THE TURKISH JOURNAL OF PEDIATRICS

A joint publication of the Turkish National Pediatric Society and the Turkish and International Children's Center

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This Journal is listed in *Current Contents, Index Medicus, Abstracts on Hygiene and Communicable Diseases, Tropical Diseases Bulletin,* the *CAB Abstracts* database and the *Excerpta Medica* database *EMBASE.*

VOLUME: 34 NUMBER: 4 OCTOBER - DECEMBER 1992

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The Turkish Journal of Pediatrics 34: 197-202, 1992

CONGENITAL HYPOTHYROIDISM IN TURKEY: A RETROSPECTIVE EVALUATION OF 1000 CASES*

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SUMMARY: Tarım ÖF, Yordam N. (Endocrinology Unit, Department of Pediatrics Hacettepe University Faculty of Medicine, Ankara, Turkey). Congenital hypothyrodism in Turkey: A retrospective evaluation of 1000 cases. Turk J Pediatr 34: 197-202, 1992.

In this retrospective investigation, 1000 cases of congenital hypothyroidism followed-up in the Pediatric Endocrinology Unit at Hacettepe University Children's Hospital between 1964-1989 were evaluated with respect to age at diagnosis, main complaints, symptoms and physical findings. The mean age at diagnosis was 49.22 months, with 55.4 percent of patients diagnosed after two years of age and only 3.1 percent during the neonatal period. The main complaints of the patients were growth failure (26.7%), inability to speak (21.4%), and inability to walk (18.1%). The physical signs and symptoms most commonly detected by the physician were hypotonia (72%), constipation (66.8%), cretinoid face (64.6%), and macroglossia (64.6%).

These results emphasize the necessity for routine neonatal screening programs to be established in Turkey, with the aim of detecting congenital hypothyroidism. *Key words: congenital hypothyroidism, neonatal screening.*

Among the causes of mental retardation, congenital hypothyroidism (CH) is the most easily treated. Its treatment is also economical. Since 1970, neonatal screening programs have succeeded for the most part in preventing or minimizing mental and motor retardation due to CH[1-6].

The purpose of this study was to enumerate the signs and symptoms of CH according to the age at diagnosis and to determine the relevance of neonatal screening in Turkey.

Material and Methods

The Pediatric Endocrinology Unit at the Hacettepe University Faculty of Medicine is one of the referral centers in Turkey for this particular disorder. Congenital hypothyrodism was diagnosed in 1000 patients who had been followed-up in our department between 1964-1989.

The diagnosis was confirmed in all patients by the measurement of serum protein-bound iodine and buthanol extractable iodine or serum thyroxine and thyroid-stimulating hormone levels in accordance with the facilities of the laboratory. There were 535 females (53.5%) and 465 males (46.5%).

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All patients were evaluated taking into account sex, age at diagnosis, main complaints, symptoms and physical findings related to CH elicited by history and physical examination (hypotonia, cretinoid face, macroglossia, dry skin, constipation, umbilical hernia, cold intolerance, neonatal jaundice and goiter).

Results

The mean (± SD) age at diagnosis was 49.22 ± 49.17 months (range: 18 days to 15 years), with 3.1 percent of patients diagnosed during the first month of life, 9.4 percent between 1-3 months of age, 8.6 percent between 4-6 months of age, 9.5 percent between 7-11 months of age, and 14 percent between 1-2 years of age.

The majority of patients (55.4%) were older than two years of age at the time of diagnosis.

The main complaints of the patients were directly related to hypothyroidism or at times completely unrelated to CH (fever, seizures, diarrhea, etc.). As seen from Table I, the most frequent complaints listed are growth failure and inability to speak and walk. Constipation, jaundice, and large tongue were the most common

Table I: Main Complaints of Patients With Congenital Hypothyroidism

	0-3 Months (125)		4-6 Months (86)		> 6 Months (789)		Total (1000)	
Complaint	n	%	n	%	n	%	n	%
1. Growth failure	–	–	19	22.1	248	31.4	267	26.7
2. Inability to speak	–	–	–	–	214	27.1	214	21.4
3. Inability to walk	–	–	–	–	181	22.9	181	18.1
4. Constipation	30	24.0	16	18.6	87	11.1	133	13.3
5. Large tongue	20	16.0	21	24.4	57	7.2	98	9.8
6. Hypoactivity	11	8.8	14	16.3	56	7.2	81	8.1
7. Abdominal swelling	12	9.6	10	11.6	31	3.9	63	6.3
8. Swelling in the neck	12	9.6	–	–	36	4.6	48	4.8
9. Mental retardation	–	–	–	–	44	5.6	44	4.4
10. Hoarse cry	17	13.6	9	10.5	8	1.0	34	3.4
11. Inability to sit	–	–	–	–	33	4.2	33	3.3
12. Jaundice	28	22.4	–	–	–	–	28	2.8
13. Delay in tooth eruption	–	–	–	–	28	3.6	28	2.8
14. Anorexia	1	0.8	–	–	18	2.3	19	1.9
15. Umbilical hernia	9	7.2	8	9.3	1	0.1	18	1.8
16. Others (edema, cough, vomiting, fever, diarrhea, etc.)	17	13.6	21	24.8	75	9.4	113	11.3

Table II: A Comparison Between the Signs and Symptoms in 1000 Patients With Congenital Hypothyroidism (CH) Followed up at the Hacettepe University Children's Hospital and those in 141 CH Patients Reported by Raiti and Newns[8]

		0-3 Monts		4-6 Months		> 6 Months		Total	
Symptoms		n	%	n	%	n	%	n	%
1. Hypotonia	a	77	61.6	67	77.9	576	73.0	720	72.0
	b	22	55.0	11	47.8	24	30.8	57	40.4
2. Constipation	a	81	64.8	71	82.6	472	66.8	624	62.4
	b	26	65.0	11	47.8	46	58.6	83	58.9
3. Cold intolerance	a	24	19.2	14	16.3	300	38.0	338	33.8
	b	x	x	x	x	x	x	x	x
4. Feeding problems	a	x	x	x	x	x	x	x	x
	b	24	60.0	14	60.9	27	34.6	65	46.1
5. Respiratory symptoms	a	x	x	x	x	x	x	x	x
	b	12	30.0	3	13.0	1	1.2	16	11.3
Signs									
1. Macroglossia	a	86	68.9	70	81.4	490	62.1	646	64.6
	b	26	65.0	21	91.3	78	100.0	125	88.7
2. Cretinoid face	a	79	63.2	66	76.7	501	63.5	646	64.6
	b	10	25.0	21	91.3	78	100.0	109	77.3
3. Dry skin	a	63	50.4	62	72.1	513	65.0	638	63.8
	b	x	x	x	x	x	x	x	x
4. Umbilical hernia	a	81	64.8	70	81.4	216	27.4	367	36.7
	b	27	67.5	15	65.2	34	43.6	76	53.9
5. Neonatal jaundice	a	71	56.8	47	54.7	204	25.9	322	32.2
	b	11	27.5	4	17.4	12	15.4	27	19.2
6. Goiter	a	18	14.4	1	1.2	92	11.7	111	11.1
	b	x	x	x	x	x	x	x	x
7. Hoarse cry	a	17	13.6	—	—	—	—	17	1.7
	b	9	22.5	7	30.4	16	20.5	32	22.7

a : Hacettepe study
b : Raiti & Newns study[8]
x : no data

complaints in the 0-3 month-old infants, while a large tongue, growth failure, and constipation were observed mostly in the 4-6 month old infants.

The signs and symptoms detected by the physician either by obtaining the history of the patient or by physical examination, and which supported the diagnosis of CH, are shown in Table II. The most common symptom was hypotonia and the most common sign was a cretinoid face. The most common symptom found in the 0-3 month and in the 4-6 month-old patients was constipation, while the most common physical signs were macroglossia and umbilical hernia.

Discussion

The most striking result of our study was that the mean age of diagnosis was 49.22 months. The fact that inability to speak and walk were the main complaints in 39.5 percent of our patients, was due to a delay in diagnosis.

The physical findings of CH are very rarely observed during the neonatal period. Cretinoid face and other findings appear after 4-6 weeks of age, even in cases where thyroid agenesis is present, while it takes 3-6 months for hypoplasia or ectopia of the thyroid gland to develop[7]. However, the mean age of diagnosis in our patients exceeded the time required for the symptoms and physical findings of hypothyroidism to appear. This time differential may be attributed to the socio-economic or cultural level of families and also the difficulties encountered in diagnosis by physicians.

Cretinoid face, macroglossia, hypotonia, constipation, and umbilical hernia were noted with increasing frequency among the complaints listed by parents and physicians, the older the patient was at diagnosis.

The symptoms and findings of congenital hypothyroidism with respect to age at diagnosis were investigated extensively by Raiti and Newns[8] in a series of 141 cases (Table II). When comparing the physical findings of our patients with this series, we found that during the first three months of life, umbilical hernia ranked first, followed by macroglossia and constipation. Although they are not synonymous, the "lethargy" noted in Raiti's patients was comparable to the "hypotonia" observed in our patients. During the first three months of life, these symptoms were observed in both series and occurred in percentages whose values were near each other. Raiti claims that neonatal jaundice in hypothyroid patients lasts about two months, and therefore, the percentages obtained after three months are likely to be elicited by medical histories, rather than by physical examination. A history of neonatal jaundice was considered to be a sign in diagnosing CH in our patients.

The ratio of females to males was found to be 1.15 (535/465) in our patients instead of the 2.5-3 ratio reported in the literature[9-11]. Although there is no

explanation for the predominance of the disease in girls, the lower female/male ratio in our patients may be due to the sociocultural preference of male infants and lower prevalence in seeking medical care for girls.

The difficulties encountered in early clinical diagnosis of CH have been reported in many studies. The screening of 1,046,362 newborns in Canada and North America between 1974 to 1978 revealed that out of 239 patients with CH, only eight were clinically suspected of having the disease at the time of biochemical screening. Regarding the cumulative results of different screening programs, only five percent of 452 primary CH cases detected by screening 1,998,845 children, could be clinically diagnosed[12].

In the United States, it is noted that 30 days after the diagnosis of CH by screening, treatment was initiated in 70 percent of patients, while by the end of 45 days, 90 percent of patients had already been treated.

The intelligence quotients (IQ) of these patients measured when they were 4 and 7-years-old were within normal limits[13]. The ages at onset of treatment in countries with neonatal screening programs were: 18-days-old in Holland, 32-days-old in England, 12-days-old in West Germany, four-weeks old in Sweden, and two-weeks old in Switzerland[14]. The mean age at diagnosis in our patients was over four years. This figure did not correspond to the age reported in other countries with neonatal screening programs.

In Europe, 6500 cases of CH were detected by screening 25 million children between 1975 to 1987, showing an incidence of 1/3800[15]. Although we do not know the actual incidence of CH in Turkey, the huge number of patients diagnosed in the absence of routine screening gives the impression of a high incidence.

The results of our investigation once again prove the necessity for neonatal screening programs for CH, a disease which causes mental retardation.

We hope we can overcome the limitations of our economic resources to establish a routine screening program in the future in Turkey.

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The Turkish Journal of Pediatrics 34: 203-210, 1992

EFFECTS OF INTRAVENOUS IMMUNOGLOBULIN ON CLINICAL AND IMMUNOLOGICAL FINDINGS OF PATIENTS WITH HUMORAL IMMUNODEFICIENCY DISEASES*

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SUMMARY: Ersoy F, Tezcan İ, Sanal Ö. (Immunology Unit, Hacettepe University Institute of Child Health, Ankara, Turkey). Effects of intravenous immunoglobin on clinical and immunological findings of patients with humoral immunodeficiency diseases. Turk J Pediatr 34: 203-210, 1992.

We evaluated nine patients with humoral immunodeficiency (6 immunodeficiency with hyper-IgM, 2 X-linked agammaglobulinemia, 1 common variable immunodeficiency) who were being treated with intravenous immunoglobulins (IVIG). After the use of the IVIG regimen in a dose of 250-300 mg/kg/4 weeks for one year, the severity and frequency of infections, even in patients with chronic lung disease, decreased significantly. An improvement in pulmonary function tests was observed in four patients who had airway obstruction prior to IVIG therapy. Side effects such as chills and fever were observed in 21 of 91 infusions, particularly in the early months of therapy. Preinfusion administration of aspirin and diphenhydramine prevented these side effects. The inversion of the $CD4^+/CD8^+$ ratio was detected in most patients during both intramuscular gammaglobulins (IMIG) and IVIG therapy. *Key words: Intravenous immunoglobulin, hypogammaglobulinemia, T cell subsets.*

Patients with antibody deficiency are susceptible to infections particularly due to pyogenic microorganisms. Immunoglobulin concentrates were first used in 1952 for the treatment of primary immunodeficiency disease[1]. Since 1952, intramuscular gammaglobulins (IMIG) have been used in humoral immunodeficient patients. In recent years, intravenous forms of immunoglobulins (IVIG) have been developed for immunoglobulin substitution therapy[2-6]. Intravenous immunoglobulin preparations have several advantages among which can be cited the opportunity to allow the use of larger amounts of antibody, avoidance of proteolytic antibody degradation at the intramuscular injection site, and the rapid achievement of high serum levels of specific antibody.

Material and Methods

We evaluated ten patients with primary humoral immunodeficiency who were administered IVIG. Six patients had immunodeficiency with hyper-IgM (ID with

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Supported in part by Sandoz Pharmaceuticals.

hyper-IgM), three had X-linked agammaglobulinemia (XLA), and one had common variable immunodeficiency (CVI) (Table I). All patients were diagnosed using the WHO criteria[7]. The ages of the patients ranged between 8 and 21 years (mean 13.4 years). In one out of ten patients, IVIG therapy was withdrawn after the first infusion due to an anaphylactoid-like reaction. Thus nine patients completed the one year IVIG program. Eight out of nine patients had been receiving IMIG (approximately 0.6-0.8 cc/kg/4 weeks) prior to IVIG therapy.

Table I: Diagnosis and Infection Scores of Patients

	Age (Years)	Diagnosis	Infection Scores During One Year	
			IMIG	IVIG
1. ECK	17	ID with hyper IgM	25	40
2. FC	10	ID with hyper IgM	65	30
3. HK	10	ID with hyper IgM	35	5
4. ACA	14	ID with hyper IgM	*	15
5. ERK	19	ID with hyper IgM	15	10
6. DH	9	ID with hyper IgM	15	10
7. AAR	21	XLA	25	10
8. UYŞ	8	XLA	25	5
9. ME	13	CVI	30	5

* The patient was put on IVIG immediately after diagnosis was established.

The patients initially received monthly doses of 250-300 mg/kg of IVIG (Sandoglobulin). This product was prepared by pepsin treatment with a pH of 4.0. The dose was increased to 400 mg/kg/month in two patients (FÇ, ECK) due to persistent infections and low serum IgG levels.

Most of the monthly infusions were administered in the Immunology Clinic at Hacettepe University Children's Hospital. A medical history was obtained from each patient and a physical examination was performed. Complete blood counts and quantitative immunoglobulin measurements were taken prior to every IVIG infusion. Vital signs were monitored periodically during infusions. Patients with repeated adverse reactions received aspirin and diphenhydramine prior to infusion.

Eight patients received monthly doses of 0.6-0.8 cc/kg of IMIG prior to the IVIG regimen. Pulmonary function tests, chest and sinus radiography, liver function tests, delayed-type hypersensitivity skin tests and T lymphocyte subset studies were performed before and after one year of IVIG therapy.

We used a modified infection scoring system described by Blore and Haeney[8] to evaluate the frequency and severity of infections (Table II). Infections occurring the previous year while on IMIG therapy were evaluated retrospectively from the patients follow-up records. For each patient, scores obtained during the IVIG regimen were compared with those obtained during administration of the IMIG regimen.

Table II: Scoring System

Major Infection	Minor Infection
Score: 10	Score: 5
Pneumonia	Otitis media
Meningitis	Conjunctivitis
Septicemia	Skin infections
	Sinusitis

Serum immunoglobulins were determined by using a nephelometer (Behring, Germany). Pulmonary function studies were performed using a spirometer (Collins, U.S.A.).

Pan T ($CD3^+$) cells, helper T ($CD4^+$) cells and suppressor T ($CD8^+$) cells were examined using monoclonal antibodies (OKT3, OKT4, OKT8; Behring-Werke Institute) according to the standard technique[9]. Delayed-hypersensitivity skin reactions were evaluated using candida antigen (prepared at the Hacettepe University Pediatric Allergy Laboratory) of 1:10 dilution; phytohemagglutinin (PHA-P, Burroughs-Welcome Lab.) 10 µg/0.1 ml; PPD (Refik Saydam Hygiene Institute, Ankara) 5U/0.1 ml; tetanus fluid tetanus toxoid (Refik Saydam Hygiene Institute, Ankara) 2 lf/ml.

The Student's paired t-test was used for statistical analysis. A p value below 0.05 was considered significant.

Results

Infection scores of the patients decreasred significantly during the duration of IVIG treatment ($p = 0.017$) (Table I). No life-threatening infections were observed during the administration of either of the two forms of therapy.

Serum IgG levels of all patients, with the exception of one (ME), were below 250 mg/dl prior to IVIG therapy (Table III; Fig 1). Following IVIG therapy, serum IgG levels began to increase and plateaus were generally reached three or four months after the initiation of IVIG therapy. At the end of one year, most patients

Table III: Immunologic Features of Patients Prior to and Following One Year of IVIG Therapy

	Serum IgG Level (mg/dl)		T Cell Subsets (%)					
	Prior to IVIG	One Year After IVIG	Prior to Therapy			One Year After Therapy		
		254	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$
1. ECK*	63.6	400	37	38	0.9	44	40	1.1
2. FÇ*	173	330	ND	ND		51	43	1.2
3. HK	166	426	40	40	1	39	48	0.8
4. ACA	UD	410	57	25	2.2	30	51	0.6
5. ERK	179	290	31	42	0.7	33	39	0.8
6. DH	170	327	27	41	0.6	19	61	0.3
7. AAR	160	700	38	47	0.8	42	66	0.6
8. UYS	248	732	30	47	0.6	24	58	0.4
9. ME	602		45	46	0.9	37	46	0.8
	Controls n:30		66.9±13	45.6±2.2	1.8±0.5			

ND : Not done
UD : Undetectable

* Dose of IVIG increased to 400 mg/kg.

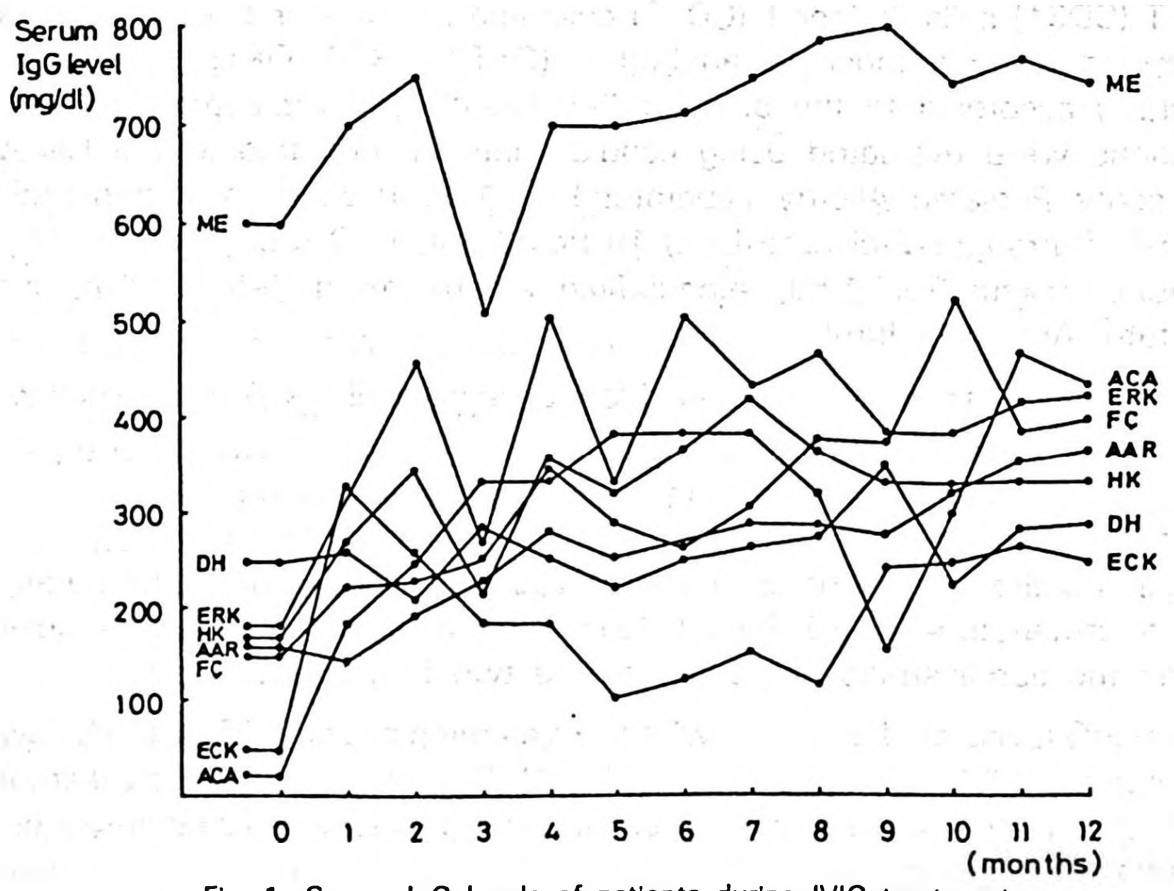

Fig. 1: Serum IgG levels of patients during IVIG treatment.

had serum IgG levels of 300 mg/dl or higher. Serum IgA and IgM concentrations were not altered during the course of IVIG therapy.

Prior to IVIG therapy, chest radiographs revealed peribronchial thickness and increased shadowing in the middle zones in eight patients, and left paracardiac and retrocardiac atelectasis in one. Reduced middle zone shadowing was observed in six patients after one year of therapy with IVIG. However, there was no significant change in the chest X-ray of the patient with atelectasis.

The sinus radiographs of eight patients receiving IVIG therapy showed opaqueness. We found an improvement in the condition of four patients following one year of treatment with IVIG.

Pulmonary function studies were able to be performed in seven out of nine patients. Moderate airway obstruction was found in two patients (ME, AAR), moderate obstruction and restrictive dysfunction in one patient (ACA), small airway obstruction in one patient and normal pulmonary functions in three patients prior to IVIG therapy. After one year of therapy with IVIG, one patient with moderate obstruction (ME) and one patient with small airway obstruction (ECK) had normal pulmonary function tests, while there were signs of improvement in the other two patients (ACA, AAR).

During IMIG therapy, six out of eight patients had reversed $CD4^+/CD8^+$ ratios (Table III). Reversed $CD4^+/CD8^+$ cell ratios were found in seven of the patients after one year of treatment with IVIG. The values were lower, but statistically insignificant when compared with previously observed ratios.

We did not find any significant changes in the complete blood count, liver function tests or delayed-type hypersensitivity skin tests.

Adverse reactions such as chills, fever, peripheral cyanosis and vomiting were observed after 21 of 91 infusions. In one patient, an anaphylactoid-like reaction was seen during the first infusion, and IVIG therapy was discontinued. No correlation was found between the adverse reactions and the rate of gammaglobulin infusions.

Discussion

Gammaglobulin replacement therapy and the administration of antibiotics are recommended in treating humoral immunodeficiency disorders associated with IgG deficiency. In recent years, intravenous forms of gammaglobulin have become available and are widely used in the treatment of primary and secondary immunodeficiencies and autoimmune disorders[10].

There is a paucity of controlled trials in regard to the best regimen in the treatment of primary humoral immunodeficiencies with IVIG. Recently, it has been claimed that maintaining a serum IgG level of 500 mg/dl or higher is most beneficial for

these patients[6]. Therefore, higher IVIG doses are required resulting in a problem in treating patients in developing countries since the administration of IVIG therapy is costly. Our patients received monthly doses of 250-300 mg/kg of IVIG and most of them had serum IgG levels below 500 mg/dl, but above 300 mg/dl. These levels were much higher than those of patients receiving IMIG, as was expected.

After the administration of the said monthly doses, a significant reduction in infection scores was found. We also observed an improvement in the chest and sinus radiographs and pulmonary function tests of most of the patients receiving the IVIG regimen in monthly doses of 250-300 mg/kg. In two out of nine patients, the IVIG doses were increased to 400 mg/kg because of low serum IgG levels and persistent recurrent sinopulmonary infections. Since the catabolic rate and half-life of serum IgG varies from patient to patient, most authors suggest that the regimen should be adjusted to the individual patient. Our observations suggest that a dose of 250-300 mg/kg/month can help in controlling recurrent sinopulmonary infections seen in most humoral immunodeficient patients and even those with chronic lung disease.

Twenty-three percent of intravenous infusions were associated with adverse reactions such as fever, cyanosis and chills, and most were observed during the first months of therapy. One patient was excluded from the study because of an anaphylactic reaction which occurred during the first infusion. According to several reports, the incidence of adverse reactions varies between 2.5 and 59 percent. Aggregated IgG, IgE anti-IgA antibodies and leukocyte antigens may be involved in the cause of these side effects[11-13]. Further studies are needed to understand the real mechanism behind this phenomenon.

IVIG therapy has varying immunomodulating effects. Hashimoto et al[14] reported that there was a suppressive effect of gammaglobulin on in vitro PWM-induced immunoglobulin synthesis. In vivo effects of gammaglobulin on immune functions were examined by Durandy et al[15], and they did not observe any changes in delayed-hypersensitivity skin tests, B or T cell surface markers or T cell proliferative responses. In our study, six patients out of eight had reversed $CD4^+/CD8^+$ ratios during IMIG therapy. At the end of one year of therapy with IVIG, reversed $CD4^+/CD8^+$ ratios were found in seven out of nine patients. These ratios were lower than those observed in patients receiving IMIG (not significant). We did not observe any change in delayed hypersensitivity skin tests. Ballow et al[16] found a proportional decrease in the number of $CD4^+$ cells, a proportional increase in $CD8^+$ cells and a significant reduction in $CD4^+/CD8^+$ ratios after four months of IVIG therapy. Since secondary immunologic abnormalities may be seen during gammaglobulin therapy, the interpretation of diagnostic immunological tests performed on patients receiving gammaglobulins should be done carefully.

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The Turkish Journal of Pediatrics 34: 211-218, 1992

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS IN SIBS*

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SUMMARY: Söylemezoğlu O, Tınaztepe K, Bakkaloğlu A, Saatçi Ü. (Pediatric Nephrology and Nephropathology Units, Department of Pediatrics, Haccetepe University Faculty of Medicine, Ankara, Turkey). Membranoproliferative glomerulonephritis in sibs. Turk J Pediatr 34: 211-218, 1992.

Idiopathic membranoproliferative glomerulonephritis (MPGN) is a chronic renal disease with variable clinical expression and several distinct morphological subtypes. Two sibs, aged 10 and 13, presented with clinical and laboratory findings of MPGN at the time of admission. After an interval of one year, the diagnosis of MPGN was established by renal biopsies. The complement pathway was unremarkable. HLA typing in the unrelated parents and the two male sibs revealed common HLA A2,A11,Bw60, DR2,DQw1 antigens in the brothers. Of these antigens, A2 has been reported previously in cases of MPGN. The other antigens regarding this disease need to be evaluated from the standpoint of genetic importance. *Key words: membranoproliferative glomerulonephritis, sibling, renal failure, childhood, familial.*

Membranoproliferative glomerulonephritis (MPGN) was first recognized in the mid 1960's[1]. The disease occurs after two years of age, and it may be associated with hypertension and nephrotic syndrome in addition to urinary abnormalities[1]. Mild to moderate renal insufficiency may be observed, but the typical patient usually reveals no evidence of renal failure at diagnosis.

On the basis of morphological characteristics, Habib et al[2] divided the glomerular changes seen in patients with MPGN into two types. Type I was characterized by a double contour appearance of the capillary walls due to mesangial cell interposition with nonargyrophilic subendothelial deposits which were finally granular with electron microscopy (EM) and immunofluorescent microscopy. Type II was characterized by linear dense deposits within the basement membrane. Strife et al[3] described a third variety (Type III) which had some characteristics of Types I and II. Most cases are truly idiopathic. The evidence obtained up until now as for genetic factors predisposing to MPGN is an apparent association of Type I with inherited deficiency of complement components (C6,

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C3)[4-6], and the rarity of the disease in blacks[7]. Although the presence of MPGN in siblings has been reported previously, documentation is incomplete in most cases[5,8,9]. The aim of this report is to present biopsy-proven MPGN in sibs and to emphasize the familial aspect of the disease.

Case Reports

Case 1 (M.Y.)

A 10 year-old-boy was admitted in December 1990, for evaluation of hypertension, oliguria, proteinuria and hematuria. There was no relevant past history. Physical examination revealed peripheral edema and a blood pressure of 160/100 mmHg. The protein excretion rate was 76 mg/m^2/h, and there was microscopic hematuria. The blood chemistry revealed serum creatinine 10.6 mg/dl, BUN 96 mg/dl, serum total protein 5.4 g/dl, albumin 2.6 g/dl, and uric acid 11 mg/dl. The serum C3 and C4 levels were 10 mg/dl and 14 mg/dl, respectively (normal C3, 60-120 mg/dl; C4, 20-40 mg/dl). Serologic investigations including ASO titer, hepatitis B surface antigen (HBsAg) and antibody (HBsAb), and antinuclear antibody (ANA) were negative. Serum immunoglobulins were within normal limits for the age of the patient.

We were not able to perform a renal biopsy during the acute clinical stage of the disease. Drug therapy included corticosteroids and cyclophosphamide. The tentative diagnosis of rapidly progressive glomerulonephritis necessitated prompt dialysis. During the follow-up period, the patient was enrolled in a hemodialysis program. The clinical and laboratory status improved after six months of therapy and renal functions could be maintained without dialysis. One year after the onset of disease, a renal biopsy was performed following admission of the patient's brother to the hospital who had similar clinical manifestations and a diagnosis of biopsy-proven MPGN. At the time the biopsy was taken, laboratory investigations revealed creatinine clearance 17 ml/min/1.73 m^2, C3 64 mg/dl, C4 24 mg/dl and total hemolytic complement pathway CH50 33 U/ml (normal 15-55 U/ml):

Renal biopsy findings (light microscopy): The hematoxylin and eosin stained semiserial sections showed 10 glomeruli on the average. All glomeruli were smaller than normal. Five showed complete sclerosis, while the remaining glomeruli had occluded capillary lumens with variable mesangial cellularity. The tubuli showed atrophy, areas of thyroidization, and dilatation. Interstitial mononuclear inflammatory cell infiltration was present. The arteriole walls and small-sized arteries showed hyaline thickening. The PAS (periodic-acid Schiff) and trichrome stained sections revealed an additional number of sclerosed glomeruli. In one or two relatively less damaged glomeruli, a pattern suggestive of membranoproliferative glomerulonephritis was present. In addition to glomerular sclerosis, trichrome staining also showed red dots, suggestive of immune deposits. Silver

with or without counterstain demonstrated complete or nearly complete sclerosis of the many glomeruli. One or two glomeruli without sclerosis had a double-contour appearance.

Diagnosis: End-stage glomerulonephritis with a few preserved patterns of membranoproliferative glomerulonephritis (Fig. 1-3).

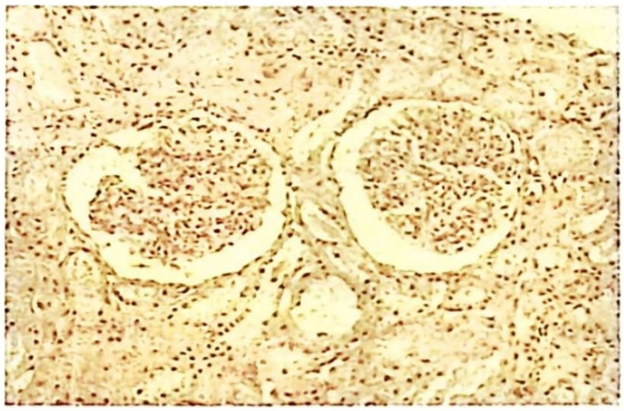

Fig. 1. Enlarged glomeruli showing mesangial expansion, increased cellularity and an accentuated lobular pattern. (Hematoxylin-eosin stain).

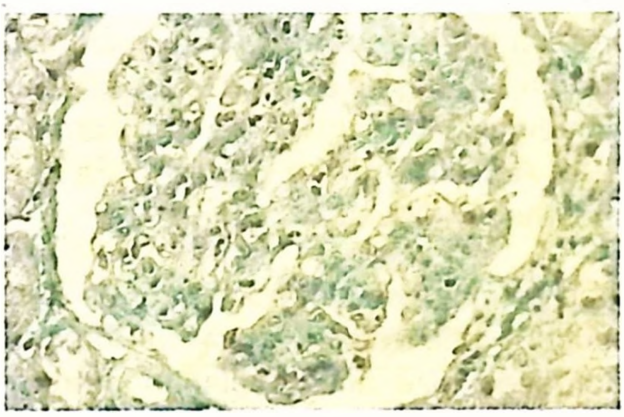

Fig. 2. The glomerulus under higher magnification shows an enlarged mesangial matrix with increased cellularity admixed with neutrophiles and a thickened basement membrane in places (Masson's trichrome stain).

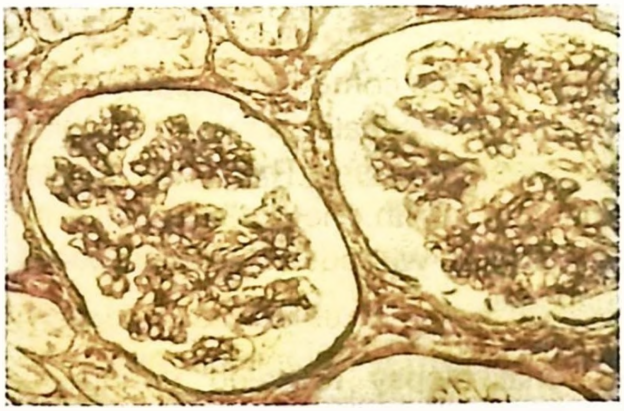

Fig. 3. The increased amount of mesangial matrix with thickening of the basement membrane and a double contour appearance at some points are seen. (Jones silver methenamine with HE).

Fig. 4. Irregular granular desposition of C3 is seen in the peripheral capillary basement membrane zone and some of the areas of the mesangium in the glomerulus (Direct Immunofluorescence microscopic study).

Direct immunofluorescence study of the renal biopsy revealed peripheral deposition of complement (C3) in the basement membrane zone, granular in pattern. The Igs were not demonstrated.

Note: In this patient, end-stage glomerulonephritis is not used as a clinical term, but pathologically, to indicate the late and non-specific nature of glomerular

sclerosis, which as in this patient, may have formed as a result of the progression of MPGN.

Case 2 (F.Y.)

The older brother of Case 1, who is 13-years-old was referred to our hospital for evaluation of edema, hypertension and proteinuria in December 1991. His blood pressure was 150/95 mmHg. Urine analysis revealed microscopic hematuria and proteinuria 48 mg/m^2/h. Serum creatinine was 2.3 mg/dl, uric acid 9 mg/dl, total protein 6.6 mg/dl, albumin 3.2 mg/dl, and BUN 60 mg/dl. Serologic investigations including ANA, anti-DNA, antiglomerular basement membrane antibody (anti-GBM Ab), HBsAg and HBsAb were all negative. The serum C3 level was 33 mg/dl and the C4 level 24 mg/dl.

Biopsy findings (light microscopy): The hematoxylin and eosin stained semiserial sections showed 20 glomeruli on the average. Involvement was diffuse with increased size and lobulation due to cellular proliferation. In the majority of glomerular tufts capillary lumens were obliterated. The proliferation of cells was mainly of the endomesangial type, but several polymorphonuclear leukocytes were also present. PAS staining showed an increase in the mesangial matrix with a thickened basement membrane. Even with this stain, reduplication in some areas could be seen when examined carefully. Trichrome stain showed red dots within the capillary walls, suggestive of immune deposits.

In some areas, methenamine-silver stain showed double contoured "splitting" of the basement membrane. The epithelium of the tubuli revealed a hyaline droplet change, and a vacuolar appearance in some. Casts were rare. The brush border and the tubular basement membrane were intact. Only in one dot-sized area of the interstitium, a few inflammatory cellular infiltrates without eosinophils were present. The vessel walls appeared unremarkable.

Direct immunofluorescence study of the renal biopsy revealed peripheral depositons of C3 (++), C1q (+), and IgA (+) in the basement membrane zone and some in the mesangium (Fig. 4).

The patient was treated with one gm methylprednisolone intravenously for three consecutive days. This was followed by a six-month prednisolone regimen. Serum complements C3, C4, and CH50 levels were within the normal range three months following the onset of the illness. The patient's clinical and laboratory status improved, and he is at present in remission, and under no medication.

A summary of the initial clinical and laboratory findings are mentioned in Table I. The HLA typing of the members of the family is displayed in Table II.

Table I: Initial Clinical and Laboratory Findings of Patients

	Patient 1	Patient 2
Anemia	+	−
Edema	+	−
Hypertension	+	+
Hematuria	+	+
Proteinuria (*)	+	+
BUN	96 mg/dl	60 mg/dl
Serum creatinine	10.6 mg/dl	2.3 mg/dl
C3	10 mg/dl	33 mg/dl
C4	14 mg/dl	24 mg/dl
HBsAg	−	−
HBsAb	−	−

* Proteinuria > 40 mg/m^2/hr.

Table II: HLA Typing of the Patients and Parents

Case 1	: HLA A2, A11, B39, Bw60, DR2, DRw13, DQw1
Case 2	: HLA A2, A26, A11, Bw60, DR2, DQw1
Mother	: HLA A11, A31, B39, B35, DR2, DR7, DQw1, DQw2
Father	: HLA A2, A26, Bw60, DRw13, DQw1

Discussion

Membranoproliferative glomerulonephritis is an uncommon disease which rarely occurs in siblings[10,11]. The literature suggests that the incidence in siblings is variable, but that definite conclusions cannot be drawn regarding genetic predisposal to MPGN[8,9,11]. The sib pairs reported by Van Acker et al[8] were members of six separate families, while Berry et al[9] noted a familial incidence of about four percent.

Although predisposition to MPGN occurring in siblings may reflect a common environmental exposure, it is more likely that it indicates a genetic basis for the disease. The presented sib pairs were shown to have biopsy-proven MPGN, which could reflect exposure to a common environmental stimulus or alternatively a genetic predisposition manifest with or without an enviromental trigger.

Evidence to support the view that genetic factors predispose to MPGN has been limited to the rarity of the disease in blacks[7] and the reported association with

deficiency of complement components C3, C6, C7, C8[4-6]. The demonstration of circulating immune complexes in 50 percent of patients with MPGN and the presence of granular deposits of immunoglobulins and complement in the glomerular capillaries provide evidence of an immunological basis for the disease[12]. In our patients, there was suggestive evidence of classical pathway activation in the acute stage. In addition, the presence of C3, C1q and IgA depositions in immunofluorescence microscopy of the renal biopsies was another finding supporting the immunological origin of the disease. Complements C3, C4, and CH50 were at normal levels in the unrelated parents and also in the two brothers which exclude inherited complement deficiency conditions.

The role of genetic factors in the etiology of glomerulonephritis is unclear. Because of the importance of gene products of the major histocompatibility complex in both immune recognition and effector functions, the protein polymorphism in this region has been studied in most immune-related diseases including a number of types of glomerulonephritis[13]. Noel et al[13] reported an insignificant increase in the frequency of HLA-B7 in Type II MPGN, while Rashid et al[14] found insignificant increases in HLA-A2 and HLA-Bw44 in MPGN patients. Recently, Welch et al[15] reported an elevated frequency of HLA-B8, DR3 and C4A*Qo alleles. They also mentioned that the extended haplotype B8, DR3, SCO1, GLO2 is clearly not a necessary factor in the development of MPGN since most patients do not carry this haplotype, which may be also present in some healthy siblings and parents. The common HLA antigens of our patients were A2,Bw60,DR2 and DQw1, but only the presence of HLA-A2 is similar to reports in the literature[14]. There was no evidence of primary immunoglobulin deficiency in our patients and no repeated infections. Changes in the population of cytotoxic/suppressor T cells may theoretically lead to immune-related renal disease. We also examined the T cell subsets of the whole family and found that they were all in normal numbers.

The clinical manifestations of the disease were similar in both siblings which can be attributed to genes linked to common haplotypes. Although renal functions progressed to renal failure in the first case, in the second case, the symptoms disappeared after drug therapy. To explain these differences in outcome, it may be postulated that MPGN is of multigenic origin. Thus the response to a gene functionally predisposing to MPGN might be modified by other genes which control pertinent immune responses resulting in differences in the mode in which the disease is expressed.

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The Turkish Journal of Pediatrics 34: 219-224, 1992

USE OF SINGLE VOIDED URINE SAMPLES TO ESTIMATE QUANTITATIVE PROTEINURIA IN CHILDREN*

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SUMMARY: Mir S, Kütükçüler N, Cura A. (Nephrology Unit, Department of Pediatrics, Ege University Faculty of Medicine, İzmir, Turkey). Use of single voided urine samples to estimate quantitative proteinuria in children. Turk J Pediatr 34: 219-224, 1992.

Quantitation of protein excretion in urine is used for diagnostic and prognostic purposes and also to assess the effects of therapy in children. The method in common use is to measure urinary protein in a 24-hour urine sample, which may be time consuming and is often inaccurate. The aim of this study was to determine if the urine protein/creatinine ratio in a single-void urine sample had a high correlation with the quantity of protein in a 24-hour urine specimen. We found that there was an excellent correlation between the protein content of a 24-hour urine excretion and the protein/creatinine ratios in single morning urine samples of 50 patients. We also discovered that a protein/creatinine ratio greater than 4.9 could signify "nephrotic-range" proteinuria, while a ratio less than 2.5 indicated nephritic syndrome or other renal diseases. We concluded that the determination of urinary protein/creatinine concentration ratios in a single morning urine sample under most clinical circumstances, especially in nephrotic syndrome, could replace the measurement of protein excretion in 24-hour urine specimens. *Key words: protein/creatinine ratio, 24-hour urine sample, single voided urine sample, nephrotic-range proteinuria.*

Quantitation of proteinuria in children has diagnostic and prognostic importance, and is used to assess the effects of therapy. The quantity of protein excreted in the urine varies during the day. Proteinuria is related more to changes in the glomerular filtration rate and tubular reabsorption than to the plasma concentration of albumin, volume of urine voided daily and volume of extracellular fluid. In children and adolescents there are several additional factors that may also change the degree of proteinura, namely stress, exercise, temperature and the upright postural position[1,2].

The most common method for quantitating urinary protein excretion makes use of a 24-hour urine sample collection. However, since the amount of protein can fluctuate from day to day, a 24-hour urine sample collection must be carried out on three different days to obtain an accurate measurement.

In practice, it may not only be difficult to obtain 24-hour urine collections from children but also from adults, for this method can be rather time consuming, cumbersome and, on occasion, because of forgetfulness, unreliable.

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In recent years, there have been several studies conducted with the aim of excluding the urine volume factor in the quantitation of proteinuria. Some authors have reported that the protein/creatinine ratio in a single voided sample of urine is a successful method used to assess the degree of proteinuria. They found an excellent correlation between 24-hour urine protein excretion and the protein/creatinine ratio in a single random urine sample[2]. However, the methods used and their clinical assessment have not as yet been completely identified.

The aim of our study was to determine if a correlation exists between protein concentration in a 24-hour urine sample and the protein/creatinine ratio in a single urine sample and the role that the protein/creatinine ratio plays in clinical management.

Material and Methods

A total of 50 subjects comprising outpatients and hospitalized patients who were being followed in the Nephrology Unit of the Department of Pediatrics at the Ege University Faculty of Medicine were enrolled in this study. There were thirty boys and twenty girls whose ages ranged between one to twelve years (mean 4.5 ± 0.6 yrs.). Twenty-six patients had minimal change nephrotic disease (MCND), 16 had either membranoproliferative glomerulonephritis (MPGN), membranous glomerulopathy (MG) or focal glomerulosclerosis (FGS), and eight had acute nephritic syndrome (ANS). Studies were carried out on the patients during the period of active disease or during the remission period following treatment. Sixteen patients with MCND and seven patients in the MPGN, MG, FGS group were in the active phase of the disease, while the others were in remission.

All patients were examined. Their respective medical histories, along with their physical and routine laboratory findings were scrutinized. Each patient was asked to submit a morning urine sample in one container, while in the other container urine specimens voided over a 24-hour period were also to be submitted. Protein and creatinine concentrations were measured in the single voided and 24-hour urine samples. Urine protein was measured using the Prudy method[3]. The creatinine excretion rate was determined by the Jaffe reaction (picric acid)[4]. The measurements were all expressed in milligrams per deciliter (mg/dl). A protein concentration exceeding 0.05 g/kg in the 24-hour collected urine sample was considered to be representative of "nephrotic range" proteinuria, while values less than 0.05 g/kg were termed "abnormal proteinuria".

The Student's *t* test was used for statistical analysis.

Results

The protein concentrations in the 24-hour urine samples exceeded 0.05 g/kg (mean 0.068 g/kg) in twenty-three patients. The mean protein/creatinine ratio in

the single voided urine samples was 8.47. The remaining 27 patients had protein concentrations in 24-hour urine excretion measuring less than 0.05 g/kg (mean 0.017 g/kg). The mean protein/creatinine ratio was 1.66 (Table I).

Table I: Mean 24-Hour Protein Excretion and Protein/Creatinine Ratios in Morning Urine Specimens of Both Groups

Patients	N	Mean 24-h Protein Excretion (g/kg)	Mean protein/creatinine Ratio (single urine)
NEPHROTIC SYNDROME (proteinuria > 0.05 g/kg/day)	23	0.068 ± 0.018	8.47 ± 2.40 (> 4.9)
ABNORMAL PROTEINURIA (proteinuria < 0.05 g/kg/day)	27	0.017 ± 0.009	1.66 ± 0.31 (< 2.5)

When we compared the amount of protein in 24-hour urine excretion with the protein/creatinine ratio in single morning urine samples of all 50 patients, it was found that they were well correlated ($p < 0.01$) (Table II). In addition, the protein/creatinine ratio in the single voided urine specimens of the 23 patients with nephrotic-range proteinuria and the remaining 27 subjects were compared,

Table II: Analysis of 24-Hour Protein Excretion and Protein/Creatinine Ratios in Morning Urine Samples of Patients

	N	Mean
Proteinuria in 24-h collected urine (g/L)	50	1.79 ± 1.57
Protein/creatinine ratio (single urine sample)	50	7.91 ± 6.90 $p < 0.01$

and were found to be significantly different ($p < 0.01$). The protein/creatinine ratios in the single-void urine samples of each group of patients were analyzed, and we found that this ratio was more than 4.9 in all patients who were diagnosed as having nephrotic syndrome according to clinical and laboratory findings. On the other hand, the ratio of the patients who did not have nephrotic proteinuria was less than 2.5 (Fig. 1).

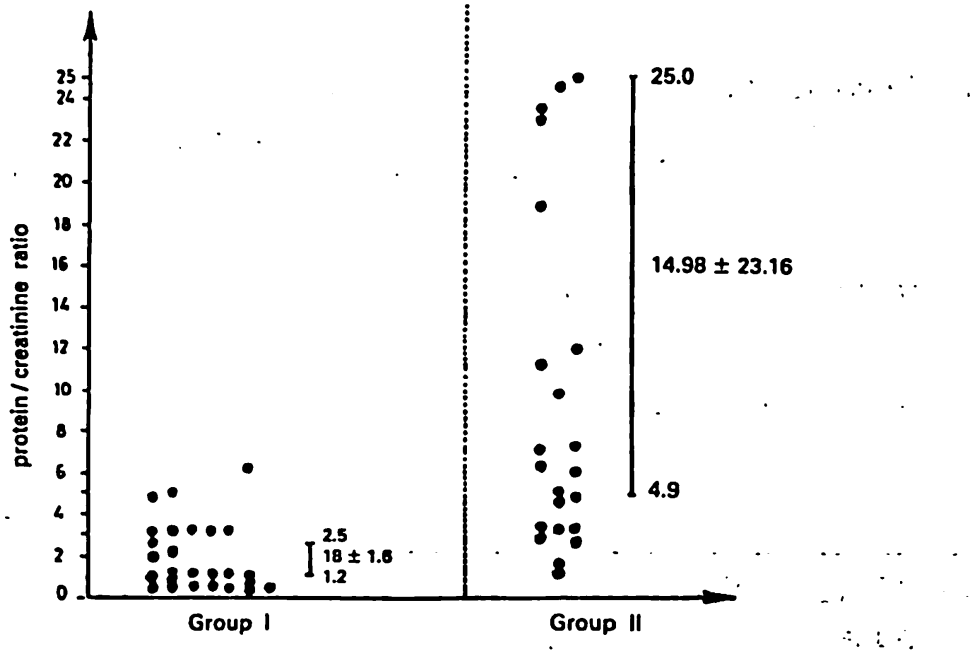

Fig. 1: Analysis of protein/creatinine ratios in morning urine specimens of patients with nephrotic syndrome (Group II) and the other group with abnormal proteinuria (Group I).

Discussion

In pediatric nephrology, measurements of the protein content of a timed 24-hour urine collection is the definitive method of establishing the presence of nephrotic syndrome, whatever the morphologic structure. It is thought that this method is more reliable. It has been reported that urine protein concentration is usually higher in daytime samples than in early morning urine samples in patients with proteinuria[2].

It has been proposed that the daily protein excreted in the urine must be measured per kilogram. Reports in the literature indicate that different amounts of protein excretion in the urine such as 0.05-0.10 and 0.20 g/kg/day, cause the nephrotic syndrome[5]. The expected nephrotic range proteinuria changes according to the proposed degree of proteinuria, however, most authors have reported that minor degree nephrotic-range proteinuria is a value of 0.05 g/kg/day[5]. In our study, we have also used this minor degree measurement to indicate nephrotic proteinuria.

Of 50 patients, 23 had protein concentrations in 24-hour urine excretion in excess of 0.05 g/kg (mean 0.068 g/kg) (Table I). Clinical and laboratory findings of this group of patients evidenced the nephrotic syndrome pattern. The arithmetical average was not very high because the ages and weights of the patients varied.

Twenty-seven patients who had abnormal proteinuria, had protein concentrations in 24-hour excretion with a mean value of 0.017 g/kg, which was a great deal less than the figure associated with minor degree proteinuria. All these results support the opinion that in 24-hour urine specimens, minor degree nephrotic-range proteinuria occurs when the value is 0.05 g/kg.

In the management of nephrotic syndrome, the degree of proteinuria must be assessed along with other clinical findings. Nephrotic syndrome may persist with all its biological changes even though the edema may have disappeared in the patients. Therefore, the degree of proteinuria is a very significant factor when evaluating these patients. A single voided urine sample that would give reliable information regarding the degree of proteinuria would be of great help to the pediatrician.

Ginsburg[6] discovered that the 24-hour protein excretion rate could be estimated from the observed protein/creatinine ratio by multiplying this ratio by the expected creatinine excretion rate which is calculated by using the formulas derived by Cockroft and Gault. He also reported that there was an excellent correlation between it and the 24-hour protein excretion rate. Many other authors have reported that their results correlated very well with the protein/creatinine ratio in single voided urine samples. This method is now used in their daily practice.

In studies conducted on renal disease by Niinomi[7] in 11 patients and by Watana[8] in 41 patients, values for 24-hour urine protein excretion and the protein/creatinine ratio in a random urine sample demonstrated a high correlation. This method is more accurate in determining proteinuria especially in infants and small children. White et al[9] also expressed their results in terms of protein/creatinine ratios of early morning urine samples, and found an extremely good linear correlation with the protein excretion rate in 24-hour urine excretion. Shaw[10] has reported that the protein/creatinine ratio of random urine samples should be used to supplement dipsticks in screening for proteinuria in cases where misclassification could be serious. Wilkin[11] has measured the 24-hour urinary excretion of albumin and the protein/creatinine ratio in early morning and random samples in 14 diabetic subjects and found a significant correlation for early morning samples, but no correlation with the random samples of outpatients. Most investigators are of the opinion that the results of early morning urine samples are more reliable[6,7]. It has been reported that the protein/creatinine ratio of a single urine specimen represented a highly accurate method of assessing renal function in pregnant and preeclamptic women, and was more practical than 24-hour collection[12].

In our study, we also estimated the protein/creatinine ratio in single-void morning urine samples of all 50 subjects and found that there was a high correlation with the proteinuria in 24-hour urine excretion ($p < 0.01$) (Table II). The protein/creatinine ratios in the single voided urine specimens of the patients with nephrotic-range proteinuria were compared with the other group of patients and it was noted that they were significantly different ($p < 0.01$). According to these results, which comply with reports in the literature, it is clear that the protein/creatinine ratio in single morning urine samples represents an accurate and reliable method of assessing proteinuria.

In order to make use of protein/creatinine ratios in single urine specimens in daily practice, we especially have to know the minimum value of this ratio for nephrotic-range proteinuria. Ginsberg[6] reported that when this ratio was more than 3.5, it signified nephrotic-range proteinuria. In Watana's[8] study, the minimum value of this ratio for nephrotic-range proteinuria was two. In our study, the arithmetical mean of the protein/creatinine ratio was 8.47 in the subjects with nephrotic syndrome and 1.66 in the other group (Table I). The protein/creatinine ratio of both groups of patients were examined, and we observed that nephrotic syndrome was present when this ratio was $\geqq$ 4.9, while this ratio was less than 2.5 in the abnormal proteinuria group. We concluded that the subjects with ratios between 2.5 and 4.9 had to be carefully examined and followed up (Fig. I).

We suggest that the determination of urinary protein/creatinine concentration ratios in single morning urine samples under most clinical circumstances, especially in nephrotic syndrome, can replace the measurement of protein excretion in 24-hour urine samples. But, it would be more reliable if urinary protein/creatinine concentration ratios are examined in several random single voided urine samples during normal daytime activities in the same subject and for a few days.

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The Turkish Journal of Pediatrics 34: 225-230, 1992

ANALYSES OF SERUM VITAMIN D – BINDING PROTEIN, CERULOPLASMIN AND COPPER LEVELS IN PRETERM INFANTS*

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SUMMARY: Paşaoğlu H, Kurtoğlu S, Muhtaroğlu S. (Departments of Biochemistry and Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey). Analyses of serum vitamin D-binding protein, ceruloplasmin and copper levels in preterm infants. Turk J Pediatr 34: 225-230, 1992.

The cord blood specimens of 12 preterm and 20 term babies were investigated. We determined serum calcium (Ca), phosphorus (P), magnesium (Mg), vitamin-D binding protein (DBP), ceruloplasmin (Cp) and copper (Cu) levels in two groups. We found that Ca, P, and MG levels of cord sera did not differ between the groups ($p > 0.05$), but DBP, Cp and Cu values showed a significant decrease in the preterm group ($p < 0.05$). The Cu and Cp values of the preterm infants correlated with those of the term infants.
Key words: preterm baby, DBP, Cp, Cu.

It has been documented that early neonatal hypocalcemia is a common occurrence in the first week of life in preterm infants[1], while absorption and activation of vitamin D are observed 24 hours after birth in preterm infants born after 31 weeks of gestation. Early neonatal hypocalcemia is unlikely to be caused either by impairment of parathyroid hormone secretion or vitamin D activation[2]. Vitamin D and its metabolites circulate in the blood bound to a specific vitamin D-binding protein (DBP). Vitamin D-binding protein is similar to other binding proteins, such as ceruloplasmin (Cp), in that it is produced in the liver[3,4]. During the last trimester of pregnancy, most of the zinc (Zn) and copper (Cu) is transported through the placenta to the developing fetus[5]. Copper deficiency has been found in preterm infants[6-8]. Copper is a trace element that plays an important role in many metabolic processes related to body growth, the blood system, and bone mineralization[7,9]. Recently attention has been focused on calcium (Ca), phosphorus (P), Zn, and Cu nutrition in newborns, and on its relation to physical growth and dietary intake[10-12].

In this study, we examined the DBP, Cp, Cu, Ca, P, and magnesium (Mg) levels in cord blood of preterm and term infants to determine liver maturity and mineral values in preterm infants.

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Material and Methods

Cord blood specimens were obtained from 20 term and 12 preterm infants who were born in the Department of Obstetrics at Erciyes University Faculty of Medicine from May to August. Since Specker et al[13] reported seasonal differences in infants who were less than six months of age, we decided to conduct our study in the summer.

Gestational ages were determined using the scoring system devised by Dubowitz et al[14], which ranged from 26 to 35 weeks (mean ± SD; 33.5 ± 1.5) The mean birth weight of the preterm group was 2221.7 ± 125.2 g (range 750 to 2500 g).

Cord serum Ca and P concentrations were determined using the Encore standard Autoanalyzer (Baker, GB), and Mg and Cu levels were measured by atomic absorption spectrophotometry (Hitachi Z-8000)[15]. Vitamin D-binding protein values were assessed by the single radial immunodiffusion technique according to the method of Bouillon et al[16].

DPB antiserum and standard were provided by Prof. Bouillon of Leuven, Belgium. Cp levels were measured by the p-phenylenediamine oxidase method[17].

All data were expressed as a mean ± SD. For statistical analyses, the Student's *t* test and regression analysis were used.

Results

The cord serum DBP, Ca, P, Mg, Cu, Cp values of the preterm and term groups are listed in Table I.

The serum DBP, Cp and Cu levels of the preterm group were found to be significantly decreased, but the Ca, P, and Mg values did not differ between the groups.

Table I: Cord Serum DBP, Ca, P, Mg, Cu and Cp Levels in Preterm and Term Infants

	Preterm	Term	
n	12	20	
M/F	8/4	10/10	P
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	
DBP (mg/l)	268 ± 30	301 ± 45	$p < 0.02$
Ca (mg/dl)	10.0 ± 0.6	10.3 ± 0.7	$p > 0.05$
P (mg/dl)	4.6 ± 1.3	4.8 ± 0.7	$p > 0.05$
Mg (mg/dl)	2.3 ± 0.6	2.2 ± 0.4	$p > 0.05$
Cu (ug/dl)	37.5 ± 10.9	49.8 ± 14.3	$p < 0.02$
Cp (mg/dl)	14.5 ± 5.8	20.6 ± 6.4	$p < 0.01$

In the preterm infant samples, the correlation found between the serum Cu and Cp values was $n = 12$, $r = 0.674$, $p < 0.05$, while the correlation in term infants was $r = 0.78$, $p < 0.001$.

Discussion

Vitamin D-binding protein is actively synthesized in fetal liver after the 10th gestational week, and its prenatal serum level is half that of the maternal level[18]. It has been reported that DBP concentrations are at normal adult values in cord blood of term infants, but that preterm infants have low serum DBP concentrations[19], a finding which has been confirmed by other investigators[20].

Lichtenstein et al[21] have demonstrated that starting from birth to 18 months of age, DBP concentrations increased with age. Workers have found that formula-fed infants have higher serum concentrations of all measured vitamin D metabolites and DBP than breast-fed infants[21].

Hillman et al[22] have reported that DBP values increased linearly from 29.7 ± 2.5 to 40 weeks of gestational age. Auconi et al[23] have reported that the mean value of DBP serum levels steadily increases from the 32nd to the 35th week of gestation. This pattern of increase is similar to the patterns of serum concentrations of a number of proteins produced in the liver such as Cp, and therefore Cu[24,25].

Our data demonstrated that DBP levels of preterm babies are lower than those observed in term babies. These results are similar to reports in the literature[22,23].

In our study, we found no difference in the cord serum Ca, P and Mg levels between the preterm and term infants, although the Cu and Cp levels were found to be decreased in the preterm group of infants. Studies have demonstated the same results in cord blood[2,4]. However, when compared with cord blood levels, serum calcium concentrations were found to decrease significantly during the first 24 hours after birth and remained low until the forth day. In addition, serum 25-OH D levels are found to decrease in preterm infants. Hillman[24] has shown that in 57 very early preterm infants studied, serum Cu concentrations remained low for the first 9-12 weeks of postnatal life. He suggested that the ability to increase serum Cu and Cp concentrations is a maturational process, with less mature infants having longer delays.

We examined the Cu-Cp correlation both in preterm and term infants, and found our results to be similar to Hillman's findings[24].

The concentration of copper is significantly higher in term infants than in adults, and it is believed that low copper and ceruloplasmin values in newborn infants reflect an immaturity of the ceruloplasmin synthetic mechanism rather than copper deficiency[26].

Both term and preterm infants begin life with low serum Cu and Cp values. Term infants increase their copper concentration to adult levels by increasing Cp production in mobilizing liver stores by one month of age[24]. Copper concentration in the liver of preterm infants does not decrease, but total stores are limited by a smaller liver size[5, 27]. If sufficient quantities of Cu are not provided in a bioavailable form in postnatal life, a deficient state may develop in preterm infants[8].

Infants of very low birth weight are at risk of developing many serious nutritional deficiencies including Cu deficiency. Copper deficiency of premature infants results in bone changes, neutropenia, anemia and poor weight gain. We recommend that facilities for measurement of plasma Cu and Cp be made available to all neonatal units, and that it should be considered as part of routine investigations in the class of infants mentioned above. It is important that early diagnosis is arrived at, and that treatment is administered before major clinical features appear.

In addition to Cu, vitamin D supplementation is important for the preterm infant.

Acknowledgments

We wish to thank Prof. R. Bouillon of the Laboratorium Voor Experimentele Geneskunda en Endocrinologie, Leuven, Belgium, for his help in providing DBP antiserum and DBP standard serum.

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The Turkish Journal of Pediatrics 34: 231-238, 1992

CRANIOSYNOSTOSIS: A REVIEW OF 143 SURGICALLY-TREATED CASES*

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SUMMARY: Çolak A, Tahta K, Bertan V, Erbengi A, Sağlam S, Gürçay Ö, Özgen T, Benli K, Özcan OE. (Department of Neurosurgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Craniosynostosis: a review of 143 surgically-treated cases. Turk J Pediatr 34: 231-238, 1992.

In this study, 143 cases of craniosynostosis are presented. There were 109 males and 34 females. The major complaints were skull deformity (92 patients), proptosis (38 patients) and microcephalus (32 patients). Neurological examination revealed the presence of optic atrophy in 24 patients and papilledema in 20 patients. Seventy-four patients (53%) had three or more suture closures, with the sagittal suture being the most commonly involved (20% of patients). All patients underwent surgery. Suture removal was performed in 131 patients (91.7%), suture removal plus orbital decompression in 34 (23.8%), and linear craniectomy plus wrapping in 12 (8.3%). The reoperation rate was 6.2 percent. During the follow-up period, preoperative papilledema and proptosis improved in 88.2 and 78.9 percent of patients, respectively. Skull deformity disappeared in 46.9 percent of patients, but remained unchanged in 16.6 percent. *Key words: craniosynostosis, exophthalmos, hydrocephalus, suture removal, wrapping.*

With the use of advanced techniques and approaches, craniosynostosis is becoming one of the more popular entities[1-9]. Craniosynostosis is defined as the premature closure of one or more cranial sutures, producing a deformity of the skull[8-18]. Three classic theories have been advanced to explain craniosynostosis. Virchow[19] believed that craniosynostosis was a primary malformation and the cranial base deformity was secondary to it. Moss[20] postulated that the cranial base malformation was a primary abnormality, resulting in secondary premature fusion of the cranial sutures. The most recent theory proposes that a primary defect in mesenchymal blastema results in both craniosynostosis and an abnormal cranial base[11]. According to Virchow[19] compensatory growth of the skull occurs parallel with the plane of the fused suture. During the first several months of life, when the brain has reached 80 percent of its mature size, its development can be affected if two or more sutures are closed prematurely[6,9,10].

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In these cases, surgical intervention should be carried out as soon as a diagnosis is established. Several different surgical techniques have been used to correct this deformity[3,6,7,9-16].

In this report, we investigated patients according to age, sex, complaint, clinical features and neurological and neuroophthalmological findings. Surgical indications and results are discussed and compared with other reports in the literature.

Material and Methods

This retrospective study comprised 143 patients with craniosynostosis who were investigated and underwent surgery between 1965-1989 in the Department of Neurosurgery at Hacettepe University Faculty of Medicine.

Diagnosis was established according to clinical and neuroradiological findings.

The surgical techniques used in these patients were: suture removal carried out with a median width of two cm; parasagittal linear craniectomy about one cm in width, and the wrapping of the craniectomy edges with an inert film.

Results

Of the 143 patients, 109 were male and 34 female. The age distribution ranged from two weeks to nine years, with a median age of 23.4 months (Table I).

Table I: Age Distribution at Surgery

Age	No. of Patients	
0-6 months	42	(29.4%)
7-24 months	26	(18.2%)
2-5 years	56	(39.1%)
6-10 years	19	(13.3%)
Total	143	(100.0%)

The most frequently encountered complaints on admission were skull deformity (92 patients), proptosis (38 patients) and microcephalus (32 patients) (Table II).

Neurological examination revealed papilledema in 20 patients and optic atrophy in 24 patients. The other findings are summarized in Table III. Although 107 out of 143 patients had a normal head circumference, 135 patients had an abnormally shaped head (Table IV). We found that 74 patients had more than three suture closures, with the sagittal suture being the most commonly involved in 28 patients (Table V). Only the involved suture was removed in 23 patients while all were removed in 108 patients.

Table II: Complaints on Admission

Complaint	No. of Patients	
Skull deformity	98	(68.6%)
Proptosis	38	(26.6%)
Microcephalus	32	(22.4%)
Visual disturbance	23	(16.1%)
Headache	16	(11.2%)
Seizure	6	(4.2%)

Table III: Neuroophthalmological Findings

	No. of Patients		
Vision	143		
Normal		115	(80.5%)
Decreased		28	(19.5%)
Fundoscopic Findings	143		
Papilledema		20	(14.0%)
Atrophy		24	(16.7%)
Normal		99	(69.3%)
Exophthalmos	63		
Slight		30	
Severe		33	

Table IV: Head Circumference and Shape

	No. of Patients		
Head Circumference	143		
Normal		107	(74.8%)
Increased		25	(17.5%)
Decreased		11	(7.7%)
Head Shape	143		
Normal		8	(5.6%)
Abnormal		135	(94.4%)

Table V: Suture Involvement

Involved Suture	No. of Patients
Three or more	76 (53.1%)
Only sagittal	28 (19.6%)
Bilateral coronal	11 (7.7%)
Coronal and sagittal	10 (7.0%)
Coronal and metopic	9 (6.3%)
Sagittal and metopic	6 (4.2%)
Only coronal	3 (2.1%)
Total	143 (100.0%)

The surgical techniques used are shown in Table VI. The most frequent complications were: wound infection (five patients), cerebrospinal fluid fistula (three patients), and leptomeningeal cyst formation (one patient). There were ten postoperative deaths due to hemodynamic imbalance (eight patients), sepsis (one patient), and bleeding diathesis (one patient).

Table VI: Surgical Procedures

	No. of Patients	
Suture Removal	131	(91.7%)
Only involved suture	23	(16.1%)
All sutures	108	(75.6%)
Suture removal + Orbital Decompression	34	(23.6%)
Linear craniectomy + Wrapping	12	(8.3%)

Primary craniosynostosis was observed in 142 patients and secondary craniosynostosis due to subdural hematoma in one.

Follow-up examinations revealed normal fundoscopic findings in 17 patients with preoperative papilledema. Although exophthalmos remained unchanged in six out of 52 patients, it disappeared in 43. Table VII shows the preoperative and follow-up findings of all patients.

A repeat operation was performed in nine patients because of resynostosis of the sutures. In eight of them, the sutures were removed, and a linear craniectomy was performed in one. One patient was operated on three times and the others twice.

Table VII: Findings at Follow-up

Preoperative Findings	No. of Patients*	Postoperative Findings	No. of Patients
Papilledema	17	Normal	15 (88.2%)
		Optic atrophy	2 (11.8%)
Proptosis	52	Decreased	5 (9.6%)
		Unchanged	6 (11.5%)
		Normal	41 (78.9%)
Skull Deformity	115	Complete Improvement	54 (46.9%)
		Marked Improvement	33 (28.7%)
		Slight Improvement	9 (7.8%)
		Unchanged	19 (16.6%)

* Number of cases whose follow-up examination was possible.

Findings of raised intracranial pressure were found in 52 patients (36.5%). Associated congenital anomalies consisted of corpus callosum agenesis (one patient), low posterior hair line and phimosis (one patient), clavicula abnormality (one patient), and encephalocele (one patient). One patient with cystic fibrosis also had craniosynostosis and patent ductus arteriosus. One patient had puberty precox. Four patients had hypertelorism and this condition was corrected in two of them by a combined surgical procedure performed by a team of neurosurgeons and plastic and reconstructive surgeons. One patient had a family history of hyperthyroidism. The mother of this patient had received propicyl therapy during her pregnancy. Hyperthyroidism could cause premature fusion of cranial sutures[11].

Discussion

Craniosynostosis occurs in approximately 1 per 1900-2000 live births[6,9-11,13,17], and there is a male preponderance accounting for 76 percent of patients, even though some authors report a slight female preponderance for brachycephaly[7,9,13,17]. In our series, the male/female ratio was 3.5/1.

Radiographic and/or clinical evidence of raised intracranial pressure was found in most of the reported cases[4-6,9,10,13]. It is documented that this pressure drops to normal after surgical treatment[3,4,6,10,13]. In our series, the incidence of increased intracranial pressure was 36.5 percent at the time of diagnosis, which was similar

to the series of Renier et al[4], but different from others reported in the literature[6,9,10,13]. It is important to look for signs of intracranial hypertension especially in older children in order to discover the premature suture closure.

Although some authors have emphasized the coexistence of craniosynostosis with hydrocephalus, there is no mention of hydrocephalus in large series such as that of Schillito and Matson[9,10,18]. We observed only one case of craniosynostosis associated with hydrocephalus. Seizure is rare in patients with craniosynostosis unless increased intracranial pressure is present[6]. The incidence of seizure becomes higher with prolonged duration of increased intracranial pressure. In our series, seizure was found in six patients (4.2%), all of whom also had elevated intracranial pressure.

Papilledema, and optic atrophy which have been reported as rare entities in many series[6,9,10,15], were observed in 44 out of 143 of our patients. After surgical intervention, we observed that papilledema disappeared more in the younger patients than in the older ones. Myriathopoulos[17] proposed that papilledema only occurs when more than one suture is synostozed. We found in our series of 122 patients, that three or more sutures were involved. According to Winston[6], proptosis is associated only with coronal synostosis, which is in contrast to observations, since proptosis is seen in all types of suture closures. Forty-two out of our 63 cases with proptosis had three or more suture closures. Findings at follow-up examination revealed that papilledema disappeared in 15 out of 17 patients (88.2%), and proptosis was no longer evident in 41 out of 52 patients (78.8%). These results are similar to those reported in the literature[6,9,10,13]. Therefore, orbital decompression should be added to removal of sutures in patients with proptosis.

Surgical treatment is undertaken to decrease intracranial hypertension and prevent an abnormal appearance[6,9-11,13]. There are therefore only two surgical indications: increased intracranial hypertension and reconstruction of a cranial deformity. The general strategy regarding surgery is to perform a linear craniectomy. A parasagittal linear craniectomy is one of the preferred surgical techniques used to preserve the sagittal sinus and prevent resynostosis[6,8,9,10,13]. In our study, a parasagittal linear craniectomy, with or without wrapping, was performed in 12 out of 143 patients and resynostosis was observed in one (8.6%). Some authors have advocated several different approaches to prevent resynostosis such as wrapping, application of chemical solutions, and suturectomy[8,9,11,13]. Ingraham et al[8] was the first to advance the opinion that wrapping material was a foreign substance and could be a source of infection in the body. Therefore, wrapping is not necessary if an appropriate craniectomy is performed. In our series, wrapping was performed in 12 patients, and infection was observed in four of them (33.3%).

Suture removal was the preferred procedure in our series. The rate of reoperation was 6.2 percent. In these cases, operative techniques consisted of suture removal (8 patients) and parasagittal linear craniectomy (one patient). It has been reported that the rate of repeat operations ranges from 4 to 40 percent[8-10]. In our series, this ratio was lower than the reports in the literature. It is our opinion that this low ratio is due to wide suture removal performed with a median measuring two cm in width.

In conclusion, we believe that surgical intervention must be performed as early as possible, not only to prevent deformity and improve the appearance of the child, but also to prevent damage to the brain due to increased intracranial pressure. We are also of the opinion that suture removal should be preferred as the surgical technique used to correct this abnormality.

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The Turkish Journal of Pediatrics 34: 239-244, 1992

EFFECTS OF ANTICONVULSANT DRUGS ON THYROID HORMONES IN EPILEPTIC CHILDREN*

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SUMMARY: Deda G, Akıncı A, Teziç T, Karagöl U. (From the Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Effects of anticonvulsant drugs on thyroid hormones in epileptic children). Turk J Pediatr 34: 239-244, 1992.

Serum total and free thyroid hormones, reverse T3 (rT3), thyroxin binding globulin (TBG) and thyroid stimulating hormone (TSH) concentrations were measured in 35 epileptic patients receiving anticonvulsants (phenobarbitone, phenytoin). There was a significant reduction found in total thyroxine (TT4), free thyroxine (FT4), total triiodothyronine (TT3), free triiodothyronine (FT3) and rT3 in the group treated with, phenytoin. The thyroid hormone levels were within normal limits in the group receiving phenobarbitone. *Key words: anticonvulsant drugs, thyroid functions.*

It is widely known that long-term administration of anticonvulsant drugs affects blood thyroid hormone levels[1]. Despite a reduction in serum TT4 and FT4 concentrations, most studies have emphasized that patients receiving anticonvulsants appear to be clinically euthyroid with normal reference TSH levels[2].

In 1961, studies revealed a decrease in protein-bound iodine in adults undergoing phenytoin therapy, which was attributed to the displacement of T4 from its binding to TBG[3,4]. More recent investigations have demonstrated that adults treated with phenytoin also have decreased TT4, FT4 and T3 levels[3].

The long-term use of phenobarbitone has been shown to produce a drop in the serum T4 concentration which coincides temporarily with hepatic enzyme induction[5].

The aim of this study was to determine the effect on thyroid function of long-term anticonvulsant treatment with phenytoin and phenobarbitone, placing particular emphasis on the direct measurement of serum TT4, FT4, TT3, rT3, TBG and TSH concentrations.

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Material and Methods

This study was conducted in epileptic children who were receiving anticonvulsant therapy for a mean period of 2-3 years.

We examined two groups, one consisting of 20 patients who received only phenobarbitone and the other, consisting of 15 patients, who were only receiving phenytoin. The age distribution of the patients receiving phenobarbitone ranged between 2.5-8 years (mean 6.9 years). Fifteen healthy children, whose ages were between 4-12 years (mean 8 years), were the control subjects. (Table I).

Table I: Mean Serum Concentrations and Period of Treatment With Anticonvulsant Drugs

	Phenobarbitone		Phenytoin
Serum concentration of drug (μ g/ml)	23.64 ± 7.3 (11.26 – 34.64)		10.62 ± 4.6 (8.78 – 14)
Period of drug use (yrs.)	2.3 ± 1.2 (1.4 – 4.5)	$p > 0.05$	2.5 ± 1.8 (1.5 – 6) ($p > 0.05$)

All patients were examined by a pediatric endocrinologist, and except for short stature and delayed skeletal maturation, none of them showed clinical findings of hypothyroidism.

The serum TT3, TT4, FT3, FT4, TSH, rT3 and TBG levels were measured in all patients by the radioimmunoassay technique using commercially available kits (Diagnostic Product Corporation for TT3, TT4, FT3, FT4; IRMA for TSH, Biodata for rT3 and GMBH for TBG).

Serum phenobarbitone and phenytoin levels were measured in all patients by the radioimmunoassay technique of Baxter.

The results were analyzed statistically using Student's *t* test.

Results

In group I (patients on phenytoin), TT_4 levels were lower when compared with the control group, and the difference was statistically significant ($p < 0.01$). In group II (patients on phenobarbitone), TT_4 levels did not differ and when compared with the control group, the difference was not statistically significant ($p > 0.05$). The difference in TT_4 levels was also statistically significant in groups I and II ($p < 0.01$). FT_4, TT_3, FT_3, and rT_3 levels were lower in group I when compared with group II and the control group, and the difference was statistically

significant ($p < 0.05$). Between group II and the control group, there was no difference with regard to these hormones ($p > 0.05$). There were also no significant variations in the TSH levels of the three groups ($p > 0.05$). In groups I and II, the TSH levels were found to be within normal ranges. The TBG levels were found to be lower in group I when compared with group II and the control group and the results were statistically significant ($p < 0.01$) (Table II). Although, there was a significant decrease in the thyroid functions of group I, no clinical signs of hypothyroidism were detected.

Table II: Mean Serum Concentrations of TT_4, TT_3, FT_4, FT_3, rT_3, TSH and TBG in Serum During Anticonvulsant Therapy in Epileptic Children and Controls.

	Phenytoin Group I n = 15		Phenobarbitone Group II n = 20		Control n = 15
TT_4 nmol/1 (58 – 61)	62 ± 21.10[E] (46 – 80)	$p < 0.01$	105 ± 16.23 (66 – 105)	$p > 0.05$	137 ± 11.90 (95 – 146)
TT_3 nmol/1 (1.32 – 2.87)	1.30 ± 0.77[*] (1.02 – 1.33)	$p < 0.05$	2.34 ± 0.47 (1.7 – 2.7)	$p > 0.05$	2.45 ± 0.57 (2.2 – 2.9)
FT4 pmol/1 (10.3 – 18.9)	10.28 ± 4.3[*] (7.2 – 12.6)	$p < 0.05$	16.68 ± 5.9 (9.8 – 16.7)	$p > 0.05$	15.57 ± 4.6 (15 – 17.6)
FT3 pmol/1 (2.14 – 5.34)	2.25 ± 1.95[*] (1.95 – 4.1)	$p < 0.05$	4.85 ± 1.7 (2.05 – 6.1)	$p > 0.05$	0.42 ± 0.12 (2.5 – 6.6)
rT3 nmol/1 (0.20 – 0.56)	0.26 ± 0.96[*] (0.17 – 0.22)	$p < 0.05$	0.48 ± 0.77 (0.25 – 0.45)	$p > 0.05$	0.42 ± 0.12 (0.27 – 0.49)
TSH µu/1 (0.3 – 4.5)	2.08 ± 1.38[*] (1.05 – 3.8)	$p < 0.05$	2.29 ± 1.05 (1.5 – 2.9)	$p > 0.05$	2.02 ± 0.7 (1.7 – 2.2)
TBG mg/1 (14.7 – 36.3)	18.10 ± 7.5[E] (10.5 – 19.2)	$p < 0.01$	31.75 ± 6.6 (26.4 – 32.9)	$p > 0.01$	29.5 ± 4.4 (27.8 – 34.5)

E Compared with control ($p < 0.01$)
* Compared with control ($p < 0.05$)
* Compared with control ($p > 0.05$)

There was no difference seen in the duration of the anticonvulsant therapy between groups I and II (Table I).

When we attempted to make a correlation between the concentration of anticonvulsants and thyroid functions, we found that in the patients on phenytoin there was a negative correlation between TBG levels and phenytoin serum concentration ($r = 0.55$) ($p < 0.01$) (Fig. 1), while there was no correlation found between the duration of the anticonvulsant therapy and the levels of thyroid hormones. However, there was a negative correlation found between FT_4 levels and serum phenytoin concentrations ($r = 0.62$) ($p < 0.01$) (Fig. 2).

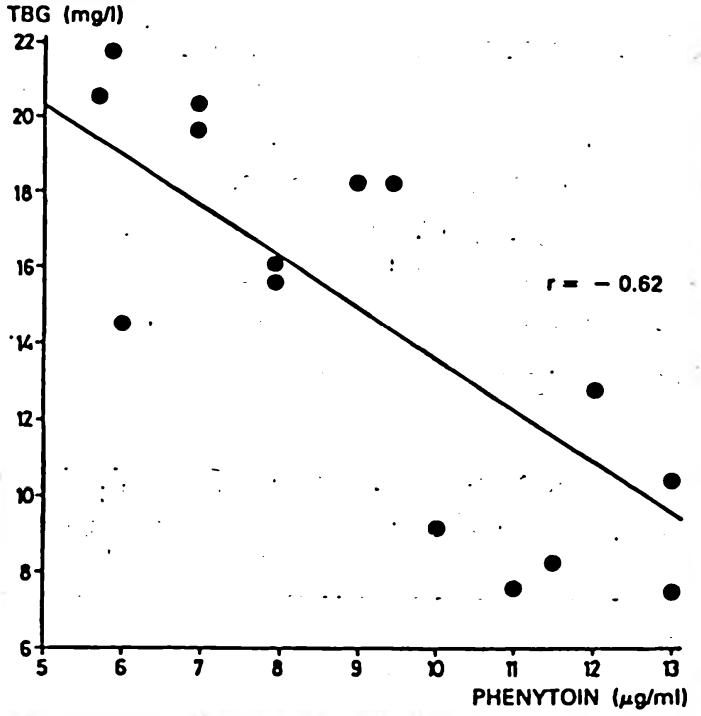

Fig. 1: Correlation between serum levels of TBG and phenytoin (r:-0.62) ($p < 0.01$)

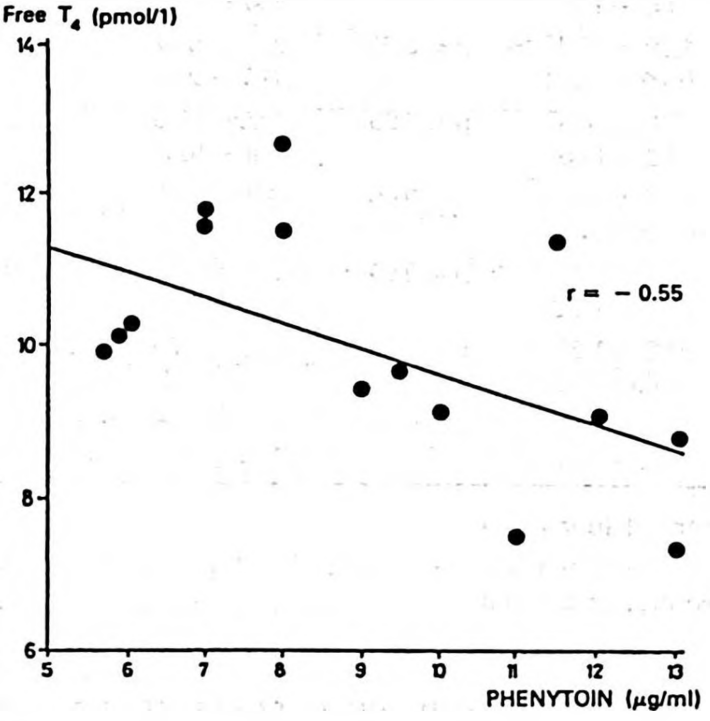

Fig. 2: Correlation between serum levels of phenytoin and FT_4 (r:-0.55) ($p < 0.01$)

Discussion

Anticonvulsants are known to induce the hepatic microsomal enzyme system resulting in the catabolization of thyroid hormones. During chronic use of phenobarbitone, deiodinating activity increases in the hepatic microsomes and the degradation of the thyroid hormones is aggravated. At the same time, phenobarbitone has an activating effect of up to 100 percent on the fecal clearance of T4[1]. On the other hand, during chronic use of phenobarbitone, T4

levels may remain compensatorily within normal limits. It was shown previously that phenobarbitone had no significant effect on thyroid functions[2]. In our study, the TT4 and FT4 levels in the group on phenobarbitone were not significantly different than those in the control group (Table II).

It has been reported that the use of phenytoin alone or in combination with carbamazepine results in a significant decrease in thyroid functions[3-5]. Results of other studies indicate that despite the decrease in TT4, and FT4 levels, TT3 and FT3 levels have been found to be normal in patients taking phenytoin[6]. This result was believed to be related to the sufficient conversion of peripheral T4 → T3 in spite of an increased catabolism of T4[7]. In some studies, as a result of the increased peripheral utilization and clearance of thyroid hormones related to phenytoin, a decrease was detected in FT4, FT3 and rT3 levels[2].

In our study, TT4, FT4, TT3, FT3 and rT3 levels revealed a statistically significant decrease in group I when compared with the control group and group II (Table II).

Despite the decreasing effect of anticonvulsants on thyroid hormone levels, most patients in the euthyroid state have normal TSH levels[8]. Some investigators have found high TSH levels in patients taking phenytoin[9]. An insufficient increase in TSH levels, in spite of the drop in T4 and T3 levels, has not been clearly explained. But normal TSH values reveal that the intrapituitary conversion of T4 to T3 is normal.

Surks et al[10] showed that phenytoin caused insufficient TRH → TSH stimulation. In our study, serum TSH levels were within normal limits in groups I and II.

It is known that phenytoin decreases TBG by an unknown mechanism. Although, the affinity of phenytoin to TBG in serum is less than T4, once the concentration of phenytoin reaches a certain level in serum, it is bound to TBG[8]. In our study, the TBG levels were found to be reduced in group I, and there was a negative correlation found between phenytoin serum concentrations (Fig. 1). This finding shows that the depressant effect of phenytoin on TBG is not related to the duration of therapy, but correlated with the serum concentrations of phenytoin. The same correlation is also seen in FT4 levels (Fig. 2). We found that serum thyroid hormone levels of the patients on phenobarbitone did not differ significantly, but that they had decreased significantly in the patients receiving phenytoin therapy. This decrease was mainly due to the serum concentration of phenytoin rather than to the duration of therapy.

There are some reports indicating that anticonvulsants not only affect thyroid hormones subclinically, but also cause clinical hypothyroidism[11]. In conclusion, we recommend that thyroid functions be monitored in patients receiving anti-convulsant therapy.

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The Turkish Journal of Pediatrics 34: 245-250, 1992

TWO-DIMENSIONAL AND DOPPLER ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF ABSENT PULMONARY VALVE SYNDROME (SURGERY WITHOUT CATHETERIZATION)*

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SUMMARY: Özkutlu S, Özme Ş, Atalay S, Saraçlar M, Bilgiç A, Yurdakul Y. (Department of Pediatric Cardiology, Hacettepe University Institute of Child Health, Ankara, Turkey). Two-dimensional and Doppler echocardiography in the diagnosis of absent pulmonary valve syndrome (surgery without catheterization). Turk J Pediatr 34: 245-250, 1992.

The majority of severely affected infants with absent pulmonary valve syndrome develop varying degrees of respiratory distress. Cardiac catheterization and angiocardiography are still performed in the diagnosis of these infants prior to surgery. However, considering the high risks of these invasive investigations for severely symptomatic infants, diagnosis using only noninvasive methods becomes important. In this regard, we present three cases of absent pulmonary valve syndrome, diagnosed pre-operatively by both two-dimensional and Doppler echocardiography. The diagnosis was confirmed by cardiac catheterization and angiocardiography in two cases and by surgery in a symptomatic infant. Therefore, we are of the opinion that the two-dimensional and Doppler echocardiograpic methods are most reliable in diagnosing absent pulmonary valve syndrome, and that severely symptomatic infants can be referred for surgery without catheterization. *Key words: two-dimensional echocardiography, Doppler echocardiography, absent pulmonary valve syndrome.*

Congenital absence of the pulmonary valve is a rare cardiac malformation usually associated with tetralogy of Fallot (TOF)[1-3]. Patients generally present in early infancy with cyanosis or respiratory distress or both[4]. Clinical findings may be complicated by respiratory insufficiency due to tracheobronchial compression by the dilated pulmonary arteries[4]. This syndrome has been diagnosed by cardiac catheterization and angiocardiography. In a few recent reports, it was emphasized that since echocardiographic features of absent pulmonary valve syndrome appear to be unique, diagnosis can be established by the use of noninvasive methods[5-7].

When considering the high risks involved for severely symptomatic infants undergoing cardiac catheterization, it is important that only noninvasive methods be used in arriving at a diagnosis before surgery is undertaken. To illustrate this

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point, we present three cases of congenital absence of the pulmonary valve diagnosed by both two-dimensional and Doppler echocardiography. The diagnosis was subsequently confirmed by cardiac catheterization, angiocardiography and cardiac surgery in two patients and by surgery in the severely symptomatic infant.

Material and Methods

Among the patients referred to the Department of Pediatric Cardiology of the Hacettepe University Institute of Child Health, three patients were diagnosed as having absent pulmonary valve syndrome by the use of both two-dimensional and Doppler echocardiography. In addition, cardiac catheterization and angiocardiography were performed in two patients. The ages of the patients ranged between two months and seven years. All patients underwent cardiac surgery.

The echocardiographic examination included M-mode, two-dimensional, contrast and Doppler studies using a Toshiba-Sonolayer-S SSH 60 A Scanner with 2.5, 3.75 and 5 MHz transducers.

Case Report

Clinical manifestations and laboratory findings of these patients are presented in Table I, and some echo findings in Table II. Other echo findings were as follows:

In all patients right ventricular enlargement and subaortic ventricular septal defect, also demonstrated by contrast studies, were noted. In the short-axis view at the level of the great arteries an echo-dense structure at the level of the pulmonary annulus, suggestive of valve tissue and dilated pulmonary arteries, was observed

Table I: Clinical and Laboratory Data of Patients

Case No.	Age Sex	Symptoms	Murmur	ECG	X-ray	Pressure (mm Hg)	Angiocardiography
1	4 yr. M	No	To-and-fro	Right axis RV Hypertrophy	Cardiomegaly	RVP : 110/5 PA : 28/9	Dilated main PA and branches, VSD PR
2	7 yr. M	No	To-and-fro	RV Hypertrophy	Cardiomegaly Pulmonary Pressure	RVP : 110/5 PA : 35/4	Dilated main PA and branches Narrow PA annulus VSD PR
3	2 Mo. F	Dyspnea Cough Cyanosis	To-and-fro	Right axis RV Hypertrophy	Cardiomegaly Prominent RPA		

RV : right ventricle
RPA : right pulmonary artery
PA : pulmonary artery
PR : pulmonary regurgitation

Table II. Echo Findings

Case No.	Diameter of PA Annulus (mm)	Diameter of Main PA (mm)	Diameter of LPA (mm)	Diameter of RPA (mm)	Diameter of Ao Annulus (mm)	Systolic Gradient By Doppler Echo (mm Hg)
1	12	30	27	17	20	75
2	15	46	17	22	22	67
3	8	14	12	18	11	68

PA : pulmonary artery
LPA : left pulmonary artery
Ao : aorta

in each patient. In the subcostal position, the right and left pulmonary artery branches were visualized more clearly (Fig. 1).

In the parasternal short-axis view, retrograde systolic and anterograde diastolic flow patterns in the main pulmonary artery were recorded by continuous-wave Doppler echocardiography (Fig. 2). Diameters of the pulmonary arteries and the systolic gradient across the pulmonary annulus measured by Doppler echocardiography are noted in Table I.

Surgical confirmation of the diagnosis was available in all three patients.

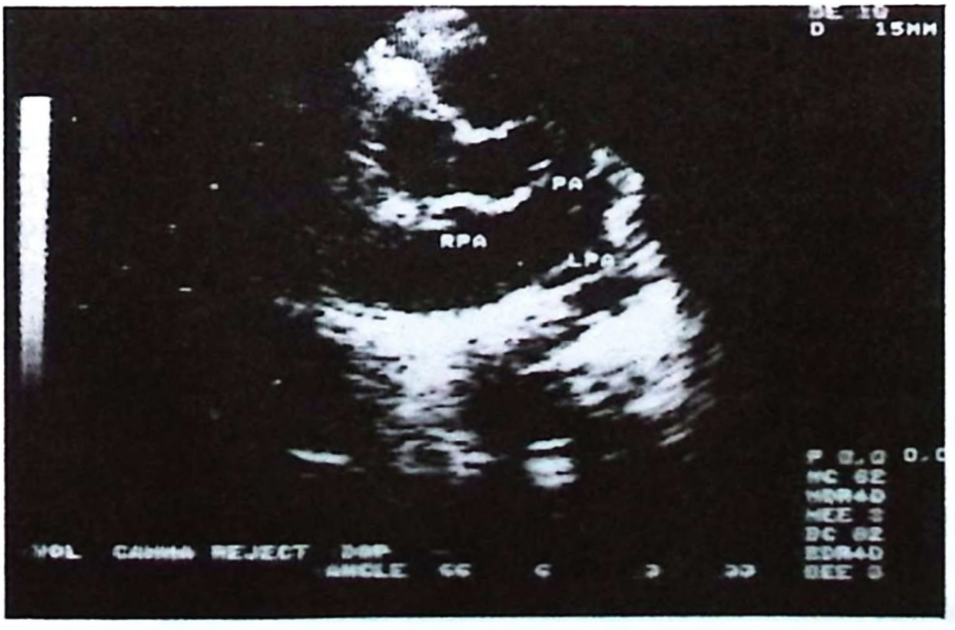

Fig. 1: Case 3. Two-dimensional echocardiogram in the subcostal position. The main and right pulmonary arteries are markedly dilated. (PA: pulmonary artery, RA: right pulmonary artery, LA: left pulmonary artery).

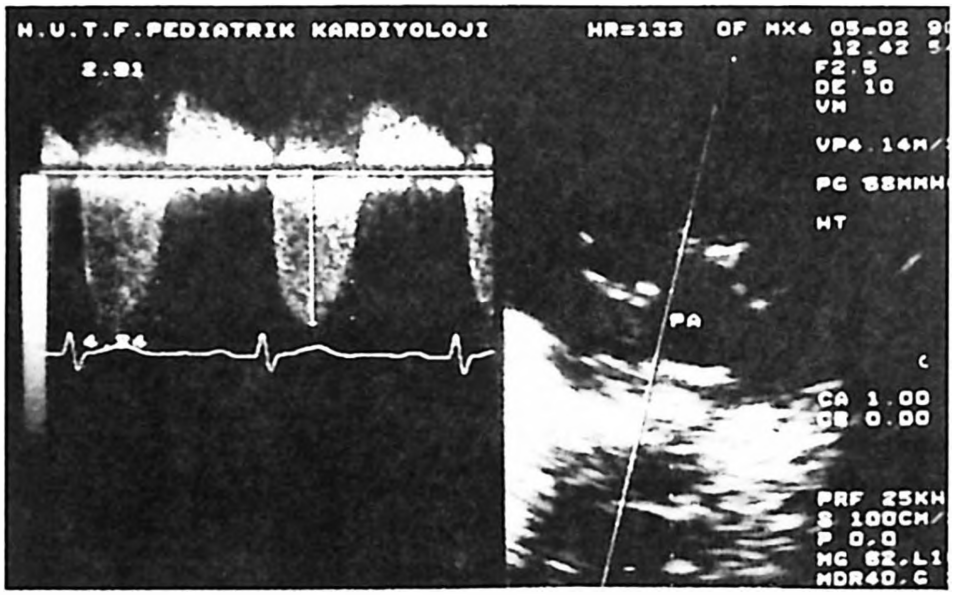

Fig. 2: Same patient. Two-dimensional and continuous-wave Doppler echocardiogram in the parasternal short-axis view showing antegrade systolic flow (below the baseline) and retrograde diastolic flow (above the baseline) in the main pulmonary artery.

Discussion

The absent pulmonary valve syndrome was first described by Chevers in 1847[8]. This anomaly can be associated with other congenital anomalies such as TOF, ventricular septal defect (VSD), patent ductus arteriosus (PDA), atrial septal defect (ASD), double outlet right ventricle (DORV), endocardial cushion defects (ECD), tricuspid atresia and transposition of the great arteries (TGA)[4]. It is rarely present as an isolated lesion[4]. The cases presented were associated with VSD. Only 15 cases without VSD have been reported in the literature[4].

In most of our patients, symptoms of respiratory distress were present in infancy and early childhood due to the compression of the trachea by a pulmonary artery aneurysm. While two cases were asymptomatic and were referred to our hospital for evaluation of a to-and-fro murmur detected on physical examination, the third had cyanosis and dyspnea.

There are reports of a few patients who have been diagnosed only by two-dimensional echocardiography or by both two-dimensional and Doppler echocardiography[5-7]. Ventricular septal defect, aortic overriding and right ventricular dilatation can be demonstrated by two-dimensional echocardiography. In the parasternal short-axis view of the great arteries, main pulmonary artery dilatation and dysplastic or rudimentary pulmonary valve elements can be recorded[4-7]. In the cases presented, normal septal-aortic continuity, VSD and right ventricular dilatation were seen. In all three cases, it was demonstrated in the short-axis view of the great arteries, that the main pulmonary artery was dilated, the annulus was

stenotic and the pulmonary valves were rudimentary. In the subcostal position, branches of the right and left pulmonary arteries were visualized far more clearly.

With Doppler echocardiography in the parasternal short-axis view, a retrograde systolic flow pattern was recorded in the main pulmonary artery and antegrade diastolic flow patterns in the main pulmonary artery and in the right ventricular outflow tract.

The distinction between the resemblance of the Doppler flow pattern in the main pulmonary artery in absent pulmonary valve syndrome and the flow pattern in PDA can be made in the absence of a diastolic flow at the right ventricular outflow tract unless pulmonary insufficiency in association with PDA is present[9].

Since 1982, neonates and infants with certain types of congenital heart disease such as critical aortic valve stenosis, pulmonary atresia or stenosis, aortic arch obstruction, aortic atresia, total anomalous pulmonary venous connection, and truncus arteriosus are referred for surgery only after echocardiographic evaluations are made. Of course, this decision depends upon the confidence and skill of the referring cardiologist[10,11]. When considering the high risks involved in catheterization of symptomatic newborns and small infants, the importance of referring these patients for surgery without undergoing catheterization increases.

Therefore, it is our opinion that the two-dimensional and Doppler echocardiographic methods are most reliable for diagnosing absent pulmonary valve syndrome and that severely symptomatic infants may undergo surgery without catheterization, thus avoiding the high risks of this invasive procedure.

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The Turkish Journal of Pediatrics 34: 251-254, 1992

A CASE OF JUVENILE CHRONIC MYELOID LEUKEMIA WITH XX / XXX MOSAICISM*

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SUMMARY: Yeşilipek MA, Lüleci G, Oygür N, Berker S, Yegin O. (Departments of Pediatrics and Medical Biology, Akdeniz University Faculty of Medicine, Antalya, Turkey). A case of juvenile chronic myeloid leukemia with XX/XXX Mosaicism. Turk J Pediatr 34: 251-254, 1992.

Cytogenetic abnormalities are rarely found in patients with juvenile chronic myelogenous leukemia (JCML). In patients with chromosomal abnormalities, chromosomes 7 and 8 are usually involved. A case of JCML with 47 XXX and a 46 XX karyotype is described and the literature is reviewed. To our knowledge, this is the first case ever to have been reported. *Key words: juvenile chronic myeloid leukemia, chromosome, XXX karyotype.*

Juvenile chronic myeloid leukemia (JCML) is a clonal panmyelopathy associated with an elevated white blood cell count, hepatosplenomegaly, and decreased leukocyte alkaline phosphatase and high fetal hemoglobin levels[1-7]. In cytogenetic studies, JCML is distinguished from the adult form of the disease because the leukemic cells lack the Philadelphia (Ph') chromosome marker[1,3,5,7,8]. The majority of patients have no cytogenetic abnormalities, but in cases where they are present, chromosomes 7 and 8 are the most commonly involved[1,7].

We present a case of JCML with the 46 XX/47 XXX mosaic karyotype, that to our knowledge, has not been previously reported in the literature.

Case Report

A seven-year-old girl was admitted to our clinic with a history of pallor, cough, lassitude, and loss of appetite. Physical examination revealed bilateral otitis media, chronic tonsillitis, polymicrolymphadenopathy (one right axillary lymph node exceeded 3 x 1 x 1.5 cm in size). The liver was enlarged 4 cm and the spleen 6 cm below the costal margins. Ecchymoses and petechial skin lesions were observed on both extremities.

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Laboratory studies revealed hemoglobin 6.5 g/dl, white blood cell count 26,000/mm^3, and hematocrit value 21%. The peripheral blood smear showed a decreased thrombocyte count, and 13% blasts, 1% promyelocytes, 2% myelocytes, 6% metamyelocytes, 45% PMN band forms, 15% lymphocytes, 18% monocytes, and 12 normoblasts per 100 white blood cells, some of which were in a very early stage of differentiation. Bone marrow aspiration demonstrated hypercellularity with 11.5% blast cells, 7.5% promyelocytes, 5.5% myelocytes, 15% metamyelocytes, 15% PMN band forms, 2% pronormoblasts, 27.5% normoblasts, 2% lymphocytes, 14% monocytes, and no megakaryocytes. Hemoglobin electrophoresis revealed hemoglobin F 30.7%, hemoglobin A_2 0.2%, and hemoglobin A_1 69%. The heterophile antibody test was negative, while the direct Coombs test was initially positive, but after three weeks, was found to be negative. Hemoglobin A_2 levels were normal in both parents.

Cytogenetic analysis was carried out using the direct bone marrow technique, and chromosomes were banded by GTG[9,10]. In accordance with the normal 46 XX karyotype, the 47 XXX configuration was observed in 35 out of 100 cells examined (Fig. 1).

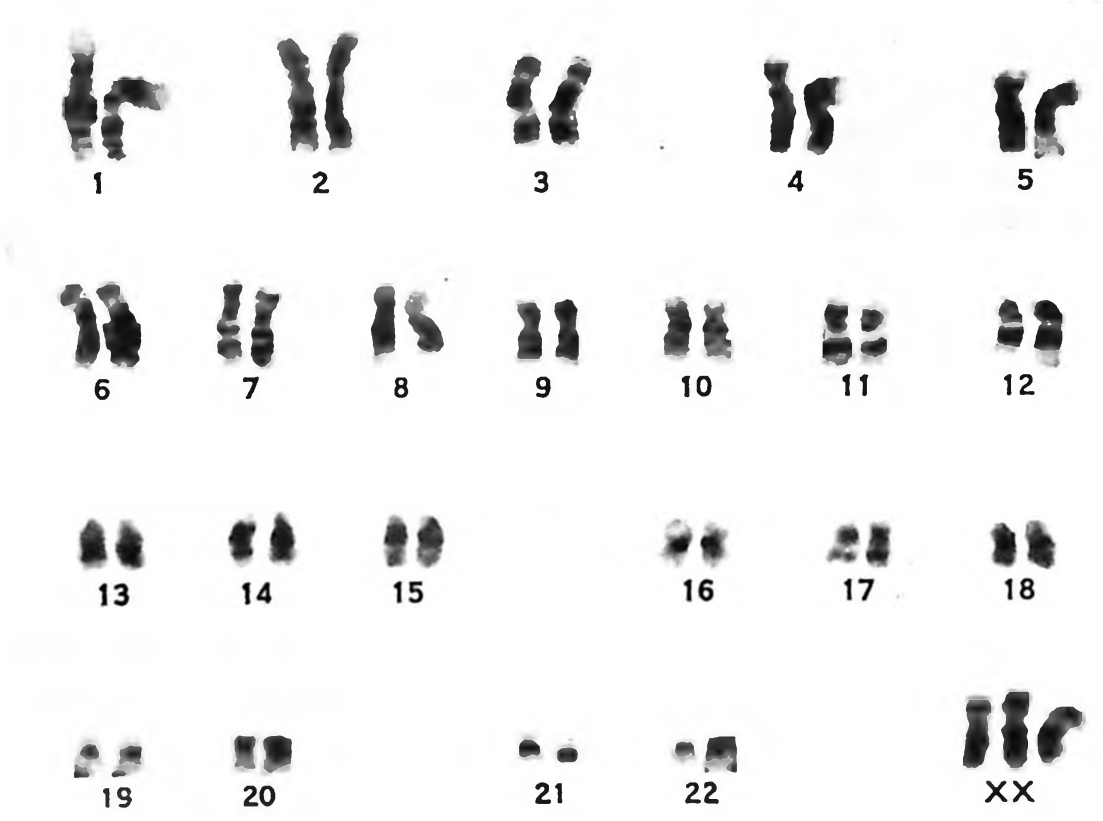

Fig. 1. Karyotype of the patient.

Discussion

Chronic myelocytic leukemia (CML) is a rare type of childhood leukemia. Three different forms of the disease have been described: the adult, juvenile, and congenital or infantile types[8].

JCML differs from the adult form of CML by its presentation in the first year of life, cutaneous manifestations, lymphadenopathy, hemoglobin level, immunologic deficiency, prominent involvement of the monocytic series, a relatively rapid course and absence of the Ph' chromosome[1,3,7]. Monocytosis and the presence of the early form of normoblasts are the most striking feature in peripheral blood smears[3,7]. These features confirm that JCML is a panmyelopathy which involves granulocytes, monocytes, erythrocytes and platelet precursors[1,5,11]. In addition, there are reports regarding the association between the pathogenesis of JCML, and neurofibromatosis and persistent Epstein-Barr virus infection[1,3,4,12]. An elevated fetal hemoglobin level is another characteristic of JCML[1,3,7]. Castro-Malaspina et al[3] found that fetal hemoglobin levels were increased in 53 percent of the patients they studied. We also observed a fetal hemoglobin level of 30.7 percent in our patient. JCML has a heterogenous cytogenetic pattern. Most patients have normal karyotypes and the Ph' chromosome is always missing.

In a minority of patients, chromosome abnormalities have been documented by cytogenetic studies of marrow cells including an extra-minute chromosome, condensed G-group chromosome, trisomy C, missing Y chromosome, and various translocations and deletions[3,5,11]. We found the 46 XX/47 XXX mosaic karyotype while making a cytogenetic analysis of the marrow cells of our patient. To the best of our knowledge, this assocaiton with JCML has not been previously reported, and it may be coincidental, therefore, it requires further investigation.

Acknowledgement

We wish to thank Prof. Hugo Castro-Malaspina (U.S.A) for being a consultant in this case.

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The Turkish Journal of Pediatrics 34: 255-258, 1992

INTUSSUSCEPTION DUE TO ECTOPIC PANCREATIC TISSUE IN A NINE – MONTH – OLD CHILD*

*Bedii Salman MD**, Nesrin Beşbaş MD***, Turgay Coşkun MD***
*Dilek Yılmazbayhan MD****, Faik Sarıalioğlu MD*****

SUMMARY: Salman B, Beşbaş N, Coşkun T, Yılmazbayhan D, Sarıalioğlu F. (Departments of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, and Diyarbakır State Hospital, Diyarbakır, Turkey). Intussusception due to ectopic pancreatic tissue in a nine-month-old child. Turk J Pediatr 34: 255-258, 1992.

Ileo-colic intussusception was diagnosed in a nine-month-old male infant who presented with abdominal distention, irritability, and bilious vomiting. After reduction of the invaginated segment, a mass measuring one cm was palpated at the antimesenteric border of the terminal ileum. Pathological examination of the mass revealed ectopic pancreatic tissue, which most likely caused the intussusception. *Key words: intussusception, ectopic pancreas.*

Intussusception, the most common cause of acute abdomen in children under one year of age seldom results from recognizable lesions[1,2] such as Meckel's diverticulum, ectopic pancreatic tissues, polyps, enterogenous cysts, or tumors, which are generally observed in patients over one year of age[3-5].

In this paper, we report a case of intussusception caused by ectopic pancreatic tissue with the aim of stressing the possibility of its occurrence even in a nine-month-old infant.

Case Report

A nine-month old boy was admitted with complaints of abdominal distention, irritability and bilious vomiting which began two days prior to admission. The patient was found to be dehydrated at the time of admission. A sausage-like mass was easily palpable in the right lower quadrant of the abdomen.

Following digital rectal examination, a strawberry jelly-like stool discharged through the anus. Plain abdominal radiographs revealed wide-based air-fluid levels with intestinal loops over the bony pelvis.

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The patient was hospitalized with the diagnosis of intussusception. The hemoglobin level, white blood cell count and routine urinalysis were all within normal limits. Blood biochemistry revealed hyponatremia with a serum Na^+ level of 126 mEq/L. Because of wide-based air-fluid levels, reduction of the invaginated intestinal segment by barium enema was not attempted, and surgical treatment was planned. Following fluid and electrolyte replacement, an emergency laparotomy was performed through a transverse abdominal incision and an ileo-colic intussusception was detected. Intussusception located in the mid-transverse colon was easily reduced. After reduction of the ileo-colic intussusception, a mass measuring one cm in diameter and located at the antimesenteric border of the terminal ileum and ten cm proximal to the ileo-cecal valve was discovered (Fig. 1). Although the reduced intestinal segment was in good

Fig. 1: Macroscopic appearance of the resected intestinal segment.
Note the nodule located at the antimesenteric edge of the small intestine.

condition, a resection and anastomosis were performed to remove the mass. The pathological examination of the specimen revealed the mass to be composed of acini, ductuli and islands of Langerhans consistent with the histological appearance of pancreatic tissue (Figs. 2, 3). The postoperative course was uneventful.

Discussion

Only two to eight percent of intussusceptions is the result of a recognizable cause[2], which is usually encountered in patients over one year of age[3,4]. Although

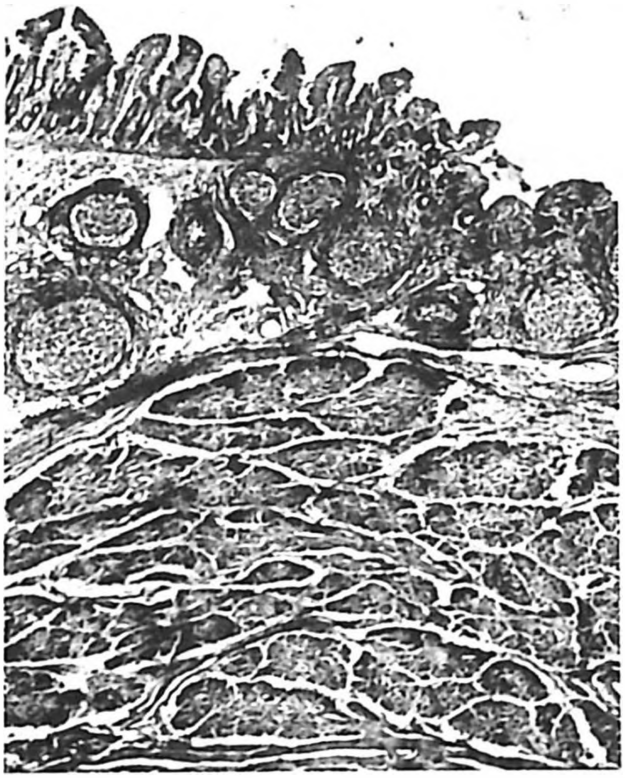

Fig. 2: Microscopic appearance of the intestinal mucosa with underlying lymphoid hyperplasia and ectopic pancreatic tissue (H.E. x 32).

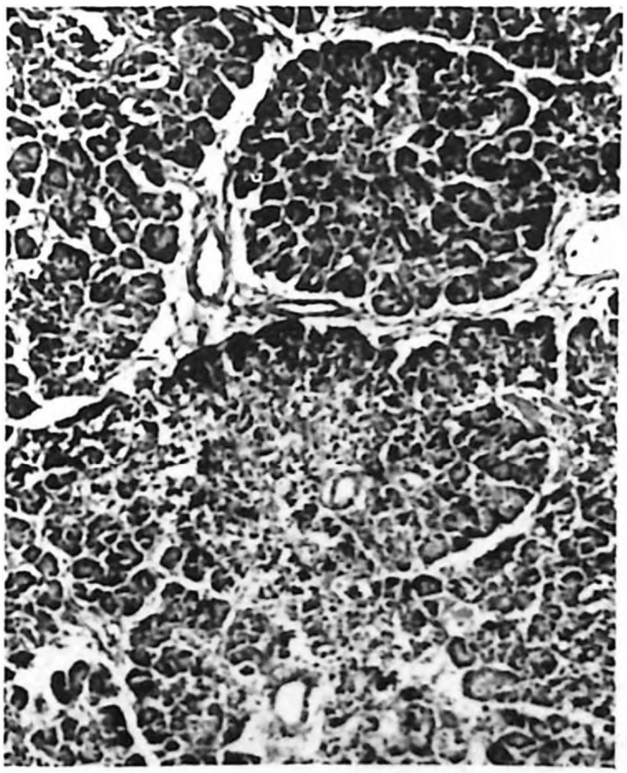

Fig. 3: Microscopic appearance of the nodule. Note the typical structure of the pancreas with acini, ductuli and islands of Langerhans (H.E. x 125).

reports of many large patient series have listed various recognizable causes, ectopic pancreatic tissue is rarely included[2,5].

In the case presented, the small-sized mass, which could hardly be palpated because of intestinal edema, urged us to perform a resection and anastomosis. Subsequent microscopic examination of the specimen revealed ectopic pancreatic tissue.

In the light of the findings regarding this patient, we conclude that in young infants who generally suffer from idiopathic intussusception, the proximal intestine should be examined carefully, even if manual reduction is easily accomplished.

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The Turkish Journal of Pediatrics 34: 259-263, 1992

PRIMARY LYMPHEDEMA PRECOX OF THE PENIS AND ITS SURGICAL TREATMENT: A CASE REPORT*

*Haluk Mıdıoğlu MD***, Ali Barutçu MD***, Sacit Karademir MD**
*Atay Atabey MD***

SUMMARY: Mıdıoğlu H, Barutçu A, Karademir S, Atabey A. (Department of Plastic Surgery, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Primary lymphedema precox of the penis and its surgical treatment: a case report. Turk J Pediatr 34: 259-263, 1992.

Primary penile lymphedema occurs infrequently and is seen in conjunction with a similar process in the scrotum. The accepted form of treatment is surgery since conservative medical treatment is of little value. Different surgical techniques have been described, but no single procedure has emerged as the ideal treatment. Radical excision of all lymphedematous tissues and reconstruction using local penile flaps yield excellent functional and cosmetic results.

We treated a 13-year-old boy with primary penile lymphedema precox using radical excision and reconstruction with local penile flaps. At follow-up two years later, functional and cosmetic results were satisfactory. *Key words: primary lymphedema, penis, surgical treatment.*

Lymphedema, characterized by an abnormal collection of interstitial lymph fluid can be defined as a swelling caused by improper drainage of lymph from the affected region[1-3].

Lymphedema is commonly divided into two main types: primary and secondary. The primary type is described as a collection of lymph in interstitial tissue from a functional overload on the lymphatic system. This overload is a result of a decrease in flow due to malformation of the lymphatics[1,4-6]. Lymphedema precox (Meige's disease), a subtype of primary lymphedema which develops at puberty, constitutes 80 percent of all primary cases of the disease.

Different methods of treating penile lymphedema have been described, but no single procedure has emerged as the ideal treatment.

We treated a patient with lymphedema precox of the penis by radical excision of all lymphedematous tissues and reconstruction using local penile flaps. This simple technique has some advantages, and functional and cosmetic results are satisfactory.

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Case Report

We present a 13-year-old patient who had been suffering from swelling of the penis for two years. Physical examination revealed that the penis was greatly enlarged, thickened and indurated. It measured 8 cm in circumference and 15 cm in length. The glans was not visible under an enlarged prepuce, but could be palpated within the mass (Fig. 1). The remainder of the physical examination was unremarkable and the results of extensive laboratory investigations were negative. There was no leg involvement and lymphangiographs demonstrated normal lymphatics and nodes. The genital lymphangiographs revealed what appeared to be lymphedema precox radiographically.

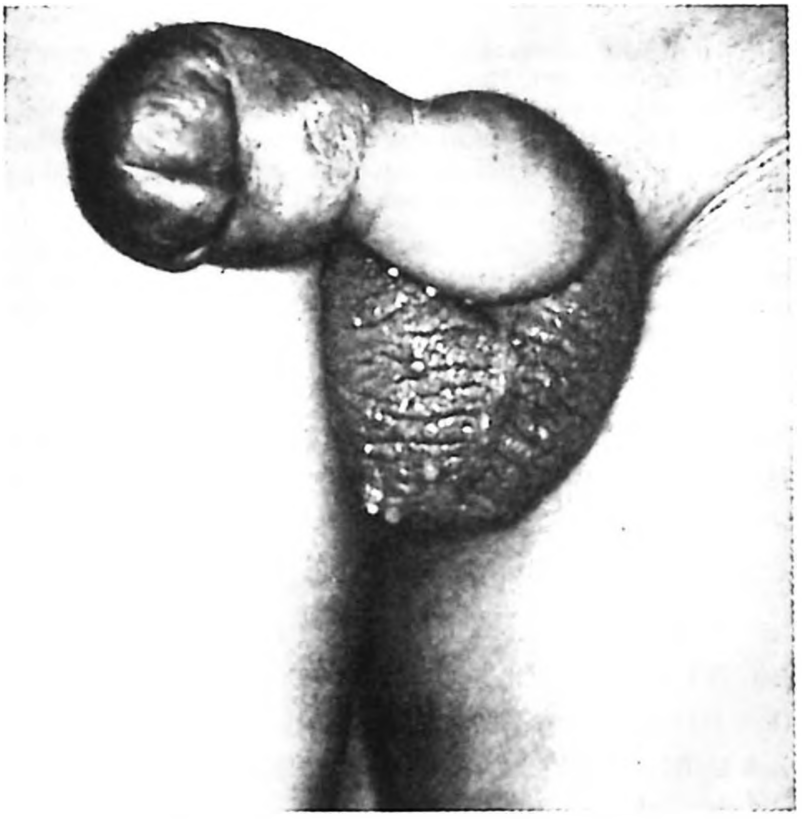

Fig. 1: Preoperative view of the case.

Under general anesthesia, a foley catheter was introduced into the urethra. A skin incision was made down to the fascia and a lazy-S incision on the dorsal surface from the root of the penis proximally to the balanopreputial groove. The urethra was dissected and all the diseased lymphedematous tissues and skin were excised and closed with local penile flaps after circumcision and thinning (Fig 2).

The postoperative course evidenced no complications or recurrence. In addition the functional and cosmetic results were satisfactory (Fig. 3).

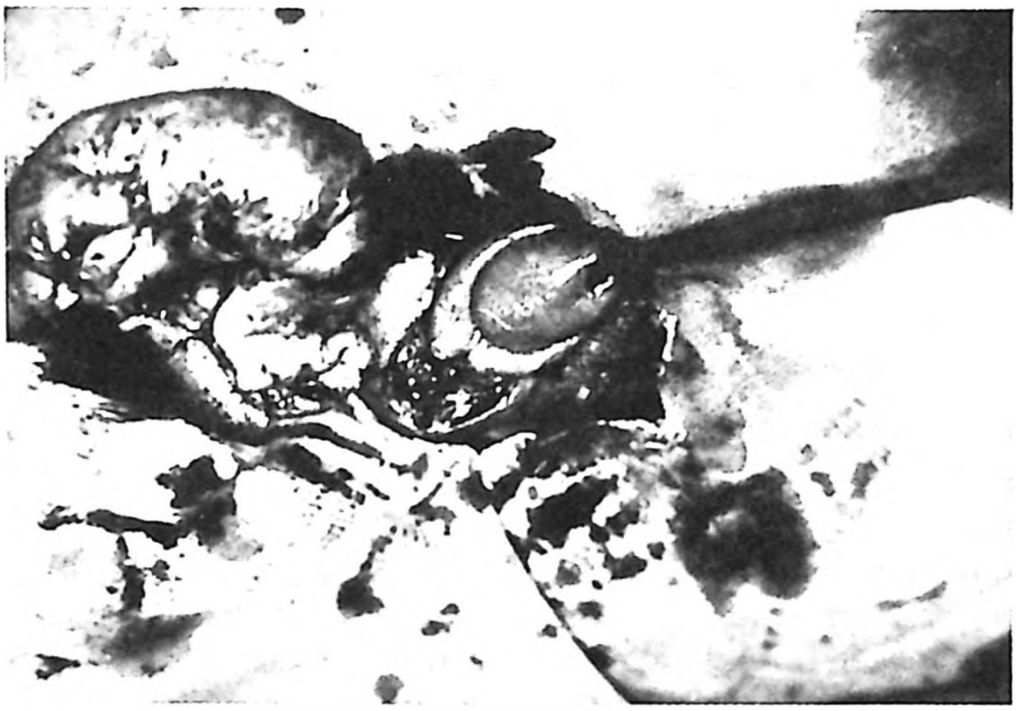

Fig. 2: After excision of lymphedematous tissues.

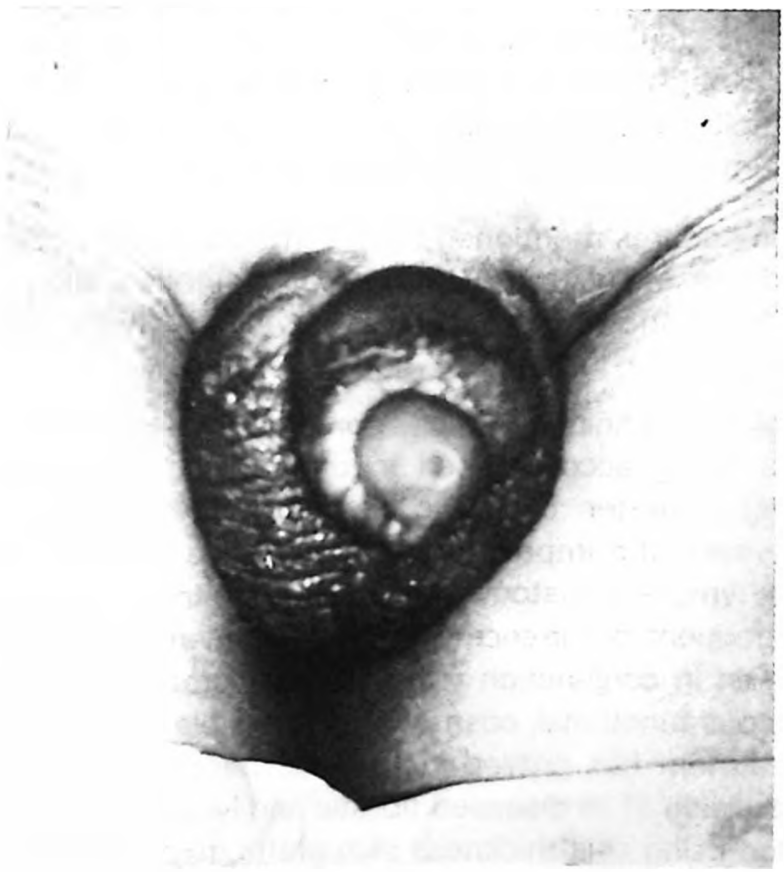

Fig. 3: Late postoperative view of the patient.

Discussion

Various methods of treating penile lymphedema have been described, but no single procedure has emerged as the ideal treatment[1,6-10].

There are two main principles involved in the surgical treatment of lymphedema. The first is physiological, while the second consists of excisional procedures[3,9,11].

Physiological procedures include lymphangioplasty, bridging methods, and lymphaticovenous shunts and flaps, where the aim is to drain the lymph from the diseased areas to areas of normal lymphatic drainage.

Excisional procedures comprise the following: 1) Removal of all diseased tissues and reconstruction using split thickness skin grafts or flaps. 2) staged subcutaneous excision beneath flaps[2,3,8,10].

The accepted form of treatment is surgery since conservative medical management is of little value. In 1823, Delpech[11] described a case of genital lymphedema successfully treated by excising all lymphedematous tissues and reconstructing the penile and scrotal coverage with local thigh flaps.

Multiple variations of Delpech's original technique have been described by Feins[8], and Tapper and associates[7], but they all share a common theme, excision of the superficial lymphatics, subcutaneous tissue and skin at the level of Buck's fascia on the penis. Reconstruction and coverage varies following this type of radical excision using split thickness skin grafts, flaps (local, rotational, scrotal, fasciocutaneous, myocutaneous, cutaneous) or their combinations[2,3,10,12].

All the surgical procedures mentioned have some associated complications such as hematoma, edema, infection, abscess formation, urethral injury, painful erection and recurrence, but in the radical excisional technique, these complications may occur infrequently[1,3,6-8].

This simple excisional technique also has some advantages such as removal of all diseased tissues being accomplished in one stage, a shorter hospitalization period, less costly, better cosmetic and functional results, and no graft contracture. However, the important disadvantage is that this technique is not applicable to all lymphedematous patients[1,6-8]. Primary lymphedema of the genitalia is an infrequent occurrence. Penile lymphedema is still more infrequent, and is usually seen in conjunction with a similar process in the scrotum. This condition has serious functional, cosmetic and possible malignant consequences. Conservative treatment has proved ineffective, necessitating surgical intervention. Complete excision of all diseased fibrotic and lymphedematous tissues, skin and reconstruction using split thickness skin grafts, flaps or their combinations is the operative procedure of choice for primary lymphedema of the genitalia. The results of this procedure are excellent if all involved tissues are removed.

Excisional procedures produce excellent results, and in our opinion, are to be preferred in most cases of genital lymphedema.

We treated a patient with lymphedema precox of the penis by radical excision of all lymphedematous tissues and reconstruction using local penile flaps. There has been no evidence of complications or recurrence postoperatively, and the functional and cosmetic results were satisfactory.

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The Turkish Journal of Pediatrics 34: 265-268, 1992

LETTERS TO THE EDITOR

WOLMAN DISEASE: SUGGESTIONS FOR EFFECTIVE TREATMENT

To the Editor:

Wolman disease is a relatively rare genetically-determined metabolic disease caused by lack of acid esterase-lipase. The disease is characterized by storage of neutral lipids (triglycerides and cholesterol esters) in the reticulo-endothelial system and other cells and diffuse subcapsular calcifications in the adrenals (producing a characteristic X-ray appearance). In its classical form, it results in death at around the age of 3-4 months. It is remarkable that the cells devoid of acid lipolytic activity (in their lysosomes) are capable of neutral lipolysis of the same substrates in another cellular compartment. In fact, Salvayre et al (*Eur J Biochem* 170: 453, 1987) have shown, in a tissue culture study, that only lipids of extracellular origin (those which are normally catabolized in lysosomes) remain undergradated in these cells.

My own autopsy observations (cf. Huber A, Klein D (eds). In *Neurogenetics and Neuroophthalmology,* 1981, pp. 325-332, and Pediatrics 83:1074, 1989) indicated that the organs most severely affected by lipid deposition were the small intestine and liver, which suggested that in the infants most of the damage was due to feeding with milk and other neutral fat-containing materials. The major symptomatology was also centered in the intestinal tract.

These data led me to suggest a dietary regime (as described below) for treating these infants. I believe that my suggestion does not pose any ethical dilemmas. The untreated disease causes early death, so that: (a) no control series is possible, (b) any treatment proposal prolonging life is fully justifiable.

Since the disease is rather rare, the possibility of obtaining a large enough sample in order to draw valid conclusions must depend on wide international and inter-institutional cooperation.

For over a year, a female infant afflicted with Wolman disease and treated by the dietary treatment described below survived far beyond the 3-4 month predictable life span. Although otherwise normal, in time my patient developed EFA (essential fatty acid) deficiency which is now treated by an established procedure, not against dietary treatment.

This treatment consists of strict cessation of breast feeding and avoidance of foods containing fats or oils (triglycerides and cholesterol esters). Formula feeding should be as much as possible free of neutral lipids, but should contain all vitamins.

In order to avoid dermatological complications and stunted growth due to EFA deficiency, about 10 μ of 1 / 100 sunflower oil should be rubbed lightly once a day on the skin of one arm of infants with a body weight below 5 kg, while 20 - 25 μ of the solution should be applied to infants with a body weight between 5 - 10 kg (or 3 μ / body weight). The site where the oil is applied should be alternated on consecutive days between arms, forearms, thighs and legs.

At present, it is not known whether percutaneous administration of EFA should continue uninterruptedly or if 3-4 weeks of treatment should be followed by an intermission of one or more weeks. It is proposed that this point should be tested in different cases.

In order to be able to learn about the best treatment modalities from a sizable group of patients, it is suggested that treatment of patients and its effects be reported to me every 3-6 months. A report in the name of all participants (after consultation, of course) will be published in due time. Alternately, pediatricians can combine their efforts and results and publish them independently. In addition, I would be grateful for any information which could be provided about cases of this disease, which information will be considered confidential.

Professor Emeritus Moshe Wolman

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THERAPEUTIC TRIAL IN WOLMAN DISEASE

To the Editor:

I am pleased to learn that Dr. Wolman is still very much active regarding the disease that bears his name[1].

I have so far examined six infants with Wolman's disease; the first patient at the Boston Children's Hospital in 1962 and five others at the Hacettepe Children's Hospital. All the patients had the same compaints, that is, protuberant abdomen, marked hepatosplenomegaly (spleen exceeding liver size), diarrhea and growth retardation commencing shortly after birth. The parents of the children diagnosed at the Hacettepe Children's Hospital were related and three families had a history of another child with similar complaints who died before reaching the age of six months. All these observations were compatible with the recessive inheritance pattern of the disease, in which deficiency of acid esterase-lipase is essential.

As a result of this enzyme deficiency, degradation of triglycerides and cholesterol esters can not take place. Therefore, storage of neutral lipids and cholesterol esters in the hepatocytes and in the adventitial cells of almost all organs occurs which causes the symptomatology[2,3]. Punctate calcifications of enlarged adrenal glands in infants with the above symptomatology are very helpful in diagnosis.

To my knowledge, all children with the infantile form of the disease have died in early infancy, and the replacement of acid esterase has not been tried in this disease, as has been accomplished in Gaucher disease[4,5]. Therefore, any suggestion in treating these children should be welcomed such as Dr. Wolman's, which had previously been proposed differently[6]. Even though the proposed treatment dose not seem to solve the problem, because with the exception of diarrhea most of the symptoms are already present at birth, it is a start.

Dr. Wolman's approach might be criticized from the ethical point of view that "the risk of treatment is not negligeable"[7]. But, I agree with the concept in the editorial published in The Lancet[8], that a new form of threatment should be tried when we are faced with a life-treatening disorder such as in Wolman disease. However, I believe our efforts should be mobilized towards prenatal diagnosis of this disease, since acid esterase can be determined in amniotic fluid[9] and in fibroblasts[6]. Bone marrow transplantation seems to provide hope in Gaucher disease[10,11]. Why not try it in Wolman disease ?

Professor Şinasi Özsoylu

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ANNOUNCEMENTS

MEETINGS

ÜRGÜP, 1 - 4 OCTOBER 1992

9th KIDNEY DISEASES AND TRANSPLANTATION CONGRESS

Inquiries to: Dean of Faculty of Medicine
Gazi University
ANKARA 06510, TURKEY

PARIS, 3 - 7 OCTOBER 1992

EUROPEAN TUTORIAL ON HAEMATOPATHOLOGY: LEUKAEMIA AND LYMPHOMAS

Inquiries to: Chairman
G. Flandrin
Centre Hayem, Hôpital Saint Louis
1 Avenue Claude Vellefaux
PARIS 75010, FRANCE

LONDON, 14 OCTOBER 1992

SUPPORT FOR FAMILIES OF WOMEN AND CHILDREN WITH HIV (SYMPOSIUM)

Inquiries to: Symposium Secretary
RPMS Institute of Obstetrics and Gynaecology
Queen Charlotte's and Chelsea Hospital
Goldhawk Road
LONDON W6 OXG, ENGLAND

VALENCIA, 22 - 24 OCTOBER 1992

CONGRESS '92 OF THE EUROPEAN SOCIETY FOR SOCIAL PEDIATRICS (ESSOP)
Theme: Health Promotion in Action

Inquiries to: Organizing Secretariat
Natalia Cerni
Prensa Congreso Pediatría Social
IVESP Juan de Garay, 21
VALENCIA 46017, SPAIN

ANTALYA, 25 - 29 OCTOBER 1992

FIRST INTERNATIONAL CONGRESS ON ADOLESCENCE DISORDERS AND NEW APPROACHES

Inquiries to: Congress Secretariat
Prof. Sevim Dinçer Cengiz, MD
Meşrutiyet Caddesi 3/12
ANKARA, TURKEY

LONDON, 13 NOVEMBER 1992

ADAPTATION TO EXTRAUTERINE LIFE (SYMPOSIUM)

Inquiries to: Symposium Secretary
RPMS Institute of Obstetrics and Gynaecology
Queen Charlotte's and Chelsea Hospital
Goldhawk Road
LONDON W6 OXG, ENGLAND

LONDON, 25 NOVEMBER 1992

THE DEATH OF A CHILD (SYMPOSIUM)

Inquiries to: Symposium Secretary
RPMS Institute of Obstetrics and Gynaecology
Queen Charlotte's and Chelsea Hospital
Goldhawk Road
LONDON W6 OXG, ENGLAND

LONDON, 30 NOVEMBER - 4 DECEMBER 1992

NEONATAL COURSE FOR SENIOR PAEDIATRICIANS

Inquiries to: Symposium Secretary
RPMS Institute of Obstetrics and Gynaecology
Queen Charlotte's and Chelsea Hospital
Goldhawk Road
LONDON W6 OXG, ENGLAND

SAMOS, 27 MAY - 1 JUNE 1993

SEVENTH INTERNATIONAL CLINICAL GENETICS SEMINAR ON DYSMORPHOLOGY AND THE GENETICS OF CARDIOVASCULAR DISORDERS

Inquiries to: Dr. C. Bartsocas
Dept. of Pediatrics
"P. & A. Kyriakou" Children's Hospital
ATHENS GR - 11527, GREECE

AN AEGEAN CRUISE ON THE ARCADIA, 2 - 6 SEPTEMBER 1993

19th ANNUAL MEETING OF THE INTERNATIONAL STUDY GROUP OF DIABETES IN CHILDREN AND ADOLESCENTS (ISGD)

Inquiries to: Dr. C. Bartsocas
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DULU, 7 - 10 SEPTEMBER 1993

XIV MEETING OF THE EUROPEAN SOCIETY FOR PEDIATRIC HEMATOLOGY AND IMMUNOLOGY (ESPHI'93)

Inquiries : Secretary General
Dr. Marjatta Lanning
Department of Pediatrics
University of Oulu
OULU SF - 90220, FINLAND

İZMİR, 24 - 27 OCTOBER 1993

XXI CONGRESS OF THE UNION OF MIDDLE EASTERN AND MEDITERRANEAN PEDIATRIC SOCIETIES (UMEMPS)

Inquiries to : Organizing Secretariat
Dr. Atilla Büyükgebiz
Dept. of Pediatrics
Dokuz Eylül University Hospital
P.O. Box 4
BALÇOVA, İZMİR 35330, TURKEY

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