven (32.3%) of the 34 HSP patients -who were found not to be associated with FMF- carried MEFV mutations.

Conclusions: Alterations in the MEFV gene are important susceptibility factors for the development of HSP. HSP-like vasculitides seem to be an important feature of FMF but are usually unrecognized. Thus, HSP patients should be followed cautiously with regard to FMF.

YIM OP-18

IDENTIFICATION OF 90 FAMILIES WITH PEDIATRIC RHEUMATIC DISEASES-AFFECTED SIBPAIRS: RESULTS OF THE PRINTO SURVEY

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Pediatric rheumatic diseases (PRD) are multifactorial complex polygenic diseases that can be categorized as complex genetic traits. The availability of DNA from families in which there are two or more siblings with PRD represents an important source for the identification of susceptibility genes.

The objective of this survey was to investigate the genetic basis of the PRD, other than juvenile idiopathic arthritis (JIA), through the analysis of families with affected sibpairs.

Methods: All Centers belonging to the PRINTO network were asked to complete an on-line survey requesting information on age, gender and PRD diagnosis for each affected sib.

Results: 119/277 (43%) worldwide rheumatologic centers belonging to the PRINTO network responded to the survey. 90 families with at least 2 children with PRD were identified (10 triplets). Among 190 patients recruited, 72 (38%) were male and 118 (62%) female, with a mean age at visit of 15.5±8.3 years. The diagnosis distribution was as follows: systemic lupus erythematosus (JSLE) 36% (5 triplets), familial Mediterranean fever 13%, localized scleroderma 5%, Behçet's syndrome 4% (2 triplets), iridocyclitis 4%, and other PRD 38%. In 66/90 families (73%), there was concordance for disease subtype (57 sibpairs and 9 triplets).

Conclusion: We identified a relevant number of PRD familial cases. JSLE represents the most frequent PRD, other than JIA, in which familial cases can be identified. The analysis of DNA through a genome-wide screen will be useful to identify the genes involved in PRD susceptibility and pathogenesis.

YIM OP-19

EXPERIENCE WITH THE USE OF TUMOR NECROSIS FACTOR ANTAGONISTS IN CHILDREN WITH TAKAYASU ARTERITIS

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Objective: To report our experience with the use of tumor necrosis factor (TNF) antagonists in the treatment of children with Takayasu arteritis (TA).

Methods: Five patients (4 girls, 1 boy), who met the American College of Rheumatology classification criteria for TA were started with infliximab (IFX) because of disease relapse during conventional therapy (4 patients) or as first-line therapy together with steroids (1 patient). Infliximab was administered at the dose of 5 mg/kg at weeks 0, 2 and 6, and every 6 weeks thereafter. Methotrexate or azathioprine therapy was associated to prevent production of anti-chimeric antibodies. Outcome measures included acute phase reactants, changes in prednisone dosage, Doppler ultrasound and magnetic resonance (MR) angiography.

Results: Median age at diagnosis was 12.9 years (range 7.6–21). Median duration of IFX therapy was 18 months (range 6-27). At the end of IFX therapy, all but one patient had reduced prednisone dose, 3 patients had normalization of acute phase reactants, and in all patients imaging studies did not show new vascular lesions and/or worsened vessel wall enhancement. One patient was switched

to etanercept after 10 infusions of IFX because of incomplete clinical response. This patient was further switched to adalimumab 4 months later due to etanercept inefficacy and is currently doing better. Another patient had a disease relapse after an initial response to IFX and was then switched to adalimumab for 2 months without improvement. No patient experienced major adverse events during anti-TNF therapy.

Conclusion: Our results show that anti-TNF agents represent a promising therapeutic option for children with TA. A controlled trial is warranted to further evaluate the efficacy and safety of these drugs in TA.

YIM OP-20

WHICH IS THE BEST IMAGING MODALITY TO CAPTURE BONE EROSIONS IN JIA?

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Background: *M*ore sensitive imaging modalities are required in juvenile idiopathic arthritis (JIA) to assess joint damage.

Objectives: To compare joint magnetic resonance imaging (MRI), sonography (US) and conventional X-ray sensitivity in evaluating bone erosion and to relate imaging results with clinical parameters.

Methods: 39 JIA patients followed at the Gaslini Rheumatologic Department underwent radiographs, US and MRI of wrist (23 pts) or hip (16 pts) in the same day. MRI, US and X-ray scores were completed independently by two readers. The relationship between imaging scores and clinical data (number of limited joints (LOM), severity of joint involvement, CHAQ, and JADI) was evaluated.

Results: 10 male and 29 females were evaluated [mean age: 12.5±3.7 (range: 5.6-18.5); mean duration of JIA: 5.9±3.9 years]. The inter-reader intraclass correlation coefficients were excellent for MRI (ICC wrist: 0.97; hip: 0.92) and radiography (ICC wrist: 0.97; hip: 0.91). 80.6%, 41.7%, and 36.1% of the patients had erosions identified on MRI, X-ray and US, respectively. 13 patients, with erosions identified only by MRI, were not identified on X-ray or US. All 7 patients negative on MRI were also negative on X-ray. Spearman's correlation between MRI and X-ray scores was satisfactory (r_s=0.85). Wrist MRI and X-ray scores correlated highly with LOM score (r_s=0.71 and r_s=0.79); hip MRI and X-ray correlated with JADI-A (r_s=0.52 and r_s=0.61). The correlations between MRI and X-ray scores and clinical indicators of disease activity were low, as expected.

Conclusion: MRI appears to be the most sensitive modality to capture bone erosion compared to US and radiography.

YIM OP-21

CLINICAL AND BIOLOGICAL FEATURES OF SoJIA PATIENTS WITH COMPLETE OR INCOMPLETE RESPONSE TO ANAKINRA TREATMENT

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Aim: To identify among systemic onset juvenile idiopathic arthritis (SoJIA) patients possible differences between complete and incomplete responders to Anakinra.

Patients & Methods: 20 SoJIA patients were treated with Anakinra at the starting dose of 1 mg/kg/day. The mean follow-up was 1.10 year (range 0.3 -2.1). Complete response was defined as the absence of systemic and joint manifestations and complete normalization of acute phase reactants at follow-up. Other patients were considered as incomplete or non-responders. Serum levels of 27 different cytokines (IL-1 to 18, IFN, TNF, MIF), growth factors (VEGF, VCAM-1, GM-CSF), and other soluble molecules (IL1RII, pentraxin) were analyzed at day 0 and day 7 using Bio-Plex cytokine multiplexable bead assays (BioRad). Monocytes from SoJIA patients and healthy donors were activated with 1 μg/ml LPS for 3 h. Intracellular and secreted pro-IL-1β and IL-1β were determined by western blot and ELISA with or without ATP stimulation for 15'.

Results: 9 SoJIA patients were classified as *complete responders,* and 11 patients as *incomplete or non-responders*. At baseline, complete responders displayed a lower number of active joints ($p = 0.04$) and increased neutrophil counts ($p = 0.03$) and IL-9 serum levels ($p=0.04$). Incomplete and non-responder patient group was characterized by higher levels of VCAM and GM-CSF. The magnitude of IL-1β secretion from monocytes from SoJIA patients after LPS and ATP stimulation did not differ from healthy controls and among responder and non-responder patients.

Conclusions: *T*he response to Anakinra seems to identify different populations in the groups of SoJIA, possibly characterized by distinct clinical and biological features.

YIM OP-22

THE LONG-TERM OUTCOME OF JUVENILE IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM): A MULTICENTER, MULTINATIONAL STUDY OF 557 PATIENTS

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Objective: To investigate the long-term outcome of a multicenter cohort of patients with juvenile IIM seen over a 20-year period.

Methods: All patients with juvenile IIM and disease duration >2 years seen at participating centers after 1980 were identified. Subsequently, patients were located and asked to undergo a cross-sectional assessment. The study included retrospective assessment of onset features, disease course and drug therapies, and cross-sectional assessment of disease activity, muscle strength, functional ability, accumulated damage, and health-related quality of life (HRQL). Patients who died were retrospectively assessed, including damage assessment, until the last visit before death.

Results: 654 patients (96% with JDM) were identified in 30 centers in 5 countries (Italy, UK, Mexico, Brazil, Argentina) and 557 of them (85%) underwent study assessments. At cross-sectional assessment: 42% and 54% of patients had abnormal muscle strength (MMT and CMAS, respectively); 46% and 61% of patients had ongoing disease activity (MITAX and DAS, respectively); 47% and 55% of patients had abnormal CHAQ score and parent global assessment, respectively; 69% of patients had cumulative damage (MDI) in one or more organ system (57% skin, 37% muscle, 28% skeletal); and 11% and 5% of patients had a HRQL (CHQ) in the physical and psychosocial domain, respectively, > 2 standard deviations below the mean of healthy children.

Conclusion: At >2 years after onset, a substantial proportion of patients with juvenile IIM had persistently active disease and cumulative organ damage. Reassuringly, only a few patients had major impairment in HRQL.

YIM OP-23

ROLE OF INTRACELLULAR METHOTREXATE ASSESSMENT FOR THERAPY OPTIMIZATION IN JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: Methotrexate (MTX) has become the most commonly used second-line agent in the treatment of more severe forms of JIA. The individual effective dose ranges between 7.5-20 mg/m^2/week. Optimization of the initial treatment (dose, route of administration) is highly clinically relevant. The dose-finding process may be unnecessarily prolonged with suboptimal dosing while aggressive higher-dose therapy increases toxicity risk. MTX bioavailability is influenced by many intrinsic as well as compliance factors. Previous studies have shown that concentration of MTX polyglutamates in erythrocytes (EMTX) may reflect MTX bioavailability and could help to guide early MTX therapy as well as further drug monitoring.

Aim: We compared EMTX concentrations in clinical responders and non-responders to evaluate possible usefulness of EMTX assessment in optimization of MTX therapy and in drug monitoring.

Patients and Methods: Follow-up evaluation of disease activity during routine clinic visits (core sets of JIA outcome measures)(1) was used to assess efficacy of MTX therapy in 28 JIA patients with various onset subtypes (12 boys, 16 girls, mean age 9.7 years, mean disease duration 3.6 years). Therapy response was defined as full-response (inactive disease), partial response (≥ pedACR 50) and no response (≤ pedACR 30) after mean MTX therapy duration of 2.2 years. Patients were treated with a stable dose of MTX titrated according to clinical effect and administered orally (p.o., n = 12) or subcutaneously (s.c., n = 17). EMTX was measured by HPLC with fluorescence detection (2).

Results: Table 1 summarizes the data on dosing and EMTX values in patients grouped according to the response to therapy. Despite higher dosing in the groups with partial response and nonresponse, EMTX values did not differ between groups. Consequently, dose-normalized EMTX levels were lower in patients with insufficient response due to decreased systemic bioavailability of MTX and/or other differences in the kinetics of EMTX accumulation. In two additional cases, unexpectedly low EMTX concentrations were found and noncompliance was confirmed by the patients.

Conclusion: Our preliminary study shows that differences exist in the kinetics of EMTX accumulation between responders and nonresponders to MTX therapy. Nonresponders may require higher therapeutic concentrations of MTX polyglutamates than responders. Consequently, dose escalation of MTX guided by EMTX concentrations could be advantageous. Until this concept is tested in a prospective trial, we can recommend monitoring of EMTX only for evaluation of patient compliance.

Table I. Dosing of MTX and concentrations of MTX polyglutamates in erythrocytes (EMTX).

	Responders	Partial responders	Nonresponders	P-value*
N	16	4	8	–
Route of admin.	6 p.o./10 s.c.	1 p.o./3 s.c.	3 p.o./5 s.c.	–
Dose (mg/m^2 BSA)	10.4 (8.9–11.9)	12.5 (6.8–18.1)	15.7(11.0–20.4)	< 0.02
EMTX (nmol/L)	88.0 (72.1–104)	68.0 (39.5–96.4)	71.6 (38.7–104)	0.36
EMTX/Dose	9.1 (7.1–11.1)	5.7 (2.5–8.8)	4.5 (2.9–6.1)	< 0.01

Data are shown as the mean (95%-CI for the mean). *One-way ANOVA.

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YIM OP-24

EVALUATION OF INTEROBSERVER AGREEMENT IN CLINICAL EXAMINATION IN JUVENILE IDIOPATHIC ARTHRITIS

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Objective: Currently the management of juvenile idiopathic arthritis (JIA) and the outcome of clinical trials are reliant on clinical examination to confirm the extent of joint involvement. Delay in diagnosis or under-assessment of severity can seriously affect outcome, nor is over-treatment desirable. The aim of this study was to evaluate agreement in musculoskeletal examination between pediatric rheumatologists (PR) in children with JIA.

Methods: We compared the examinations made by 9 blinded consultant PR from the UK Eire and Canada in 9 children with JIA, giving 5427 joint and 891 entheses examinations. Children at the time of examination had either mild disease activity or were considered in remission in the clinical setting, but had variable severity and duration of JIA in the past. Examiners were given a standard written summary of the clinical history and were encouraged to examine in their own established examination style, but to report their findings using the Core Outcome Variables. Analysis was by kappa statistics (κ) and percentage of agreement (%) of the enthesitis scores, and a combined score of active and restricted joints, giving 36 paired comparisons between consultants.

Results: The percentage of these joints reported as abnormal ranged from 2.8 to 14.8% for the different consultants, and 2.0-26.3% for enthesitis.

Agreement		Slight	Fair	Moderate	Substantial
	n	15	20	1	0
	κ	0.01–0.20	0.20–0.38	0.43	–
	p	13<0.05 2=NS	<0.05	<0.05	–
Arthritis	%	82–95	84–95	96	–
	n	14	14	7	1
	κ	0.04–0.19	0.20–0.32	0.41–0.60	0.73
	p	8=<0.05 6=NS	<0.05	<0.05	<0.05
Enthesitis	%	75–94	77–96	83–96	90

Conclusions: Overall, there was low agreement between examiners in their assessment of joints and entheses in children with mild disease activity where examiners used their own examination technique. A standardized examination technique for clinical trials and awareness of the limitations of musculoskeletal assessment in clinical practice are essential.

OP-1

GENE EXPRESSION PROFILING IN UNTREATED NEW ONSET SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS REVEALS MOLECULAR HETEROGENEITY THAT MAY PREDICT MACROPHAGE ACTIVATION SYNDROME

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Systemic juvenile idiopathic arthritis (sJIA) has been strongly associated with macrophage activation syndrome (MAS). To better understand the pathogenesis of sJIA and to facilitate the search for MAS biomarkers, we examined gene expression profiles from 17 untreated new onset sJIA patients. Five of the 17 patients showed biologic evidence of subclinical MAS and two eventually developed overt MAS. Peripheral blood mononuclear cells were isolated using a Ficoll gradient and total RNA was analyzed using Affymetrix GeneChips®. Two hundred twenty-five differentially expressed genes were identified (T-test; $p<0.01$; Bonferroni correction) that distinguished sJIA (n=17) from healthy controls (n=30). Clustering analysis of these genes identified three main expression patterns that correlated with normal versus high (which included subclinical MAS) serum ferritin levels. The first cluster contained genes involved in the synthesis of hemoglobins and structural proteins of erythrocytes consistent with immature nucleated red blood cells likely reflective of red cell turnover. Also included were transcripts indicating immature granulocytes. A second cluster was enriched for genes involved in cell cycle regulation and apoptosis. The third cluster was enriched for genes implicated in innate immunity including those involved in the negative regulation of the TLR/IL1-induced inflammatory cascades and markers of the alternative pathway of macrophage differentiation. The alternative pathway leads to the development of scavenger macrophages with enhanced phagocytic activity. Additional differentially expressed genes of interest included SH2D1A, Rab27a, and LYST. We conclude that gene expression profiling can be utilized to identify candidate blood biomarkers for MAS in sJIA.

OP-2

INVESTIGATION OF EFFECTIVENESS OF 10 M. WALKING, TIMED UP AND GO, AND SIT AND STAND TESTS IN PATIENTS WITH JUNENILE IDIOPATHIC ARTHRITIS: A COMPARISON WITH HEALTHY CONTROLS

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Background: Children with juvenile idiopathic arthritis (JIA) experience joint swelling, pain and limited mobility, which contribute to decreased physical activity, fitness, and function, increasing their risk for disability. Exercise programs aimed to maintain or improve range of motion, strength, and endurance are considered vital to the management of arthritis in children. However, little is known about the validity of assessment tests that measure these parameters in children with JIA.

Objective: The aim of this study was to investigate the results of velocity, endurance, flexibility and dynamic balance tests in children with JIA and compare results with those of healthy children.

Methods: 11 JIA and 20 healthy children were included in this study. Disease activity, disease duration and number of active joints of the patients were recorded. 10 m. walking test for velocity, sit and stand test (SST) in a chair for 30 sec. for endurance, and timed up and go test (TUG) for flexibility and dynamic balance were applied in both groups. Function was measured by means of Childhood Health Assessment Questionnaire (CHAQ).

Results: Significant differences were found between the two groups (10 m. Walk: $p<0.030$, SST: $p=0.000$, TUG: $p<0.004$). Children with JIA accomplished the 10 m. walking and TUG tests 46% and 33% more slowly, respectively, than controls, and 38% less on SST compared to the control group. There was a correlation between CHAQ and 10 m. walking test ($p<0.007$) and CHAQ and TUG ($p<0.014$). There were correlations between disease activity and TUG ($r=0.614$, $p<0.045$) and number of active joints and 10 m. walking test ($r=0.664$ $p<0.045$). Disease duration of patients did not affect results of any of the three tests.

Conclusion: These tests are easy to administer in the clinical setting. They clearly demonstrated the difference between patients with JIA and the control group. We concluded that these tests, which measure endurance, velocity and balance, should also be considered in addition to other parameters of functional ability while preparing the assessment tests for pre- and post-treatment in patients with JIA.

OP-3

ASSESSMENT OF 25 PATIENTS WITH THE DIAGNOSIS OF CHILDHOOD POLYARTERITIS NODOSA (PAN) ACCORDING TO THE NEW CLASSIFICATION CRITERIA

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Objectives: To review 25 patients' files with the diagnosis of PAN or PAN-like disease, according to the most recent criteria for childhood vasculitis as defined recently (S Ozen et al, ARD 2006).

Methods: Patients were divided in two groups as one group of 15 (8F/7M) patients meeting the criteria and one group of 10 patients (6F/4M) who did not meet these criteria due to the lack of typical histological features. Clinical, laboratory and radiological symptoms at presentation were recorded, as well as treatments and follow-up, in order to compare both groups.

Results: No differences were found between the groups in terms of follow-up (5y2m vs 4y10m) and onset symptoms: mean age at onset (8y8m in PAN patients vs 8y1m), fever (in 14/15 patients vs 8/9), skin nodules (12/15 vs 8/10), soft tissue swelling (7/15 vs 7/10), livedo reticularis (3/15 vs 4/10), arthralgia (8/15 vs 7/10), arthritis (2/15 vs 5/10), myalgia (10/15 vs 6/10), and abdominal pain (6/15 vs 4/9). Laboratory findings were similar: leukocytosis ($16x10^9$/L vs $19x10^9$/L), thrombocytosis ($458x10^9$/L vs $517x10^9$/L), C-reactive protein (157 mg/L vs 126 mg/L), and presence of antinuclear antibodies (4/15 vs 2/7). Patients of both groups received similar treatments, mainly oral steroids (10/15 patients vs 8/10) with comparable initial dosage (1.9 $mg.kg^{-1}.d^{-1}$ vs 1.68) and efficacy (8/10 patients vs 8/8). Parenteral steroids were administered (4/10 vs 2/10) with comparable efficacy (3/4 vs 2/2). Intravenous immunoglobulins were infused (6/15 vs 4/10) with the same efficacy (3/6 vs 2/4). The situation of patients of both groups at last visit was comparable: complete remission without treatment (5 vs 5), complete remission under treatment (6 vs 2), partial remission under treatment (2 vs 1), and lost to follow-up (2 vs 1). One patient with a very unusual clinical presentation died of septic shock in the group with typical histology.

Conclusion: Although PAN-like patients did not show typical histological findings, they shared the same initial presentation and course with the PAN patients. The difference between groups may be due only to non- contributive biopsies.

OP-4

ACUTE KAWASAKI DISEASE IS ASSOCIATED WITH REVERSE REGULATION OF SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (SRAGE) AND ITS PROINFLAMMATORY LIGAND S100A12

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Objective: RAGE serves as a pattern recognition receptor for a number of endogenous ligands that are potent inducers of inflammation. Activating endothelial cells and leukocytes, RAGE augments recruitment of leukocytes to sites of inflammation, which is a key process especially in vasculitis. Soluble receptor for advanced glycation end products (sRAGE) acts as a naturally occurring inhibitor of RAGE by neutralizing proinflammatory ligands, e.g. S100A12. This neutrophil-derived protein has been reported to be associated with Kawasaki disease (KD) and to provoke proinflammatory responses. In this study, we investigated for the first time circulating sRAGE in an acute inflammatory disorder and compared these data directly with concentrations of the proinflammatory RAGE-ligand S100A12.

Methods: Serum concentrations of sRAGE and S100A12 were analyzed by specific ELISAs in 50 children with KD. In 28 of the patients, levels were analyzed longitudinally over the course of the disease.

Results: KD patients had decreased levels of sRAGE during active disease, especially those more severely affected and not responding to treatment. In addition, sRAGE correlated negatively to proinflammatory S100A12, which was found elevated in patients with active KD. S100A12/sRAGE ratio showed significant differences between responders and non-responders after intravenous immunoglobulin (IVIG) therapy.

Conclusions: Inverse regulation of both sRAGE and its proinflammatory ligand S100A12 seems to be a relevant molecular mechanism promoting systemic vasculitis. Calculating the S100A12/sRAGE ratio might help to detect patients with KD at risk for non-response to IVIG therapy.

OP-5

APOPTOSIS OF REGULATORY T CELLS (T_{reg}): HOMEOSTATIC CONTROL OF T_{reg} AND LOSS OF T_{reg} IN DERMAL LESIONS OF LUPUS PATIENTS (CLE)

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$CD4^+CD25^+FOXP3^+$ regulatory T cells (T_{reg}) are potent immunosuppressive T cells. Reduced peripheral blood T_{reg} numbers have been reported to be associated with pediatric autoimmune disease. Mechanisms of T_{reg} -reduction during autoimmune disease are not clear. We have recently reported high sensitivity of T_{reg} towards CD95L-mediated apoptosis[1]. However, a T_{reg} subpopulation remains consistently apoptosis-resistant. Gene micro array and 6-color flow cytometry analysis including FOXP3 revealed that naïve T_{reg} with an apoptosis-resistant phenotype constitute this so far neglected T_{reg} population. We demonstrate the importance of naïve T_{reg} for the homeostasis of T_{reg} and translate our findings into cutaneous lupus erythematosus (CLE). Analysis of CLE-patients revealed a significant loss of T_{reg} in the skin compared to other inflammatory skin diseases and peripheral blood. To elucidate the underlying mechanism, we tested for alterations in migratory and cell death properties of CLE-derived

T_{reg}. Based on the high apoptosis sensitivity of memory T_{reg} compared to apoptosis-resistant naïve T_{reg}, we present a new hypothesis for paucity of T_{reg} in the dermal lesion during autoimmune disease.

1. Fritzsching et al., Cutting Edge, Journal of Immunology l. 2005 Jul 1; 175 (1): 32-6.

OP-6

HUMAN BONE MARROW MESENCHYMAL STEM CELLS SUPPORT POLYCLONAL STIMULATION OF HUMAN B CELLS

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To investigate the possible application of bone marrow (BM) mesenchymal stem cells (MSCs) in systemic lupus erythematosus (SLE), an autoimmune disease in which B cells play a pivotal role, we studied the interaction of B cell subsets isolated from healthy donor and pediatric SLE patients with human BM MSCs. We isolated from peripheral blood of healthy donors: a) immature transitional B cells, b) naïve B cells, c) IgM memory and d) switch memory B cells. BM MSCs promoted proliferation and differentiation into immunoglobulin secreting cells of transitional and naïve B cells stimulated with CpG 2006 in the absence of BCR triggering, and strongly enhanced proliferation and differentiation of both memory B cell populations. Furthermore, both proliferation and differentiation into plasma cells of CD19+ B cells isolated from pediatric SLE patients were enhanced by BM MSCs upon polyclonal stimulation. Inhibition of T cell proliferation by MSCs was suggested to be dependent on INF-γ. To test whether INF-γ could have an effect on the B cell response under the influence of MSCs, we co-cultured B cell subsets with MSC in the presence of human recombinant INF-γ̃. After four days of culture, both proliferation and differentiation into plasma cells of all B cell subsets stimulated with CpG, soluble CD40L and anti-Ig were inhibited in both healthy donors and SLE patients. These data show the complexity of the cross-talk between MSCs and B cells and how the microenvironment in which the interaction takes place could influence the outcome of the immune response.

OP-9

FAMILIAL JUVENILE IDIOPATHIC ARTHRITIS: CLINICAL FEATURES AND LOCALIZATION TO CHROMOSOME 13q

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Objective: To delineate the clinical features of familial juvenile idiopathic arthritis (JIA) in Saudi patients and to localize the underlying gene.

Methods: All included patients fulfilled the ILAR criteria for JIA. We defined familial JIA patients as belonging to a family with more than one sibling diagnosed with JIA. Familial autoinflammatory diseases including certain subgroups of JIA (i.e. spondyloarthropathies), familial Mediterranean fever or known syndromes associated with articular manifestations were excluded. All patients were assessed with respect to: age of onset of JIA, disease activity, disease damage and laboratory variables. DNA was obtained from all patients and a whole genome scan was performed using the Affymetrix Gene Chip Mapping 10K 2.0 Array for linkage analysis.

Results: Eleven affected siblings (9 female/3 male) with JIA belonged to four apparently unrelated families. All patients were from the same geographical area. The mean age at onset was 2.4 years, and mean age at diagnosis was 3.5 years. The mean duration of follow up was 6.4 years. All patients presented with multiple joint involvement at diagnosis. One third of the patients had a polyarticular onset subtype, and the remainder had a systemic onset subtype. All patients had elevated inflammatory markers and rheumatoid factor was positive in 38% of them. Radiological evaluation revealed significant osteopenia, joint space narrowing and erosions. Genome-wide parametric linkage analysis of the four families using an autosomal recessive model of inheritance localized the disease to a ~4cM region of chromosome 13q with a combined multipoint LOD score of 9.87.

Conclusion: Familial JIA has similar clinical features to the more common sporadic JIA. Localization of familial JIA to chromosome 13q and subsequently cloning of the underlying gene may provide further insight into the immunopathologic features of this disease. Thereby, opportunities for earlier diagnosis and detection of carrier status may provide the basis for reduced morbidity and disease prevention.

OP-13

EXTREMELY SKEWED X-CHROMOSOME INACTIVATION IN JUVENILE IDIOPATHIC ARTHRITIS

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Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease, with an incidence between 7-21/100,000. The genetic basis of JIA is unknown. It rarely manifests familial recurrence, but the monozygotic twin data suggest that there is a considerable genetic basis, which is likely to involve multiple epigenetic events (*Autoimmun Rev*, 5:279, 2006). We identified an association between extremely skewed X-chromosome inactivation (XCI) patterns and female predisposition to autoimmunity (*Arth&Rheum*, 52:1564, 2005*; Eur J Hum Gene*t 14:791, 2006). Since JIA is thought to have an autoimmune etiology, we studied the XCI patterns of 72 female patients diagnosed with JIA and 183 female controls. The control group was comprised of newborns (n=91) and children with no history of an autoimmune condition (n=92). To determine XCI status, androgen receptor locus was analyzed by methylation sensitive *Hpa* II digestion followed by PCR. A male control (46, XY) was used for complete digestion. Extremely skewed (>90% skewing) XCI was observed in DNA from the peripheral blood cells in 9 of 56 informative patients (16.1%), and in 4 of 124 informative controls (3.2%, P=0.0039). When patients and controls with 80-89% skewing were also included in the analysis, 14 patients (25.0%) and 12 controls (9.7%, P=0.0108) displayed skewed XCI. These results show that there is a significant association (odds ratio 16.9, 95% confidence interval 6.2-45.8) between extremely skewed XCI and JIA. "Loss of mosaicism" for X-linked gene expression could be considered as a potential mechanism in break-down of self tolerance.

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OP-16

OUTCOMES IN JUVENILE IDIOPATHIC ARTHRITIS: HOW ARE OUR PATIENTS DOING?

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Objective: To investigate the outcomes of a cross-sectional cohort of juvenile idiopathic arthritis (JIA) patients with long-standing disease.

Methods: Consecutive patients with disease duration ≥5 years seen between September 2003 and March 2007 were evaluated. Assessments included physician's and parent's global assessments, joint counts, CHAQ, Juvenile Arthritis Damage Index (JADI), Poznanski score of radiographic damage, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and health-related quality of life (CHQ).

Results: 308 patients (242 girls) were studied. Thirty-one had systemic arthritis, 60 RF-negative polyarthritis, 6 RF-positive polyarthritis, 84 extended oligoarthritis, 116 persistent oligoarthritis, and 11 psoriatic arthritis. 23.4% of patients had inactive disease, 51.3% had CHAQ = 0 and 74.7% were in Steinbrocker class I; 3% of patients had CHAQ >1.5 and 3.6% were in Steinbrocker classes III or IV. 35.4% and 27.3% of patients, respectively, had articular and extra-articular damage in at least 1 site. 32.7% of patients with wrist disease had radiographic damage, defined as Poznanski score below -2 units. 20% and 13.8% of patients, respectively, had a CHQ-Physical score 1 and 2 SD below the mean of healthy controls and 10% and 1.3% of patients, respectively, had a CHQ-Psychosocial score 1 and 2 SD below the mean of healthy controls.

Conclusion: Our findings show that most JIA patients have persistently active disease at the last follow-up and confirm a tendency towards marked improvement in functional outcome. However, the degree of impaired function and cumulative damage observed is still considerable. Reassuringly, only a few patients have a major impairment in their quality of life.

OP-17

PRELIMINARY AGREEMENT OF THE PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY (PRES) ON THE EUSTAR/EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF SYSTEMIC SCLEROSIS IN CHILDREN (JSSC)

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Background: Juvenile systemic sclerosis (JSSc) is a multisystem disease leading to significant disability and mortality. The aim of the study was to verify the agreement of a group of PRES pediatricians on the use of the EUSTAR/EULAR recommendations for the management of SSc in children.

Methods: An EUSTAR/EULAR task force of 18 SSc international experts, including 2 pediatric rheumatologists and 2 representatives of patients with SSc, developed, through a web-based Delphi survey, a set of 26 research questions for the literature research. Systemic literature research was performed on Pubmed, Medline, EmBASE and Cochrane Database. Retrieved manuscripts were evaluated according to Jadad classification (1).

A final set of 14 recommendations for the treatment of SSc was developed and subsequently evaluated by a panel of 18 pediatric experts on JSSc to test their agreement on the appropriateness of these recommendations for children. Through a Delphi survey, they were asked to approve, disapprove or state the lack of experience for each of the 14 recommendations.

Results: For 9 recommendations concerning the use of cyclophosphamide, prostanoids, calcium channel blockers, corticosteroids, methotrexate, ACE and proton pump inhibitors, prokinetics and rotating antibiotics, a consensus greater than 85% among experts was reached. For the recommendation on continuous intravenous epoprostenol for SSc-related pulmonary arterial hypertension (PAH), the majority of experts had no experience. As far as new experimental drugs (i.e. bosentan for PAH and digital ulcers, sitaxentan and sindenafil), the experts expressed interest for future applications in pediatric clinical trials although there was not enough experience at present to recommend their use.

Conclusion: Most of the recommendations for the management of SSc in adults can be extended to JSSc. An international cooperation, following standardized operative procedure (2), is needed to validate the strength of these and future recommendations.

OP-19

RESULTS OF A MULTINATIONAL SURVEY REGARDING PREFERENCES OF PEDIATRIC RHEUMATOLOGISTS IN THE TREATMENT OF JUVENILE SYSTEMIC SCLEROSIS

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Introduction: To date, there have been no prospective or retrospective studies regarding effective treatment for patients with juvenile systemic sclerosis (jSSc). The aim of the survey was to obtain an understanding of the current treatment flow for patients with jSSc.

Methods: The survey consisted of 14 questions. The questions aimed to evaluate preferences regarding the effectiveness of the treatments for the different organ involvements of jSSc. The responders could score the effectiveness of the listed treatment from 1 to 5, with 1 being the most effective. For some topics, only a "yes" or "no" response was required. The survey was sent out to participants of the mailing lists of the Juvenile Scleroderma Working Group of the PRES, the Paediatric Rheumatology Bulletin Board and to members of the PRINTO.

Results: We received 65 responses that could be evaluated. The regional distribution of the responding centers were: 33 from Europe, 13 from North America, 11 from South America, 2 from Australia, 1 from Saudi Arabia, and in 5 cases the responder could not be identified. A list of second-line agents was offered from which to choose. Cyclophosphamide with 1.8 achieved the highest mean score for controlling overall disease activity, with 1.6 for control of pulmonary interstitial involvement and 1.7 for renal involvement. Methotrexate reached the highest score with 2.2 regarding the control of skin involvement. 66% of the responders would add corticosteroids to the disease-modifying agent, and 65% of them would prefer an oral corticosteroid. To control Raynaud phenomenon, the Ca-antagonists and i.v. Iloprost were viewed as equally effective with a score of 2.5. Bosentan reached 2.9, local therapy 3.6 and aspirin 4.0. Bosentan reached the highest score with 1.9 for the treatment of pulmonary hypertension. 78% of the responders would not anticoagulate the patients with pulmonary hypertension. 70% viewed autologous bone marrow transplantation as a realistic and effective rescue therapy. 65% of the responders routinely use ACE inhibitors to prevent a potential renal crisis and 87% treat gastroesophageal reflux with omeprazole. From the prokinetic agents, if needed, 41% would apply cisapride. 91% prescribe physiotherapy and 86% occupational therapy to mobilize the patients.

Discussion: This survey represents preferences in the treatment of jSSc. In some items, preferences differed from those in adult rheumatology. Prospective studies are needed to prove if the preferences really present the best choice of treatment.

OP-21

MODIFIED EURO-LUPUS NEPHRITIS TREATMENT PROTOCOL

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Cyclophosphamide (CYC) and glucocorticoids has been the landmark in the treatment of lupus nephritis. However, long-term treatment with CYC is associated with significant side effects. We aimed to evaluate the efficacy and importance of short-term intravenous (IV) CYC treatment as a remission induction treatment followed by azathioprine (AZA) or mycophenolate mofetil (MMF) as a maintenance treatment in children.

Twenty-six patients (23 girls, 3 boys) with biopsy proven Class III (7 patients) and IV (19 patients) lupus nephritis were included in the study. Detailed clinical and laboratory data, treatment modalities and outcomes of patients were evaluated. All patients received three methylprednisolone (MP) IV pulses on alternate days, followed by oral prednisone 0.5-1 mg/kg/day and 6 monthly IV pulses (500 mg/m^2) of CYC. Azathioprine or MMF was started as a remission maintaining treatment in 20 and 3 patients, respectively; 3 patients received only low dose oral steroid as maintenance therapy. In 8 of 20 patients, treatment was switched to MMF because of AZA-related toxicity or unresponsiveness.

The mean age at the time of diagnosis was 16.21±3.49 years (range: 4.5-21) and the mean duration of follow-up was 49.6±27 months (range: 8-122). Eighteen patients (66.6%) had complete remission, 5 (18.5%) had partial remission, 1 (3.7%) continued to have active disease and 2 (7.4%) progressed to end stage renal disease. Nine of the patients (50%) with complete remission had received AZA and switching to MMF increased complete remission rate (additional 6 patients, 33%). There were no side effects.

In conclusion, short-term (6 months) IV bolus CYC treatment followed by AZA is a safe and effective treatment in children with severe lupus nephritis, and MMF use increases the remission rate in resistant cases. Further studies are needed to define the role of MMF in the treatment armamentarium of children with lupus nephritis.

OP-22

HEPTAVALENT CONJUGATE PNEUMONOCOCCAL VACCINE IN CHILDREN WITH CHRONIC RHEUMATIC DISEASES UNDER IMMUNOSUPPRESSIVE THERAPY: SEROCONVERSION, SAFETY AND EFFICACY (PRELIMINARY DATA)

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Introduction: Streptococcus pneumoniae (SP) is the most common cause of severe respiratory tract infections in children with chronic rheumatic diseases (CRD).

Aim: To study the seroconversion, safety and efficacy of heptavalent pneumococcal conjugate vaccine (PCV7) in children with CRD receiving long-term (≥6 months) immunosuppressive therapy.

Material: 56 children (F:45), aged 1.5-18 yrs (10.7±0.7 yrs) with CRD received 2 doses of PCV7, with a 4-8 week interval. Serum IgG antibodies to 23 more frequent serotypes of SP (including PCV7 serotypes) were measured by indirect ELISA pre-vaccination and 47±2.3 days post-vaccination (just before the second dose).

Results: Before vaccination, 59% of children were found to have protective titer (>250 mU/ml) (20% of children ≤5 yrs vs 67.4% of children >5 yrs, p=0.0107). One month after the first dose, 96% of children achieved protective titer (geometric mean titer (GMT): 1776). Children with a non-protective titer pre-vaccination exhibited a 3 to 800-fold rise of the titer after the first dose. Although the GMTs were lower in children ≤5 yrs compared to those >5 yrs (1079 vs 1973, p=0.024), the magnitude of antibody increase was similar between the two groups. No significant difference in GMTs was found between children with different therapeutic regimens (1 DMARD ± prednisone or 2 DMARDs ± prednisone or anti-TNF +1 DMARD ± prednisone). 5.4% of patients reported mild local reactions. No patient experienced exacerbation or relapse of underlying disease post-vaccination. No patient reported respiratory tract symptoms or invasive infections during the 6-month period of follow-up.

Conclusions: Children with CRD receiving long-term immunosuppressive therapy respond satisfactorily to PCV7 without serious adverse reactions or disease exacerbations.

OP-24

THE EXPRESSION OF ASC IN RENAL TISSUES OF FMF PATIENTS WITH AMYLOIDOSIS: A POTENTIAL ROLE FOR ASC IN AA TYPE AMYLOID DEPOSITION

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease, characterized by recurrent inflammatory attacks of fever and serositis. The most serious complication is deposition of AA type amyloid, mainly in the kidneys. Colchicine reduces not only the frequency and severity of attacks, but also prevents the development of amyloidosis. The FMF gene, MEFV, encodes a protein termed as pyrin, which appears to play an important role in the inflammatory pathways. The two pyrin-interacting proteins thus far characterized, ASC and PSTPIP1, are both primarily cytosolic. When cells are co-transfected with both pyrin and ASC, pyrin is recruited to ASC specks. Speck formation is accelerated in the presence of pyrin. The aims of this study were to address the effect of mutant forms of pyrin on ASC speck formation; to assess the impact of colchicine on the process of speck formation; and to determine whether the expression of ASC is altered in glomeruli of FMF patients with amyloid deposition.

The preliminary results of this study have demonstrated that mutant forms of pyrin increase and colchicine prevents speck formation. Kidney tissues from 15 patients diagnosed to have secondary amyloidosis due to clinical FMF were stained with anti-ASC antibody. Kidney specimens from 5 patients with a diagnosis other than FMF and 5 focal glomerulosclerosis patients were used as controls. In the FMF group, ASC expression was higher in glomeruli, especially at sites of amyloid deposition, although there was no ASC expression in glomeruli in the control specimens. Thus, there may be more ASC specks in the person with FMF and they can cause AA type amyloid nucleation unless their concentration is somehow decreased with colchicine usage. We suggest that expression of ASC in a critical amount or at a critical time may be important in the pathogenesis of amyloid formation in predisposed tissues.

OP-26

REGISTER FOR PEDIATRIC PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME: CLINICAL AND IMMUNOLOGICAL FEATURES OF 107 CHILDREN

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Objectives: To obtain data on the association of antiphospholipid antibodies (aPL) with clinical manifestations in childhood and enable future studies to determine impact of treatment and long-term outcome of pediatric antiphospholipid syndrome (APS).

Methods: The Ped-APS Register is a collaborative project of the European Forum on Antiphospholipid Antibodies and the Lupus Working Group of the Paediatric Rheumatology European Society. To be eligible for enrollment, the patient must meet the preliminary criteria for the classification of pediatric

APS, and the onset of APS must have occurred prior to the patient's 18th birthday.

Results: As of April 1, 2007, there were 107 cases registered from 13 countries. Fifty were boys and 57 girls, with mean age at diagnosis of 10.9 years. Fifty (47%) patients had underlying autoimmune disease. Venous thrombosis occurred in 60 (56%), arterial thrombosis in 36 (34%), small vessel thrombosis in 7 (7%), and mixed arterial and venous thrombosis in 4 (4%) patients. Associated clinical features in pediatric APS included hematological manifestations (n=42), skin disorders (n=27) and non-thrombotic neurological manifestations (n=17). Laboratory investigations revealed positive IgG aCL in 66/91 (73%), IgM aCL in 52/86 (60%), IgG anti-ß$_2$GPI in 19/41 (46%), IgM anti-ß$_2$GPI in 19/38 (50%), and LA in 65/93 (70%) patients.

Discussion: Deep veins in the lower extremities and cerebral arteries were the most common sites of thrombosis associated with aPL in children. Patients with underlying autoimmune disease showed stronger associations with hematological manifestations than patients with primary APS.

OP-27

THE LONG-TERM SAFETY OF ETANERCEPT IN CHILDREN WITH POLYARTICULAR OR SYSTEMIC JUVENILE RHEUMATOID ARTHRITIS

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Background: Etanercept (ETN), a soluble tumor necrosis factor (TNF) receptor, has been approved for use in children with polyarticular-course juvenile rheumatoid arthritis (JRA).

Objective: To evaluate the long-term safety of ETN in children with polyarticular or systemic JRA.

Methods: This 3-year, open-label, non-randomized registry included patients, age 2-18, with polyarticular-course or systemic JRA. Patients treated with methotrexate (MTX), ETN, or methotrexate/etanercept in combination (MTX/ETN) were eligible. Co-administration of non-biologic disease-modifying antirheumatic drugs (DMARDs) was allowed. ETN was administered subcutaneously at a dose of 0.4 mg/kg (max 25 mg) twice weekly for up to 36 months.

Results: 601 patients were enrolled: 198 received MTX, 105 ETN, and 298 MTX/ETN. 131 MTX patients (66%), 51 ETN patients (49%), and 146 MTX/ETN patients (49%) discontinued the registry. In the MTX, ENT, and MTX/ENT groups, 24 (12%), 7 (7%), and 11 (4%) patients, respectively, discontinued because of remission, 35 (18%), 7 (7%), and 51 (17%) because of an insufficient therapeutic effect, and 3 (1.5%), 2 (1.9%), and 1 (0.3%) because of adverse events. 159 patients (26%) have completed the 3-year registry to date. The rates of serious adverse events and medically important infections per 100 patient-years were 5.25, 8.36, and 5.78, and 0.95, 1.97, and 1.98, respectively, for patients receiving MTX, ETN, or MTX/ETN. One case of lupus (MTX) and 2 cases of sepsis (ETN and ETN/MTX) were reported. No cases of lymphoma, malignancy, tuberculosis, or death were reported.

Conclusion: Safety data from this ongoing registry support the use of ETN in this patient population for up to 3 years.

OP-28

EFFICACY AND SAFETY OF ABATACEPT IN CHILDREN AND ADOLESCENTS WITH ACTIVE JUVENILE IDIOPATHIC ARTHRITIS (JIA): RESULTS OF DOUBLE-BLIND WITHDRAWAL PHASE

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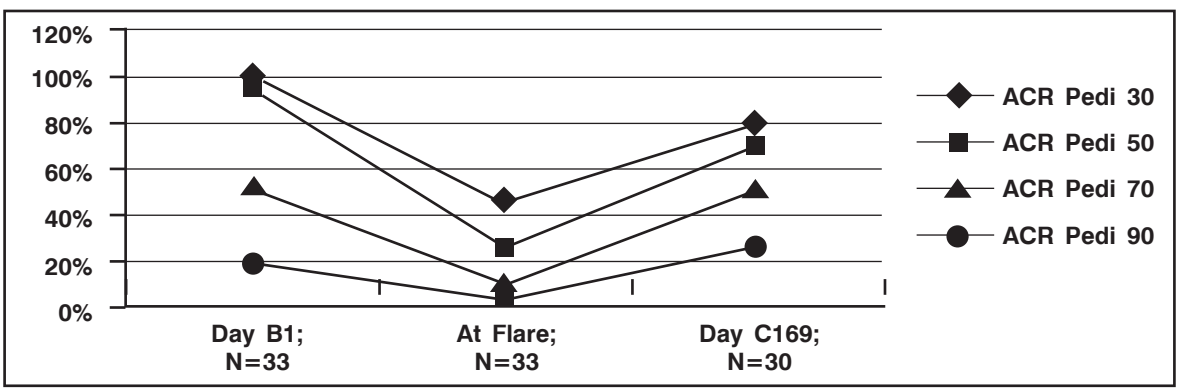
Background: Abatacept (ABA) previously demonstrated efficacy in the open-label (OL) phase of this study in patients with polyarticular JIA (Period A).

Objectives: To evaluate safety and efficacy of ABA in children with polyarticular JIA and an inadequate response to disease-modifying antirheumatic drugs (DMARDs).

Methods: At the end of Period A, ACR Pediatric (Pedi) 30 responders were randomized in a double-blind fashion 1:1 to ABA 10 mg/kg or placebo (PBO) (Period B). Patients who flared or completed therapy were offered OL ABA therapy (Period C). Safety was assessed at each visit.

Results: Of 190 patients treated in Period A, 123 (64.7%) were ACR Pedi 30 responders; 122 were randomized. Baseline demographic and clinical characteristics were similar between groups. In Period B, 33/62 (53.2%) of PBO-treated patients flared and switched to ABA; 12/60 (20%) of ABA-treated patients flared (p=0.0002 for ABA vs PBO); all but one restarted ABA. No patient discontinued due to adverse events (AEs); 31 (50%) PBO- and 10 (16.7%) ABA-treated patients discontinued due to flare/lack of efficacy; one ABA-treated patient withdrew consent. Two PBO patients experienced serious AEs (SAEs): hematoma in one, varicella and encephalitis in another – neither discontinued. No patient receiving ABA had a SAE. Overall, 54.8% of PBO- and 61.7% of ABA-treated patients had an AE; incidence of infection AEs was similar (PBO, 43.5%; ABA, 45.0%). Two patients from each group had mild/moderate infusional AEs.

Conclusion: The significantly higher flare rate in PBO- versus ABA-treated patients supports efficacy of ABA in patients with JIA. ABA was well tolerated.



OP-29

TWO-YEAR EFFICACY OF ADALIMUMAB IN CHILDREN WITH JUVENILE RHEUMATOID ARTHRITIS (JRA): RESULTS OF A PHASE III STUDY

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Objectives: This analysis evaluated long-term efficacy of adalimumab in JRA.

Methods: A Phase III study of adalimumab was conducted in 171 JRA patients aged 4–17 years. At the end of a 16-week, open-label phase [body-surface-area–dosed adalimumab, 24 mg/m^2 BSA; max 40 mg/dose], patients with ACR Pedi 30 were randomized (stratified by methotrexate [MTX] use) to adalimumab or placebo every other week for an additional 32 weeks or until flare (primary endpoint). Patients could then enter a BSA-dosed, open-label extension (OLE). Efficacy was assessed (ITT NRI). Patients who flared were non-responders for ACR Pedi responses at Week 32 of the double-blind period. Because of differing exposure times in the OLE, these data were analyzed as observed.

Results: At Week 16, 84/77/58/27% achieved ACR Pedi 30/50/70/90. During the double-blind period, significantly more placebo patients flared. Adalimumab patients demonstrated greater ACR Pedi 30/50/70 responses (60/59/56%) at Week 48 (end of double-blind period) vs. placebo (35/35/28%). Of 133 patients in the double-blind phase, 128 enrolled in the OLE. Treatment duration in the OLE varied because of different entry times; a small subset reached 136 weeks. Week-24 observed data showed maintenance of response, with 97% (114/117) reaching ACR Pedi 30, 93% (109/117) ACR Pedi 50, 80% (94/117) ACR Pedi 70, and 56% (66/117) ACR Pedi 90. At Week 56, patients demonstrated maintenance of response (94/93/81/60% had ACR Pedi 30/50/70/90). Results were similar in MTX and non-MTX strata.

Conclusion: With or without MTX, adalimumab provides substantial, sustained improvement in JRA over 2 years.

OP-30

LEFLUNOMIDE IS AN EFFECTIVE ALTERNATIVE IN THE TREATMENT OF PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background: Leflunomide (LEF) is a second-line agent not yet licensed for treatment of juvenile idiopathic arthritis (JIA), despite a Phase III study showing an effectiveness in treating polyarticular course JIA equal to that of methotrexate (MTX). In clinical practice, LEF is added to MTX in patients with inadequate response to MTX, or is started instead of MTX in patients who cannot tolerate MTX, but still need a second-line agent.

Objectives: To evaluate the effectiveness and side effects of LEF in our clinic population.

Methods: We retrospectively reviewed charts of our patients who received LEF to treat JIA in the last 6 years. We evaluated the reason for starting LEF and the effectiveness of this therapy.

Results: Fifty-eight patients with JIA received LEF, 33 of them female. The reason for starting LEF in 12 cases was insufficient response to MTX and in the other 46 cases MTX was switched to LEF because of side effects. The MTX side effect in 38 cases was dyspepsia. The mean MTX dose was 14.89 mg/m^2/week before the change in therapy. The mean LEF

dose was 16.64 mg/day (0.34 mg/kg/day). Mean duration of LEF therapy was 1.45 years (range 0.04 to 5.28). At the end of the follow-up period, LEF was stopped in 17 patients because of remission, in 13 because of side effects, and in 1 because of non-response; 1 patient was lost to follow-up. Twenty-six patients were still taking LEF. Sixteen of the 17 patients in whom LEF was discontinued received monotherapy. In the whole group, the mean CHAQ score decreased from 0.54 at the initiation of LEF to 0.19 at the end of the follow-up period. The number of swollen joints decreased from 1.4 to 0.84. Nine of the 58 patients developed transient increase in transaminases. Side effects that led to discontinuation of the therapy were diarrhea in 5 cases, abdominal pain or dyspepsia in 5, and hair loss, tiredness and hypertonia in 1 case each.

Conclusion: LEF was a well-tolerated medication in 78% of these preselected patients. In 29% of the patients, a remission could be achieved and LEF was discontinued. LEF is a reasonable alternative medication for patients who cannot tolerate MTX.

OP-31

PRELIMINARY EVIDENCE FOR SUSTAINED BIOACTIVITY OF IL-1 TRAP (RILONACEPT), A LONG-ACTING IL-1 INHIBITOR, IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

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Background: Non-controlled studies in SJIA demonstrated clinical responses with a short-acting interleukin-1 (IL-1) inhibitor, suggesting that IL-1 plays a pivotal role in SJIA. IL-1 Trap (rilonacept) is a long-acting soluble receptor-based IL-1 blocker.

Objective: To obtain long-term data from an ongoing double-blind (DB) placebo-controlled study of IL-1 Trap in SJIA subjects during the open label (OL) phase.

Methods: Twenty-one children, 5 to 20 yrs old, mean disease duration of 3.1 yrs., with both active articular and systemic features, received either weekly 2.2 or 4.4 mg/kg IL-1 Trap or placebo (PBO) subcutaneously (SC) for 4 wks in the DB phase. OL treatment occurred after 4 wks in the DB or a minimum of 2 wks, if rescue in DB was clinically warranted. The study is ongoing and remains blinded. OL dose was as per the DB dosing cohort. Pre-study background steroid and disease-modifying antirheumatic drug (DMARD) doses were stable. Data from OL are presented for all 21 subjects, including the last observation of 12 current subjects. Discontinuations were due to loss of efficacy or to adverse events (AEs) of worsening pancytopenia, ISR, mood alteration, and MAS. Seven of the 21 subjects had previously received but inadequately responded to anakinra.

Conclusion: Improvement was observed in all 6 of the ACR Ped core variables upon OL treatment, with ACR Ped 30, 50, 70 responses of 76.2%, 61.9%, and 33.3%, respectively, after 4 wks. After a median of 42 wks OL treatment for 12 subjects who remain in the study, ACR Ped 50 and 70 increased to 83.3% and 83.3%. Fever and/or rash observed in all subjects at baseline completely resolved. WBC, platelet, and Hb improved substantially. D-dimer and ferritin were dramatically reduced, and elevated CRP was nearly normalized. Preliminary evidence was obtained for the durability of clinical and biological activity of IL-1 Trap in some patients with SJIA. IL-1 blockade was generally safe and well-tolerated.

OP-32

RILONACEPT (IL-1 TRAP) DEMONSTRATES IMPROVEMENT IN HEALTH-RELATED OUTCOME MEASURES IN SUBJECTS WITH CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS) IN A PLACEBO-CONTROLLED TRIAL

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Background: IL-1β inhibition with rilonacept has been shown to rapidly improve the clinical and laboratory signs and symptoms associated with Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). Short- term (6 wk) treatment of FCAS/MWS subjects with rilonacept 160 mg weekly demonstrated marked (85%) decreases (improvements) in the 21-day mean key symptom score (KSS, 0-10 scale of rash, fatigue, feeling of fever/chills, joint pain and eye redness/ pain) and mean serum amyloid A and C-reactive protein levels (94% and 92%, respectively).

Methods: Two randomized, double-blind (DB), placebo-controlled (PC) studies were conducted sequentially in a population of 47 subjects with FCAS/MWS. Study A was a 6-week comparison in which subjects received weekly subcutaneous (SC) injections of either 160 mg rilonacept or placebo (PBO). In study B, all subjects initially received rilonacept followed by a 9-week, DB, PC, randomized withdrawal comparison. Outcomes measures such as Physicians' Global Assessment (PGA) as measured by no disease activity to severe disease activity, graded 0-10 points and subjects' assessment of Limitation of Daily Activities (no limitation to much limitation, graded 0-10 points) are reported here as mean change in points from baseline. An additional open label extension study included 4 pediatric subjects.

Results: Forty-four (44) of 47 enrolled subjects completed both studies. In A, subjects treated with rilonacept experienced a mean decrease of 4.2 points in PGA of disease activity (Baseline 5.61); for PBO subjects PGA of disease activity increased by 0.2 points (baseline 4.78) ($p<0.0001$ vs PBO). Limitation of daily activities was reduced by 2.2 points (73%; baseline 3.03) in rilonacept-treated subjects vs. 0.8 points (33%; baseline 2.39) in PBO subjects ($P=0.0063$ vs PBO). In B, subjects randomized to PBO experienced gradual return of PGA of disease activity, with mean increases of 3.4 points (baseline 1) compared to a 0.1 point increase for subjects who remained on rilonacept (baseline 1.29; $p<0.0001$ vs. PBO). Limitations of daily activities in the rilonacept-treated subjects were unchanged but in PBO subjects increased with a mean change of 0.7 points (baseline 0.1; $P=0.0533$ vs PBO). Adverse events were infrequent and mild. No serious infections, autoimmune diseases, malignancies or deaths were reported.

Conclusion: In this first PC study in CAPS, rilonacept markedly improved signs and symptoms of CAPS, which was reflected in significant improvement in PGA as well as subjects' assessment of Limitation of Daily Activities due to disease.

OP-33

IL-1RA (ANAKINRA, KINERET®) IN SEVERE SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS (ANAJIS ANAKINRA VERSUS PLACEBO RANDOMIZED DOUBLE-BLIND TRIAL)

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Background: Patients with systemic onset juvenile idiopathic arthritis (SOJIA) and a severe, persistently active course are often poorly responsive to existing treatments including methotrexate and etanercept. There is some preliminary evidence of dramatic, quick improvement in some patients treated with interleukin (IL)-1 receptor antagonist (IL-1RA) anakinra.

Objectives: To evaluate the safety and efficacy of anakinra in patients with SOJIA and insufficient response to non-steroidal anti-inflammatory drugs and corticosteroid treatment.

Methods: This was a multicentric randomized double-blind trial. The primary objective was to compare the efficacy of a 1-month treatment with anakinra (2 mg/kg subcutaneously daily, maximum 100 mg) to a placebo between 2 groups of 12 patients each (1 group treated with anakinra and 1 group treated with placebo). Secondary objectives included pharmacokinetic analyses, tolerance and efficacy assessment over 12 months in the 24 patients, assessment of treatment effect on serum amyloid A and cytokine expression by PBMC, and anti-pneumococcal antibody response following immunization by Pneumo23®.

Results: Inclusions started in June 2006. At the end of March 2007, 23 patients had been enrolled. The 24th and last patient's enrollment has been planned in April. Five patients stopped treatment between 5 days and 6 months for intolerance to painful subcutaneous injections (1 case), lack of efficacy (2 cases) or a disease flare when the dose of prednisone was reduced (2 cases). There were 3 severe adverse events (2 infections, 1 vertebral collapse) but anakinra treatment was not interrupted and the outcome was favorable in all cases.

In May 2007, after the last patient has reached 1-month treatment, we will request the trial to be unblinded in order to analyze differences in response at 1 month between patients treated with anakinra and patients who received a placebo (primary objective). By the end of August 2007, the follow-up will be 6 to more than 12 months in 21 patients and 4 to 6 months in the last 3 patients.

Conclusion: Preliminary analyses of the results of this randomized double-blind trial should provide important information regarding tolerance and efficacy of IL-1RA treatment in patients with severe SOJIA.

OP-34

PROPOSAL FOR DIAGNOSTIC GUIDELINES FOR INCOMPLETE AND ATYPICAL KAWASAKI DISEASE (KD)

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S Oliveira[1], MC Pietrogrande[1], U Unsal[1], S Ozen[1], S Magni Manzoni[1], L Lepore[1]
R Barcellona[1], F De Benedictis[1], S Martino[1], E Stenboeg[1], S Pasic[1], A Boncompagni[1]
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Background: Lacking a specific diagnostic test, KD is still recognized by puzzling clinical signs. Several children, despite an incomplete (I) form (fever and 2 or 3 clinical manifestations) or atypical (A) onset (surgical, neurological), develop coronary artery (CA) damage. In infants, other febrile illnesses (OFI) with rash (e.g. adenovirus, cytomegalovirus, and enterovirus infections, streptococcal and staphylococcal toxin-mediated disease) mimic KD, delaying intravenous immunoglobulin (IVIG) therapy with increased risk of coronary injury. At onset, systemic juvenile idiopathic arthritis (JIA) may also resemble KD.

Aim: To individualize preliminary diagnostic guidelines for I- and AKD.

Material and Methods: We identified through chart review 241/1466 (16%) children discharged with KD diagnosis not fulfilling CDC criteria. Of these 241, 188/241 (78%) (M 109, F 78, median age at onset 20 months) had IKD and 53/241 (22%) (M 31, F 22, median age at onset: 37.5 months) AKD. 79 patients (M 41, F 38, median age at onset: 50 months) with OFI with rash mimicking KD (adenovirus, systemic JIA, cytomegalovirus) discharged from the same units and a sample of 319 patients with typical (T) KD were included in the study for comparisons. Demographic data, ESR, CRP, platelet count, albumin and sodium levels, clinical manifestations, coronary involvement, ASA and IVIG administration were recorded. Descriptive statistics, chi-square test or the Fisher's exact test, and the analysis of variance (ANOVA) were performed as appropriate. Bonferroni's correction (P_B) was applied as *a posteriori* adjustment and the Scheffé test was used for *post-hoc* comparisons after the ANOVA.

Results: Comparison of quantitative variables showed that patients with A/IKD have a younger age at onset (P=0.0002), higher levels of ESR (median, 76 mm/h) (P=0.0003), γGT (median: 21 UI/l) (P=0.019), and platelet count (455.5 n×10^3/mm^3) (P<0.0001) with respect to OFI (median values: age at onset: 50 months; ESR: 60 mm/h; γGT: 15 UI/l and PLT count: 325.0 n×10^3/mm^3). Analyzing the clinical manifestations, the frequency of conjunctivitis (63.5%; P_B<0.0001), lip and oral changes (64.7%; P_B<0.0001), and extremity changes (27.4%; P_B<0.0001) was significantly higher in A/IKD than in patients with OFI (conjunctivitis: 31.6%; lip/oral changes: 20.2%; extremity changes: 3.8%). TKD had very high frequency of the same clinical manifestations (conjunctivitis: 93.9%; lip/oral changes: 92.0%; extremity changes: 82.0%). In contrast, lymphadenopathy was significantly (P_B<0.0001) more frequent in OFI (65.8%) than in A/IKD (37.8%); conversely, lymphadenopathy was even more frequent in TKD (79.9%). Cardiovascular involvement (dilatation or aneurysms) was detected only in the groups of AKD (17/50; 34.0%), IKD (54/187; 28.9%), and in TKD (85/319; 26.6%), while absent in OFI.

Conclusions*:* The presence of mucosal changes, non-exudative conjunctivitis and extremity changes, increase in the number of platelets and ESR and γGT levels, and a younger age at onset may help in differentiating A/I KD from other common childhood febrile diseases.

OP-37

PEDIATRIC GRANULOMATOUS ARTHRITIS REGISTRY: A PROGRESS REPORT

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Pediatric granulomatous arthritis (PGA) designates a chronic inflammatory condition characterized by a triad of arthritis, uveitis and dermatitis with epithelioid cell granulomas on skin or synovial biopsy. The familial (Blau syndrome) and sporadic (early onset sarcoidosis) forms share an identical phenotype and are strongly associated with *CARD15* mutations.

An International Registry/Repository was established in spring 2005. The presence of arthritis or systemic granulomatosis with histologically confirmed granulomas was required for inclusion. Identified clinical information was collected; *CARD15* genotyping was performed in probands and relatives. Two years after inception, 35 pedigrees comprising 93 individuals had been collected (15 Europe, 13 USA, 5 S America, 2 Australia).

Eighteen pedigrees (5 multiplex) had the classic phenotype. Cutaneous presentation was most common. Chronic persistent uveitis was present in 26 cases, often complicated by cataract and glaucoma. Additional features were liver granulomas (1), erythema nodosum (1) and palpable purpura (1). Seventeen pedigrees had atypical disease: panniculitis (3), polyarthritis (1), bone involvement (2), systemic granulomatosis (4), CNS disease (1), cranial neuropathy (1), isolated dermatitis (1), Mikulicz syndrome (1), aortitis (1), and kidney involvement (1). Eight patients had uveitis.

At the moment of writing, *CARD15* genotyping had been performed in 87 cases. *CARD15* mutations were found in 100% of affected cases with the classic phenotype, and not in any cases with atypical disease variants; there were no asymptomatic carriers.

In conclusion, our International Registry combining sporadic and familial pedigrees with PGA provides a resource to further define the spectrum of pediatric granulomatous inflammatory diseases and their relation to *CARD15* mutations.

OP-39

AUTOINFLAMMATORY GENE MUTATION IN BEHÇET'S DISEASE [BD]

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Introduction: BD shares clinical similarities with well-recognized auto-inflammatory disorders. In addition, some defects of innate immunity, FMF (familial Mediterranean fever) mutations and the R92Q-TRAPS (TNF receptor associated periodic syndrome) mutation were reported to be increased in patients with BD.

Patients and Methods: To test additional auto-inflammatory genes as possible susceptibility factors for BD, we analyzed 97 DNA samples from BD patients and 51 matched healthy controls for MVK, CIAS1 and PSTPIP1 genes, responsible for MKD (mevalonate kinase deficiency), CAPS (cryopyrin associated periodic syndromes) and PAPA (pyogenic sterile arthritis, pyoderma gangrenosum and acne), respectively. Over 90% of known mutations were screened using restriction fragment length polymorphism and/or sequencing.

Results: Mutations were identified in 4 patients. Two of them had paired mutations in the MVK gene

(V377I/V377I, V377I/ S135L) and shared typical BD and MKD features. One was heterozygote for V377I. Another patient had the V198M mutation in the CIAS1 gene in association with typical BD and no sign of CAPS. No mutations were identified in the control group. PSTPIP1 analyses revealed a novel exon 10 variant insertion (c.741+33_741+34insGT). This insGT was identified in 2/97 patients and 1/51 controls ($p>0.054$) calling for a polymorphism rather than a true mutation. RNA from this patient was not available to test whether this insertion could affect the gene expression.

Discussion: We conclude that MVK, CIAS1 and PSTPIP1 genes are not likely to be involved in BD. The two BD patients with two MVK mutations probably have both diseases.

Poster Presentation

BASIC:

• Genomics

PP - 1

IL-1 GENE FAMILY ASSOCIATIONS IN sJIA

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The systemic subtype of juvenile idiopathic arthritis (sJIA) can be the most severe and is potentially fatal. Patients have a characteristic daily spiking fever and elevated levels of inflammatory cytokines, including members of the interleukin-1 (IL-1) gene family. IL-1 is a large gene family with eight naturally occurring forms, a receptor antagonist, four receptors and a receptor accessory protein. IL-18 is also a member of the IL-1 family and has its own receptor, receptor accessory protein and antagonist. There are also a number of proteins that are integral to the activity of IL-1, including caspase-1 and cryopyrin. Members of the gene family have been shown to be associated with various inflammatory and autoimmune diseases and treatment with the IL-1 receptor antagonist, Anakinra, has shown remarkable improvement in some sJIA patients.

This work describes the most complete and thorough investigation to date of the involvement of the IL-1 family in sJIA. Publicly available genotyping data and a tagging SNP (tSNP) approach were used to examine association with a total of 20 candidate genes. The tSNPs were genotyped in 130 sJIA patients and 146 healthy controls and examined by single marker and haplotype analysis.

Novel significant associations were found with *IL18BP, IL1RAcP, IL1R2* and the *IL1* ligand cluster. These results indicate that there may be aberrant control of the activity of the IL-1 family in patients with sJIA causing the increased susceptibility to the disease. These findings could lead to new diagnostic, pharmacogenetic and therapeutic targets.

PP - 2

FAMILIAL AUTOINFLAMMATORY DISEASE LOCI AS CANDIDATE SUSCEPTIBILITY GENES FOR SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS

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Background: A novel approach for the selection of candidate juvenile idiopathic arthritis (JIA) susceptibility genes is to extrapolate from rare monogenic diseases that have an overlapping phenotype. In the present study, genes for four of the familial autoinflammatory syndromes were investigated in UK Caucasian JIA cases and unrelated controls. These are: *PSTPIP1 (p*yogenic

arthritis, pyoderma gangrenosum, and acne [PAPA] syndrome), *CIAS1* (cryopyrin associated periodic syndrome [CAPS]), *MEFV* (familial Mediterranean fever [FMF]) and *CARD15* (Blau syndrome).

Methods: For the *PSTPIP1* gene, DNA was available for 115 systemic-onset JIA patients, 711 other JIA patients, and 617 healthy controls. For the *CIAS1, MEFV* and *CARD15* genes, DNA was available for 175 systemic-onset JIA patients, 735 other JIA patients, and 733 healthy controls. Six SNPs were genotyped in *PSTPIP1*, 23 SNPs in *CIAS1*, 19 SNPs in *MEFV*, and 13 SNPs in *CARD15*. Genotyping was performed using the Sequenom MassArray iPlex platform.

Results: This is a work in progress and as such only data for the *PSTPIP1* gene is currently available. Single point analysis shows carriage of the minor allele of two SNPs, rs8030698 and rs4078354, to be significantly associated with systemic-onset JIA (OR 1.5, 95% CI 1.0-2.3, p=0.03; OR 1.6, 95% CI 1.1-2.6, p=0.02). Association with 4 PSTPIP1 SNPs has also been found with juvenile psoriatic arthritis. No significant haplotypic associations were observed.

Discussion: These data support the approach of extrapolation from autoinflammatory monogenic syndromes to JIA. Replication of positive findings will be required in independent cohorts of JIA cases and controls.

PP - 3

TNFα -308 GA/AA GENOTYPES ARE ASSOCIATED WITH HIGH INFLAMMATORY ACTIVITY AND HIGH SERUM TNFα IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS

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Objectives: To examine whether clinical measures of juvenile idiopathic arthritis (JIA) activity and tumor necrosis factor (TNF)α serum levels are associated with TNFα-308 genotypes.

Material and Methods: Patients with diagnosis of JIA were recruited. A protocol was applied including demographic, clinical data (including visual analogue scale [VAS]) and patient's functional status. We measured erythrocyte sedimentation rate (ESR) and TNFα serum levels (ELISA). Determination of TNFα gene polymorphisms at position -308 was made by polymerase chain reaction (PCR). Genotyping of the same polymorphism was also performed in a sample of controls.

Results: Eighty patients were evaluated: 51 patients presented the oligoarticular subtype, 15 polyarticular, 7 systemic, 5 enthesitis-related arthritis and 2 psoriatic arthritis. In the JIA group, 66 (82.5%) patients presented the -308 GG genotype and 14 (17.5%) the -308 GA/AA genotype, and in the control group 48 (75.0%) patients presented the -308 GG genotype and 16 (25%) the -308 GA/AA genotype (p-value=0.27). Patients with the polyarticular subtype presented a higher frequency of the -308 GA/AA genotype (40%). Patients with the -308 GA/AA genotypes had a slight, but significant, higher degree of functional impairment (CHAQ=0.375 *vs* 0; p<0.05). In addition, patients with the -308 GA/AA genotype had a significantly higher ESR (29.4 *vs* 13.7, p<0.05) and TNFα levels (406.0 *vs* 99.6, p<0.01), but not VAS (p=0.53).

Conclusions: These results suggest that the TNFα-308 GA/AA genotypes are associated with a lower functional capacity, polyarticular involvement, higher inflammatory activity and higher TNFα serum levels in JIA patients, although they do not appear to have a relevant role in the susceptibility for JIA.

PP - 4

NOVEL MUTATIONS OF CAMPTODACTYLY ARTHROPATHY COXA VARA PERICARDITIS (CACP) SYNDROME

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The CACP syndrome is an autosomal recessive disease characterized by congenital camptodactyly, noninflammatory arthropathy, synovial hyperplasia, coxa vara, and thickening of the pericardium.

The causative gene for CACP (1q25-31) consists of 12 exons and encodes for a mucin-like glycoprotein named "proteoglycan-4" (PRG-4), which acts as the major surface lubricant for joints and tendons.

Four unrelated patients with a phenotype resembling CACP syndrome were referred to our Laboratory of Immunology for mutational analysis of *CACP* gene. The genomic region was amplified by polymerase chain reaction (PCR) and most of *CACP* coding regions were sequenced, with the exception of 1450 bp within exon 6 due to highly repetitive motifs.

Four novel homozygous mutations within the *CACP* gene were identified. In two patients we found two different 5 bp deletions (3896_3900delTTAGG; 2754_2758delGACAA) both causing a frame-shift with premature stop signal, probably resulting in a truncated protein. Moreover, in the remaining patients, we detected one point mutation at a splice site junction (IVS8+3A>G) and a single nucleotide substitution 7 bp after the wild-type stop codon (4222G>A). The evaluation of these mutations on CACP protein change is still ongoing.

CACP syndrome is a rare disorder often misdiagnosed with other pediatric connective tissue diseases. Genetic analysis is not widely available. To date only coding mutations have been reported. We identified a new set of *CACP* molecular aberrations. In particular, the finding of two non-coding mutations causing CACP phenotype emphasizes the need for awareness of this particular mutational mechanism of disease.

PP - 5

BCLI GLUCOCORTICOID RECEPTOR GENE POLYMORPHISM AND OSTEOPENIA IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS IN SAINT-PETERSBURG

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Low bone mineral density (BMD) or osteopenia (OP) for age is a well-known syndrome in children with juvenile idiopathic arthritis (JIA).

The aim of our study was to investigate the relationship between BclI glucocorticoid receptor gene polymorphism and bone mineralization in children with JIA.

Seventy-eight JIA children (59 girls, 19 boys) were included in our study. BclI glucocorticoid receptor gene polymorphism and serum levels of intact osteocalcin, parathyroid hormone, Ca, Ca2+, phosphate, and common alkaline phosphatase were tested in all patients. Uppercase letters represent absence, and lowercase letters represent presence, of gene restriction site. BMD was detected by dual-energy X-ray absorptiometry (Hologic QDR-4500C) in lumbar spine (L1-L4) with national referent database (L. A. Scheplyagina, 2005). OP was defined as BMD lower than at least 1 SD.

Using the data of BMD we divided the children into two groups: with OP – 20 children (25.6%) and without OP - 58 children (74.4%). For statistical

analysis of the allelic frequency distribution in this polymorphism, the two groups were compared using chi-square test and Fisher's exact test.

The distribution of BclI polymorphism revealed significant differences in genotypes between JIA girls with and without OP (CC-25.0% and 46.8%, GC-25.0% and 40.4%, GG-50.0% and 12.8%, respectively, p=0.017) and all children with and without OP (CC-30.0% and 48.3%, GC-35.0% and 41.4%, GG-35.0% and 10.3%, respectively, p=0.035). We revealed the same significant differences in allele distribution.

Conclusion: In our study, we revealed that G allele and GG genotype are associated with OP in JIA children.

PP - 6

BCLI GLUCOCORTICOID RECEPTOR GENE POLYMORPHISM AND JUVENILE ARTHRITIS COURSE AND TREATMENT

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Juvenile arthritis (JA) is heterogeneous group of joint diseases with individual course and treatment. Some patients receive only nonsteroid anti-inflammatory drugs (NSAID) and others receive glucocorticosteroids.

The aim of our study was to determine whether BclI polymorphism was associated with JA course and treatment.

We included in our study 122 JA children, 43 boys (35.2%) and 79 girls (64.8%). Glucocorticoids were administered in 30 children (24.6%), 3 boys and 27 girls. All children were divided into three groups based on disease course: 62 children (50.8%) had progressive course, 44 children (36.1%) had recidive course and 16 children (13.1%) had regressive course with rapid longitudinal remission (more one year). BclI glucocorticoid receptor gene polymorphism was detected by polymerase chain reaction with restriction assay. Uppercase letters represent absence, and lowercase letters represent presence of gene restriction site.

We detected significant differences in BclI genotype distribution between JA girls with progressive and regressive course (CC-40.4% and 0.0%, GC-36.2% and 100.0%, GG-23.4% and 0.0%, respectively, p=0.023). We determined no differences between genotype and allele distributions between children who received NSAID or glucocorticoids.

Conclusion: In our study, we revealed that GG genotype and G allele were associated with JA progressive course.

PP - 7

HYPERCOAGULABILITY: INTERACTION WITH INFLAMMATION

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Familial Mediterranean fever (FMF) patients in clinical remission are reported to have increased baseline inflammation. Normal function of the natural anticoagulant pathways is particularly needed in diminishing inflammatory responses. In the presence of subclinical inflammation, natural anticoagulant response may be exaggerated. We aimed to observe the anticoagulant–procoagulant status in attack-free FMF patients. Twenty-seven FMF patients diagnosed in accordance with Tel-Hashomer criteria and 26 healthy controls were included. All patients were attack-free under regular colchicine treatment. Amyloidosis, autoimmunity, accompanying liver and renal disease, and vasculitis were excluded. No predisposing factors for thrombosis were present. Acute phase reactants (APRs), anticardiolipin antibody positivity, prothrombin time (PT), activated prothrombin time, thrombin time (TT) and D-dimer, protein C activity, activated protein C resistance, free protein S, antithrombin, lupus anticoagulant, human prothrombin fragment F 1 + 2, and human thrombin/antithrombin III complex were analyzed in

all subjects. APRs were comparable with controls. Autoimmune markers were negative in all. Anti-streptolysin titers were significantly different from the control group. PT, TT, protein C activity, and F 1 + 2 levels were significantly different from those of healthy controls. Shortened PT and TT and decreased protein C activity vs increased levels of F 1 + 2 suggested a hypercoagulable state in our patients. The hypercoagulable state detected in FMF patients suggests that screening with abnormal coagulation tests may be beneficial for tracing the future consequences of subclinical inflammation in these patients. Studies covering larger groups of patients are needed to verify the currently observed hypercoagulable status in FMF.

PP - 8

MEFV GENE MUTATIONS IN FAMILIAL MEDITERRANEAN FEVER AND RENAL AMYLOIDOSIS: A RETROSPECTIVE MOLECULAR STUDY

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Objective: Familial Mediterranean fever (FMF) is an autosomal recessive disorder, and the gene responsible for the disease, MEFV, located on chromosome 16 p13.3, encodes a protein called pyrin or marenostrin. About 90 MEFV mutations have been associated with FMF, with the M694V, V726A, M694I in exon 10, and E148Q in exon 2 mutations being the most frequently encountered. Amyloidosis is the most devastating complication of the disease, usually affecting the kidneys, leading to chronic renal failure. Most previous genetic studies showed that the M694V mutation in the MEFV gene may be a major risk for developing amyloidosis.

Materials: In this study, the frequencies of six (M694V, M694I, M680I, V726A, E148Q and R761H) FMF-related MEFV mutations were investigated in FMF patients with (n=55) and without (n=236) amyloidosis.

Methods: Mutation identification was performed according to described polymerase chain reaction (PCR) and restriction-enzyme digestion or amplification mutation system techniques.

Results: The most frequent mutation was the M694V in both groups. Of the 55 FMF with amyloidosis patients, 25 (45.5%) were homozygous for M694V and 12 were compound heterozygous for different combinations of MEFV mutations (M694V/M680I, V726A, E148Q) and 18 had one identifiable mutation. Seventy-two (30.5%) of 236 FMF patients were homozygotes, of whom 63 (26.6%) were M694V/M694V and 9 were M680I/M680I. We found a higher statistically significant prevalence of FMF with amyloidosis in M694V homozygotes patients than in FMF without amyloidosis patients (p=0.006).

Conclusion: Previous studies have implicated heredity, ethnicity and environment as factors affecting the risk of developing amyloidosis. Additionally, two major studies from Turkey suggested an association between the development of amyloidosis and M694V homozygosity. Our findings also demonstrated a significantly higher frequency of the M694 mutations among FMF patients suffering from amyloidosis.

• Cytokines and inflammatory mediators

PP - 9

CXCR6-CXCL16 INTERACTION IN THE PATHOGENESIS OF JUVENILE IDIOPATHIC ARTHRITIS

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Objective: To examine the role of CXCR6/CXCL16 and their interaction with CXCR3/CXCL10 in driving lymphocyte migration into inflamed joints of children with oligoarticular juvenile idiopathic arthritis (JIA).

Methods: CXCR6 expression was evaluated in lymphocytes from synovial fluid (SF) and peripheral blood (PB) of 23 patients by flow cytometry and by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The functional capability of CXCR6 was analyzed in purified T cells isolated from SF by migration assays. CXCR6 and CXCL16 expression in synovial tissue (ST) was analyzed by immunohistochemistry.

Results: T cells isolated from SF of patients with JIA co-expressed CXCR6 and CXCR3 and were functionally active, as shown in the chemotactic assays in which they exhibited a definite migratory activity in response to CXCL16 and CXCL10. Immunohistochemical analysis of ST with an anti-human CXCL16 showed that the chemokine was intensively expressed on the surface of macrophages, synoviocytes and endothelial cells, preferentially in the synovial lining, while CXCR6 expression was detected in the lining and sub-lining cells, particularly on lymphocytes, synoviocytes and endothelial cells.

Conclusions: Taken together, these data suggest that T cells co-expressing CXCR6 and CXCR3 act coordinately with respective ligands and are involved in the pathophysiology of JIA-associated inflammatory processes.

PP - 10

DRAMATIC RESPONSE TO IL1RA (ANAKINRA) THERAPY IN 3 CASES OF SoJRA AND STUDY OF IL1BETA PRODUCTION AFTER IN VITRO LYMPHOCYTE STIMULATION

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The efficacy of interleukin (IL)-1 receptor antagonist (Anakinra) in systemic onset juvenile rheumatoid arthritis (SoJRA) has been suggested since 2004, but to date, has not been confirmed in controlled trials. Anakinra has been shown to be very effective in genetic disorders of inflammation that are characterized by hyper-production of IL1beta (e.g. CINCA). Thus, we evaluated the clinical response to Anakinra in three patients affected by SoJRA and we measured the IL1beta production in vitro as compared to controls and to autoinflammatory syndrome patients.

Three patients with SoJRA refractory to immunosuppressive therapies and anti-tumor necrosis factor (TNF)alfa inhibitors, with severe steroid-related side effects were treated with Anakinra. Peripheral blood mononuclear cells were stimulated in vitro with LPS and the production of cytokines was evaluated after 24 hours. The results were compared with six healthy controls and three patients affected by autoinflammatory syndromes. The production of IL1beta in vitro appeared to be higher than in controls, and similar to that in autoinflammatory patients.

An immediate improvement in clinical condition was observed after Anakinra administration, with disappearance of fever, arthritis and rash. Acute phase reactants showed a rapid decrease until normalization in two out of three cases, and a slower decrease in the third patient. Anakinra was safe and well tolerated and allowed the withdrawal of other therapies, with a relevant sparing of steroids. Our data confirm the critical role of IL1 in the pathogenesis of SoJRA both on the clinical and on the bench side.

PP - 11

S100A12 AS A BIOMARKER IN FEVER OF UNKNOWN ORIGIN

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Objectives: Fever of unknown origin (FUO) is frequently a diagnostic challenge in the pediatric population. Patients present with fever and non-specific signs of inflammation. Differential diagnosis includes systemic onset juvenile idiopathic arthritis (SOJIA), an autoinflammatory syndrome associated with activation of phagocytic cells and an oversecretion of the proinflammatory cytokine interleukin (IL)-1β, but in the initial phase hard to differentiate from severe systemic infections. In this study, we compared the serum levels of the phagocytic proinflammatory protein S100A12 in the initial phase of SOJIA with some of its important differential diagnoses.

Methods: Serum samples from 60 SOJIA, 17 familial Mediterranean fever (FMF), 18 neonatal-onset multisystem inflammatory disease (NOMID), 17 Muckle-Wells syndrome (MWS), 19 acute lymphoblastic leukemia (ALL), 5 acute myeloblastic leukemia (AML), and 83 patients with systemic infections were included. Samples were obtained at presentation before initiation of anti-inflammatory or antibiotic treatment. Serum concentrations of S100A12 were analyzed using an ELISA system established in our laboratory. Normal serum levels were determined in 45 healthy controls.

Results: The mean serum level of S100A12 at initial presentation of SOJIA was 7,190 ng/ml (95% confidence interval ± 2685), in FMF 6722 ng/ml (± 4955), in NOMID 720 ng/ml (± 450), in MWS 150 ng/ml (± 60), in systemic infections 473 ng/ml (± 160), in ALL 110 ng/ml (± 60), and in AML 60 (± 30) compared to 50 ng/ml (± 10) in healthy controls. Sensitivity and specificity of S100A12 to distinguish SOJIA from severe infections were 85% and 89%, respectively.

Conclusions: S100A12 as a marker of granulocyte activation is highly overexpressed and secreted in patients with SOJIA. The measurement of S100A12 serum levels provides a diagnostic tool in the evaluation of FUO, which helps in differentiating SOJIA from its most relevant differential diagnoses.

PP - 12

DIFFERENTIAL EXPRESSION OF MRP8/14 IN AUTOINFLAMMATORY SYNDROMES

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Objectives: Familial Mediterranean fever (FMF), neonatal-onset multisystem inflammatory disease (NOMID), and Muckle-Wells syndrome (MWS) are autoinflammatory syndromes associated with activation of phagocytic cells and an oversecretion of the proinflammatory cytokine interleukin (IL)-1β. In this study, we compared the serum levels of the phagocytic proinflammatory proteins MRP8/14 during inflammatory phases and in the course of these diseases.

Methods: Serum samples from 17 FMF, 18 NOMID, and 17 MWS patients were included. Samples were obtained during inflammatory episodes before initiation of anti-inflammatory treatment or during low inflammatory activity. Serum concentrations of MRP8/14 were analyzed using an ELISA system established in our laboratory.

Results: The mean serum levels of MRP8/14 in inflammatory episodes in FMF were 343,208 ng/ml (± 202,209) and significantly higher than in NOMID 2,828 ng/ml (± 583) and in MWS 3,205 ng/ml (± 584). MRP8/14 levels decreased during low inflammatory activity and correlated to inflammation markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Conclusions: MRP8/14 as a marker of phagocyte activation is highly overexpressed and secreted in patients with FMF. Measurement of MRP8/14 serum levels might provide a diagnostic tool in the evaluation of patients with probable FMF, and might serve as a biomarker of inflammation in autoinflammatory diseases.

PP - 13

THE ROLE OF CHEMOKINES IN HENOCH-SCHÖNLEIN PURPURA

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Background: The pathogenesis of Henoch-Schönlein purpura (HSP) is incompletely understood and the role of chemokines is unknown.

Objective: To investigate the levels of CC chemokines, eotaxin, TARC, and CXC chemokine IP-10 in HSP.

Methods: Three groups of children were enrolled in the study: HSP in active stage (n=26), HSP in remission phase (n=26) and healthy children (n=18). Levels of eotaxin, TARC, and IP-10 were determined in plasma using ELISA.

Results: No significant difference was observed in the plasma level of eotaxin and TARC levels between the HSP and healthy children (>0.05). We also could not find any significant difference in eotaxin and TARC levels between acute phase of

the disease and convalescent phase ($p>0.05$). We have suggested significant decreases in plasma IP-10 in the acute phase of the disease compared with the convalescent phase ($p<0.05$). There was also a significant difference in IP-10 levels between active stage and healthy controls (<0.05). We could not find any significant correlation between chemokine levels and system involvement (>0.05).

Conclusion: Our study shows that plasma level of eotaxin and TARC levels do not differ between the HSP and healthy children. However, decreasing the release of the Th1 chemokine IP-10 in HSP active stage may show that in HSP, there is no shift to Th1 lymphocytes in children with HSP. Further investigations are warranted to more fully explore and understand the production of and potential role of these chemokines in HSP.

PP - 14

CHARACTERIZATION OF INTRA-ARTICULAR HMGB1 EXPRESSION DURING THE COURSE OF COLLAGEN-INDUCED ARTHRITIS

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Introduction: High Mobility Group chromosomal Box protein 1 (HMGB1) is a structural nuclear protein which promotes inflammation when present extracellularly. Aberrant, extracellular HMGB1 expression has been demonstrated in human and experimental synovitis. The aim of the present study was to elucidate the temporal and spatial expression of HMGB1 compared to that of the central mediators, tumor necrosis factor (TNF) and interleukin (IL)-1β, during the course of collagen-induced arthritis.

Methods: Dark Agouti rats were immunized with homologous type II collagen and synovial tissue specimens were obtained at various time points prior to and during the course of clinical arthritis. Local cytokine responses were assessed by immunohistochemistry and by *in situ* hybridization.

Results: A distinct nuclear expression of HMGB1 was demonstrated at early disease-preceding time points. Preceding clinical onset by a few days, cytoplasmic HMGB1 expression was evident in synoviocytes within the non-proliferative lining layer. Pronounced cytoplasmic and additional extracellular HMGB1 expression coincided with the progression of clinical disease. In advanced arthritis, the number of cells with cytoplasmic HMGB1 expression was quantitatively comparable to cells expressing TNF and IL-1β. Interestingly, although abundantly expressed throughout the inflamed synovium at a protein level, upregulation of HMGB1 mRNA was mainly restricted to areas of cartilage and bone destruction.

Conclusion: These new findings implicate a role for HMGB1 in both inducing and perpetuating inflammatory events of significant importance in the destructive processes in chronic arthritis.

PP - 15

INCREASED TNFα PRODUCTION IN PARVOVIRUS B19 POSITIVE JUVENILE IDIOPATHIC ARTHRITIS PATIENTS

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Objectives: Even though human parvovirus B19 (HPV B19) has been highly investigated in rheumatic diseases, its role in the pathogenesis of juvenile idiopathic arthritis (JIA) remains unclear. The goal of our study was to assess a possible association between HPV B19 infection and secretion of tumor necrosis factor α (TNFα) in JIA patients from Latvia.

Methods: Blood samples obtained from 29 (17 girls, 12 boys) JIA patients were analyzed for HPV B19 infection: presence of anti HPV B19 IgG and IgM against VP2 protein by the enzyme immunoassay method and HPV B19 DNA in plasma and leukocytes by nested polymerase chain reaction. TNFα was detected by ELISA assay. Mean age of patients was 7.6 years. Blood samples from 28 subjects with noninflammatory conditions were analyzed as controls.

Results: The prevalence of HPV B19 infection in the JIA group was increased compared to controls, but the difference was not significant. A significant association was found between HPV B19(+) JIA and high TNFα production when compared to HPV B19(-) JIA, which showed lower levels of TNFα production (82.75% vs. 31%, $p<0.05$). Among controls, high TNFα production level was detected in 64.3% of HPV B19(+) subjects compared to 8.35% in HPV B19(-) subjects.

Conclusion: The HPV B19 virus infection may influence TNFα production in JIA patients.

PP - 16

BIOLOGICAL THERAPY IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA) IN LATVIA

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The new therapeutic strategy in JIA resistant to traditional therapy is biologics, which have been applied in Latvia since 2004.

Objective: To determine the use and therapeutic efficacy and safety of biologics in JIA patients in Latvia.

Materials and Methods: Data from all 32 patients, 4 to 18 years old, with JIA (2 pts with Still disease, 30 pts with polyarthritis) unresponsive to prior therapy started receiving Enbrel with methotrexate. The JIA diagnosis was confirmed according to ILAR criteria. In both patients with Still disease, Enbrel was discontinued due to lack of response, and Anakinra was started, with good therapeutic response. One patient with polyarthritis was intolerant to Enbrel. Therapeutic efficacy was evaluated in the period of 3 to 6 months according to the definition of *Giannini et al.* by using the software program SPSS and Microsoft Excel.

Results: 29 (14 boys, 15 girls) patients with JIA polyarthritis improved after Enbrel therapy according to the global assessment of the severity of disease by the physicians ($p<0.01$), the global assessment of overall well-being determined by the parent ($p<0.01$), and by the scale of severity of pain ($p<0.01$). The decrease in the number of affected joints was valid. Laboratory analysis confirmed a decrease in C-reactive protein (CRP) ($p<0.05$). Severe infectious or opportunistic diseases were not registered.

Conclusion: Enbrel has been determined safe and effective in the treatment of JIA polyarthritis, but Anakinra was effective in cases of Still disease.

• Humoral aspects – autoantibodies

PP - 17

EVALUATION OF ORGAN-SPECIFIC AUTOIMMUNITY IN PATIENTS WITH JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE)

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Introduction: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease characterized by the presence of several autoantibodies, including the organ-specific ones. The lack of reports describing the association between lupus and organ-specific autoimmune diseases in pediatric populations inspired this study.

Objective: To evaluate the presence of organ-specific antibodies in a juvenile SLE (JSLE) population.

Methods: Thirty-seven patients with JSLE were investigated for the presence of organ-specific autoantibodies. The diseases evaluated were: diabetes mellitus type 1-DM1 (anti-insulin – IAA and anti-glutamic acid decarboxylase - anti-GAD); autoimmune thyroiditis (anti-thyroglobulin - TGA and anti-thyroid peroxidase - TPO); celiac disease (antiendomysium - EMA); primary biliary cirrhosis (anti-mitochondrial – AMA); and autoimmune hepatitis (anti-liver-kidney microsomal type 1 - LKM1 and anti-smooth muscle - SMA). Frequency of rheumatoid factor (RF) and antineutrophil cytoplasmic antibody (ANCA) were also determined.

Results: Ten patients (27%) presented at least one of the autoantibodies evaluated. Two patients (5.4%) had positive antibodies for DM1, one presented anti-GAD and the other IAA; thyroiditis antibodies were detected in six patients (16.2%), two of them were positive for both TGA and TPO; and one patient had positive antibody for celiac disease. Autoantibodies for autoimmune hepatitis (anti-LKM1 and SMA) and for primary biliary cirrhosis (AMA) were negative. RF and ANCA were positive in four (10.8%) and three (8.1%) patients, respectively.

Conclusion: The association between JSLE and organ-specific autoimmune diseases such as diabetes, thyroiditis and celiac disease may stimulate the search for common genetic factors involved in their etiopathogenesis.

PP - 18

CLONAL EXPANSION OF SYNOVIAL B CELLS AND DIFFERENTIATION INTO PLASMA CELLS IN JUVENILE IDIOPATHIC ARTHRITIS

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The presence of antinuclear antibodies in early-onset pauciarticular arthritis (EOPA), one of the most frequent forms of juvenile idiopathic arthritis (JIA), might reflect a participation of B cells in the pathogenesis. However, B cells are not yet well characterized in this disease.

Flow cytometric analysis of matched synovial fluid and peripheral blood samples of 23 patients with EOPA-JIA demonstrated the accumulation of activated memory B cells in the synovial fluid. Plasma cells/plasmablasts could be detected in one-third of the analyzed synovial fluid samples. The presence of plasmablasts in the synovial fluid of several patients prompted us to analyze whether clonal relatedness could be found between the memory B cell population and the plasma cell population. Therefore, we amplified and further sequenced the kappa light chain rearrangements of individual memory B cells and plasma cells of the synovial fluid of two patients. Clonal relatedness, indicated by the usage of identical kappa light chain CDR3 regions within different B cells, could be separately found in the memory population as well as in the plasma cell population. Additionally, the appearance of memory B cells and plasma cells using identical CDR3 regions could be demonstrated in both patients, suggesting clonal differentiation of memory B cells into plasma cells.

Oligoclonal memory B cells accumulate in the synovial fluid of EOPA patients and differentiate into plasma cells at this site of inflammation. Further work has to elucidate if the arising plasma cells might participate in the production of autoantibodies.

PP - 19

ANTI-MELANOMA ANTIGEN B2 (MAGE-B2) ANTIBODY: A POTENTIAL BIOMARKER FOR ACTIVE SLE AND LUPUS NEPHRITIS

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Introduction: Renal involvement is present in 75% of pediatric patients with systemic lupus erythematosus (SLE); however, markers specific for SLE nephritis remain elusive. Anti-melanoma-associated antigen (MAGE) B2 antibody may be a novel biomarker of lupus nephritis. The purpose of this study was to determine the association of anti-MAGE B2 antibody with active SLE and nephritis.

Methods: Using two pediatric SLE patient sera with high-titer autoantibodies to perform serologic analysis of recombinant cDNA expression library (SEREX) made with a human epithelioma (HEp-2) cell line, antibodies to MAGE B2 were found. The presence of anti-MAGE-B2 antibody was determined in 40 pediatric patients meeting 1997 criteria for SLE, in 23 adult controls, and in 16 patients with juvenile rheumatoid arthritis (JRA). Immunoscreening, performed by SEREX and Western Blot analysis using patient plasma at 1:250 dilution, detected antibodies to recombinant MAGE B2 protein.

Results: Seventeen (43%) of 40 pediatric SLE patients had detectable anti-MAGE-B2 antibody, compared to 0 of 14 JRA patients and 2 (9%) of 23 control adult patients ($p=0.0004$). Of the 17 SLE patients who had anti-MAGE B2 antibodies, 59% had active nephritis compared to 21 in those without the antibody ($p=0.024$). SLE disease activity (SLEDAI and BILAG) scores were also higher in anti-MAGE B2 antibody-positive patients ($p=0.028$, $p=0.011$, respectively).

Conclusion: Anti-MAGE B2 antibody may be a potential SLE biomarker specific to SLE nephritis and disease activity. A prospective study of the anti-MAGE B2 antibody in lupus nephritis with a larger cohort of patients is underway.

PP - 20

DETERMINATION OF ANTI-CYCLIC CITRULLINATED PEPTIDE (ACCP) AND ANTI-MODIFIED CITRULLINATED VIMENTIN (MCV) IN CHILDREN WITH EARLY ARTHRITIS

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Objective: There are some difficulties in the diagnosis of early juvenile arthritis (JA). There are no serological markers that can help in the diagnosis and determination of the method of treatment. Importance of rheumatoid factor (RF) in the diagnosis of JA is lower than in adults, because its frequency in arthritis in childhood is 15-20%. Some reports about the diagnostic value of ACCP and anti-MCV in JA of varied duration have been published in recent years.

Methods: ACCP was tested in sera from 38 patients with early JA (duration less than 6 months) by ELISA using commercial kit (Axis Shield Diagnostics Limited, UK; cut- off: 5.0 U/ml). Anti-MCV was tested in serum from 60 patients with JA by ELISA using commercial kit (Orgentec, Germany; cut off: 25.0 U/ml).

Results: Serum from 10.5% of patients was ACCP-positive. Frequency of ACCP in the group of patients was higher than in the control group of healthy

children, but lower than in adults with RA (82.4%). Frequency of ACCP was higher in the group of early JA than in patients with late course of JA. All patients with ACCP had polyarthritis, RF-positive. 28.3% of patients with early JA had increased levels of anti-MCV and five patients (from 17 who had anti-MCV) had levels higher than 100 U/ml. We revealed significant correlations of anti-MCP with ACCP, RF, CRP, and number of affected joints.

Conclusion: We assume that ACCP and anti-MCV may be indicators of polyarticular course of JA with severe outcome and prognosis, especially in the early stage of disease.

PP - 21

THYROID AUTOIMMUNITY IN YOUNG PATIENTS WITH RHEUMATIC DISEASES

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Autoimmune thyroiditis is more frequent than is usually believed in the course of other autoimmune diseases. Nevertheless, it is scarcely studied, especially in children. We studied 440 patients (308 females, 132 males, median age 12.6 yrs, range 2.4–18.9 yrs). 290 children had juvenile idiopathic arthritis (JIA): 184 oligoarticular, 76 polyarticular, 17 systemic onset, and 13 psoriatic arthritis. Ninety-six children had juvenile-onset spondyloarthropathies (JSpA), 21 systemic lupus erythematosus (SLE), 16 Behçet syndrome (BS), 12 localized scleroderma (LS), and 5 Sjögren syndrome (SS). 196 age- and sex-matched children served as controls. All patients underwent antithyroglobulin (TgA) and antiperoxidase (TPOA) antibody testing. All patients with positive TPOA and/or TgA values had thyroid function tests (TSH, FT4 and FT3) and a thyroid sonography. Positive TPOA and/or TgA were found in 45 out of 440 patients (10.23%): 21/184 oligoarticular JIA (11.4%), 5/76 polyarticular JIA (6.6%), 1/17 systemic JIA (5.9%), 10/96 JSpA (10.4%), 3/21 SLE (14.3%), 3/16 BS (19%), 1/12 LS (8.3%), and 1/5 SS (20%). Ultrasound examination showed non-homogeneous thyroid parenchyma in 21/45 (46.6%) and thyroid nodules in 4/45 patients (8.8%); thyroid ultrasound was normal in 20/45 patients (44.4%); 37/45 children were euthyroid, 3 oligoarticular JIA patients and 1 with JSpA showed subclinical hypothyroidism (TSH > 5 μU/ml, normal FT3 and FT4); 1 with systemic JIA, 1 with JSpA, 1 with LS and 1 with SS showed hypothyroidism. In the control group, 3/196 children had positive thyroid antibodies (1.5%). Therefore, it is clinically important to screen pediatric patients with rheumatic diseases for the coexistence of thyroid disorders.

• Innate immune response

PP - 22

HUMAN SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR I (sTNF-RI) AND INTERLEUKIN-I RECEPTOR ANTAGONIST (IL-I RA) IN DIFFERENT STAGES OF ACUTE RHEUMATIC FEVER

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Acute rheumatic fever (ARF) is a multisystem inflammatory disorder that follows nasopharyngeal infection caused by group A streptococci (GAS). Recent studies have demonstrated elevated proinflammatory cytokine concentrations in ARF and rheumatic heart disease. Serum concentrations of two anti-inflammatory cytokines, interleukin-I receptor antagonist (IL-I Ra) and human soluble tumor necrosis factor receptor I (sTNF-RI), were investigated in children with ARF at the time of admission (n=21) and after three months following the cessation of treatment (n=15). Serum levels of

IL-1RA and sTNF-RI were found to be significantly higher during acute phase and remission period of ARF when compared to age-matched healthy controls. These data suggest that this increase might probably serve to protect a balance between anti-inflammatory and proinflammatory cytokines in ARF.

CLINICAL:
• JIA
PP - 23

INFLIXIMAB IN JUVENILE IDIOPATHIC ARTHRITIS: LITTLE FROM JORDAN

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Prescribing biologic therapies in children with juvenile idiopathic arthritis (JIA) has been recently introduced in Jordan. We report results of Infliximab use in four children with JIA refractory to methotrexate treatment: three with systemic onset- and one with extended oligo-JIA. The dose ranged between 3-5 mg/kg/8 weeks. The mean follow-up was 21.5 months (range 12-30 months). Two patients showed ACR 70, one ACR 50 and the fourth had ACR 20 when assessed one year after treatment. They all tolerated treatment well. Even though it is described in few cases, Infliximab use in these patients showed significant clinical improvement and was usually well tolerated.

PP-24

FREQUENCIES OF ALLELIC POLYMORPHISMS IN GENES ENCODING CTLA4, IL6, -10, MIF AND TGFß IN DIFFERENT SUBTYPES OF JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: Associations of polymorphisms in genes encoding regulatory cytokines or receptors with autoinflammatory diseases have been reported in: (i) IL6 and MIF with systemic JIA, (ii) TGFß with progressive joint destruction in RA, (iii) IL10 with limiting inflammatory response in JIA, and (iv) CTLA4 with diabetes as well as autoimmune thyroiditis. We studied the polymorphisms CTLA4 (-49 A/G; +318 C/T), IL6 (-174 G/C), IL10 (+592 A/C), TGFß (+509 C/T) and MIF (-173 C/G) in a large cohort of German JIA patients with different subtypes of JIA.

Material and Methods: 906 DNA samples from the DNA database of the "Gesellschaft für Kinder- und Jugendrheumatologie (GKJR)" and 500 healthy Caucasians of a population-based study were amplified with gene specific PCR and genotyped based on allele specific restriction fragment length polymorphism. Statistics were performed with SPSS using chi^2 and Fisher's exact tests.

Results: CTLA4 allele frequencies showed no differences in any JIA subtype. IL6 promoter region showed increased frequencies of the GC genotype in oligoarticular, systemic and polyarticular (seronegative) JIA. MIF promoter GC genotype was significantly increased in both polyarticular and extended oligo JIA. IL10 polymorphism showed the AC genotype significantly increased in seronegative polyarticular and persistent oligoarticular JIA, while TGFß CT genotype was associated with all subtypes except enthesitis-associated and psoriatic JIA.

Discussion: Associations in the German cohorts (JIA and controls) differ from those observed in Great Britain and Italy. There seems to be a significant diversity within gene frequencies even in healthy individuals from different regions of Europe, complicating the interpretation of different studies.

PP - 25

SURVEY ON IMMUNIZATION IN CHILDREN AND ADOLESCENTS WITH RHEUMATIC DISEASES

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There are very limited data on the safety and efficacy of vaccines in children and adolescents with inflammatory rheumatic diseases and guidelines for immunization are missing. The immunosuppressive therapy often necessary for these patients gives rise to additional uncertainty. In addition, many colleagues consider vaccination to increase the risk of relapse of the rheumatic illness. As a consequence, there are substantial variations in practicing vaccination in these patients, resulting in insufficient vaccination coverage rates.

Methods: A survey on the vaccination status of JIA patients and vaccination procedures was performed in the pediatric rheumatology centers in Germany.

Results: Every third patient was incompletely vaccinated (see figure).

Between the 28 centers participating, there were remarkable differences concerning: (i) vaccination procedures and (ii) the assessment of contraindications resulting from immunosuppressive therapies.

Conclusion: To date, there are no evidence-based strategies for the vaccination of JIA patients. Apart from live vaccines, these patients should be immunized according to the Standing Immunization Commission of the Robert Koch Institute recommendations whenever possible. However, the time of vaccination must be carefully selected, taking disease activity and treatment into account.

PP - 26

IS JUVENILE DRY POLYARTHRITIS A NEW CLINICAL ENTITY OR AN ATYPICAL PRESENTATION OF A KNOWN CHRONIC RHEUMATISM?

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Juvenile dry polyarthritis (JDPA) is characterized by a progressive stiffness of peripheral joints without effusion or biological inflammation. This exceptional clinical picture calls into question whether JDPA is a novel disease or an atypical picture of an identified rheumatism. We report herein a longitudinal study of eight patients (5 girls and 3 boys) with JDPA.

The patients were followed for a mean of 6.4 years. Mean age at disease onset was 7.3 years and diagnosis delay 1.2 years. Patients always reported a progressive flexion contracture of digits at disease onset. When referred, 8/8 presented with generalized symmetrical joint stiffness, complaining about pain (7/8) and prolonged morning stiffness (8/8). There was no sign of joint inflammation, no or few synovitis and no effusion. ESRs were subnormal and autoantibodies negative. Patients were unresponsive to NSAIDs; however, methotrexate (MTX, 10-15 mg/m^2/wk) induced a clear pain release (8/8), allowing an efficient reduction of polyarticular stiffness under intensive physiotherapy. In the absence of pain and despite MTX therapy, X-rays showed a progressive polyarticular destructive course over time in 6/7 patients. Finally, one patient developed a sclerodermiform cutaneous dystrophy over wrists and ankles. Importantly, familial history of psoriasis or psoriatic arthritis (PsA) was found in five patients, and two patients developed psoriatic lesions during the disease course.

This suggests that JDPA might be an atypical form of juvenile-PsA, lacking psoriasis over years. JDPA patients should benefit from early treatments like physiotherapy plus MTX combined with anti-TNFalpha, which are used in adult PsA patients, limiting both joint structural damage and contractures.

PP - 27

EARLY DIAGNOSIS OF TEMPOROMANDIBULAR JOINT INVOLVEMENT IN JUVENILE IDIOPATHIC ARTHRITIS: A PILOT STUDY COMPARING CLINICAL EXAMINATION AND ULTRASOUND TO MAGNETIC RESONANCE IMAGING

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Background: Temporomandibular joint (TMJ) arthritis is a common manifestation of juvenile idiopathic arthritis (JIA). TMJ arthritis in children can severely affect growth and function of the jaw. Because it is often asymptomatic, a screening method needs to be developed to detect TMJ arthritis before destruction and growth disturbance occur.

Objectives: To study the validity of specialized clinical rheumatological and dental examinations and an ultrasound (US) technique as screening methods for early diagnosis of TMJ arthritis as compared to the gold standard magnetic resonance imaging (MRI).

Methods: Thirty consecutive patients with a confirmed diagnosis of JIA were included into this pilot study. Rheumatological and dental examinations were compared to MRI as the gold standard and to US of the TMJ as a new technique. Presence of joint effusion and/or synovial enhancement on MRI were considered signs of active arthritis.

Results: MRI signs of active TMJ arthritis were present in 19/30 patients (63%). Any TMJ pathology was present in 19/30 patients (63%) at the rheumatological, in 18/30 patients (60%) at the dental examination and in 10/29 patients (34.5%) with US. The positive predictive value was 0.74 for the rheumatological examination, 0.72 for the dental examination and 0.52 for the US. The negative predictive value was 0.55, 0.5 and 0.2 for rheumatological, dental and US examination, respectively.

Conclusion: A normal clinical or US examination was not able to reliably exclude active TMJ arthritis in our patients with JIA. Of the methods tested, US was the least useful for the diagnosis or exclusion of TMJ arthritis.

PP - 28

METHOTREXATE IS AN EFFECTIVE TREATMENT OPTION FOR JUVENILE IDIOPATHIC ARTHRITIS ASSOCIATED UVEITIS

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Background: Uveitis occurs in 10-15% of patients with juvenile idiopathic arthritis (JIA). When topical treatment fails, a second-line agent is used to control the disease. Currently there is no controlled study regarding the effectiveness of second-line agents.

Objectives: The aim of the survey was to create a cross-sectional cohort to learn about the efficacy of methotrexate (MTX) in the treatment of JIA-associated uveitis.

Methods: Via e-mail survey, the international pediatric rheumatologic community was questioned regarding the use and efficacy of MTX in the treatment of JIA-associated uveitis.

Results: Eight centers reported 80 patients with JIA-associated uveitis treated with MTX. Twenty-five were male. The mean age of the patients was 11.57 years (range 2.25-20.17 years). In 68 patients, uveitis evolved in a mean 1.79 months after the onset of arthritis, and in 12 patients uveitis evolved in a mean 1.34 months before the onset of arthritis. The type of uveitis was described as anterior in 70, intermediate in 4, posterior in 5 and panuveitis in 1; 137 of 160 eyes were involved. The mean time to initiating MTX was 2.57 months after diagnosis of arthritis or uveitis. MTX was initiated in 10 cases because of arthritis, in 11 cases because of arthritis and uveitis and in 59 cases for uveitis only. In 66 cases, uveitis was non-responsive to local therapy, in 16 cases high dose of systemic glucocorticoids were needed to control the uveitis, and 12 patients already received another second-line agent before starting MTX treatment. The mean MTX dose was 12.66 mg/week. The mean duration of MTX therapy was 4.47 months (range 0.22-84.5 months); in 47 cases it was administered orally and in the other cases subcutaneously. The response was rated good in 42 patients; 38 of them received MTX as monotherapy. In 31 cases another agent was added to improve the response; in 29 cases a tumor necrosis factor blocking agent, in 20 cases it was infliximab. Local steroid eyedrops could be reduced in 63 cases and systemic steroids could be reduced in 46 cases.

Conclusion: In 38 of 80 cases, MTX was effective to control uveitis as a monotherapy. MTX appears to be the first choice of the second-line agents to treat JIA-associated uveitis.

PP - 29

MACROPHAGE ACTIVATION SYNDROME IN JUVENILE IDIOPHATIC ARTHRITIS

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Macrophage activation syndrome (MAS) is a severe complication of juvenile idiopathic arthritis (JIA) usually described in longstanding diseases. Here, three patients, in different clinical forms and stages of JIA diagnosed with bone marrow biopsy, will be presented to discuss heterogeneity of this complication.

Case 1: A 17-month-old boy, suffering from fever for one month presented with petechiae and hepatomegaly. Laboratory evaluation was as follows: hemoglobin (Hb): 8.5 g/dL, WBC: 2350/mL, platelet count: 19, 300/mL, ESR: 5 mm/h, AST 204 U/L, ALT 106 U/L, ferritin: 119, 913 ng/ml, fibrinogen 1.09 g/l, and D-dimer 1.03 mg/mL. Methylprednisolone pulse and cyclosporine A were used with success.

Case 2: A 14-month-old boy presented with left hip arthritis and high fever. He was treated with the diagnosis of septic arthritis. At the end of third week of hospitalization, together with unremitting fever, laboratory evaluation was as follows: Hb: 7.54 g/dL, WBC: 2960/mL, platelet count: 46, 500/mL, ESR: 9 mm/h, AST 339 U/L, ALT 127 U/L, ferritin: 79, 810 ng/ml, fibrinogen 1.62 g/l, and D-dimer 3.99 mg/ml. Prednisone 2 mg/kg/day was used with success. He is now on follow-up with methotrexate.

Case 3: An 11-year-old girl was followed with the diagnosis of oligoarticular JIA whose disease progression could not be controlled with intraarticular steroid, methotrexate and oral prednisone. Sulfasalazine was added with weekly increments. At the fourth week, she presented with vomiting, high fever and hepatosplenomegaly. Laboratory evaluation was as follows: Hb: 7.6 g/dL, WBC: 2640/mL, platelet count: 95, 000/mL, ESR: 2 mm/h, AST 953 U/L, ALT 586 U/L, ferritin: 2420 ng/ml, fibrinogen 1.5 g/l, and D-dimer: 1.3 mg/mL. Sulfasalazine was withdrawn, methylprednisolone pulse was instituted. She is now on follow-up with methotrexate and etanercept.

PP - 31

INCIDENCE AND PREVALENCE OF JUVENILE IDIOPATHIC ARTHRITIS IN CATALONIA (SPAIN)

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Objective: To determine the incidence and prevalence of juvenile idiopathic arthritis (JIA) in Catalonia (North East Spain).

Methods: Prior to the initiation of the study itself, an educational program addressed to all general pediatricians in Catalonia was designed. A review of the different forms of presentation of JIA was summarized, discussed with pediatricians and made available on-line. From October 2004 until October 2006, all data of the newly diagnosed patients were collected. Twenty-four different hospitals collaborated with the main investigators. October 2006 was established as the cut-off date for prevalence calculation. Data from all patients with the diagnosis of JIA were introduced in the database regardless of their actual age. For classification purpose, the Edmonton criteria were used.

Results: The two-year incidence rate for JIA was 5.08 (4.42-5.84)/10^5 children ≤16 yrs. A bimodal pattern was present with a peak at 2 yrs and a second peak at 10 yrs. The percentages of the different subtypes were as follows: systemic 6.3%, oligoarticular 36.3%, polyarticular 11.3%, psoriatic arthritis 20%, enthesitis and arthritis 15.8% and undifferentiated 11.3%. Only patients younger than 16 yrs old were used to calculate prevalence. JIA was present in 36.5 (31.6 – 42.0)/10^5 children. Distribution of the different subtypes showed more patients classified as oligoarticular subtype and less as psoriatic arthritis in the prevalent cases (oligo=52.8%; psoriatic=9.6%). Girl to boy ratio was 2.3/1.

Conclusion: Incidence and prevalence of JIA are similar to those found in other countries in the south of Europe. Different subtypes of the disease were present at the same percentages described in other epidemiological studies.

PP - 32

ANA AS A RISK FACTOR FOR JIA-ASSOCIATED UVEITIS IS HIGHLY DEPENDENT ON METHOD

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Introduction: Positive antinuclear antibodies (ANA) are reported to be an important risk factor for development of uveitis in children with juvenile idiopathic arthritis (JIA) and influences ophthalmologic screening programs for uveitis. Enzyme-linked immunoassays (ELISA) for automated identification of antigen-specific ANA (E-ANA) are increasingly used as a more standardized alternative to the traditional immunofluorescence method on Hep-2 cells (IF-ANA). Clinical implications of the different ANA methods with respect to uveitis in JIA need attention.

Material/Method: Sera of 116 children with JIA and 49 healthy children were analyzed with both E-ANA and IF-ANA method. Patients were prospectively recruited and followed at regular intervals from onset of disease from 1997-2004.

Results: Five of 115 (4%) patient sera were E-ANA positive, and 74 of 115 (63%) were positive using the IF-ANA method. Of the five E-ANA positive, three were IF-ANA negative. Fifteen of the patients developed uveitis, with a mean observation time of six years. Analyses of risk factors for uveitis show

that F-ANA titer > 1/320 and young age at onset of arthritis are significantly associated with increased risk of uveitis. Arthritis subtype, gender, positive E-ANA and IF-ANA titer >1/80 are not significantly associated with the development of uveitis.

Conclusion: Positive ANA in children with JIA is highly dependent on the analyzing methods. Without specifications of method, the clinical value of ANA in JIA and in risk stratification for uveitis screening must be questioned.

PP - 34

ADAPTED VERSIONS OF THE SHARP-VAN DER HEIJDE SCORE ARE RELIABLE AND VALID FOR ASSESSMENT OF RADIOGRAPHIC PROGRESSION IN JIA

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Objective: To develop adapted versions of the Sharp/van der Heijde (SvdH) radiographic scoring system for use in juvenile idiopathic arthritis (JIA), and to investigate their validity in children with polyarticular disease.

Methods: Wrist/hand radiographs of 177 patients with polyarticular-course JIA obtained at first observation and then at 1, 3, 5, 7 or 8, and 10 years were assessed independently by two pediatric rheumatologists according to different adapted versions of the SvdH method. To facilitate score assignment, each patient radiograph was compared with a bone age-related standard. Validation procedures included analysis of reliability, construct validity, and score progression over time.

Results: Interobserver and intraobserver agreement on longitudinal score values and score changes were good for all score versions, with intraclass correlation coefficient >0.85. Score changes over time were moderately-to-strongly correlated with the clinical indicators of long-term joint damage and with the amount of long-term radiographic damage measured with carpometacarpal ratio, thereby demonstrating good construct validity. A steady increase in scores over time was observed, with joint space narrowing being the most common form of damage throughout the disease course. The inclusion of five new areas appeared to increase the overall construct validity of erosion scores.

Conclusion: Our results show that the adapted versions of the SvdH score are reliable and valid for the assessment of radiographic progression in JIA and support the use of quantitative measures of radiographic damage in pediatric rheumatology care and their inclusion in future observational studies and therapeutic trials in JIA.

PP - 35

LIPID PROFILE AND HOMOCYSTEINEMIA IN LONG-TERM JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Accelerated atherosclerosis may contribute to cardiovascular mortality in adults with rheumatoid arthritis. In patients with long-term JIA, data on lipid profile is inconclusive. Therefore, we studied plasma lipid and homocysteine levels in patients with long-term JIA and the possible association with disease activity, drug treatment, and sera levels of folate and vitamin B12.

Subjects and methods: Plasma lipid profiles, homocysteine and apolipoprotein levels were determined in 30 JIA patients according to 1997 ILAR revised criteria, after 12h overnight fast. Disease activity was arbitrarily established as the presence of active synovitis in >1 joint associated with elevated ESR/CRP. Statistical comparisons were performed using *t* test, and P<0.05 was considered significant.

Results: Thirty JIA patients (1 systemic, 24 polyarticular, 3 oligoarticular), with mean age of 22.6+5.9 yrs (range 11-32 yrs) and mean disease duration of 12.4±5.9 yrs (range 1-24 yrs) were evaluated. Seven subjects were under low dose CE therapy (<5 mg/kg/d) and 13/30 (43.3%) had active JIA. High levels of total cholesterol were detected in 4 (13.3%) patients, of LDL in 8 (26.6%), and of triglycerides in 2 (6.6%); 5 (16.6%) had increased apolipoprotein B/apolipoprotein A1 ratio. Interestingly, 12/30 (40%) subjects had low HDL. Elevated homocysteine levels were observed in 5/30 (16.6%) patients, and all 5/5 had lower serum folate (P=0.009); only 1/5 was on methotrexate (MTX) (p=0.03). There was no relationship between homocysteine levels and disease activity.

Conclusion: Adverse lipid profile is frequent in long-term JIA and elevation in levels of homocysteine in 1/6 patients may be an additional cardiovascular risk factor.

PP - 36

SEXUAL FUNCTION IN MALE PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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In JIA, joint impairment and reduced muscular strength may affect activities of daily living including eating, bathing, dressing, toileting, and transferring. An individual's sex life may be similarly hampered. Therefore, the aim of this study was to evaluate musculoskeletal influence in sexual function of male patients with polyarticular JIA.

Patients and Methods: Polyarticular JIA male patients according to 1997 ILAR revised criteria with inactive disease were studied. As a control group, 70 age-matched male individuals with the same socioeconomic status were studied. All patients and control subjects were subject to a self-applied questionnaire for screening their sexual life (satisfaction, practice and functional aspects).

Results: Thirty polyarticular JIA male patients, with mean age of 21.1 ± 3.7 yrs (range 16-26 yrs) and mean disease duration of 13.8 ± 2.82 yrs (range 10-20 yrs) were evaluated. Desire and satisfaction were preserved in all subjects. Concerning masturbation, 26/30 (87%) patients reported regular practice, although 3/26 (12%) had concomitant pain: 1/3 (34%) genital and 2/3 (66%) in hips and feet. In the control group, 59/70 (84%) regularly masturbated and 5/59 (8%) had genital pain. Regular sexual intercourse was mentioned by 25/30 (83%) JIA patients, 13/25 (52%) associated with pain: 12/13 (92%) in joints (hips and knees), 1/13 (8%) in genitalia. Likewise, 60/70 (86%) control subjects reported regular intercourse, but only 2/60 (3%) had pain (p<0.001) due to previous hand trauma.

Conclusion: Despite long-term disease, morbidity and functional dysfunction, joint pain did not compromise sexual life of our polyarticular JIA patients, including desire, satisfaction, regular masturbation and intercourse practice.

PP - 37

TUBERCULIN SKIN TEST (TST) IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Introduction: Screening for tuberculosis (TB) using TST is mandatory before anti-tumor necrosis factor (TNF) therapy for JIA. Therefore, we evaluated TST reaction in JIA children considering prior BCG immunization, disease activity and CE/immunosuppressor therapy.

Methodology: According to ILAR criteria, 25 JIA patients were evaluated after obtaining informed consent. JIA disease activity was arbitrarily established as active synovitis >1 joint plus erythrocyte sedimentation rate (ESR) >20 mm. TST was performed using 2 tuberculin U/dose of PPD - RT23 according to WHO recommendations; induration ≥5 mm read 48h later was considered positive. Chest X-rays were suspect when apical lesions, reticulonodular infiltrates or pleuritis was evidenced. Mann Whitney and Fisher tests were used for statistical comparisons and $P < 0.05$ was considered significant.

Results: Twenty-five JIA patients (4 systemic, 11 polyarticular, 10 oligoarticular), with mean age of 10.2±4.3 yrs (range 2.5-16 yrs) and mean disease duration of 4.2±3.6 yrs (range 0.5-13 yrs) were evaluated. All children received neonatal BCG immunization; none had TB or a positive history for TB exposure. Six children were using low-dose CE (mean 5.5±2.0, range 2.5-7.5 mg) while 1 was taking 1.7 mg/kg/d; 20/25 (80%) were on immunosuppressors (20 MTX, 3 cyclosporine); 5/25 (20%) had active JIA. Only 5/20 TST-negative children had active JIA whereas positive TST occurred in 5/25 (20%) patients, none with active disease (P=1.0): 30 mm in 1 child, whose X-ray was suspect but CT was normal; 15 mm in 1; 8 mm in 1; and 10 mm in 2. CE/immunosuppressors did not interfere with TST response (P=1.0).

Conclusion: In a Brazilian cohort of JIA children, neonatal BCG vaccination, disease activity and CE/immunosuppressor intake had no effect on TST interpretation.

PP - 38

ATLANTO-AXIAL SUBLUXATION IN A PATIENT WITH POLYARTICULAR JIA: CLINICAL AND RADIOLOGICAL RESPONSE TO INFLIXIMAB

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A nine-year-old boy with polyarticular juvenile idiopathic arthritis (JIA) underwent MRI of the cervical spine for persistent neck pain, restriction, elevated inflammatory indices, and an increased atlanto-odontoid distance on cervical X-rays and CT. MRI showed an atlanto-odontoid distance of 10 mm suggesting an atlanto-axial subluxation. He was treated with steroids (prednisone 0.5 mg/kg) and indomethacin (3 mg/kg) with complete erase of joint arthritis except for cervical spine involvement. Considering the potential life-threatening complication of atlanto-axial subluxation, infliximab (5 mg/kg) was initiated in addition to steroids. After three infusions of infliximab, the neck pain and decreased range of motion completely resolved, and steroid therapy was gradually withdrawn. A follow-up MRI of the neck showed a reduction of atlanto-odontoid distance (6 mm). However, the persistence of increased tissue density anterior to the cervical spine and the persistent elevation of inflammatory markers were consistent with active disease. Infliximab therapy was continued with six other infusions every eight weeks as sole therapy (total 9 infusions).

Complete clinical control of the disease was achieved three months after the last infliximab infusion, with a normalization of inflammatory markers, and a further reduction of atlanto-odontoid distance to a normal value (5 mm) was measured on MRI.

Atlanto-axial subluxation is a characteristic radiological abnormality of the axial skeleton in JIA often leading to pain and neck functional limitations.

This is the first case of polyarticular JIA with atlanto-axial subluxation that showed a complete remission after tumor necrosis factor (TNF) blocker therapy.

PP - 39

AUDIT OF LEG LENGTH DISCREPANCY IN A TERTIARY PEDIATRIC RHEUMATOLOGY CENTER

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Introduction: Leg length discrepancy (LLD) in juvenile idiopathic arthritis (JIA) due to accelerated growth of an affected leg may result in long-term mechanical back and limb pain and abnormalities of gait. In addition, hip or knee flexion contractures cause relative shortening of the extremity.

Method: The following were audited: (1) The clinic letters and therapy notes of 50 consecutive patients referred to pediatric rheumatology therapists, and (2) Referrals for shoe raises over the last 30 months.

Results: (1) From 50 consecutive patients, two were found to have a LLD. (2) Twenty-eight patients were referred for a shoe raise in the last 30 months (mean age: 8y 8m, range: 2y 8m – 17y 1m). Of these, 17 had oligoarticular JIA, 4 polyarticular JIA, 1 enthesitis-related arthritis, 1 juvenile psoriatic arthritis, and 4 other. Sixteen patients had had joint injections. Fourteen patients had a 5 mm raise, 10 patients had a 10 mm raise, and 4 patients had a raise ≥ 10 mm. Seven patients demonstrated an improvement in LLD over this time. Raises ≤ 5 mm are usually fitted inside the shoe allowing for ease of changing shoes and re-ordering as the child grows. Raises ≥ 10 mm are added to the outside of the shoe, which is likely to result in poorer adherence.

Conclusions: Leg length should always be measured where there is or has been disease in the lower limbs. It should be measured regularly during active disease, following joint injections and when the child is growing, and the appropriate raise supplied.

PP - 40

UNSUCCESSFUL TREATMENT WITH EXTRACORPOREAL PHOTOPHERESIS (ECP) OF A PATIENT WITH SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS (SoJIA)

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Background: ECP, originally used to treat cutaneous T cell lymphoma, has also been applied to the treatment of autoimmune diseases. Although the exact mechanisms whereby ECP modulates immunity are not fully understood, some studies suggest that ECP induces expansion of T-reg.

Objectives: To investigate the biological and clinical response to ECP in a five-year-old girl with SoJIA.

Methods: The patient was three years old at the onset of the disease. Oral prednisone, methotrexate and etanercept, administered for two years, produced unsatisfactory control of the disease. Only high dose steroids controlled symptoms. ECP was started at the age of five with simultaneous administration of oral prednisone at 1 mg/kg/day dose. Fifteen applications, two every week for the first month and two every 15 days in the following months, were performed. T-regs were assessed three times - before, in the middle, and at the end of ECP.

Results: The child did not improve clinically. ESR and CRP remained elevated and she also developed a significant anemia. Before starting ECP, the number of CD4+CD25+ cells (T-reg) was low (13.3%) and the percentage of T-reg did not change in the course of treatment (9% in the second determination and 11.4% in the last).

Conclusion: Treatment with ECP of a child with SoJIA did not improve the clinical course and did not result in any increase of the number of T-reg.

PP - 41

HIGH PREVALENCE OF ALGIC-DYSFUNCTIONAL PATHOLOGY OF MASTICATORY MUSCLES IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Background: JIA may affect any joint, including the temporomandibular joint (TMJ). TMJ can be involved unilaterally or bilaterally, early or late in the course of disease and it may be the first affected joint. TMJ arthritis seems to be a more frequent manifestation in patients with JIA than previously recognized, owed to the paucity of clinical symptoms and poor sensitivity of conventional radiological studies used for diagnosis.

Objectives: To investigate the involvement of TMJ in JIA.

Methods: Six hundred and eighty children with JIA consecutively diagnosed between 1992 and 2005 by the Rheumatology Unit of our hospital were referred for orthodontic evaluation of TMJ involvement including orthopanoramic X-rays, TMJ stratigraphy and scintigraphy, MRI, 3D-CT and electromyography of masticatory muscles.

Results: One hundred and fifty-seven patients (23%) were clinically symptomatic and radiological studies confirmed TMJ involvement; 426 (62.6%) had no TMJ clinical symptoms but accurate clinical

examination, electromyography and imaging studies revealed involvement of masticatory muscles and especially of the external pterygoid. Ninety-seven patients (14.2%) were clinically asymptomatic and radiological studies were all negative. Two hundred and ten patients, 47 symptomatic and 163 asymptomatic, required orthodontic treatment with improvement of muscle contractions and algic-dysfunctional pathology.

Conclusion: TMJ is functionally or anatomically involved in the majority (85.7%) of our children with JIA. Algic-dysfunctional pathology of masticatory muscles is detectable in more than 60% of children with JIA in the absence of TMJ symptoms.

PP - 42

IMPROVING THE CEILING EFFECT OF THE CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ): A STUDY IN CHILDREN WITH JIA

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Objective: To study the ceiling effects of a Dutch translation of the revised version of the CHAQ (Lam et al., 2004) among seven different versions and response options of Dutch translations of the CHAQ.

Methods: Seven versions of the CHAQ were tested in two convenience samples of children with juvenile idiopathic arthritis (JIA) (n=89). The questionnaires were completed with pen and paper or through an interview by a physical therapist. The distribution of the scores was analyzed for normality and ceiling effects.

Results: The results confirmed the ceiling effect of the Dutch translation of the original CHAQ. Removing the questions about aid and assistance increased the ceiling effect, while adding eight more demanding items, as proposed by Lam et al., reduced it. Ignoring the original domain sub-scores and calculating instead the average of the individual items resulted in the version with the largest (30 items) and the version with the smallest (38 items) ceiling effect. The revised CHAQ showed a more normal distribution than either of the versions and response options of the original CHAQ, but the score range was very narrow.

Conclusion: A CHAQ version with 38 items calculated as the average of the sum score showed the best properties to assess functional status in children with JIA. This version showed a smaller ceiling effect than the original CHAQ and the widest score range of all seven versions. The advantage of this version is that historic data sets can still be compared with the results from the revised version of the CHAQ.

PP - 43

JUVENILE IDIOPATHIC ARTHRITIS FROM THE VIEWPOINT OF THE ADOLESCENT PATIENT: EXPLORATION BY DIALOGICAL SELF-ASSESSMENT

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Most literature demonstrates, somewhat counterintuitive, that growing up with juvenile idiopathic arthritis (JIA) has little impact on the psychosocial functioning of adolescents. The discrepancy between these findings and our clinical experience gave us reason to search for a more subtle care and research method directly related to the adolescent patient's own experience.

At present, in the Wilhelmina Children's Hospital of the University Medical Centre Utrecht, The Netherlands, a large scale study into the stories told by adolescents with JIA about themselves –using Hermans' Self Confrontation Method- is being conducted. With this dialogical self-assessment, insight in the personal emotions and experiences can be gained, and in addition a self-assessment can have a positive influence on the integration of the disease in the life of the adolescent. Especially since many patients with arthritis experience psychological distress in early adulthood, we want to point out the importance of gaining more insight into the personal experiences of the adolescent patient. Some preliminary results of this study will be discussed, comparing the self-narratives of some adolescents with JIA to the stories healthy adolescents tell about themselves. In addition, the special value of the self confrontation method as a counselling tool will be illustrated in a case study.

PP - 44

ANTIOXIDANT STATUS IN JUVENILE IDIOPATHIC ARTHRITIS

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Juvenile idiopathic arthritis (JIA) is the most commonly diagnosed rheumatic disease in children. Reactive oxygen species (ROS) have been implicated in its pathogenesis. Oxidative free radical production may contribute to tissue damage at inflammation sites. However, the role of ROS in JIA is not yet fully understood. The aim of this study was to investigate antioxidant status including superoxide dismutase (SOD), catalase and ceruloplasmin in 32 patients with JIA and 20 healthy age-matched controls. In addition, erythrocyte sedimentation rate (ESR), platelet count, serum C-reactive protein (CRP) and rheumatoid factor (RF) levels were determined. Plasma SOD levels were unchanged, catalase levels were lower and ceruloplasmin levels were higher in patients with JIA than healthy children (0.89±0.03 vs 0.9±0.02 enzyme unit/mg, $p>0.05$; 12.6±3.2 vs 5.05±0.66 enzyme unit/mg, $p<0.01$; and 74.6±5.2 vs 28.3±4.9 mg/dL, $p<0.001$, respectively). CRP ($p<0.05$) and RF levels ($p<0.001$), ESR ($p<0.05$) and platelet counts ($p<0.05$) were significantly higher in patients with JIA than healthy subjects. There were significant negative correlations between catalase and CRP, ESR and platelet counts. There was a positive correlation between ceruloplasmin and ESR, CRP and platelet counts. These results provide some evidence for a potential role of decreased (catalase) or unchanged (SOD) enzymic antioxidants in JIA by its inflammatory character. These results suggest that oxidant stress plays a very important role in the pathogenesis of JIA.

PP - 45

IS THE COUNT OF ACTIVE JOINTS, AS CURRENTLY DEFINED, A "PURE" MEASURE OF DISEASE ACTIVITY IN JUVENILE IDIOPATHIC ARTHRITIS?

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Background: The count of joints with active disease is one of the six core set measures included in the ACR Pediatric definition of improvement. In this definition, a joint is defined as active if it displays swelling (SW) or, if no swelling is present or detectable, restricted motion (RM) plus either tenderness (TEN) or pain on motion (POM). However, it is unclear whether the presence of RM + TEN/POM equates to the presence of SW as indicator of active disease, particularly in patients with long-standing disease in whom the presence of RM and/or TEN/POM may be due to joint damage rather than to disease activity.

Objective: To investigate the relative role of the count of joints with SW and RM+TEN/POM as indicators of disease activity in long-standing juvenile idiopathic arthritis (JIA).

Methods: 302 patients with disease duration > 5 years were studied. The Spearman's correlation of count of joints with SW and TEN/POM + RM was compared with other joint counts and conventional measures of JIA activity and damage.

Results: The count of joints with SW was better correlated with the active joint count than the count of joints with TEN/POM (r_s 0.89 vs. 0.64). The counts of joints with SW and TEN/POM were poorly correlated each other (r_s 0.32). The count of joints with SW correlated better with activity measures, whereas the count of joints with TEN/POM correlated better with damage measures.

Conclusion: Our results show that the count of joints with TEN/POM is an imperfect indicator of disease activity in JIA.

PP - 46

THE CLINICAL MEANING OF CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ) DISABILITY IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Objective: To investigate the time course of CHAQ disability in children with JIA and identify predictors of long-term functional outcome.

Methods: Patients who were followed for > 1 year and had > 2 CHAQ completed were included. Predictor variables were: sex, onset age, ILAR category, age at visit, disease duration, joint counts, ANA, ESR, CRP, and baseline CHAQ. At each visit, CHAQ scores were divided into 3 categories: 0-0.49, 0.5-1.5, and 1.51-3, representing disability states 1, 2, and 3, respectively. Predictor analysis was conducted with multivariate analysis, using disability state (1 vs 2 or 3) at last visit as outcome variable.

Results: 227 patients had 1356 CHAQ completed. Mean number of CHAQ per patient was 6 (2-19) and mean follow-up was 4.1 years. Initial disability state was 1, 2 and 3 in 49.8%, 40.1% and 10.1% of patients, respectively. Three longitudinal patterns of disability were observed: 1) a stable state; 2) a steady improvement or deterioration; 3) a fluctuating state. Disability state at last visit was 1, 2 and 3 in 74%, 22.9%, and 3.1% of patients, respectively. The strongest predictor variables were an age < 4.8 years and a restricted joint count > 10.

Conclusion: In spite of a wide variability in the course of physical functioning, at last follow-up, three-fourths of patients had no disability and a small proportion had severe disability. Younger age at disease onset and a greater number of joints with limited range of motion were the strongest predictors of long-term functional disability.

PP - 47

RADIOLOGICAL PROGRESSION IN PATIENTS WITH JUVENILE IDIOPATIC ARTHTRITIS TREATED WITH TNF INHIBITORS

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Studies to evaluate radiological progression were performed in children with juvenile idiopathic arthritis (JIA) treated with methotrexate. To our knowledge, this has not been done in children treated with biologics. The Poznanski score is a well- recognized method to evaluate radiological progression in children. The aim of the study was to evaluate if children with JIA treated with TNF a inhibitors had a better outcome regarding radiological progression than those treated with methotrexate as monotherapy and patients without these drugs.

A total of 51 patients were evaluated, divided as group 1: patients treated with TNF a inhibitors (17 patients), group 2: with methotrexate (18 patients) and group 3: without these drugs (16 patients). All three groups were comparable with respect to sex and age. Retrospectively, the Poznanski scores at the start of treatment and last visit were reviewed independently by two of the authors and data were compared regarding disease activity, functional ability and time of onset of TNF treatment. Statistics used were descriptive tests, chi square, Student's t and Pearson correlation. In all patients treated with TNF a inhibitors, Childhood Health Assessment Questionnaire (CHAQ) was used to evaluate functional ability.

Difference in Poznanski score for group 1 was -1.99E-02, for group 2 -4.80E-02 and for group 3 -8.66E-02. Difference in Poznanski score between the three groups was F 3.8; p 0.029.

Conclusion: Treatment with TNF a inhibitors was shown to be more effective in reducing radiological progression in children with JIA and, if started early, was related with a significant improvement in functional ability. A multicenter study is in progress to increase the number of patients and statistical relevance.

PP - 48

ACHIEVEMENT OF COMPLETE DISEASE CONTROL IN THE FIRST 5 YEARS PREDICTS A MORE FAVORABLE LONG-TERM OUTCOME IN POLYARTICULAR JIA

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Objective: To investigate the relationship between achievement of complete disease control (CDC) and long-term outcome in children with polyarticular juvenile idiopathic arthritis (JIA).

Methods: 123 patients who were followed for ≥ 5 years and had a yearly assessment between the first observation up to 5 years were studied. At each visit, the presence of CDC (defined as active joint count = 0 and ESR < 20 mm/hour) was assessed. Based on achievement of CDC in the first 5 years, patients were divided into three groups as: 1) patients who never achieved CDC (n=62); 2) patients who achieved CDC only once (n=40); and 3) patients who achieved CDC more than once

(n=21). Long-term outcome was assessed 6 to 18 years after first observation through joint counts, CHAQ, Poznanski score of radiographic damage, Articular and Extraarticular Juvenile Arthritis Damage Index (JADI-A and JADI-E), and ESR.

Results: The Table shows the comparison of mean values of long-term outcomes in the three patient groups (Kruskal-Wallis test).

Conclusion: Patients who achieved CDC in the first 5 years had a better long-term outcome than those who did not. These results underscore the importance of tight control of disease activity over time in the improvement of the long-term outlook of children with JIA.

	No. active joints	No. restricted joints	CHAQ	Poznanski score	JADI-A	JADI-E	ESR
Group 1	5.0	7.4	0.50	-2.0	3.7	0.8	19.7
Group 2	2.4	2.6	0.26	-0.9	1.5	0.5	21.7
Group 3	3.1	2.4	0.22	-1.1	0.2	0.4	13.6
P	0.02	0.03	0.17	0.15	0.004	0.37	0.03

PP - 49

IRIDOCYCLITIS IS RARE IN THE ABSENCE OF ANA AMONG ITALIAN JIA PATIENTS WHO HAD ANA STATUS CHECKED WITH REPEATED DETERMINATIONS

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Objective: To evaluate the frequency of iridocyclitis in our patients with juvenile idiopathic arthritis (JIA) and its relationship with the presence of antinuclear antibodies (ANA).

Methods: A total of 749 patients who were seen between 1985 and 2004 and were followed for at least six months were identified. ILAR category frequency was as follows: 11.9% systemic arthritis, 52.5% oligoarthritis, 16.6% rheumatoid factor (RF)-negative polyarthritis, 1.7% RF-positive polyarthritis, 4.8% psoriatic arthritis, 6% enthesitis-related arthritis (ERA), and 6.5% undifferentiated arthritis. All patients had at least two ANA determinations made > 3 months apart. Patients were defined as high-positive (HP) if they had ≥ 2 positive results on indirect immunofluorescence at a titer ≥ 1:160. Patients who had ≥ 1 positive results at lower titer were defined as low-positive (LP). Patients were defined as ANA-negative if they had negative results in all determinations made during follow-up.

Results: 480 patients (64%) were ANA-positive: of them, 452 (60.3%) were HP and 28 (3.7%) LP; 269 patients (35.9%) were ANA-negative. Overall, 126 patients (16.8%) had iridocyclitis, 5 of whom (all with ERA) had acute iridocyclitis. Excluding the latter patients, the frequency of iridocyclitis was 24.6% (111/452), 21.4% (6/28), and 1.5% (4/269) in HP, LP and ANA-negative patients, respectively.

Conclusion: In our JIA patients who had their ANA status checked on repeated occasions, iridocyclitis was very uncommon in the absence of ANA. The large majority of our ANA-positive patients had ≥ 2 positive determinations at a titer ≥ 1:160. The optimal threshold for ANA positivity in JIA deserves international consensus.

PP - 50

DEVELOPMENT AND INITIAL VALIDATION OF A NEW MULTIDIMENSIONAL ASSESSMENT QUESTIONNAIRE FOR JUVENILE IDIOPATHIC ARTHRITIS

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Objective: To devise a new multidimensional assessment questionnaire for children with juvenile idiopathic arthritis (JIA), named Juvenile Arthritis Multidimensional Assessment Report (JAMAR).

Methods: The JAMAR includes a 15-item questionnaire for assessment of physical function, a 10-item questionnaire for assessment of health-related quality of life, three visual analogue scales for rating of well-being, pain and disease activity, two 5-point scales for rating of morning stiffness and disease outcome versus previous assessment, one 3-point scale for rating of disease activity state, a self-report joint assessment tool, multiple-choice questions devoted to report of treatment side effects, treatment compliance and difficulties at school, and a final question about the satisfaction with the outcome of the illness.

Results: The questionnaire was devised by six experienced pediatric rheumatologists, who reached consensus on the domains and items to be included in the tool, thus establishing its content validity. To assure face validity, the questionnaire was shown to 14 physicians who were not part of the JAMAR group and to four physiotherapists, and their opinion on its suitability was sought. To date, a total of 55 parents and 26 patients have completed the questionnaire. None of them has reported difficulties in understanding its components.

Conclusion: We have developed a new multidimensional assessment tool for JIA that is proposed for use in standard clinical care. Preliminary validation analyses have shown that the JAMAR is feasible and has good content and face validity. Evaluation of reliability, construct validity and responsiveness of clinically important change is in progress.

PP - 51

AGREEMENT BETWEEN DIFFERENT SPECIALISTS IN THE ASSESSMENT OF RADIOGRAPHIC JOINT DAMAGE IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Objective: To compare the judgement of different musculoskeletal specialists on the amount of radiographic joint damage in children with JIA.

Methods: One pediatric rheumatologist, one pediatric radiologist, and one pediatric orthopedic surgeon, who had > 5 years of experience in childhood chronic arthritis, independently evaluated 60 bilateral radiographs of the hands and wrists taken in JIA patients with polyarthritis. Each specialist scored the amount of radiographic damage on a 5-point scale (0=no abnormalities; 5=mutilating bone changes and/or ankylosis) (specialists' score). Radiographs were previously divided into five classes of severity according to the modified Sharp-

van der Heijde (mSH) score, assigned by two pediatric rheumatologists not involved in this study. Agreement between specialists was evaluated using weighted kappa (<0.40=poor agreement; 0.41-0.60=moderate agreement; 0.61-0.80=substantial agreement; >0.80 excellent agreement) and overall agreement (percentage of observed exact agreement). Correlation between specialists' and mSH score was assessed by Spearman's correlation coefficient (<0.4=low; 0.4-07=moderate; >0.7=high).

Results: Kappa value (overall agreement) was 0.64 (45%) between the rheumatologist and the radiologist, 0.61 (48%) between the rheumatologist and the orthopedic surgeon, and 0.63 (52%) between the radiologist and the orthopedic surgeon. Spearman's correlation between specialists' and mSH score was 0.87 for the rheumatologist, 0.90 for the radiologist, and 0.84 for the orthopedic surgeon.

Conclusions: We found a fair agreement between different musculoskeletal specialists in the assessment of radiographic damage in children with JIA. The 5-point scale that we devised represents a simple and reliable tool that enables a quick standardized assessment of radiographic joint changes in clinical practice.

PP - 52

PHYSICIAN AND PARENTAL RATINGS OF INACTIVE DISEASE ARE FREQUENTLY DISCORDANT IN JUVENILE IDIOPATHIC ARTHRITIS

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Objective: To investigate discrepancy between physician and parental rating of inactive disease in children with juvenile idiopathic arthritis (JIA) and determinants of discordance.

Methods: Study data were obtained from the clinical database generated at the study unit. Each visit included a standardized assessment of JIA outcome measures. One visit for each patient was selected for the analysis. Three definitions of inactive disease were applied to the data: a physician-based definition (physician global assessment = 0); a parent-based definition (parent global assessment = 0); and a formal definition, based on fulfillment of newly developed criteria for inactive disease in JIA.

Results: Of 1, 237 visits made by 537 patients that included both physician and parent global assessments, 265 fulfilled the physician-based definition and/or the parent-based definition of inactive disease. Concordance between physicians and parents in rating the disease as inactive was seen in 40% of the visits, whereas in 60% of the visits the two assessments were discordant. Parents tended to disagree with physicians in rating the disease as inactive if the child had pain or functional impairment, whereas physicians tended to disagree with parents in the presence of active joint symptoms. Only 2/3 of the 79 visits that fulfilled the formal definition of inactive disease also met the parent-based definition of inactive disease.

Conclusion: We found frequent discordance between physician and parental ratings of inactive disease in children with JIA, which suggests that parental rating of their child's disease activity should be considered for inclusion in the definition of clinical remission for JIA.

PP - 53

ONCE WEEKLY DOUBLE-DOSE ETANERCEPT IS AS EFFECTIVE AS TWICE WEEKLY USUAL DOSE IN RETAINING AND INDUCING REMISSION IN JIA

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Background: Etanercept at the dose of 0.4 mg/kg twice weekly has been shown to be effective in juvenile idiopathic arthritis (JIA). Studies in adults show that a double dose once weekly is effective enough to induce and retain remission. A pharmacokinetic model indicates that the same dosing regimen could be used in children (1).

Methods: Patients with JIA in remission were switched to etanercept at the double dose of 0.8 mg/kg subcutaneously once weekly. In addition, etanercept was initiated in patients in the once weekly double dose. Disease activity was evaluated at the start of the study and re-evaluated after three months by means of the internationally used PRINTO-score. Efficacy was assessed using the preliminary definition of improvement of Giannini et al. (2).

Results: Fourteen JIA patients (5 systemic, 4 polyarticular rheumatoid factor (RF)-, 1 polyarticular RF+, 3 oligoarticular extended, 1 psoriatica), in remission, were included. Mean age was 13.3 years, mean disease duration 7.0 years and mean etanercept use 2.2 years. After three months, all patients showed values of the PRINTO-score that were equal to the values at the start of the study, except one who did show equal values after six months. Three JIA patients (mean age 15.3 years, mean disease duration 3.2 years; 2 polyarticular RF+, 1 polyarticular RF-) started etanercept in a double dose. All showed major improvement on the PRINTO-score, meeting the requirements of the ACR 50.

Conclusion: Etanercept in a once weekly double dose can induce and retain remission in JIA.

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PP - 54

DEVELOPMENT AND PRELIMINARY TESTING OF A NEW COMPOSITE DISEASE ACTIVITY SCORE FOR JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Objective: To devise and test the Juvenile Arthritis Disease Activity Score (JADAS).

Methods: The JADAS is composed of the following measures: 1) physician's global assessment; 2) parent's global assessment; 3) joint count; and 4) acute phase reactant. Several versions of the JADAS were tested: a 3-item version, which included active (act) or swollen (sw) joint count, assessed in all joints or in a maximum of 10 joints; and a 4-item version, which included erythrocyte sedimentation rate (ESR) (divided by 10) or C-reactive protein (CRP). For both ESR and CRP, values above 10 were equalized to 10. The different versions of the JADAS were tested by calculating their Spearman's correlation with juvenile idiopathic arthritis (JIA) outcome measures not included in the score.

Results: Spearman's correlations are shown in the table.

	Version of the JADAS					
	Act71	Act10	Sw68	Sw10	Act10–ESR10	Act10–CRP10
Parent's pain assessment	0.66	0.70	0.67	0.70	0.68	0.67
CHAQ	0.59	0.59	0.56	0.56	0.60	0.58
Active joint count	–	–	0.78	0.76	–	–
Swollen joint count	0.80	0.77	–	–	0.76	0.76
Tender joint count	0.80	0.79	0.74	0.73	0.78	0.78
Restricted joint count	0.67	0.64	0.59	0.58	0.63	0.64
Morning stiffness	0.53	0.55	0.53	0.55	0.55	0.56
ESR	0.50	0.50	0.50	0.51	–	0.60
CRP	0.55	0.54	0.54	0.54	0.63	–

Conclusion: The different versions tested showed similar statistical performances, which leads us to propose the 4-item JADAS composed of physician's global assessment, parent's global assessment, active joint count, and ESR, all measured on a 0-10 scale and yielding a 0-40 total score, for use in future studies.

PP - 55

ADVANCED BONE AGE ON THE AFFECTED SIDE IS ASSOCIATED WITH GREATER RADIOGRAPHIC PROGRESSION IN JIA PATIENTS WITH UNILATERAL WRIST DISEASE

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Objective: To verify our clinical impression that juvenile idiopathic arthritis (JIA) patients with unilateral wrist disease often have an advanced bone age on the affected side and that advancement in skeletal maturation is associated with more severe radiographic progression.

Methods: 21 patients with unilateral wrist disease and 21 patients with bilateral wrist disease who underwent a bilateral hand/wrist radiograph were evaluated. Bone age in each wrist was assessed on radiograph made at first observation by an experienced pediatric endocrinologist according to Greulich & Pyle atlas. Radiographic damage was assessed at baseline and last follow-up visit by measuring carpo-metacarpal ratio (Poznanski score).

Results: Bone age on the affected side was advanced by > 6 months in 12/21 patients (57.1%) with unilateral wrist disease and in 8/21 (38.1%) and 7/21 (33.3%) patients with bilateral wrist disease on the right and left side, respectively. Comparison of chronological-bone age lag and radiographic damage on baseline and follow-up films in patients with unilateral and bilateral wrist disease is shown in the table.

	Chronological-bone age lag (years)	Baseline Poznanski score	Follow-up Poznanski score
Unilateral-affected side	1.06[#]	-1.94[$£]	-4.4[§]
Unilateral-unaffected side	0.67	-0.47[£]	-1.9[§]
Bilateral-average L/R wrist	0.23[#]	-0.62[$]	-2.7

[#]p=0.05; [$]P=0.006; [£]p=0.004; [§]p=0.02.

Conclusion: Our results confirm that JIA patients with unilateral wrist disease often have advanced skeletal maturation on the affected side and that this is accompanied by a greater destructive course. This indicates that these patients warrant a careful radiographic follow-up and an early aggressive therapy aimed at suppressing joint inflammation in the wrist to prevent progression of joint damage.

PP - 56

LEVELS OF SOLUBLE INTERLEUKIN-2 RECEPTOR AND RESPONSE TO ANTI-TNF TREATMENT IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background: Recent data in adults with rheumatoid arthritis suggest that low baseline level of soluble interleukin-2 receptor (sIL2R) may predict a good response to anti-tumor necrosis factor (TNF) treatment.

Aim: To relate the sIL2R level and the response to anti-TNF treatment in children with juvenile idiopathic arthritis (JIA).

Patients-Methods: Levels of sIL2R were measured by ELISA in 29 children with persistently active JIA (systemic: 8, oligo-persistent: 2, oligo-extended: 7, poly-rheumatoid factor (RF) negative: 8, poly-RF positive: 3, psoriatic: 1, aged 2-17.5 years [x=10.2], disease duration: 68.9±10.6 mo), before and 6 months after anti-TNF treatment (etanercept=14, infliximab=12, adalimumab=3) and in 30 healthy (age- and sex-matched) children. Patients were concomitantly receiving methotrexate (22), cyclosporine (6), NSAIDs (19) and/or prednisolone (22). The response to treatment was assessed by ACRped 50 and 70 and the disease activity by a MDVAS scale (1-4).

Results: Elevated levels of sIL2R (x±SD: 1676±596.41 pg/ml) were found in all patients pre-treatment compared to the controls (480±120 pg/ml, $p<0.001$). Six months post-treatment, all patients achieved an ACRped>50 and reduced the sIL2R levels (1005±474.59, $p<0.01$) but these were still significantly elevated compared to those of the controls ($p<0.05$). No correlation was demonstrated: a) between the pre-treatment sIL2R levels and those after 6-months of treatment, MDVAS score and ACRped 50-70 (r^2:0.07, p:0.17) and b) between the difference (pre- and 6 months post-treatment) of sIL2R levels and MDVAS score.

Conclusions: Baseline sIL2R levels are not a prognostic marker of response to anti-TNF treatment in children with JIA.

PP - 57

DOES THE INCOME OF THE FAMILY AFFECT THE COURSE OF JIA: A LINK TO HYGIENE HYPOTHESIS?

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Among the juvenile idiopathic arthritis (JIA) subtypes, persistent oligoarthritis has been reported to be more frequent among North American and European patients as compared to other populations. On the other hand, recent studies have shown that the cytokine profile of persistent oligoarthritis is towards the T-helper 2 type. We have analyzed whether the socioeconomic level correlated with persistent oligoarthritis course of JIA.

We applied a questionnaire to a group of 50 JIA patients presenting to our center in Ankara, Hacettepe University, Pediatric Nephrology and Rheumatology Department. A number of issues relating to the socioeconomic level were queried. The results showed that the higher income families were statistically more in the persistent oligoarthritis group (44.4%) as compared to the other JIA subtypes (15.6%) ($p>0.05$). A persistent oligoarthritis was 4.32 times more common among higher income families.

These preliminary results in this small group suggest that the socioeconomic level is probably a confounding factor in the persistent oligoarthritis course, which can be explained by the hygiene hypothesis. Other social factors are being evaluated.

PP - 58

THE IMMUNOPATHOLOGY OF EARLY UNTREATED JUVENILE IDIOPATHIC ARTHRITIS: COMPARING OLIGOARTICULAR AND POLYARTICULAR DISEASE

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Aim: To explore the cellular expression of the synovial membrane in early untreated juvenile idiopathic arthritis (JIA), and define the histology of the disease subtypes.

Methods: All patients had at least one swollen knee joint requiring intra-articular steroid injection. Participants were defined according to ILAR criteria, with disease duration <1 year, and no previous treatment. Synovial biopsies from the knee were obtained from 31 JIA patients. The density and distribution of inflammatory cells, osteoclast mediators and markers of growth and repair were all subsequently assessed by immunohistochemistry and quantified using standard scoring system.

Results: Clinically, there was no correlation between degree of joint swelling and clinical symptoms, the time of presentation and ultrasound findings. Synovial hypertrophy in patients with oligo disease was as evident as in those with poly disease. Polys had significantly greater mean scores for B-cells (1.7 vs 1.0) and vessels (6.9 vs 2.6) than the oligos ($p<0.05$). Positive correlations between vessel score and the number of swollen joints were observed in oligo ($p=0.025$) and poly ($p=0.038$).

Conclusion: This novel study has shown that polys had significantly more B-cells and vessels than the oligos in our untreated population.

	Poly	Oligo
Number of patients	11	20
Age (years)	9 (4-16)	4.4 (1-16)
Sex (M/F)	(3/6)	(5/17)
Number of swollen joints	13 (5-36)	2.2 (1-4)
WBC	9.7 (5-11.8)	8.7 (5.4-15.7)
Hb	11 (7.2-12.8)	9.9 (10-12.4)
ESR	24.3 (13-110)	14.5 (2-37)
CRP* (mg/l)	14.5 (1-42.3)	8.6 (2-20.4)
Plt	409.6 (303-578)	339.7 (222-489)
ANA (+/–)	(4/5)	(12/8)
measurement	40 (40-80)	71.1 (40-320)
Rheumatoid factor	1 positive, 10 negative	All negative

PP - 59

HEALTH-RELATED QUALITY OF LIFE IN RUSSIAN CHILDREN WITH JUVENILE RHEUMATOID ARTHRITIS

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Background: Health-related quality of life (HRQOL) measurement is an important health outcome in clinical practice improvement strategies, and even children aged 5 years can reliably and validly self-report their HRQOL (J. Varni et al., 2007).

Methods: We used the modified Piers-Harris Children's Self-Concept Scale and Dembo-Rubinstein Scale of Self-Efficacy and Outcome Expectations to evaluate the self-assessment of HRQOL in 130 children (88 girls) with juvenile rheumatoid arthritis (JRA) and in 113 (78 girls) healthy children (HLT) aged 5-18 years. The subscales of behavior (BE), schooling (SC), intellectual level (IL), appearance (AP), anxiety (AN), popularity (PO), happiness (HA), health status (7 issues), and psychosocial status (6 issues) were analyzed using chi-square, Kolmogorov-Smirnov tests and multivariate exploratory techniques.

Results: The results demonstrate that HRQOL measure for children with JRA is lower than for HLT. For children younger than 10 years, it concerns only two health status subscales: rehabilitation medicine (MED) and physical development and mobility (MOB). For teenage girls, the difference is significant in subscales AP, PO, HA, MED, MOB, rehabilitation nursing, nutrition, pain and psychology (PSY); for teenage boys – in subscales AP, MED and MOB only. There were no differences in subscales of communication, neuropsychology, social issues, vacation/educational activity, pastoral care subscales of psychosocial status, BE, SC, IL, activities of daily living and AN.

Conclusion: Gender, duration of the disease and glucocorticoid treatment, body height and mass, SSD and NAIS are the most important factors influencing the HRQOL.

PP - 60

CHRONIC ACTIVE UVEITIS IN JIA: LESSONS FROM A CLINICAL SCREENING SERVICE

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Current screening for chronic active uveitis (CAU) in juvenile idiopathic arthritis (JIA) is not evidence-based and does not reflect recent changes in care. Providing the evidence base will require study of a large number of patients in many centers.

Aim: To audit the screening program (SP) for patients attending a single pediatric rheumatology center to inform the future development of a multicenter study of the SP.

Methods: Clinical details of JIA and eye data from the SP were collected prospectively in the clinics. In cases where eye care occurred in another hospital, the ophthalmology records were reviewed.

Results: Of 310 JIA patients, 217 (70%) entered the SP; 158 in this center, 59 in their local hospital. Exclusions from SP referral were age (35), disease type (26), pending (12) or inappropriately missed (7). First JIA symptom to first SP visit was a median of 159 days (52-3247). Subsequent median screening interval was 196 days (48-1139). Of 987 SP visits in 158 children, 45% were screening visits and 55% for the management of CAU. CAU occurred in 31 children, identified in half at their first SP visit. CAU occurred in 36% of children with extended oligoarthritis, other (25%), rheumatoid factor (RF) negative polyarthritis (24%), enthesitis-related arthritis (ERA) (20%), psoriatic arthritis (11%), classification unknown (14%), and least often in persistent oligoarthritis (10%).

Discussion: Half the patients had uveitis at first eye screen, a median of 5 months after their first JIA symptom. CAU was seen in a high proportion of patients with disease types often considered less at risk or excluded from screening programs.

PP - 61

RE-ESTABLISHMENT OF CLINICAL BENEFIT IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS AFTER ABATACEPT WITHDRAWAL AND SUBSEQUENT RE-INTRODUCTION

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Background: When juvenile idiopathic arthritis (JIA) abatacept (ABA)-responders were randomized to ABA or placebo (PBO) for up to 6 months (double-blind Period B), the PBO group had a flare rate significantly higher (>2.5-fold) than those continuing on ABA. Here we present interim results from PBO-treated patients who flared and subsequently received ABA in the open-label extension of this study (Period C).

Objectives: To evaluate safety and efficacy of ABA in children with polyarticular JIA, with an inadequate response to disease-modifying antirheumatic drugs.

Methods: All 33 PBO-treated patients who flared during Period B opted to receive ABA 10 mg/kg in Period C. Safety (including immunogenicity) and efficacy were assessed through 6 months.

Results: Upon re-introduction of ABA, a return toward prior levels of clinical response was observed, determined by ACR Pediatric 30, 50, 70 and 90 scores (Figure). Three patients were excluded from Day C169 assessments: two discontinued and one did not have the Day C169 evaluation. During the first 6 months of Period C, there were no discontinuations due to adverse events (AEs), no acute (within 1 hour of dosing) infusional reactions and no auto-immune events in this cohort. One patient had a serious AE (fruit allergy) and remained on ABA therapy with no recurrence.

Conclusion: Re-introduction of ABA after withdrawal of up to 6 months was associated with clinical improvement in patients with JIA, and was not associated with infusion reactions or untoward safety findings.

PP - 62

PREGNANCY OUTCOME IN WOMEN AFFECTED BY JUVENILE IDIOPATHIC ARTHRITIS (JIA) EXPOSED TO BIOLOGICAL AGENTS

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Introduction: JIA is a disease that includes 8 ILAR categories different from those of adult rheumatoid arthritis (RA). Methotrexate (MTX) has shown efficacy and safety in treatment of JIA. In the last few years, a more specific and effective therapeutic approach has emerged with biological agents (anti-tumor necrosis factor [TNFα]). AntiTNFα approved for RA are: the p75TNFαR (etanercept), the monoclonal antibodies against TNFα: chimeric (infliximab) and human (adalimumab). Etanercept is the only antiTNFα registered for JIA. In our center during the last seven years, infliximab and adalimumab have been used off-label in an open prospective study for the treatment of refractory JIA not only in pediatric age but also in young adults. These drugs have shown a dramatic clinical benefit. Nevertheless, some patients do not respond to the first antiTNFα. Failure may be due to adverse events (AE), inefficacy or loss of efficacy.

Purpose: To underline the capability to become pregnant, without negative influence by antiTNFα, and to describe the pregnancy outcome of some of our young patients who became pregnant during the antiTNFα treatment.

Methods: Seven women affected by refractory JIA (1 systemic onset, 2 psoriatic arthritis, 2 poly RF, 2 oligo extended) became pregnant during the antiTNFα therapy. Mean age: 25 yrs (range: 19.7-28.3); mean onset age: 12 yrs; mean yrs between disease onset and introduction of antiTNFα: 12.8 yrs (range: 5.1-24.7); mean treatment duration: 3 yrs (range: 0.9-6). All patients had a long-lasting refractory polyarticular disease not responsive to MTX and one or more other DMARDs (2 or 3 previous failed treatments). Two patients had been treated with only 1 biologic agent: pt 1 received etanercept for 18.3 months, and pt 2 for 2 months, interrupted for pregnancy. Four patients had switched to a second TNFα blocker (for the reasons reported above). Pt 1 received 7 infusions of infliximab, suspended because of AE and switched to etanercept for 3.7 months, then pregnancy. Pt 2 received 24 infusions of infliximab, suspended because of lack of efficacy and switched to etanercept for 41.6 months, then pregnancy. Pt 3 received 4 infusions of infliximab, suspended because of AE and switched to etanercept for 48.1 months, then pregnancy. Pt 4 received 4 infusions of infliximab, suspended because of loss of efficacy and switched to adalimumab for 28.5 months, then pregnancy. One patient had been treated with 3 TNFα blockers: she received 16 infusions of infliximab, suspended because of AE and loss of efficacy, switched to adalimumab for 40 months, suspended because of loss of efficacy, and switched to etanercept for 4 months, then pregnancy.

Results: Three patients decided on elective termination; three patients had a normal pregnancy resulting in live born infants, full term, with no structural abnormalities and still in good health; one patient is actually in the 2nd trimester of pregnancy without any complications. No abnormalities were observed in the live born infants or in the fetuses of the pregnancies ended with elective termination. Regarding the patients who proceeded with the pregnancies, two interrupted the biologic treatment as soon as they became grave index positive; the third one suspended the biologic agent (etanercept) during the third month, as soon as she became aware of the pregnancy. The patient who is still pregnant did not suspend immediately but after the second month of pregnancy because of the persistently active disease.

Conclusions: For female patients affected by JIA, the availability of antiTNFα has raised important questions about fetal safety if a woman becomes pregnant while under treatment. Few case reports or studies regarding limited populations affected by Crohn's disease or RA treated with antiTNFα have been published. There does not seem to be an increased risk of pregnancy loss. No malformations were reported except three cases of tetralogy of Fallot, intestinal malrotation, and delayed development. In our experience, the pregnancy outcome in women affected by JIA exposed to antiTNFα produced no abnormalities.

PP - 64

OUTCOME OF JUVENILE IDIOPATHIC ARTHRITIS (JIA) PATIENTS FOLLOWED IN A SINGLE CENTER

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Objective: To determine the disease outcome of JIA patients followed in a single center.

Methods: JIA patients registered to the rheumatology department of a university hospital since 1993, first seen before the age of 16 and with a follow-up of at least 5 years, were called for evaluation. Functional, damage, pubertal, growth and socioeconomic status and complications were evaluated. Patient charts were also reviewed.

Results: 174 patients were identified. Among these, 1 had died and 58 (34 females, age 22.3±9.3, age at onset 8.4±4.4, follow-up 12.9±5.9 years) were available for evaluation. Onset/course type was oligoarticular in 15 (11 early onset, 4 extended)/7; polyarticular in 24/33; systemic in 6/3; enthesitis-related in 11/7; and juvenile ankylosing spondylitis in 2/7. There was a significant delay in puberty in 12 and growth retardation in 14 patients. Among the 40 patients over the age of 18, 7 were not able to work, 17 were attending or graduated from college, 19 graduated from middle school, 8 were married, and 4 had a child. The 1 patient who had died had amyloidosis, 5 had uveitis and 2 had joint

prosthesis. During the last visit, 47 were still using DMARDs, 11 were using TNF-antagonists, and 24 had elevated acute phase reactants. Sixteen were in remission, 5/16 without any medication. Mean HAQ score was 2.2±8.8, articular JADI was 6.1±8.0 and extra-articular JADI was 0.5±0.9.

Conclusion: JIA remains a disease which impairs functional and socioeconomic status of patients, with 83% of patients still under treatment after a follow-up of 13 years.

PP - 65

TUMOR NECROSIS FACTOR α (TNFα) ANTAGONISTS IN THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS (JIA) PATIENTS WITH SECONDARY AMYLOIDOSIS

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Objective: This retrospective survey aimed to evaluate the efficacy of TNFα antagonists in JIA patients with secondary amyloidosis, treated in a single center.

Methods: We treated 8 such patients (M:F 4:4, age 28.1±9.6) with TNFα antagonists. The onset was systemic in 4, polyarticular in 3 and oligoarticular in 1. Two received infliximab, 5 infliximab and etanercept, and 1 etanercept and adalimumab successively.

Results: Mean disease duration was 19.6±9.8 years, and amyloidosis duration was 4.6±8.6 years. After treatment for 19.2±10.9 months, creatinine level increased from 0.92±0.4 to 0.98±0.4 mg/dl, and proteinuria decreased from 2.3±2.4 to 1.2±1.9 g/day. Serum creatinine level increased in 1/8, and was stable in 7/8 patients. Seven of 8 had proteinuria when TNFα antagonists were started, 3/8 in the nephrotic range. Proteinuria disappeared in 3/7, decreased in 3/7, and increased in 1/7 patients.

Three of the 8 patients died: 1, who was previously treated with etanercept for 19 months and was on the 3rd month of adalimumab, died with sepsis; 1 died with massive bleeding from bladder 6 months after stopping infliximab due to cardiac failure; and 1 died with bleeding following hip prosthesis surgery and fondaparinux treatment for anticoagulation, 26 months after stopping infliximab for financial reasons. Other adverse events were retinal vein thrombosis in 1 patient and mild upper respiratory tract infection in 3 patients.

Conclusion: This limited experience suggests that treatment with TNFα antagonists over one year might reduce proteinuria and stabilize serum creatinine levels; however, further experience is required to determine their efficacy and safety.

PP - 66

THE RELATIVE ROLE OF ESR AND CRP AS MARKERS OF DISEASE ACTIVITY IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Objective: To investigate the relative role of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as markers of disease activity in JIA.

Methods: The clinical database in study units was examined to search for visits in which both ESR and CRP were determined. Correlation between ESR and CRP and other JIA outcome measures was compared by Spearman's correlation test. Sensitivity and specificity of ESR and CRP in discriminating visits with high (HDA) or low disease activity (LDA), defined according to therapeutic decisions made by the attending physician, were

compared. Concordance between quartiles of ESR and CRP was evaluated using unweighted kappa (<0.40=poor agreement; 0.41-0.60=moderate agreement; 0.61-0.80=substantial agreement; >0.80 excellent agreement).

Results: 848 visits were evaluated. Spearman's correlations between ESR and CRP and other JIA outcome measures were similar, although ESR correlated better with physician's and parent's subjective assessments and CRP correlated better with joint counts. Sensitivity and specificity in distinguishing visits with HDA from visits with LDA were 0.69 and 0.74, respectively, for ESR, and 0.69 and 0.68, respectively, for CRP. The ability of ESR and CRP in discriminating visits with HDA from visits with LDA was similar among patients with oligoarthritis and polyarthritis, whereas in patients with systemic arthritis, ESR appeared to be a more reliable indicator of LDA and CRP a more reliable indicator of HDA. Kappa value for concordance between ESR and CRP was 0.56.

Conclusion: ESR and CRP proved equally reliable as markers of JIA activity, although their significance appeared to be different in different activity states among patients with systemic arthritis.

PP - 67

IDENTIFICATION OF 254 FAMILIES WITH JUVENILE IDIOPATHIC ARTHRITIS AFFECTED SIBPAIRS: RESULTS OF THE PRINTO SURVEY

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Juvenile idiopathic arthritis (JIA) is a disease with a complex genetic trait. The availability of DNA from families with two or more siblings with JIA might help to identify susceptibility or resistance genes. The objective was to investigate the genetic basis of the JIA through the analysis of families with JIA sibpairs.

Methods: All centers belonging to the PRINTO network were asked to complete an on-line survey requesting information on age, gender and JIA subtype of each affected sib.

Results: 119/277 (43%) worldwide centers responded to the survey. 254 families with at least 2 children with JIA were identified (19 triplets); 336/527 (64%) were female with mean age at visit of 13.6±6.5 years. The ILAR subtype distribution was: systemic arthritis 2.7%, oligoarthritis 47% (persistent 38.6%, extended 8.4%), polyarthritis rheumatoid factor (RF) negative 23%, polyarthritis RF positive 2.3%, enthesitis-related arthritis 16.2%, psoriatic arthritis 6.7%, and undifferentiated arthritis 2.1%. In 159/254 families (63%) there was concordance for disease subtype (149 sibpairs and 10 triplets). The distribution of JIA subtype in the concordant families was similar to that reported above.

Conclusion: We identified a relevant number of JIA familiar cases despite the modest extent to which JIA is familial (estimated JIA sibling risk ratio 15). The concordance and distribution within the pairs for disease subtype is similar to that previously reported in literature. The analysis of DNA through a genome-wide screen will be useful to identify the genes involved in JIA susceptibility and pathogenesis.

PP - 68

ELECTROPHYSIOLOGICAL EVALUATION FOR CARPAL TUNNEL SYNDROME IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: Juvenile idiopathic arthritis (JIA), the most common form of childhood arthritis, encompasses a heterogeneous group of clinical arthropathies. Neurologic complications in children with JIA have been reported. Among those, carpal tunnel syndrome (CTS) -median nerve entrapment in the carpal tunnel- was mentioned in only two case reports. In this preliminary study, our aim was to investigate CTS in patients with JIA.

Material and Methods: Twenty-one patients with the diagnosis of JIA were included in the study. All patients underwent electrophysiological evaluation. The presence or not of wrist arthritis was also noted and the patients were divided into two groups accordingly. Their electrophysiological data were compared.

Results: Patients were classified to have systemic arthritis (9.5%), oligoarthritis (47.6%), polyarthritis (38.1%) and enthesitis-related arthritis (4.8%). Mean values for age were 13.1±4.8 years and age of disease onset was 8.6±2.8 years. Sedimentation rate and C-reactive protein were 25.1±17.9 mm/hour and 1.5±2.5 mg/dL, respectively. Sensory examination of the patients revealed no abnormality. Forty-two hands with JIA were evaluated. Mean median nerve motor and sensory distal latencies and conduction velocities were within normal limits according to our laboratory normative data. No statistically significant differences were detected between the groups ($p>0.05$).

Conclusion: Although CTS may be seen in JIA due to wrist synovitis or biomechanical changes in the wrist joint, it is a rare entity. In this study, no abnormalities in median nerve conduction studies were detected. Furthermore, there was no difference between JIA patients with and without wrist arthritis.

PP - 69

LONG-TERM EFFICACY AND SAFETY OF ADALIMUMAB IN CHILDREN WITH JUVENILE RHEUMATOID ARTHRITIS (JRA): CONVERTING FROM BODY-SURFACE-AREA DOSING TO FIXED DOSING

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Background: Adalimumab has been shown to substantially improve signs and symptoms of JRA.

Objective: To evaluate differences in the efficacy and safety of adalimumab in JRA when converting from body surface area (BSA) dosing to weight-based fixed dosing (FD).

Methods: Patients in the 32-week, double-blind period of a Phase III study of adalimumab in JRA (patients 4–17 years of age) were eligible to continue subcutaneous every other week (eow) adalimumab (24 mg/m^2 BSA; max 40 mg/dose) in an open-label extension (OLE). After ≥16 weeks of OLE, patients were converted from BSA- to FD based on body weight (<30 kg received 20 mg eow; ≥30 kg received 40 mg eow). ACR Pedi responses and safety results before and after the dosing conversion were compared.

Results: Of 133 patients completing the double-blind period, 128 entered the BSA-dosed OLE period. Of these, 106 entered the FD period. 53/106 received either the same dosage or less of adalimumab after conversion [dosage groups combined for analysis because only 3 decreased dosage]. 53/106 received an increased amount. ACR Pedi 30/50/70 responses achieved before the conversion were maintained for 16 weeks following conversion (Table). Safety profiles were also comparable. No deaths, opportunistic infections, malignancies, demyelinating diseases, or lupus-like reactions were observed.

Conclusion: Adalimumab was efficacious and well-tolerated in the treatment of JRA. The substantial percentages of ACR Pedi 30/50/70 responses achieved during BSA dosing were maintained during 16 weeks of FD.

Adalimumab ACR Pediatric Response Rates: Conversion From BSA Dosing to Weight-Based Fixed Dosing

Response	Time on FD	Patients with same/decreased dosage N1/N2* (%)	Patients with increased dosage N1/N2* (%)
ACR Pedi 30	Wk 0	48/48 (100)	49/50 (98)
	Wk 16	46/48 (96)	45/47 (96)
ACR Pedi 50	Wk 0	46/48 (96)	47/50 (94)
	Wk 16	46/48 (96)	45/47 (96)
ACR Pedi 70	Wk 0	42/48 (88)	44/50 (88)
	Wk 16	42/48 (88)	43/47 (92)

Observed data. *N1=responders, N2=pts with data available at time point.

PP - 70

APPLYING CASPAR CRITERIA TO PATIENTS WITH JUVENILE PSORIATIC ARTHRITIS (JPsA)

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Introduction: The CASPAR criteria were recently found to be highly specific in the diagnosis of adult PsA, and consist of established inflammatory articular disease with at least 3 points from the following: current psoriasis (assigned a score of 2; all other features were assigned score of 1), history of psoriasis (unless current psoriasis was present), family history of psoriasis, dactylitis, and juxtaarticular bone formation.

Objective: To compare the existing classification criteria for the diagnosis of juvenile psoriatic arthritis (JPsA) with the CASPAR criteria.

Methods: Data were collected retrospectively from chart review of 117 patients who met the ILAR or Vancouver criteria for a diagnosis of JPsA and 64 patients who met the ILAR criteria of JIA (control group). Patients were then classified according to: ILAR, Vancouver and CASPAR criteria for PsA. The sensitivity and specificity of each criterion were compared at presentation and during follow-up. JIA patients with a first-degree relative with psoriasis or patients with a diagnosis of enthesitis-related arthritis (ERA) were excluded from the control group. Ten patients with JPsA were excluded as rheumatoid factor (RF) status was unavailable (required for CASPAR).

Results: During follow-up, all 99 of the 107 patients who fulfilled the ILAR criteria for JPsA also fulfilled the CASPAR criteria. 106/107 who fulfilled the Vancouver criteria (98 patients definite and 9 probable) met the CASPAR criteria. At presentation, more patients met the CASPAR (80 patients) than the ILAR (69 patients) or Vancouver (71 patients) criteria. None of the patients with JIA fulfilled any criteria for JPsA. Using the Vancouver criteria as the gold standard, during the course of the illness, the CASPAR criteria was highly sensitive (0.98) and highly specific (1), while at presentation, CASPAR was more sensitive than the Vancouver criteria to detect patients who would go on to develop definite JPsA (sensitivities of 0.74 vs 0.66, respectively). Both Vancouver criteria and CASPAR were highly specific (1).

Conclusion: The CASPAR criteria are highly specific to patients with JPsA with the highest sensitivity to early diagnosis.

PP - 71

JUVENILE PSORIATIC ARTHRITIS (JPSA): IS IT A SEPARATE DISEASE?

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Objectives: To compare the clinical features and outcome between patients with JPsA and juvenile idiopathic arthritis (JIA).

Methods: Fifty-four children who fulfilled the diagnostic criteria for JPsA (Vancouver or ILAR criteria), 32 with <5 joints in the first 6 months of disease (oligo–JpsA) and 22 with >5 joints (polyarticular–onset [poly-JPsA]) were compared to 54 JIA patients (ILAR criteria) who were matched by gender, age and date of diagnosis and articular pattern. JIA patients were excluded if they had: a positive rheumatoid factor (RF), enthesitis-related arthritis or first-degree relative with psoriasis.

Results: There was no difference in the mean age of onset of patients with oligo–JpsA and oligo-JIA (mean age 6.35±3.6 vs 6.5±3.9 years; p=0.49); or between poly-JpsA and poly-JIA (mean age 8.9±4.4 vs 8.6±4.4 years; p=0.25). Lengths of follow-up were similar for both groups: 6.6±3.8 years vs 6.7±3.9 years for the oligoarticular groups and 5.8±3.5 vs. 6.3±4.1 years for the polyarticular groups. There was no difference in the percentage of patients who developed extended oligoarticular arthritis between the oligoarticular groups (37.5% vs 34%; p=1) or in the percentage of patients who were ANA-positive (57% vs. 36%; p=0.31). The only differences were that oligo-JPsA patients were more likely than oligo-JIA patients to have dactylitis (21% vs 0%; p<0.01) and nail pitting (50% vs 18.7%; p<0.05). However, in polyarticular patients, the percentages with dactylitis were similar (18% vs 36%; p=0.25).

Outcome: Frequency of uveitis was identical in both groups of oligoarticular patients (18.7%), but there was a trend for a higher rate of uveitis in patients with poly-JPsA as compared to poly-JIA (22.7% vs 4.5%; p=0.1), while contractures were more frequent in poly-JIA as compared to poly-JPsA (45% vs 18%; p=0.058). At last follow-up, mean CHAQ scores were similar in both the polyarticular (0.19 ±0.3 for JPsA vs 0.18±0.29 for JIA; p=0.325) and oligoarticular (0.137±0.33 vs 0.1±0.29; p=0.7) groups.

Conclusions: We found that the only differences between patients with JPsA and JIA were: 1) Oligo-JPsA was associated more frequently with dactylitis than oligo-JIA; 2) Poly-JIA patients were more likely to develop contractures than poly-JPsA patients, while mean CHAQ scores were similar; and 3) Poly-JPsA patients were more likely to develop uveitis than poly-JIA (trend only). We suggest that JIA and JPsA are similar diseases and rheumatologists should reconsider the need to divide JIA based on the presence of psoriasis.

PP – 72

SYMPTOMS AT PRESENTATION TO PEDIATRIC RHEUMATOLOGY: ASSOCIATION WITH DELAY FROM DISEASE ONSET [RESULTS FROM THE CHILDHOOD ARTHRITIS PROSPECTIVE STUDY (CAPS)]

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Aim: To study the association between delay to pediatric rheumatology assessment and presenting disease characteristics using children recruited to CAPS, a prospective inception cohort of inflammatory arthritis (IA) in children.

Methods: CAPS recruits children <16 years with new IA in at least 1 joint persisting for 2 weeks from five UK tertiary referral centers. Demographics, disease features, joint counts, Childhood Health Assessment Questionnaire (CHAQ), physician's

global assessment, parent's general evaluation of well-being, blood tests and interventions are collected at presentation, 6 months and then yearly. Delay to presentation was defined as time from reported symptom onset to first presentation to a pediatric rheumatologist. Differences between disease characteristics in children with more/less than the median total delay within the cohort were compared using chi-squared and Wilcoxon rank-sum statistics.

Results: 507 children were analyzed: median age at onset 6.8 years, 65% girls, 233 oligoarthritis, and 68 rheumatoid factor (RF)-negative polyarthritis. Median total delay was 4.6 months (IQR 2.3, 9.5). Most delay occurred before referral; 62% were seen within 4 weeks of referral date. Median total delay was longest for psoriatic arthritis (8.6 months) and shortest for systemic arthritis (1.6 months). Children with delay >4 months had higher median active joint counts (2 vs 1, p=0.005) but lower median erythrocyte sedimentation rate (ESR) (14 vs 32 mm/hr, p<0.001).

Conclusions: Children with systemic arthritis had the shortest delay to specialist rheumatology care. Children with joint pain/stiffness but normal ESR had longer delays, suggesting that if blood tests do not indicate inflammation, the diagnosis of JIA may be overlooked.

PP - 73

PREDICTORS OF SEVERE CHAQ ONE YEAR FOLLOWING PRESENTATION TO PEDIATRIC RHEUMATOLOGY: RESULTS FROM THE CHILDHOOD ARTHRITIS PROSPECTIVE STUDY (CAPS)

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Background: The pattern of inflammatory arthritis (IA) is variable both in terms of presentation and outcome. This analysis identified predictors of severe Childhood Health Assessment Questionnaire (CHAQ) score one year following first presentation to a pediatric rheumatologist.

Methods: CAPS recruits children <16 years with new IA in ≥ 1 joint persisting for ≥ 2 weeks from five UK tertiary referral centers. Data regarding demographics, disease features, joint count, CHAQ, physician's global assessment (PGA), parent's general evaluation of well-being (PGE), erythrocyte sedimentation rate (ESR) and treatment are collected at first presentation, 6 months, and then yearly. Independent predictors of severe CHAQ (defined as CHAQ ≥ 0.75) at one year were identified using multivariable logistic regression models, adjusting for differences in treatment.

Results: 275 children were included: median age at presentation 7.5 years, 68% girls, 51% oligoarthritis. During the first year, 84% received NSAIDs, 62% intra-articular corticosteroids, 39% methotrexate, and 20% oral corticosteroids. Mean presenting CHAQ score was 0.85, which decreased to 0.57 at one year; 51% had severe CHAQ at presentation but only 35% at one year. The strongest predictor of severe CHAQ at one year was severe CHAQ at presentation (OR 3.3 95% CI: 1.4, 7.8). Age, gender, joint count, PGA, and PGE at presentation were not predictive, after adjusting for CHAQ score.

Conclusion: Although CHAQ score improved in most children, the strongest predictor of a persistent severe CHAQ at one year was a severe CHAQ at presentation. Follow-up beyond one year will assess whether CHAQ at presentation will continue to be a predictor of future poor outcome.

PP - 74

INFLIXIMAB TREATMENT IN JUVENILE RHEUMATOID ARTHTRITIS-INDUCED AMYLOIDOSIS

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Amyloidosis is an important complication of juvenile rheumatoid arthritis (JRA), which is resistant to immunosuppressive treatments. A currently used agent, infliximab (Remicade), is an antitumor necrosis factor (TNF) therapy effective in both induction and maintenance of remission in JRA. We report a case of systemic JRA who developed amyloidosis despite immunosuppressive therapy, successfully treated with infliximab.

A 14-year-old-girl was admitted with a history of fatigue, fever, anorexia, weight loss, arthralgia, and morning stiffness. Physical examination revealed symmetric polyarthritis of knees, wrists, elbows and ankles, loss of finger extension, nonpruritic maculopapular skin rash, retinal soft exudates, hepatosplenomegaly, respiratory distress and hypertension. On laboratory investigation there was a mild normocytic, hypochromic anemia. The acute-phase reactants were elevated and tests for rheumatoid factor and ANA were positive. Proteinuria was as high as 120 mg/m^2/h, and renal biopsy revealed deposition of amyloid. The patient was treated with infliximab (3 mg/kg/dose) and followed up for 24 months. Her systemic manifestations resolved rapidly and acute-phase reactants became normal. Amyloidosis regressed 20 months after the first anti-TNF treatment and with 12 infusions of infliximab. Proteinuria resolved almost completely.

In conclusion, the result suggests that anti-TNF therapy may be effective in the treatment of amyloidosis caused by renal involvement in JRA, which is resistant to other immunosuppressive treatment.

PP - 75

OPTIC NEUROPATHY IN A PATIENT WITH HLA B27-ASSOCIATED RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is a systemic disease with a high mortality rate. Cerebral involvement in RA is neither common nor fully understood. We herein describe a 14-year-old girl with RA who presented with optic neuropathy and pseudotumor cerebri. Her medical history included swelling and painful shoulder, ankle and hip joints for three years. She also complained of decreased vision in the right eye for two days. On physical examination she had limited movements in shoulder, ankle and sacroiliac joints. The ophthalmologic examination revealed a visual acuity of 3/10 in the right eye. Color vision test was abnormal and visual field test showed diffuse scotoma in the right eye. Fundus fluorescein angiography showed normal findings. The patient had high C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) level and positive rheumatoid factor, HLA B27 and anticardiolipin IgM antibody. Results of lumbar puncture were normal except for increased opening pressure associated with pseudotumor cerebri. Brain magnetic resonance imaging showed nonspecific multifocal hyperintensities in the white matter. Cerebral angiography was normal. The patient was treated with intravenous pulse methylprednisolone and cyclophosphamide. Improvement in visual functions was excellent. In conclusion, optic neuropathy is a rare complication of RA. We described an association between optic neuropathy, pseudotumor cerebri, anticardiolipin antibody and RA. RA should always be a consideration in the differential diagnosis of patients with optic neuropathy.

PP - 76

A NOVEL AND PROACTIVE APPROACH TO EVALUATE THE SAFETY OF NSAIDS IN JUVENILE IDIOPATHIC ARTHRITIS (JIA) PATIENTS

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Clinical trials evaluating NSAID use for JIA treatment have not studied rare or delayed safety effects, as these trials are generally short-term. Furthermore, such safety effects have not been detected via standard voluntary postmarketing surveillance, but these data are limited. To better evaluate safety data from various sources, we designed the Celebrex Postmarketing Program. The intent of this Program is to identify adverse events (AEs), including events with longer latency, which may be associated with NSAID use in the JIA population. The four major components of the Program are:

• A multi-center, prospective observational registry to collect long-term (>3 years) safety, efficacy, and developmental data on JIA patients treated with celecoxib or non-selective NSAIDs as utilized in the "real world".

• A 6-week randomized open label clinical trial to evaluate the effects of treatment with celecoxib or naproxen on blood pressure in patients with JIA.

• Proactive and routine survey of physician network(s) to ascertain occurrence of cardiovascular events in JIA patients receiving NSAIDs.

• A Panel of Pediatric Experts to review all data that are generated from the above- listed sources and standard postmarketing surveillance. The mission of the Panel will be to identify any safety issue(s) with celecoxib in the JIA population.

The Celebrex Postmarketing Program may serve as a model to proactively generate and monitor safety data in order to identify AEs that may be associated with NSAID treatment for JIA or with other medications and disease states.

PP - 77

ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES (aCCP-Abs) IN JUVENILE IDIOPATHIC ARTHRITIS (JIA): A MONOCENTRIC PROSPECTIVE STUDY OF A 369 PATIENT COHORT

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Background: aCCP-Abs are specific for rheumatoid factor (RF)+ adult rheumatoid arthritis (RA). Less than 10% of JIA are RF+ polyarthritis. We expect that only this ILAR category tests positively for aCCP-Abs (aCCP+).

Objective: To determine, in the different JIA ILAR categories, aCCP sensitivity, specificity and correlation with disease characteristics.

Methods: In a cross-sectional study, aCCP-Abs were determined by a commercial second-generation ELISA in sera randomly collected from 507 patients of our Center. 180 JIA patients were also prospectively studied.

Results: 369 JIA (mean age 16.9±9.4 years, range 1.9-49.8; mean disease duration 10.2±9.2 years, range 0.5-41.5; mean age at disease onset 7.1±4.9 years, range 0.7-16.3) and 138 disease controls (38 RA and 100 children [35 with connective tissue diseases, 65 with other rheumatic conditions]) were tested. Overall, 77/507 (15.2%) patients tested aCCP+: 25/28 (89.3%) RF+ RA, 2/10 (20%) RF- RA, 47/369 (12.7%) JIA, including 23/28 (82%) RF+ polyarthritis, 24/341 (7%) other JIA ILAR categories ($p<0.01$), and only 3/100 (3%) controls with other juvenile onset rheumatic diseases. aCCP+ JIA patients showed: significant older onset age (8.7±5.1 vs. 6.8±4.8 years, $p<0.05$) and lower

ANA positivity (41.7% vs. 55%, p<0.05). Gender, disease duration and activity, need of biological drugs and DMARDs did not differ significantly between aCCP+ and aCCP- JIA patients.

Conclusion: aCCP-Abs can be detected almost exclusively in polyarticular RF+ JIA. As in adult RA, the majority of polyarticular RF+ JIA (82%) but only a few patients of other JIA ILAR categories (7%) tested aCCP+. It is possible that aCCP-Abs, in some cases, develop before RF, identifying JIA patients at greater risk of poor evolution.

PP - 78

EWING'S SARCOMA: PRESENTING AS AN ERRONEOUS JIA HIP MONOARTHRITIS DIAGNOSIS

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A five-year-old girl, referred to our Center with a diagnosis of juvenile idiopathic arthritis (JIA), presented with a six-month history of pain in the right gluteus, also during the night, extending to groin with lameness and hyperpyrexia. Clinical assessment showed: analgesic flexion and tenderness to intorsion and extortion of the right hip and increased CRP (8 mg/dl) and ESR (69 mm) at 1st hour. Hip X-ray and CT were negative and ultrasonography showed a small quantity of synovial fluid in the right hip.

At the first evaluation in our Center, despite the presence of defined monoarticular arthritis of the right hip with aspecific increase in inflammatory levels, the JIA diagnosis was questioned for the following reasons:

- arthritis location (isolated hip arthritis in oligoarticular JIA is rare, especially at onset);

- age and gender (hip monoarthritis can be an onset symptom in teenage males in enthesitis-related arthritis [ERA] subset);

- night and mechanical pain (versus inflammatory morning pain in JIA).

The following investigations were performed:

- Hip radiography: lytic lesion with periosteal reaction at the right iliac wing;

- TC99 scintigraphy: hyper-captation at the right iliac wing;

- CT: osteolytic lesion with extraosseous soft tissue mass;

- MR: T1 and STIR high signal intensity and T2 low signal at the right iliac wing area, and bone marrow edema.

Biopsy of osteolytic lesion and extraosseous soft tissue mass showed a mesenchymal malignant tumor uniformly composed of sheets of small round cells closely packed and numerous and thin blood vessels and immunochemistry was positive for antibody anti-CD99.

PP - 79

CLASSIFICATION OF JIA- WHAT CAN THE ADULT CLASSIFICATION CRITERIA TEACH US?

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The ILAR classification (IC) of juvenile idiopathic arthritis (JIA) (1997) distinguishes childhood arthropathies from adult disease and identifies distinct subgroups, but is still evolving. Using the adult classification criteria as tools, the performance of the IC with disease evolution over time and different approaches to defining subgroups were examined.

Methods: Clinical, radiographic and laboratory information was collected on 172 cases (111 girls), mean age 6.4 years (0.9-15.8) at disease onset, with median disease duration of 6.9 years

(0.6-37.4). The cases were classified using the IC, Ankylosing Spondylitis (AS) (1966 New York), Spondyloarthropathy (Spond) (ESSG 1991) and Rheumatoid Arthritis (RA) (1987 ARA).

Results:

Conclusions: The diagnostic categories EO, RFN and PO contain a broad a mix of classification features and are distinctive only by the number and timing of joint involvement; ERA and Ps significantly overlap. The concept of spondyloarthropathy and rheumatoid factor-negative RA may be of equal value in JIA as in adult disease.

JIA Subgroup (% of JIA subgroup) RF=rheumatoid factor		Number rejected as other	Reason for rejection (may be both)		Adult classification		
			Ps	ERA	AS	Spond	RA
Systemic	10	0	0	0	0	0	0
Persistent Oligoarthritis (PO)	42	12 (28.6)	6	6	0	4 (9.5)	0
Extended Oligoarthritis (EO)	42	11(26.2)	5	6	1 (2.4)	1 (2.4)	34 (97.1)
Psoriatic Arthritis (Ps)	10	6 (60.0)	–	6	0	4 (40)	8 (80.0)
Enthesitis–Related Arthritis (ERA)	28	10 (35.7)	7	–	5 (18)	15 (54)	15 (53.6)
RF – Polyarthritis (RFN)	35	8 (22.9)	6	3	1 (2.9)	1 (2.9)	28 (80.0)
RF + Polyarthritis (RFP)	6	1 (16.7)	0	0	0	0	6 (100.0)
Other	43	–	–	–	3 (7.0)	11 (25.6)	24 (55.8)
Totals	172	43	24	21	7 (4.0)	23(13.5)	94 (54.6)

PP - 80

MULTIDISCIPLINARY ARTHRITIS SCHOOL FOR 10-12-YEAR-OLD CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA) AND THEIR PARENTS

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Since 1999, children aged 10-12 years with JIA have been offered an arthritis school course in our Department. Parents attend a parallel course. Each class consists of 5 - 7 children. The aim of the course is to let children and parents meet with "equals" and to improve knowledge and understanding of and coping with the disease. Lessons contain different issues presented by a multidisciplinary team.

Patients and Methods: 18 children (14 girls, 4 boys) with a mean disease duration of 3.3 years answered a multiple choice (MC) test with questions regarding arthritis before and after the course. Children and parents were asked to make statements about the course.

Results: The children improved the number of correct answers by 20% at the end of the course, with 74% being correct. Children found it easier to participate in physical activities and dare more when together with JIA-children than with healthy peers, even in the same activity. Children mistakenly regarded a low fitness as a cause of active disease. Children found it easier to talk to other children with JIA about management of medicine, blood tests and pain. Parents found it rewarding to meet and exchange experience with other parents.

Conclusion: Generally, we found a high rate of satisfaction with attending the arthritis school both for children and parents. The MC test shows that the children benefit and learn more about their disease from the course. Even children with active disease or pain are eager to participate in physical activities in the arthritis school rather than in gym classes together with their healthy peers.

1. Kristensen O, Gyldenlove H, Herlin T, Arthritis Rheum 2001; 44: S324.

PP – 81

THE IMPACT OF JUVENILE IDIOPATHIC ARTHRITIS ON THE FOOT: DO PROBLEMS PERSIST AND WHAT TREATMENTS ARE PROVIDED?

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Background: Foot problems are common in juvenile idiopathic arthritis (JIA), previously reported in over 90% of cases. This pilot study aimed to investigate the prevalence of foot morbidity and audit foot-care in patients managed on DMARD and biologic regimens.

Methods: 30 consecutive JIA patients completed the Juvenile Arthritis Foot Disability Index (JAFI), CHAQ, and pain VAS. Foot deformity score, active and limited joint counts and walking speed were measured. Foot-care provision over the previous 12 months was determined from the medical records in 23/30 participants.

Results: Children received biologic agents in 35%, DMARDs in 65%, and 90% of participants had received multiple intra-articular corticosteroid injections. Median (range) values for foot disease outcomes are presented in the Table:

Outcome (range)	JIA patients (n=30)
$JAFI_{IMPAIRMENT}$ (0-4)	1 (0-3)
$JAFI_{ACTIVITY\ LIMITATION}$ (0-4)	1 (0-4)
$JAFI_{PARTICIPATION\ RESTRICTION}$ (0-4)	1 (0-3)
CHAQ (0-3)	0.38 (0-2)
VAS Pain (0-100)*	22 (0-79)
Foot deformity score (0-38)	6 (0-20)
Active joints (0-77)	0 (0-7)
Limited joints (0-77)	0 (0-31)
Walking speed (m/s)	1.09 (0.84-1.38)

The JAFI scores represent mild foot-related impairment and disability. Gait defects, deformity or abnormal foot posture, and/or active foot disease were the main reasons for referral. 43% of children received specialist podiatry care comprising footwear advice, orthotic therapy, and silicone digital appliances together with intrinsic muscle strengthening exercises.

Conclusions: Despite DMARD/biologic regimens and specialist podiatry care, foot- related impairment and disability persists in JIA children. Further study is required to determine the long-term consequences of these changes found during childhood in the foot.

PP - 82

AGREEMENT BETWEEN PHYSICIANS AND PARENTS IN RATING PHYSICAL DISABILITY OF CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Objective: To investigate concordance between physicians and parents in rating the degree of disability of children with juvenile idiopathic arthritis (JIA).

Methods: The attending physician and a parent were asked to rate independently the level of physical disability of 155 patients with disease duration ≥ 5 years on a 6-point scale ranging from 1=no disability (i.e. the child can do without difficulty all activities that children of his/her age can do) to 6=severe disability (i.e. all activities are difficult for the child). At study visit, measures of JIA activity and damage were assessed. Agreement was evaluated with weighted kappa (<0.40=poor agreement; 0.41-0.60=moderate agreement; 0.61-0.80=substantial agreement; >0.80 excellent agreement). Physician/parent evaluations were divided in 3 groups: 1) concordance; 2) positive discordance= parent assessment over-rated relative to physician assessment; 3) negative discordance= parent assessment under-rated relative to physician assessment. Factors affecting concordance/discordance were evaluated by means of Kruskal-Wallis or chi-square/Fisher's test.

Results: Concordance, positive discordance and negative discordance were observed in 107 (69%), 29 (18.7%) and 19 (12.3%) evaluations, respectively. Kappa value was 0.69. Positive discordance was associated with greater intensity of pain (p=0.01) and higher CHAQ score (p=0.004), whereas negative discordance was associated with more severe joint disease (p<0.001), higher frequency of Steinbrocker functional class > II (p<0.001), and greater articular damage (measured with Juvenile Arthritis Damage Index) (p=0.0009).

Conclusion: Physicians and parents revealed fair concordance in rating physical disability of children with JIA. Parent over-rating was associated with worse parent-centered outcomes, whereas physician over-rating was associated with worse physician-centered outcomes.

PP - 83

WHICH JOINTS ARE MOST SUITABLE FOR INCLUSION IN A REDUCED JOINT COUNT FOR JUVENILE IDIOPATHIC ARTHRITIS?

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Objective: To select the joints that should be included in a reduced joint count for juvenile idiopathic arthritis (JIA).

Methods: The frequency of involvement of the 71 joints assessed in standard articular examination was evaluated in 2769 patients stored in the PRINTO database, 632 patients enrolled in the PRINTO methotrexate (MTX) trial, and 396 unselected patients seen in the authors' clinic. Based on the frequency of involvement of the different joints, 3 reduced joint counts were devised, which included 47, 35, and 27 joints. Validity of reduced and complete counts of active joints was compared by assessing their Spearman's correlation with the physician's global assessment of disease activity, measured on a 10-cm visual analogue scale.

Results: The following joints, which were affected in > 5% of patients in all 3 study cohorts or were considered of primary clinical importance, were selected for inclusion in variable combinations in reduced joint counts: temporomandibular, cervical spine, shoulder, elbow, wrist, metacarpophalangeal (MCPs), proximal interphalangeal (PIPs), hip, knee, ankle/subtalar, and metatarsophalangeal. Spearman's correlations between complete and reduced active joint counts and physician's global assessment in the 3 study cohorts are reported in the Table.

	PRINTO database (N=2769)	MTX trial (N=632)	Clinic patients (N=396)
71 joints	0.65	0.32	0.68
47 joints	0.65	0.31	0.68
35 joints	0.64	0.29	0.68
27 joints	0.64	0.29	0.67

Conclusion: Correlations between complete and reduced joint counts and physician's global assessment were comparable, which suggests that the simpler and more feasible 27-joint count is a good surrogate of the complete joint count in children with JIA.

PP - 84

A NEW MULTI-CENTER REGISTRY TO MONITOR LONG-TERM SAFETY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) INCLUDING CELEBREX IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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NSAIDs have been used for more than 30 years to relieve pain and inflammation in JIA, and it is estimated that 80-90% of JIA patients will use an NSAID at some point. Yet little is known about the long-term safety of chronic NSAIDs in children with JIA. Randomized Controlled Trials (RCTs) of NSAIDs in JIA are considerably smaller than adult RA trials: the median JIA study size is 59 patients (range: 18-242) and of 12 weeks' duration (range: 4-24), and, like most RCTs, may not be generalizable to typical JIA populations. To address the lack of routine clinical long-term safety data on NSAIDs, including celecoxib, in JIA, we are constructing a prospective observational registry. This multi-center Registry will enroll a quasi-inception cohort of patients aged 2-17 years and >10 kg prescribed (not more than 6 months prior) either celecoxib (n=200) or other NSAID(s) (n=200). Pediatric rheumatologists will enter demographic, developmental, clinical, and safety information in a secure web-based database quarterly for the first 12 months, and twice annually thereafter until the final patient completes 12 months of follow-up. The aim is to follow at least 50% of patients 2 years and at least 15% for 3 years. Concomitant medications and treatment switches are permitted, and patients will be followed for residual effects even if NSAID treatment is discontinued. When complete, the registry should provide substantial (660 patient-years minimum) routine clinical safety data on NSAIDs, including celecoxib, used in JIA, and will facilitate appropriate therapeutic decision-making for doctors and patients.

PP - 85

WHICH AREAS IN THE WRISTS AND HANDS SHOULD BE INCLUDED IN A RADIOGRAPHIC SCORING SYSTEM FOR JUVENILE IDIOPATHIC ARTHRITIS?

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Objective: To identify the areas in the wrist and hand joints that are most suitable for inclusion in a radiographic scoring system for juvenile idiopathic arthritis (JIA).

Methods: A total 568 bilateral hand/wrist radiographs made in 177 patients with polyarticular JIA were examined. The frequency of involvement of the 30 and 32 areas included in the joint space narrowing (JSN) and erosion components, respectively, of the Sharp-van der Heijde (SH) score was assessed. Ten new areas (5 in each side) for erosion not included in the SH score, which were found to be common sites or radiographic changes in our previous experience, were also assessed. Films were read independently by two pediatric rheumatologists and the average of their assessments was used in the analysis.

Results: The range of frequency of JSN and erosion in the proximal interphalangeal (PIP), metacarpophalangeal (MCP) and wrist areas is shown in the Table.

	JSN (%)	Erosion (%)
PIP areas	13.1–23.5	4.7–16.1
MCP areas	5.4–12	4.2–8
Wrist original areas	23.7–34.3	9–21
Wrist new areas	–	12.7–26.4

Conclusion: The frequency of radiographic damage was greater in wrist areas, followed by PIP and MCP areas. The new areas for erosion were among the commonest sites of structural changes, which supports their inclusion in a pediatric version of the SH score.

PP - 86

EPIDEMIOLOGY OF JIA

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Juvenile idiopathic arthritis (JIA) is one of the most common chronic illnesses in children. The disease subtypes in order of frequency are oligoarticular JIA (50%-60%), polyarticular JIA (30%-35%), systemic onset JIA (SoJIA) (10%-20%), juvenile psoriatic arthritis (2%-15%) and enthesitis-related arthritis (1%-7%). In this report, we evaluate our patients according to subtypes and other epidemiologic specialties.

Forty-two patients with diagnosis of JIA have been followed in our unit since 2004.

Twenty-three (54.7%) were girls, 19 (45.2%) were boys. Mean age was 120.4±57.6 months (min 12, max 204 months). The frequencies of the disease subtypes were 23/42 (54.7%) oligoarticular, 7/42 (16.6%) polyarticular and 12/42 (28.5%) SoJIA. Thirteen (30.9%) of the patients were followed-up in other centers after the initial diagnosis. Twenty-eight (66.6%) of the patients were still on follow-up. One patient died because of macrophage activation syndrome (MAS) and multiorgan failure. Four of the patients were also diagnosed as MAS. Currently, 7 patients are in full remission without any drug, 13 patients are on nonsteroid anti-inflammatory drug + steroids + methotrexate with a ratio of 6/28 (21%) in remission. Total follow-up without any iridocyclitis was 10.5± 11.1 months. There were no seasonal differences according to the time of presentation of the disease.

In conclusion, although the frequency of oligoarticular form is similar to the reported series, frequencies of systemic onset and polyarticular subtypes were higher, with a similar rate of remission, in our single center experience.

PP - 88

LONG-TERM SAFETY AND EFFICACY OF ETANERCEPT IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA): RETROSPECTIVE REVIEW OF THE SPANISH EXPERIENCE

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Introduction: Previous clinical trials have demonstrated the efficacy and safety of etanercept in children with polyarticular JIA intolerant or resistant to methotrexate (MTX).

Objective: To evaluate long-term, real-setting efficacy, safety and QoL of etanercept treatment over 60 months in JIA patients.

Methods: Multicenter, observational retrospective registry, with 60 months of follow-up. Data were collected from baseline (demographics, medical history, disease characteristics) to 60 months every year [biochemistry, hematological, ESR, CRP, number of active joints, physician's global assessment (PGA), parent/patient assessment of pain (PAP), functional disability (CHAQ)]. The efficacy was evaluated using PAVIA index.

Results: 158 patients were included (40.4% males). Median age was 12 years (1-23), and 5 years (0.67 -16) at disease onset. 97.5% had received previous treatments (95.6% MTX). At the analysis, 132, 114, 75, 44, 48 and 6 patients were at month 6, 12, 24, 36, 48 and 60, respectively. Significant improvements were observed in every variable from baseline to the 60th month. Mean number of tender and swollen joints decreased from 8 to 0.3 and 7.6 to 0.8, respectively, PGA 6 to 0.3, PAP 5.7 to a 0.3, CHAQ 1.61 to 0.1; ESR 40 to 12 mm/hr, and CRP 10 to 1.7 g/l.

PAVIA:

	6m	12m	24m	36m	48m	60m
PAVIA 30 (%)	87.2	92	94.6	91.3	89.5	100
PAVIA 50 (%)	64.1	83	85.7	91.3	89.5	100
PAVIA 70 (%)	64.1	61.4	71.4	82.6	78.9	100

Most of the adverse events (AE) were mild; only 5 were serious.

Conclusion: In JIA patients, long-term etanercept treatment has been shown to be safe and highly effective, achieving early significant improvements in every variable.

PP - 89

ASSESSMENT OF DISEASE ACTIVITY IN JUVENILE IDIOPATHIC ARTHRITIS (JIA): THE NUMBER AND THE SIZE OF JOINTS MATTERS

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Introduction: Assessment of disease activity in JIA is complex. The children are often too young to actively contribute. No validated disease activity score is available for JIA. Studies of variables included in the PRINTO core set of outcomes show that the physician global assessment (GA) seems to be a potentially suitable dependent variable comparable between patients. The impact of the number of active joints and joint size in assessment of disease activity has rarely been studied.

Aim/Method: The aim was to study the physician GA as a dependent variable in relation to the other variables included in the core set of outcomes and to evaluate the impact of large and small joint

activity on the physician's assessment. Prospectively collected variables included in the core set of outcomes from one randomly chosen hospital visit were studied for each of 312 patients with JIA from the Nordic countries.

Results: Spearman's rank order correlation showed that the number of active joints was strongly associated with physician GA. The median physician GA score rose markedly for each active large joint. Although small joints were also statistically important in assessing disease activity, the impact of small joint activity was less than that for large joints. Among laboratory data, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and platelet count correlated only weakly to physician GA.

Conclusion: In preparation for the construction of a disease activity score for children with JIA, this study demonstrates that the number as well as the size of joints matter.

PP - 90

PULMONARY FUNCTION TESTING IN PEDIATRIC PATIENTS TREATED WITH METHOTREXATE FOR JUVENILE IDIOPATHIC ARTHRITIS

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Methotrexate has been found to cause interstitial lung disease in adults with rheumatoid arthritis, but there are hardly any reports on pulmonary side effects in pediatric patients. We have performed annual pulmonary function testing (PFT) in all our patients with juvenile idiopathic arthritis (JIA) who were treated with methotrexate. Here we report on the subgroup of 26 patients (14 girls and 12 boys, ages 9-18 years at last PFT) for whom results of PFT were available prior to and during methotrexate therapy. Methotrexate therapy was given for 1-8 years (mean 4.0 years). PFT results were analyzed by paired t-test.

Both vital capacity as well as forced expiratory volume in 1 second showed no significant changes during the course of therapy. However, total lung CO diffusion capacity showed a declining trend in those patients who were treated with methotrexate for more than 4 years.

The majority of PFT parameters demonstrated no significant effect of methotrexate therapy in pediatric patients with JIA, but there may be an effect on the CO diffusion capacity in patients treated for more than 4 years. Further analysis is ongoing and will include patients in whom due to their younger age PFT could only be performed after the onset of methotrexate therapy.

PP - 91

INFLUENCE OF IMAGE GUIDANCE ON THE EFFICACY OF INTRA-ARTICULAR CORTICOSTEROID THERAPY IN JUVENILE IDIOPATHIC ARTHRITIS: A PROSPECTIVE COHORT STUDY

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Background: Intra-articular corticosteroid therapy is an integral part of the management of children with juvenile idiopathic arthritis (JIA). Factors which influence response to intra-articular steroids are still being defined.

Aim: To determine whether the use of image guidance to direct intra-articular steroid therapy in children with JIA influences the probability of arthritis of injected joints becoming inactive or the duration of response obtained.

Methods: Prospective cohort study of children with JIA undergoing intra-articular corticosteroid therapy of selected joints with or without image guidance at a single institution.

Results: One hundred and thirteen patients (81.4% female) underwent 291 intra-articular steroid injections. Ninety-four joints were injected using image guidance. Response rates at the first post-injection visit were 69.2% and 78.2% for the image-guided and non-image-guided groups, respectively (p=0.095). In survival analysis, the method of injection did not influence risk of relapse (Hazard Ratio 0.986, 95%CI: 0.74-1.32). The median duration (95% CI) of response for the image-guided and non-image guided groups was 27.1 (19, 44.86) and 28.4 (23.86, 35.86) weeks, respectively.

Conclusions: We found no evidence that the use of image guidance for the administration of intra-articular triamcinolone acetonide in patients with JIA significantly alters its efficacy, either in initial response rate or duration of response. We therefore do not recommend the routine use of image guidance when using triamcinolone acetonide in the treatment of JIA involving the elbows, wrists, knees ankles or subtalar joints.

PP - 92

NON CT-GUIDED INTRA-ARTICULAR STEROID TREATMENT OF ACTIVE TEMPOROMANDIBULAR JOINT INVOLVEMENT IN JUVENILE IDIOPATHIC ARTHRITIS

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Background: Temporomandibular joint (TMJ) involvement is a threatening complication of juvenile idiopathic arthritis (JIA). Intra-articular corticosteroid injections (IACS) are used as first-line therapy for persistent oligoarthritis and have been found to be effective in all joints, including the small ones. The aim of our study was to evaluate the safety and efficacy of IACS treatment in children with JIA and TMJ involvement by using a non-computer tomography-(CT) guided procedure.

Methods: 11 JIA patients, aged 5-18 years, with evidence of active TMJ involvement received 0.5 mg/kg of triamcinolone acetonide unilaterally (8) or bilaterally (3). Clinical symptoms (jaw pain at rest and at maximal mouth opening, morning stiffness, TMJ crackles) and signs (jaw deviation and limitation in function) were assessed at baseline and at 3, 6, and 12 months after treatment.

Results: At 12 months follow-up, the treatment was clinically successful in 9/11 patients. Six out of 7 patients with symptoms prior to IACS had complete resolution. 4/8 children with deviation of mouth opening improved. Among 4 patients with function limitation, 3 had complete resolution at 2 months, but unfortunately, 1 relapsed at 6 months and another at 12 months. The only patient refractory to IACS treatment was the oldest one (18 years) with disease duration of 11 years. A slight subcutaneous atrophy was observed in 1 patient, 6 months after injection.

Conclusion: IACS treatment of active TMJ arthritis is safe and effective, if performed as early as possible, at the first clinical and MRI evidence of arthritis. We found no need for a CT-guided procedure.

PP - 93

BMD VALUES IN IDIOPATHIC OSTEOPOROSIS (JIO) AND SECONDARY OSTEOPOROSIS IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Purpose: Osteoporosis in children is increasingly being seen and is an often undiagnosed condition. Diagnosis is usually made after occurrence of several fractures with minimal trauma or when radiograph demonstrates hypodense bones. Controlled, prospective studies to evaluate the results of prevention and therapy in children are still lacking.

Methods: We prospectively followed up three groups of patients, aged 8-15 years: A) 20 children referred to our Clinic due to two or more fractures without serious trauma diagnosed as juvenile idiopathic osteoporosis (JIO group); B) 20 JIA patients (JIA group); and C) 35 healthy age-matched volunteers as a control group (C group). JIA and JIO groups were treated with alfacalcidol given orally 1 mcg/ day during one month, 0.5 mcg/day for the next two months, and 0.25 mcg during the last three months of treatment. Oral calcium 125 mg/day on alternate days was added during the six-month therapy period. Lumbar BMD (DXA) measures and calcium metabolism parameter evaluation were done in all patients at enrollment and after one year of follow-up in the JIA and JIO groups.

Results: Our results have shown significantly lower BMD in JIA compared to controls (BMD 0.693 ± 0.151 vs. 0.787 ± 0.108; $p<0.05$). In JIO group, 7 children had same location refracture; of the other 13, 3 had 2, 6 had 3, 3 had 4 and only 1 had 5 fractures in different bone locations. There were no vertebral fractures. At enrollment, lumbar BMD in the JIO group showed osteoporosis or osteopenia in 16 patients: BMC 42.21±6.23 g; BMD 0.65±0.43 mg/cm^2; BMDvol 0.215±0.06; Z score – 0.255±0.74 significantly lower ($p<0.05$) compared to controls but not to JIA group. Lower levels of calcium, but within normal range, was the only change in calcium metabolism parameters in both JIO and JIA groups. One year after enrollment and six months after therapy regimen, we found significant improvement in lumbar DXA: BMC 45.21±4.27 g; BMD 0.96±0.23 mg/ cm^2; BMDvol 0.312±0.05; Z score –0.005±0.36 ($p<0.05$) in JIO group and BMC 47.32±3.17 g; BMD 0.895±0.18 mg/ cm^2; BMDvol 0.310±0.15; Z score –0.005±0.36 ($p<0.05$, Wilcoxon rank signed test) in JIA group. Calcium metabolism parameters followed monthly showed slight increase in calcium serum and urine levels, within normal range, and without significant changes. All patients were continuously followed during the next three years after the treatment regimen was applied and there were no new fractures registered and no bone pain complains.

Conclusions: The promising results achieved using alfacalcidol and calcium in our study indicate that it could be one of the treatment options for JIO and secondary osteoporosis in JIA in childhood. Optimal achievement of peak bone mass during childhood and adolescence is important to minimize future fracture risks.

PP - 94

VITILIGO IN TWO PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Vitiligo is a common skin disorder characterized by depigmentation of the epidermis. The disorder has been associated with certain autoimmune and rheumatic disease syndromes but not with juvenile idiopathic arthritis (JIA). We here report two patients with JIA and vitiligo.

Case 1: An 8-year-old girl with seronegative polyarticular JIA, with involvement of the elbows, wrists, fingers, knees and ankles. Although widely spread vitiligo was distinctly localized over the knees, elbows and finger joints (left 2nd MCP and PIP), depigmentation over the knees had appeared two years before the first symptoms of arthritis.

Case 2: A 14-year-old girl with extended oligoarticular JIA, and ANA and IgM-RF negative, and with severe arthritis of the temporomandibular joint (TMJ), knees, ankles and fingers. She had severe depigmentation in the face over the affected TMJ, and on knees and ankles. Both girls had a partial response to topical tacrolimus (Protopic) for the skin disorder.

Conclusion: Anatomical distribution of the lesions in skin in the two patients resembled to some extent that of the affected joints. Several variations of vitiligo in patients with classical immune and rheumatic disease have been described by the coexistence of lesions affecting particular areas of the skin, which overlies sets of internal structures characteristically involved in these diseases. The functional significance of the curious linkages of affected skin tissues and joints remains to be determined but may be explained by the sharing of the same vitiligo-autoimmune disease gene locus.

PP - 95

ANAKINRA TREATMENT FOR SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS (SOJIA)

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Introduction: SOJIA accounts for increased morbidity and mortality compared to other forms of JIA [Schneider 1998]. A significant number of patients have ongoing disease activity despite aggressive treatment. Case reports using anakinra, an interleukin-1 receptor antagonist, have suggested efficacy in refractory SOJIA.

Methods: Retrospective data collection on 7 patients from 3 centers in the UK who met ILAR classification criteria for SOJIA and received anakinra for refractory disease.

Results: Median age of disease onset was 5 years 4 months (2 years 1 month - 14 years). Median age starting anakinra was 8 years 6 months (5 years 2 months to 15 years 1 month). Previous failed treatment included methotrexate (n=6), cyclosporine (n=4), immunoglobulin (n=5), infliximab (n=2) and etanercept (n=2). Median duration of treatment with anakinra was 9 months (3 to 27 months). Median follow-up was 28 months (10 months to 6 years 5 months). Hemoglobin, total white cell count, platelet count and erythrocyte sedimentation rate normalized in all patients. Three patients required a dose of 2 mg/kg to achieve disease remission. Prednisolone dose (mg/kg), and active and restricted joint counts reduced from a median of 0.75, 8 and 6 pre- anakinra to 0.1, 6 and 2 at 6 months post-anakinra, respectively (n=6). Anakinra was stopped in one patient after 3 months due to injection site pain. One patient developed severe presumed viral gastroenteritis during treatment but continued with anakinra.

Conclusions: All patients had a good clinical response to anakinra. One serious adverse event of viral gastroenteritis was seen.

PP - 96

CLINICAL FEATURES AND THE RISK FACTORS FOR UVEITIS AND RATE OF COMPLICATIONS IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Purpose: To evaluate the clinical features and determine the risk factors for uveitis and rate of complications in patients with juvenile idiopathic arthritis (JIA).

Methods: This was a prospective study of all patients with JIA examined by either of two ophthalmologists from October 2005 to March 2007. All patients were also under the care of the Pediatric Rheumatology Division at Hacettepe Children's Hospital. Age of diagnosis of JIA, disease onset subtype of JIA, antinuclear antibody titers, idiopathic factor titers, age of diagnosis of uveitis, and complications from uveitis were recorded.

Results: Eighty-five patients with JIA had eye examinations; 29 (34.1%) developed uveitis. Twenty-nine patients had uveitis on the initial eye examination. Of these, 23 (79.3%) had oligoarticular, 5 (17.2%) had polyarticular and 1 (3.5%) had systemic-onset JIA. The prevalence of uveitis was significantly higher in patients with oligoarticular JIA. The mean age at onset of arthritis in the uveitis patients was 3.31 years, which was significantly lower than in the non-uveitis group (5.1 years). Antinuclear antibodies (ANA) were positive in 26 (89.7%) of the 29 uveitis patients, confirming ANA as a significant determinant for uveitis in JIA. Since 24 of the patients with uveitis were girls, female gender seems to be a risk factor for developing uveitis. Uveitis was bilateral in 2 of 29 patients (6.9%). Ten (34.4%) of the 29 patients developed serious sight-threatening complications during the follow-up period.

Conclusions: This study confirmed that oligoarticular onset, ANA positivity, female gender and young age are risk factors for developing uveitis in patients with JIA. Rheumatoid factor was not found to be a risk factor.

PP -97

EVALUATION OF DEMOGRAPHIC, CLINICAL, LABORATORY, AND RADIOLOGIC FEATURES AND COMPLICATIONS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Aim: The aim of our study was to determine the disease subtypes at diagnosis and at last evaluation on the basis of ILAR criteria, to investigate the clinical, laboratory and radiological features, and to report the complications in children with juvenile idiopathic arthritis (JIA) followed-up in our rheumatology clinic.

Methods: Totally, 293 patients were investigated in terms of their ages, gender, age at diagnosis, duration of follow-up, height and weight Z scores, duration of treatment, symptoms on admission, features of joint involvement, HLA tissue types, eye involvement, joint deformities, accompanying diseases and complications.

Results: Fifty-nine of the cases were male and 58 were female. Mean age at diagnosis was 9.5±4.12 years. At diagnosis, 39 patients were classified as oligoarticular type, 30 patients as enthesitis-related arthritis, 17 as systemic-onset JIA, 16 as seronegative polyarticular type, 8 as extended oligoarticular type, 4 as psoriatic arthritis and 3 as seropositive polyarthritis. At the end of follow-up, the number of patients with seronegative polyarthritis had increased while the number with systemic-onset arthritis had decreased. The most common symptom at admission was arthralgia in 79.4%. The height and weight standard deviation scores at last visit were lower than the scores at diagnosis; however,

this was not statistically significant (p>0.05). HLA B27 was found as positive in 32.4% of the patients. Forty-two of the patients were evaluated with sacroiliac MRI and sacroiliitis was detected in 19 of them. Eighteen (15.4%) of the cases had permanent joint deformities. Macrophage activation syndrome developed in 2 cases.

Conclusion: JIA is a multi-systemic chronic inflammatory disease that can lead to mortality and lifelong morbidities like growth retardation and joint deformities. The progress of the disease should be closely followed in order to screen and prevent complications. The higher frequency of enthesitis-related arthritis among our patients is an interesting feature and can be investigated in detail in a more specific study.

PP - 98

THE EFFECT OF FOLIC ACID SUPPLEMENTATION ON PLASMA HOMOCYSTEINE LEVELS IN PATIENTS DIAGNOSED AS JUVENILE IDIOPATHIC ARTHRITIS, UNDER METHOTREXATE THERAPY

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Methotrexate (MTX), the most common disease-modifying anti-rheumatoid drug, has been used for a long time in the treatment of juvenile idiopathic arthritis (JIA). MTX shows its effects and toxicity by antifolate action. MTX decreases folic acid level in plasma and erythrocytes by inhibition of dihydrofolate reductase activity and increases plasma homocysteine levels by inhibiting methylene tetra folate reductase activity. Hyperhomocysteinemia is an independent and important risk factor in the development of premature vascular defects and arterial and venous thrombosis. Folic acid decreases some of the toxicities of MTX. It is proposed that folic acid supplementation decreases homocysteine levels.

Aim: To investigate the effect of folic acid supplementation on plasma homocysteine (tHcy) levels in patients diagnosed as JIA under MTX therapy for an extended time.

Patients and Methods: We investigated 30 patients under MTX treatment and folic acid supplementation (5 mg/week).

Results: Sixteen patients were male and 14 were female, with median age 10.8±4.65 years. The control group consisted of 9 male and 11 female patients with median age 10.45±3.95 years. There was no statistically significant difference in terms of folic acid and vitamin B12, but tHcy level was significantly higher in the patient group (10.04±2.09 vs 8.85±1.95 μmol/L, p=0.04).

Conclusion: In case of investigation of folic acid supplementation effect on tHcy, it is considered that hyperhomocysteinemia is independent of folic acid deficiency in the patient group with high homocysteine levels but with normal folic acid levels. However, a negative correlation was detected between tHcy and folic acid level in patients with folic acid supplementation, indicating that folic acid supplementation is effective in decreasing homocysteine levels.

PP - 99

INVESTIGATION OF PULMONARY INVOLVEMENT IN JIA PATIENTS

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Aim: We aimed to evaluate the pulmonary involvement in patients diagnosed as juvenile idiopathic arthritis (JIA) with Pulmonary Function Tests (PFT) and High Resolution Chest Tomography (HRCT).

Patients and Methods: We investigated 31 Turkish children diagnosed as JIA, followed up regularly from our rheumatology outpatient clinic between 2002 and 2005. Posteroanterior (PA) chest roentgenogram, PFT and HRCT were carried out in

all patients. For the full adaptation of patients and sensitive evaluation of tests, PFT were measured with Micromedicals Microloop 3535 10 times.

Results: Thirteen of the cases were female and 18 were male. The mean age was 12.6 years, and the mean age at diagnosis was 8.87 years. According to ILAR criteria, 32% of the patients were diagnosed as systemic–onset disease, 23% as enthesitis-related arthritis, 26% as oligoarthritis and 19% as polyarthritis. Pulmonary involvement was detected on HRCT in 8 patients (26%), and of them, bronchiectasis was seen on PA chest roentgenogram in only one patient (3%). Among the patients with pulmonary involvement, interstitial involvement was detected in 4 patients, bronchiectasis in 3 patients and air trapping in 1 patient. Pulmonary involvement was significantly higher in males ($p<0.01$). Pulmonary involvement was seen in 3 of the 10 patients with systemic onset disease, in 3 of the 6 patients with polyarthritis and in 2 of the 8 patients with oligoarthritis; no pulmonary involvement was seen in patients with enthesitis-related arthritis. With PFT, restrictive type of functional disturbance was seen in 13 patients; however, no pathology was detected on HRCT in 2 of them. There was no significant difference in terms of hemoglobin, leukocyte and platelet levels between the patients with or without pulmonary involvement; however, C-reactive protein (CRP) levels were significantly higher in patients with pulmonary involvement.

Conclusion: HRCT is more sensitive then PA chest roentgenogram in detecting pulmonary involvement in JIA, and PFT are not as reliable as HRCT. Patients with elevated CRP levels in particular must be evaluated with HRCT.

PP - 100

SYSTEMIC ACTIVITY AND BONY EROSIONS PREDICT INADEQUATE LONG-TERM RESPONSE TO ANTI-TNF AGENTS IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background: Anti-tumor necrosis factor (TNF) agents are indicated in children with juvenile idiopathic arthritis (JIA) refractory to methotrexate. Improvement occurs in two-thirds of patients, but it may be short-lived. Prediction of poor response may prove valuable in clinical practice.

Purpose: To identify predictive factors for poor long-term response to anti-TNF agents in children with refractory JIA.

Methods: Inclusion: children with JIA who started anti-TNF therapy ≥ 2 years ago. Patients refractory to one anti-TNF agent were switched to another. Exclusion: patients who abandoned treatment for non-medical reasons. Primary end-point was failure to achieve improvement (ACR-Pedi30) at 1 and 2 years after the initiation of anti-TNF therapy. Recorded variables at anti-TNF therapy onset included sex, age, JIA type, number of active and limited joints, ESR, bony erosions, CHAQ, systemic symptoms (fever, rash, serositis), and use of corticosteroids. Univariate and multivariate analyses were performed.

Results: Fifty-six children were included. Features at anti-TNF therapy onset: 34 girls, age 12, disease duration 3 years; 30 systemic JIA, 16 polyarticular JIA; 19 active joints, 11 limited joints; ESR 33 mm/h; erosions in 23 patients; CHAQ >0.5 in 26; systemic symptoms in 10; and corticosteroids in 30. Seventeen (30%) patients did not reach improvement at 1 year and 24 (43%) patients at 2 years. Multivariate analysis showed systemic symptoms and erosions were associated with no improvement at 1 year ($p=0.02$ and $p=0.006$) and 2 years ($p=0.05$ and $p=0.01$) after initiation of therapy.

Conclusion: Systemic symptoms and bony erosions at the onset of anti-TNF therapy predict long-term unfavorable response in children with JIA.

PP - 101

CERVICAL SPINE INVOLVEMENT AS THE ONLY MANIFESTATION OF JUVENILE IDIOPATHIC ARTHRITIS

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Background: Cervical spine arthritis is a common manifestation in polyarticular and systemic onset juvenile idiopathic arthritis (JIA), but involvement of the cervical spine can occur in any subgroup of JIA. Isolated affection of cervical spine in JIA, without inflammation of other joints, is rare, and the diagnosis of JIA can be missed.

Case Report: A 12-year-old girl presented to our clinic with a three-month history of right-sided cervical swelling and limited range of motion in the cervical spine. Neither ultrasound examination of the swelling nor an ENT evaluation had led to a diagnosis thus far. At the time when symptoms started, she had a painful swelling of the right MTP I after a long walk which resolved within 2 weeks without any treatment. Her family and personal histories were unremarkable except for a diagnosis of psoriasis made by a dermatologist about 3 months prior to the first articular symptoms. The rheumatologic examination confirmed the limited motility of her cervical spine but was completely normal for all other joints. Laboratory exams showed an elevated ESR (24 mm/hour), a positive test for rheumatoid factor and a positive ANA serology (1:160). Conventional radiographs were normal. The MRI showed arthritis in the upper part of the cervical spine (C_0 to C_2) accentuated on the right side.

Conclusions: Persistent torticollis has to be investigated thoroughly and imaging studies are mandatory so that a correct diagnosis can be made. Arthritis of the cervical spine has to be treated aggressively to avoid complications such as ankylosis or instability of the cervical spine. Although cervical spine involvement is commonly seen in children with polyarticular joint involvement, our case demonstrates that cervical spine arthritis may occasionally be the only manifestation of JIA.

PP - 102

A CASE OF SUB-CLINICAL ELBOW AND TMJ INVOLVEMENT IN JUVENILE IDIOPATHIC ARTHRITIS

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A girl born in 1995 had been followed since 1997 for an ANA-negative pauciarticular juvenile arthritis. Right knee involvement in 1997 and 3 flares (September 2000, July 2003, January 2005) marked the disease, on left knee, right knee again and left ankle, respectively. Inflammatory markers were increased at every occasion. Three- monthly general and eye and six-monthly temporomandibular specialist examinations never showed any other clinical involvement. At every visit, the patient was treated with intra-articular triamcinolone acetonide. In the intercurrent periods, periodical evaluations showed a remission state: normal ESR, CRP, serum proteins, and no clinically involved joints or other organs. In July 2005, the girl presented with complaint of a slight pain in her left elbow, which was found to show a synovial hypertrophy with a synovial cyst in the trochanter. Two months later the temporomandibular joint (TMJ) was also shown to be involved with an advanced state of condylar erosion. The case focuses our attention on two topics, smouldering disease and deceiving joints. We often deal with cases in which patients in apparent clinical remission show episodic undefined slight inflammation-related signs or symptoms. While the most commonly involved joints have an easy and early clinical access, the clinical impact or detectability of some others (e.g. TMJ and elbow) are not similarly so obvious. At the moment, for most clinical settings, the best suggestion seems to always remember these "hidden" joints. Detection of pain, motion reduction or asymmetry, palpable

joint rubbing in the TMJ or softening or bulging of the trochanter fossa, and slight pain or asymmetry in the elbow range of motions must require an instrumental evaluation: ECHO and power Doppler scan, computed tomography and magnetic resonance imaging will define the picture, providing an answer to an early clinical suspicion.

PP - 103

CIRCULATING DENDRITIC CELLS IN PERIPHERAL BLOOD AND SYNOVIAL FLUID OF CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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The role of dendritic cells (DC) in development of adult rheumatoid arthritis has been suggested. Thus far, this problem has been poorly explored in juvenile idiopathic arthritis (JIA). Therefore, we aimed to assess circulating blood DC (BDC) in this disease. In 47 JIA children, BDC absolute counts and ratios were assessed in both peripheral blood and synovial fluid. The results were correlated with several laboratory and clinical JIA-specific parameters. Additionally, BDC were assessed in peripheral blood of 22 healthy controls. Using the panel of monoclonal antibodies against BDC antigens (BDCA), three BDC subpopulations were determined: myeloid type 1 (BDCA1+/HLA-DR+/CD11c+/CD19-), myeloid type 2 (BDCA3+/HLA-DR+/CD14-) and plasmacytoid (BDCA2+/HLA-DR+/CD123+). We found a profound deficiency of BDC in the blood of JIA children (mean BDC count more than 3-times lower than in healthy children; $p<0.001$). This concerned all subpopulations examined. Moreover, lower BDC numbers correlated with higher disease activity ($p=0.024$) and higher thrombocyte counts ($p=0.007$). BDC ratios correlated inversely with levels of anti-nuclear antibodies (ANA) ($p=0.021$). Importantly, both BDC percentages and counts in JIA synovial fluid were significantly higher than in peripheral blood of both JIA ($p<0.0001$) and healthy children ($p<0.001$). These results show that the number of BDC in peripheral blood is significantly decreased in JIA, probably due to their accumulation in tissues involved in the inflammatory process. It is likely that circulating BDC migrate to joints, participating in mediation of local immune response, and in turn, in maintaining the prolonged inflammatory process.

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PP - 104

SYNOVIAL FLUID T CELLS ARE RESISTANT TO rAd-BASED SUPPRESSION OF PROLIFERATION

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Introduction: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. There are various subtypes of JIA, with major differences in both severity and outcome. Both T cells and dendritic cells (DC) are key cell types contributing to the pathology of JIA. We have found CD4+CD25+ regulatory T cells (Treg) in the synovial fluid (SF) of children with JIA and DC in a semi-mature state in SF. Using a method previously developed in our laboratory to generate tolerogenic DC from healthy peripheral blood monocytes (PBMC), we have adapted it to generate tolerogenic DC from synovial cells of children with arthritis, and we have investigated the ability of T cells from the joint to be suppressed.

Materials and Methods: Human monocyte-derived DC grown from SF from children with JIA were infected with replication deficient adenoviral (rAd) constructs (E1-E3-deleted) and then matured. CFSE-labelled T cells were cultured with either autologous

DC (adenoviral infected or control) and stimulated with PHA, or were seeded with allogeneic DC. T cell proliferation was measured by CFSE dilution using flow cytometry.

Results: Proliferation of T cells when co-cultured with adenoviral-infected DC was inhibited both in healthy volunteers (allogeneic response) and samples from PB from children with JIA. However, only minimal or no significant reduction in T cell proliferation was seen when T cells were from the SF compartment. The effect was not due to direct rAd infection of T cells.

Conclusions: We have shown that tolerogenic DC from synovial cells of children with arthritis can be generated in vitro. These DC were able to inhibit T cell proliferation when T cells were obtained from PB. Our data suggest that T cells from the joint were resistant to this suppression. The mechanisms of this resistance will be important to elucidate since this may provide new therapeutic targets for childhood arthritis.

PP - 105

EARLY JUVENILE ARTHRITIS (JA) – RESULTS OF TWO-YEAR PROSPECTIVE OBSERVATION

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Objective: To determine prospectively clinical and functional status, laboratory parameters, and ultrasound picture in patients with early JA two years after the onset of disease.

Material and Methods: The study included 128 (50 boys, 78 girls) patients with early JA. The age of patients ranged from 1.5 to 16 years (mean 8.1±5.1 years). Disease duration was from 2 weeks to 6 months (3.1+1.5 months). We investigated 384 pairs of joints (knee, hip, ankle) in 128 patients by using ultrasound.

Results: The majority of children had mono-oligoarthritis (68.8%), with polyarthritis at a rate of 21.4% and the systemic form of JA at 10%. 37% were ANA positive and 13.2% were positive for rheumatoid factor (RF). After two years, 57% of patients had oligoarthritis and 43% polyarthritis; no patient had systemic signs. 71.4% of patients had functional disability (FD) of 0-1 Steinbrocker class and 28.6% of 2 class; no patient had 3-4 class. Remission was noted in 52.3% of children, intermitting course - in 19.1% of patients with polyarthritis. The presence of arthritis was confirmed by ultrasound in practically all patients. In the early stage of disease, fibrin was detected in 15% of joints. Initial signs of arthritis were revealed in 14 joints without clinical manifestation.

Conclusions: Two years after the onset of disease, half of the patients had remission. Most of them have a satisfactory outcome without serious disability. The patients with polyarthritis have serious course and prognosis in spite of DMARD administration. They need more aggressive treatment in the early stage of the disease.

PP - 106

HODGKIN'S LYMPHOMA IN JIA PATIENTS TREATED WITH ANTI-TNF AGENTS

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Tumor necrosis factor (TNF) blocking agents are widely used in the treatment of methotrexate-refractory juvenile idiopathic arthritis (JIA). The long-term risks of taking these and other biologic medications are still unknown. There has been recent controversy regarding the possibility that these agents may increase the risk of lymphoma in adults with rheumatoid arthritis (RA). We herein describe the occurrence of Hodgkin's lymphoma in two JIA patients treated with anti-TNF agents.

Case 1 is a 9-year-old boy diagnosed with ANA-positive extended oligoarthritis and uveitis at age 11 months. The uveitis was refractory to multiple medications, and he was eventually treated with high-dose infliximab, to which he responded. At age 9 years (3.5 years after starting infliximab), he was diagnosed with classical Hodgkin's lymphoma, nodular sclerosing subtype, Stage IVB.

Case 2 is an 11-year-old girl who presented with rheumatoid factor (RF) positive polyarthritis. She was treated with oral and subcutaneous methotrexate (for 4.3 years) and etanercept (for 3.8 years), to which she responded well. However, at age 15 years, she was diagnosed with classical Hodgkin's lymphoma, Stage II.

To our knowledge, these are the first reports of Hodgkin's lymphoma associated with anti-TNF use in JIA. These cases indicate that these agents may also be a risk factor for lymphoma development in JIA patients as well as adults with RA. Careful long-term surveillance of all pediatric patients taking anti-TNF and other biologic agents is needed.

PP - 107

SUBCHONDRAL GEODE OF THE ELBOW: UNUSUAL FINDING IN JUVENILE RHEUMATOID ARTHRITIS (JRA)

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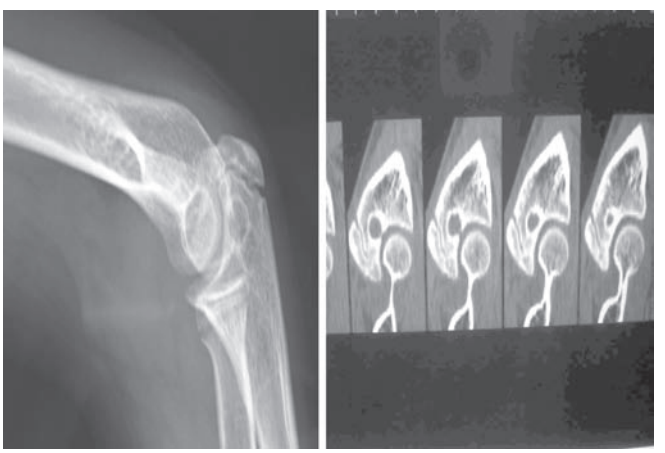
Bone cysts are an usual finding in rheumatoid arthritis. They are typically present in long-lasting and aggressive forms of the disease, more frequently described in knees, hips and hands. Opposite to synovial extra-bone cysts, they are not frequent in childhood arthritis. A PubMed search found only one report of such lesions, from Turkey in 1975 (1). Consequently, the X-ray finding (Fig. 1) of a lytic lesion in a just turned aspecifically painful elbow of a 12-year-old girl with a smouldering JRA since 5 years led to a further evaluation. A TC scan (Fig. 2) showed a subchondral well-defined, fluid-containing, sclerotic-edged lesion in the trochanter, with a clear communication with the joint space, which appeared to be involved by a synovial hyperplasia. This led to the diagnosis of subchondral geode. The intrusion of the synovial fluid into the bone through a marginally eroded joint as a means to compensate for the inflamed joint intra-articular high pressure or a bone-eroding rheumatoid nodule are the hypotheses put forward to explain these arthritic cysts. While rheumatoid nodules are not seen in JRA, the peculiarity of the elbow is to be a small but formerly weight-bearing joint, which has maintained a tight and strong capsular apparatus. This could explain the clinical paucity of an involved elbow, a high intra-articular pressure, and consequently, the possibility to have a bone cyst formed even in presence of a smouldering, not specifically aggressive or long-lasting disease.

1. Pitamic T, Votava-Sprem A. Bone cysts (geodes) in rheumatoid arthritis of children Reumatizam. 1975; 22 (2): 56-60.



PP - 108

GHRELIN LEVELS AND FOOD INTAKE IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA) UNDER ANTI-TNF IN RELATION TO DISEASE ACTIVITY

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Aim: To investigate whether the adverse effect of tumor necrosis factor (TNF) on appetite and weight gain is related to the suppression of GHRELIN, a stomach- secreted orexigenic peptide.

Patients-Methods: The nutritional status, appetite, food intake and serum GHRELIN levels (SG) were prospectively studied in 52 (44 females) children with JIA in relation to their disease type and activity as well as anti-TNF treatment. Body weight and height, several anthropometric parameters and resting energy expenditure (EE) were measured. Appetite-related sensations score (hunger, satiety, desire for food) were assessed using a specific software. The disease activity was assessed by a MDVAS scale (1-4). A 24-hour food recall was analyzed and the Actual Caloric Intake (ACI) was expressed as % of the calculated EE. STG was assessed by ELISA.

Results:

All patients	Range	Mean±SD
GHRELIN pg/ml	27.8-338.3	103.05±59.1
EE	850-2190	1350±300
ACI%	0.31-2.88	1.34±0.64

No correlation was demonstrated between STG and EE or ACI%. The lower STG levels were observed in patients with a): systemic JIA (8/52) (69.005±25.6), compared to other disease types ($p<0.005$), and b) MDVAS 2-3 (7/52) (71.6±24.9) compared to those with MDVAS 0-1 ($p<0.01$). Higher STG levels were found in patients under anti-TNF (14/52) (137.84±92, 8) compared to those without anti-TNF ($p<0.05$). Concomitant prednisolone treatment did not significantly affect the STG levels.

Conclusion: The elevated STG observed in patients under anti-TNF may be attributed to the neutralization of TNF action on growth retardation in systemic or active JIA.

PP - 109

HEARING LOSS AND MIDDLE EAR INVOLVEMENT IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Objective: Evaluation of the hearing status and middle ear function of patients with juvenile idiopathic arthritis (JIA).

Methods: The study group was comprised of 19 JIA patients aged between 5 to 23 years. The control group was comprised of 15 healthy subjects aged between 5 to 22 years. All subjects were examined audiologically using otoadmittance measurements, pure-tone audiometry, high frequency audiometry and transient evoked otoacoustic emission tests.

Results: There were a statistically significant number of ears (32%) with abnormal tympanograms in the JIA group while all tympanograms were normal in the control group. Individually, there was no subject with a conductive or sensorineural hearing loss in either group. But as a group, patients with

JIA showed statistically significant elevation of air conduction thresholds at frequencies of 250 Hz, 500 Hz, 6000 Hz, 12500 Hz; and larger air-bone gaps at 500 Hz and 2000 Hz ($p<0.05$). Comparison of bone conduction thresholds and otoacoustic emission tests between groups did not reveal any statistically significant difference ($p>0.05$).

Conclusion: This study suggests a dual effect of disease on both the middle and inner ear of JIA patients. Presence of abnormal tympanograms together with worse air conduction thresholds at lower frequencies as well as larger air bone gaps at frequencies of 500 and 2000 Hz suggest subclinical middle ear involvement, while hearing losses at high frequencies suggest inner involvement at an early stage.

PP - 110

MACROPHAGE ACTIVATION SYNDROME: THE SPANISH MULTICENTRIC STUDY

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Introduction: Macrophage activation syndrome (MAS) is a severe complication of systemic onset juvenile idiopathic arthritis (SoJIA).

Objective: To describe the clinical characteristics and outcome of patients diagnosed with MAS and SoJIA included in the Spanish MAS Registry.

Patients and Methods: Data were recorded via standard protocol and data record form submitted to all centers attending children with rheumatic diseases.

Results: Information was available on 31 patients (16 boys and 15 girls) who suffered 37 MAS episodes. 27 presented only 1 episode, 3 had 2 and 1 had 4 episodes. The time between episodes ranged from 9 to 33 months. The median age was 5.9 years (1-23 years). The most frequently recorded symptoms were fever (97%), followed by skin rash (49%), central nervous system dysfunction (41%) and gastrointestinal abnormalities (15%). The most frequent abnormal laboratory findings included thrombopenia (78%) and elevated levels of hepatic enzymes (70%). All episodes but one were treated with steroids, 15 with cyclosporine A, and 6 with etoposide. One patient received a liver transplant before diagnosis. The mortality rate was 6.5% (2/31).

Comments: MAS is a severe, potentially lethal complication of SoJIA. The clinical and laboratory abnormalities characteristic of systemic JIA complicate its diagnosis. Awareness of this complication may allow the diagnosis and institution of therapy early in the course of the disease.

PP - 111

RECURRENT SYSTEMIC-ONSET JUVENILE IDIOPATIC ARTHRITIS: A CASE REPORT

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Introduction: Systemic-onset juvenile idiopathic arthritis (JIA) is a subset of JIA that describes patients with intermittent fever, rash, and arthritis. Children with this illness comprise between 10-20% of all cases of JIA. Systemic complications are more common in this subtype of JIA than in any other type.

Case Description: The authors report the case of an 18-year-old girl, with a 2-week history of intermittent high spiking fever, maculopapular rash, inflammatory arthralgias, myalgias, fatigue and anorexia. She described two previous episodes suggesting systemic-onset JIA at the age of 6 and 4. Physical examination showed oligoarthritis,

cervical lymphadenopathy and abdominal pain on deep palpation, without hepatosplenomegaly. Laboratory evaluation revealed leukocytosis with neutrophilia and lymphopenia, high ESR, CRP and liver function markers, and markedly elevated serum ferritin. Spleen size was at its upper ultrasound limit and a small pericardial effusion was observed on echocardiography. The chest, hands and feet radiographic study, urinalysis, autoantibodies, seric immunoelectrophoresis, rheumatoid factor, complement, serological evaluation, and blood and urine cultures were all normal, without evidence of acute infection. Initial therapy with NSAIDs and low-dose corticosteroid was ineffective. Clinical and laboratory response was achieved with prednisolone 1 mg/kg/day. Successful effort was made to minimize the dosage and duration of therapy.

Conclusion: Patients with systemic-onset JIA require close supervision and monitoring. Its course and prognosis are highly variable. Some children have recurrences, even in adulthood, after years of appearing disease-free. Recurrent disease after the age of 16 is not adult-onset Still's disease.

PP - 112

CD45RA, CD45RACD4 AND CD45RACD8 T CELLS IN PERIPHERAL BLOOD IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Aim: The aim of the study was to find the relation between CD45RA, CD45RACD4 and CD45RACD8 T cells in the acute phase of juvenile idiopathic arthritis (JIA) and in remission.

Material and Method: Blood of 30 children in acute phase of JIA and 28 children in remission was tested. Age of the children in acute phase was 3.0-17.5 years (mean 12.1 y) and of the children of remission was 3.5-17 years (mean 13.3 y). There were two control groups: 30 healthy children and 10 children with reactive arthritis.

Results: In acute phase, number of CD45RACD4 and CD45RACD8 T cells was increased and CD45RA was decreased. In remission and in children with reactive arthritis, the number of CD45RACD4 and CD45RACD8 T cells was decreased and the number of CD45RA T cells returned to normal. The increase in the number of CD45RACD4 and CD45RACD8 T cells is also confirmed in the exacerbation of JIA.

Conclusion: 1) The subpopulations of CD45RA, CD45RACD4 and CD45RACD8 T cells in peripheral blood in children with JIA are different from those of healthy children and children with reactive arthritis. 2) There is a correlation between the subpopulation of T cells and exacerbation of JIA.

PP - 113

ADVERSE EVENTS TO TNF-a BLOCKERS IN JUVENILE IDIOPATHIC ARTHRITIS

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Objective: To register adverse events (AE) in JIA patients treated with tumor necrosis factor (TNF)-a blockers.

Method: 101 patients were enrolled in the period of 1/11/1999 to 1/11/2006. TNF-a blockers were etanercept (ETN), infliximab (IFM) and adalimumab (ADA). All patients were followed prospectively according to a standardized protocol. Medical records were reviewed carefully for any observed AE. AE were divided into 8 subtypes (fever, rash, GI-discomfort, injection and infusion complications, general discomfort, weight gain and central nervous system symptoms). AE were graded into 5 degrees according to time and degree: 1: <24 hours, 2: without medical attendance, 3: need of medical attendance, 4: admission to hospital, and 5: life-threatening.

Results: Patients were treated between 1 and 73 months, average 18.5 months.

AE were seen in 74% of ETN-treated, with the most frequent AE being fever (54%) without serious signs of infection. 7% developed serious AE, all with full recovery. AE were seen in 63% of the IFM-treated, and in 50% of ADA-treated. Most frequent AE was fever (INF: 53%/ADA: 50%). Infusion reactions to IFM were seen in 17%. There were no deaths, and no AE as demyelination or malignancy. In total, 0.1 AE per patient per month were registered.

Conclusion: Treatment was in general well tolerated. By far the most frequent AE was fever with only mild symptoms of infection. All patients had full recovery and there was no malignancy.

Table A:	Etanercept	Infliximab	Adalimumab
Number of patients	89	30	8
Treatment duration, month	(2-73) 21.4	(1-41) 12.8	(1-25) 9
Total treatment duration, month	1902	385	72
Number of patients without AE	23	11	4
Number of patients with AE	66	19	4
Number of patients with AE grade 1-2	38	7	2
Number of patients with AE grade 3	23	12	2
Number of patients with AE grade 4-5	6	0	0
Number of AE/treatment months	(214/1902=) 0.12	(41/385=) 0.11	(10/72=) 0.14
Number of AE/treatment years	1.35	1.28	1.67

PP - 114

METHOTREXATE MONITORING IN A TERTIARY CENTER: IS IT ALL WORTHWHILE?

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Aim: The aim was to review the results of the current methotrexate (MTX) monitoring program in a tertiary pediatric rheumatology center.

Method: Retrospective audit of all patients with juvenile idiopathic arthritis (JIA) commenced on MTX from June 2002 - December 2006.

Results: 84 patients in total. All blood results documented at 2 weeks after commencing MTX were normal. 6/84 (7.1%) patients developed a neutropenia, median 1.5 (range 0.5-1.8 $X10^9$/L) within median of 5.5 months (range 3-22). 8/84 (9.5%) patients developed an abnormal alanine transferase (ALT), median result 97.5 (range 82-364 U/L) with a median time of 11 months (range 3-30).

Discussion: Currently, the timing of blood tests in patients taking MTX varies between individual centers. At this tertiary center, current MTX monitoring consists of the first blood test taking place 2 weeks after MTX is commenced. Thereafter, blood tests are checked monthly for 6 months and if results are normal they are changed to every 2 months. BSPAR guidelines state "FBC and LFTS should be checked regularly." This study in this center provides further information with a median time to abnormal results of between 5.5-11 months. The results of this survey suggest that the blood test after 2 weeks is not necessary and that it may be possible to start monitoring later than the current BSPAR guidelines advise.

Blood test	Number of patients with abnormal results No. (%)	Abnormal Results Median (range/units)	Time to result (months) Median (range)
Neutrophils	6 (7.1)	1.5 (0.5-1.8 $X10^9$/L)	5.5 (3-22)
ALT	8 (9.5) (n=84)	97.5 (82-364 U/L)	11 (3-30)

PP - 115

CLINICAL AND LABORATORY PROFILE OF SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS

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Aim: To study the clinical and laboratory profile of systemic onset juvenile idiopathic arthritis (soJIA).

Materials and Methods: Out of 300 children with JIA who attended between Jan 2004 and Dec 2006, 79 patients (49 male, 30 female) fulfilling the ILAR criteria for soJIA were analyzed.

Results: Age distribution was as follows: 0-5 yrs - 30, 6-10 yrs - 25, 11-16 yrs - 20, above 17 yrs - 4. Fifty-five children were less than 10 years. Mean duration was 1 year and 10 months. Lymphadenopathy was present in 51 (64.5%), followed by rash in 41 (51.9%) and hepatosplenomegaly in 39 (49.4%). All three features were present in 9 (11.4%). Serositis and eye involvement were not seen.

Polyarticular involvement was observed in 68.4% and pauciarticular in 31.6%. Joints commonly affected were knee (n:62) (78.5%), wrist (n:50) (63.3%), ankle (n:44) (55.7%), elbow (n:30) (38%), PIP in hands (n:27) (34.2%), feet (n:26) (33%), MCP (n:25) (31.6%), DIP of hands (n:11) (14%) and cervical spine (n:23) (29.1%).

Investigations showed anemia in 34 (43%), leukocytosis in 28 (35.4%) and thrombocytosis in 14 (17.7%). Raised C-reactive protein, erythrocyte sedimentation rate and anti-streptolysin O were seen in 68, 61, 24 (86%, 77%, 30%), respectively, and ANA were positive in 4 (5%). HLA class I typing was done in 13 patients and A_2 allele was the commonest.

Conclusion: soJIA was more common in boys. The majority of children were below 10 years. Fever with lymphadenopathy, and polyarticular presentation with involvement of knee, wrist and ankle was common. No serositis or uveitis was seen in these children.

PP - 116

SAFETY OF OVER 8 YEARS OF CONTINUOUS ETANERCEPT THERAPY IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS

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Background: The study included patients with juvenile rheumatoid arthritis (JRA) who were treated with etanercept, a soluble TNF receptor, for more than 8 continuous years.

Objective: Assessing the long-term safety of etanercept in patients with JRA.

Methods: Patients with JRA who participated in a double-blind, randomized controlled trial (RCT) of etanercept were eligible to enroll in a multicenter open-label extension (OLE) study. Data from the RCT and the OLE were included in this analysis. Safety was assessed in all patients receiving at least one dose of etanercept. Safety assessments included the incidence of serious adverse events (SAEs), medically important infections (MIIs), and deaths.

Results: 69 patients with JRA enrolled in the RCT; 58 of these (84%) enrolled in the OLE. 42 patients entered the 4th year and 26 (38%) entered the 8th year of continuous etanercept exposure. The most common reason for withdrawal from the OLE was patient/guardian refusal (N=10, 14.5%). 9 patients (13.0%) withdrew because of a suboptimal response status, 5 (7.2%) because of AEs, and 5 (7.2%) because of physician decision. 16 patients (23%)

reported a total of 39 SAEs. The overall rate of SAEs (0.12/pt-yr) did not increase with long-term exposure to etanercept (Years 1-8, 0.00-0.20/pt-yr). No cases of lupus, demyelinating disorders or malignancies were reported. The overall rate of MIIs was 0.03/pt-yr. No infections were opportunistic. No deaths were reported.

Conclusion: These data suggest the safety profile of etanercept therapy is maintained with long-term use for up to 8 years in this population of patients with JRA.

PP - 118

THE IMMEDIATE EFFECTS OF WRIST ORTHOSES ON GRIP PRESSURE AND PINCH STRENGTHS IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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The wrist is one of the most commonly involved joints in juvenile idiopathic arthritis (JIA). As an adjunct to the medical treatment, wrist orthoses are used to stabilize the joint, prevent deformities and contractures, reduce pain, and allow function through proper positioning. The changes in grip and pinch strengths over time give an indication of the hand function. In addition, these measurements are also used to follow disease activity and determine the effectiveness of the medical and rehabilitative treatments. There is little information about the effects of wrist orthoses on hand strengths in patients with JIA.

Aim: This study was conducted to investigate the immediate effects of wrist orthoses on grip pressure and pinch strengths of patients with JIA.

Method: A total of 49 patients with JIA were included into the study. Patients were divided into two groups according to their ages: G1 (n:19): 1-16 years of age and G2: 17-39. Measurements were taken on a total of 86 hands. An adapted sphygmomanometer, which measures up to 510 mmHg, was designed and used for grip pressure measurements. Pinch strengths were evaluated with B&L pinch-meter. Grip pressure, lateral pinch, palmar pinch, and tip-to-tip pinch strengths were measured with and without an orthosis. A standard protocol was used during the measurements.

Results: The only significant difference was seen in palmar pinch in the whole group and G2.

PP - 119

THE CORRELATION BETWEEN GRIP STRENGTH AND GRIP PRESSURE IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Grip strength measurements are done to evaluate the functional status of a patient and to assess disease activity and effects of the medical and rehabilitative treatments. Standard Jamar Dynamometer is a well known and the most widely used hydraulic instrument to measure grip strength. An adapted sphygmomanometer is a pneumatic instrument and is used to measure grip pressure. It is custom-made and contains an elastic bag. Although they measure similar variables, they cannot be used in place of one another. In general, in painful conditions and in hands with prominent deformities and contractures, the use of an adapted sphygmomanometer is advocated. When considering the patients with the juvenile idiopathic arthritis (JIA), the use of the Jamar Dynamometer may cause additional problems. It is heavy and squeezing the handles is difficult for small-handed children. However, when a measurement is done by only one of these instruments, it will be useful to obtain an

idea regarding a corresponding value on the other instrument.

Aim: This study was conducted to determine whether a correlation exists between grip strength and grip pressure and obtain regression equations for patients with JIA.

Method: A total of 56 patients participated in the study. They were divided into two groups according to their ages: G1: 1-16 years of age and G2: 17-39 years of age. Measurements were taken in 33 and 75 hands in G1 and G2, respectively. Standard measurement protocol was used.

Results: Good correlations were seen in both groups. In G1, regression equation was found as follows: {Grip strength(kg)=-2.134+0.113(grip pressure)}.

PP - 120

ELECTRONIC DATABASE SYSTEM INSTEAD OF PAPER-BASED DOCUMENTATION FOR CHILDHOOD CHRONIC ARTHRITIS

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The complete documentation of patient data is essential for the chronic diseases such as juvenile idiopathic arthritis to enable a perfect long-lasting follow-up. In order to avoid illegible and incomplete documentation, we wanted to establish an electronic medical record system (EMRS) in the pediatric rheumatology outpatient clinic of our hospital that would provide multiple ways of generating notes. We created an EMRS using SQL database, which is running under Microsoft Windows 98. The database was specially designed for pediatric rheumatology patients and modules were prepared by two pediatric rheumatologists. Modules were programmed for basic patient data, general history, vaccination status, history of rheumatic disease, physical examination, joint examination shown on "homunculus", laboratory investigation, treatment, and special notes for each visit. This EMRS facilitates patient management in the outpatient clinic, and furthermore enables the quick statistical analysis for scientific researches. In conclusion, information in patient records is legible and complete, and it helps to provide what is needed to verify level of service.

PP - 121

JUVENILE IDIOPATHIC ARTHRITIS (JIA) IN ADULTHOOD IN A TERTIARY REFERENCE CENTER

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Introduction: Health outcomes in JIA have been actively researched in the last decade, and a diminished frequency of severe physical disability has been shown; however, patients who enter adulthood with active disease do not seem to have decreased.

Objective: To evaluate the impact of adult JIA in a tertiary rheumatologic center.

Materials and Methods: All consecutive JIA patients aged >18 years referred to our Center in two weeks were assessed with: HAQ; SF36; active joint count; VAS (0-100 mm) for: pain, patient and physician global health (GH) assessment; and radiological evaluation (Steinbrocker).

Results: Data of 79 enrolled patients are shown in the Table.

			Poly		Oligo			
	All JIA	Systemic	RF+	RF-	Persist.	Extend.	Psoriatic	ERA
	79	15	5	10	23	15	3	5
Age	27 (18-39)	29 (18-35)	21 (18-27)	27 (18-38)	26 (18-38)	25 (18-31)	34 (18-39)	27 (18-34)
Active arthritis (%)	94	100	100	80	100	93	100	80
VAS-pain	30 (0-98)	48 (0-98)	27.8 (2-54)	34 (1-66)	26 (0-83)	18 (1-52)	21.3 (0-62)	32.4 (6-82)
VAS-patient-GH	67 (0-100)	30 (0-98)	67.8 (40-99)	58.2 (0-88)	74 (20-100)	76 (40-95)	56.7 (40-80)	68.6 (10-90)
VAS-physician-GH	30 (0-98)	27 (0-90)	16.6 (0-42)	18.3 (0-53)	27 (0-80)	10 (1-32)	39 (2-94)	23.4 (2-85)
% Anatomic class: III-IV	59	87	100	67	14	71	100	75
HAQ	0.5 (0-2.6)	0.9 (0-2.6)	0.9 (0-2.5)	0.5 (0-0.9)	0.1 (0-0.6)	0.4 (0-1.6)	1 (0-1.8)	0.2 (0-0.9)
SF36-physical-health	65 (1.3-98)	54 (1.3-94.3)	67 (43-94)	60 (29-93)	76 (43-98)	61 (15-90)	38 (22-67)	60 (16-80)
SF36-mental-health	64 (11-100)	60 (11-97)	70 (29-99)	54 (14-85)	79 (18-100)	73 (20-97)	47 (21-86)	55 (12-97)

Conclusion: Our hospital-based study shows a selection bias toward the most serious cases, but underlines the importance of JIA still active in adulthood, confirming the need for a more aggressive treatment to improve outcomes in future.

PP - 122

EFFICACY OF A SECOND ANTI-TNF-ALPHA AFTER FAILURE WITH A FIRST (ETANERCEPT VS INFLIXIMAB) IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Introduction: Although clinical benefit has been shown with etanercept and infliximab in JIA, some patients do not respond to a first anti-TNF-alpha because of adverse events (AE), inefficacy or loss of efficacy.

Objectives: To determine the efficacy of a second anti-TNFalpha in JIA after failure of the first.

Methods: All prospective JIA patients who failed a first anti-TNFalpha and switched to a second were assessed at baseline and after 3-6 months of each treatment, with: tender/swollen joint count, erythrocyte sedimentation rate (ESR), patient global health, and DAS28.

Results: 32 patients were enrolled: onset age: 7±5.2 (0.6-15.9) years; age at beginning of first anti-TNFalpha: 19.9±7 (5.2-31.3) years; duration of first anti-TNFalpha treatment: 15±11.9 (1.5-56.1) months.

Cause of switch	Etanercept→Infliximab	Infliximab→Etanercept
Adverse Events	4	14
Inefficacy/Loss of efficacy	7	7
# Total	11	21

Each variable collected significantly improved during the first treatment, worsened at its suspension, and again improved during the second treatment ($p<0.01$).

	Baseline	After 3-6 months with first anti-TNFalpha	After first anti-TNFalpha suspension	After 3-6 months with second anti-TNFalpha
DAS28	5.2±1.1 (2.66-7.36)	3.8±1.2 (1.45-6.27) ($p<0.001$)	4.8±1.3 (2.64-8.28) ($p=0.08$)	3.4±1.4 (0.53-8.42) ($p<0.001$)

After 3-6 months with second anti-TNFalpha, there was no significant difference in DAS28 from that registered during the first treatment ($p=0.2$). DAS28 good/moderate response was around 70% with both treatments. No significant difference was found when stratifying the population for type and reason for the shift.

Conclusion: Data show that in JIA patients, failure of an anti-TNFalpha therapy due to adverse events, inefficacy or loss of efficacy does not preclude a good response to another anti-TNFalpha agent.

• Spondyloarthropathies
PP - 123

HIP INVOLVEMENT IN JUVENILE ANKYLOSING SPONDYLITIS: CLINICAL AND RADIOLOGICAL EVOLUTION AND RELATIONSHIP TO SACROILIITIS

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Aim: To investigate clinical and radiological features of hip involvement in patients with juvenile ankylosing spondylitis (JAS) and relationship between hip involvement and sacroiliitis.

Methods: Clinical, radiographic and laboratory findings of 130 patients with JAS treated and followed at the Institute of Rheumatology in Belgrade since 1965 were analyzed. All patients met the modified New York criteria for ankylosing spondylitis. Anteroposterior radiographs of the pelvis and lateral view of the lumbar spine were carried out in all patients and graded according to the New York classification criteria for AS. Hip involvement was defined by radiographic changes or clinical findings. Statistical analysis was performed using x^2 test with Yateson's correction.

Results: Among 130 patients, 122 were male and 8 female. Mean age at disease onset was 12.1±3.6 years and at last examination 31.3±9.8 years; and mean disease duration at the time of diagnosis was 10.7±6.7 years and at last examination 19.2±7.2 years. Hip involvement was the initial manifestation in 13% of patients and was found in advanced form of the disease in 50.7% patients; involvement was unilateral in 24.2% and bilateral in 75.8% of patients according to clinical and radiological examination. Radiological findings of hip involvement were: early changes in 28.8% and advanced in 71.2%: constructive 30.3%, destructive 34.8% and ankylosing in 6.05% of patients. The percentage of grade IV sacroiliitis was significantly higher in patients with hip involvement than in patients without, 75% vs 25% ($p<0.05$). Only 12.1% of patients had hip joint replacement. HLA-B27 was present in 97.55% of patients tested.

Conclusion: Hip involvement in JAS was the initial manifestation in 13% of patients and after 20 years, 51% of patients had severe extraspinal manifestation. Significantly higher radiographic changes in sacroiliac joints (grade IV) were found in patients with hip involvement ($p<0.05$). Involvement of the hip and sacroiliitis was closely related to the disease duration.

PP - 124

IS CRMO A SUBGROUP OF SPONDYLOARTHROPATHY DURING CHILDHOOD?

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Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a syndrome generally affecting children and adolescents. Its etiology is not yet known and it is usually characterized with recurrent inflammation of the metaphysis of long bones and clavicles. Recently, this rare syndrome is thought to be a subgroup of spondyloarthropathies.

Case Report: An 11-year-old girl presented to our hospital with the complaints of migratory pain of the large joints and loss of range of motion for 20 days. She had been diagnosed as chronic osteomyelitis two years ago although no microbial growth had been detected. Later, a new lesion had been seen at the sternoclavicular junction and she again had been diagnosed as chronic nonspecific osteomyelitis with the help of bone scintigraphies. Her immune profile was found to be normal. There was consanguinity between her parents. On her physical examination, two incision scars at the left upper leg and right clavicular region were present, palmoplantar yellow-white lesions, and excoriated and pustular crusted lesions were also present on the abdomen, neck, and upper and lower extremities. She was limping and anterior flexion of the body was extremely limited due to pain. Laboratory findings were as follows: Hb 12.8 g/dl, leukocytes 9500/mm^3, platelets 464000/mm^3, erythrocyte sedimentation rate 56 mm/hr, C-reactive protein 5.5 mg/dl, antinuclear antibody, rheumatoid factor, HLA-B27 were negative, and levels of IgM, IgG, IgA, IgE and C3, C4 levels were within normal limits. NBT 100% and MEFV mutations were -/-. Histopathological examination of cutaneous and subcutaneous dermis was pustular dermatitis. Bilateral active sacroiliitis was present in the sacroiliac MRI. Bone scintigraphy revealed chronic osteomyelitis. Although our patient's clinical and laboratory findings were consistent with the criteria of the European Spondylarthropathy Study Group (ESSG) for spondyloarthropathy, she had recurrent noninfectious osteomyelitis and cutaneous lesions leading us to revise the decision to a rare and unexpected diagnosis of CRMO. Significant improvement in pain and range of motion was achieved with NSAID and steroid.

In conclusion, it was shown that CRMO might present with the findings of spondyloarthropathy at the beginning of the disease and it might be a subgroup of spondyloarthropathies.

PP - 125

COMPARISON OF PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER ASSOCIATED JUVENILE ANKYLOSING SPONDYLITIS (FMF-JAS) TO JUVENILE ANKYLOSING SPONDYLITIS (JAS)

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Objectives: From an ongoing study comparing FMF-associated AS with AS, patients with juvenile onset from both groups were assessed separately. All patients were diagnosed before age 16, had bilateral sacroiliitis and had been followed in the same clinic since diagnosis.

Methods: 6 FMF-JAS (group 1) (M/F: 4/2, mean age: 16±2 years) and 7 JAS (group 2) (M/F: 5/2, mean age: 26±5 years) patients were surveyed. Enthesopathy was evaluated using B mode and power Doppler ultrasonography. Disease activity index (BASDAI), function index (BASFI) and radiology index scores (BASRI) were recorded.

Results: In 4/6 FMF-JAS patients, both diseases were diagnosed simultaneously, in 2/6, FMF was diagnosed 4 years before JAS. The mean disease

duration for FMF was 10±5 years, for associated JAS 5±3, and for the second group 15±7 years. Age at onset of AS for both groups was 11±3 years. Mean duration of follow-up was 3±3 versus 11±5 years for groups 1 and 2, respectively. A family history of FMF was present in 2/6 FMF-AS patients, and family history of AS was present in 2 other patients in each group. None of the patients had amyloidosis, IBD, or psoriasis, while 1 patient with JAS had uveitis. All patients from both groups had peripheral arthritis; however, acute 'red' monoarthritis was more common in group 1. A more significant decrease in lumbar flexion, a higher enthesitis score (4.25±1.98 vs. 1.86±1.95), and more severe radiological hip involvement were noted in JAS patients. There was no significant difference in BASRI, BASFI and BASDAI scores. HLA B27 was positive in all JAS and 2/6 of the FMF-JAS patients. Three from the first and 4 from the second group are currently receiving anti-TNF therapy.

Conclusion: There was no major difference in the expression of JAS with or without concomitant FMF. A longer disease course for JAS and early introduction of anti-TNF therapy in FMF-JAS patients may account for the slightly increased limitation of motion observed in the former group.

PP - 126

ACTIVITY DETECTION IN JUVENILE-ONSET SPONDYLOARTHROPATHIES (JSPA) BY INFRARED THERMOGRAPHY

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Introduction: JSpA is a term that refers to a group of pediatric disorders characterized by enthesopathy and arthropathy. Children usually present with undifferentiated SpA and progress to differentiated forms over time. The hallmark of JSpA is sacroiliitis.

Aim: To define the sensitivity and the clinical utility of infrared thermography in disease activity detection in JSpA.

Methods: We studied 24 children (17M, 7F, mean age 14 yrs, range 8-19 yrs) with active sacroiliitis, diagnosed by bone scintigraphy and confirmed by MRI, and 10 children with scoliosis. The thermographic analyses were performed with Digital Infrared Camera Land FTI 6 (plane array 256x256, HgTeCd sensor), with spectral band within 3-5 μm, time resolution of 0.05 s, and temperature sensitivity of 0.1 K. The temperature measurement noise was reduced to about 0.03 K by averaging 32 images each time with a delay of 30 ms. Emissivity of the skin was estimated as $\varepsilon = 0.95$. The measurements were performed in a temperature and humidity controlled room (within 1°C of 24° and 60% of humidity, respectively). The subjects observed 15 min of acclimation in the measurement room before thermographic observation.

Results: Nineteen of the 24 patients with active sacroiliitis were abnormal thermographically. None of the 10 children with scoliosis had increased sacroiliac activity on thermography.

Conclusions: The thermographic technique examined was of little help in the diagnosis of early sacroiliitis but might be more helpful in the objective serial assessment of sacroiliitis in individual patients with active disease.

PP - 127

SONOGRAPHIC EVALUATION OF ENTHESOPATHY IN PATIENTS WITH ENTHESITIS-RELATED ARTHRITIS: A PRELIMINARY REPORT

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Aim: Sonographic evaluation of enthesitis and related soft tissue complications is well known in the adult population; however, a similar study in the pediatric age group has not been reported. Therefore, the purpose of this study was two-fold: our first aim was to present our early sonographic experience with regard to the follow-up of enthesitis-related arthritis (ERA) patients and secondly, we aimed to analyze whether US findings could be related with any of the disease-related parameters.

Patients and Methods: Ten ERA patients (9 male, 1 female) were enrolled in the study. The physical examination included assessment of joint/tendon tenderness and swelling and Schober test. Laboratory testing included acute phase reactants and HLA-B27. Sacroiliitis was confirmed by either magnetic resonance imaging or scintigraphy. Sonographic measurements of bilateral knee and ankle joints were performed by the same physician using a linear array probe of 8–16 MHz.

Results: Seven patients were found to have sonography-proven enthesopathy in at least one joint. The mean quadriceps/patellar/achilles tendon and plantar fascia (right and left) thickness values (mm) of the patients were as follows: 7.32±1.46, 6.92±1.23; 3.73±0.62, 3.93±0.61; 4.85±0.77, 4.86±0.83; and 3.06±0.81, 2.74±0.69, respectively. There was a negative correlation between the Schober and tendon thickness values, but this correlation did not reach statistical significance. The mean tendon thickness values of the patients were not different when a comparison was performed with regard to the presence or not of HLA-B27 and sacroiliitis.

Conclusion: Sonographic follow-up of ERA patients seems to be easy and convenient. Further analyses with larger groups will provide a better understanding of the relation between the tendon properties and the disease-related parameters.

• Autoinflammatory syndromes
PP - 128

CLINICAL PRESENTATION AND CARDIAC OUTCOME OF RHEUMATIC FEVER AT ALFATEH CHILDREN'S HOSPITAL - BENGHAZI, LIBYA (REVIEW OF 10 YEARS)

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Objective: To review the clinical presentation, investigations and cardiac outcome of patients with rheumatic fever admitted to Alfateh Children's Hospital.

Design: Retrospective case series observational study.

Setting: Medical departments of Alfateh Children's Hospital in Benghazi.

Patients and Method: 110 patients with confirmed rheumatic fever according to modified Jones criteria who admitted from Jan 1994 – Dec 2003.

Data was collected by retrospectively reviewing medical records and information regarding history, clinical presentation, investigation, and treatment recorded. Serial echocardiogram reports of patients with carditis were also followed for two years when available.

Main Results: Total number of patients was 110; 30 (27%) were admitted more than once, 67 (60%) were male and 43 (40%) female. HlO sore throat was present in 85 (77%); none received a 10-day course of oral antibiotics. The most common clinical presentations were 64% with migratory

arthritis, 43% with fever, and 41% with carditis (the most common acute cardiac lesion: 63% mitral regurgitation, 33% mitral+aortic regurgitation and 4% aortic regurgitation). Serial echocardiograms of 38 of them were followed for two years and the results were as follows: 34% mild mitral regurgitation, 31% with normal heart, 21% mild mitral+aortic regurgitation, 5% moderate mitral regurgitation, 2.5% severe mitral regurgitation, 2.5% mitral valve prolapse, and 2.5% with aortic valve replacement. About 8% presented with chorea. No patient had erythema marginatum or subcutaneous nodules.

Conclusion: A good prognosis was observed in our patients. Both the incidence and the deleterious effect of rheumatic fever on the heart decreased but it can still result in significant heart damage. Primary and secondary prophylaxis by proper antibiotic is essential to prevent occurrence and recurrence of rheumatic fever.

PP - 129

EVALUATION OF THE CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF CHILDREN WITH FMF

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Familial Mediterranean fever (FMF) is an autoinflammatory syndrome with multiple mutations of the MEFV (Mediterranean fever) locus. More than 50 mutations have been described in MEFV.

Objectives: The aim of the study was to evaluate the clinical and epidemiological features of children with the diagnosis of FMF. These features were also compared with the commonly seen mutations and their relationships with the disease severity scores were studied.

Methods: The clinical and epidemiological features of 158 children followed by the pediatrics unit were evaluated. The diagnosis was made according to the Tell-Hashomer criteria. The commonest 3 mutations were studied in 123 of the children; no mutations were studied in 22 patients. For the remainder, either 5 common mutations or full genetic analysis of the MEFV gene was performed. For every patient, a clinical and epidemiological data-related file was reported. Laboratory data of the patients were also collected for the evaluation of the inflammatory response.

Results: A total of 158 children were included in the study. Of these patients, 83 (52.5%) were females and 75 (47.5%) were males. Mean age of the children was 128.14±42.48 months (48-222 months). The age of onset was 4.23±3.08 years (1-16 years). Familial consanguinity was present in 31% of the patients. The presence of FMF in family members was found in 52.9% of the cases. The most common clinical findings were abdominal pain (94.9%), chest pain (65.2%), arthritis (55.1%) and erysipelas-like erythema (46.8%). In 52.5% of the patients, attacks were seen 1-2 times per month, and the duration of the attacks was between 48 and 72 hours in 33.5% of the patients. The severity score was found to be mild in 4%, moderate in 82% and severe in 14%. There was a correlation between the severity score and hepatosplenomegaly. In 25.9% of the patients there was leukocytosis and all had increased sedimentation rates during the attacks. There was a significant increase in the hemoglobin values of the patients after a regular treatment with colchicine. Total response to colchicine was seen in 60.8% and partial response in 39.2%. None of the patients was accepted as unresponsive. The disease severity score was significantly higher among females. The commonest mutation was M694V/M694V (57.7%). One of the patients had E148Q/S647T genotype and to our knowledge S647T was the first mutation defined by our study. The genotype and phenotype relations were evaluated according to the most common 3 mutations (M694V, M680I, V726A). Patients who were homozygous for M694V mutation had the most severe disease score and highest sedimentation rate values. Arthritis and erysipelas-like erythema were significantly high among patients homozygous for the M694V mutation. Although common in Turkey, 20.7% of the patients had been misdiagnosed as rheumatic fever before their admission.

PP - 130

EFFICACY OF THE TREATMENT WITH ANAKINRA IN TRAPS PATIENTS: A PILOT STUDY

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Aim: To analyze the efficacy and safety of Anakinra in tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS) patients.

Patients and Methods: Three children (mean age 10.6, range 9-13) and a 33-year- old man were enrolled. Two children with cysteine mutations (C52Y, C55Y) had prolonged and frequent fever attacks requiring high cumulative doses of steroids. One child with R92Q mutation and the adult patient with C43A mutation displayed a chronic disease course, with persistent elevation of acute reactants (including SAA), muscular-articular manifestations and daily steroid and NSAID administration. The patient with C52Y mutation was already treated with etanercept that was suspended one year before because of loss of efficacy. Patients were treated with 1 mg/kg/day of Anakinra, subcutaneously.

Results: All TRAPS patients started Anakinra treatment during the active phase of their disease. The mean follow-up was 7.5 months (range 5-13). Mean CRP at T0 was 10.8 mg/dl (5-18), 1.9 mg/dl (0.3-3.9) after 7 days and 0.8 mg/dl (0.3-2) at follow-up. The same behavior was observed for other acute phase reactants (WBC, ESR, SAA). Patients' evaluation of global disease severity (VAS) was 5.8 (1-9.5) at T0, 0.7 (0.3-1) after 7 days and 0 at follow-up. During treatment, no patient presented significant fever episodes. Patients with C52Y, C55Y and R92Q mutations did not need steroid during follow-up. Patient C43A is on 5 mg/day of prednisone (starting dosage 12.5 mg). No major adverse reactions or severe infections were observed.

Conclusions: Continuous treatment with Anakinra is able to effectively control both clinical and laboratory manifestations in severe TRAPS patients.

PP - 131

RHEUMATOLOGIC PRESENTATION OF APECED SYNDROME

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Introduction: The autoimmune polyglandular syndrome type 1, also known as APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), is due to disease-causing mutations in the autoimmune regulator (AIRE) gene. The leading clinical triad is adrenal insufficiency, hypothyroidism and mucocutaneous candidiasis. The syndrome is well known by the endocrinologist, but less so by other pediatric specialities, especially when manifesting differently from the classical triad.

Clinical Cases: (1) A German girl initially presented with recurrent fevers and polyarthritis at 1 year of age, followed by hepatitis (2 years), oral candidiasis, hypothyroidism (3 ½ years), and intestinal malabsorption, hypoparathyroidism and vitiligo (4 years). Stabilization was achieved under azathioprine, antifungal agents and hormone substitution.

(2) An Italian boy initially presented with recurrent fevers and chronic urticaria at a few months of age, was diagnosed with autoimmune hepatitis (w/o autoantibodies) at age 6; oral and esophageal candidiasis was found on gastroscopy for unexplained pernicious anemia. Good response to azathioprine plus low dose corticosteroids, antifungal treatment and parenteral substitution of vitamin B12 was obtained. In both cases, mutations (homozygote and compound heterozygote) were identified in the AIRE gene.

Conclusion: In childhood, the APECED syndrome may present with nonspecific signs and symptoms such as recurrent fevers, arthritis and hepatitis with or without autoantibodies. Oral candidiasis beyond early infancy is seldom recognized as a clue to the correct diagnosis especially when the patient is already under immunosuppressive agents.

PP - 132

RECURRENT PERICARDITIS IN A CHILD WITH HYPER IgD SYNDROME RESPONDING TO ETANERCEPT

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Hyper-IgD and periodic fever syndrome (HIDS) is an autosomal recessive autoinflammatory syndrome caused by mutations in the mevalonate kinase gene (MVK). It is characterized by self-limited recurrent attacks of fever, lymphadenopathy, abdominal pain, arthralgia, and skin rash. Attacks begin in infancy and last approximately 3-7 days.

Treatment of HIDS patients is mainly supportive and very difficult. Favorable experiences with etanercept have been reported. We observed a 12-year-old boy affected by HIDS who was successfully treated with etanercept but developed a recurrent pericarditis.

The boy, born of healthy Italian parents, was diagnosed as having HIDS at the age of 10 years by demonstration of an homozygous missense mutation on exon 11 of the MVK gene. He was also screened for MEFV and TNFRSF1A gene mutations with negative results. A therapy with etanercept at the dosage of 0.4 mg/kg twice weekly was started. Attacks disappeared and no side effects were registered. Two years later, the patient presented fever, precordialgia and orthopnea. Pleural and pericardial effusions were demonstrated. He was started on prednisone 2 mg/kg/day with good clinical and laboratory response. Etanercept was interrupted. Four months later, a relapse occurred. Colchicine 1 mg/day and ibuprofen were added to prednisone. At present, after prednisone tapering, the patient is symptom-free.

In this patient, etanercept was successful in aborting the attacks of HIDS. It is not clear if a possible link between TNF blockade and the pathogenesis of pericarditis exists, although the relapse occurring after etanercept suspension reduces this possibility. Further investigation of this therapy is necessary.

PP - 133

EFFECTS OF NATURAL ISOPRENOID COMPOUNDS ON MEVALONATE PATHWAY INHIBITORS-INDUCED INFLAMMATION

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Mutations in mevalonate kinase gene (MVK) lead to mevalonic kinase deficiency (MKD) - a rare inborn disorder of the biosynthesis of cholesterol and isoprenoids - characterized by a recurrent autoinflammatory syndrome (HIDS, OMIM_ 260920) and, in most severe cases, by psychomotor delay (MA, OMIM_ 610377). It is thought that a deficiency in some isoprenoids or in the prenylation of some proteins accounts both for the inflammatory and the neurological phenotypes. Although the genetic defect has been known for a decade, we still do not know the molecular mechanisms underlying the inflammatory phenotype, and thus we lack an etiologic treatment for MKD. It is intriguing that drugs like aminobisphosphonates (N-BPs) and statins, which are able to inhibit the cholesterol-isoprenoids pathway, could cause undesirable inflammatory reactions, including fever, in humans.

Thus, we decided to use these drugs to set-up an "in vitro" and "in vivo" model for isoprenoids-deficiency related inflammation. Moreover, we evaluated the effects of some natural isoprenoid compounds – geraniol and farnesol – on the inflammatory response in these models, in order to identify new possible targets for an etiologic therapy of the disease.

We observed that N-BP/statin alone - and much more in the presence of bacterial muramyl-dipeptide (MDP) or lipopolysaccharide (LPS) as second inflammatory boost - led to an inflammatory reaction both in cell and in murine model.

Preliminary results about the use of natural isoprenoids show that treatment with geraniol and farnesol had reverted the inflammatory phenotype in both models, suggesting a probably role for these isoprenoid compounds in the treatment of MKD.

PP - 134

PROTRACTED FEBRILE MYALGIA IN CHILDREN AND YOUNG ADULTS WITH FAMILIAL MEDITERRANEAN FEVER (FMF): ANALYSIS OF 20 PATIENTS AND SUGGESTED DIAGNOSTIC CRITERIA

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Background: Protracted febrile myalgia (PFM) is a rare and underdiagnosed dramatic manifestation of FMF.

Aim: To present an analysis of children with PFM, and propose clinical criteria for diagnosis.

Methods: A multicenter retrospective cohort study of children with PFM was performed. Clinical and laboratory data were obtained by medical record review, in addition to a MEDLINE search of all reported cases.

Results: The study group included 15 patients with PFM and 5 case reports. PFM occurred as the presenting sign of FMF in 40%. FMF was diagnosed clinically in all and by genetic analysis in 85%. M694V allelic involvement was noted in 94%. PFM occurred at a mean age of 10±4.4 years and was characterized by severe generalized muscle pain in all patients and fever in 79%. Mean duration to diagnosis was 14.7±7 days. Mean erythrocyte sedimentation rate was 102±24 mm/h; mean C-reactive protein was 16.4±5.7 mg%. Creatine kinase was normal. Treatment included corticosteroids (9 patients) and nonsteroidal anti-inflammatory drugs (NSAIDs) (9 patients) with a symptomatic relief achieved in a mean of 7.25±5 days and 5±4 days, respectively (p=0.33) (mean severity score 2.55 and 2.22, respectively, p=0.4). Symptomatic relief in 2 untreated patients was achieved in a mean of 45.5 days.

Conclusions: Based on our data, we propose diagnostic criteria including: severe disabling myalgia of at least 5 days in a young patient with FMF, associated with fever, elevated levels of inflammatory markers and presence of at least one M694V mutation. Treatment with NSAIDs is as efficacious as with steroids.

PP - 135

THE EVALUATION OF BONE MINERAL DENSITY IN PREPUBERTAL CHILDREN

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Aim: To investigate bone mineral density (BMD) in prepubertal patients with familial Mediterranean fever (FMF) under colchicine therapy and to determine the relationship between bone mass and laboratory and demographic features of the disease.

Patients and Methods: We investigated 220 patients diagnosed as FMF according to Tel-Hashomer criteria, who were followed up regularly from our rheumatology outpatient clinic between April 2005-September 2005. The patients were

investigated in terms of most common mutations (M694V, M680I, V726 A). Age, gender, family history, age at presentation, age at diagnosis, clinical findings, and colchicine treatment initiation time were recorded. The control group consisted of 24 healthy children. L1-L4 lumbar vertebrae BMD were studied with DEXA method. BMD was calculated as g/cm^2. The results were evaluated according to the International Clinical Densitometry Community. BMD was accepted as low in cases of Z scores below -2.

Results: Of 32 patients, 12 (37%) were female and 20 (63%) were male. The mean age was 6.88±1.42 years. The mean age of the control group was 7.1±1.97 years. M694V/N heterozygous mutation was detected in 6 (25%), M694V/M6801 heterozygous mutation in 3 (12.5%), M694V/M694V homozygous mutation in 12 (50%), M694V/V726A heterozygous mutation in 2 (8.33%), and V726A/N heterozygous mutation in 1 (4.17%) of the patients. There was no statistically significant difference in terms of height, weight, body mass index, bone age, Ca, P, and ALP values between patient and control groups. BMD and Z scores were significantly lower in patients with FMF when compared to control group (p 0.001). BMD and Z scores were not correlated with gender, disease duration, body mass index, bone age, Ca, P, ALP, PTH, 25 OH Vit D, or Ca/creatinine ratio in spot urine.

Conclusion: BMD was found to be low in patients with FMF and is significantly lower in patients with delayed diagnosis and treatment. Moreover, colchicine therapy can positively affect BMD.

PP - 136

ANAKINRA IN COLCHICINE RESISTANT FAMILIAL MEDITERRANEAN FEVER

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Colchicine can reduce disease activity and prevent amyloidosis in the vast majority of familial Mediterranean fever (FMF) patients. However, some fail colchicine therapy. The recent implication of IL-1beta in the pathogenesis of FMF prompted us to try anakinra in a 14-year-old FMF patient whose disease was resistant to colchicine (2 mg/day). She had experienced attacks since the age of 2. With age, the attacks became frequent (every 3-10 days), prolonged (12 to 88 hours) and more severe. The episodes consisted of an abruptly rising fever exceeding 40°C accompanied by chills, anorexia, abdominal and retrosternal pain, and arthritis. Blood tests showed elevated inflammatory markers, with further increase during attacks.

After clinical confirmation of therapeutic compliance, patient and parents gave written informed consent for a trial of daily anakinra 100 mg subcutaneous. Colchicine was initially maintained at 2 mg daily.

In the 15 months after initiation of anakinra treatment, fever, abdominal pain and arthralgias did not recur, even after gradually reducing the daily colchicine dose to 1 mg. The only possible side effect of anakinra treatment was an occasional mild urticarial rash on the hands and face, which could be controlled well with oral anti-histamines. ESR improved markedly and CRP normalized completely. Furthermore, there was a reduction in serum IL-1α, IL-1β and IL-8 levels. All other cytokines measured (IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-18, IFN-γ and TNF-α) were either not elevated or did not change upon treatment with anakinra.

This is the first report of a child with colchicine-resistant FMF successfully treated with anakinra. Similar results had been reported in one adult FMF patient. Serious side effects of anakinra are rare. It therefore seems to be a safe agent for treatment of auto-inflammatory disorders. However, increased susceptibility to infections may still pose a real risk and patients obviously need to be monitored closely when anakinra treatment is initiated. We conclude that IL-1 blockade in patients with colchicine-resistant FMF is potentially beneficial. Recently, etanercept was shown to be effective in some colchicine-resistant FMF patients. A prospective trial comparing the two approaches in such patients is warranted.

PP - 137

TONSILLAR EXUDATE IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER: A REVIEW OF FOUR CASES

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Familial Mediterranean fever (FMF) is an autosomal recessive disease (MEFV gene) characterized by recurrent fever and inflammatory serositis. PFAPA syndrome is a periodic fever with adenitis, pharyngitis and aphthous stomatitis. We reviewed the files of 4 patients diagnosed with FMF who presented, at the onset, clinical symptoms similar to PFAPA syndrome rather than to FMF. The diagnosis of FMF was based on typical clinical and laboratory features. Patients included 3 males and 1 female with a mean age at onset of 10.5 months. In the early stage of the disease, the number of attacks per month was higher and their typical attack was characterized by fever > 39 °C with the presence of tonsillar exudate with negative throat cultures, abdominal pain and cervical adenopathy. Leukocytosis and C-reactive protein (CRP) elevation were noted during attacks in all patients. On investigation of MEFV, two compound heterozygosity (M694V-V726A) and one heterozygosity (M680I) were detected. One patient did not present MEFV mutation, but FMF was diagnosed according to Tel Hashomer criteria. All patients responded well to colchicine, and amyloidosis was not documented in any patient. The frequency of attacks slowly increased with disease progression, and clinical profile of attacks changed. In addition to intermittent fever, all patients had abdominal pain, 1 had headache and tonsillar exudate with adenopathy disappearance.

In conclusion, in the early stage of disease, FMF was confused with PFAPA in our patients. Many atypical cases of FMF emerge: we report the tonsillar exudates as an unusual presentation in childhood.

PP - 138

FAMILIAL MEDITERRANEAN FEVER: CLINICAL AND GENETIC CHARACTERIZATION IN A SOUTHERN ITALY POPULATION

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Familial Mediterranean fever (FMF) is an autosomal recessive disease (MEFV gene) characterized by recurrent attacks of fever and inflammation of serosal membranes. The aim of this study was to explore the magnitude of the FMF problem and to describe clinical phenotypic and genotypic profile in a population of Southern Italy (Calabria, Sicily). Twenty-four patients diagnosed as FMF between January 1997 and January 2007 in the Department of Pediatrics, "G. Martino" Hospital, were included. The diagnosis of FMF was based on typical features. The FMF mutations were investigated in all patients.

Result: Of the 24 patients, 10 (41.6%) were females, 14 (58.4%) were males, and the age ranged from 9 months to 52 years. A positive family history for FMF was noted in 9 (37.5%) patients. The mean onset age was 131 months (from 8 months to 30 years). Sixteen patients (66.7%) were symptomatic below the age of 5 years. Abdominal pain was observed in 24 (100%), fever in 22 (91.6%), thoracic pain in 10 (42%) with pleuritis in 2 (8.3%), arthralgias in 6 (25%) and headache in 4 (16.6%). The most frequent mutation was the M680I/M680I. Clinical presentation was different with respect to genotypes. Patients had no chronic renal disease suggestive of amyloidosis.

Conclusion: It was noted that the FMF patients in this study had a broad spectrum of mutation combination, which might reflect the intercultural interactions of ancient ethnic groups that lived in Southern Italy; these mutations were different with respect to clinical presentations.

PP - 139

MOST PATIENTS HAVE AN ATYPICAL PRESENTATION IN FAMILIAL MEDITERRANEAN FEVER

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Familial Mediterranean fever (FMF) classically presents with abdominal pain, fever and arthralgia lasting for up to three days. Hamburg has a large ethnic population with a high prevalence for the FMF trait. The aim of our study was to evaluate the primary clinical presentation of our patients with the diagnosis of FMF. We assumed that a larger proportion of patients do not have the classical symptoms of FMF. We evaluated retrospectively all charts of patients who fulfilled the criteria for FMF and were followed in the last three months in our pediatric rheumatologic center. Data for demographics, symptoms at first presentation, and the results of the molecular biologic examination were assessed. We treated 36 patients with FMF, 23 of them with Turkish origin. The mean age at onset of the first symptoms was 5.04 years (range 0.3-12.1). The mean age at diagnosis of FMF was 7.95 years (2.3-15.5). Twenty-one of the patients had a positive family history for FMF. Eighteen patients had just one symptom of FMF at time of diagnosis of FMF; in 9 cases it was arthritis, in 5 cases fever attacks, in 2 cases abdominal pain, and in 1 case each pleuritis or myalgia. Ten patients presented with two symptoms; 5 patients with abdominal pain and fever attacks, 3 patients with arthralgia and fever attacks, 1 with fever and arthritis and 1 with arthritis and abdominal pain. In 8 cases, the expected presentation of fever, abdominal pain and arthralgia/arthritis occurred. The molecular biologic examination revealed a mutation in 32 cases; in 12 cases a homozygous mutation was present. Only in 8 of the 36 patients were all three of the classical symptoms of FMF present at the time of the diagnosis. It is important to emphasize that if the ethnical background for FMF is present in a patient, even if the patient is monosymptomatic regarding FMF, a high suspicion for FMF is warranted.

PP - 140

BENEFICIAL CLINICAL RESPONSE TO INTRAVENOUSLY ADMINISTERED PAMIDRONATE IN CHILDREN WITH CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS

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Background: Chronic Recurrent Multifocal Osteomyelitis (CRMO), first described in the early 70s, is an aseptic local multifocal inflammation of the long bones and clavicles of children and adolescents, characterized by recurrent episodes of painful bony swellings. Radiographic changes are consistent with osteomyelitis and the lesions are ascribed by some authors as part of the spectrum of the SAPHO syndrome. Other pathologies, such as histiocytosis X, leukemia, neuroblastoma, rhabdomyosarcoma and bacterial osteomyelitis or discitis need to be excluded. Bisphosphonates administered intravenously have been reported to have beneficial effects in adults with chronic sterile osteomyelitis. There are no reports to date on their potential beneficial effects in children with CRMO.

Objectives: To report our preliminary clinical experience with the use of intermittently administered intravenous pamidronate in children with severe CRMO.

Methods: Four children with CRMO were treated with intravenous pamidronate administered daily for three consecutive days at 3 to 4 monthly intervals, at a dose of 0.5 mg/kg (max 15 mg) on day 1 and 1 mg/kg (max 30 mg) on days 2 & 3. Response to treatment was determined by changes in clinical symptoms, particularly pain, and by changes in analgesia medication.

Results: Three girls and one boy, with a median age at diagnosis of 12.3 years (10.5-14.2 years) demonstrated a beneficial clinical response to treatment after even the first course of infusions, with significant relief of pain, increased activity and improved well-being. Analgesia could be tapered and eventually discontinued. We observed no adverse events except for a transient mild acute phase reaction in two of the patients.

Conclusion: Our preliminary data suggest that intermittently administered intravenous pamidronate is associated with a beneficial clinical response and no significant adverse effects in children with severe CRMO. Whether or not the treatment is able to alter the natural history of the inflammatory disorder in the long-term remains to be established.

PP - 141

INFANTILE-ONSET PANNICULITIS WITH UVEITIS AND SYSTEMIC GRANULOMATOSIS: A NEW CLINICOPATHOLOGIC ENTITY

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We hereby report on four children with infantile onset lobular panniculitis, uveitis and systemic granulomatous inflammation. To our knowledge, this is a previously undescribed pediatric condition.

Patients were recruited through the International Registry of Pediatric Granulomatous Arthritis (PGA) established in 2005 to define the clinical spectrum and frequency/penetrance of CARD15 mutations in patients with PGA. Arthritis or systemic granulomatosis with histologically confirmed granulomas was required for inclusion in the Registry.

Clinical manifestations in four children included infantile-onset panniculitis, fever, hepatosp-lenomegaly, arthritis, uveitis and anemia. Histolo-gically, the subcutaneous nodules showed a non-vasculitic non-cytophagic lobular panniculitis. Giant and epithelioid cell granulomas were found in liver (pt 1), synovium (pt 2), lymph node, colon, subcutaneous fat (pt 3), and dermis and lung (pt 4). Primary pancreatic disease, infections, α1-antitrypsin deficiency, autoimmune disease, complement deficiency and hemophagocytosis were excluded. Immunoglobulin levels and neutrophil function were normal. No CARD15 mutations were found.

Despite steroid and cyclosporin treatment, the course was progressive in patient 1 with severe lung involvement and death from respiratory insufficiency at age 14. In patients 2, 3 and 4 the administration of anti-TNF MoAbs allowed better disease control.

We propose infantile onset panniculitis with systemic granulomatosis as a clinicopathologic entity which may be part of the spectrum of pediatric granulomatous inflammatory diseases. The response to anti-TNF MoAbs in three of our patients is of note.

	Patient 1	Patient 2	Patient 3	Patient 4
Age at onset	6 weeks	12 months	1 week	4 months
Painful panniculitis	+	+	+	+
Fever	+	+	+	+
Hepatosplenomegaly	+	+	+	+
Uveitis	panuveitis	panuveitis	anterior uveitis	anterior uveitis
Arthritis	oligoarticular	polyarticular	oligoarticular	polyarticular
Epithelioid cell granulomata	liver	dermis, synovium	lymph node, salivary gland, colonic submucosa, subcutaneous fat	dermis, lung
Treatment	steroids, cyclosporine, IVIG	steroids, MTX, TNF-antagonists	steroids, IVIG, TNF-antagonists	steroids, colchicine, cyclosporine, soluble TNF receptor, thalidomide
Course	respiratory failure and death	response to anti-TNF MoAbs	moderate response to anti-TNF MoAbs	response to anti-TNF Moabs

PP – 142

PATIENT WITH CHRONIC INFANTILE NEUROLOGIC CUTANEOUS ARTICULAR (CINCA) SYNDROME TREATED SUCCESSFULLY WITH ANAKINRA ON AN ALTERNATE-DAY REGIMEN FOR MAINTENANCE

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Introduction: In this report, we describe a patient with CINCA syndrome who is being successfully treated with Anakinra.

Case Report: A 2.5-year-old girl presented with febrile attacks which recurred 1-2 times every month, a persistent macular rash on her face and trunk that had started 15 days after she was born and that increased during febrile attacks, frontal bossing, and left knee arthritis. She had a history of pericarditis when she was 17 months old, and she later started complaining of headaches. She had no family history of consanguinity. Sequencing of the third exon of CIAS1 gene showed that she carries D303N mutation. Following the start of Anakinra 2 mg/kg/day, her rash disappeared within 2 days, and 3 weeks later her acute phase reactants were normal. During treatment she had to stop Anakinra twice, due to upper respiratory infections, and each time the rash reappeared, once with arthritis. In the eighth month of treatment, she started having Anakinra injections every other day. Now, in the eleventh month of treatment, she is still having 2 mg/kg Anakinra injections every other day and she is well except for a few rashes. Her height and weight, which were below 10th percentile, are now at the 50th percentile.

Conclusion: Anakinra was shown to be effective and fast-acting in controlling inflammatory activity and symptoms in a patient with CINCA syndrome. Variability in clinical severity has been known in CIAS1-related autoinflammatory disorders. Efficacy of every-other day Anakinra treatment in this patient may suggest that IL-1 blockade could also be titrated according to the severity of inflammatory findings.

PP - 143

CHRONIC NON-BACTERIAL OSTEOMYELITIS IN CHILDREN

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Objective: Chronic recurrent multifocal osteomyelitis (CRMO) in children is a chronic non-suppurative inflammation involving multiple sites. Clinically, however, there are children affected by chronic non-bacterial osteomyelitis (CNO) who do not experience multiple lesions or a recurrent course. The goal of this study was to characterize the long-term outcome of children with the full spectrum of CNO.

Methods: We followed 30 children diagnosed with CNO for a mean of 5.6 years using a clinical score, multiple imaging approaches and diagnostic biopsy including extensive microbial analysis.

Results: Nine patients had unifocal non-relapsing disease, 3 unifocal lesions with relapses, 9 multifocal lesions without relapses and 9 multifocal lesions with relapses (CRMO). Granulocytes were present significantly more often in CRMO- than in unifocal and nonrecurrent lesions. Pustulosis was more frequent in multifocal cases regardless of recurrence. Mean duration of therapy in 15 children with a single occurrence was 9.2 months. Naproxen treatment was generally effective. Naproxen treatment in 12 patients with relapses lasted 25 months. However, 7 of these were not effectively treated with naproxen alone. Five were treated with oral glucocorticoids for 27 days in addition to naproxen, which induced remission in 4 lasting at least 1.5 years. Longitudinal growth of affected bones was not altered, except for the development of hyperostosis.

Conclusion: CNO is a spectrum of inflammatory conditions, with CRMO being the most severe. The majority of children with CNO have a favorable outcome of disease. Oral glucocorticoids may be necessary in severe recurrent cases. The diagnostic role of MRI is being discussed.

PP - 144

LONG-TERM EFFICACY AND TOLERABILITY OF ANAKINRA IN 4 PATIENTS AFFECTED BY CINCA SYNDROME

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Chronic infantile neurologic cutaneous articular (CINCA) syndrome is a rare autoinflammatory disease in which a mutation of gene CIAS1, involved in regulation of inflammation and in IL1β production, is detected in about 60% of cases.

Effectiveness of IL1-Ra (Anakinra) in CINCA syndrome has been widely described in the last few years, but its long-term tolerability and efficacy are still unknown. In our study, we analyzed the clinical and laboratory course of 4 Italian patients affected by CINCA syndrome treated with daily injections of Anakinra (1 mg/kg/day) for a mean period of 27 (±3) months. The patients, aged 7-22 at the beginning of the therapy, 50% CIAS1 mutated, were all refractory to previous treatments.

Clinical and laboratory remission was achieved after 3 months in all patients, with or without CIAS1 mutation. Some chronic CNS and ocular manifestations also responded to the treatment: papilledema disappeared in 2/2 cases; an improvement of sensorineural hearing loss was documented by audiometry in 1/2 cases; and in 1/1 case, Anakinra induced a regression of chronic uveitis. No flares were observed in all patients during the period of Anakinra daily administration.

The only side effects observed were a local reaction at the site of injection (3/4 patients) and oral aphthosis refractory to treatment (1/4 patients). Withdrawal of treatment or alternative day therapy induced an immediate flare in all patients, promptly reverted by reinitiating therapy.

In summary, our study demonstrates that a long-lasting treatment with Anakinra appears to be safe and highly effective in patients with CINCA syndrome.

PP - 146

A CASE OF FAMILIAL NEUROSENSORIAL IMPAIRMENT WITH VASCULITIS: A NEW PHENOTYPE OF CIAS1 PATHIES?

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We describe an 18-year-old female presenting with fever, persistently increased acute phase reactants, and painful episodic aphthosis since she was three. Urticarial, then ecchymotic painful rash on lower extremities appeared since the age of five; skin biopsy showed leukocytoclastic vasculitis. At age six, celiac disease was diagnosed. Two ischemic episodes occurred at the ages of 7 and 14, respectively, the first characterized by diplopia and ptosis, and the second with gaze palsy and low vision. MRI and SPET showed ischemic lesions. An important familial history of vasculitis with neurosensorial impairment, rash, multiple abortions, celiac disease and migraine/headache, with apparent dominant inheritance, was present. Several hypotheses were evaluated (SLE, Behçet, CADASIL, MELAS, Moyamoya, thrombophilic disorders, multiple sclerosis, Sneddon syndrome). Autoinflammatory disorders were suspected, but, at that time, no specific diagnosis was possible. Recently, a mutation in CIAS1 was found even though clinical features were somehow different from the already described autoinflammatory syndromes caused by CIAS1 mutations (in particular CINCA and Muckle-Wells); thus, a generic diagnosis of CIAS1pathy was made.

Clinical and molecular spectrum of CIAS1pathies is widely heterogeneous. Cutaneous rash, fever with early-onset, and neurologic and neurosensorial involvement have to suggest CIAS1 disorders, in particular if familial history is present. Ischemic events have been described in CINCA, although chronic meningeal inflammation seems to be more frequently the cause of neurosensorial impairment. Association with celiac disease, previously described, may indicate a role of the genetic disorder of inflammation in inducing celiac features.

PP - 147

HYPERIMMUNOGLOBULINEMIA D SYNDROME-CASE REPORT

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Hyperimmunoglobulinemia D syndrome is an autosomal recessive affection included in the hereditary autoinflammatory disorders, associated with recurrent episodes of fever, abdominal distress (pain, vomiting, diarrhea), rash, arthralgias and lymphadenopathy. Laboratory investigations show elevated Ig D > 100 mg/dl and positive inflammatory tests.

This is the case report of a 14-year-old male with a long history of recurrent hospitalizations since 2 years of age for fever, abdominal pain, vomiting, diarrhea, arthralgias, cervical lymphadenopathy, rash and positive inflammatory tests. These symptoms occurred every 2 months.

The causes of periodic fever syndrome in children are reviewed. The diagnosis of hyper-Ig D syndrome was based on elevated serum concentration of Ig D. This case report is presented in view of the diagnostic difficulties and the rarity of the syndrome.

PP - 148

INTERLEUKIN-1 INHIBITION AS A THERAPEUTIC STRATEGY FOR CHILDHOOD AUTOINFLAMMATORY SYNDROMES

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Inhibition of inflammatory reactions mediated by interleukin-1 (IL-1) through human IL-1 receptor antagonist (rA), named anakinra, a recombinant form of the naturally occurring IL-1rA, which acts as a specific blocker of IL-1 signaling, has been proven effective in adult rheumatoid arthritis. Anakinra, administered subcutaneously at a daily dose of 1 mg/kg, can be used to control at least two childhood autoinflammatory syndromes: hyper-IgD syndrome (HIDS) and CINCA syndrome (CINCAs), conditions in which serum IL-1 levels appear strongly related to the clinical picture and its severity.

Case 1: A 7-year-old female with HIDS had a history of recurrent episodes of high fever combined with abdominal pain and inconstant exanthema beginning in the 3rd month of life. Anakinra was administered with no other drug during a febrile attack and continued daily. After 24 hours, the clinical picture changed suddenly with disappearance of fever and other inflammatory signs. Blood tests reflected the clinical improvement 10 days after the first anakinra injection (WBC 9,740/mm^3, N 53.3%, ESR 33, CRP 4.1 mg/l). In a follow-up of 18 months, we observed a reduction in the mean number of febrile attacks per month, of febrile days per each attack and - above all - of febrile days per month (more than 50%) in comparison with the semester before anakinra administration.

Case 2: A 7-year-old male with CINCAs had a history of persistent urticaria, growth failure with knee abnormality, pseudopapilledema, cerebral atrophy, and marked neutrophil leukocytosis starting on the 2nd day of life. Anakinra was administered with no other drug. After the first week, knee mobility improved substantially, while febrile peaks and urticarial rash decreased and disappeared definitely. The laboratory results showed the clean drop in neutrophil leukocyte number (WBC 12,400/mm^3, N 50.4%) in addition to improved inflammatory markers (ESR 6, CRP 6.5 mg/l). Twenty-four months after anakinra introduction, parents and teachers confirmed a psycho-intellectual progress, which was reflected in the central nervous system evaluation with magnetic resonance imaging.

Though further studies appear necessary to verify long-term anakinra efficacy in childhood autoinflammatory syndromes, we have observed in our experience, respectively, a reduction in the overall number of febrile days in HIDS and control of clinical/laboratory manifestations in CINCAs.

PP - 149

A VARIANT MUCKLE-WELLS SYNDROME WITH A NOVEL MUTATION IN CIAS1 GENE RESPONDING TO ANAKINRA

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Muckle-Wells syndrome (MWS) is a subset of autoinflammatory diseases. It is characterized by recurrent inflammatory crises associated with fever, abdominal pain, persistent urticaria, arthralgia, sensorineural deafness and possible development of multiorgan amyloid A protein (AA) type amyloidosis. Mutations in the CIAS1 gene have been reported in MWS. Interleukin 1B (IL 1B) probably plays a major role in the pathophysiology of the disease, and IL 1B blockade may be therapeutic in this syndrome.

We report here a Turkish child with MWS treated with anakinra. A novel mutation (I480F) was identified in exon 3 of the CIAS1 gene in this patient. The resolution of inflammatory symptoms, normalization of serological values and improvement in hearing was noted with anakinra treatment. This is the first case report on MWS treated with anakinra from Turkey.

PP - 150

RECURRENT REACTIVE ARTHRITIS AS UNUSUAL PRESENTATION OF HIDS (HYPER IgD SYNDROME)

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Background: HIDS is an autosomal recessive disease characterized by recurrent episodes of fever, lymphadenitis, and abdominal pain with raised IgD levels and caused by a mild deficiency of mevalonate kinase (MVK). Herein we re port a case of HIDS with recurrent episodes of arthritis as the only symptoms of the disease.

Case History: A 4.5-year-old girl presented with recurrent joint swelling, pain and limitation of movement since the age of 3 years. Each episode followed upper airways viral infections. On physical examination, she had painful arthritis on left knee, left shoulder and right 2nd and 3rd MCPs. Lab tests showed ESR 79 mm/h, CRP 124 mg/L, WBC 11320/mm^3, Hb 10 g/dl, and Plts 381000/mm^3. Rheumatoid factor, ANA, serology for CMV, Parvovirus B19, EBV, adenovirus, and Coxsackievirus were negative. IgD levels were very high (2560 mg/L). Arthritis resolved over 15 days on naproxen. Analysis of MVK mutations allowed identification of two heterozygous missense changes: the c.748G>A in exon 7, leading to V250I, and the c.1006G>A in exon 9, leading to G336S. Each of these mutations had already been observed separately in two Italian patients affected with MVK deficiency (MKD).

PP - 151

PROTRACTED FEBRILE MYALGIA: CASE REPORT

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A 12-year-old girl was admitted to the pediatrics clinic with fever and severe myalgia in upper and lower extremities lasting 10 days. We describe a case of protracted febrile myalgia without diagnosis of familial Mediterranean fever (FMF). Her genetic diagnosis was homozygous for M694V mutation. We emphasize that protracted febrile myalgia in some cases of FMF could be the first symptom during childhood.

PP - 152

A FATAL TURKISH CASE OF CINCA-NOMID SYNDROME DUE TO THE NOVEL VAL-351-LEU CIAS1 GENE MUTATION

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Chronic infantile neurologic, cutaneous, articular (CINCA) syndrome is a severe inflammatory disease associated with mutations in CIAS1. In this report, we describe a Turkish patient afflicted by CINCA-NOMID syndrome. CIAS1 genetic analyses revealed the presence of the novel and de novo missense Val-351-Leu (V351L) in exon 3 as responsible for the disease. Our patient had some interesting features, such as bilateral symmetric calcifications on globi pallidi, which has not been previously reported in CINCA-NOMID patients, and the presence of secondary AA amyloidosis, despite both his young age and colchicine treatment.

CINCA syndrome is seen rarely in our country and to the best of our knowledge, this is first Turkish patient reported.

PP - 153

CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS (CRMO) IN 12 HUNGARIAN CHILDREN

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Background: Chronic recurrent multifocal osteomyelitis is a rare chronic inflammatory disorder with multiple radiographically confirmed osteomyelitic changes in absence of pathogens, autoantibodies or antigen specific T cells. It may manifest only as multifocal bone lesions but is frequently associated with other inflammatory conditions. The histopathologic confirmation is relevant for the diagnosis. Because of the unique clinical features of the patients and the recently elucidated genetic evidence (the susceptible gene is located on chromosome 18q21.3-18q22), it was added to the autoinflammatory syndromes.

Methods: (Case reports) In our retrospective analysis of 12 Caucasian patients (7 girls, 5 boys) at a mean of 12 years after diagnosis, the onset of the disease was at a median 7.5 years of age (range: 1-16y). Three girls had only bone lesions; synovitis was present in 6, and psoriasis in 2. The most affected regions were the metaphyses of the tubular bones and vertebral bodies in 7 and 5 patients, respectively; 3 epiphyseal involvements were seen in triplets. Only 2 children had symmetric lesions, and 5 had more than one lesion per bone. Three patients had vertebra plana, and 1 14-year-old girl had consequent neurological dysfunction. Ulnar overgrowth was present in 2 and sacroiliitis in 3 children. The histopathological examination of 9 patients showed reparative changes in bones: lymphocytes, plasma cells, histiocytes and a few granulocytes.

Results: CRMO is considered to be a self–limited process, but the treatment is controversial. We treated 10 patients with steroids and methotrexate successfully. The genetic determination is in progress, which may help us to understand more about the clinical outcome of CRMO.

PP - 154

THE RELATIONSHIP BETWEEN DISEASE SEVERITY SCORE AND GENETIC MUTATIONS IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Aim: To investigate distribution of genetic mutations among pediatric-aged patients with familial Mediterranean fever and to determine the effects of these mutations in clinical progress and development of complications.

Patients and Methods: We investigated 192 Turkish children (106 boys, 86 girls), diagnosed as FMF according to Tel-Hashomer criteria, who were followed up regularly from our rheumatology outpatient clinic between 1999 and 2005. Disease severity scores (early onset of symptoms, frequency and severity of joint involvement, existence of erysipelas-like erythema and the dose of colchicine needed to control the symptoms) were calculated according to defined criteria. The patients were investigated in terms of the three most common genetic mutations (M694V, M6801, V726A). The control group consisted of 70 healthy children.

Results: The mean age of the cases was 11.34±4.29 years. 96.87% had abdominal pain, 80.72% had fever, 62.5% had joint involvement, 34.89% had chest pain and 40.8% had myalgia. The mean value of disease severity score was 05±2.1. M694V homozygous mutation was the most commonly encountered mutation (32.3%). No mutations could be defined in 28.1% of the cases. The mean age at disease onset was significantly lower in the M694V homozygous and heterozygous group, when compared to the group in which no mutation could be defined ($p<0.05$). There was no statistically significant

difference in terms of disease severity scores between M694V homozygous and heterozygous group (p>0.05). However, when compared to the group in which no mutation was detected, disease severity score was significantly higher in the M964V homozygous group (p=0.0001) and M694V heterozygous group (p=0.048). The frequency of arthritis and erysipelas-like erythema was also significantly higher in the M694V homozygous group when compared to others (p<0.05).

Conclusion: M964V mutation was found to be related with earlier onset of disease, more severe disease and development of arthritis and erysipelas-like erythema.

PP - 155

FAMILIAL MEDITERRANEAN FEVER AND MULTIPLE SCLEROSIS: FIRST CASE REPORT IN ITALY

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The association between familial Mediterranean fever (FMF) and some vasculitides such as nodose polyarthritis (NAP), Schönlein-Henoch syndrome (SHS) and Behçet's disease (BD) is known, but there have been few associations made between FMF and multiple sclerosis (MS).

The first case in Italy of an association between FMF and MS is described herein: L.M. is a 24-year-old woman who started to manifest recurrent episodes of fever with abdominal pain at the age of 13. The episodes lasted 3-4 days, 6-7 times. She was hospitalized several times and her appendix removed was removed. In November 2005, FMF was considered, and a genetic test showed the presence of same on the MEFV gene, in a composed heterozygosis, of the mutations M680I and V726A. She was therefore administered therapy with colchicines (1 mg/day), thus resolving symptomatology. In February 2006, an alteration in sensitivity occurred, together with a lack of strength in the right arm, and an electric shock-like sensation when bending her head forward (Lhermitte's sign). These symptoms gradually disappeared over a period of 20 days. In October 2006, an altered sensitivity was observed in the left leg. The presence of numerous demyelinating lesions shown by encephalic MRI and cervical rachis led to an MS diagnosis, based on McDonald's criteria.

In conclusion, owing to the low number of reports on the subject, it is not currently possible to establish whether a correlation between the two pathologies exists, or if it is a mere coincidence. The only elements in common are recurrence and inflammation.

PP - 156

GROWTH IN CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER: EFFECTS OF ATTACK FREQUENCY AND COLCHICINE TREATMENT

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There are few studies evaluating the growth of children with familial Mediterranean fever (FMF). While one study denotes that growth of these children does not differ from healthy children, another study concludes that colchicine treatment improves height z-score. We evaluated the effects of attack frequency and colchicine treatment on height, weight and body mass index (BMI) in children with FMF.

Hospital records of 83 children with FMF (M/F: 41/42, mean age at diagnosis 10.6±4.8 years) were evaluated retrospectively. Age at diagnosis, follow-up period, attack frequency before and after treatment, height SDS, weight SDS and BMI of 33 children (M/F: 19/14) diagnosed during the prepubertal period and followed up at least 6 months were recorded.

Age at diagnosis and follow-up period were 85.3±30.8 (12-144) and 46.2±39.8 (6-174) months, respectively. While attack frequency was significantly different before and after treatment (7.2±5.3 vs 1.3±1.6 per year, p=0.000), height SDS (0.20±1.10 vs 0.19±1.19, p=0.743) and weight SDS (-0.07±1.18 vs -0.02±1.11, p=0.561) were not

different. However, BMI increased significantly after treatment (16.2±2.6 vs 17.3±3.1, p=0.035).

These results indicate that colchicine treatment with a mean duration of four years does not adversely affect height and weight SDS. On the other hand, increase in BMI might be considered as a positive effect of colchicine treatment on anthropometric development.

PP - 157

PROTEINURIA INCIDENCE IN CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER

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Proteinuria in familial Mediterranean fever (FMF) may be due to amyloidosis, non-amyloid renal pathologies or acute phase response during the attacks. Two-thirds of patients with FMF have persistent inflammation in between attacks. In this study, we evaluated the incidence and severity of proteinuria before and after colchicine treatment as well as during the attacks in children with FMF.

Hospital records of 83 children with FMF (M/F: 41/42, mean age at diagnosis 10.6±4.8 years) were evaluated retrospectively. Proteinuria was present in 3 of 51 patients (5.6%) with recorded urinalysis including 1 patient with FSGS. Proteinuria was determined in 8 of 61 children (13.1%) during follow-up. When the 2 patients with proteinuria at the onset with long-term follow-up were included, the rate of proteinuria increased to 10/61 (16.4%). When we exclude the patient with amyloidosis (proteinuria level 259 mg/m^2/h), the rest had mild proteinuria (6.1±2.2 mg/m^2/h). Mean yearly attack numbers were 10.3±6.5 vs 7.4±4.4 (p=0.233) and 2.6±3.2 vs 1.2±1.6 (p=0.211) before and after colchicine treatment, respectively. The age at diagnosis was also not different in those with and without proteinuria (8.9±3.8 vs 10.7±4.9 respectively, p=0.374). On the other hand, among the 4 patients presenting with a FMF attack, 2 (50%) had proteinuria.

These results indicate that proteinuria rate might be increased as a reflection of acute phase response during FMF attacks. On the other hand, the considerably high rate of proteinuria (13%) during the attack-free periods could be regarded as an indicator of subclinical inflammation.

PP - 158

IS THERE AN ASSOCIATION BETWEEN FAMILIAL MEDITERRANEAN FEVER AND CELIAC DISEASE?

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Background: Based on the fact that some chronic inflammatory diseases were found to be associated with familial Mediterranean fever (FMF), we have investigated whether there could also be any relation between celiac disease (CD) and FMF.

Methods: The study was composed of two parts. In the first, the presence of CD in 50 patients (30F, 20M; mean age: 12.9±3.8) with FMF was investigated. Clinical characteristics of the patients were noted. Serum IgA level and antigliadin antibody (AGA) IgA, IgG, and anti-endomysial antibody (EMA) IgA antibodies were tested, and intestinal biopsy was done in suspicious cases. In the second part, 15 patients with CD (9 F, 6M; mean age: 13.5±3.3 years) were evaluated for the presence of FMF, and MEFV gene mutation analysis was performed in all of them. Six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the MEFV gene were studied.

Results: Part I: Three patients had diarrhea suggesting CD, four patients had low IgA levels, one had positive AGA IgA, six had AGA IgG and one had EMA IgA. Intestinal biopsy was performed in only one patient and was normal. Overall, CD was detected in none of the 50 FMF patients. Part II: None of the patients with CD had complaints

consistent with FMF. Four of the 15 patients (26.7%) were found to carry MEFV mutations. Three of them had heterozygous p.E148Q mutation and one had heterozygous p.M680I mutation.

Conclusion: None of the FMF patients had concomitant CD. Furthermore, none of the CD patients were diagnosed to have concurrent FMF. Patients with CD had MEFV mutation frequency similar to that of the normal population in Turkey. Therefore, in light of our study results, no relation between CD and FMF was observed.

PP - 159

A GENE MUTATION FREQUENCY IN FMF PATIENTS AND DECREASED RESPONSE TO COLCHICINE THERAPY IN M694V CARRIERS

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Objective: Above 90 MEFV mutations have been identified in FMF, and the various mutations were shown to have different clinical, diagnostic, prognostic and therapeutic implications. The aim of study was to analyze MEFV gene mutations and response to therapy.

Materials: This study included 236 FMF children. The six MEFV mutations (M694V, M694I, M680I, V726A, E148Q and R761H) were investigated in all patients.

Methods: Mutation identification was performed according to described PCR and restriction-enzyme digestion or amplification mutation system techniques.

Results: The most frequent mutation in the study group was the M694V. Seventy-two (30.5%) of 236 FMF patients were homozygotes, 44 (18.6%) were compound heterozygotes, 88 (27.3%) had only a single mutation, and no mutation was identified 32 (13.6%) patients.

For evaluation of the mutation-specific difference in the phenotypic expression of the disease and response to therapy, 236 patients were divided into three groups according to the presence of M694V mutation on both alleles (homozygotes), on only one allele (heterozygotes), and on none of the alleles. Partial response was determined in 33 (52.4%), 34 (41.5%), and 18 (19.8%) of patients with M694V/M694V, M694V/Other and Other/Other, respectively, whereas for complete response, these values were 24 (38.1%), 43 (52.4%), and 62 (68.1%), respectively. The response to colchicine therapy was lower in the M694V homozygous patients when compared with the other groups ($p=0.001$). No differences were found between these groups with respect to the other phenotypic features.

Conclusion: Previous studies have demonstrated that mutation in M694V, especially homozygosity of M694V, was associated with severity of disease and the necessity of high-dose colchicine to control attacks. Our results also support that homozygosity of M694V is associated with lower response to colchicine therapy.

PP - 160

MACROPHAGE ACTIVATION SYNDROME - FAVORABLE OUTCOME WITH PULSE STEROIDS

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Macrophage activation syndrome (MAS) is a rare, potentially fatal clinical syndrome caused by activation and uncontrolled proliferation of T lymphocytes and macrophages with overproduction of cytokines.

Case report: We describe a 19-year-old female with systemic onset juvenile idiopathic arthritis (soJIA) who developed MAS. She was in remission for one year and relapsed two weeks before admission in a regional hospital. She presented with non-remitting fever, splenomegaly, lymphadenopathy, arthralgia, and myalgia. Several antibiotics, NSAID, MTX and sulfasalazine were introduced but high temperature and malaise continued and she progressively deteriorated. Laboratory findings indicated high suspicion on MAS: drop down of ESR, profound depression of WBC and PLT, Hb, hyperferritinemia, hypertriglyceridemia, hypoproteinemia, hypoalbuminemia, raised liver cell enzymes and abnormalities of clotting profile. She developed overt clinical signs of DIC. Bone marrow examination confirmed diagnosis of MAS: numerous well differentiated macrophages phagocytosing hematopoietic cells. We raised GC dosage, introduced two weeks before in the regional hospital, and gave her 1 g i.v. three consecutive days with platelets substitution. She improved clinically thereafter and GC dosage was reduced. Laboratory analyses gradually returned to normal. On the last visit, she was without any signs of disease and all laboratory examinations were within range.

Conclusion: MAS is an uncommon life-threatening condition triggered sometimes by soJIA. MAS appears to be more frequent than is recognized. Early recognition and introduction of high dose GC are of essential importance for favorable outcome.

PP - 161

HEREDITARY SYSTEMIC AUTOINFLAMMATORY DISORDERS: EXPERIENCE FROM A TERTIARY CENTER IN SPAIN

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Introduction: Hereditary systemic auto-inflammatory disorders (HSAD) are a group of rare disorders with recurrent attacks of inflammation.

Objective: To describe 9 patients with genetically confirmed HSAD.

Methods: Retrospective chart review.

Results: Genetic testing was performed in 29 children. Mutations were detected in 31%. The main characteristics are displayed below.

Conclusion: Recent advances in genetic testing facilitate confirmation of HSAD, allowing specific treatment strategies and genetic counselling. An important number of cases with autoinflammatory diseases failed to reveal mutations.

PP - 162

SYSTEMIC AUTOINFLAMMATORY DISEASES: EXPERIENCE IN PATIENTS WITH POSITIVE MUTATIONAL ANALYSIS

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Introduction: Systemic autoinflammatory diseases are a heterogeneous group of genetically determined diseases characterized by seemingly unprovoked inflammation, in the absence of autoimmune or infective causes.

In recent years, some mutations have been identified associated with: familial Mediterranean fever (FMF), hyper-IgD syndrome (HIDS), tumor necrosis factor receptor superfamily 1A-associated periodic syndrome (TRAPS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome (CINCA).

Objective: To describe clinical findings and mutations found in patients with systemic autoinflammatory diseases.

Methods: We made a revision of clinic histories from patients with positive genetic studies and disease. Mutational analysis was carried out in Barcelona's Clinic Hospital (Spain) and study requests were made in our center.

Results: The genetic study was done in 30 patients. Ten cases (30%) presented mutations.

Table 10 patients with mutations and disease.

Conclusion: Progress in PFS knowledge allows classification of the patients, evaluation of different treatments and opportunity to offer genetic advice.

PP - 163

PFAPA SYNDROME REGISTRY: CLINICAL DESCRIPTION AND GENETIC TESTING

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Introduction: PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome is defined by criteria based on unspecific symptoms after the exclusion of other fever syndromes.

Aim: To better describe the clinical and laboratory features, and follow a cohort of PFAPA patients.

Methods: PFAPA patients were included in an international web-based registry by completing a questionnaire with demographic and clinical data, laboratory values and treatment. **Results:** We included 82 PFAPA patients (sex ratio: 1/0.78, median age at onset: 2.1 years). The most prevalent clinical manifestations were pharyngitis (91%), adenitis (86%) and aphthous stomatitis (69%). 59% of the patients presented all 3 clinical features ("complete PFAPA"), and 77% presented additional symptoms: gastrointestinal 68%, osteo-articular 41%, skin rash 20%, splenomegaly 7% and genital aphthosis 5%. Patients with complete PFAPA had a higher rate of aphthae and additional symptoms (gastrointestinal, osteo-articular, genital aphthae). 44 patients had a negative genetic testing; one patient was heterozygote for the MEFV gene.

Conclusion: Our study shows that PFAPA may present with many different and unspecific clinical manifestations and important variations between the affected patients. This heterogeneity of the clinical presentation is responsible for the long delay to diagnosis, which is more than double the age at disease-onset. In about half of our patients, the exclusion of other periodic fever syndromes was done using clinical criteria and in 56% by genetic testing. With a better clinical definition of this syndrome, the usefulness of genetic testing may be further evaluated.

BASIC:

• Autoimmune diseases: Pathogenesis

PP - 165

IL-17 PRODUCING CELLS ARE ENRICHED IN JUVENILE IDIOPATHIC ARTHRITIS (JIA) SYNOVIAL FLUID BUT ARE RECIPROCAL TO REGULATORY T CELL (TREG) NUMBERS

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Introduction: The prevailing model of autoimmune pathology in JIA has had a central role for interferon gamma (IFNγ) secreting T cells within the joint. However, recent data have demonstrated a new subset of T cells, Th17, that are critical to produce arthritis in animal models, though their role in humans is unclear.

Methods: Peripheral blood (PBMC) and synovial fluid mononuclear cell (SFMC) samples from 18 JIA patients (3 polyarthritis, 2 systemic, 13 oligoarthritis) and 5 healthy controls (PBMC) were analyzed for IL-17 and Foxp3 expression. SFMC samples were depleted of CD25+ cells, and proliferation to anti-CD3 and PHA was assessed using CFSE with intracellular cytokine staining for IL-17 also performed.

Results: IL-17+ T cells are enriched in SFMC, 1.9% of CD4+ T cells vs 0.57% and 0.48% in JIA and adult healthy control PBMC, respectively. The frequency of IL-17 cells in the joint showed subtype-specific associations. Foxp3+ cells were inversely related to the frequency of IL-17+ T cells but not IFNγ+ cells ($r=-0.737$, $p=0.01$). Depletion of CD25+ cells led to increased proliferation of IL-17+ cells in response to mitogens, and this was reversed by addition of CD25+ cells.

Conclusions: We have demonstrated that Th17 cells are enriched within the joints of children with JIA. Remarkably, Th17 numbers are inversely related to Treg, but only within synovial fluid. We are investigating the possibility that the link between enhanced Treg numbers and a milder form of JIA may be a result of Treg suppression of Th17 cells.

PP - 166

CHITOTRIOSIDASE ACTIVITY IN JUVENILE SARCOIDOSIS

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Background: Sarcoidosis is an inflammatory disorder of unknown etiology identifiable by the formation of confluent noncaseating granulomas. It is characterized by lymphocyte and macrophage activation and migration into involved organs. Chitotriosidase belongs to the chitinase protein family and is secreted by activated macrophages. The chitinases are able to catalyze the hydrolysis of chitin or chitin-like substrates such as 4-methylumbelliferyl chitotrioside.

Methods: Chitotriosidase activity was determined using the substrate 4-methylumbelliferylb-DNN'N''-triacetylchitotriosiose (MUbGlc-Nac, SIGMA Chemical Co). The substrate was incubated with the serum in a citrate/phosphate buffer. The reaction was stopped by adding glycine buffer. The fluorescence of 4-methylumbelliferone was evaluated by fluorimeter at excitation 365 nm and emission 430 nm.

Results: We report about chitotriosidase measurements in patients with juvenile sarcoidosis. They presented a serum chitotriosidase level up to 1658 nmol/h/ml at disease onset before therapy. Erythrocyte sedimentation rate (ESR) and angiotensin converting enzyme (ACE) were elevated. Under medication, clinical activity improved, and ESR and ACE normalized. The chitotriosidase levels were below 700 nmol/h/ml. The chitotriosidase level in normal healthy donors was < 500 nmol/h/ml.

Conclusion: Serum chitotriosidase levels could be a marker for disease activity in sarcoidosis. Chitotriosidase might represent the collaboration of macrophages in the pathogenesis of sarcoidosis.

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PP - 167

CHITOTRIOSIDASE ACTIVITY IN JUVENILE IDIOPATHIC ARTHRITIS

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Background: Juvenile idiopathic arthritis (JIA) is an inflammatory joint disease of unknown etiology. The pathogenesis is driven by T and B-cells. The role of macrophages remains unclear. Chitotriosidase belongs to the chitinase protein family and is secreted by activated macrophages. The chitinases are able to catalyze the hydrolysis of chitin or chitin-like substrates such as 4-methylumbelliferyl chitotrioside.

Methods: Chitotriosidase activity was determined using the substrate 4-methylumbelliferylb-DNN'N''-triacetylchitotriosiose (MUbGlc-Nac, SIGMA Chemical Co). The substrate was incubated with the serum in a citrate/phosphate buffer. The reaction was stopped by adding glycine buffer. The fluorescence of 4-methylumbelliferone was evaluated by fluorimeter at excitation 365 nm and emission 430 nm.

Results: We report about chitotriosidase measurements in patients with JIA. The chitotriosidase level in synovial fluid was up to 2000 nmol/h/ml at disease onset before therapy. The level in sera was below 600 nmol/h/ml.

Conclusion: Serum chitotriosidase levels could represent the activity of macrophages in the synovial fluid in JIA. Chitotriosidase represents the collaboration of macrophages in JIA.

References: Renkema GH, Boot RG, Muijsers AO, Donker-Koopman WE, Aerts JM (1995) Purification and characterization of human chitotriosidase, a novel member of the chitinase family of proteins. J Biol Chem 270 (5): 2198-2202.

Michelakakis H, Dimitriou E, Labadaridis I (2004) The expanding spectrum of disorders with elevated plasma chitotriosidase activity: an update. J Inherit Metab Dis 27(5):705-706.

PP - 168

FAS AND BCL-2 EXPRESSION ON PERIPHERAL MONOCYTES FROM JUVENILE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE)

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Introduction: JSLE patients have high expression of Fas and Bcl-2 proteins on peripheral lymphocytes. Monocyte functions are not fully characterized in lupus, although some evidences suggest that these cells are involved not only in tissue damage, but also in humoral abnormalities. Furthermore, the induction of T cell apoptosis is regulated in part by monocytes.

Objective: To evaluate the expression of Fas and Bcl-2 proteins on CD14 monocytes from patients with JSLE.

Methods: Forty-three patients with JSLE and 35 sex- and age-matched healthy volunteers were studied. Subjects with suspicion of any infection were excluded. Disease activity was determined using SLEDAI score and serum levels of anti-dsDNA (ELISA). Monocytes were isolated from fresh blood and stained with CD14 PE-labeled moAb and FITC-labeled Fas and Bcl-2 molecules. Mean percentages of Fas+CD14+ or Bcl-2+CD14+ among CD14 cells were determined by flow cytometry. Statistical analysis was done using nonparametric Kruskal-

Wallis test and Spearman's rank. P values ≤ 0.05 were considered significant.

Results: Mean percentages of monocytes expressing Fas membrane protein and cytoplasmic Bcl-2 protein were significantly lower in JSLE patients compared to healthy controls (93.6 ± 6.9 vs 96.7 ± 2.5%, p=0.01; 25.2 ± 18.2 vs 34.5 ± 16.6, p=0.006, respectively). There was a statistically significant inverse correlation between percentage of CD14+ cells positive for Fas antigen and SLEDAI score (r= -0.55, p=0.01) and anti-dsDNA antibodies (r= -0.37, p=0.02).

Conclusion: The lower expression of Fas and Bcl-2 proteins on JSLE monocytes may indicate altered apoptosis process on these cells and a possible role in lupus etiopathogenesis.

PP - 169

C1q-DEFICIENCY IS ASSOCIATED WITH IMPAIRED PHAGOCYTOSIS: A CASE REPORT

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We report the case of a 4-year-old Turkish female with recurrent erythematous skin lesions, mucocutaneous candida infections, hepatitis, recurrent bronchopneumonias and hemiparalysis diagnosed as selective complete C1q-deficiency. The clinical picture of C1q-deficiency consists of SLE-like symptoms and recurrent bacterial or monilial infections. Deficiency of the defense collagen C1q is associated with autoimmunity due to inefficient clearance of apoptotic cells. During immunosuppressive, antimycotic and antibiotic treatment, most symptoms of the patient improved but did not disappear. Further laboratory evaluation revealed clearly impaired phagocytic activity against *E. coli* in granulocytes and monocytes while respiratory burst reaction was normal. Substitution of plasma restored ability of phagocytosis *in vitro*. Here, we show that impaired phagocytosis due to lacking opsonization through C1q is a clinical hallmark in C1q-deficiency, explaining the propensity for recurrent infections and supporting the hypothesis of the molecular mechanisms regarding apoptotic debris-driven autoimmunity.

PP - 170

THE ROLE OF REGULATORY T CELLS IN DISEASE REMISSION OF PROTEOGLYCAN-INDUCED ARTHRITIS BY AUTOLOGOUS BONE MARROW TRANSPLANTATION

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Introduction: Autologous bone marrow transplantation (aBMT) can induce drug-free disease remission in severely ill juvenile idiopathic arthritis (JIA) patients, but relapses often occur in time. We turned to proteoglycan-induced arthritis (PGIA), a chronic relapsing remitting arthritis model, to explore whether regulatory T cells (Tregs) play a role in tolerance induction after aBMT. Furthermore, we investigated the possibility of expanding Tregs *in vitro* for therapeutic use.

Methods: Arthritis was induced in balb/c mice by two i.p. injections of human proteoglycan in DDA. On day 39, recipient mice were conditioned by 7.5 Gy irradiation and received BM from: 1) healthy donor, 2) sick syngeneic donor, 3) T cell depleted BM from sick donor. Sick untreated mice were used as controls. On a weekly basis, repopulation of CD4+CD25+ Tregs was assessed in peripheral blood by FACS staining. For the *in vitro* expansion of Tregs, CD4+CD25+ was stimulated with a TLR2 ligand, anti CD3 and IL-2.The

functionality of the expanded Tregs was tested in a suppression assay.

Results: Conditioning followed by aBMT led to rapid decrease of arthritis. Interestingly, best long-term results were achieved with BM, containing T cells, of sick donors. A relative increase in CD4+CD25+ was observed shortly after aBMT, corresponding with clinical improvement. Furthermore, Tregs were expanded successfully and suppressed proliferation of responder T cells.

Discussion: PGIA provides an interesting model for unraveling the mechanism of disease remission by aBMT. Tregs may be involved and are now being tested as a therapeutic tool for the enhancement and maintenance of disease remission.

PP - 171

FAMILIAL ANTIPHOSPHOLIPID SYNDROME: INFLUENCE OF A PRO-INFLAMMATORY GENOTYPE AS A RISK FACTOR FOR CLINICAL MANIFESTATIONS

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A 12-year-old girl was referred to our unit because of low back pain and macroscopic hematuria. Further work-up revealed a renal vein thrombosis, and thrombophilia tests led to the diagnosis of primary antiphospholipid syndrome, with the presence of anti-β2GPI antibodies. During follow-up, she presented an acute myositis with arthritis, with a good outcome under corticotherapy and hydroxychloroquine. Thereafter, she presented a new thrombosis of the sural vein despite anticoagulation with warfarin. At 3 years since diagnosis, her renal function is normal and she is clinically asymptomatic, under the same treatment. No new features of systemic lupus erythematous (SLE) or other connective tissue diseases have appeared.

The presence of headaches in the past medical history of the proband and in two siblings led us to investigate all family members (mother, who had a spontaneous abortion, father, and 10 siblings). Interestingly, 6 other cases out of 12 had positive antiβ2-GPI antibodies (3 at medium-high titer). A study of cytokine (*IL1b, TNFa, TGFb1, IL6, IL10, IFN*g) gene polymorphisms and Toll-like receptor 4 (TLR-4) gene polymorphism was performed in all family members by allele specific polymerase chain reaction.

Among aPL-positive subjects, the presence of the wild type TLR-4 gene and of cytokine polymorphisms associated with a high pro-inflammatory response (IL1b +3954 C/T) was found only in the index case.

This case report supports the notion that inflammatory processes might represent second hits able to trigger aPL-associated thrombotic events, as well as the previously published link between TLR-4 and the same aPL-mediated effects.

PP - 172

DEFECTIVE T CELL REGULATION IN POLY-ARTICULAR JUVENILE IDIOPATHIC ARTHRITIS IS NOT RESTORED BY ETANERCEPT-TREATMENT

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Introduction: Anti-TNFalpha treatment has become a leading therapy in rheumatoid and juvenile idiopathic arthritis (JIA) patients. Infliximab seems effective in adult rheumatoid arthritis in part by modulation of defective regulatory T cells (T_{reg}). In children, etanercept is clinically very effective, although arthritis tends to relapse immediately after etanercept is stopped. We examined the effect of etanercept on (induced) regulatory T_{reg} in JIA.

Methods: Blood of 15 patients with poly-articular JIA was obtained before and after 3 months of etanercept treatment. Frequency and characteristics of T_{reg} were analyzed by flow cytometry and PCR. Function of T_{reg} was evaluated in suppression assays. Responses to human heat shock protein 60 (HSP60) were studied in proliferation assays and by determining cytokine profiles in supernatants. Direct effects of etanercept on T_{reg} were studied in incubation experiments.

Results: Although etanercept significantly increased the frequency of CD4+CD25^{bright} T cells after 3 months of therapy, the frequency of Foxp3+CD4+ T_{reg} was unaffected. Expression of GITR, CTLA-4, CCR4 on T_{reg} did not change during treatment. We observed diminished suppression of proliferation by T_{reg} in suppression assays of patients compared to healthy controls. This was not normalized after etanercept treatment (n=5). Proliferative responses to human HSP60 significantly decreased after etanercept. The quality of the self HSP60 response remained rather pro-inflammatory.

Conclusions: We found indications of disturbed T cell regulation in polyarticular JIA. The clinical benefit of etanercept seems not the result of effects on (induced) T_{reg} in JIA. Our results indicate that etanercept downregulates T cell responses to auto-antigens and may also downregulate other effector cells.

	FMF	Granulomatous arthritis	TRAPS	MWS	HIDS
Patients (n)	4	2	1	1	1
M/F	2/2	1/1	0/1	0/1	0/1
Age onset (y)	2.85 (0.4-4.2)	0.6 (0.4-0.9)	14.7	11	0.1
Evolution (y)	5.5 (3.7-10.8)	16.8 (11.8-22)	1.7	4.7	7
Basic data (n)	Fever (4)	Arthritis (2)			Fever
	Arthritis (4)	Uveitis (2)			Adenitis
	Serositis (3)	Cutaneous (2)	Fever	Fever	Splenomegaly
	Cutaneous (3)	Granulomas (2)	Adenitis	Urticaria	Diarrhea
Genes	MEFV	NOD2	TNFRSF1A	CIAS1	MVK
Mutations (n)	E148Q (2)				
	P180R (1)	C495Y (1)			
	I591T (1)	R334Q (1)	R92Q	R488K	V377I/I268T
Therapy	Colchicine (4)	Steroids (2) Methotrexate (2) Adalimumab (1)	Steroids	NSAIDs	Steroids Cytotoxic drugs
Outcome (n)	Good (2)				
	Partial (1)	Bad (1)			
	Unknown (1)	Partial (1)	Good	Good	Multiorgan failure

PP - 173

MESENCHYMAL STEM CELLS: POTENTIAL USE IN AN ANIMAL MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS NZB/NZW F1

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Human bone marrow mesenchymal stem cells (MSC) are self-renewing multipotent cells that contribute to the generation of BM stroma. These cells can be easily expanded *in vitro* without losing the multipotent differentiation potential. Recently, their capacity to modulate an immune response, being able to inhibit dendritic cell maturation, T cell proliferation and natural killer activity, has been described. These properties open the possibility to use MSCs in inhibiting autoreactive immune responses. In this context, we investigated the potential use of murine BM MSCs to treat the animal model of systemic lupus erythematosus (SLE) NZB/NZW F1. In order to evaluate the capacity of BM MSCs to modulate the development of serum autoantibodies, we co-cultured marginal zone and mature follicular B cells, isolated from spleens of NZB/NZW F1 and balb/c mice, with BM MSCs. We evaluated the effects on B cell proliferation and differentiation into plasma cells. Furthermore, to test their effects on the pathogenesis of the disease, we intravenously injected BM MSCs in young and old NZB/NZW F1 mice. We scored the disease with the evaluation of the following parameters: 1) weight change, 2) serum IgG autoantibodies, and 3) proteinuria levels.

					FMF			MWS	TRAPS	HIDS
CASE	1	2	3	4	5	6	7	8	9	10
SEX	♂	♂	♂	♂	♂	♂	♂	♀	♀	♂
AGE	14	9	14	4	2	6	8	0.1	6	0.3
FEVER	–	15	30	15	15	30	15	Initial	Variable	30
SEROSITIS	+	–	diarrhea	–	diarrhea	–	–	+	–	diarrhea
ARTHRITIS	–	+	+	–	–	–	+	–	+	+
SKIN	–	–	+	+	+	–	+	+	+	–
UVEITIS	–	–	–	–	–	–	–	–	–	–
ADENITIS	–	+	+	+	+	+	+	+	+	+
MEGALIAS	+	–	+	–	–	–	–	–	–	+
REACTANT	–	+	+	+	+	+	+	+	+	+
GENE			MEFV		MEFV	MEFV	MEFV	CIAS–1	TNFRSF1A	MVK
MUTATION			M694V		I591T	M694I	P369S R408Q	V198M	R92Q	I268T V377I

• Autoinflammation: Pathogenesis

PP - 174

IDENTIFICATION OF CRITERIA FOR PERFORMING MVK GENETIC ANALYSIS IN PFAPA PATIENTS

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PFAPA is characterized by apparently unprovoked episodes of fever, aphthous stomatitis, pharyngitis, and adenitis with periodic recurrence. This clinical picture may partially overlap with other autoinflammatory syndromes, like mevalonate-kinase deficiency (MKD), but the prognosis of PFAPA is the most benign.

Aims: To evaluate the clinical overlap between PFAPA and MKD in our series, and to identify clinical and immunological criteria to select PFAPA patients for genetic analysis of MVK.

Patients and Methods: 67 patients affected by PFAPA were consecutively referred to the Otorhinolaryngology Unit (ORL) of our Hospital. Clinical, immunological (IgA and IgD measure) and genetic (direct sequencing of MVK) data from this group were compared with a series of 6 MKD patients under care at the pediatric department of our Hospital.

Results and Discussion: 5/6 MKD patients had had clinical features compatible with PFAPA, thus suggesting a possible overlap between MKD and PFAPA. However, MVK mutations were found in none of the PFAPA patients. IgA and IgD levels were significantly higher in MKD than in PFAPA, but not sufficiently sensitive nor specific for the diagnosis of the disease. Although there was a wide overlap of symptoms between the two groups, MKD patients seem to have an earlier onset and a more complex clinical picture. Moreover, extra-tonsillar symptoms dominated the clinical outline in all MKD patients, leading the patient to be referred to pediatricians instead of an ORL specialist.

In conclusion, typical PFAPA does not require genetic investigation. Subjects with early onset and predominant extra-tonsillar symptoms should undergo genetic testing.

PP - 175

MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) GENE POLYMORPHISM AND SERUM MIF LEVELS IN THE SYMPTOM-FREE PHASES OF ITALIAN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Background: Macrophage migration inhibitory factor (MIF) is a ubiquitously expressed cytokine playing a critical role in the regulation of many immunologic responses. A single-nucleotide G-to-C polymorphism at the position -173 in the MIF gene (*MIF*) promoter region has been associated with increased serum MIF levels and poorer response to steroids in systemic onset-juvenile idiopathic arthritis. The potential role of MIF in familial Mediterranean fever (FMF) has not yet been investigated.

Objective: To examine *MIF*-173 polymorphism and serum MIF concentrations in a group of Italian patients with FMF during a symptom-free phase of their disease and to compare these results with healthy controls of the same ethnic origin.

Methods: Genomic DNA for MIF and serum MIF concentrations were evaluated in 17 patients with FMF recruited in the Center of Periodic Fevers of our university (9 males and 8 females, mean age: 33.8±28.1 years, mean age at diagnosis: 28.1±26.2). No patient had current evidence of infection or was receiving steroids; all patients were treated with colchicine. *MIF*-173 polymorphism was genotyped using polymerase chain reaction. Serum MIF levels were measured by enzyme-linked immunosorbent assay provided from R&D Systems (detection limit: 31.25 pg/ml) in a symptom-free period. The control group for *MIF* polymorphism consisted of 169 healthy Italian individuals with no inflammatory/autoimmune disease or history of infectious disease; in 41 of them, serum MIF levels were tested. Genotype and allele frequencies were analyzed using the c^2 test or Fisher's exact test, while the comparison of serum MIF concentrations, expressed as mean results ± standard deviation, was performed with Mann-Whitney U test. Statistical significance was set at $p<0.05$.

Results: Frequency of *MIF*-173 CG genotype was higher in patients with FMF than in controls (41.2% vs 12.4%, $p=0.005$): the C allele was more frequently observed in the group of FMF patients (32.4%, $p<0.005$). Mean serum MIF concentrations were higher in patients with FMF than in controls, independent of genotype analysis, with high statistical significance (85.7±22.7 ng/ml vs 6.03±13.3 ng/ml, $p<1\cdot10^{-5}$).

Conclusions: *MIF*-173-*C allele is more represented and likewise MIF serum concentrations appear to be remarkably elevated in patients with FMF. However, no statistically significant correlation has been observed between *MIF*-173*C allele and serum MIF levels. These observations suggest that cytokine activation pathways might result in misregulation, leading to subclinical inflammation between attacks in FMF. Our results have to be considered preliminary and justify further research into the definition of the exact role of MIF in the autoinflammatory syndromes.

PP - 177

CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES: REPORT OF TWO BRAZILIAN CASES, INCLUDING A RARE NON-EXON 3 CIAS1 MUTATION

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Introduction: Cryopyrin-associated periodic syndromes comprise three clinical syndromes linked to mutations in CIAS1 gene: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystemic inflammatory disease (NOMID). We describe here patients with FCAS and NOMID, with the corresponding molecular defect.

Methods: Exons and flanking intronic regions of CIAS1 were amplified by PCR, purified and sequenced using an automated capillary sequencer.

Results: Patient 1 is an 8-year-old girl who presented at 20 days of age with an erythematous and macular rash involving face, chest, abdomen, limbs, palms and soles. At 3 months of age, she developed recurrent fever, exacerbated by cold weather. Clinical diagnosis was FCAS. She presented elevated acute phase reactants. Arthritis of large joints and unilateral anterior uveitis appeared during follow-up. Brain MRI was normal. DNA sequencing revealed the T436I CIAS1 mutation, previously reported in a NOMID patient. Patient 2 is a 7-year-old boy who developed after birth a papular exanthema involving chest, abdomen and extremities. Daily fever episodes appeared shortly. Persistent anemia, leukocytosis, thrombocytosis, and high acute phase reactants were seen. Examination revealed low weight and height, frontal bossing and marked swelling of knees with patellae prominence. Cognitive and motor difficulties and chronic intracranial hypertension were noted. NOMID was diagnosed. CIAS1 analysis revealed a G755R change, located in exon 4. Cryopyrin mutations outside exon 3 are exceedingly rare.

Conclusion: T436I CIAS1 mutation can manifest as FCAS or NOMID. Rare non-exon 3 G755R change can be found in Brazilian patients with cryopyrinopathy.

PP - 178

TNF RECEPTOR-ASSOCIATED PERIODIC FEVER SYNDROME (TRAPS) CAUSED BY A NOVEL MUTATION (C30F) ASSOCIATED WITH A COMMON R92Q LOW-PENETRANCE MUTATION IN TNFRSF1A

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Introduction: TRAPS is the most common of the autosomal dominant periodic fever syndromes. It is caused by mutations in the TNFRSF1A gene, which encodes for the type 1 TNF-receptor (TNFR1). We describe here a Brazilian patient with TRAPS associated with a novel TNFRSF1A mutation.

Methods: The exons 2 to 5, encoding the extracellular portion of TNFR1 and flanking intronic regions, were amplified by PCR, purified and sequenced using an automated capillary sequencer.

Results: The patient is a 9-year-old girl from São Paulo, Brazil. She has presented recurrent fevers since she was 3 years old, lasting 3 to 7 days, and recurring every other week. Episodes were associated with mild abdominal pain, nausea, vomiting and generalized myalgia. Recurrent conjunctivitis and erysipelas-like skin lesions in lower limbs were also present. Laboratory studies showed persistent normocytic normochromic anemia, thrombocytosis, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Antinuclear antibody was positive (1:80). Physical examination was unremarkable, except for height in percentile 3 and weight in percentile 10 – 25. IgD level was within normal range. PCR for familial Mediterranean fever related gene (MEFV) excluded four mutations (M680I; M694V; M694I; V726A; and one polymorphism (E148Q). Mutational screening of TNFRSF1A revealed the novel C30F mutation and the common R92Q low-penetrance mutation. The R92Q is seen in 5% of the general population, and is associated with an atypical inflammatory phenotype.

Conclusion: The novel TNFRSF1 mutation C30F was associated with TRAPS in a Brazilian patient, in conjunction with the R92Q low-penetrance change.

• **Other**

PP - 179

SveReFo (SWEDISH RHEUMA FORUM)

Karin Berggren[1]

[1]Organisation Swedish Rheuma Forum

What is SveReFo?

A forum for health professionals and physicians working in the field of rheumatology in Sweden.

The aim of the forum is to build a basis for the different professionals working in the field of rheumatology. The Association was established in 1989 with members from the Associations for: nurses, occupational therapists, physical therapists, social workers and rheumatologists. One representative of the Swedish Rheumatism Association is an additional member.

The goals of SveReFO are to:

• Make it possible to compare professional notes

• Arrange contact with groups for research projects

• Stimulate further development and research for an individual and between the different professional groups

• Create economical conditions for inter-disciplinary work

• Work for international collaboration

KOD no eksik?

SWEDISH RHEUMA FORUM (SveReFo)

Karin Berggren[1]

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Swedish Rheuma Forum (SveReFo) is a forum for health professionals working in the field of rheumatology in Sweden. The aim of the forum is to build a basis for the different professionals working in the field of rheumatology. The Association was established in 1989 with members from the Associations for: nurses, occupational therapists, physical therapists, rheumatologists and social workers. A representative of the Swedish Rheumatism Association for patients is an additional member. The main goals of SveReFo are to: stimulate development and research for individuals and between different professional groups**, ar**range contact with groups for research projects, create economical conditions for interdisciplinary work and research, and work for international collaboration**.** Members of the Board are elected for two years with the possibility to be re-elected for an additional two years. Two persons from each of the different health professions are elected. Board meetings are held four times a year.

Scholarships to support individual progress as well as to develop collaboration between the different member groups working within the field of rheumatology are distributed once a year. Approximately 5-10 persons per year have received scholarships over the years.

A Newsletter is distributed to the members by e-mail twice a year with short presentations from different working places within rheumatology, reports from meetings, conferences, scholarship reports, calendar, web site addresses and other information such as new treatment strategies. Information is also available from SveReFo's web site: www.severefo.nu.

National educational meetings are arranged every two years to give the members a possibility to meet each other and receive education in different fields with special focus on interdisciplinary and team work. The content of the meetings are lectures given by invited speakers and a smaller poster session. Informal contacts and discussions as well as social activities are stimulated. Since 1989, at least 10 meetings have been arranged. The evaluation of the latest meeting, in 2006, was very positive and will be presented.

Inter-professional- and teamwork is the focus of SveReFo and the members of the board have great hopes that these activities will stimulate the care and the rehabilitation of people with rheumatological disorders. Evaluation of the activities of SveReFo for 20 years, between 1989-2009, is now discussed.

PP - 180 **(duplicate of YIM OP-10)**

SINGLE INJECTION OF MESENCHYMAL STEM CELLS DECREASES PROGRESSION OF PROTEOGLYCAN-INDUCED ARTHRITIS

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PP - 182

PACHYDERMATODACTYLY: A POLYARTICULAR JIA MIMIC

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Pachydermatodactyly is an infrequently rec-ognized disorder characterized by painless fusiform swelling of the soft tissues around the PIP joints of the hands.

We report 2 Caucasian males who developed bilateral hand PIP swelling at the ages of 12 and 13 and were diagnosed with polyarticular juvenile idiopathic arthritis (JIA), and then sent to our pediatric rheumatology center for further assessment because of lack of improvement after therapy with NSAIDs.

There were no systemic manifestations, described discomfort, or characteristic early morning stiffness. Aside from PIP swelling with lateral aspect predominance, no other articular changes were noted. Pt #1 presented with 6 involved PIP joints and Pt #2 with 4; both hands were affected at our assessment but involvement at earlier onset had been unilateral in both children. There were no history or current findings of psychiatric disease, carpal tunnel syndrome, Ehlers Danlos syndrome or tuberous sclerosis. Pt # 2 had been diagnosed with mild Asperger syndrome. Inflammatory markers were unremarkable and all autoantibodies were negative. X-rays showed soft tissue swelling in both patients. Pachydermatodactyly was considered to be the diagnosis in both children.

A contrast enhanced MRI of Pt #1 showed no enhancing synovium or other abnormalities aside from soft tissue swelling around the affected PIP joints, and a skin biopsy showed hyperkeratosis and dermal fibrosis, further supporting this diagnosis.

Most clinical reports of pachydermatodactyly are found in the dermatology literature.

Pediatric rheumatologists should be aware of these typical findings in order to avoid further unnecessary diagnostic and/or therapeutic interventions.

PP - 183

SYNOVIAL CYSTS IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Introduction: Synovial cysts are recognized as a complication of JIA and are most often located in the popliteal fossa (Baker's cyst). Bicipital cysts, however, are rare. They present as a soft tissue swelling on the flexor aspect of the upper arm and are caused by effusion from the shoulder bursa. Ultrasonography (US) has proved to be a valuable diagnostic tool for detection of synovial cysts.

Methods: A retrospective analysis of medical history and imaging of patients with bicipital cysts seen in the department from 1999 - 2006.

Results: All patients had systemic onset JIA (SoJIA). Six patients (5 males / 1 female) aged 2-7 years presented with a bicipital cyst and three of these patients also had episodes with popliteal Baker's cyst. All patients were severely affected with a median no. of swollen joints of 6 (5 – 14) and all patients had systemic symptoms at presentation. Relapse of bicipital cysts within 2-6 months occurred in five patients, despite intensive systemic therapy and intracystic corticosteroid injection. Relapse in one patient with Baker's cyst was complicated by rupture of the cyst. In five patients, a US scan showed either an anechoic cystic process with a grape-like structure or a classic anechoic intramuscular cystic process.

Conclusion: We observed bicipital cysts in patients with SoJIA all in a severe stage of their disease. Three patients in addition had Baker's cysts, which presented unrelated to the bicipital cysts. The effect of corticosteroid injections was marked and rapid but the cysts relapsed within 2-6 months. US is a feasible tool for bedside diagnosis of synovial cysts.

PP - 184

CLINICAL STRATIFICATION AND MONITORING OF LOCAL INFLAMMATION IN JUVENILE ARTHRITIS USING THE SYNOVIAL FLUID PROTEOME

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Aim: The synovial fluid (SF) proteome was investigated to isolate a subset of biomarkers that are significantly over- or underexpressed in juvenile idiopathic arthritis (JIA) patients. The SF proteome could be used to stratify clinical subgroups of arthritis patients and may provide further insight into the local inflammatory features of this multi-factorial condition.

Method: In this study, we analyzed matched SF and plasma samples obtained from 32 JIA patients: 16 with oligoarticular arthritis, 5 extended oligoarticular and 11 polyarticular disease. Samples were labeled with Cy dyes to differentiate plasma and SF, and subjected to protein separation by two-dimensional difference in-gel electrophoresis (2D DIGE). Progenesis software analysis of plasma and SF gel scans was used to highlight joint-specific proteins differentially expressed across disease classifications. Proteins of interest were identified by nanoelectrospray-ionization mass spectrometry.

Results: 2D DIGE reveals ~900 spots per gel within the pH 4-7 range for synovial fluid and plasma. On comparison of plasma and synovial gel scans, a subpopulation of spots, uniquely expressed in synovial fluid, were identified. Hierarchical clustering based on the expression levels of a defined set of proteins segregates oligoarticular and polyarticular disease. Identified proteins of interest include PRO2619, transthyretin, properdin and alpha-1 antitrypsin.

Conclusions: Since localized and systemic aspects of this disease can be differentiated, therapeutic intervention could be directed at the most prevalent symptoms of this disease. Definition of protein profiles that discriminate clinical subgroups of arthritic disease may present a method to manage JIA more effectively at an earlier stage.

PP - 185

PROANTHOCYANIDIN ATTENUATES METHOTREXATE-INDUCED RENAL OXIDATIVE STRESS IN RATS

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Background: Methotrexate (MTX) has important side effects for which there is no definitive prophylaxis or preventive treatment. This study was designed to investigate whether proanthocyanidin has a protective effect on the MTX-induced renal oxidative stress in rats.

Methods: Twenty-eight albino rats were randomized into experimental and control groups and divided into four groups. To the first group, MTX was given as a single dose (20 mg/kg) intraperitoneally. To the second group, in addition to MTX application, proanthocyanidin (PA, 100 mg/kg) was given orally every day by gavage. To the third group, PA alone was administered. The fourth group was the control. All animals were sacrificed 4 days after the intraperitoneal injections. Histopathologic examination of kidney tissues was then performed, and tissue malonaldehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels were measured.

Results: In the MTX group, MDA levels in the kidney tissue were found significantly higher than in other groups. There was no change in the levels of SOD and GPx. The histopathologic examination of

the kidney tissues revealed no significant differences between groups. MDA levels in the PA+MTX-administered group were significantly lower than levels in the group administered MDA alone.

Conclusion: These results suggest that PA may protect the kidney tissues from MTX-induced oxidative stress. This attenuation of oxidative stress factor may result from the antioxidant properties of PA.

PP - 186

FINAL DIAGNOSES OF PATIENTS REFERRED TO A TERTIARY REFERRAL CENTER WITH RHEUMATIC COMPLAINTS

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Aim: To evaluate the final diagnosis among patients referred to a tertiary referral center in the Eastern Mediterranean region with a possible diagnosis of a rheumatic disease.

Materials and Methods: Our center is the main referral center for the central, east, north and south regions of Turkey. Medical records of all patients referred to our center with a suspicion of rheumatic disease were retrospectively evaluated for a period of 6 months. The follow-up period was at least 24 months.

Results: Among a total of 147 new referrals during the study period, 26 patients were lost to follow-up. The main complaints of 131 patients [57 (43.5%) girls, 74 (56.5%) boys; mean age at presentation 8.25±4.19 years] were joint pain (57.3%), abdominal pain (48.1%), fever (32.8%) and skin eruptions (22.9%). The most common referral diagnoses were familial Mediterranean fever (FMF, 35.9%), Henoch-Schönlein purpura (HSP) and juvenile idiopathic arthritis (JIA). The distribution of the final diagnoses was as follows: FMF (16.8%), HSP (16.8%), JIA (9.2%), acute rheumatic fever (3.8%), systemic lupus erythematosus (3.1%), other vasculitides (6.1%), other rheumatic diseases (3.1%), gastrointestinal disorders (8.5%) and other non-rheumatic diseases or no diseases (32.6%). The ratios of correct diagnosis on referral for FMF and JIA were 59.5% and 33.3%, respectively.

Conclusion: The distribution of rheumatic diseases in a center from the Eastern Mediterranean region has been presented for the first time. FMF is probably the most frequent disease; however, the referring physicians are over-diagnosing it at the expense of missing other diseases. Almost one-third of the referred patients were determined to have non-rheumatic disorders. The high frequency of HSP and the rarity of fibromyalgia in this area are other interesting conclusions.

PP - 187

COMMON VARIABLE IMMUNODEFICIENCY MIMICKING SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS

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Common variable immunodeficiency (CVID) is the most common symptomatic primary antibody deficiency syndrome. It is characterized by recurrent infections, especially of the respiratory tract, with onset in childhood or young adulthood. CVID patients also have a higher prevalence of autoimmune diseases. A four-year-old boy was referred to the Pediatric Rheumatology Department with fever of unidentified origin lasting for two months. He had a course of 3-weeks of intravenous antibiotics prior to admission without any improvement. Physical examination revealed hepatosplenomegaly, lymphadenopathy, and arthritis of the right knee. The fever pattern was intermittent. Serologic markers for salmonellosis, brucellosis, hepatitis A, B, C, Epstein-Barr virus, cytomegalovirus, toxoplasmosis, and HIV were negative. Repeated cultures of the blood were also negative. A bone marrow aspiration showing hypercellularity with increased number of myeloid precursors excluded malignancy. Given the lack of an infectious proof by cultivation and serology, systemic onset juvenile idiopathic arthritis was suspected. The diagnosis of immune deficiency was considered when hypogammaglobulinemia was

found. Immunological studies showed decreased levels of IgG, decreased number of peripheral blood B lymphocytes, increased percentages of CD8 lymphocytes, and a reduced CD4/CD8 ratio. He was diagnosed as CVID. Intravenous immunoglobulin substitution therapy resulted in the remission of arthritis and fever, as well as of hepatosplenomegaly and lymphadenopathy.

PP - 188

LUPUS ANTICOAGULANT ASSOCIATED WITH CMV INFECTION

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Remission of proteinuria following corticosteroid therapy has greater prognostic value than renal histology in nephrotic syndrome. The management of steroid-resistant nephrotic syndrome is difficult; most patients failing to achieve remission show progressive renal damage. Treatment with levamisole, cyclophosphamide, cyclosporine, and mycophenolate mofetil is beneficial in some of the patients with frequent relapses or steroid dependence. Calcineurin inhibitors (cyclosporine, tacrolimus) are able to induce remission in some patients, but there is a significant risk of nephrotoxicity.

A 4-year–old boy admitted to our hospital with the complaint of abdominal distension. He was diagnosed as nephrotic syndrome after the physical examination and laboratory investigation. He had severe proteinuria and did not respond to first-line steroid treatment. Renal biopsy was reported as focal segmental glomerulosclerosis. He had steroid-resistant idiopathic nephrotic syndrome and the treatment was arranged with cytotoxic therapy. Since he did not show a good response to this treatment, it was finally changed to tacrolimus protocol. During this therapy he had CMV infection (CMV IgM- and CMV PCR-proven infection). Lupus anticoagulant positivity was demonstrated during CMV infection.

It is recognized that the presence of IgG and IgM anticardiolipin antibodies (aCL) and lupus anticoagulant (LAC) is associated with thrombosis in patients with antiphospholipid syndrome (APS). Auto-antibodies to beta(2)-glycoprotein I (beta(2)-GPI) and/or prothrombin (FII) have been involved in the expression of lupus anticoagulant (LA) activity, an *in vitro* phenomenon associated with an increased risk of arterial and/or venous thromboembolic events. However, LA activity sustained by anti-FII antibodies has a much weaker association with thrombosis than LA activity sustained by anti-beta(2)-GPI antibodies. Gharavi *et al*. suggested a relationship between CMV infection and antiphospholipid antibodies production in a murine model. Our patient also had LAC during CMV infection, but it became negative after treatment of the CMV infection.

CLINICAL:

- **SLE**

PP - 189

SEVERE CLINICAL COURSE OF SYSTEMIC LUPUS ERYTHEMATOSUS IN THE FIRST YEAR OF LIFE

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Background: Systemic lupus erythematosus (SLE) affects predominantly young females of reproductive age and very rarely occurs before the age of 10. Herein, we describe the clinical features of patients with infantile SLE (iSLE) with onset during the first year of life.

Methods: The charts of patients followed since 1984 at the Department of Pediatrics of Padua, who met the criteria for the SLE diagnosis, were reviewed. The clinical and laboratory characteristics at disease onset of patients with iSLE from this series and those found by a systematic literature search on PubMed and EmBASE were analyzed and compared with classic juvenile SLE (jSLE).

Results: Of 13 patients with iSLE, 7 were females and 6 males. The age at disease onset ranged from 6 weeks to 11 months. In comparison with jSLE, iSLE showed a significantly higher prevalence of systemic symptoms at presentation, renal, cardiovascular and pulmonary involvement, and shorter time between symptom onset and diagnosis. As far as laboratory features, anemia and thrombocytopenia were more frequent in iSLE while ANA and anti-dsDNA antibodies were not significantly different. The overall prognosis in iSLE was very poor: 5 infants died 2-31 months after the onset and 5 had significant organ damage (2 renal failure, 2 CNS impairment and 1 digital amputation for gangrene).

Conclusion: SLE can start as early as during the first year of life. Since the course in these patients is quite aggressive, SLE should be considered in the differential diagnosis of infants with renal, pulmonary and/or cardiac system involvement and hematological changes.

PP - 190

PROMPT AND STEADY IMPROVEMENT IN PROTHROMBIN LEVELS AFTER CYCLOPHOSPHAMIDE THERAPY IN PEDIATRIC LUPUS ANTICOAGULANT HYPOPROTHROMBINEMIA SYNDROME (LAHPS)

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Lupus anticoagulant hypoprothrombinemia syndrome (LAHPS) is a well-known, albeit rare, condition, usually associated with systemic lupus erythematosus (SLE). LAHPS probably develops as a result of the presence of anti-Factor II antibodies. The mechanism appears to be mediated by the presence of antiphospholipid antibodies. Considering the strict linkage between the presence of antiprothrombin antibodies and lupus anticoagulant (LAC), some authors suggest cross-reactivity between the antiphospholipid antibodies and phospholipid epitopes in the prothrombin molecule. Others suggest that antibodies bound to prothrombin in circulation accelerate clearance rather then interfere with prothrombin function.

We describe two pediatric SLE patients with hypoprothrombinemia, LAC, moderate thrombocytopenia and bleeding, who showed a dramatic response to cyclophosphamide therapy with documented normalization of prothrombin levels (Figures 1 and 2).

No consensus exists for the treatment of LAHPS. Corticosteroids have been a successful first-line treatment. IVIG treatment has been shown to be effective in the setting of acute bleeding. In some patients, weaning from corticosteroids has led to a recrudescence of bleeding, requiring the addition of immunosuppressive therapy, usually azathioprine. Our patients have been successfully treated with corticosteroids but Factor II deficiency reappeared after tapering of steroids. Both children achieved normal Factor II levels with cyclophosphamide therapy. This effect was long–lasting, a phenomenon that has not been documented in children.

Our cases show that when bleeding occurs in SLE patients in the absence of severe thrombocytopenia, the possibility of hypoprothrombinemia should be considered and prothrombin time measured. Management may require the use of intravenous cyclophosphamide.

PP - 191

APOPTOSIS AND HEAT-SHOCK PROTEIN-70 (HSP-70) IN LUPUS NEPHRITIS (LN): A CLINICOPATHOLOGICAL PRELIMINARY STUDY

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Abnormalities of apoptosis have been implicated in the pathogenesis of systemic lupus erythematosus. Recent studies have also revealed the anti-apoptotic effect and regulatory function of heat-shock proteins (HSP). In this study, we investigated the relationships among glomerular apoptosis, HSP-70 and histopathological findings in 30 cases with LN. There were 27 females and 3 males, aged from 4 to 60 years. Twenty-seven renal biopsies, three renal necropsies and four kidney samples from control cases were studied using light and immunofluorescence microscopy. Apoptosis was determined by in situ DNA nick end labeling technique and HSP-70 were identified by immunohistochemistry. Activity (AI) and chronicity (CI) indices and total pathological scores (TPS) were also calculated. There was a correlation between TPS and serum creatinine ($p<0.05$). No correlation was found between apoptosis and proteinuria or anti-DNA levels. Patients with Class III and IV showed a higher apoptosis index than those of cases with Class II and V and control subjects ($p<0.05$). HSP-70 staining was found to be less intense in cases with high apoptotic scores. HSP-70 showed no correlation with TPS scores, proteinuria or serum creatinine. In conclusion, apoptosis was increased in Class III and IV LN. A decrease in HSP-70 expression, though not statistically significant, in cases with high apoptotic scores implies a relationship between apoptosis and HSP-70. Further studies are needed to clarify this relationship between HSP-70 and apoptosis in patients with LN.

PP - 192

JUVENILE SLE: DIFFERENT TYPES OF CLINICAL DEBUT

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Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with variable clinical features at onset. A cohort of juvenile SLE (JSLE) (onset before 16th birthday) showed four different types of debut.

Methods: Prospective registry of demographic, clinical and serologic data of patients with definitive diagnosis of JSLE during a 15-year period was collected at onset and during the course of disease. The patients were classified according to the number of systems involved in the presence of immune abnormalities as oligosystemic (<4) or multisystemic (>4). Other groups were catastrophic debut when life-threatening complications developed, antiphospholipid syndrome and ANA-negative groups. Different clinical associations were identified in those groups of patients.

Results: 147 JSLE patients with a sex ratio of F5: M1 with a mean age of 8.4 years (4-16) were included. Fifty-nine developed JSLE during the first decade of life and another 88 between 11-16 years. Frequency of a multisystemic debut in the first decade was 61% vs 74% in older patients. Oligosystemic debut was observed in 39% vs 26%, respectively. The multisystemic onset was more common in males (96% vs 73%). Four of 147 developed ANA-negative JSLE (3%). 15% had a catastrophic onset while 26% developed complications related to antiphospholipid syndrome. Differences in clinical manifestations were observed based on age of onset and sex. During the first decade of life, sex ratio was F4: M1. The systems involved more frequently were: hematologic, articular, renal and skin. In patients older than 10 years, the sex ratio was F6.4: M1. The most common systems affected were: articular,

skin, hematologic and renal. Hematologic and renal involvements were more frequent in younger patients while skin was more commonly affected in older patients. Oligosystemic onset was more common in females (27% vs 4%) and 62% were older and 11th years. The more commonly involved systems were skin, articular, hematologic and renal. An increase in frequency of serositis and neurological complications was observed. An equal number of males developed JSLE in the first two decades of life. Only 4% had an oligosystemic debut. The most common systems involved were articular, renal, skin and hematologic. Complications related to antiphospholipid syndrome were: deep venous thrombosis, arterial thrombosis, stroke, and Evans syndrome. Acute renal failure, seizures, bleeding and thrombotic complications were related to a catastrophic onset. Three of 147 died promptly after diagnosis.

Conclusions: The clinical manifestations in JSLE are quite variable. Some patients do not fulfill the diagnostic criteria or develop atypical manifestations, and thus a high index of clinical suspicion is required to confirm the diagnosis. The timing of diagnosis may impact the prognosis. Detection of autoantibodies and biopsies have an important diagnostic value. Antiphospholipid antibodies should be investigated in all patients.

PP - 193

INFLUENCE OF GENDER AND AGE OF ONSET ON THE OUTCOME IN CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: To determine the influence of gender and age of onset on outcome in children with systemic lupus erythematosus (SLE).

Methods: Medical records of children with SLE treated at King Faisal Specialist Hospital and Research Center were reviewed. Outcome measures included Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index score (SLICC/ACR), renal disease requiring dialysis or transplant, and death related to SLE. Patients were classified based on age at disease onset into early onset (≤ 5 years) and late onset (> 5 years). Data was analyzed and comparison was made according to the gender and age groups.

Results: Eighty-nine patients (76 girls, 13 boys) were investigated, and 12 of them had early onset disease. The median disease duration was 5 years. The median ages at onset and diagnosis of the cohort were 9.5 and 10 years, respectively. There was no difference in the median of age, age at diagnosis, disease duration and follow-up between the different groups. Logistic regression analysis showed significant association of high SLICC/ACR score with early onset disease and male gender. While renal disease requiring dialysis or renal transplant was associated significantly with male gender independent of age of disease onset, death related to SLE was influenced by early onset disease.

Conclusion: Male children with early onset disease in this cohort had poorer outcome. This finding indicates that gender and early onset disease may influence the long-term outcome of SLE in children.

PP - 194

REMITTING SYMMETRICAL PITTING EDEMA OF HANDS AND FEET IN A TWELVE-YEAR-OLD GIRL WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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To our knowledge, this is the first case of remitting symmetrical pitting edema in SLE in pediatric age; at least three cases have been reported in adult age. Our patient is a 12-year-old girl who was admitted to our unit with a 1-month history of edema of hands followed by edema of feet and legs.

Physical examination revealed pitting edema of hands and feet and swelling of the pretibial region and of the forearm, as well as arthritis and tenosynovitis of proximal interphalangeal and wrist joints. She complained of pain and functional impairment of left arm and shoulder. There were no other abnormal physical signs. The diagnosis of SLE was based on 4 of the American Rheumatism Association criteria: arthritis, leukopenia, anti-dsDNA and ANA positivity.

She was initially treated only with anti-inflammatory drugs and hydroxychloroquine and then, after exclusion of hematological diseases, she received steroid (prednisone 1 mg/kg/day). After only 2 weeks of steroid treatment, pitting edema and articular symptoms disappeared completely. Pitting edema of the distal limbs is a rare manifestation of SLE and it has to be differentiated from remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, which may occur in other rheumatic diseases.

PP - 195

DIFFUSE LUPUS NEPHRITIS WITH A SILENT CLINIC

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The renal involvement of systemic lupus erythematosus (SLE) is a multi-faceted process in terms of clinical and morphological expressions. In the absence of clinical renal involvement, microscopic evidence of renal disease is called silent lupus nephritis (SLN). We present a case of SLN with severe renal histopathological changes even during the second flare of the illness.

A 12-year-old girl was admitted with fatigue, fever, arthralgia, dyspnea, and weight loss. SLE diagnosis was established with malar rash, serositis, positive LE cell and ANA. She was treated with 2 mg/kg/day prednisone but very low complement C3 level persisted over 2 months despite full-dose prednisone therapy. Renal biopsy showed class IV-G (A/C) (active and chronic lesions, diffuse global proliferative and sclerosing LN) according to the International Society of Nephrology/Renal Pathology Society 2003 classification of LN. She was instituted on pulse cyclophosphamide on a monthly base, pulse methylprednisolone and prednisone, and then maintained with azathioprine and alternate-day prednisone. At the end of the second year, she ceased treatment and low complement C3 (76 m/dl), C4 (10 mg/dl) and high anti dsDNA (1/1280 IFA) indicated disease activity without any systemic findings. Urinalysis and renal functions were normal. A second renal biopsy revealed again class IV-G (A/C). The patient resumed a serologic remission with mycophenolate mofetil and prednisone. She is still in remission with azathioprine and low-dose prednisone during her fifth year of follow-up.

We suggest that every SLE patient with active serological markers should undergo renal biopsy in order not to miss the silent renal involvement of SLE.

PP - 196

IMMUNOGLOBULINS PROFILE IN JUVENILE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE)

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Introduction: The association between autoimmune diseases and humoral immuno-deficiencies is reported with frequencies varying from 7 to 42%. Whereas patients with common variable immunodeficiency show an increased prevalence of lupus, the frequency of IgA deficiency in SLE patients ranges from 1 to 4%. Lack of reports evaluating the prevalence of humoral immunodeficiencies in pediatric lupus patients stimulated this study.

Objective: To evaluate the titers of immunoglobulins in a JSLE population.

Methods: Thirty-seven patients with JSLE had immunoglobulin (IgG, IgA, IgM) serum levels determined. Exclusion factors were secondary humoral immunodeficiency causes, such as nephrotic syndrome and intestinal malabsorption.

Results: Seven patients (18.9%) presented IgG levels below normal range for age (mean level: 572.3 mg/dl, range: 317 to 717 mg/dl); 11 patients (27%) presented low levels of IgA (mean level: 61 mg/dl, range 1 to 89.3mg/dl); and 9 patients (24.3%) low levels of IgM (mean level: 42.7 mg/dl, range: 23 to 72 mg/dl). Two patients had a complete IgA deficiency (IgA below 7 mg/dl). Seven patients (18.9%) presented abnormal levels of two immunoglobulins (IgG and IgM in 3; IgG and IgA in 1; and IgM and IgA in 3). None of the patients evaluated had low levels of the three immunoglobulins simultaneously.

Conclusion: This preliminary study showed low immunoglobulin levels in 19/37 (51.3%) evaluated patients. Diagnosis of selective IgA deficiency was made in two patients. Further studies are necessary for determining the prevalence of humoral immunodeficiencies in patients with juvenile-onset systemic lupus.

PP - 197

SEVERITY OF FLARES, SEVERITY OF ONSET AND ATYPICAL ONSET AS PREDICTORS OF POOR OUTCOME IN PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Only a few studies have focused on pediatric systemic lupus erythematosus (p-SLE) prognosis and its correlation with risk factors, and only two papers took into account clinical features at onset as cause of increased risk of organ damage. The aim of our study was to clarify if atypical onset or the explosiveness of onset and/or of flares influences the severity of the organ damage in p-SLE. Here, atypical onset refers to organ involvement present at onset of p-SLE, but not included in ACR criteria. Severe episode refers to the features included in ACR/SLEDAI severe flare tool. Organ damage indicates any non-reversible change, not related to active inflammation occurring since onset of SLE ascertained by clinical assessment, present for at least 6 months (SDI).

We considered 29 p-SLE patients with a mean follow-up of 10.9 years. Two patients showed an atypical onset with gastrointestinal involvement; 12 patients presented severe onset or severe episodes during the follow-up. Of these 14 patients (with atypical onset or severe episodes), 12 (86%) showed organ damage (>0 SDI) mostly with CNS, cutaneous and renal involvement. In contrast, 15 patients with

typical onset had no severe episode; in this group, we observed only one patient (6.6%) with cutaneous organ damage ($p<0.0001$).

We conclude that there is a significative correlation between organ damage, atypical onset and the severity of onset and flares in p-SLE. Future diagnostic approaches and therapeutic options should take into account this strict correlation.

PP - 198

PEDIATRIC LUPUS ERYTHEMATOSUS: LONG-TERM FOLLOW-UP AND PROGNOSTIC IMPACT OF ANTIPHOSPHOLIPID ANTIBODIES

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Objectives: The aim of our study was to describe the initial symptoms and the long-term follow-up of pediatric onset systemic lupus erythematosus (p-SLE), as well to evaluate the prognostic impact of antiphospholipid antibodies (aPL).

Methods: This French retrospective study included 56 patients with p-SLE. Chi-square test, Fisher's exact test, incidence rate ratio and Kaplan-Meier survival curves were used to compare aPL-positive and aPL-negative patients considering the value of SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for SLE) at the end of follow-up, the occurrence of thromboses, organ system involvements, and need for immunosuppressive treatment (associated with corticosteroids).

Results: Anticardiolipin antibodies and lupus anticoagulants were detected in 49% and 35% of patients, respectively. These antibodies were frequently transient or intermittent (10 and 15 cases, respectively), and only rarely persistent over time (5 cases). The thrombotic risk was significantly higher and occurred earlier in the presence of aPL, especially if aPL were persistent ($p<0.05$). The association between aPL and neurological, renal, and hematological manifestations or need for immunosuppressive treatment was not statistically significant. After a mean follow-up of 7.2 years, 54.5% of patients had a SDI score ≥ 1. The risk of damage (SDI$\geq$1) in aPL-positive patients was 3 times higher than in aPL-negative patients ($p<0.05$). Four of the six fatal cases occurred in the aPL-positive group.

Conclusions: The presence of aPL in p-SLE could represent not only a risk factor for thrombosis but also a poor prognostic factor overall.

PP - 199

FACTORS ASSOCIATED WITH THE DEATH OF PATIENTS HOSPITALIZED FOR JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: We assessed the factors associated with death in patients hospitalized for juvenile systemic lupus erythematosus (JSLE) and evaluated the autopsy reports.

Methods: A total of 57,159 hospitalizations occurred in our institution from 1994 to 2003, with 169 of them involving 71 patients with JSLE. The most recent hospitalization of these patients was evaluated.

Results: Patients were divided into two groups based on mortality during hospitalization: those who survived (N = 53) and those who died (N = 18). The main causes of hospitalization were JSLE activity associated with infection in 52% and isolated JSLE

activity in 44%. Univariate analysis showed that a greater risk of death was due to severe sepsis (OR = 17.8, CI = 4.5-70.9), SLE disease activity index (SLEDAI) ≥8 (OR = 7.6, CI = 1.1-53.8), general infections (OR = 6.1, CI = 1.5-25), fungal infections (OR = 5.4, CI = 3.2-9), acute renal failure (OR = 5.1, CI = 2.5-10.4), acute thrombocytopenia (OR = 3.9, CI = 1.9-8.4), and bacterial infections (OR = 2.3, CI = 1.2-7.5). Stratified analysis showed that severe sepsis and SLEDAI ≥8 were not confounding variables. In the multivariate analysis, logistic regression showed that the only independent variable in death prediction was severe sepsis (OR = 98, IC = 16.3-586.2). Discordance between clinical diagnosis and autopsy was observed in 6/10 cases.

Conclusions: Mortality of hospitalized JSLE patients was associated with severe sepsis. Autopsy was important to determine events not detected or doubtful in deceased patients and should always be requested.

PP - 200

PANCREATITIS IN PATIENTS WITH JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: To describe three patients with juvenile systemic lupus erythematosus (JSLE) and pancreatitis.

Methods: Retrospective analysis of medical records from three adolescents with JSLE, emphasizing the pancreatic involvement, its relation to previous corticosteroid use, treatment and outcome.

Results: The three patients studied (ages 10.2, 10.8 and 14.8 years old) presented fever, weight loss, alopecia, musculoskeletal complaints and pericarditis. They developed pancreatitis symptoms, confirmed by laboratory test and radiological studies. The interval between the beginning of JSLE and pancreatitis was 3.5 months. All patients presented renal failure during the episode of pancreatitis. This involvement was not persistent, despite the presence of anti-DNA and C3 and C4 abnormalities. Two patients had started on corticosteroids one day before the beginning of pancreatitis (one orally and one with methylprednisolone pulse). In the third patient, the medicine had not yet been started. All cases were submitted to fasting, parenteral nutrition and antibiotics. Laparotomy was done in one of them. The resolution of the illness occurred after 10.3 days (median). Methylprednisolone pulses were used for pancreatitis treatment in two patients. The third patient received this medicine two weeks after the pancreatitis resolution with no recurrences. The median of hospitalization was 45 days. One patient developed diabetes mellitus.

Conclusions: Pancreatic involvement, a severe manifestation of the disease, occurred early in the follow-up of JSLE. In these cases, the pancreatitis was possibly associated with the illness, since all patients improved with corticosteroid therapy.

PP - 201

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) IN CHILDREN WITH SICKLE CELL DISEASE (SCD): A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Objective: To describe the first manifestations of SLE and the tolerability of its treatment in children with sickle cell disease (SCD).

Study Design: A French multicenter retrospective study of children less than 18 years of age, with coexisting SLE and SCD. Clinical data were provided by the centers of the French study group on sickle-cell, and patients were identified over a 5-year period (2000-2005).

Results: SLE was recorded in 6 African children (3 boys, 3 girls). The median age at the time of diagnosis of SLE was 9.3 years (range: 4 -12 years). The mean

interval between onset and diagnosis ranged from 0 to 4 years. At SLE onset, patients presented with arthralgia (4 patients), renal disease (3 patients), pericarditis (2 patients), fever (2 patients), eruption (2 patients) and/or persistent fever (2 patients). Renal involvement consisted of glomerulonephritis type III or IV, according to the WHO classification, and presented with hemolytic and uremic syndrome (HUS) in 1 patient. Anti-double stranded DNA and antiphospholipid antibodies were present in 6/6 and 3/5 patients, respectively. Prednisone was initiated in 5 patients, associated with cyclophosphamide in 2 of them. After the initiation of steroids, severe vaso-occlusive events (VOE) (2-fold increase in frequency of painful crisis, acute chest syndrome, stroke, renal infarct) and septicemia occurred in 2 patients. Exchange transfusion programs led to the regression of pain episodes. The only patient who did not experience any complication was the one who received hydroxyurea before the initiation of steroids.

Discussion: Young age at onset, low sex ratio F/M and occurrence of HUS are non- classical features in childhood-onset SLE. The diagnosis of SLE in SCD children may be delayed because of atypical presentation and overlap of some clinical manifestations, especially arthralgia, between the two diseases. Long-term administration steroid treatment may result in severe side effects.

Conclusion: SLE should be searched in SCD children presenting with persistent arthralgia or atypical symptoms. Chronic transfusions regimen should be considered before starting steroid therapy in order to prevent VOE.

PP - 202

MACROPHAGE ACTIVATION SYNDROME IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS: AN UNDERRECOGNIZED COMPLICATION?

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Objective: To describe the characteristics of patients with macrophage activation syndrome (MAS) complicating juvenile systemic lupus erythematosus (JSLE).

Methods: A systematic review was conducted of the published cases of MAS occurring in patients with JSLE and confirmed through a bone marrow aspirate.

Results: 8 patients were identified in the literature. An additional patient seen by the authors was included. The age at onset/diagnosis of SLE ranged from 10 to 17 years. In 5 patients, the onset of SLE and MAS was simultaneous; in 3 other patients MAS occurred at 6 weeks, 3 months, and 7 months after onset. Fever was recorded in all patients; hepatomegaly, splenomegaly and lymphadenopathy were detected in 2/8, 2/8 and 5/8 patients, respectively. 3/8 patients developed CNS dysfunction and 1/8 patients hemorrhagic complications. Heart, lung or kidney involvement was seen in 4/9 patients. Leukopenia, neutropenia, anemia and thrombocytopenia were recorded in 6/7, 6/6, 6/7, and 7/7 patients, respectively. Increased transaminases, lactic dehydrogenase, and triglycerides were observed in 6/7, 6/6, and 3/5 patients, respectively. Hypofibrinogenemia was seen in 3/6 patients. 5/5 patients had elevated levels of ferritin, which ranged from 426 to 9853 μg/L. Treatment for MAS included corticosteroids, cyclosporine, intravenous immunoglobulins, cyclophosphamide, etoposide, plasma-exchange, and rituximab. Seven patients experienced full recovery, and 2 died.

Conclusion: Little information is available regarding MAS in JSLE. Analysis of a larger patient sample is needed to better characterize the clinical and laboratory picture of the syndrome and the lupus context in which it most commonly occurs.

PP - 203

NEURO-PSYCHIATRIC INVOLVEMENT IN PEDIATRIC SLE

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Aim: The diagnosis of neurological involvement in systemic lupus erythematosus (SLE) is complex because of the wide spectrum of manifestations. 14-80% of patients with SLE suffer from neuropsychiatric complications. We have analyzed these features in our pediatric SLE patients.

Methods: All patients fulfilled the ACR criteria for SLE. Physical examination was performed by a pediatric rheumatologist and subsequently by a neurologist. MRI was performed in all, and MRA and EEG only in selected cases. The burden of disease was assessed by the Symptom Distress Check List (SCL-90-R) questionnaire.

Results: The female/male ratio was 14/1. The mean ages at the time of diagnosis and evaluation were 11.4 (range: 6-16) and 15.8 (range: 6-22), respectively. Four of the patients had overt neurological signs/symptoms at onset or admission: one had hemiparesis, one loss of consciousness, one convulsions and one vertigo. Complaints included headache, mild hearing loss, forgetfulness, and visual disturbances. The examination of the neurologist revealed a few signs that were missed: one patient had hand tremor and one had hypoesthesia; however, these patients had normal MRI findings. Overall, 2/3 of the patients in this cohort displayed neurological symptoms and/or signs. However, MRI showed pathological findings only in the four patients who had overt neurological symptoms. The patient with vertigo had multiple infarcts due to antiphospholipid antibodies and Factor V Leiden heterozygosity. According to the SCL-90-R questionnaire, four patients had significant depression and two had significant anxiety. 37.5% of adolescents expressed a decline in school performance. One of these patients was the one with vertigo. MRI findings in patients with depression/anxiety were normal.

Conclusions: Neuropsychiatric involvement is not rare in pediatric SLE. MRI is probably not required in patients who do not have any neurological symptoms or signs, or in patients with nonspecific headache. Further studies will enlighten the indications for more advanced work-up with MRA or SPECT.

PP - 204

SIMPLE MEASURE OF IMPACT OF LUPUS IN YOUNGSTERS©-RESPONSIVENESS TO CHANGE IN SLE ACTIVITY

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Background: We have previously described the development of "Simple Measure of the Impact of Lupus Erythematosus in Youngsters©" (SMILEY©), a novel, brief, valid and reliable health-related quality of life (QOL) tool for children with systemic lupus erythematosus (SLE). SMILEY© has parallel child/parent reports with 5 faces-scale responses and percentage scores. Higher scores mean better QOL.

Objective: To determine responsiveness of child-report of SMILEY to change in SLE activity.

Methods: In this longitudinal multi-center study, we conducted three prospective assessments of children 2-18 years with SLE. We examined their QOL with

child-report SMILEY©. We evaluated SLE activity with both Physician Global Assessment (PGA) and subject (child) global assessment of SLE activity (ASLE). We calculated Spearman rho and one-way ANOVA between change (ch) in child SMILEY© (chSMILEY©) and corresponding changes in SLE activity (chASLE, chPGA).

Results: Median interval between the first two evaluations (Eval12) was 4 months and between the first and third (Eval 13) was 7 months. For Eval 12, chSMILEY© correlated significantly with both chASLE ($r=0.4$, $p=0.002$, $n=49$) and chPGA ($r=0.5$, $p<0.01$, $n=47$). ANOVA was significant for chSMILEY© with both chASLE ($p=0.02$) and chPGA ($p=0.009$). For Eval 13, chSMILEY© correlated significantly with chASLE ($r=0.5$, $p=0.002$, $n=32$). ANOVA was significant for chSMILEY© with both chASLE ($p<0.05$, $n=32$) and with chPGA when chPGA$\neq 0$ ($n=15$) ($p<0.05$).

Conclusion: Child-report SMILEY© is responsive to change in SLE activity on preliminary analysis and will be an important adjunct to clinical care and research. We are currently examining the responsiveness of parent report of SMILEY© to change in SLE activity.

PP - 205

ASSOCIATION OF AUTOIMMUNE HEPATITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILDHOOD

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The association of systemic lupus erythematosus (SLE) and autoimmune hepatitis (AIH) is controversial. Liver abnormalities are common in patients with SLE, and sometimes the differential diagnosis with AIH may pose problems. Lack of antibodies to dsDNA and histopathology may be helpful. Here we present two patients with overlap features of AIH and SLE.

Case 1: A 14-year-old girl presented with jaundice, hepatosplenomegaly, malaise, polyarthralgia, arthritis, and butterfly rash at the age of 12 years. Laboratory tests revealed severe liver dysfunction, Coombs(+) hemolytic anemia and ANA, anti-dsDNA positivity. Liver biopsy showed chronic hepatitis with severe inflammatory activity. She satisfied the international criteria for both SLE and AIH and was diagnosed as an overlap syndrome involving AIH and SLE. Clinical and laboratory features of SLE improved with high-dose steroid and azathioprine; however, remission was not achieved for liver disease. Rebiopsy performed after three years of therapy revealed ongoing chronic hepatitis with high activity.

Case 2: A 6-year-old girl was diagnosed as AIH with clinical and laboratory findings, and the liver biopsy showing chronic hepatitis. Although her clinical and laboratory findings remained stable, she developed full-blown SLE at 16 years of age, at which time she presented with fever, butterfly rash, livedo reticularis, hepatosplenomegaly, and fusiform swelling of the proximal interphalangeal joints. Laboratory tests revealed liver dysfunction, high levels of sedimentation rate and C-reactive protein, a positive Coombs test, low levels of complement, and ANA and anti-dsDNA positivity. Clinical symptoms and laboratory findings of SLE improved with steroid and remission for liver disease was achieved.

We believe that these two patients represent AIH-SLE overlap syndrome. Children with liver dysfunction and SLE should be investigated for AIH. A diagnostic and therapeutic dilemma exists for patients with AIH-SLE overlap syndrome.

PP - 206

PREGNANCY OUTCOME IN WOMEN WITH INHERITED/ACQUIRED THROMBOPHILIA

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A relationship between acquired/inherited thrombophilia and obstetrical complications has been reported, and thromboprophylaxis seems to reduce the incidence of adverse pregnancy outcomes. To confirm the efficacy of thromboprophylaxis in women with acquired/inherited thrombophilia and previous placental insufficiency, we studied 419 women, mean age 35 years, with previous placental insufficiency (more stillbirth, fetal loss (FL) >20th wk of pregnancy, abruptio placentae, intrauterine growth restriction (IUGR), preeclampsia). Other independent risk factors for stillbirth and late FL were excluded. To identify inherited thrombophilic conditions: fibrinogen, ATIII, protein C-S, FV-R506Q, C677T-MTHFR and G20210A-PT gene mutations, and to identify acquired thrombophilia: homocysteine, platelet count, and aPL (LA, aCL) were assessed. ANA, ENA, aTG, thyroid antimicrosomal Abs were also tested. Therapeutic protocol was: ASA 50 mg/day (6th-25th wk of gestation) and heparin 2500 U x 3/day or LMWH 4000 U/day (10th-15th wk or, in case of previous history of thrombosis, from 6th wk to delivery). Prevalence of thrombophilic defects in our study population is shown in Figure 1. Prevalence of one or more inherited or acquired defects was 43.8% and 51.1%, respectively. We evaluated 622 previously untreated and 310 treated pregnancies. Treatment led to a significant reduction ($p<0.00001$) of FL<20th wk from 46.6% to 6.8%; FL>20th wk from 16.2% to 4.2%; IUGR from 32.4% to 17.4%; and of preeclampsia from 18.4% to 2.8%. These results were confirmed also considering inherited and acquired thrombophilic defects separately. In conclusion, our study confirmed: i) the relationship between inherited/acquired thrombophilia and adverse pregnancy outcome, and ii) the reduction of adverse pregnancy outcome with thromboprophylaxis.

PP - 207

SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS WITH UNUSUAL COMPLICATIONS

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by a broad range of manifestations. We report a refractory case of SLE with multisystem presentation who developed macrophage activation syndrome (MAS).

A 13-year-old girl was diagnosed as SLE with Class IV lupus nephritis and CNS involvement. She received pulse methylprednisolone, prednisone, and cyclophosphamide therapy. On the 40th day of hospitalization, she developed fever, pancytopenia, hypofibrinogenemia, hyperferritinemia and hypertriglyceridemia. Bone marrow aspiration revealed hemophagocytosis, which was consistent with MAS. A dramatic clinical improvement was achieved in a couple of weeks with high-dose intravenous immunoglobulin administration and methylp-rednisolone therapy. Despite aggressive immunosuppressive treatment she developed vesicular skin lesions in the second month of hospitalization and skin biopsy showed bullous dermatitis, which was consistent with SLE. Skin lesions improved in two weeks with hydroxychloroquine and mycophenolate mofetil (MMF) therapy. However, MMF had to be withdrawn because of the severe side effects. Rituximab was given for persistent nephrotic proteinuria, thrombocytopenia and recurrent cardiac and CNS manifestations. Although the systemic features responded to therapy, she progressed to renal failure a year after the diagnosis.

Conclusion: We present an unusual case of SLE with bullous lesions and MAS. The association of MAS and bullous lesions in children with SLE has not been reported previously. The recognition of MAS is difficult in SLE patients. Suspected cases should be evaluated carefully with clinical features and serologic markers for differential diagnosis.

PP - 208

PERITONITIS AS THE PRIMARY MANIFESTATION AT ONSET OF CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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According to the French Pediatric-Onset SLE Study Group, as reported in J Pediatr (2005; 146:648-53), approximately 20% of children experience abdominal symptoms at onset (defined as within one month of presentation). One child of their 155 patient study group was noted to have peritonitis at onset.

In our cohort of 74 children with SLE, the percentage of children with abdominal symptoms at onset is similar, but 3 of these 74 children initially sought medical attention for recurrent sever abdominal pain, nausea and vomiting, and were then diagnosed as having peritonitis.

All were female, 2 were African/American and 1 African/Caribbean, and presentation was between the ages of 13 – 15 years. All children had ascites documented by imaging studies, which was exudative in 2 of 2 patients in whom paracentesis was performed. None had pancreatitis, cholecystitis, intestinal pseudo-obstruction, oral ulcers, evidence of gastrointestinal bleeding, or significantly abnormal liver function studies. Clinical nephritis subsequently developed in 2 of 3 patients.

Peritonitis in 2 children responded solely to high-dose intravenous methylprednisolone, whereas 1 also required the addition of mycophenolate mofetil for complete resolution. None has experienced further episodes of peritonitis.

Although the most common earliest signs at presentation of pediatric SLE are fever, arthritis, and characteristic malar rash, abdominal symptoms are not uncommon, and some of those children who present with severe abdominal discomfort, nausea, and vomiting may have peritonitis.

PP - 209

BISPHOSPHONATE TREATMENT IN A MALE PATIENT WITH LUPUS NEPHRITIS, META-STEROIDAL LOW BONE MINERAL DENSITY AND HYPOGONADISM

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Children with lupus nephritis (LN) display a higher risk of bone loss and osteoporosis due to overall disease activity, steroid treatment and secondary endocrine abnormalities.

We report a 16-year-old male patient with LN diagnosed at the age of 8 years according to the revised ACR criteria for diffuse global glomerulonephritis (class III), non-erosive arthritis, malar rash, photosensitivity, and hemolytic anemia combined with positive anti-nuclear, anti-dsDNA, and anti-phospholipid antibodies, who was treated with variable combinations of corticosteroids and immuno-suppressant drugs. At 11 years, the child underwent dual-energy X-ray absorptiometry (DEXA) to measure bone mineral density (BMD) in lumbar spine (L_2-L_4), femoral neck (FN) and total femur (TF). Supplements of calcium (1 g/day) and cholecalciferol (800 IU/day) were decided due to low BMD. Subsequent DEXA controls were performed after 2 years and then annually. At the age of 14, when the median cumulative dose of corticosteroids administered until that time was 40.9 g, bisphosphonate treatment (25 mg neridronate every month) was initiated due to the observation of meta-steroidal low BMD for age; unfortunately, febrile reactions necessitated cessation of neridronate infusions after 6 months. At the age of 15, alendronate was started (70 mg firstly administered every 15 days, then increased to 70 mg every 7 days), while a statural growth arrest was observed. At the age of 16 - when treatment included low-dose prednisone (7.5 mg/day), azathioprine (75 mg/day), hydroxychloroquine (200 mg/day) and low-dose aspirin (100 mg/day) - 1 year since alendronate initiation - BMD was improved in all sites,

but insufficient in terms of Z-score at L_2-L_4. This was probably due to secondary hormonal deficiency, particularly hypogonadism (patient's Tanner stage was P_1G_1, testicular volume 6 ml, and serum testosterone level pre-pubertal, 1.12 ng/ml). These results are summarized in the following table:

Bisphosphonate therapy can contrast bone mineral loss and prevent pathological fractures in patients receiving long-standing corticosteroids for LN. Our experience confirms the importance of periodic BMD and hypothalamus-pituitary function assessments to diagnose hormonal insufficiencies precociously.

PP - 210

OSTEOMYELITIS AND MULTIPLE AVASCULAR NECROSIS (AVN) OF BONE IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Introduction: Avascular necrosis (AVN) of bone is a rare musculoskeletal manifestation in patients with systemic lupus erythematosus (SLE). The poorly vascularized bone is a well-recognized predisposing factor to osteomyelitis, but coincidental development of AVN and bone infection in SLE has rarely been described.

We present a 17-year-old girl who was admitted to our Department in June 2006 with a 3-week history of polyarthralgia, fever, headache and facial rash. Diagnosis of SLE was made according to ACR criteria and treatment with methylprednisolone was started. She did not respond well, and hydroxychloroquine and azathioprine were introduced. Three months later, she was readmitted because of right knee pain, weakness and myalgia with increased acute inflammatory parameters. SLE laboratory features were negative. Four days later she developed fever with painful and swollen right lower extremity. She was diagnosed by MRI as having bilateral tibial AVN and distal femoral and proximal tibial osteomyelitis. Biopsy and drainage of right distal femur and knee were performed, and the culture revealed the presence of *Staphylococcus aureus*. Owing to severe side effects to clindamycin and ciprofloxacin, therapy was modified to rifampicin and cloxacillin intravenously, which she is still receiving. Methylprednisolone was tapered to 0.2 mg/kg and azathioprine was stopped. At present, SLE is in complete clinical and laboratory remission and there are no clinical signs of infection.

PP - 211

A CASE WITH IgA BULLOUS DERMATOSIS: A RARE PRESENTATION OF SLE

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Bullous dermatosis is a rare subset of SLE in children. We report a 7-year-old girl who was referred with vesiculobullous lesions during the course of the treatment of chronic arthritis diagnosed as juvenile idiopathic arthritis with low-dose steroid for two years. On presentation, she had active arthritis and a widespread urticarial, erythematous eruption associated with tense blisters, erosions, and crusting on the face, trunk and limbs. Laboratory results showed marked eosinophilia, elevation in erythrocyte sedimentation rate, CRP and IgE level. Serology for hepatitis B and C virus and HIV were negative. In addition, C3 level was slightly below normal range and C4 level was normal. IgA dermatosis was diagnosed by skin biopsy showing linear IgA deposition with subepidermal blisters. Five boluses of methylprednisolone were administered followed subsequently with prednisone 2 mg/kg/d, dapsone and colchicine. The lesions healed, but at follow-up, two relapses were observed. At the last relapse, she had widespread blistering from head to foot with oral ulcers. Laboratory evaluation

showed low levels of C3 and C4, ANA (-), anti dsDNA (+), anti-histone (+), hemolytic anemia and thrombocytosis. She was resistant to dapsone, colchicine, methotrexate and oral steroid. After addition of oral cyclophosphamide, the patient was discharged with remission of skin lesions.

This patient featured unusual skin lesions diagnosed as severe IgA dermatosis during low-dose, long-term oral steroid therapy of chronic arthritis, which was superposed with oral ulcers, positive SLE serology, hemolytic anemia and thrombocytosis.

SLE should be considered in the differential diagnosis of children presenting with generalized bullous eruptions.

PP - 212

PREGNANCY OUTCOME IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE): A BRAZILIAN MULTICENTER COHORT STUDY

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Objective: To determine pregnancy outcome and fetal loss risk factor in JSLE.

Methods: 315 female JSLE (ACR criteria) patients followed in 12 Brazilian Pediatric Rheumatology Centers were consecutively selected for this study. Menarche was observed in 298 (94.6%) of these patients.

Results: A total of 28 unplanned pregnancies occurred in 24/298 (8%) JSLE patients. The age at the first sexual intercourse was 16.4 ± 1.8 years (13–20.1) and age of the first pregnancy was 18.1 ± 1.8 years (14-21.7). Twenty-seven pregnancies occurred after lupus onset and 3 of them were in the first trimester of pregnancy during the study. The outcomes of 24/27 pregnancies that occurred after the onset of lupus resulted in fetal losses in first trimester in 5/24 (21%), live births in 18 (75%) and neonatal death in 1 (4%). Remarkably, the frequencies of diffuse proliferative glomerulonephritis, proteinuria ≥ 0.5 g/day and arterial hypertension in the first pregnancy evaluation were higher in pregnancies resulting in fetal losses than in live births (60% vs. 5%, p=0.02; 60% vs. 5%, p=0.02; 60% vs. 5%, p=0.02; respectively). Furthermore, JSLE pregnancies with fetal losses had a significantly higher mean SLEDAI at the first evaluation compared to those with live births (9.40 ± 7.47 vs. 3.94 ± 6.00, p=0.049). Despite the contraceptive prescriptions, 4 pregnancies were inadvertently exposed to intravenous cyclophosphamide therapy; these resulted in 3/5 (60%) of the fetal losses versus 1/18 (5%, p=0.020) of the live births.

Conclusions: Fetal losses were associated with active disease and nephritis, reinforcing the importance of contraception in young lupus patients.

PP - 213

AN UNUSUAL PRESENTATION OF CHILDHOOD SLE

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The thrombotic microangiopathy associated with anti-phospholipid antibody syndrome (APS) is characterized by occlusions of small vessels affecting the skin and other major organs. We report a pediatric patient who developed thrombotic microangiopathy and purpura fulminans due to APS secondary to systemic lupus erythematosus (SLE).

A 12-year-old girl was admitted with the complaints of fever, fatigue, hair loss, and arthritis of joints of hands and feet for two months. On the day of admission, the patient developed purpuric lesions on her legs that increased within hours. The physical examination revealed hair loss, bilateral ecchymotic, tender lesions on the legs, and swelling and erythema of both ankles.

The ANA titer was 1/160 and anti-dsDNA antibody level 752 IU/ml (0-100), anti-phospholipid IgM and IgG were positive, and complements were very low. She was diagnosed as SLE and secondary anti-phospholipid syndrome causing purpura fulminans. Intravenous methylprednisolone was given followed by oral prednisolone, and heparin was started. On the 9th day, she had developed new purpuric lesions, and a short lasting diplopia attack. The brain MRI revealed bilateral acute ischemic lesions of the centrum semiovale. Thus, cyclophosphamide was added and plasmapheresis was started. The skin biopsy showed leukocytoclastic vasculitis and thrombosis. After 5 sessions, her findings remitted and the patient was discharged with oral prednisolone and enoxaparin. Her antiphospholipid antibodies became negative.

We suggest that prompt treatment and plasmapheresis with clearing of the autoantibodies were efficient in reversing the course in this patient.

PP - 214

DRUG-INDUCED LUPUS: A RARE DISORDER IN CHILDHOOD

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Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin; however, various drugs have been reported to cause symptoms and laboratory findings that closely resemble SLE, known as drug-induced lupus erythematosus (DILE).

A 7-year-old boy was admitted to our hospital with the complaints of fever, loss of appetite, diffuse arthralgias, myalgias, weight loss, and swelling of the finger and toe joints. He had experienced recurrent seizures since four years of age and had used multiple antiepileptic agents. Six months ago -while on single oxcarbazepine therapy- he began to complain of diffuse arthralgias and morning stiffness. Naproxen was commenced for his pain in another center and his symptoms regressed. Three months later, valproic acid was added due to ongoing seizures and one month later levetiracetam was given and oxcarbazepine reduced. Forty-five days after the onset of valproic acid treatment (while on triple therapy), his current complaints began and continued for about one month. Oxcarbazepine was stopped before the day of admission. Physical examination revealed generalized lymphadenopathy, hepatosplenomegaly, arthritis in his proximal interphalangeal joints, wrists and ankles, and limitations and pain in all of his joints with motion. Laboratory tests were as follows: urinalysis: normal; Hb: 10.7 g/dl; WBC: 2800/mm^3; Plt: 28400/mm^3; ESR 87 mm/h; CRP 7.6 mg/dl (0-0.8); C3 and C4: normal; direct Coombs +++; ANA ++++ (1/1000); anti histone ab +; and anti nucleosome ab +. Anti dsDNA was normal. DILE was diagnosed based on the clinical and laboratory findings. Valproic acid was stopped as the causative etiologic factor.

Oxcarbazepine was the possible triggering factor for SLE in our patient and valproic acid made the second hit, resulting in DILE. This case is presented to draw attention to the rare association between DILE, oxcarbazepine and valproate.

PP - 215

PERSISTENT PULMONARY HEMORRHAGE AS THE SOLE PRESENTING CLINICAL MANIFESTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Pulmonary hemorrhage is a rare but potentially fatal presenting feature of systemic lupus erythematosus (SLE). In this report, we describe a 16-year-old girl with pulmonary hemorrhage as the sole initial presenting manifestation of SLE. She had refractory hemoptysis and required multiple blood transfusions. Despite the combined treatment of pulse methylprednisolone and intravenous cyclophosphamide, she developed generalized weakness and tonic-clonic seizures. Additional treatment with plasmapheresis resulted in rapid radiological and clinical improvement. Pulmonary hemorrhage is a rare complication of SLE and carries a high mortality rate. The pathogenesis of this fatal complication is not clearly defined, but is presumed to be mediated immunologically. It commonly occurs in association with other extrapulmonary manifestations of SLE. Here we report a girl with pulmonary hemorrhage as the initial manifestation of SLE, who followed a complicated course.

PP - 216

CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS IN 64 SOUTH INDIAN CHILDREN

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Aim: To analyze the clinical and immunological profile of childhood onset systemic lupus erythematosus (cSLE).

Materials and Methods: Prospective analysis of 64 patients with cSLE fulfilling the 1997 ACR criteria was conducted between Jan 2004 - Dec 2006. A complete clinical examination and hematological, biochemical, immunological and other relevant investigations were done to determine cardiopulmonary, renal, neurological and gastrointestinal involvement, and results were compared with other studies from 3 continents.

Results

Conclusion: cSLE is common in girls above 10 years and rare in those less than 5 years. Constitutional, mucocutaneous manifestations are common at presentation; neuropsychiatric and renal manifestations dominate during the course of illness. All 7 out of 10 rheumatoid factor (RF)-positive children had cardiopulmonary and gastrointestinal manifestations.

Conclusion: cSLE is common in girls above 10 years and rare in those less than 5 years. Constitutional, mucocutaneous manifestations are common at presentation; neuropsychiatric and renal manifestations dominate during the course of illness. All 7 out of 10 rheumatoid factor (RF)-positive children had cardiopulmonary and gastrointestinal manifestations.

PP - 217

STUDY OF NEUROPSYCHIATRIC MANIFESTATIONS IN CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS

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Aim: To analyze neuropsychiatric manifestations in childhood systemic lupus erythematosus (cSLE).

Materials and Methods: The study was a prospective analysis of 64 cSLE patients fulfilling ACR criteria and was conducted during Jan 2004 - Dec 2006. Follow-up period was 1 month to 3 years. The clinico-laboratory features were analyzed. Immunological investigations and electroencephalogram (EEG) were done for all patients. MRI or CT scan of brain was done for relevant patients and results compared with the study done by Steinlin et al., Canada.

Results: Twenty-nine (45%) had neuropsychiatric manifestations. Mean age was 13.2 vs 13.3 yrs. Female :male ratio was 4.3 :1. Neuropsychiatric events were observed as initial presentation in 34% and during the course in 66% of patients in our study; these values were 48% and 52% in Steinlin's study. Seizure occurred in 41% vs 20%, and lupus headache in 28%, cerebral infarcts in 17% in our study versus 22% and 15% in their study. Our results showed depression in 7%, and polyradiculopathy, peripheral neuropathy in one each (3%). Steinlin reported peripheral neuropathy as 5% and movement disorder as 3% in their patients. Other rates included sleep disturbances (17%) and psychosis (10%) in our patients, EEG abnormalities (20%), MRI brain infarct (20%) and cerebral atrophy (7%). ANA positivity was present in 97%, anti-dsDNA 69%, anti-Sm antibody 26%, anti-cardiolipin antibody Ig G 17%, and Ig M positive 24%. One (3%) had lupus anticoagulant positivity.

Conclusion: Forty-five percent had neurop-sychiatric manifestations. Seizure was the most common manifestation and none had movement disorders in our study. EEG was abnormal in half of our patients who had seizures and in 33% of patients in the study done by Steinlin et al.

PP - 218

MUCOCUTANEOUS MANIFESTATIONS IN CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: To analyze the mucocutaneous manifestations in childhood systemic lupus erythematosus (cSLE).

Materials and Methods: Prospective analysis of 64 patients with cSLE, fulfilling ACR criteria, was done during the period Jan 2004 to Dec 2006. A detailed evaluation was done and results were compared with the study of Wananukul et al.

Results: Male :female ratio was 1 :4.3. Mean age was 13.2 years vs 11.9 years. Mucocutaneous lesions were present in 54 (84.4%) vs 77%. Specific skin lesions were present in 70%. Out of 33 who had acute lesions, 39% had malar rash in our study and 74% in their study. Twelve (22%) had generalized maculopapular rash and one had subacute cutaneous lupus erythematosus lesions in our study and none in the compared study. Two (4%) had discoid lupus erythematosus (DLE) lesions in contrast with 19% in their study. Out of 47 who had nonspecific skin lesions, alopecia was present in 60%, oral ulcers in 52%, and photosensitivity in 30% in our study; these rates were 32%, 46%, and 40%, respectively, in their study. Vasculitic lesions were present in 41%, as purpura 22%, leg ulcer 5%, skin infarct 9%, urticarial lesions 4%, gangrene 2%, dyschromic nails 19%, diffuse hyperpigmented lesions 14%, lupus panniculitis 5%, and Raynaud's phenomenon, ecchymosis, and hypopigmented lesions 2% each. In the compared study, vasculitis was noted in 42%. ANA was positive in 98% and anti dsDNA in 69% of our patients compared to 93% and 46%, respectively, in Wananukul et al.'s study.

Conclusion: Malar rash and discoid lesions were less common and generalized maculopapular rash and alopecia more common in our patients compared to those of Wananukul et al.'s study group.

PP - 219

A CASE OF POLYARTHRITIS, RAYNAUD'S PHENOMENON AND MUSCLE WEAKNESS

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We present the case of a 10-year-old girl with the symptoms of polyarthritis, Raynaud's phenomenon and ***muscle weakness. D***iagnostic workup included detection of strongly positive antinuclear antibodies (ANA) and detection of autoantibodies against the U1 small nuclear ribonucleoprotein (anti-RNP).

The patient was diagnosed with mixed connective tissue disease (MCTD). MCTD is characterized by overlapping symptoms of lupus erythematosus, systemic sclerosis and dermatomyositis. Pediatric presentations account for 23% of all cases, which makes MCTD an important pediatric differential diagnosis. Here we describe the diagnostic procedure and therapeutic management of a typical case of pediatric-onset MCTD. Moreover, we discuss controversy regarding the specificity of RNP autoantibodies for the diagnosis and debate the significance of the separate entity of the mixed connective tissue disease.

• Vasculitis

PP - 220

CUTANEOUS POLYARTERITIS NODOSA IN CHILDREN - INCEPTION COHORT RESULTS FROM SICKKIDS TORONTO

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Cutaneous polyarteritis nodosa (cPAN) is a severe necrotizing vasculitis in children. The main pathologic feature of the disease is necrotizing vasculitis involving primarily small- and medium-sized arteries. The etiology of the disease is unknown. Strong associations with infections like hepatitis and Strep infections are documented in cPAN.

Objective: To define the clinical, laboratory and long-term follow-up characteristics of the disease in an inception cohort.

Methods: Retrospective cohort study was performed including consecutive patients seen at SickKids with the diagnosis of cPAN from 1991 to 2007.

Results: 19 patients were found to have cPAN. Male/female ratio was 11/8 (ratio 1.37:1). Mean age at the diagnosis of the disease was 9.5 years (range: 11 months – 16 years and 7 months). All patients had fever, rash and lymphadenomegaly. Laboratory features included elevated ESR in 15/19 patients (mean: 51 mm/h, range 1-131 mm/h), high WBC in 9/19 patients (mean 10.6, range 4.3–21.4), and low Hb in 12/19 patients (mean 115, range 86-153). Skin biopsy was performed in 14 patients and results in 13 were consistent with cPAN. Patients were followed either without treatment (n=6), or with non-steroidal anti-inflammatory drugs, i.e. indomethacin (n=2), or indomethacin and/or prednisone. Two patients required cyclophosphamide treatment, either due to unresponsive disease or relapse. Mean follow-up time for all patients was 29 months (range 1–73 months).

Conclusion: Cutaneous PAN is a rare vasculitis in childhood. In our patients, we found elevated inflammatory markers. Skin biopsy results were consistent in all but one patient. Some of our patients were treated with prednisone; however, two of our patients had relapse and one of our patients needed cyclophosphamide for resistant disease. Future research should be directed towards determining predictors of disease severity, as the course of cutaneous PAN ranges from mild to severe disease requiring cyclophosphamide treatment.

PP - 221

CHILDHOOD CUTANEOUS PAN AND MONONEURITIS MULTIPLEX

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Cutaneous polyarteritis nodosa (CPAN) has been described as a distinct entity with cutaneous lesions without systemic involvement. A few of the childhood reports, similar to the adult reports, include mononeuritis multiplex as a feature of the disease. Here we report a case of CPAN with mononeuritis multiplex and aim to discuss whether childhood CPAN definition should include mononeuritis multiplex.

An 8-year-old girl presented with a one-year history of tender nodules on her extremities together with livedo reticularis. Fever and arthritis were also present. Laboratory examination was as follows: urinalysis: normal, biochemical analysis: normal, Hb: 9.61 g/dl, WBC: 6950/μL, platelet count: 360000/μL, ESR: 75 mm/h, CRP: 9.5 mg/dl (N<0.5), ANA: (+), anti ds DNA: (-), C3: 149 mg/dl, C4: 27 mg/dl, VDRL: (-), ASO: 40 IU/ml (N<200), HBs Ag: (-), anti HCV IgM and G: (-), anti cardiolipin Ig M and G: (-), and ANCA: (-). A skin biopsy specimen from a nodule showed changes consistent with necrotizing arteritis. Tender nodules subsided with prednisone 1 mg/kg but livedo reticularis persisted. During an upper respiratory tract illness she suffered from myalgia and pins and needles in her left hand. Electromyography revealed mononeuritis multiplex. Renal and mesentery angiography was normal. Mononeuritis was successfully treated with 2 mg/kg prednisone. She is now in remission with methotrexate.

This case is presented to point out that mononeuritis multiplex is not only a systemic feature of PAN but could also be a feature of CPAN.

PP - 222

SYSTEMIC VASCULITIS COMPLICATING THE FOLLOW-UP OF UNDIFFERENTIATED CONNECTIVE DISEASE

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This case report concerns a female patient, 18 years old, who at the age of 11 years presented fever, precordial pain associated with increased inflammatory indexes and ASLT, and pericarditis. Rheumatic carditis was diagnosed. Steroid and oral cephalosporins were administrated for 10 days with disappearance of symptoms. She began prophylaxis with i.m. benzathine penicillin. After 1 month, the girl had a new episode of pericarditis and arthralgias. Steroid was re-started, but after 6 months the girl presented malaise and fever again and so was admitted to our hospital. Increased inflammatory indexes, with ANA, ENA, anti-DNA, and ANCA negativity, and normal kidney were detected, without pericarditis. An undifferentiated connective tissue disorder was diagnosed and MTX was started. Five years later, the girl presented microhematuria, mild proteinuria with p-ANCA positivity and elevated CRP. Anti-glomerular basement membrane antibody was negative. A renal biopsy disclosed a "pauci-immune" glomerulonephritis. Chest CT showed hemorrhagic pulmonary involvement, confirmed by bronchoscopy, and millimetric nodules. The girl was treated with cyclophosphamide and prednisone therapy with remission of pulmonary involvement. She is on prednisone and azathioprine with no further abnormalities of urine or pulmonary involvement. p-ANCA titer is decreasing progressively. According to ACR criteria, Wegener granulomatosis was diagnosed first, for the presence of 2 of the 4 required criteria (abnormal urinalysis and abnormal chest X-ray). On the other side, according to recent EULAR/PRESS Endorsed Consensus Criteria, is it possible to consider microscopic polyangiitis as an alternative diagnosis?

PP - 223

CUTANEOUS VASCULITIS AFTER MYCOPLASMA PNEUMONIAE (MP) INFECTION

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A 9-year-old girl was admitted to our clinic for Henoch-Schönlein purpura-like skin lesions. After 8 days of fever and 6 days of clavulanate-amoxicillin, when body temperature had returned to normal, maculopapular rashes appeared, starting from the lower extremity of the legs up to chest, back and arms. Physical examination and X-ray findings were consistent with a pulmonary infection localized in the right lung. Laboratory findings showed microhematuria (20 RBC/uL), but no proteinuria and a mild elevation in CRP; serological tests showed recent *Mycoplasma pneumoniae* (MP) infection, confirmed by pharyngeal swab positivity for MP. The patient underwent macrolide treatment (15 mg/kg/dose twice a day) for 15 days. Remission of skin lesions was obtained in about 7 days, evolving to ecchymoses.

Mycoplasma pneumoniae is a bacterial agent responsible for respiratory infections. It can lead to two kinds of complications: one caused by the invasion of respiratory tissue, for example pleuritis; the other one mediated by an autoimmune mechanism, such as vasculitis or reactive arthritis. The second one usually manifests with an average delay of 10 days from the beginning of the respiratory symptoms. Furthermore, a relation between MP and glomerulonephritis is reported in the literature (Said–Pediatric Nephrology 1999). For these reasons, it is necessary to treat MP properly with macrolides for suspected mycoplasma respiratory infection, to avoid complications, and continued monitoring of renal function is needed even after remission of cutaneous symptoms to exclude any possible damage.

PP - 224

RENAL INVOLVEMENT IN HENOCH-SCHÖNLEIN PURPURA

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Introduction: Henoch-Schönlein purpura (HSP) is the most common vasculitis in the pediatric age and renal involvement is the main cause of morbimortality during a long-term follow-up.

Objectives: To verify the frequency, association with other clinical signs and symptoms, and time of appearance.

Methods: This is a cross-sectional study that comprised children and adolescents assisted in our service in 2005.

Results: There were 25 patients, 13 female (52%), with mean age at symptoms onset 6.2 years (2-13 years). The most common clinical signs and symptoms in the first week were palpable purpura, arthritis and abdominal pain. The most common evolutive signs and symptoms were purpura, arthritis and dark urine. Eight patients (32%) had nephritis that appeared 1-14 months (mean 3 months) from HSP onset, but one patient developed nephritis within 35 months. Renal biopsy was performed in only two patients (one showed mesangial glomerulonephritis and the other diffuse proliferative). Six out of these eight patients needed immunosuppression (prednisone, azathioprine, cyclophosphamide, mycophenolate mofetil).

Conclusion: Renal involvement in HSP is not infrequent and may arise a long time after disease onset, which makes a long follow-up essential in these patients. The need for frequent immunosuppression leads us think that renal involvement in HSP may not be as benign as suggested in the literature.

PP - 225

CHILDHOOD STROKE SIGNS CNS VASCULITIS

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Vasculitis of the central nervous system (CNS) is a catastrophic condition in children and presents the clinician with a diagnostic challenge. CNS vasculitis may occur as an isolated phenomenon of unknown cause (primary CNS vasculitis) or may be associated with an identifiable systemic condition (secondary CNS vasculitis). Stroke is the main topic of CNS vasculitis. We report a 12-year-old Caucasian boy who presented with a one-month history of multiple recurrent strokes with hemiparesis and nervus VI palsy. The blood cell count, erythrocyte sedimentation rate (ESR), chest X-ray and chest CT were normal. The titers for ANA and ANCA were negative. The differential diagnosis included infection and malignancy. The MRI revealed multiple non-hemorrhagic infarctions. Conventional angiography was typical for vasculitis. Therapy with prednisolone, cyclophosphamide and mycophenolate mofetil resulted in clinical remission.

CNS vasculitis is a differential diagnosis for stroke. Therefore, CNS vasculitis should not be underestimated because of its catastrophic complications.

PP - 226

CHILDHOOD STROKE SIGNS TAKAYASU'S ARTERITIS: DIAGNOSTIC DELAY CAN CAUSE CATASTROPHIC COMPLICATION

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Takayasu's arteritis (TA) is a granulomatous inflammation of the aorta and its major branches. Clinical presentation in adults is characterized by symptoms due to stenosis or aneurysms of the involved vessels. Children may present with organ-specific or with nonspecific systemic features. Therefore, connecting the symptoms with the diagnosis may be a challenge in pediatric patients. Tremendous complications can develop when the diagnosis is missed and the consecutive treatment is delayed. We present a 9½-year-old girl who developed eight episodes of stroke before diagnosis of TA was established and proper anti-inflammatory treatment was initiated. TA in children has a different presentation from that in adults and may cause catastrophic complications. Therefore, TA has to be considered in children presenting with stroke.

PP - 227

QUANTITATIVE DETECTION OF CIRCULATING ENDOTHELIAL CELLS-FLOW CYTOMETRIC DETECTION IS NOT THE SAME AS MAGNETIC BEAD EXTRACTION

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Introduction: Circulating endothelial cells (CECs) are biomarkers for endothelial cell (EC) injury. There are two key techniques that are used to quantify CECs: immunomagnetic bead extraction and flow cytometry. Previous studies suggested comparable CEC counts obtained using these two techniques. However, we question whether they are identifying the same population of cells, and with comparable levels of sensitivity.

Methods and Results: Immunomagnetic bead extraction of CD146+ cells subsequently stained with FITC-conjugated ULEX was compared to flow cytometry of CD146+ cells using previously published protocols. Using immunomagnetic beads, we demonstrated similarity in size (15-50 μm) and morphology between detached cultured human umbilical vein endothelial cells (HUVEC) and CECs from a child with active vasculitis. HUVEC and CECs were considerably larger than the monocytic cells extracted from peripheral blood mononuclear cells (PBMCs) (<10 μm). By spiking whole blood with HUVEC, we were able to reliably retrieve them using immunomagnetic beads over the range 10-100000 HUVEC/ml of blood, with >60% recovery rate over the pathophysiological range (100-1000 HUVEC/ml). In contrast, flow cytometry was unable to detect HUVEC spiked in whole blood using the linear forward and side scatter acquisition settings (optimized for PBMCs) suggested by previous studies. HUVEC were detected using standard EC logarithmic flow cytometric acquisition gates, although sensitivity using this latter setting was lower than bead extraction: HUVEC were only detected after addition of greater than 1000 HUVEC/ml, always with <25% recovery rate.

Conclusions: We have shown that CECs detected using immunomagnetic beads are a different cell population from the flow cytometry defined CD146+ cells described in previous studies. HUVEC and CECs are detected in a standard flow cytometric EC acquisition gate, but at considerably lower sensitivity than immunomagnetic bead CEC quantification. Thus, the two techniques are not directly comparable, and we urge caution when comparing results from studies using these different techniques.

PP - 228

RENAL INVOLVEMENT IN HENOCH-SCHÖNLEIN PURPURA: A MULTIVARIATE ANALYSIS OF INITIAL PROGNOSTIC FACTORS

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Objectives: To identify initial predictive factors for renal involvement in children and adolescents with Henoch-Schönlein purpura (HSP).

Methods: Over a period of 21 years, medical records of 142 patients with a diagnosis of HSP admitted in our University Hospital were reviewed. The initial predictive factors evaluated in the first three months included: demographic data, clinical features (persistent palpable purpura, arthritis, abdominal pain, severe abdominal pain, gastrointestinal bleeding, orchitis, central nervous system involvement and pulmonary hemorrhage), laboratory tests (serum levels of IgA) and treatment (corticosteroids, intravenous immunoglobulin and immunosuppressives). Patients were divided in two groups with presence or absence of nephritis,

and were evaluated according to univariate and multivariate analysis.

Results: Nephritis was seen in 70 patients (49.3%). Of note, univariate analysis revealed that severe abdominal pain (p=0.0049; OR 1.6; CI 1.18-2.21), gastrointestinal bleeding (p=0.004; OR - 1.6; CI 1.10–2.26) and corticosteroids use (p=0.0012; OR - 1.7; CI 1.28–2.40) were associated with a higher incidence of renal involvement. It was remarkable that in the multivariate analysis, the logistical regression showed that the only independent variable in the prediction of nephritis was severe abdominal pain (p<0.012; OR 2.593; CI 1.234–5.452).

Conclusions: Severe abdominal pain represented a significant predictor of HSP nephritis. Therefore, pediatric patients with this clinical feature should be rigorously followed due to their higher risk of renal involvement.

PP - 229

EXPERIENCE WITH A COMMUNITY MODEL FOR IMPROVING THE AWARENESS AND CARE OF KAWASAKI DISEASE IN MUMBAI, INDIA

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We report our experience with a Registry for Kawasaki disease (KD), established Jan 2003 under the auspices of the local pediatric association (MBIAP).

In addition to data collection, the multi-pronged approach consists of a) physician awareness initiatives, including a mailer titled "Spend a minute, Save a Heart", b) assistance with diagnosis including tele/net support, c) bilingual parent information brochures titled "Mom Dad and Kawasaki disease", d) pharma liaison for IVIg, occasionally at concession, e) publicity through a scorecard column in the monthly newsletter and a poster at the annual conference, and f) assisting other cities to set up similar models.

Prior to the registry, there was 1 reported case. To date, 109 cases have been registered by 63 pediatricians with 75 confirmed KD (11 in 2003 rising to 26 in 2006). An important motive to report is to seek endorsement before recommending IVIg. Thirty-four cases with alternative diagnosis have allowed us to enumerate disorders simulating KD. We observed equal sex distribution and 10 children were below one year. 57/75 cases were diagnosed before Day 10, with the earliest on Day 4 and the latest on Day 30. 68/75 received IVIg, of which 2 needed repeat IVIg and 1 additional infliximab. 8/67 patients followed for 6 weeks had persistent ECHO abnormalities, 5 of whom were diagnosed before Day 10. No mortality or hitherto unreported features were observed.

We confirm our belief that such models are feasible with keen scientific interest and minimum resource. They help increase awareness of seemingly rare diseases, determine their local burden, educate physicians/laypersons, provide a database for research, and rationalize usage of costly drugs.

PP - 230

EXPERIENCE WITH INFLIXIMAB IN A 14-MONTH-OLD BOY WITH UNCLASSIFIED VASCULITIS

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Background: Juvenile idiopathic arthritis is the main indication for treatment with TNF-α blockers in children. Nowadays, they are used in other inflammatory diseases but there are few reports on patients treated below 2 years.

Case Report: One month after an episode with intermittent fever for 2 weeks and a maculopapular rash, a 4-month-old boy presented with a septic status with low cardiac output. Infectious etiology was ruled out. Myocardial infarction and a giant aneurysm of the left coronary artery were diagnosed. He developed severe arterial hypertension, transient renal failure and necrotizing peripheral vasculopathy. All autoantibodies tested were negative; a skin biopsy was not performed because of the poor clinical condition. Treatment with immunoglobulins (IVIG) was not

effective. When we saw the boy 5 months later in the outpatient department, he was clinically fine but showed ongoing inflammatory activity with elevation of ESR, CRP and leuko- and thrombocytosis. IVIGs and steroid pulse (30 mg/kg) were given followed by prednisolone (1 mg/kg). Two months later he developed bloody stools. Whole body MR-angiography and colonoscopy were inconspicuous. Infliximab (5 mg/kg) was started at the age of 14 months. After 2 doses, prednisolone could be decreased to 0.25 mg/kg, he gained weight again, and repetitive stool tests for occult blood were negative.

Conclusion: Our case shows that TNF-α inhibitors can be an effective treatment in children with systemic vasculitis not responding to conventional therapies, and they seem to be safe even in this age group.

PP - 231

APOPTOSIS AND HEAT-SHOCK PROTEIN-70 (HSP-70) IN HENOCH-SCHÖNLEIN NEPHRITIS (HSN): A PRELIMINARY STUDY

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There have been increasing reports on the role of apoptosis and heat-shock proteins (HSP) in renal disease. The data are limited in cases with Henoch-Schönlein nephritis (HSN). In this study, we investigated the relationships between glomerular apoptosis, HSP-70 and histopathological findings in 18 cases with HSN. There were 9 females and 9 males, aged from 5 to 20 years. Eighteen renal biopsies from patients with HSN and four kidney samples from control cases were investigated by light and immunofluorescence microscopy. Apoptosis was determined by in situ DNA nick end labeling technique and HSP-70 were identified by immunohistochemistry. Patients were divided into crescentic (9 cases) and non-crescentic (9 cases) groups. Apoptotic index and HSP-70 staining were not different statistically between the two groups. No correlation was found between apoptosis and serum creatinine or proteinuria. HSP-70 was mainly stained in the nuclei and cytoplasm of glomerular visceral epithelial cells, proximal and distal tubules, and some cortical collecting tubules, while no staining was detected in medullary collecting tubules. HSP-70 staining revealed no correlation with proteinuria or serum creatinine. The intensity of HSP-70 staining in patients with HSN was slightly higher than in control subjects but showed no significant correlation with apoptotic index. In conclusion, the relationship between HSP-70 and apoptosis in the presented cases was not clearly evident.

PP - 232

MANNOSE BINDING LECTIN (MBL) POLYMORPHISMS AND AGE AT ONSET OF KAWASAKI DISEASE (KD)

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Background: Kawasaki disease (KD) is a systemic febrile vasculitis most likely triggered by an infectious agent. Mannose binding lectin (MBL), a protein of the innate immune system, is involved in the inflammatory response. MBL levels are regulated by polymorphisms in the promoter (H/L and X/Y) and in exon 1 (A/B/C/D) of the MBL gene. Deficiency in MBL due to gene point mutation seems to predispose to infections.

Aims: 1. To evaluate MBL polymorphisms in KD patients and in controls. 2. To correlate MBL mutations linked with low or normal protein

synthesis with age of patients at KD onset and disease severity.

Patients and Methods: 124 children discharged with the diagnosis of KD (72 M, 52 F) (age range 5-71 months, median 37.5) entered the study. 12/124 patients (9.6%) had coronary disease. Blood samples from 138 age- and sex-matched healthy children were used as controls. KD patients and controls were Caucasians, all of Italian ancestry. Genomic DNA was extracted from EDTA blood samples using QIAmp DNA Blood kit (Qiagen, Hilden, Germany). Typing of MBL gene exon 1 (mutant codons 52, 54 and 57) and promoter (codons –221 and –550) was performed by PCR and restriction fragment length polymorphism (RFLP). For exon 1 the wild type was designated as allele A while B, C and D were mutants in codon 54, 57 and 52, respectively. For the promoter, the wild type was designated as allele L (position –550) and allele Y (position –221) while H and X were the two mutants, respectively. Statistical evaluation was performed by SPSSX (ver.10.0) using Fisher's exact or chi-square tests, as appropriate. In KD patients, serum MBL concentrations were measured using a double enzyme immunoassay (Antibodyshop-Denmark).

Results: As already shown by our group, MBL "low" mutations were more common in KD than in controls. The median age at KD onset in patients with low mutation was 39 months, while in those with wild type it was 25 months ($p<0.005$). No correlation was found between CRP levels, platelet count, Hb, and MBL polymorphisms. When analyzing the correlation between MBL levels and response to IVIG therapy, 8/49 patients (16.3%) with normal MBL levels required additional IVIG infusions (2 or 3), while in the group with low MBL mutations, only 1 patient out of 19 (5.2%) required a second infusion.

Conclusions: A "low" mutation of the MBL gene seems to be associated with a higher risk of KD. Conversely, patients with "normal" MBL develop KD at an earlier age than those with low mutation. As suggested by the need of additional IVIG therapy, "normal" MBL patients develop a more severe course of the disease, possibly due to MBL pro-inflammatory action.

PP - 233

EXPERIENCE WITH THE USE OF TUMOR NECROSIS FACTOR ANTAGONISTS IN CHILDREN WITH TAKAYASU ARTERITIS

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Objective: To report our experience with the use of tumor necrosis factor (TNF) antagonists in the treatment of children with Takayasu arteritis (TA).

Methods: Five patients, 4 girls and 1 boy, who met the American College of Rheumatology classification criteria for TA were started with infliximab (IFX) because of disease relapse during conventional therapy (4 patients) or as first-line therapy together with steroids (1 patient). Infliximab was administered at the dose of 5 mg/kg at weeks 0, 2 and 6, and every 6 weeks thereafter. Methotrexate or azathioprine therapy was associated to prevent production of anti-chimeric antibodies. Outcome measures included acute phase reactants, changes in prednisone dosage, Doppler ultrasound and MR angiography.

Results: Median age at diagnosis was 12.9 years (range 7.6–21). Median duration of IFX therapy was 18 months (range 6-27). At the end of IFX therapy, all but one patient had reduced prednisone dose, 3 patients had normalization of acute phase reactants, and patient imaging studies in all showed no new vascular lesions and no worsened vessel wall enhancement. One patient was switched to etanercept after 10 infusions of IFX because of incomplete clinical response. This patient was further switched to adalimumab 4 months later due to etanercept inefficacy and is currently doing better. Another patient had a disease relapse after an initial response to IFX and was then switched to adalimumab for 2 months without improvement. No patient experienced major adverse events during anti-TNF therapy.

Conclusion: Our results show that anti-TNF agents represent a promising therapeutic option for children with TA. A controlled trial is warranted to further evaluate the efficacy and safety of these drugs in TA.

PP - 234

LONG-TERM EFFICACY OF RITUXIMAB IN A CHILD WITH A SEVERE DIGESTIVE C-ANCA/PR-3 ASSOCIATED VASCULITIS

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While the efficacy of rituximab for adult ANCA-associated vasculitis is disputed, it has not been evaluated in children. A severe digestive vasculitis was diagnosed in a 47-month-old girl with positive C-ANCA (>1/640e) and proteinase 3 specificity. There was no other organ involvement. Remission was obtained after methyl-prednisolone pulse therapy (1 g/1.73m^2 x 3) followed by 2 mg/kg/d of steroid and 6 intravenous pulses of cyclophosphamide (700 mg/m^2/pulse). Azathioprine was then started. Nine months after the diagnosis, while the child received prednisone 0.4 mg/kg/d, a clinical relapse occurred. c-ANCA and PR3 were also positive again. Methyl-prednisolone pulses were performed, followed by 1 mg/kg/d of prednisone and 4 intravenous cyclophosphamide pulses. Because of the important cumulative dose of cyclophosphamide (272 mg/kg), this treatment was stopped, and 4 infusions of rituximab were administrated (375 mg/m^2/injection/week) followed by a total blood peripheral B lymphocytes depletion. A second relapse occurred 5 months after the last injection of rituximab concomitant with the increasing of peripheral B lymphocytes. Improvement was obtained after 4 pulses of steroid associated with a unique injection of MabThera. After depletion, peripheral B lymphocytes were again detectable after 8 months following the last MabThera injection. With an actual follow-up of 18 months after the last infusion of rituximab, the child is still in clinical remission with a 0.25 mg/kg dose of prednisone and c-ANCA/PR3 is negative. Rituximab might be a promising cyclophosphamide-sparing therapy in severe vasculitis c-ANCA/PR3+ in children. Such treatment should be evaluated in larger prospective studies.

PP - 235

KAWASAKI DISEASE: NOTES FROM AN ITALIAN STUDY

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By general agreement, the diagnosis of Kawasaki disease is still set in presence of high fever for more than 5 days, plus at least four of the following: skin rash, conjunctivitis, mucositis, cervical adenopathy and alterations in hands and/or feet, though around 10% of patients show "incomplete" forms, in which not all the classical criteria are met. The main sequela of the disease is coronary aneurysm, showing from 25% of not treated to 4-9.5% of properly treated patients. As far as we know, treatment effectiveness against coronary aneurysms mainly depends on the length of the disease before treatment administration, the threshold seeming to be the 10th day of fever. 54 patients treated for Kawasaki disease in the Paediatric Regina Margherita Hospital of Turin, Italy, from 1999 to 2005 were studied. Our patients mimic literature cases for general features, rate of complete vs incomplete cases, and clinical aspects (Tables I, II and III). The patients with incomplete forms (12/54), the frequency of which was above expected, were recognized, admitted and treated later than the patients with classical forms, and showed a clear increase in aneurysmal complications (Tables II and IV). The high percentage of aneurysmatic complications, far exceeding that reported, seems to be mainly due to an initial delay in diagnosis and treatment (Table IV). Self-referral was more frequent than family pediatrician admission, more for incomplete cases (Table II).

Conclusions: Our data seem to underline that greater family pediatrician awareness of the disease and of its incomplete forms is paramount for an early referral and treatment of Kawasaki disease to reduce the risk of aneurysms. A careful examination of patients, especially babies younger than one year, for the secondary signs of the disease (such as the scaly perineal rash, relevant irritability, sterile urine leukocytes), often peculiar, can lead to an early diagnosis, basic for an effective treatment.

PP - 236

SUCCESSFUL TREATMENT OF DIGITAL ISCHEMIA AND GANGRENE WITH ILOPROST IN A CHILD WITH POST-STREPTOCOCCAL POLYARTERITIS NODOSA

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Prostacyclin is a potent endogenous vasodilator that inhibits platelet adhesion and aggregation, and prevents smooth muscle proliferation. The use of the prostacyclin analogue, iloprost, for the treatment of severe digital ischemia in pediatric post-streptococcal cutaneous polyarteritis nodosa (PAN) has not been previously reported.

Case Discussion: A previously healthy 7-year-old girl presented with fever, arthritis and myalgias one week after diagnosis of streptococcal pharyngitis. She failed to respond to NSAIDs, IV solumedrol 30/mg/kg pulses and a tapering course of oral prednisone. Her vasculitis progressed and she developed tender subcutaneous nodules, diffuse livido reticularis and varying intensity of tender ischemia of all digits. Digital ischemia worsened despite treatment with low-dose aspirin, one dose of infliximab, one IV cyclophosphamide pulse and twice daily enoxaparin sodium injections. She developed gangrene of three digits. She was started on IV iloprost infusions at incrementally increasing doses. Digital perfusion improved within 24 hours of the first infusion, and ischemia resolved entirely during the 9-day iloprost course. Eventually, she had limited auto-amputation of the distal aspects of the three digits with gangrene. Following iloprost, she was treated with oral cyclophosphamide and sildenafil for three months, with resolution of all clinical symptoms.

Comment: Iloprost treatment was impressively effective in our patient with severe digital ischemia associated with post-streptococcal PAN.

PP- 237

UNUSUAL CAUSE OF ACUTE NEUROLOGIC DEFICIT IN CHILDHOOD: PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

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Primary central nervous system vasculitis (PCNSV) of childhood is a rare disorder. The most common signs and symptoms are acute severe headache and focal neurologic deficit. It should be suspected in children who have an acquired neurologic deficit that remains unexplained after an initial basic evaluation. Diagnosis usually depends on brain magnetic resonance imaging (MRI) and conventional angiography of cerebral vasculature. In this report, we describe an 8-year-old boy who presented with vertebrobasilar insufficiency and impaired consciousness. The patient was admitted to the hospital with acute onset of behavior changes, ataxia, and dysarthria. On physical examination, he had muscle weakness, impaired consciousness, bilateral fascial weakness, bilateral Babinski sign and nystagmus. Brain MRI showed pontine infarction and millimetric lacunae on thalamus. Conventional angiography revealed widespread vasculitic changes of medium-sized vessels and occlusion of basilar artery. Biochemical, microbiological and serologic markers did not reveal any risk factor for prothrombotic conditions, infections, metabolic diseases or systemic vasculitis. The patient had good response to steroid and immunosuppressive treatment. He had good neurologic outcome throughout two years

follow-up. The control MRI did not show any new lesion, and MR angiography revealed basilar arterial recanalization. In conclusion, PCNSV should be kept in mind in children with acquired neurological deficit of unknown etiology.

PP - 238

UNILATERAL CERVICAL MASS AS A MAIN CLUE RAISING THE DIAGNOSTIC SUSPICION OF KAWASAKI SYNDROME

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Kawasaki syndrome (KS) is a relevant cause of cervical lymphadenopathy in childhood, though recognized with delay in many clinical scenarios.

We report a 6-year-old boy who was hospitalized after a 5-day history of painful left cervical swelling and a 3-day history of fever unresponsive to amoxicillin per os. Blood tests revealed: WBC count 17, 590/mm^3 (N 83%), ESR 87, and CRP 64.7 mg/l (n.v. <3). Empiric treatment with ceftriaxone (firstly 40 mg/kg/day, then increased to 85 mg/kg/day) and teicoplanin (8 mg/kg/day) was started and continued, despite a mild non-specific skin rash that appeared the following day. The clinical picture was still characterized by high fever, severe neck pain, stiffness and increased left cervical adenopathy. Neck echography revealed more than 10 enlarged cervical lymph nodes with a maximal diameter of 20 mm. Neck CT scan revealed no evidence of fistulization in the soft tissues. Three days later, blood tests showed worsening of inflammatory markers (WBC 22, 130/mm^3, N 82.4%, ESR 87, CRP 128), while hemoculture, Mantoux-intradermoreaction, Epstein-Barr virus, cytomegalovirus, *Toxoplasma gondii*, *Bartonella henselae* serologies, anti-streptolysin O titer, pharyngeal swab, angiotensin converting enzyme and anti-nuclear antibodies were all negative. On 7th illness day, the non-fluctuant unilateral left laterocervical mass persisted, and the child developed right knee arthritis, non-exudative bilateral conjunctivitis and lip fissures. Edema of hands and perineal desquamative eruption emerged on the 8th day, leading to the final diagnosis of KS. The complete resolution of symptoms was obtained with intravenous gammaglobulin and oral high-dose aspirin; the cervical mass completely disappeared in a 7-day period with no consequence on neck motility. Ten days after gammaglobulin infusion, blood tests confirmed the amelioration of inflammatory markers (WBC 5, 100/mm^3, N 45%, ESR 36, CRP 5.9) with PLT count of 645, 000/mm^3. No heart coronary abnormality was observed at the cardiologic follow-up.

Cervical lymphadenopathy is the least common clinical sign of KS, being present in approximately 50 to 70% patients. Difficulty in diagnosing KS in febrile children with exclusive cervical adenopathic involvement represents a huge concern for clinicians. Unilateral cervical lymphadenopathy mimicking acute suppurative infections, especially if unresponsive to antibiotic therapy, should suggest a diagnosis of KS.

PP - 239

CLINICO-EPIDEMIOLOGICAL PROFILE AND MANAGEMENT OF HENOCH SCHÖNLEIN PURPURA AT ALFATEH CHILDREN HOSPITAL-BENGHAZI (5-YEAR REVIEW)

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Background: Henoch-Schönlein purpura (HSP) is an inflammatory disorder characterized by generalized vasculitis of small vessels of skin, gastrointestinal (GIT) system, kidney, joints, and rarely the lungs and central nervous system (CNS). It is the most common vasculitis in children.

Objective: To determine the epidemiology, clinical presentation, management and outcome of HSP at Alfateh Children's Hospital.

Setting: Medical Department of Alfateh Children's Hospital from Jan 2001-Dec 2005.

Patients and Method: A case series observational study in which the files of 117 patients with diagnosis of HSP were retrospectively studied for age, sex, residence, date and duration of admission, clinical presentations, investigations and management.

Results: 117 patients were admitted with diagnosis of HSP over a 5-year period, accounting for 0.2% of total hospital admissions. Male to female ratio was 1.2:1. The age range was from 1-13 years, and median age was 4.7 years. There were clusters of patients observed between October and January. The mean duration of admissions was 6 days. 15% of patients had recurrence of admission. The most common clinical features were purpuric skin rash (100%), 66% with joint involvement, 56% with GIT symptoms, 28% with renal involvement, 26% with edema, and 5% with scrotal swelling; none of the patients had significant CNS manifestation. 22% of patients presented with low Hb, 40% leukocytosis, 23% thrombocytosis, and 52% high ESR. Surgical consultations were needed in 17%. Surgical intervention before admission was 3.5%. Steroid was given to 38% of the patients, all for GIT complaints, and 88% of them improved within 1-3 days.

Conclusion: Our patients presented at younger age, with slightly less GIT involvement, but with similar clinical features and laboratory findings. Steroid was very helpful in treating patients with GIT symptoms.

Recommendation:

• Early administration of steroids in cases of HSP with GIT symptoms.

• Further studies are needed to search the infectious causes of HSP and role of steroids in management.

Cases should be followed for recurrence of disease and early treatment of renal complication.

PP - 240

COMPLEMENT FACTOR I DEFICIENCY ASSOCIATED WITH RECURRENT INFECTIONS, VASCULITIS AND IMMUNE COMPLEX GLOMERULONEPHRITIS

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Here we report complement factor I deficiency in an 11-year-old girl from a consanguineous Turkish family, who presented with recurrent pyogenic infections, vasculitic eruptions and immune complex glomerulonephritis. A moderately low C3 level together with the clinical picture suggested a deficiency affecting regulation of complement activation. Analysis of hemolytic activity revealed absence of alternative pathway activity and subsequent analysis showed no detectable factor I (<2%) together with a low level of factor B and a moderately low level of factor H, indicating

consumption secondary to the factor I deficiency. Mutation analyses revealed change of a cysteine to a tyrosine (TGT->TAT, C237Y, numbering without signal peptide) in exon 5, which encodes for LDLR1 domain. Our patient and two siblings were homozygous, and two siblings and both parents were heterozygous for this mutation.

Factor I inhibits complement activation beyond C3 by cleavage of C3b in the presence of cofactors. Complement factor I deficiency is frequently associated with recurrent pyogenic infections mainly affecting the upper and lower respiratory tract, or presenting as meningitis or septicemia, while rheumatic disorders have not been a prominent feature. This report emphasizes the importance of screening for complement deficiencies in cases with recurrent infections and rheumatic disorders. When properly diagnosed, these patients and family members may benefit from antibiotic prophylaxis and vaccination against encapsulated bacteria.

PP - 241

LIVEDOID VASCULITIS IN A GIRL WITH FACTOR V LEIDEN MUTATION

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Livedoid vasculitis (LV) is an uncommon condition that most commonly affects middle-aged women. It is characterized by purpuric macules and papules on legs and feet. The histological feature of this condition is the deposition of fibrinoid material in the superficial vessel walls. As a consequence, areas of necrosis involving the epidermis and dermis may occur. Onset of LV in childhood is rare. Differential diagnosis includes scleroderma, lichen sclerosis and pseudo-Kaposi syndrome. Various abnormalities of coagulation have been observed in patients with this disorder. An association of LV with factor V Leiden mutation has been reported in adults. Factor V Leiden is due to a single mutation in the factor V gene product, resulting in resistance to activated protein C. Different mutations have been described.

An 8-year-old girl presented with a two-year history of intermittent painful eruption around both ankles. These eruptions were associated with ulceration, which would then heal to leave atrophic scars. She was otherwise well. On physical examination, there was a livedoid rash with hyperpigmentation around her ankles, feet and distal legs. Cribriform ulcerations and atrophie blanche were present. All investigations, including C3, C4, PT, aPTT, homocysteine, anticardiolipin antibody, anti-dsDNA and cANCA, were unremarkable. Heterozygous factor V Leiden mutation was found. Histology showed evidence of thrombosis of blood vessels. After two months of treatment with pentoxifylline and low-dose aspirin, a slight decrease in pain and ulcerations was registered. No new lesions were observed.

The role of mutant factor V in livedoid vasculopathy must be elucidated.

PP - 242

EVALUATION OF EPIDEMIOLOGIC, CLINICAL, AND LABORATORY FINDINGS, TREATMENT AND PROGNOSIS IN CHILDREN WITH HENOCH-SCHÖNLEIN'S PURPURA

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Aim: To evaluate the general features of children with Henoch Schönlein's Purpura (HSP) followed-up in our clinic.

Method: 377 children with HSP, diagnosed according to ACR (American College of Rheumatology) criteria were evaluated retrospectively. Age, gender, season at admission, etiologic, epidemiologic, clinical, and laboratory features, treatment, and prognosis were recorded.

Results: Male: female ratio was 1.16. The mean age was 7.89±3.11 years. The mean duration of follow-up was 12.13±14.30 months. 30.8% of the cases had admitted in spring, 27.9% in autumn, 26% in winter and 15.4% in summer. As a predisposing factor, 37.66% of the cases had upper respiratory tract infection. Possible etiological agents were detected in 118 of the cases; most common was Streptococcus infection (22.5%). The others were Mycoplasma, Chlamydia, Parvovirus, cytomegalovirus, Ebstein-Barr virus, hepatitis A, B virus and Giardia. 74.8% of the cases had admitted with purpura, 17% with joint pain/swelling and 8.2% with abdominal pain. During follow-up, palpable purpura had occurred in 100%. 62.1% of the cases had gastrointestinal system (GIS), 62.6% had joint, 31.8% had renal, 30.3% had soft tissue, 7.7% had genitourinary system, and 0.53% had central nervous system involvement. There was leukocytosis in 42.2%, anemia in 13.5%, and thrombocytosis in 22.7% of the cases. CRP was elevated in 93.1% and ESR in 86.7%. 72.6% of the cases who received steroid therapy had severe GIS involvement, 25.8% had persistent rash and frequent relapse and 4.7% had renal involvement. 23.6% had hematuria, 18.0% had proteinuria, 5.6% had hypertension, 3.2% had melena, 2.9% had acute renal failure, 0.8% had invagination, 0.8% had hematemesis, 0.53% had encephalopathy and convulsions, and 0.26% had perforation after invagination. In 81% of the cases, there was full recovery. In 10%, recovery occurred after relapses and in 6% disease became chronic. Chronic glomerular disease developed in 2.1%.

Conclusion: Even though HSP is a benign type of vasculitis, long-term follow-up is required since it can have short- and long-term effects.

PP - 243

EVALUATION OF FACTORS RELATED WITH RELAPSE IN CHILDREN WITH HENOCH SCHÖNLEIN'S PURPURA

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Aim: Henoch Schönlein's Purpura (HSP) is a disease that usually spontaneously resolves in 4-6 weeks. However, relapses sometimes can occur after the acute phase and the disease can become chronic. In this study, we aimed to evaluate the risk factors related with relapses.

Method: We investigated retrospectively the patient files of 377 cases with HSP, diagnosed according to ACR (American College of Rheumatology) criteria. Patients were grouped as cases with relapse and cases with no relapse. These two groups were compared in terms of age, gender, persistence of purpura, mild abdominal pain, severe abdominal symptoms, joint involvement, renal involvement, early steroid therapy, coexistence of familial Mediterranean fever (FMF), predisposing infections, and hemoglobin, leukocyte, thrombocyte, ESR, CRP, ASO, IgA and C3 levels.

Results: Relapse occurred in 13.8% of the cases. The mean duration till the occurrence of relapse was 9.96±9.84 months. Female: male ratio was 2.25. Among the cases with relapse, 36.5% had proteinuria, 34.6% had rash, 30.7% had abdominal pain, 30.7% had microscopic hematuria, 23% had occult blood in feces, 13.4% had arthritis and 3.8% had macroscopic hematuria. There was no

significant difference in terms of age between the groups. Female gender was significantly predominant among cases with relapse ($p<0.01$). There was no significant difference in terms of persistence of rash, gastrointestinal symptoms, joint involvement and existence of predisposing infection between the groups ($p>0.05$). Renal involvement was significantly higher in cases with relapse ($p<0.01$). Even though the frequency of early steroid therapy was higher in cases with relapse, there was no statistically significant difference ($p>0.05$). There was no significant difference in terms of anemia, thrombocytosis, IgA, C3, ESR and CRP levels between the groups ($p>0.05$). With logistic regression analysis, leukocytosis was found to increase the relapse risk 2.25-fold.

Conclusion: Relapse in HSP is related with female gender, existence of leukocytosis and renal involvement.

PP - 244

INVESTIGATION OF PREDICTIVE RISK FACTORS RELATED WITH RENAL INVOLVEMENT IN CHILDREN WITH HENOCH SCHÖNLEIN'S PURPURA

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Aim: Renal involvement in Henoch Schönlein's Purpura (HSP) is important in prognosis. In our study, we aimed to define the risk factors related with renal involvement in children with HSP.

Method: We retrospectively evaluated 377 cases with HSP, diagnosed according to ACR (American College of Rheumatology) criteria. The patients were grouped as cases with renal involvement and cases without renal involvement. These two groups were compared in terms of age, gender, persistence of purpura, mild abdominal pain, severe abdominal symptoms, involvement of joints, early steroid therapy, coexistence of familial Mediterranean fever (FMF), predisposing infections, and hemoglobin, leukocyte, thrombocyte, ESR, CRP, ASO, IgA and C3 levels.

Results: The mean age of the cases with renal involvement was statistically higher than the other group ($p<0.01$). Female gender was predominant among the group with renal involvement ($p<0.01$). Persistence of rash and gastrointestinal symptoms did not differ statistically between the two groups ($p>0.05$). Relapse rate was higher in cases with renal involvement (p:0.019). There was no difference between the groups in terms of joint involvement ($p>0.05$). Frequency of early steroid therapy was significantly higher in cases with renal involvement ($p<0.01$). There was also no difference in terms of anemia and thrombocytosis, whereas renal involvement was significantly higher in cases who had leukocytosis and elevated ASO ($p<0.05$). C3 and IgA levels did not differ between the groups ($p>0.05$). When the effects of these parameters on renal involvement were evaluated with logistic regression test, severe gastrointestinal system involvement was also demonstrated to be a risk factor in development of renal involvement.

Conclusion: Female gender, age, occurrence of relapse, severe gastrointestinal involvement, existence of leukocytosis at disease onset, early steroid therapy, and history of streptococcic upper respiratory tract infection are risk factors in development of renal involvement.

PP - 245

THE EVALUATION OF GASTROINTESTINAL INVOLVEMENT IN PATIENTS WITH HENOCH-SCHÖNLEIN PURPURA WITH CLINICAL, LABORATORY PARAMETERS AND DOPPLER ULTRASONOGRAPHY

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Henoch-Schönlein Purpura (HSP) is a vasculitic syndrome seen frequently in the childhood. It is characterized by skin, joint, gastrointestinal and renal involvement.

Aim: To evaluate the gastrointestinal involvement in patients diagnosed as HSP with clinical, laboratory parameters and ultrasonographic features.

Patients and Methods: We investigated 30 patients admitted to our hospital's rheumatology outpatient clinic between November 2004 and October 2005 diagnosed as HSP. Abdominal Doppler ultrasonography was carried out between 7-10th day after the onset of the disease.

Results: The mean age of the patients was 7.66±2.61 years (range: 3.3-13.4 years). Female/male ratio was 1.32. Fourteen patients (46%) had abdominal pain. Guaiac test was positive in 6 (20%) patients. In the patients with the complaint of abdominal pain, duodenum wall thickness (DWT) was 2.44±0.52 mm, duodenum diameter (DD) 24.89±2.92 mm, and stomach wall thickness (SWT) 2.63±2.67 mm; in the patients with no abdominal pain, DWT was 2.64±0.33 mm, DD 26.38±2.67 mm, and SWT 2.46±0.34 mm. There was no statistically significant difference in terms of Doppler ultrasonographic findings between the patients with and without abdominal pain ($p>0.05$). Among the patients in which Guaiac test was negative, DWT was 2.61±0.32 mm, DD 25.97±2.83 mm, and SWT 2.45±0.31 mm. Among the patients in which Guaiac test was positive, DWT was 2.3±0.72 mm, DD 24.52±2.85 mm and SWT 2.52±0.39 mm. There was no statistically significant difference in terms of Doppler ultrasonographic parameters between the Guaiac test positive and negative patients.

Conclusion: There is no correlation between severity of clinical findings and ultrasonographic parameters. Therefore, ultrasonography is not routinely suggested; however, it can be used in cases suspected to have gastrointestinal system complications.

PP - 246

ACUTE CHOLECYSTITIS AT INITIAL PRESENTATION OF POLYARTERITIS NODOSA

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Polyarteritis nodosa (PAN) is a systemic vasculitic disease characterized by necrotizing inflammation of small- and medium-sized arteries. Although gastrointestinal involvement is common, the symptomatic involvement of the hepatobiliary system is rare. Gallbladder vasculitis has been reported in about 1.6–2.7% of the patients with PAN.

A 16-year-old female patient was hospitalized for right upper quadrant pain and fever. Abdominal ultrasonography disclosed a thickening of the gallbladder. She underwent cholecystectomy. On histologic examination, the majority of the medium-sized arteries in the gallbladder showed considerable thickening of the vessel wall with intense fibrointimal proliferation and lymphocytic infiltration with fibrinoid necrosis. No abundance of eosinophils, microabscesses or giant cells were found. Veins were unaltered and spared. There was no ulceration of the mucosa. These histological features were consistent with PAN. Corticosteroid therapy was initiated. After one month, clinical and laboratory findings returned to normal.

This case represents one of the rarest forms of PAN in childhood. Our report emphasizes that gallbladder

vasculitis may occur at initial presentation of PAN and that a complete clinical and laboratory evaluation should always be performed to distinguish the systemic from the isolated form of the disease.

PP - 247

SUCCESSFUL TREATMENT OF POLYARTERITIS NODOSA WITH LAMIVUDINE

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Childhood polyarteritis nodosa (PAN) is characterized by necrotizing vasculitis of arteries. It may be associated with hepatitis B antigenemia; in these patients, benefit of antiviral treatment has been previously reported. We present a pediatric patient with childhood PAN associated with HBsAg. This patient was an 11-year-old girl who presented with constitutional findings, myalgia, arthritis, abdominal pain, hypertension and elevated acute phase reactants. HBsAg and HBeAg were positive and she had elevated titers of HBV DNA. She was diagnosed as childhood PAN according to clinical findings and characteristic microaneurysms on angiograms. Antihypertensive treatment was started immediately. The patient received lamivudine along with a short steroid regimen. She responded very well with full clinical and laboratory remission.

In childhood PAN associated with hepatitis B, antiviral treatment along with a short course of steroids is beneficial, as suggested in the adult literature.

PP - 248

LOW SPECIFICITY OF ACR CRITERIA FOR EARLY DIAGNOSIS OF TAKAYASU ARTERITIS (TA) IN A YOUNG GIRL

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The diagnosis of TA is based on the presence of at least three of the six ACR criteria defined in 1990: age at disease onset < 40 years, claudication of extremities, decreased brachial artery pressure, blood pressure difference >10 mmHg, bruit over subclavian arteries or aorta, and arteriogram abnormality.

A 16-year-old girl was admitted to our department because of malaise and fever of unknown origin and sharp dorsal pain that worsened with fever. A cardiac murmur was detected. She did not present decreased pulsation of any peripheral pulse or significant increase in the differential systolic blood pressure between the two arms. CRP, ESR and complement were repeatedly elevated. Echocardiography revealed a bicuspid shaped aortic valve with regurgitation, and dilatation of aortic root. Chest and abdominal CT revealed wall thickening of the aortic arch, of its primary branches and of all thoracic and abdominal aortic portion. MRI angiography revealed a marked dilatation of both ascending and descending aorta with valve strip immobility and valve regurgitation during the diastolic phase. Although our patient had just one of the clinical ACR criteria, diagnosis of TA with bicuspid aortic valve regurgitation was made based on MRI angiography images. The patient started oral prednisone and methotrexate. She quickly improved, her pain ameliorated and she had no further fever.

The early diagnosis of TA may be difficult since early symptoms are nonspecific and the ACR criteria are probably not sufficient in early disease stages or in young patients.

PP - 249

HENOCH-SCHÖNLEIN PURPURA IN CHILDHOOD: A RETROSPECTIVE ANALYSIS OF 430 CASES

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Henoch-Schönlein purpura (HSP) is an IgA-mediated autoimmune vasculitis of children. It often presents with symptoms including purpuric rash, abdominal pain, renal involvement or arthritis. In this retrospective study, we aimed to examine the clinical and laboratory features of HSP.

This study consisted of 430 children (mean age: 7.7±2.8 years; range: 1-14 years; male/female: 225 / 205) with HSP between the years 1995 and 2005. The mean follow-up time was 16.4±22.1 months (range: 6-112 months). At onset, purpura was present in 423 patients (98.4%), arthritis / arthralgias in 295 (45.4%), abdominal pain in 130 (30.2%), gastrointestinal bleeding in 100 (22.8%), renal involvement in 192 (44.7%; 9 nephrotic syndrome, 6 nephritis), scrotal edema in 6 (2.7% of 225), intussusception in 4 (0.09%) and central nervous system involvement in 3 (0.07%). The most frequent laboratory abnormalities were high erythrocyte sedimentation rate (240 patients, 55.8%) and leukocytosis (107 patients, 24.9%). One hundred and four patients (24.2%) received corticosteroids. Recurrences occurred in 22 children (4.9%). All children recovered completely.

In conclusion, although a small percentage of HSP children exhibited severe nephropathy, the prognosis of HSP is excellent in childhood.

PP - 250

CHURG-STRAUSS SYNDROME IN A 12-YEAR-OLD BOY

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A 12-year-old boy was hospitalized because of persistent febrile temperature and leg pain. At the age of four he had the first sign of allergic diathesis – an expressed local reaction to insect bites. When he was eight, obstructive bronchitis was first diagnosed. A diagnosis of asthma followed at the age of nine, accompanied by pollinosis and allergic rhinitis. Skin prick tests were positive for grass pollen and cereals. Treatment with budesonide inhalation powder and intranasal spray was started. At the age of 10, pansinusitis became a continuous problem; the treatment – antibacterial and lavation – had little effect. After one-and-a-half years, chronic pansinusitis and nasal polyposis were diagnosed and confirmed by a computer tomography investigation. Shortly thereafter, the general status of the child's condition abruptly worsened; he was hospitalized with headache, vomiting and volatile rash; CRP was 102 mg/dl. The patient was operated on with a suspicion of abscessus – bilateral functional endoscopic sinus surgery was performed. Polypous tumor was found in ethmoidal cells and mucous-purulent secretion in sinuses.

During the first-mentioned hospitalization, eosinophilia was 32.5%. Churg-Strauss syndrome was diagnosed according to clinical and laboratory criteria, supported by nasal and sinus biopsy findings. Methotrexate and oral prednisolone were started. In the first year, every attempt to stop prednisolone resulted in an exacerbation of the disease. Intravenous methylprednisolone pulses were given three times. At two years, control over the disease was achieved with 7.5 mg oral prednisolone per day and 5 mg methotrexate per week; the asthma is treated with budesonide and formoterol, 320/9.0 μg/dose twice a day.

PP - 251

THE OUTCOME AND THERAPEUTIC DIFFICULTIES IN A CHILD WITH CHURG STRAUSS SYNDROME AND NECROTIZING CUTANEOUS LESIONS

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Churg Strauss syndrome (CSS) is an extremely rare vasculitis of childhood associated with asthma and allergies. We present a 14-year-old boy with CSS who was first admitted to our hospital at 2 years of age because of recurrent attacks of fever, asthma, pneumonia, aphthous stomatitis and biopsy-proven vasculitic skin lesions lasting since he was 3 months old. Eosinophilia with highly elevated immunoglobulin E level (1640 U/ml) and allergy to certain foods and pollens were found. Serum complement levels were normal with negative antinuclear antibody, anti-DNA, and p and c antineutrophil cytoplasmic antibodies. With the diagnosis of CSS, he was started on oral prednisolone therapy. In the following 4 years, he was admitted to the hospital several times with recurrent attacks of infections and flare-up of vasculitic lesions under steroid therapy and was given oral cyclophosphamide for 3 months. At the end of 5 years, he had severe lesions on cheeks, auricles and extremities that rapidly developed into necrosis. The lesions were limited with intravenous cyclophosphamide pulse therapy and healed in 3 months with scar formation on extremities and partial amputation of left auricle after an intensive wound care including surgical debridement. Maintenance therapy with azathioprine and low dose oral prednisolone maintained remission for two years when he had another relapse with mild symptoms. Azathioprine was replaced with mycophenolate mofetil and remission was achieved thereafter. In conclusion, more aggressive immunosuppressive therapy for longer periods should be given in CSS in order to prevent severe attacks.

PP - 253

HENOCH-SCHÖNLEIN PURPURA SECONDARY TO ASCARIASIS IN TWO SIBLINGS

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Infectious diseases and parasites are believed to be involved in the pathogenesis of Henoch-Schönlein purpura (HSP) by triggering the immune complex mechanism via antigenic stimulation. Here we present two siblings with HSP and ascariasis. A 7- year-old boy applied to the emergency room with abdominal pain, edema of the feet, arthralgia of ankles and vasculitic purpuric rash over the extensor surfaces of both legs. Occult blood was positive in stool examination. The boy was diagnosed as HSP based on dermal, musculoskeletal and gastrointestinal findings. Prednisolone (2 mg/kg) was started for gastrointestinal involvement. On second day of admission, an adult worm of *Ascaris lumbricoides* came out through his mouth. Mebendazole treatment was initiated and steroid discontinued. On the same day, the 9-year-old brother of the patient was brought to emergency room with very similar complaints of dermal and gastrointestinal involvement. His rash over the legs was more prominent and skin biopsy revealed leukocytoclastic vasculitis. Not surprisingly, this patient also excreted several adult worms of *Ascaris lumbricoides* with stool and he was given mebendazole.

Occurrence of the similar symptoms characteristic for HSP and diagnosis of ascariasis in these two siblings strongly suggest a direct causal relation between the infestation and vasculitis, which is an association reported relatively rarely in the literature.

PP - 254

INCOMPLETE KAWASAKI DISEASE IN A CASE OF FAMILIAL MEDITERRANEAN FEVER (FMF): COINCIDENCE OR CO-OCCURRENCE?

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There have been several reports of a "FMF-vasculitis" association, but not with Kawasaki disease (KD), which is a common systemic childhood vasculitis. The diagnosis of KD is based purely on clinical criteria. Presence of coronary artery abnormalities validates the diagnosis of incomplete KD (IKD) when the clinical criteria of KD are not met. Here, we present a 5-year-old girl admitted to the hospital with the complaints of fever and abdominal pain. She denied recurrent attacks of abdominal pain with fever, but she had transient erysipelas-like erythema around ankle and leg pain 5 months ago. Physical examination revealed a temperature of 38.5°C, respiratory rate of 40 breaths/minute, and pulse rate of 160 beats/minute. She had multiple cervical and inguinal lymphadenopathies smaller than 5 mm. Grade I systolic murmur was heard on auscultation. Laboratory examination disclosed: hemoglobin 7.9 g/dl, white blood cell count 12, 800/mm^3, platelet count 853, 000/mm^3, erythrocyte sedimentation rate 60 mm/hr, and C-reactive protein 70 mg/L. Urinalysis revealed sterile pyuria. Colchicine was started with the diagnosis of FMF that was confirmed with the detection of homozygous MEFV gene mutation (M694V/M694V). Echocardiography revealed aneurysmal dilatation of left and right coronary arteries of 0.30 and 0.36 cm in diameter, respectively. Thus, the patient was diagnosed as IKD and intravenous immunoglobulin and acetylsalicylic acid were started. The patient responded well to this treatment. We present this patient since it is the first case of FMF with IKD in children. However, the question of coincidence or co-occurrence remains to be answered.

PP - 255

CEREBRAL AND PULMONARY INVOLVEMENT: RARE MANIFESTATIONS IN HENOCH-SCHÖNLEIN PURPURA WITH FAMILIAL MEDITERRANEAN FEVER

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Although Henoch-Schönlein purpura (HSP) is a multisystemic disease, pulmonary and/or cerebral involvement is extremely rare. It has been shown that HSP is more frequent among familial Mediterranean fever (FMF) patients.

Here, we report a case with HSP with renal, pulmonary and central nervous system involvement in whom the diagnosis of FMF was made after the onset of HSP. A 7-year-old boy was referred to our hospital with a 2-day history of purpuric rash on the lower extremities, abdominal pain and arthralgia. He had been diagnosed as thalassemia major since he was 6 months old. A percutaneous renal biopsy was performed because of hematuria and nephrotic range proteinuria and revealed Class VA HSP nephritis with IgA deposition. Oral prednisolone was started at a dosage of 2 mg/kg/day for renal involvement. On the 10th day of his diagnosis, he developed dyspnea. He had nodular involvement in his chest X-ray compatible with pulmonary vasculitis. Plasmapheresis was performed along with bolus steroid and oral cyclophosphamide therapy. After his clinical improvement, on the 60th day of his initial presentation, he was referred to our hospital

because of sudden onset of left hemiparesis and facial paralysis. Magnetic resonance imaging demonstrated occlusion of right cerebral artery and acute ischemia in basal ganglia. During his follow-up, recurrent abdominal pain and fever episodes occurred. He was diagnosed as having FMF clinically and this was confirmed by MEFV mutation analysis.

In conclusion, FMF should also be considered in the evaluation of children with atypical HSP.

PP - 256

TLR EXPRESSION IN PERIPHERAL BLOOD SAMPLES OF PATIENTS WITH HENOCH-SCHÖNLEIN PURPURA AND BEHÇET'S DISEASE

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Clinical data implicates infections in the pathogenesis of Behçet's disease (BD) and childhood Henoch Schönlein purpura (HSP), which is the most common childhood vasculitis in the eastern Mediterranean region. Even penicillin prophylaxis has been used to control the course in these diseases.

We aimed to study Toll-like receptor (TLR) 2 and 4 expression in these two diseases. HSP was diagnosed according to the EULAR/PRES endorsed criteria for HSP and BD was diagnosed according to International criteria. Fresh cells were isolated from peripheral blood during active disease after appropriate consent. The expressions of CD14+, TLR2, TLR4+ on peripheral mononuclear cells were measured by flow cytometric analysis. Samples from 10 healthy patients served as controls. The mean age of HSP patients was 8.8±3 and that of BD patients was 29.8±10.6 years. TLR 2 and 4 expression was significantly increased in only two HSP patients, who both had very severe disease with very high acute phase reactants and Class IIIB HSP nephritis. Both had very high ASO titers and a history of recent infection. TLR expression in the remaining HSP patients including two with nephritis (Class IIIA and II) and BD patients were not significantly different than controls. A history of URTI or elevated ASO was present in 65% of those tested.

We were not able to detect marked TLR expression in most of our HSP and BD patients. Thus, the local site of inflammation should be studied to assess the role of TLR in these vasculitides. Whether the increased expression in severe HSP is important will be enlightened with further studies.

PP - 257

UNUSUAL PRESENTATION OF KAWASAKI DISEASE: PROLONGED FEVER AND HEMORRHAGIC PLEURAL EFFUSION

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Kawasaki disease is a self-limited vasculitis, the diagnosis of which is based on established clinical criteria. However, other signs and symptoms can occur in conjunction with or even in the absence of the classic signs, leading to a delay in the diagnosis, which significantly increases the possibility of appearance of serious coronary complications. We present a 2-year-old boy with fever, vomiting, diarrhea and painful cervical lymphadenitis. After a few days he developed abdominal distension, tachypnea, pulmonary infiltrate, pleural effusion, hepatomegaly, ascites, and gallbladder hydrops. Admitted to the hospital, he developed rash, conjunctival hyperemia and worsening of dyspnea. The pleural effusion increased, and thoracocentesis was performed. The fluid was sero-hemorrhagic and microbiologic screening was negative. In the subsequent days, he developed swelling of hands, feet (followed by hyperemia and palmoplantar pruritus) and scrotum, proteinuria, hypoalbuminemia, anemia and elevated ESR, CRP and hepatic enzymes. On the 20th day of the disease, the fever rose

again and arthritis of hands was noted. With the suspicion of Kawasaki disease, he was treated with immunoglobulin and aspirin, resulting in clinical improvement. Despite clinical control of symptoms, the echocardiogram showed impressive coronary dilatation. Methylprednisolone pulse was administered for three days. Angiotomography showed a giant aneurysm in the right coronary and two others in the left coronary. Myocardial scintigraphy was normal. Respiratory manifestations and association with hemorrhagic pleural effusion are relatively uncommon features in Kawasaki disease. In this case, the presentation of these atypical manifestations could have contributed to the difficulty and delay in the diagnosis and treatment. A strong clinical suspicion can influence the prognosis of cases with unusual presentation.

PP - 258

MACROPHAGE ACTIVATION SYNDROME ASSOCIATED WITH EBV-INDUCED NECROTIZING VASCULITIS

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Vasculitis is a term associated with inflammation of blood vessels. Necrotizing vasculitis is an inflammatory condition of blood vessels characterized by tissue death, scarring, and proliferation of the walls of the blood vessels. The exact cause of vasculitis is not known; however, it is asserted that causes may include infectious agents and autoimmune diseases.

A 6-year-old girl admitted to our hospital with skin lesions, loss of appetite and fatigue. Physical examination revealed a discomfort outlook, irritability, 38.7°C fever, disseminated erythematous skin lesions, oropharyngeal hyperemia, hepatomegaly, and sub-icterus on conjunctiva. Laboratory investigation showed WBC: 18, 000/μL, Hb: 10.8 g/dl, AST: 450 IU/L, ALT: 520 IU/L, indirect bilirubin: 1.7 mg/dl, direct bilirubin: 0.2 mg/dl, and prothrombin time (PT): 12 seconds. Serological viral study was negative except for Epstein-Barr virus (EBV). EBV IgM and EBV PCR were detected as positive. The skin biopsy was reported as necrotizing vasculitis, so the patient was diagnosed as EBV-induced necrotizing vasculitis. On the follow-up management, she had the clinical and laboratory findings of macrophage activation syndrome (MAS).

The exact incidence of MAS in childhood systemic inflammatory disorders is unknown. Although MAS may occur without any detectable precipitating factor, it has been related to a number of triggers, including exacerbation of the underlying disease, nonsteroidal anti-inflammatory drug toxicity, and viral infections.

Sawhney et al. reported 9 patients with MAS and 2 of them had EBV infection identified as a trigger. Our patient also had MAS triggered by EBV infection. She had fever, pancytopenia, hepatosplenomegaly, liver insufficiency and coagulopathy, purpuric lesions, and irritability. Bone marrow aspiration supported MAS. In the beginning, antinuclear antibodies were negative but in the long-term management ANA became positive after a year. She responded well to steroid therapy and is still in remission.

• Juvenile Dermatomyositis
PP - 259

JUVENILE DERMATOMYOSITIS WITH SEVERE CALCINOSIS EVALUATED IN MIXED CONNECTIVE TISSUE WITH ASSUMED IG A DEFICIT

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We report a case of Mixed Connective Tissue Disease (MCTD) in a 36-year-old female. Her disease started as showing symptoms of juvenile dermatomyositis such as typical rash on face and body, pseudobulbar paralysis, and severe calcinosis. Treatment with corticosteroids and plasmapheresis resulted in achievement of long clinical remission. Over the past 17 years, symptoms of scleroderma, Raynaud syndrome, and immunological diversions suggested MCTD. The assumed Ig A deficit was demonstrated in investigation of disease activity. A total lack of Ig A1 was established. It is frequently concomitant with cutaneous, joint, and respiratory infections. The treatment of this patient was difficult and involved a team of rheumatologist, surgeons, orthopedists and kinesiotherapist.

PP - 260

TOPICAL TACROLIMUS IN JUVENILE DERMATOMYOSITIS (JDM) REFRACTORY SKIN LESIONS

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Introduction: JDM is a rare idiopathic chronic inflammatory disease that affects mainly striate muscle and skin. Cutaneous lesions may persist even after successful myositis treatment. Of note, topical tacrolimus is a new immunosuppressive agent that has been used to treat atopic dermatitis with few reports in pediatric inflammatory myopathies.

Case Reports: We report 3 JDM patients (2 males), current age from 5.8 to 10.7 years. The initial therapies administered for these patients were: oral and topic corticosteroid in 3, chloroquine in 2 and methotrexate in 2. All of them had refractory skin lesions (malar rash, extensive rash and/or cutaneous vasculitis) after significant improvement of muscle weakness. Topical tacrolimus ointment 0.1% was used twice daily after failure of previous treatment. Lesions were evaluated according to extension and severity 8 and 16 weeks after topical tacrolimus was started. At the first evaluation (8 weeks), 1 patient had complete improvement of malar rash and limbs and trunk rash, and 2 had partial improvement of malar rash and cutaneous vasculitis. At the second evaluation (16 weeks), 2 patients were in remission and 1 had persistent malar rash and moderate lumbar and gluteus rash. In the last patient, remission of skin lesions was reached only 4 months after cyclosporine use. None of them had adverse effects with tacrolimus.

Conclusion: Topical tacrolimus may be considered in JDM patients with refractory cutaneous manifestations. Further randomized controlled trials should be performed in this inflammatory disease.

PP - 261

CALCINOSIS IN JUVENILE DERMATOMYOSITIS: A MULTIVARIATE ANALYSIS OF ASSOCIATED RISK FACTORS

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Objectives: To identify associated risk factors for calcinosis in children and adolescents with juvenile dermatomyositis (JDM).

Methods: Medical records of 54 patients with JDM (Bohan and Peter criteria) were reviewed. Demographic data, clinical features: muscle strength (according to Medical Research Council), pulmonary (restrictive pulmonary disease), gastrointestinal (intestinal vasculitis and/or gastroesophageal reflux disease) and cardiac involvements (pericarditis or myocarditis), increase in serum levels of muscle enzymes, and treatment with corticosteroids and immunosuppressive drugs were assessed. Patients were divided into two groups based on presence or absence of dystrophic calcification and were evaluated according to univariate and multivariate analysis (logistic regression).

Results: Calcinosis was present in 23 (43%) patients. Six of them occurred before diagnosis of JDM and 17 after. Of note, univariate analysis revealed that cardiac (p=0.01) and pulmonary (p=0.02) involvements and immunosuppressive drug use in JDM (methotrexate, cyclosporine and/or cyclophosphamide) (p=0.03) were associated with a higher incidence of calcinosis. On the other hand, age at JDM onset, time between start of disease and treatment, female gender, gastrointestinal involvement and increased muscle enzymes serum levels were similar in JDM patients with and without calcinosis (p>0.05). Remarkably, in the multivariate analysis, only cardiac involvement (OR 15.56, CI 1.59-152.2, p=0.018) and immunosuppressive drug use (OR 4.01, CI 1.08-14.87, p=0.037) were the independent variables associated with calcinosis.

Conclusions: Calcinosis occurred in 43% of patients with JDM, frequently during the course of the disease. Dystrophic calcification was associated with severe disease with cardiac involvement and requirement of immunosuppressive therapy.

PP - 262

DERMATOMYOSITIS: COURSE AND PROGNOSIS

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Introduction: Juvenile dermatomyositis (JDM) is caused by immunocomplexes and affects mainly skin and muscles. Treatment was previously based only on corticosteroids; however, the more options available today provide a better quality and expectancy of life.

Objective: To analyze prognosis of the disease in our service.

Methods: Retrospective analysis of JDM patient files at the Pediatric Rheumatology Service of IPPMG, from March 1986 to May 2006.

Results: There were 56 patients, 17 (30%) male. Mean age at onset was 3.5 years (2-11). Signs and symptoms at presentation were weakness (66%), Gottron (55.3%), heliotrope (41%), arthromyalgia (32.1%), arthritis (28.5%), malar rash (26.8%), fever (17.8%), another kind of rash (25%) and dysphagia (12.5%). Acute phase proteins were enhanced in 51.8%. Concerning muscle enzymes, enhancement of creatine kinase was seen in 42.9%, aldolase in 26.8%, aspartate aminotransferase in 37.5%, alanine aminotransferase in 23% and lactate dehydrogenase in 55.4%. Patients were treated with prednisone (98.2%), intravenous methylprednisolone (64.2%), methotrexate (62.5%), hydroxychloroquine (19.6%), cyclosporine (19.6%), alendronate (14.3%) and anti-TNF (9%). Main complications were calcinosis (37.5%), contractures (23.2%) and lipodystrophy (12.5%). Two patients presented overlap syndrome

with scleroderma. Disease course was monocyclic in 37.5%, polycyclic in 3.6% and chronic continuous in 48.1%. At the last evaluation, 20 had dropped out, 8 were discharged, 19 were in remission (9 with and 10 without medication) and 9 still had active disease.

Conclusions: There is a predominance in female and younger children. Symptoms often begin with skin manifestations, and the most common complication is calcinosis. Almost all patients received prednisone, but chronic patients generally were treated with second-line drugs.

PP - 263

CLINICAL FINDINGS AND OUTCOME IN JUVENILE DERMATOMYOSITIS

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Juvenile dermatomyositis (JDM) is a rare childhood disease characterized by nonsuppurative inflammation of striated muscle and skin. In this study, we investigated the clinical findings, complications and prognosis in 13 patients (9 girls, 4 boys) aged between 6-14 years and diagnosed to have JDM during the last 10 years. All patients had proximal muscle weakness, characteristic rash and abnormal electromyographic findings at presentation, while 9 patients had elevated muscle enzymes and 10 patients had histopathological confirmation. All patients were given oral prednisolone. Seven patients were initiated with intravenous methyl prednisolone pulse therapy and 7 were given weekly oral methotrexate. One patient died due to sepsis 6 months later and the remaining 12 patients have been followed up for a mean of 2.8 years (2 months-10 years). Ten patients followed up for more than 1 year recovered. Three patients developed calcinosis between 1.5-7 years during the therapy with prednisolone and one with methotrexate, but did not show any improvement with bisphosphonates, diltiazem or immunosuppressive therapy. In conclusion, early diagnosis and treatment are important in the management of JDM, but more aggressive initial therapy may be of benefit in order to prevent severe complications like calcinosis.

PP - 264

ASSOCIATIONS BETWEEN HLA CLASS II HAPLOTYPE GENETICS AND AUTOANTIBODIES IN CHILDREN WITH JUVENILE DERMATOMYOSITIS (JDM) AND JDM-SCLERODERMA OVERLAP

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Aim: To investigate a large cohort of children with juvenile dermatomyositis (JDM), and those with JDM-scleroderma (JDM-SSc) overlap, using serological analysis, HLA class II genotyping and clinical characterization.

Methods: 114 children with JDM were recruited, and clinical data was collected through the JDM National Registry and Repository (UK and Ireland). Sera were assayed for ANA using standard immunofluorescence, and specific antibodies were characterized using ELISA, immunodiffusion and radioimmunoprecipitation. Patients and controls (n=537) were genotyped at HLA-DRB1 and DQB1 loci, and the DQA1 locus data derived.

Results: Over 70% of patients were ANA positive. Clear differences in serological and genetic data were demonstrated between JDM and JDM-SSc overlap groups. Associations were seen for HLA-DRB1*03

and DQA1*05, for all cases vs. controls and in particular for JDM-SSc patients. The frequency of HLA-DRB1*03-DQA1*05-DQB1*02 haplotype was significantly increased in JDM-SSc and anti-PM-Scl positive groups. All anti-U1-RNP antibody-positive patients had at least one copy of the HLA-DRB1*04-DQA1*03-DQB1*03 haplotype. Associations were observed between serology and specific clinical features. 23% of sera were positive for the novel autoantibody anti-p155/140; this was not significantly different between JDM and JDM-SSc groups.

Conclusions: We present HLA genotyping, serological profiling and clinical data on a large cohort of JDM patients and a carefully characterized subset of patients with JDM-SSc overlap. These results extend our knowledge by stratification of HLA genetic data in serological and clinical subgroups. In the future, a combination of serological and genetic typing should allow better prediction of clinical course and disease subtype in JDM.

PP - 265

EVALUATION OF ORGAN-SPECIFIC AUTOIMMUNITY IN PATIENTS WITH JUVENILE DERMATOMYOSITIS (JDM)

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Objective: To evaluate the organ-specific autoimmunity in JDM.

Methods: Twenty-nine JDM patients were investigated for the presence of several serum auto-antibodies. The diseases evaluated were: diabetes mellitus type 1-DT1 (anti-insulin antibody - IAA and anti-glutamic acid decarboxylase antibody - anti-GAD); autoimmune thyroiditis (anti-thyroglobulin antibody - TGA and anti-thyroid peroxidase antibody - TPO); celiac disease (antiendomysium antibody - EMA); primary biliary cirrhosis (anti-mitochondrial antibody - AMA); autoimmune hepatitis (anti-liver-kidney microsomal type 1 antibody - LKM1 and anti-smooth muscle antibody – SMA) and autoimmune gastritis (anti-gastric parietal cells - APCA). Frequencies of rheumatoid factor (RF), anti-neutrophil cytoplasmic antibody (ANCA), antinuclear (ANA), anti-single-stranded and double-stranded DNA, anti-Sm, anti-ribonucleoprotein (anti-RNP), anti-SSA/SSB, antiphospholipid (aPL) antibodies (anticardiolipin - aCL and lupus anticoagulant - LAC), anti-Jo-1 and anti-Scl-70 were also determined.

Results: Twenty-two patients (76%) presented at least one positive auto-antibody. None of them had association of autoimmune diseases. ANA was detected in 64% of the patients; aCL in 52% (13% > 40 GPL); ANCA in 6.6%; anti-TGA in 7%; and EMA and anti-GAD in 4%. Positivity for TPO, APCA, anti-LKM1, AMA, IAA, anti-DNA, anti-Sm, anti-SSA/SSB, LAC, anti-Jo-1 and anti-Scl70 was not observed.

Conclusion: The positivity of these auto-antibodies may be unspecific, since association of autoimmune diseases was not found in this study. On the other hand, identification of these auto-antibodies in JDM patients may be related to predictive factors for prognosis.

PP - 266

JUVENILE DERMATOMYOSITIS WITH A RARE AND REMARKABLE COMPLICATION: SINUS BRADYCARDIA

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Juvenile dermatomyositis (JDM) is characterized by proximal muscle weakness, vasculopathy of skin and muscles, and typical skin rash. Approximately 70% of adult patients with dermatomyositis have evidence of cardiac damage, and these are mostly conduction abnormalities, atrial and ventricular arrhythmias, pericarditis and myocarditis. However, cardiac involvement has been reported rarely in

children with JDM. Here, we describe an 11-year-old boy who presented with bradycardia as a result of sinus node involvement due to JDM and who recovered with the treatment of JDM without any specific drug for bradycardia. The period between the beginning of the symptoms and occurrence of bradycardia was about 4 months and it resolved at the 10th day of the treatment. In addition to malignancies and pulmonary disorders, cardiac involvement is one of the important causes of death in polymyositis and dermatomyositis.

PP - 267

DERMATOMYOSITIS IN CHILDHOOD: TWO CASES WITH DIFFERENT PRESENTATION

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Juvenile dermatomyositis is a multisystemic disease that results in nonsuppurative inflammation of muscle and skin. There is great variation in the clinical manifestation of the disease. In this report we describe two pediatric patients with different presentation, but with negative serology in common.

Case 1: A 4-year-old boy was admitted with complaints of malaise, easy fatigue, and muscle weakness especially while climbing upstairs and standing up, for a period of six months. He had an upper respiratory infection two weeks before, and after 10- day treatment with penicillin, he suddenly developed severe edema on his face, upper thorax, and upper extremities.

Case 2: A 14-year-old boy was presented with high fever, severe muscle pain, muscle weakness, dysphagia, and arthritis for one month.

Both of the patients had heliotropic rash. Laboratory findings of both patients revealed moderately elevated erythrocyte sedimentation rate, C-reactive protein, and severely elevated creatine phosphokinase and lactate dehydrogenase, but negative serologic markers for vasculitis including ANA, anti-DNA, C_3 and C_4 complement components, c and p ANCA and extractable nuclear antigens. Electromyography showed myopathic findings in both patients. Magnetic resonance imaging of upper extremity revealed subcutaneous edema in the first patient. In the second patient, IgM antibody for toxoplasmosis was positive. Muscle biopsy revealed perivascular infiltration in the first patient, and minimal perivascular infiltration and minimal deposition of IgG, IgA, IgM and C_3 in the second patient. Both of the patients showed marked improvement clinically with steroid therapy. In conclusion, juvenile dermatomyositis can present with different clinical manifestations. Herein, two patients are described, one of whom presented with severe subcutaneous edema due to inflammation and the other with severe muscle weakness and fever.

PP - 268

CALCINOSIS UNIVERSALIS COMPLICATING ADULT DERMATOPOLYMYOSITIS

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Calcinosis universalis is characterized by the deposit of calcium salts in skin, subcutaneous tissue, tendons and muscles. While it is a well-recognized pathology in juvenile dermatopolymyositis, it is a rare condition in adult patients. We report the case of a 37-year-old male who complained of hardening of the skin and movement limitation, with onset about 1.5 years before presentation. Gottron papules, facial erythema, scalp psoriasiform dermatitis, and proximal symmetrical muscle weakness were

found. On his trunk and extremities, there was widespread skin induration and knee flexion was difficult. The clinical diagnosis was verified by soft tissue ultrasound examination, X-ray examination of bones, and histological examination, all of which showed subcutaneous calcifications. The laboratory data showed an increased erythrocyte sedimentation rate, increased serum creatine phosphokinase level, and slight anemia. Immunosuppressant therapy was started in combination with calcinosis treatment (warfarin, colchicine and alendronate) and evolution at six months was favorable, with resolution of calcinosis and improved mobility.

• Scleroderma
PP - 269

THE JUVENILE SCLERODERMA INTERNATIONAL (JUSI) DATABASE: AN INSTRUMENT FOR IMPROVING RESEARCH AND STANDARD OF CARE IN A RARE DISEASE OF CHILDHOOD

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Background: Since 2001, the Juvenile Scleroderma Working Group (JSWG) of PRES has created an international database including more than 1000 children with scleroderma. At present, the JSWG is transforming the existing database into a web-based instrument for the prospective collection of clinical data and biological samples.

Objective: To provide a well-characterized cohort of scleroderma patients according to the current classification criteria and collect adequate information enabling uniform clinical assessment and diagnostic tests; to stimulate clinical and basic research projects; and to gather sufficient numbers of patients for clinical trials.

Methods: The executive committee of the JSWG of PRES after several meetings developed a consensus regarding the minimal set of clinical and laboratory data of scleroderma patients to be included in the database and agreed on the regulatory issues related to the ethical aspects and to the access modality to the data by investigators.

Results: The database has an administrative structure including a Database Executive Committee, responsible for data collection, biostatistical support and evaluation of the project's progress, and an International Advisory Committee in charge of evaluating proposed projects that require access to the database data. Regulatory aspects, reports and informed consent are defined and in agreement with the current European guidelines. Steps involved in maintaining the database include: case accumulation; case validation and information gathering; data entry, quality assurance; and updating of information. A yearly newsletter will update the database status.

Conclusions: The JUSI Database will provide a well-characterized cohort of patients with childhood onset scleroderma and facilitate research on the etiology, pathogenesis, management and treatment of this relatively rare condition.

PP - 270

DEVELOPMENT OF A MINIMAL STANDARD FOR THE EVALUATION OF PATIENTS WITH JUVENILE SYSTEMIC SCLEROSIS IN A PROSPECTIVE INCEPTION COHORT

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Introduction: Juvenile systemic sclerosis (jSSc) is a rare disease. Currently only retrospective data exist regarding organ involvement and evolution of the disease. No standard assessment of the organ involvement has been developed.

Objectives: The goal of the project is to develop a minimal standard to assess organ involvement in jSSc and to develop and follow a jSSc inception cohort. Using the standard assessments, prospective data will be collected to describe organ involvement and changes in organ involvement over time.

Methods: A group of interested pediatric rheumatologists have held two face-to-face meetings and several rounds of E-mail discussions to develop a consensus regarding the data set and study methodology.

Results: For each organ system involved in jSSc, a consensus was reached regarding aspects of physical examination and diagnostic tests, and intervals between consecutive evaluations that would be appropriate for patient care. A minimal scheme for patient evaluation and follow-up was determined, with a requirement that all diagnostic tests be available in virtually all pediatric rheumatology centers. Additional tests were suggested as optional where available. Emphasis was placed on collection of quantitative data whenever possible. An international, multicenter, prospective study of the disease manifestations and evolution of jSSc has been planned. The data set for the study will be presented.

Conclusion: A minimal standard of initial and follow-up evaluation has been proposed for jSSc. Based on this standard, an inception cohort will be developed and data on these patients will be prospectively collected in an international study group. The results of this study will not only advance our understanding of jSSc, but also help guide other physicians in their care of children with systemic sclerosis.

PP - 271

IS RECONSTRUCTIVE SURGERY BENEFICIAL IN TREATMENT OF "EN COUP DE SABRE" SCLERODERMA?

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Introduction: Linear scleroderma en coup de sabre represents a rare entity of unknown etiology that usually leads to facial deformity and, in many cases, significant impairments in social relationships and well-being of affected individuals. We describe two pediatric patients in whom facial deformity was managed with surgical reconstruction.

Case Report 1: A 4-year-old boy presented with indurated and atrophic skin lesions, extending through his frontoparietal right scalp, from forehead to mandibular angle, leading to alopecia and facial hemiatrophy. Despite treatment with topical and systemic corticosteroids, colchicine and methotrexate for two years, facial atrophy continued evolving.

Case Report 2: A 9-year-old boy presented with a five-year evolution of severe and progressive left facial atrophy and a hyperpigmented and indurated lesion extending from frontoparietal scalp to cheek.

One year later, he developed partial complex seizures responsive to anticonvulsants. Imaging by CT was normal. Despite rapid improvement in color and skin consistency with methotrexate, facial-disfiguring hemiatrophy persisted. A surgical solution was proposed for both cases using silicone expanders under neighboring scalp and forehead normal tissues. The expanded flap was rotated to substitute atrophic skin and fat, with no morbidity and partial cosmetic results, but with excellent patient satisfaction.

Conclusion: There are no gold standard clinical or surgical options to correct linear scleroderma "en coup de sabre". However, good results can be achieved using scalp and forehead expanded flaps.

PP - 272

ASSESSMENT OF CARDIOVASCULAR SYSTEM IN CHILDREN WITH SCLERODERMA

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The aim of the study was to determine whether cardiovascular system (CVS) abnormalities occur in scleroderma children with no overt clinical manifestations of CVS diseases, and to find methods of early diagnosis in these patients.

Methods: We studied 20 children with localized scleroderma (LS) and 20 children with systemic scleroderma (SSc) with no clinical signs or symptoms of CVS diseases, and 20 healthy children - control group (CG). The tests included resting 12-lead ECG, 24-hour ECG and blood pressure (BP) monitoring, as well as M-mode, 2-D and Doppler echocardiography.

Results: Resting ECG QTc (ms) in SSc and LS was significantly longer than in CG. In 24-hour ECG, mean heart rate in CG was significantly lower than in SSc and LS. Daytime mean systolic BP (mmHg) in SSc and LS was significantly lower than in CG. LV ejection fraction and shortening fraction in both study groups were normal. The proportion of mitral inflow velocity in early (E) and atrial (A) phases (E/A) was significantly lower in both study groups in comparison to CG. Myocardial performance index (isovolumic relaxation time+isovolumic contraction time/ejection time) was significantly higher in SSc and LS than in CG.

Conclusion: Numerous abnormalities of the CVS function are present in children with both SSc and LS and no overt symptoms of cardiovascular pathologies. While typical parameters of systolic LV function remain normal in these patients, the echocardiographic analysis of diastole and the assessment of myocardial performance index allow for early diagnosis of LV mechanical dysfunction.

PP - 273

A CHILD WITH LINEAR SCLERODEMA AND UNILATERAL RENAL ARTERY STENOSIS

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Linear scleroderma involves the musculoskeletal parts of the extremity in addition to the skin. Extracutaneous organ involvement is rather rare. Here, a 7-year-old girl with renal artery stenosis with linear scleroderma is reported.

Case: Stiffness had been observed in her left leg since she was 4 months old. At the age of 5, skin biopsy revealed scleroderma and she received steroid, colchicine, hydroxychloroquine and methotrexate for 1.5 years and steroid and methotrexate for the last 6 months. While she was examined for recurrent vomiting, her blood pressure measurements were found at high levels and she was referred to our clinic. Her blood pressure was 140/100 mmHg.

Stiffness and tightness was observed in her left lower extremity and lumbar area. There was flexion contracture on her left knee. Urinary analysis, complete blood count, biochemical parameters, acute phase reactant levels, serological markers and complement levels, esophagus-stomach-duodenum graphs, high resolution computed tomography findings and pupilla examinations were normal, while left ventricular hypertrophy findings were evident on her electrocardiography and echocardiography. On Doppler ultrasound, flow acceleration times of left interlobar arteries were extended and the flow velocity at the level of the left renal artery was very high. Upon these findings, MR angiography was performed, which revealed a severe narrowing at the left renal artery after branching from the aorta; a stent was placed into that segment.

Conclusion: This patient is reported since such a case with linear scleroderma and unilateral renal artery stenosis requiring endovascular intervention has not been reported before.

PP - 274

TWO CASES WITH SCLERODERMA

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Localized scleroderma is related only to the skin, while the systemic type is connected with fibrosis and induration of the other organs. Here, we report one case with localized and another with systemic type of scleroderma, both of whom have unusual clinical properties.

Case-1: A 19-month-old girl was admitted with upper respiratory tract infection findings. A scarred area with a diameter of 5cm at the 1/3 upper thigh was observed coincidentally. When the family was queried regarding that finding, it was learned that the lesion had been present since she was adopted at the age of 15 months. All laboratory findings were in normal ranges other than ANA positivity at 1/40 titer. Skin biopsy revealed plaque morphea, and local steroid and Vaseline were prescribed. The extension of the lesion was limited with the therapy.

Case-2: A 12-year-old girl complained about puffiness and shiny skin on her face, hands and feet for the last four months. Her physical examination revealed localized edema at the distal parts of her wrists, knees and face. ANA titer was 1/1280 and anticentromere antibody was (+). Other laboratory findings and nailfold capillaroscopy were normal. After a low-dose steroid treatment for eight months, she completely recovered and had no recurrence in her follow-up of two years.

Conclusion: We report two cases, one with a very early onset of localized scleroderma and another with systemic sclerosis, who recovered with low-dose steroid prescribed at the initial phase of the disease.

PP - 275

SUCCESSFUL TREATMENT OF DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS ASSOCIATED WITH E148Q MUTATION

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Diffuse cutaneous systemic sclerosis (dcSSc) is characterized by symmetrical fibrous thickening and hardening of the skin combined with fibrous changes in internal organs, such as the esophagus, intestinal tract, heart, lungs, and kidneys.

We report a 9-year-old girl who presented with walking disability, limited hand movements, cold intolerance, cyanosis of lips and fingers in cold temperature, difficulty in swallowing solid food, heartburn, dysphagia, coughing while eating and fatigue. History was not remarkable except for the presence of familial Mediterranean fever (FMF) in her father (mutation E148Q/V726A determined) and sister (V726A /-). E148Q/- mutation was present in

the patient. Clinical examination showed that she had an hyperemic lesion and induration on the left elbow, 7x5 cm area of hypopigmentation in the left axillary skin, 2x1.5 cm area of hyperpigmentation on left extensor region of the forearm, symmetrical skin thickening and hardening on the distal one-third of upper extremities, restriction of flexion and extension of left wrist, flexion of bilateral interphalangeal joints, severe induration with palpation of lower extremities and significant restricted movement of both ankles. Skin biopsy was performed for the definitive diagnosis, which revealed scleroderma.

Steroid, colchicum, rocaltrol therapy and physical rehabilitation were started, and the patient improved with these approaches. Steroid was replaced with methotrexate at the end of the first year. She had an exacerbation in the third year. She also had swallowing difficulty, for which electrotherapy was performed with good resolution of this symptom. She has been followed for six years. She does not have any movement disability or skin thickness.

Although dcSSc is a progressive disease, our patient showed improvement of her symptoms with medical treatment, electrotherapy and intense physical rehabilitation.

• Osteoporosis
PP - 276

SCURVY-RICKETS ASSOCIATION MIMICKING ARTHRITIS IN TWO SIBLINGS

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Scurvy and rickets have multiple presentations, such as musculoskeletal symptoms, asthenia, etc.; thus, they can be misdiagnosed with rheumatic diseases. We describe the case of two Moroccan sisters, aged 12 and 9 years old, with swollen ankles and bone pain, which was later found to be due to a scurvy-rickets association. They were hospitalized in our Department with suspicion of arthritis. Their past medical history was unremarkable. On admission, weight and height were at the 3rd percentile; clinical examination showed pain in the upper and lower extremities with bilateral swollen ankles. They walked with a limp and had decreased range of motion of the spine and hips bilaterally. Blood tests showed anemia, low serum calcium and vitamin D levels, and normal serum phosphate. The activities of serum alkaline phosphatase, parathormone and osteocalcin were elevated. Radiographs showed a diffuse demineralization of metaphyses of long tubular bones, with periosteal proliferation. Characteristic pseudofractures were seen in only one of the sisters.

The constellation of clinical examination, blood tests and radiological findings strongly suggested a diagnosis of rickets-scurvy association. The patients' history revealed poor dietary intake (virtually no vitamin C or calcium intake) and inadequate sunshine exposure. Treatment was started with high-dose vitamin D and vitamin C plus calcium supplementation.

Their family was educated about dietary modification. Rickets is common among North-African Muslim females. Its articular manifestations include a rheumatoid arthritis-like and ankylosing spondylitis-like picture; thus, classic nutritional deficiencies must not be omitted from the differential diagnosis of arthritis.

PP - 277

PREDICTORS OF BONE MINERAL DENSITY (BMD) IN A LARGE COHORT OF CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: Reduced bone mineral density (BMD) has been reported by several studies in children and adolescents with juvenile idiopathic arthritis (JIA). Both disease activity and drug treatments (corticosteroids) have been incriminated as factors influencing BMD.

Design: To evaluate bone mass status and to identify the predictors of reduced BMD in a large cohort of children with JIA.

Patients and Methods: 144 patients with JIA (69 oligoarticular, 47 polyarticular, 11 systemic, 17 enthesitis-related arthritis) aged 5.32±3.37 years were enrolled. There were 107 females and 37 males. In all patients, demographic and anthropometric characteristics, JIA onset, disease activity (ESR, CRP, Hb, active joint count), dose and duration of steroid treatment, concomitant medications, and DXA results (lumbar spine) were recorded. Age- and sex-specific reference values from a pooled, healthy population were used as controls to calculate Z-scores.

Results: Compared to controls, the whole group of patients with JIA showed significantly lower DXA BMD Z-scores (-0.5±1.09 **vs** 0.02±1.1; $p<0.0001$). Analyzing the JIA diagnoses, BMD was more significantly reduced in systemic (-1.64±1.35), polyarticular (-0.60±0.99), and oligoarticular (-0.39±1.07) JIA than in controls, but not in enthesitis-related arthritis (-0.01±0.95).

Reduced BMD correlated with age at disease onset ($p<0.05$), disease activity ($p<0.005$), disease duration ($p<0.05$), and corticosteroid treatment ($p<0.05$). Conversely, no significant correlation was found between BMD and NSAIDs or MTX therapy. Multiple regression analysis showed that only disease activity was the significant variable in influencing the BMD Z-score.

Conclusion: Disease duration and steroid dose, but mainly disease activity, are the more important risk factors for reduced bone mass in JIA patients. Patients with enthesitis-related arthritis, although the group was small, did not seem to be at significant risk for low bone mass. A longitudinal analysis of BMD changes over time is underway.

PP - 278

A 10-YEAR FOLLOW-UP OF ALENDRONATE TREATMENT IN YOUNG PATIENTS

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In a previous study (Study 1), we showed efficacy and short-term safety of oral alendronate (ALN) in pediatric patients with connective tissue disorders. Ten years later, we investigated bone density and long-term safety in the same patients. 43 patients (of 45 originally enrolled) have been included in this analysis (24 females), with an actual age range of 15-28 years.

Diagnoses were: SLE (12), polyarticular (9) or systemic (8) JIA, dermatomyositis (7), and others (7). Three patients were lost to follow-up. All were

treated with glucocorticoids. Two became pregnant: one underwent a voluntary abortion and the other is in the 8th month of an uncomplicated pregnancy. No side effects related to ALN use were observed during follow-up.

Twenty-four subjects continued ALN (for 0.8-6 years), and 11 are still on treatment. During follow-up, 4 fractures occurred: one after 15 months of ALN, and the other 3 after ALN withdrawal. At the last DXA, the spine BMD Z-scores were: <-2 in 6 patients, between –2 and –1 in 16, and > -1 in 20. In the 24 ALN-treated subjects, BMD Z-score was -1.2 ± 1.3, with a change of +3.1 ± 0.9 vs that at the end of Study 1. In the 19 patients never treated with ALN after Study 1, Z-score was -0.9 ± 1.1, with a change of +0.7 ± 0.8.

In conclusion, oral ALN seems to be safe also in long-term use. ALN use in childhood did not induce development or growth problems. Safety during pregnancy is still an open issue.

• Bone diseases other than osteoporosis, metabolic diseases
PP - 279

CLINICAL UTILITY OF NUCLEAR MEDICINE 99mTc-MDP BONE SCAN IN THE EARLY DIAGNOSIS OF RHEUMATOID ARTHRITIS

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Abstract: Joint X-rays may be normal in the early disease stage of rheumatoid arthritis. Bone scintigraphy is a modern diagnostic imaging study that records the distribution of a radioactive tracer in the skeletal system in planar (two-dimensional) and/or tomographic (three-dimensional) images. While radiograph shows bony erosions typical of rheumatoid arthritis in the joints when disease progresses, bone scanning is a very sensitive radioactive test procedure and can demonstrate the inflamed joint earlier than it appears in radiograph. Nine patients (7 females, 2 males, mean age 11 years) with history of pain in joints and fever of mild grade with normal X-rays were chosen for imaging for early detection of rheumatoid arthritis.

Materials and Methods: For labeled radio-pharmaceutical 99mTc-methylene diphosphonate (MDP) in usual administered activity for children, 5 to 10 mCi is used. Patients were taken under the gamma scintillation camera and flow images were acquired. Delayed images of the joints are acquired 3 hours after injection. Acquisition computer was programmed to acquire the region of interest. The spot views of the bone joints (areas of interest) are acquired for approximately 500, 000 to 1 million counts.

Observations: In bone scan of the hand, multiple focal areas of increased tracer uptake were present in the interphalangeal joints, particularly involving distal joints. There was bilaterally increased tracer uptake on scans at the first carpometacarpal joint, knee joints, hip joint and wrist. The scan appearance was typically of rheumatoid arthritis.

Results: A total of 9 patients were investigated with nuclear medicine 99mTc-MDP. In 7 out of 9 patients, increased tracer uptake was seen and scan findings were typical of rheumatoid arthritis. These results are very encouraging.

Conclusions: Bone scintigraphy for detecting rheumatoid arthritis is a very sensitive and specific radionuclide procedure used for early diagnosis. It is safe, cheaper and noninvasive, and it can take scan of the entire skeleton along with spot views. It is a gold standard radionuclide procedure clinically useful in diagnosis of rheumatoid arthritis earlier than X-ray (radiograph).

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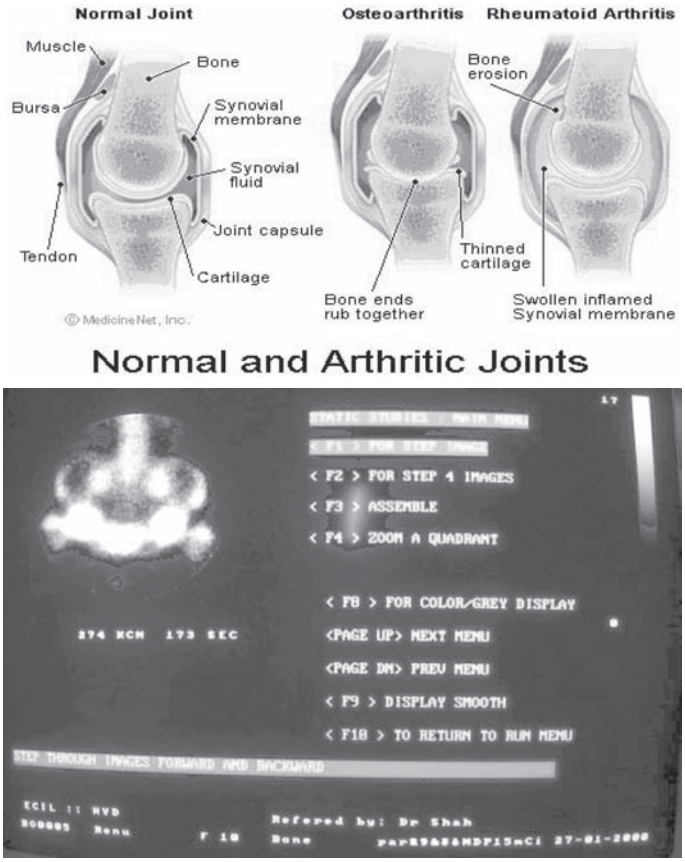

PP - 280

DIAGNOSTIC APPROACH IN A CHILD WITH CAMURATI-ENGELMANN DISEASE

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Introduction: Camurati-Engelmann disease (CED) is a rare autosomal dominant type of bone disorder. It is characterized by cortical thickening of the diaphyses of the long bones.

We present a sporadic case of CED in an 8-year-old girl who was initially suspected to have neuromuscular disorder. At the age of 3 years, she was admitted to our Department and presented with waddling and wide-based gait since she was 16 months old and began to walk. The physical examination revealed muscular hypotrophy of lower extremities and positive Gowers sign. Radiographs showed bilateral and symmetric cortical thickening, affecting the diaphysis of the long bones of the upper and lower limbs, resulting in narrowing of the medullary canal. There was increased density in the skull, ribs and scapulae. Bone scintigraphy showed increased uptake in the both femora, tibiae, fibulae and humeri. EMNG demonstrated the characteristics of myopathy in distal and chronic neurogenic lesion in proximal musculature. The patient underwent a bone biopsy that showed chronic multifocal osteomyelitis (CMO), and NSAID was started. Since the proposed diagnosis of CMO was not completely consistent with the patient's condition, and because of lack of response to NSAID, she underwent additional radiologic examination. Based on clinical and radiological findings, the diagnosis of CED was

established. Methylprednisolone, calcium carbonate and vitamin D were introduced in therapy, which resulted in clinical and radiological improvement. Now, at the age of 8 years, she is without clinical symptoms but radiographs still show characteristic features for this disease, although less extensive.

• Infection – related rheumatic diseases
PP - 281

PYOMYOSITIS: A RARE CAUSE OF LIMP

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A 3-year-old boy presented with limp, overnight right gluteus localized pain and intermittent fever, for 3 weeks. On physical examination, hip was resistant to abduction without warmth, erythema or swelling to either area. Laboratory tests showed moderate elevation of ESR and CRP and normal muscle enzyme levels. US and X-ray examinations were negative. The MRI images showed in large and medius gluteus muscles a 6 cm area lowly hyperintense in T2 and STIR sequences with intense gadolinium enhancement. A 1.3 cm oval area strongly T2 hyperintense, without enhancement, was present. MRI findings suggested muscular edema with fluid collection. Both CT-guided aspiration and biopsy were difficult to perform because of adjacency of obturator artery.

With the suspicion of infective pyomyositis, we decided to start intravenous therapy with clindamycin for 1 week, followed by oral antibiotic therapy for an additional 3 weeks. We observed a complete resolution of clinical symptoms and radiological findings in 2 weeks.

Primary pyomyositis is an uncommon infection of the skeletal muscle, caused mainly by *S. aureus*. Because of resistance of muscle to infection, risks factors are needed for occurrence of pyomyositis, including immunosuppression, local trauma or inflammation after overtraining and concurrent osteomyelitis. No risk factors were present in this case. Three stages of pyomyositis have been described, with the progression from the invasive stage to the suppurative phase and finally to systemic spread of the infection, potentially life-threatening. Therefore, early recognition, by radiological imaging (MRI is the most sensitive test) and prompt treatment are mandatory.

PP - 282

SEVERE, LONG-LASTING HENOCH-SCHÖNLEIN PURPURA INDUCED BY PARVOVIRUS B19

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A 20-year-old female was admitted, after a transient fever, for extensive, symmetric and palpable purpura on lower and upper extremities and abdomen, diffuse arthralgia with important functional impairment and severe abdominal pain. Diagnosis of Henoch-Schönlein purpura (HSP) was formalized. She was initially treated with steroids; a month later, because of severity and persistence of symptoms, we decided on intravenous immunoglobulin (IVIG) approach (1 g/kg). After an initial clinical improvement, a new episode of purpura and hematemesis occurred, and she was given a second IVIG dose. After 3 months the purpura is ongoing.

Laboratory data showed ANA and antiDNA antibodies as negative and complement levels and urine analysis as normal; IgM-anti Parvovirus (ELISA) was positive.

HSP is an inflammatory disease involving skin, joints, gastrointestinal tract and kidneys. HSP is the most common small vessel vasculitis in children and in most cases it is self-limiting within a few

weeks; little is known about the disease in adults. The etiology is unknown, although infections could have an important role as immune trigger. HSP associated with Parvovirus B19 infection has already been described; a significantly high prevalence of Parvovirus B19 NS1 gene has been reported from skin tissue of HSP. Renal diseases (in particular immune complex-mediated nephritis) can occur. In Parvovirus B19-associated adult cases, treatment of choice is IVIG in concert with anti-TNFalpha therapy; immunosuppressive therapy may lead to a persistent and/or worsening disease course. Our case suggests a particularly severe and long course of HSP-Parvovirus B19 association.

PP - 283

ETANERCEPT THERAPY AND HERPES ZOSTER (HZ)

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This case report concerns an 11-year-old boy affected by systemic juvenile arthritis, who presented HZ at the age of 10, during the third year of etanercept treatment. He showed a localized pruritic, vesicular rash involving thoracic dermatomes. In the following 15 days, etanercept was suspended and i.v. IgG, oral acyclovir and oral NSAID were administrated. Skin lesions progressively improved and pain disappeared. He continued etanercept after remission. This drug is in an anti-TNFα blocker, used for its immunosuppressive action in autoimmune diseases.

HZ occurs in individuals with primary HZV infection due to reactivation of latent virus, resident in a dorsal root ganglion, or after new exposure to HZV. Incidence increases with advancing age. It is very unusual in children younger than 10 years. Risk factors for HZ include varicella acquired during the first year of life, intrauterine infection after maternal varicella, immunosuppressive treatment for malignant diseases or to prevent transplant rejection, HIV infection, LES, onco-hematologic diseases, and systemic steroid therapy for chronic diseases. A relationship between HZ and etanercept in children with Wegener granulomatosis has been reported (Wung PK et al. – Am J Med, Dec 2005), but this aspect has not yet been studied in JIA.

Considering the above, it would be appropriate to use life-attenuated varicella vaccine in all patients who are to be treated with etanercept. It has been proven to reduce morbidity and mortality from varicella as well as the frequency of HZ (Vazquez M. et al – NEJM, Feb 2005).

PP - 284

TUBERCULOUS ARTHRITIS IS RARE FORM OF JUVENILE CHRONIC ARTHRITIS

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Isolated monoarthritis, caused by *Mycobacterium tuberculosis* in the absence of lung damage, is a very rare disease. There are few publications on this problem. In practice, tuberculous arthritis must be excluded in all children with chronic monoarthritis.

We describe 4 cases of tuberculous arthritis in children with knee monoarthritis: boys 2, 4 and 11 years old and a girl 2 years old. The presumptive diagnoses in the young children (2 and 4 years old) were oligoarticular onset of juvenile rheumatoid arthritis (JRA). They received intraarticular corticosteroid without significant effect. The presumptive diagnoses in the boy 11 years old were septic arthritis and osteomyelitis. All children had fever, acute night joint pain, high ESR (maximum 68 mm/h) and neutrophil leukocytosis of synovial fluid. We had lack of response to antibiotics and nonsteroid anti-inflammatory drugs in all patients. Standard X-ray knee examination in the disease onset showed no bone changes, but knee computed tomography and MRI detected

focal subchondral bone destruction in medial part of proximal hip epiphysis. Knee arthroscopy was done in two children with synovial and bone biopsy. Only bone biopsy was made in the 2-year-old boy. Positive Mycobacterial culture was determined in only 2 cases in 2.5 months.

The diagnosis of tuberculous arthritis was made with bone histology in 2 cases and in 1 case only by histology of intraarticular fibrinous clots. Tuberculostatic therapy was successful, and joint function was markedly improved.

PP - 286

JOINT COMPLICATIONS IN PATIENTS WITH CYSTIC FIBROSIS

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Patients with cystic fibrosis suffer from chronic infection and consequently inflammation of the respiratory tract. Microbial pathogens frequently involved are S. aureus, H. influenza, P. aeruginosa, Candida species and A. fumigatus. The chronic inflammatory reaction in the respiratory tract might trigger further inflammatory events in distant organs. In this regard, the role of Toll-like receptors might be of significant relevance in such an immune stimulation.

In a cohort of 87 patients with cystic fibrosis, we observed 6 patients who suffered from prolonged, presumably reactive arthritis. In 5 of 6, less than 5 joints of the lower extremities were affected (oligoarthritis). Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was effective in all these cases. Three of the patients did experience repetitive flares, and again NSAIDs were effective. Another patient suffered from septic arthritis; however, no bacteria were cultivable, possibly due to a preceding antibiotic treatment. One further patient suffered from a septic arthritis of the knee and osteomyelitis of the adjacent femur due to Candida albicans, which required a long-term treatment with anti-mycotic drugs. It is possible that a secondary immunodeficiency due to poor nutritional status was allowing the invasive Candida infection of the latter patient.

In conclusion, joint complications are frequent in patients with cystic fibrosis, and require a multidisciplinary diagnostic and therapeutic approach. Most of the patients exhibit a prolonged reactive type of arthritis, which can be treated with NSAIDs effectively.

PP - 287

QUALITY OF LIFE AND COGNITIVE FUNCTIONS IN ADULTS WHO PRESENTED SYDENHAM CHOREA DURING CHILDHOOD: PRELIMINARY RESULTS

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Objective: To evaluate quality of life (QOL) and cognitive functions in adults with Sydenham's chorea (SC) in remission through a QOL questionnaire and a battery of neuropsychological tests.

Methods: Participants were allocated into 2 groups: 1) individuals with SC in remission and 2) adults who presented rheumatic fever without SC during childhood. Both groups were matched according to age, gender and education. Inclusion criteria were: age older than 18 years, at least 5 years of the chorea episode, absence of neurological disease or drug use. We measured QOL using the Health Related Survey - Short Form (SF-36). Cognitive functions were assessed through a comprehensive battery, including tests for IQ, attention, verbal and visual memory, and visuospatial, motor and executive functions.

Results: Eleven individuals with SC in remission (9 females, mean age 23.2 years, mean time of remission 12.5 years, 11 years of education) and 11 individuals without SC (5 females, mean age 24.4 years, 12.4 years of education) were evaluated. Statistical analysis showed the groups were equivalent in IQ scores and educational level. Significant lower results were seen for the SC group in functions involving visuospatial and visual memory tasks (Corsi's Blocks, WMS-R Visual Reproduction). We found no significant differences between groups in QOL scores.

Conclusions: To our knowledge, this is the first report of visuospatial and visual memory deficits in individuals that presented SC during childhood. These preliminary results show that SC patients may have persistent deficits related to brain circuits involved with basal ganglia.

PP - 288

SALMONELLA-ASSOCIATED SACROILIITIS

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Infections by salmonella species are an increasing health problem worldwide. In addition to causing morbidity resulting from gastrointestinal symptoms, patients can have a variety of extraintestinal complications. One of these complications is arthritis, which can be either septic or sterile (reactive). Arthritis is an uncommon extraintestinal manifestation. The pathogenesis of this inflammatory complication is incompletely known.

Sacroiliitis due to salmonella infection is rare. The difficulty of diagnosis is that symptoms can mimic other illnesses. Magnetic resonance imaging (MRI) may be the gold standard for the diagnosis of sacroiliitis even in the early period. We present three cases of salmonella sacroiliitis (1 male, 2 female, age range: 12-14 years) in order to define the clinical features and outcome of the disease. The patients had acute asymmetric hip arthritis with predilection into low extremities, history of fever, and abdominal pain, one or two weeks earlier. Other causes of other arthritis were excluded with routine tests. The complete blood cell count, AST, ALT and creatinine kinase were normal. All had elevated levels of erythrocyte sedimentation rate and C-reactive protein. Investigation of fundus revealed no abnormality and their rheumatologic tests were also normal; HLA-B27 was negative in all patients. Stool and blood cultures for salmonella were negative, titers of Gruber Widal antibodies were extremely high, and MRI revealed sacroiliitis. The patients were treated with ciprofloxacin. Two patients recovered in two weeks after ciprofloxacin treatment; one patient continued to have moderate joint pains and was treated with nonsteroid anti-inflammatory drug.

In conclusion, sacroiliitis due to salmonella infection is rare and outcome of the patients appears generally good. We should consider salmonella infection in the differential diagnosis of sacroiliitis.

PP - 289

THE VALUE OF HEMOGLOBIN AND ACUTE PHASE REACTANTS IN ACUTE RHEUMATIC FEVER

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Introduction: Rheumatic fever (RF) is still one of the most difficult diagnoses in pediatrics, especially when it presents only with arthritis. Apart from the clinical features, laboratory abnormalities can be eventually helpful.

Objectives: The aim of our study was to associate the clinical manifestations of acute rheumatic fever (ARF) with the hemoglobin and acute phase reactants levels.

Methods: We carried out a retrospective study on 198 RF patients (111 girls, mean age at onset 121 months): 68 with carditis, 83 with arthritis without carditis and 47 with isolated chorea. Clinical features were documented and analysis of hemoglobin, erythrocyte sedimentation rate (ESR), alpha1-glycoprotein and gammaglobulin was performed.

Results: Anemia (Hb ≤10 mg/dl), and elevated ESR (≥100 mm/1st hour), alpha1-glycoprotein (≥ 140 mg/dl) and gammaglobulin (≥ 1.4 g/dl) were predominantly found in patients with clinical carditis compared to patients with arthritis and chorea ($p<0.001$, $p<0.001$, $p=0.008$, $p=0.008$, respectively).

Conclusion: In cases where patients present only arthritis, pronounced anemia and elevation of acute phase reactants can be an indication of the presence of carditis in the first weeks following the RF presentation.

• Pain Syndromes
PP - 290

BONE STRENGTH IN CHILDREN WITH GROWING PAINS AS MEASURED BY QUANTITATIVE ULTRASOUND - AN OUTCOME STUDY

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Objective: The etiology of growing pains (GP) is unknown. We previously found that bone speed of sound (SOS) measured by quantitative ultrasound (QUS) was significantly reduced in children with GP, especially in painful tibial regions, supporting a theory that GP represents a local overuse syndrome. Since GP often resolves in older children, we hypothesized that bone strength will normalize as GP improves.

Patients and Methods: We studied 30 (17 male, 13 female, mean age 13.6±2.8 years) of 39 subjects in the original cohort 5±0.2 years after the original measurement. Bone SOS was measured by QUS in mid-tibial bone (Sunlight Omnisense$^{TM\ 7000P}$). Paired Student's t-test was used to compare the first and second QUS z-score results. Pearson correlation was used to evaluate the relationship between bone SOS and frequency of GP.

Results: Sixteen (53%) subjects still had pain compatible with GP. Fourteen (88%) described the pain as less frequent and severe. Five subjects had GP episodes greater than once per week compared to 18 in the first study. Tibial SOS Z-score was significantly elevated in this study (0.84±1.4 versus -0.66±0.95, $p<0.001$). There was no significant difference in bone strength between non-symptomatic and symptomatic subjects. No correlation was found between SOS and GP frequency. No subjects developed other pain syndromes.

Conclusion: In most subjects, GP had resolved or improved after 5 years of follow-up with an increase in bone strength. This supports our hypothesis that GP represents a local overuse syndrome.

• Behçet's Disease
PP - 291

RAS (RECURRENT APHTHOUS STOMATITIS) AND HLA-B51: A PREVIEW OF BEHÇET'S DISEASE?

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We describe 3 children with recurrent aphthous stomatitis (RAS) and positive for HLA-B51 antigen.

The first child, an 11-year-old female, had only RAS since she was 2; the aphthae were almost constant, not responsive to any treatment, with remission only with thalidomide, tapered off due to a severe sensitive neuropathy. Recently, she underwent colonoscopy with histological findings of indeterminate colitis, which is not a diagnostic criterion according to ISG (International Study Group for Behçet's disease-BD) but is quite common in Italian BD patients.

The second case, a 13-year-old male, had RAS (4 episodes during the last 4 years) with cutaneous manifestation (erythema multiforme, not included in ISG criteria but already described in association with BD) and genital ulceration (although not "recurrent").

The third case, a 14-year-old female, had RAS and cutaneous manifestation (pseudofolliculitis).

According to the ISG diagnostic criteria for BD, none of our cases fit the diagnosis of BD; to date only the third case could be considered as an incomplete BD (recurrent aphthae + one diagnostic criterion), while the others could be referred to just as RAS. Nevertheless, it is believed that RAS may be a forme fruste of BD. Since high frequency of HLA-B51 has been found both in BD and in RAS, and aphthous stomatitis is part of BD, we can suppose that in these subjects with RAS and other signs of BD, the entire syndrome may actually develop in the future. Therefore, a careful follow-up is needed for these patients.

PP - 292

DISEASE PRESENTATIONS AND OUTCOME IN CHILDREN WITH BEHÇET'S SYNDROME

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Objectives: To assess the outcome of children with Behçet's syndrome (BS), all attending a single dedicated center.

Methods: Charts of around 6000 patients registered between July 1977 and February 2007 into the multidisciplinary BS outpatient clinic were reviewed. Patients who fulfilled ISG criteria and who were 16 or younger at their initial visit were re-evaluated.

Results: There were 134 juvenile patients (69 males, 65 females). The mean age at first visit was 14.2±1.8 and appearance of the first symptom was at 10.8±3.0 years. The mean time from the fulfillment of the ISG criteria to their first visit was 1.4±1.8 years. The median follow-up was 11 years. Five children (all boys) among 69 (7%) had died. Causes of death were pulmonary artery aneurysms (in 2 patients), Budd-Chiari syndrome, suicide and pneumonia. The clinical manifestations at the initial visit such as genital ulcer, papulopustular lesions, erythema nodosum and arthritis, were less frequent compared to those of the adult population in either sex. Genital ulcers were more frequent among the girls compared to the boys (p=0.014). During the follow-up, boys in particular continued to have new eye, vascular and neurological involvement. 3/41 boys and 1/29 girls with eye involvement developed bilateral blindness. Dural sinus thrombi type of neurological involvement was more common in children compared to the usual parenchymal type in adults.

Conclusions: Pediatric cases of BS accounted for approximately 0.2% of all patients. As in the adults, juvenile BS runs a more severe course and there is increased mortality among the boys.

PP - 293

ETIOLOGIC AND CLINICAL FEATURES OF UVEITIS IN CHILDREN

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Uveitis is one of the most important manifestations of rheumatologic diseases. We designed a retrospective study in order to evaluate the etiologic and clinical features and ocular manifestations of pediatric uveitis. Fifteen children (ages: 6-17 years, 6 female, 9 male) with uveitis were included in the study. Eleven of 15 patients (80%) had admitted to the ophthalmology department with initial presentation of uveitis. The etiologies of uveitis in patients were rheumatologic diseases in 9 (60%), herpes simplex and toxoplasma infections in 3 (20%) and pars planitis in 3 (20%). Of the 9 patients with rheumatologic diseases (group I), 5 had JRA and 4 had Behçet disease. The mean age of the patients in

group I was significantly lower than in those without rheumatologic disease (group II) (10.88±4.16 years and 16.5±0.54 years, respectively, $p<0.05$). Six of 9 (66.7%) patients in group I revealed findings of systemic disease on examination. Bilateral uveitis was observed in 6 patients (66.7%) in group I and in 1 patient (16.6%) in group II ($p<0.05$). Of the 9 patients in group I, 4 had intermediate uveitis, 1 had anterior uveitis and 4 had panuveitis. The etiology of panuveitis was Behçet disease in 4 patients. Of the 6 patients in group II, 2 had intermediate uveitis, 2 had anterior uveitis and 2 had posterior uveitis. None of the patients showed panuveitis in this group. Of the 5 patients who had HLAB5, 4 had the diagnosis of Behçet disease and 1 had JRA. Of the 9 patients in group I, 6 had remission, 2 had partial response and 1 had resistance to the therapy. Remission was obtained by infliximab in 2, azathioprine in 3 and CSA in 1 patient.

In conclusion, the young age of patients and the presentation of bilateral uveitis should be a warning about rheumatologic diseases. Behçet disease is frequent and the presence of HLA B5 and panuveitis was associated with Behçet disease. A close relation should be fostered between rheumatologists and ophthalmologists to effectively monitor these children.

PP - 294

SEVERE RAYNAUD SYNDROME AND ERYTHEMA NODOSUM-LIKE LESIONS AS INITIAL PRESENTATION OF BEHÇET DISEASE: A CASE REPORT

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We present the case of a 20-year-old male patient who was admitted in our clinic in November 2006 with severe Raynaud phenomenon of ulcero-necrotic lesions of the fingers in both hands and important ischemic modification at the distal phalanges **o**f the feet, which developed rapidly in a two-month period. Six months before he presented, an erythemato-nodular eruption appeared on the legs, but at the moment just several hyperpigmented plane lesions and a small ulcer on the right shank were present. Clinical investigation also revealed pseudo-folliculitis of the face and thorax, but there were no signs of oral aphthous ulceration or genital ulceration or of inflammatory eye disease. The pathergy test was positive and the biopsy that was taken from the lesion of the shank was compatible for Behçet disease. For the severe modification due to Raynaud phenomenon, we administrated 5 perfusions with iloprost (a synthetic analogue of **prostacyclin** $PGI_{2)}$ with partial remission of the ischemic lesions, and we initiated oral therapy with azathioprine, prednisone and antithrombotic drugs, with significant improvement in symptomatology after 5 months of treatment.

PP - 295

CLINICAL FEATURES OF BEHÇET'S DISEASE IN CHILDREN IN THE NAPLES AREA OF SOUTHERN ITALY

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Behçet's disease (BD) is a systemic inflammatory vasculitis of young adults with unknown etiology. A total of 16 patients were found to have BD during the period from 1995 through 2007 in the Pediatric Rheumatology Unit of the Federico II University in Naples, Italy. Diagnosis was made according to the criteria proposed by the International Study Group for Behçet's Disease. Girl: boy ratio was 10:6, the mean age at the symptom presentation was 4.6 years (range 2 to 13 years), and 2/16 (12.5%) were familial cases. The clinical manifestations at the disease onset were: oral aphthous ulcers in 6/16 patients (37.5%), skin lesions in 3/16 (19%), joint symptoms in 7/16 (62.5%), gastrointestinal symptoms in 4/16 (25%), and neurological involvement in 3/16 (19%). The mean age at diagnosis was 13 years, oral lesions were found in all patients, genital lesions in 4/14 (25%), ocular lesions in

5/16 (31.25%), skin lesions in 10/16 (62.5%), pathergy reaction in 2/16 (12.5%), arthritis in 10/16 (62.5%), gastrointestinal involvement in 8/16 (56.25%), neurological involvement in 6/16 (37.5%), recurrent epididymo-orchitis in 1/16 (6.25%) and thrombophlebitis in 1/16 (6.25%). The drugs used for the treatment of children with BD were systemic corticosteroids in 14/16 (87.5%), NSAIDs in 6/16 (37.5%), sulfasalazine in 1/16 (6.25%), thalidomide in 6/16 (37.5%), etanercept in 2/16 (12.5%) and topical agents. BD is a relatively rare rheumatologic condition. Compared with other reported series, our patients had fewer serious ocular complications and vascular manifestations, and a lower incidence of the pathergy reaction.

• New treatment strategies
PP - 296

RITUXIMAB IN JUVENILE AUTOIMMUNE DISORDERS

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Background: Some patients suffer from aggressive forms of juvenile autoimmune disorders, which are unresponsive to conventional immunosuppressive therapy. Particularly in children, treatment options that limit the need for steroids and cyclophosphamide are welcomed. Biologic agents that target specific elements of the inflammatory response have become promising treatment alternatives. Rituximab is a chimeric monoclonal antibody that binds to CD 20, a surface glycoprotein expressed by B cells. Efficacy of rituximab has been reported in non-Hodgkin's lymphoma, idiopathic thrombocytopenia and autoimmune disorders such as juvenile dermatomyositis (JDM), Wegener's granulomatosis (WG) and systemic lupus erythematosus (SLE).

Patients and Methods: Four adolescents (aged 12-17, 2 male, 2 female) suffering from JDM, WG and SLE (2) had continuous disease activity in spite of treatment with drugs such as methylprednisolone, immunoglobulins, cyclosporin A, methotrexate, azathioprine, cyclophosphamide, NSAID, and hydroxychloroquine. All patients showed therapy-related side effects such as Cushing's disease (4/4), osteoporosis (3/4), depression (1/4), and hypertension (1/4). Following a protocol established in oncology patients, rituximab 375 mg/m^2 x 4 was applied.

Results: All patients improved remarkably after rituximab therapy. Steroids could be discontinued in 3/4 adolescents. Rituximab was well tolerated with one incident of respiratory infection. Rituximab caused depletion of CD19+ B-lymphocytes in all patients.

Conclusion: Rituximab is an effective and safe treatment option in juvenile autoimmune disorders refractory to conventional therapy. This is particularly valuable in adolescents who suffer from serious steroid side effects. These results are too preliminary to substitute as standard therapy but prospective trials are warranted to gather more reliable data.

PP - 297

A PILOT STUDY OF THE EFFECTIVENESS OF AN INTENSIVE PHYSIOTHERAPY PROGRAM IN THE MANAGEMENT OF CHILDREN WITH RHEUMATOLOGICAL CONDITIONS

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Physiotherapy is a well-recognized treatment for rheumatological conditions. The Rheumatology Unit at Great Ormond Street Hospital provides a two-week intensive physiotherapy admission for children with rheumatic conditions. This pilot study explores the effectiveness of this intervention.

Methods: Twenty children were assessed before and after the completion of the program. They were followed up with a short questionnaire one month after discharge. All children had stable disease, but had biomechanical abnormalities causing pain, fatigue and loss of function. Their diagnoses included benign joint hypermobility syndrome, juvenile dermatomyositis or juvenile idiopathic arthritis.

All children were assessed for joint range of movement, muscle strength (Myometry and 0-10 Kendall scale), function (CHAQ), balance, pain, specific (SLR hold) and general (6 minute walk test) stamina, and parental assessment of well-being.

The physiotherapy included 16 90-minute exercise sessions over 10 days. The sessions were run as group sessions and consisted of a specific regimen of exercises that targeted specific muscles using a principal of a progressive resisted open chained approach. Further exercises were included that concentrated on closed chain activities, and functional and aerobic exercise. All children were progressed to 30 repetitions of each exercise and weights were added as resistance.

Results: All children substantially improved their muscle strength, specific and generalized stamina, balance, pain and function, and this was maintained for at least one month following discharge.

Conclusion: Children can significantly improve their physical functioning with an intensive physiotherapy program.

PP - 298

ANAKINRA - A NEW MAGIC DRUG FOR SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)?

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Objective: To report the preliminary results of the treatment of our SJIA patients (pts) with anakinra.

Methods: A retrospective study of pts with SJIA treated with anakinra. Anakinra was given if the standard medications (MTX, CSA, AZA, ETA etc. plus steroids) failed.

Results: 23 SJIA pts (9 F, 14 M, duration of SJIA 6.3±4.6) received anakinra 1.0-2.2 mg/kg/d for 4-16 months. In 3 of 23 pts, anakinra was stopped due to inefficacy; 19 of the 23 pts exhibited improvement of the clinical as well as of the laboratory parameters (CRP, ESR), which was dramatic in 13/19. The main side effects were injection site reactions. No serious infections were seen.

Summary & Conclusion: Anakinra led to improvement in 19 of 23 SJIA pts, which was dramatic in 13. The daily subcutaneous application led to acceptance problems in small children, which could be resolved only because of the good efficacy of anakinra. In our experience, anakinra is not a magic drug, but the most successful pharmacological treatment of SJIA today. The efficacy seems to be comparable to the results observed in the CIAS1-Associated Periodic Syndromes (CAPS), which raises the question whether some pts with SJIA suffer from a kind of hereditary autoinflammatory disease rather than from JIA.

PP - 299

BOTULINUM TOXIN A (BTX-A) AS AN ADJUNCT TO TREATMENT IN THE MANAGEMENT OF HIP INVOLVEMENT IN JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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In patients with JIA, involvement of the hip is the most important factor affecting mobility and independence. Initially, synovial hypertrophy and effusion cause pain and secondary muscle spasm; later fibrosis and periarticular contractures produce fixed flexion and adduction deformity. Intramuscular injection of BTX-A has gained widespread acceptance in the treatment of lower-extremity hypertonicity in children with cerebral palsy because of its focal effects and wide safety margin. We describe a 9-year-old girl with polyarticular JIA and celiac disease. She had severe bilateral hip involvement (right > left), with limp, pain and deformity that had led to increased lumbar lordosis. A total of 300 IU of BTX-A (Disport ®) was injected in the iliopsoas muscle and the adductors on the left side to prevent a fixed deformity. The day after the treatment, she began active assisted exercise and hydrotherapy. She had early relief of pain and improved gait. After two weeks, significant improvement was noted in external and internal hip rotation.

BTX-A injection may produce considerable benefit by decompressing the joint and releasing the joint contracture, with improvement of disuse osteoporosis and nutrition of articular cartilage. Long-term follow-up and more large clinical studies are necessary to determine the effectiveness of this form of therapy.

PP - 300

LINEAR GROWTH AND BONE MASS ACQUISITION IN JIA: INFLUENCE OF ETANERCEPT THERAPY COMPARED TO MTX

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We investigated whether etanercept may offer an advantage regarding linear growth and bone mass acquisition in juvenile idiopathic arthritis (JIA) patients compared to standard second-line treatment with methotrexate (MTX).

Two groups of active polyarticular JIA patients were enrolled in a prospective longitudinal study.

The first group included 8 patients with active polyarthritis started on MTX. A second group of 16 patients who had active polyarthritis despite MTX for at least 3 months received additional etanercept. Patients were evaluated at baseline and at 6, 12 and 18 months of therapy for disease activity (cf JIA core set criteria), anthropometric parameters (weight, height, growth velocity) and bone status and body composition assessed using DEXA.

At baseline, both groups were comparable with regard to JIA disease activity and anthropometric measures. The etanercept-treated group had a longer duration of disease and corticosteroid therapy.

A pediatricACR30 was achieved in 18 of all 24 patients (75%) at month 6 and 21 of 22 patients (95%) at month 18. The change in activity variables was not different between the two treatment groups at any time point.

Patients treated with Enbrel showed a significant increase in growth velocity after 6 months and continuously up to 18 months compared to before starting therapy. The MTX-treated patients showed a mild but non-significant increase in growth velocity throughout the study period. The Enbrel-treated patients showed a significant increase in BMD and lean body mass and decreased fat mass, in contrast with a non-significant change in the MTX group.

In conclusion, treatment with etanercept for severe polyarticular JIA may offer an advantage with regard to linear growth, bone mass and body composition.

PP - 301

LEFLUNOMIDE TREATMENT IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Objective: To evaluate the effectiveness and safety of leflunomide in patients suffering from juvenile idiopathic arthritis (JIA).

Methods: We reviewed retrospectively all the charts of JIA patients treated with leflunomide in the last 5 years in our clinic. Efficacy was determined regarding: number of active joints, number of limited joints, VAS of the physician, VAS of the parents/patient, and ESR and/or CRP after 3 and 6 months of treatment and at the last visit. All side effects and previous treatments were also registered.

Results: Twenty-one patients had been treated in the past 5 years. Mean age at the beginning of the treatment was 12.5 years (7-23). The girl/boy ratio was 4/1. Treatment received immediately before leflunomide was methotrexate in 15/21 patients (alone or in combination). The reason for the change to leflunomide was partial or null response in 8 patients and unbearable side effects in 17 (mainly gastrointestinal and mucocutaneous symptoms). 10 mg/day or 20 mg/day of leflunomide was used depending on the body weight. Mean duration of the treatment was 24.4 months (3-60). In all patients that received leflunomide for at least six months (12/21), a trend towards improvement was noticed even after 3 months, and confirmed after 6 months of treatment and at last visit. Eight patients achieved complete remission. Three patients had to stop leflunomide due to moderate side effects.

Conclusion: Leflunomide seems to be safe in JIA and efficacious for some patients. It seems to be a good alternative when intolerance to methotrexate is present. Exact pediatric dose remains to be established.

PP - 302

SULPHASALAZINE TREATMENT IN PROTRACTED FAMILIAL MEDITERRANEAN FEVER ARTHRITIS

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by self-limited attacks of fever and polyserositis. Articular involvement in early onset FMF is a common finding, characterized by nonerosive, generally asymmetric monoarthritis in large joints lasting a few days. Protracted FMF arthritis was also reported in 2.6% of Turkish patients.

An 8-year-old female with a five-year history of FMF was admitted with complaints of resistant swelling and pain in her left knee for 8 months. Erysipelas-like erythema was observed on her left lateral malleolus. MRI of the left knee showed effusion, synovial hyperplasia and multiple lymphadenopathies at popliteal fossa. Management of the patient was attempted with NSAIDs as well as intra-articular steroids and colchicine. However, arthritis and acute phase response persisted. Sulphasalazine treatment was started. Two months later, there were no complaints, knee examination was normal, and follow-up knee MRI findings showed almost total regression. Nine weeks later she admitted with left knee pain and mild swelling. Sulphasalazine dose was increased. She is being followed without any complaints or serological activation for eight months.

Despite colchicine treatment, a few cases of protracted arthritis can be seen. Synovectomy may be preferred, and thalidomide, etanercept and interferon alpha can be used as medical treatment options for colchicine-resistant FMF attacks and protracted arthritis. We tried sulphasalazine in this case of protracted FMF arthritis and achieved complete recovery. It is our belief that sulphasalazine can be a choice of medical treatment in protracted FMF arthritis.

• Miscellaneous rheumatic
PP – 303

PROTRACTED FMF ARTHRITIS PRESENTING AS SEPTIC ARTHRITIS

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In familial Mediterranean fever (FMF), arthritis is the initial symptom in 25% of patients. FMF arthritis is acute and self-limited. In 5% of cases, protracted arthritis may occur. In this report, two cases initially diagnosed as septic arthritis are presented. Our first case was a 13-year-old boy who admitted with persistent knee pain, swelling and fever. Although he had intermittent fever and arthritis attacks for the past 9 years, and had a brother who died from end stage renal failure due to amyloid nephropathy, he was operated on four times with the misdiagnosis of septic arthritis. Our second case was a 10-year-old boy who had recurrent fever, abdominal pain and myalgia attacks for the past 7 years. Because he had left knee pain, edema, and elevated acute phase reactants on admittance, he was also misdiagnosed as septic arthritis and underwent a synovectomy operation. Regarding his recurrent myalgia and fever episodes, he was started on prednisone with the diagnosis of protracted febrile myalgia, which resulted in immediate subsiding of his symptoms. Both of our cases were diagnosed as FMF with detailed history. After colchicine therapy was started, no recurrent episode of protracted arthritis was seen.

FMF must be considered in cases of protracted recurrent arthritic episodes that mimic septic arthritis. Because the diagnosis of FMF is based mainly on clinical features, we aimed to emphasize the importance of diagnosis of FMF in patients with arthritis as the only symptom to prevent unnecessary operations and patient suffering.

PP - 304

MIXED CONNECTIVE TISSUE DISEASE IN SIBLINGS

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Mixed connective tissue disease (MCTD) is one of the least common disorders in pediatric rheumatology. There has been only one report of this disorder occurring in siblings. Here we present two brothers diagnosed as MCTD.

A 12-year-old boy presented with mutilation in his fingers and toes. Physical examination revealed growth retardation; cold, pale, sclerotic fingers, three of which were necrotic and mutilated; 2 cm hepatomegaly; proximal muscle atrophy and weakness; and increased DTR in lower extremities together with symmetric sensory loss. Laboratory examinations were as follows: Hb: 10.5 g/dl, WBC: 5080/μL, platelet count: 240, 000/μL, MCV: 81fl, ESR: 70 mm/h, CRP: 0.8 mg/dl, AST 302 U/L, ALT 202 U/L, C3: 63 mg/dl, C4: 11 mg/dl, ANA: (+), and ENA RNP: (+); urinalysis and renal functions were normal. His 26-year-old brother was also growth retarded and his physical examination revealed Raynaud's phenomenon, mutilated fingers and toes together with atrophic and weak muscles. Laboratory examinations of the brother were as follows: Hb: 12.7 g/dl, WBC: 4810/μL, platelet count: 283, 000/μL, MCV: 94 fl, ESR: 24 mm/h, CRP: <0.1 mg/dl, AST 23 U/L, ALT 32 U/L, C3: 74 mg/dl, C4: 13.7 mg/dl, ANA: (-), and ENA RNP: (-); urinalysis and renal functions were normal. He was treated with pulse methylprednisolone, cyclophosphamide and prednisolone together with hyperbaric oxygen. Necrotic lesions regressed immediately with decreasing acute inflammation markers.

These brothers are presented because of rare presentation of MCTD in siblings together with mutilation in fingers and toes.

PP - 305

KAWASAKI DISEASE WITH GIANT CORONARY ANEURYSM: A CASE REPORT

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Kazım Öztarhan[1], Alper Güzeltaş[1], Rengin Şiraneci[1], Özgür Kasapçopur[2]
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Introduction: Patients with the diagnosis of Kawasaki disease having coronary aneurysms >8 mm in diameter have poor prognosis and possess an important risk factor for early myocardial infarction. We report a patient with the diagnosis of meningitis who, when reevaluated, was diagnosed as Kawasaki disease with giant coronary aneurysm on her 12th day of admission.

Case: A girl aged 3.5 months was admitted to the hospital with fever of 2 days duration, poor sucking and irritability. Fever could not be controlled with the previously prescribed penicillin antibiotics and antipyretics. She had fever of 39 °C, irritability, and bulging and pulsing anterior fontanel. Her acute phase reactant values were high. Lumbar puncture was performed and revealed 50/mm^3 of leukocytes, CSF glucose of 56 mg/dl, and protein of 39 mg/dl. She was treated with ampicillin/sulbactam and ceftriaxone, but her fever could not be controlled and antibiotics were changed to vancomycin and meropenem. First hemoculture was sterile but *Staphylococcus epidermidis* was detected in the second hemoculture. On the 9th day of her follow-up, redness over her lips and nonpurulent conjunctivitis were seen. On the 10th day, an echocardiographic evaluation was done and bilateral coronary artery dilatations of 5.5 mm (right) and 8.5 mm (left) were measured. Intravenous immunoglobulin (IVIG) (2 g/kg) and aspirin (100 mg/kg) therapies were started. Desquamation of hands and feet was seen during the second week. After first dose of IVIG, her ESR was still 75 mm/hr and she had thrombocytosis. A second dose of IVIG and 30 mg/kg of steroid were given. Her acute phase reactant values returned to normal. Fibrotic narrowings were seen in the control echocardiography. She is still on antiaggregant aspirin therapy and being followed with routine echocardiographic examinations.

In conclusion, we stress the importance of early diagnosis and treatment in Kawasaki disease with the help of clinical findings in our patient with coronary aneurysms and meningitis.

PP – 306

TWO CASES OF KAWASAKI DISEASE PRESENTING WITH PROLONGED FEVER AND HEPATITIS

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Introduction: Two patients with prolonged fever and hepatitis who were diagnosed as Kawasaki disease are presented.

Cases: The first case is a 13-month-old male with fever of 7 days, maculopapular rash and icterus. He had a history of nonpurulent conjunctivitis. He also had cervical, perioral and perineal desquamation, cervical lymphadenopathy, strawberry tongue, hepatomegaly, and activation of BCG scars. Acute phase response was high and hepatobiliary tests were abnormal. Abdominal ultrasound showed hepatomegaly. Viral markers were negative. Echocardiography was normal. Atypical Kawasaki disease with hepatic involvement was diagnosed and he was treated with 2 g/kg of IVIG and 40 mg/kg of aspirin. All clinical and laboratory findings recovered. He is being followed up without any complication.

The second case is a 13-month-old male who presented with 8 days of fever. He had been diagnosed at another hospital as tonsillitis and treated with antibiotics. His fever was still high at our first

PP - 307

MUSCLE SKELETAL INVOLVEMENT AS FIRST MANIFESTATION OF NEOPLASM DISEASES IN CHILDHOOD

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Objective: To describe the clinical and laboratory features that contributed to the diagnosis of neoplasm in patients with musculoskeletal symptoms at the onset of disease.

Methods: A retrospective analysis of medical records from patients with final diagnosis of neoplasm diseases attending the Unidade de Reumatologia do Instituto da Criança – FMUSP between January 1983 and January 2007. The data on musculoskeletal complaints, clinical examination, laboratory tests, radiological studies and diagnostic procedures were obtained.

Results: From 4893 patients, 25 (0.5%) children were studied (52% with acute lymphoid leukemia and 24% with neuroblastoma). Twenty children (80%) presented arthritis and/or arthralgia in the beginning of the illness. All patients presented systemic symptoms, such as fever (22 cases). The initial blood cell count was abnormal in 16 patients (64%), showing anemia and thrombocytopenia (12 and 5 cases, respectively). Blast cells were present in only two patients and 11 patients developed blood cell count abnormalities during follow-up. X-ray studies showed abnormalities in 11/14 patients, ultrasound in 12/18, scintigraphy in 5/5, CT in 7/9 and MRI in 3/3. Bone marrow smear was abnormal in 18/22 patients (in 3 of them, the first test was normal).

Conclusions: Musculoskeletal symptoms are common at the onset of neoplasm, especially in acute lymphoid leukemia, and this possibility should be considered in the differential diagnosis of rheumatic diseases. The laboratory tests may be normal at the onset of the illness, so serial exams should be performed. Radiological studies and bone marrow aspiration were demonstrated to be essential for correct diagnosis.

PP - 309

ARTHRITIS AND PRIMARY IMMUNE DEFICIENCIES

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Introduction: Primary immune deficiencies (PIDs) are characterized by functional and/or quantitative abnormalities in one or more of the immune system components. PIDs typically manifest as recurrent infections that usually start in childhood. Among joint manifestations, arthritis is the most common.

Case Description: The authors report 2 cases of arthritis in PID. Case 1: A 29-year-old male presented with oligoarthritis at the age of 3 years. He had repeated upper respiratory infections, conjunctivitis and gastroenteritis, and bronchopneumonia at 4 months. Chronic and relapsing arthritis was observed until the age of 16 years. Synovial fluid analysis revealed an aseptic inflammatory fluid without crystals. Biopsy showed synovial hyperplasia and capillary proliferation with neutrophilic infiltrate. Inferior limb dysmetria was one of the complications. Case 2: A 19-year-old male presented with monoarthritis at the age of 6 years. He had repeated upper respiratory infections and pneumonia at 3.5 years. Both had severe hypogammaglobulinemia and 1% of CD19+ cells and began treatment with human immunoglobulin. X-linked agammaglobulinemia (XLA) was diagnosed: a nonsense mutation (R255X) in the first case and a deletion frameshift mutation (delT in codon 344/345) in the second.

PP - 309

ARTHRITIS AND PRIMARY IMMUNE DEFICIENCIES

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Conclusion: Arthritis occurs chiefly in humoral PID, particularly in XLA, and may be inaugural. It may be related to infection or immune dysfunction. A combination of arthritis and hypogammaglobulinemia should suggest PID. Rheumatologists should be familiar with this concept so that they can request the investigations needed to support or to refute this possibility. Early diagnosis is of extreme importance.

PP - 310

SAFETY AND RESPONSIVENESS OF VARICELLA VACCINE (VV) IN PATIENTS WITH JUVENILE RHEUMATIC DISEASES

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Objective: To evaluate the safety and responsiveness of VV in children and adolescents with rheumatic diseases (RD).

Methods: Sixteen patients with low levels of varicella-zoster virus (VZV) antibodies (Ab) (13 JIA, 2 with scleroderma, 1 with vasculitis) aged 2-15 years and 17 healthy controls (3-17y) received one dose of VV BIKEN (**Aventis Pasteur**). Fifteen patients were taking methotrexate at the time of vaccination; 6 of them were also using corticosteroids and 4 other immunosuppressive drugs. Anti-VZV Ab levels were measured by ELISA 4-6 weeks and 1 year after vaccination.

Results: No overt varicella episodes were observed. Three patients developed a mild self-limited varicella-like rash (6-12 lesions) in the first 2 weeks following vaccination. None of the patients developed herpes-zoster or chickenpox during a follow-up of 18 months. When comparing the period of 3 months after and before VV, no significant differences in median values of ESR, CHAQ scores or doses of medications used were observed in the group of 16 patients ($p=0.4$). Median values of patient and physician assessment of disease activity (VAS) improved after vaccination ($p=0.004$ and 0.006, respectively). Moreover, in JIA patients, the number of active joints were significantly lower after VV ($p=0.01$). Protective VZV-Ab levels after vaccination were detected in 15/16 (93.7%) patients and 13/17 (76.6%) controls.

Conclusions: Although the number of patients studied was low, our results suggest that varicella vaccination is safe and effective even in rheumatic patients using methotrexate and corticosteroids.

PP - 311

LOSS OF EFFICACY DURING LONG-TERM INFLIXIMAB THERAPY FOR SIGHT-THREATENING CHILDHOOD UVEITIS

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Aim: To describe the efficacy and safety of Infliximab (i) for the treatment of childhood chronic uveitis (**U**) during a long-term follow-up.

Material and Methods: Eight patients (median age at **U** diagnosis: 4 yrs, range 2-12) with inflammatory chronic U, long-lasting and refractory to previous treatments, were enrolled: 4 JIA, 1 early-onset sarcoidosis, 1 Behçet disease, and 2 idiopathic uveitis. Before I treatment, all children presented active **U**: 10/16 involved eyes, despite treatment with methotrexate (5/8) and cyclosporin A (1). All were receiving oral and/or topical steroids. All patients initially received I (5 mg/kg) at t 0, 2, 6 and then every 6-8 weeks for at least 1 year (range 12-16 months). Later, the administration rate was progressively increased up to every 10 weeks if **U** did not flare.

Absence or recurrence rate of **U** throughout the study period was recorded. Spearman's correlation test was used, and Cox regression model and Kaplan Meyer curves were constructed, in order to identify predictors of outcome.

Results: Median follow-up time of treatment was 29 months (range, 12-40) and median n° of infusions 18 (range, 10-23). During the first year of treatment, 7/8 children achieved a complete remission, but all relapsed thereafter. At the first relapse of **U**, median follow-up of treatment was 12 months (range 9-18) and median n° of infusions 11 (range 8-19). The figure shows survival curve of our patients up to the first **U** flare. The number of flares showed a statistically significant association with the length of follow-up (r_s=0.84; $p<0.03$) and with the total number of infusions (r_s= 0.81; $p<0.04$). No patient developed any serious complications attributable to I, and none had to discontinue treatment due to adverse events.

Conclusions: Even if limited to a small group, infliximab appears to be an effective treatment for **U** in the short-term, but its efficacy seems to wane over time.

PP - 312

MUCOPOLYSACCHARIDOSIS TYPE I (MPS I): A FLOW CHART FOR SCREENING IN CHILDHOOD OF A SUBCLINICAL MILD FORM (SCHEIE SYNDROME)

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MPSI is a recessively inherited progressive disease caused by deficiency/absence of lysosomal enzyme α-L-iduronidase (α-L-IDUA) involved in degradation of glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate. α-L-IDUA deficiency leads to abnormal urinary excretion (uGAG) and progressive accumulation of GAGs with cellular, tissue and organ damage, leading to loss of function and progressive disability. MPSI has been classified into 3 syndromes: Hurler (H), Hurler-Scheie (H-S) and Scheie (S), corresponding to severe, intermediate and mild phenotypes. The excess of uGAG provides a useful screening test for MPSI, and diagnosis is confirmed by a low/absent IDUA activity in leukocytes. It is now possible to prevent the irreversible tissue damage, due to GAG storage, through a precocious laronidase enzyme replacement therapy. The aim of our study was to identify, pre-disease onset, with a screening program, the mild form of MPSI (S). We reviewed all published clinical studies and recorded all different presenting features. According to their frequency and specificity, we distinguished 7 major criteria (family history, cardiac disease, corneal clouding, fixed flexion deformity fingers, spinal

cord compression, carpal tunnel syndrome, skeletal abnormalities) and 6 minor criteria (recurrent ENT symptoms, joint stiffness, hearing difficulty, hepatomegaly, umbilical hernia, delayed speech development). One major or two minor criteria indicated possible MPSI (S). In these cases, according to our flow-chart à quantification of uGAG levels, if uGAG abnormal high levels à confirmation of the diagnosis via demonstration of the IDUA activity defect in leukocytes. A screening project in pediatric rheumatologic centers will contribute to a precocious diagnosis and to an early treatment avoiding irreversible damage.

PP - 313

PRIMARY ANTIPHOSPHOLIPID (aPL) SYNDROME IN A 10-MONTH-OLD CHILD

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The first formal description of aPL syndrome by the direct detection of anticardiolipin antibodies enabled Hughes and co-workers to describe in adults a group of patients who had raised levels of these antibodies and clinical features including recurrent venous thrombosis, nervous system disease and recurrent miscarriage.

The incidence of aPL in the pediatric healthy population has not been determined in a large and reliable study. The majority of aPL infection-related are IgM isotype and they are different from those seen in patients with autoimmune disease and are not associated with the typical clinical features of aPL syndrome.

We describe a 10-month-old girl, born to a healthy woman, who developed an ischemic stroke after a gastrointestinal viral infection and muscle thrombosis of the right thigh. A high positive titer of aPL and lupus anticoagulant (LA) were found during investigation. Malignancies, inherited metabolic diseases, hemoglobinopathies and other diseases with high risk of thromboembolism were excluded. Clinically, the child developed coma, left > right hemiparesis, anisocoria and seizures. She presented with normal MRI in the first evaluation and on the third day the second MRI showed ischemia in the entire left hemisphere and abnormal EEG. She was treated with anticoagulation (LMWH) with complete recovery after a 10-month follow-up. Although aPL-associated events have been described in children of all ages, even some as young as a few months of age, and because it is not a frequent condition, aPL syndrome should always be included in the differential of a child with idiopathic thrombotic disease.

PP - 314

EVALUATION OF SERUM VITAMIN B12 LEVELS IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Aim: To evaluate serum vitamin B12 levels in patients with familial Mediterranean fever (FMF) receiving long-term colchicine treatment.

Methods: Serum vitamin B12, folic acid levels and full blood count of 70 patients with FMF who received colchicine treatment for more than five years were evaluated. They had no other chronic, systemic or endocrinological disease and were not vegetarians. The results were compared with those of 80 patients with FMF that received colchicine less than 5 years and also with those of 70 healthy children.

Results: The mean age of the patients was 15.5±2.45 years; of the group that received less than 5 years of colchicine therapy 10.24±4.02 years; and of the control group 10.36±3.06 years. Serum vitamin B12 levels of the patients that received colchicine for more than 5 years (208.37±40.57) was significantly lower than of patients that received colchicine for less than 5 years (390.77±124.19) and the control group (478.31±135.76) ($p=0.0001$, $p<0.005$). Furthermore, mean corpuscular volume (MCV) was significantly higher in this group ($p=0.038$, $p<0.005$). However, MCV levels were

in normal limits in all three groups. There was no statistically significant difference in terms of folic acid, hemoglobin and hematocrit levels between the three groups.

PP - 315

RELAPSING POLYCHONDRITIS: UNSUCCESSFUL TREATMENT WITH INFLIXIMAB IN A PEDIATRIC PATIENT

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Relapsing polychondritis (RP) is a severe, chronic disorder of cartilage, very rare especially in children, characterized by recurrent episodes of inflammation of tissue cartilage.

A 14-year-old female was admitted to our department because of a 6-month history of sudden intermittent pain and swelling of the nose. She later developed redness, pain and swelling of the right ear, dysphonia and throat pain. On examination, cartilaginous parts of the right ear showed a dusky erythema and were swollen and tender. Computed tomography scanning showed circumferential deformity and edema of the proximal tracheal rings and sclerosis of the left arytenoid cartilage, with normal cricoid cartilage and vocal cords. Diagnosis of RP was made based on the diagnostic criteria of McAdam. She was treated with intravenous methylprednisolone pulses followed by oral prednisolone 2 mg/kg daily in a reducing course, which improved her symptoms. However, she relapsed as soon as steroids were tapered. Methotrexate 15 mg/kg weekly was added. During the following month, ear involvement relapsed and her voice became hoarse. Higher doses of steroids resulted in prompt improvement. Two months later, she again developed hoarse voice, throat pain, episcleritis and ear involvement. At this time, infliximab was started at 5 mg/kg dose at week 0, 2 and then biweekly. The drug was well tolerated and no immediate adverse effects were recorded. However, after three infusions, she relapsed and again developed episcleritis with respiratory difficulty and nocturnal stridor.

PP - 316

REDUCTION OF QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS WITH RHEUMATIC DISEASES

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Introduction: Rheumatic diseases have an adverse impact on the development of children and adolescents, causing physical disability, with a broader impact in other dimensions (emotional, social and school functioning).

Objective: To measure health related quality of life in a group of children aged from 2-18 with rheumatic diseases, using the generic core scale PedsQL4.0 *Pediatric Quality of Life Inventory*.

Method: PedsQL 4.0 was administered to a group of 105 children and adolescents with rheumatic diseases. The pathologies were: juvenile idiopathic arthritis (n=71), systemic lupus erythematosus (n=22), dermatomyositis (n=7) and miscellaneous (n=5). Participants in the control group were 240 apparently healthy individuals (124 girls), 60 of each age grouping (2-4, 5-7, 8-12, 13-18). The parent proxy report was administered to the respective parents or caretakers separately, on the same day.

Results: We observed significantly lower scores in patients in all aspects, when compared to the control group ($p<0.0001$): physical = 75.99 ± 22.65 vs.

95.94 ± 5.83; psychosocial = 73.33 ± 16.02 vs. 85.03 ± 9.66 and total = 74.28 ± 16.73 vs. 88.90 ± 7.35, respectively. For the PedsQL 4.0 parent proxy report, statistically significant differences were observed ($p<0.0001$) in all aspects. Parents of patients with rheumatic diseases have a good ability to assess the physical and school functioning aspects of their children. On the other hand, this capacity was less apparent when emotional and social aspects were measured.

Conclusion: Quality of life of patients with rheumatic diseases was significantly lower than in the healthy control group, showing the necessity of a comprehensive approach focused not only on the physical aspects of rheumatic diseases, but also the psychosocial.

PP - 317

RELIABILITY OF THE PEDIATRIC QUALITY OF LIFE INVENTORY 4.0 GENERIC CORE SCALE: THE BRAZILIAN VERSION

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Introduction: In the past two decades, several generic questionnaires for assessment of health related quality of life in children and adolescents have been developed. The *Pediatric Quality of Life Inventory* (PedsQL) version 4.0 is an outstanding instrument due to its reliability and flexibility of application.

Objectives: The aims of this study were to translate the generic questionnaire PedsQL 4.0 into Brazilian-Portuguese, to cross-culturally adapt it, and to evaluate its reliability and validity.

Method: Researchers followed the methodology proposed by the authors of the original version of PedsQL 4.0: 1) Translation by a board of specialists, 2) Back translation into English with evaluation from the authors of the original version, 3) Pilot study, involving 5 children and their parents from each age range (2-4, 5-7, 8-12, 13-18 years), and 4) Evaluation of reliability and validity. In this phase, the PedsQL 4.0 was administered by interviewing a group of 105 children and adolescents with rheumatic diseases and 240 controls matched by age, as well as the respective parents or caretakers.

Results: Cronbach alpha values between 0.6 and 0.9 were observed for all aspects evaluated by the questionnaire (physical, emotional, social and school functioning) showing good internal consistency. Validity was demonstrated by habitual parameters utilized in pediatric rheumatology: *Childhood Health Assessment Questionnaire* and *Childhood Health Questionnaire* (Spearman coefficient correlation of $p<0.001$). The interobserver reliability was statistically significant for all ages (0.69 to 0.88).

Conclusion: The Brazilian-Portuguese version of the PedsQL 4.0 was shown to be reliable and a valid measurement of quality of life. Its practical applicability will be of great utility for all health professionals responsible for child and adolescent care.

PP - 318

CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS (CRMO) ASSOCIATED WITH SELECTIVE IgM DEFICIENCY

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Selective IgM deficiency is a rare primary immunodeficiency disease, which can be associated with autoimmune diseases such as systemic lupus erythematosus, Crohn's disease, or hemolytic anemia. A six-year-old boy was diagnosed as CRMO based upon involvement of multiple osseous sites such as pelvic bones, vertebrae, diaphysis of tibia and both femoral metaphyses. Nonspecific chronic inflammation in bone biopsy and negative results of cultivation confirmed the diagnosis. Laboratory findings revealed significantly lower serum IgM levels (20 and 23 mg/dl) than his age-matched

PP - 319

EVALUATION OF CHILDREN AND ADOLESCENTS WITH RAYNAUD'S PHENOMENON BY NAILFOLD CAPILLAROSCOPY

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Objectives: To evaluate retrospectively the nailfold capillaroscopy (NFC) findings and their correlation with the clinical features and follow-up in patients who presented Raynaud's phenomenon (RP) without criteria for collagenosis.

Methods: In a transversal study, we evaluated 40 patients with Raynaud's phenomenon. Each patient underwent a complete medical history review and laboratory investigations, including antinuclear antibodies (ANA). We also performed a NFC by using a microscope with special light and magnification of 10 and 16X.

Results: The group comprised 34 girls and 6 boys, ranging from 4 to 16 years (mean 11.6 years). The mean follow-up time was 2.7 years. Nine out of 40 patients presented ANA positivity and 6 presented arthritis in addition to Raynaud (2 of them were ANA +). All but 6 had normal NFC (3 unspecific microangiopathy, 2 inconclusive findings and 1 scleroderma pattern). Fifteen of them were submitted to 2 or more NFC within a mean interval time of 1.9 years and all were normal, including 3 patients with arthritis, 1 with arthritis and ANA +, and 6 ANA +. The child with SD pattern was a 13-year-old girl who developed mixed connective tissue disease and ANA positivity 2 years after initial evaluation. The other children with ANA positivity will be submitted to another NFC, which has been already scheduled.

Conclusions: Raynaud's phenomenon remains without a specific diagnosis in most cases; however, NFC is extremely useful to rule out collagenosis.

PP - 320

FOUR-YEAR FOLLOW-UP OF A CHILD WITH WEBER CHRISTIAN PANNICULITIS

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We report a case of a 12-year-old boy who presented with repeating episodes of high fever; transitory synovitis of the hip and knee joints; tender nodules and erythemal lesions on the lower and upper extremities and face; facial edema; hepatosplenomegaly; and peripheral lymphadenopathy. The disease started at the age of 4, after phlegmona of the left hand. The relapses occurred several times every year with a similar clinical picture. Extended investigations for systemic infections and autoimmune diseases during multiple hospitalizations revealed only mild anemia, leukocytosis and acute phase response, associated with staphylococcal infection and HBsAg-carriage. The symptoms resolved completely after treatment with antibiotics, corticosteroids and NSAIDs in one week to one month.

The child was referred to us at the age of 8, with the same clinical picture and laboratory investigations. The symptoms and the laboratory findings resolved rapidly within a week after treatment with NSAIDs, dipyridamole and supporting therapy. The remaining clinical signs included nodular lesions, up to 3 cm, localized on the thighs, arms and cheeks. The biopsy of one nodular lesion showed non-specific histological picture corresponding to the fibrous (reconvalescent) phase of panniculitis. One month later, the disease flared again and a second biopsy of a "fresh" lesion was made. The histology revealed a lobular infiltrate corresponding to phases I and II of Weber Christian panniculitis. We started a second-line treatment with antimalarials and achieved remission lasting 4 years.

We present this case because of the rarity of the disease/syndrome and the need for a systematic approach to histological examination, which is necessary for the proper interpretation of the results.

PP - 321

A CASE OF HEREDITARY SENSORY NEUROPATHY

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The neuropathic osteoarthropathies are rare diseases in childhood.

We present a 17-year-old girl referred to us after surgery and treatment for osteomyelitis of the second metatarsal bone of the right foot. Her mother and elder sister had severe mutilating disease presenting with "relapsing osteomyelitis" and leading to amputation of both feet of her sister.

On examination we found inflammatory changes with trophic ulcers and calluses of both soles, foot edema, thickened toes with deformities and paronychia. Hands and arms had normal appearance. Neurological examination revealed an impairment of sensation for pain and temperature, but normal for touch and deep pressure perception over the distal lower extremities. Deep tendon reflexes of lower extremities were diminished. No muscle weakness or autonomic involvement was established. Despite the ulcers and recent surgical scars, she was comfortable.

X-rays and CT scans showed massive demineralization with absorption and partial fragmentation of all tarsal bones and severe subluxations. Similar changes were found by retrospective evaluation of her mother's and sister's X-rays. Laboratory examination showed the following findings: normal MRI of the spinal cord and CNS; axonal degeneration of the lower extremities; reduced/absent SNAPs of Nn. surales; and normal SNAPs of the upper extremities. Immunological investigation determined increased IgG, IgA and IgM. VDRL was negative. The clinical pattern, inheritance and laboratory data suggested type I Hereditary Sensory Neuropathy (HSAN type I).

This case is reported for the disease rarity and the challenges of presentation and diagnosis in the pediatric rheumatology office. In this particular type of HSAN, the routine genetic investigations do not contribute to diagnosis, but an extended analysis in a specialized laboratory would be of great value for the identification of the genetic abnormality in this family.

• ARHP
PP – 322

MULTIDISCIPLINARY ASSESSMENT OF CHRONIC MUSCULOSKELETAL PAIN IN CHILDREN

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Introduction: Chronic musculoskeletal pain assessment is difficult. There are no generally accepted parameters reflecting efficacy of various treatments. Most of the complex evaluations combine physiotherapy and psychology methods that differ according to their availability in different countries.

Aims: To develop a set of measures for assessment of chronic pain in Czech children (aged 10-18).

Methods: Chronic pain was defined as musculoskeletal pain lasting for more than 2 months with no identified underlying cause (idiopathic pain syndromes) or where degree of pain and disability was inappropriately severe for the diagnosis (e.g. inactive JIA). Published resources and consultations with other chronic pain teams were used as a baseline. Psychology assessment was developed and performed by a clinical psychologist and physiotherapy assessment by a pediatric physiotherapist experienced in rheumatology.

Results: The following categories were evaluated: Pain (VAS), Anxiety (SCAS), Depression (CDI), Psychosocial Wellbeing (CHQ), Catastrophic Pain Perception (Waldron-Varni Pediatric Pain Coping Inventory), School Attendance, Activities of Daily Living, Disability (CHAQ), Muscle Assessment

(MMT), Hypermobility (9-point Beighton scale), Walking and Balance Tests, Skin Perception, and Fibromyalgia (Manual Painful Point Survey). Complex evaluation of consecutive patients attending rheumatology clinics was performed (13 families). All methods were straightforward and easy to apply. Reproducibility and validity evaluation will result from the ongoing follow-up study.

Conclusion: Proper evaluation of chronic pain syndromes is important for treatment efficacy assessment. We propose a comprehensive set of measures evaluating functional as well as psychosocial aspects of chronic pain. They need further long-term prospective validation. Involvement of a multidisciplinary team with expertise in pediatric rheumatology is inevitable.