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Owner: The Turkish and International Children's Center and the Hacettepe University Institute of Child Health

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MAURICE PATE AWARD FOR 1995 TO PROFESSOR İHSAN DOĞRAMACI

UNICEF'S Maurice Pate Award for 1995 is awarded to Professor İhsan Doğramacı for his outstanding contribution in the fields of public health and child survival and development. He is only the third individual to be a recipient of this honor. Professor Doğramacı's pioneering efforts, which have spanned more than 50 years, have benefitted millions of children in Turkey and throughout the world. This award is given in memory of Maurice Pate (1894 - 1965), the first Executive Director of UNICEF.

The UNICEF Maurice Pate Award has been given as follows:

Year	Institution	Region
Prior to 1980	Various institutions	Africa, Asia, the Americas and Caribbean, Middle East and North Africa, industrialized countries and global
1981	College of Health Sciences, Bahrain	Middle East and North Africa
1982	University of the West Indies (regional institution)	Americas and the Caribbean
1983	Pan-African Institute for Development	Africa
1984	International Centre for Diarrhoeal Disease Research, Bangladesh	Global
1985	National Institute of Public Cooperation and Child Development, India	South Central Asia
1986	The League of Red Cross and Red Crescent Societies	Global
1987	The Catholic Church of El Salvador	Americas and the Caribbean
1988	Pembinaan Kesejahteraan Keluarga (Family Welfare Movement), Indonesia	East Asia and Pakistan
1989	Mademe Suzanne Mubarak, Egypt	Middle East and North Africa
1990	Professor Olikoye Ransome-Kuti, Nigeria	West and Central Africa
1991	Child-to-Child Trust, United Kingdom	Industrialized countries
1992	Bangladesh Rural Advancement Committee, Bangladesh	South Asia
1993	The People and State of Ceara, Brazil	Americas and the Caribbean
1994	All-China Women's Federation, China	East Asia and the Pacific

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Mr. James P. Grant

JAMES P. GRANT (1922 – 1995)

Murat Yurdakök
Associate Editor

James P. Grant was born in Beijing on May 12, 1922. He received a Bachelor of Arts degree from the University of California at Berkeley in 1943 and a doctorate in Jurisprudence from Harvard University in 1951. He began his career in 1946 with the United Nations Relief and Rehabilitation Administration in China. His experience in China, and the pioneering work in international public health of his father, Mr. John B. Grant, remained lifelong influences. His overseas assignments included service as Regional Legal Counsel Resident in New Delhi for United States Aid Programmes for South East (1954-1956) and Director of the United States Aid Mission in Sri Lanka (1956-1958). He was Deputy Director of the International Co-operation Administration (USAID's predecessor) with responsibility for worldwide programming and planning (1959-1962) and Deputy Assistant Secretary of State for Near East and South Asian Affairs (1962-1964). He served as Director of the USAID program in Turkey with the rank of Minister (1964-1967) and as an Assistant Administrator with the United States Agency for International Development (USAID) (1967-1969). Mr. Grant came to UNICEF from the Overseas Development Council, which he helped found in 1969, serving as its President and Chief Executive Officer. He assumed office as the third Executive Director of UNICEF, with the rank of Under-Secretary General of the United Nations, on January 1, 1980. In 1980, soon after assuming office, Mr. Grant established the Annual State of the World's Children Report, which provides an assessment of conditions and prospects for children worldwide.

An important milestone in his career was the 1989 United Nations Convention on the Rights of the Child – a Magna Carta – for children. The Convention recognized, for the first time, the economic and social as well as political rights of all children and is today the most widely ratified human rights treaty ever.

The World Summit for Children in 1990, the first meeting of its kind where leaders met to address serious social issues, stands out as one of the main highlights of his career. The Summit set 27 child health and welfare goals that have been incorporated into the national plans of more than 100 countries.

Grant resigned on January 23rd this year because of ill health. During his 15 year tenure as head of UNICEF, Mr. Grant was acclaimed for his tireless

advocacy and his unflagging commitment, vision and dedication to improving the lives of the world's least advanced the children of the developing world. His unique strategy was to emphasize simple, low-cost and practical methods for child welfare - such as immunization, oral rehydration and breastfeeding - and to inspire a worldwide movement by mobilizing the political will necessary to bring these remedies to the millions of children and mothers threatened by preventable disease and malnutrition.

Although Mr. Grant was diagnosed with cancer in May, 1993, he continued to lead UNICEF with his characteristic energy and commitment until he resigned. Over the last year, despite his illness, he met with more than 40 world leaders to seek their active support for the cause of children. Mr. Grant died of cancer on January 28, 1995, at Northern Westchester Hospital Center, Mount Kisco, New York, at the age of 72.

Mr. Grant served on the Boards of Directors of a number of organizations involved with development issues, including the Commission on Participation in Development of the World Council of Churches, the International Voluntary Service, the Pan American Development Foundation, the Institute of Current World Affairs, Save the Children and the Foreign Policy Association. He was President of the Society for International Development from 1979 to 1983.

In 1994, Mr. Grant received the Presidential Medal of Freedom the highest honor awarded by the President of the United States. He also received the "Sri Lanka Ratna" (The Government of Sri Lanka's national honor), the National Order of Merit in Education from the President of Brazil (1993), the "Hilâl-i Pakistan" from the President of Pakistan (1993), the Order of the "Aguila Azteca" from the Government of Mexico (1993), the Ecuador National Award of Merit "Illustrious Cruz of the Order" Daniel A. Carrion (Peru, 1991), the Community Prize by the Association of Italian Municipalities (1991), the First Class of the Order of the Sacred Treasure from the Japanese Government (1991), and the Commander of the National Order of Mali (1989).

Among numerous other awards he received Distinguished Public Service, USAID (1961), Rockefeller Public Service (1980), the Presidential Citation of the American Public Health Association (1989), E.H. Christopherson Lectureship Award on International Child Health from the American Academy of Pediatrics (1990), the Diplomatic World Bulletin's 1990 Award of Distinction, the Leonardo o'Oro Award, the Tolstoy Award and the United Nations Human Rights Prize (1993).

He received honorary degrees from the University of Notre Dame, Hacettepe University (1980), Maryville College (1981), Tufts and Denison Universities (1983), and the University of Maryland (1986). He was also awarded an Honorary Professorship in 1983 from the Capital Medical College of China.

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The Turkish Journal of Pediatrics 1995; 37: 299-304

EFFECTS OF SECONDARY HYPERPARATHYROIDISM ON CARDIAC FUNCTION IN PEDIATRIC PATIENTS ON HEMODIALYSIS*

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SUMMARY: Beşbaş N, Saatçi Ü, Özkutlu S, Bakkaloğlu A, Söylemezoğlu O, Özen S. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Effects of secondary hyperparathyroidism on cardiac function in pediatric patients on hemodialysis. Turk J Pediatr 1995; 37: 299-304.

Cardiovascular complications are an important cause of morbidity and mortality in chronic hemodialysis patients. In order to examine the effect of parathyroid hormone (PTH) and vitamin D on left ventricular functions, 11 patients between the ages of 13 and 18 years on regular hemodialysis were investigated using M-mode echocardiography and systolic time intervals. The ratio of the pre-ejection period to the left ventricular ejection time was found to be 0.38 ± 0.02 (range 0.25 ± 0.50) and was elevated above normal in five of the 11 patients examined. Four of these patients had hypertension and one had severe anemia. The left ventricular ejection fraction was 55 ± 2.54% and fractional fiber shortening was 31.55 ± 2.26%, both of which were within normal limits for age. Although the velocity of circumferential fiber shortening was within normal limits in the majority of cases, the mean value was 1.437 ± 0.11 circ/s, which is above normal for this age period. PTH levels were between one and 4.70 ng/ml. All of the hemodialysis patients had been receiving 1α hydroxy-cholecalciferol and had normal calcium levels. Although they had high PTH levels, most of these patients displayed normal myocardial contractility. No significant correlation was obtained between increment in PTH levels and myocardial function indices. These results imply that PTH is not the only factor affecting myocardial functions. Since all of these patients have received vitamin D therapy for long periods, we suggest that vitamin D may have prevented the deleterious effect of PTH on myocardial function. *Key words: hemodialysis, cardiac function, hyperparathyroidism, children.*

Cardiovascular complications are the leading cause of mortality in patients on maintenance hemodialysis[1]. Some experimental studies have shown that uremic toxins are capable of depressing myocardial function[2]. In addition, parathyroid hormone (PTH) may be a potent uremic toxin which in experimental conditions has several adverse effects on myocardial cell function and metabolism[3-5]. Controversy exists concerning the impact of secondary hyperparathyroidism

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(SHPT) in end-stage renal disease (ESRD) on the development of left ventricular (LV) hypertrophy and systolic dysfunctions[6,7]. It is not clear whether PTH has a direct effect or the changes are due to the lack of 1.25-dihydroxycholecalciferol (HCC)[6]. Administration of vitamin D_3 has been proven to improve LV function in hemodialysis patients, and amelioration of echocardiographic disturbances in chronic renal failure patients has been reported after 1α-hydroxycholecalciferol [1α (OH) D_3] treatment[8].

In this study we evaluated LV function in patients on maintenance hemodialysis by M-mode echocardiography, and assessed the effect of PTH on these function.

Material and Methods

Eleven uremic patients (eight girls and three boys) on maintenance hemodialysis were included in the study. The age range was 13-18 years. The patients had been on dialysis for four to 40 months (mean 19 months). All patients had arteriovenous fistulas, and the duration of dialysis was 14-18 weeks. None received digitalis and none had any signs of heart failure. Four of 11 had severe hypertension. They were all receiving diets low in protein and phosphate binders along with 0.5-1 μg/day 1α (OH) D_3.

Serum creatinine, BUN, sodium, potassium, calcium, phosphorus, uric acid, hemoglobin, PTH with X-ray and ECG were obtained before dialysis. Echocardiographic examinations were performed with a Smith-Kline Echoline 20 diagnostic ultrasonoscope combined with an Echoline 21 recorder. A 2.75-MHz transducer was used. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness (IVST), left ventricular ejection time (LVET), left ventricular pre-ejection period (LVEP), left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV), cardiac output and stroke volume were assessed. These parameters were the mean of at least three strokes. Percentiles were calculated according to the standard values for LVEDD determined by Gutgesell and Paquest[9].

Left ventricular ejection fraction (LVEF) for the LV end-systolic (ES) and end-diastolic (ED) minor diameters were obtained by the following equation:

$$EF = \frac{ES}{ED}$$

The normal rage for EF was 53-77 percent[10].

Fractional shortening (FS) was calculated by the formula:

$$\frac{LVEDD\text{-}LVESD}{LVEDD} \times 100$$

The normal range was 28-44 percent[10].

The mean velocity of circumferential fiber shortening (Vcf) was obtained by the following formula:

$$(Vcf) = \frac{LVEDD/\,LVES\,/\,IVEDD}{EF}$$

The normal range was 1.34 ± 0.03 circ/s.

The mean value for the ratio of pre-ejection period (PEP) to LVET (PEP/LVET) was 0.35 (range 0.30-0.39)[10].

Results

The mean hemoglobin value in our patients was 6.25 ± 0.38 with a range of 4.20 9.0 g/dl. Serum creatinine and BUN levels before dialysis were 7.8 ± 0.5 mg/dl (5.2 ± 9.8 mg/dl) and 75 ± 5.5 mg/dl (54 ± 120 mg/dl), respectively. The mean values for electrolytes were as follows: sodium 133 ± 1.60 mEq/L, potassium 4.8 ± 0.28 mEq/L, calcium 8.9 ± 0.2 mg/dl and phosphorus 4.5 ± 0.25 mg/dl. The C-terminal PTH levels in our cases were between 1 and 4.7 ng/ml which was well above the normal range.

X-ray and ECG findings of the patients were evaluated before dialysis. Four patients with abnormal ECG findings were noted to have hypertension and one had severe anemia.

The LV myocardial contractility indices and volume functions were assessed by M-mode echocardiography before hemodialysis. The cardiac investigations in our patients are summarized in Table I. The mean PEP/LVET ratio, which is a good index of LV function in our patients, was 0.38 ± 0.02 with a range of 0.25 ± 0.50. In the four patients with intractable hypertension and in one patient with severe anemia, this ratio was above normal. The mean LVET was 55 ± 2.54 percent (range 41.50-71.80%). The mean FS was 31.55 ± 2.26% and this was within normal limits. Vcf was 1.47 ± 0.11 circ/s (Table II), which was above the normal range for this age group (1.34 ± 0.03 circ/s).

When relations were sought between the PEP/LVET ratio, EF, FS and Vcf (which are the indices of LV contractibility functions) and Hb, serum creatinine, BUN, calcium and PTH levels, no significant correlations were found. There was a linear relationship between the stroke volume (mean 89.95 ± 12.57 ml) and cardiac output (10.0 ± 1.4 ml/min) and the serum PTH levels. A significant correlation was also found between Hb levels and stroke volumes.

Table I: Results of Cardiac Investigations in Dialysis Patients

	$\bar{X} \pm SD$	Range
LVEDD, mm	53.82 ± 2.99	37-71
LVESD, mm	31.54 ± 2.28	26-45
IVST, mm	9.54 ± 0.58	8-13
PEP ms	218.18 ± 7.84	180-260
LVESV, ml	74.53 ± 9.18	60-112
LVEDV ml	164.83 ± 20.57	66.20-308.20
Stroke volume, ml	89.95 ± 12.57	24.90-162.40
Cardiac output, 1/min	10 ± 1.4	6-14
Cardiothoracic ratio	1.18 ± 0.04	0.95-1.43

Table II: LV Function Results of Hemodialysis Patients

	$\bar{X} \pm SD$	Range	Normal Values
EF, %	55 ± 2.54	41.50-71.80	53-77
FS, %	31.55 ± 2.26	26-45	28-44
Vcf, circ/s	1.47 ± 0.11	1.09 ± 2.15	1.34-0.03
PEP/LET	0.38 ± 0.02	0.25-0.50	0.30-0.39

Discussion

Controversy exists concerning the impact of SHPT in ESRD on development of left ventricular hypertrophy and systolic dysfunction. Drüeke et al.[7] reported that myocardial contractility was reduced in dialysis patients with SHPT, which improved after parathyroidectomy. This idea has been supported by the experimental myocardial changes induced by PTH[4,5]. Gater et al.[11] assessed the LV function in chronic renal failure patients and showed that excess PTH had only a minor effect on myocardial performance and that there was no improvement even long after parathyroidectomy. Hüting et al.[12] did not show any influence of the amount of SHPT on LV function and suggested that LV ejection phase indices were not related to PTH activities in ESRD patients.

Although the C-terminal PTH levels were above normal in our study group, EF and FS values were within normal limits. The PEP/LVET ratio was normal in our cases except for the five with severe hypertension and anemia. The abnormal X-ray and ECG findings in these five patients were explained by their hypertension and anemia. Blanchard et al.[13] reported that although there were slight increases, the PEP/LVET ratio was generally within normal limits. In our patients without cardiac failure, the mean PEP/LVET was 0.38 ± 0.02, which is at the upper limit of normal. This is in accordance with the literature. In our study the mean Vcf before hemodialysis was 1.47 ± 0.11 circ/s and this was above normal for age.

It has been previously reported that maintenance hemodialysis increases Vcf significantly[14, 15]. No significant correlation was found between the PTH levels and the parameters reflecting left ventricular function ($p > 0.05$).

In another study[16], the effects of PTH and vitamin D on LV function in uremic patients on maintenance hemodialysis were examined. When the patients were given 1 µg/day 1α (OH) D_3 for six weeks, the plasma PTH levels decreased along with an increase in FS from 34.6 to 37.6 percent and an increase in Vcf from 1.25 to 1.32 circ/s. In the same study in the parathyroidectomized patients, the FS and Vcf increased from 34.9 to 36.3 percent and from 1.22 to 1.38 circ/s, respectively. The authors did not conclude whether myocardial dysfunction was due to PTH increment or the lack of 1.25 $(OH)_2$ D_3[16]. The effects of vitamin D may be related to modifications in serum Ca^{2+} levels. More direct effects on the myocardium can be deduced from experimental vitamin D3 depletion studies; this induces cardiac hypertrophy related to interstitial edema, increased collagen and decreased myofibrillar area.

All of our cases received 1α (OH) D_3 at a dose of 0.5-1 µg/day, and all had normal serum calcium levels. Since LV contractibility functions were normal in spite of increased serum PTH levels and since no significant correlation was found between the high levels of PTH and other parameters, we suggest that PTH alone is not responsible for myocardial dysfunction. The active vitamin D therapy might have prevented the myocardial dysfunction by a direct effect. The increase in cardiac output, which is due to a variety of causes in uremia, decreases after parathyroidectomy and this is related to heart rate rather than stroke volume[11].

In this study, the positive correlation between serum PTH and cardiac output and stroke volume, which are the indices of LV volume functions, imply that PTH affects these parameters. It is known that anemia is an important contributor to cardiac output and stroke volume. Anemia is inevitable in ESRD. PTH also contributes to anemia, but we were unable to demonstrate a statistical relationship between PTH level and anemia. A correlation was documented, however, between the Hb level and stroke volume.

These results imply that PTH is not the only factor affecting myocardial functions. Since all of these patients had received 1α (OH) D_3 therapy for long periods, we suggest that vitamin D may have prevented the abnormalities in myocardial function.

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The Turkish Journal of Pediatrics 1995; 37: 305-313

THE EFFECTS OF CONTRAST MEDIA ON RENAL FUNCTION IN CHILDREN: COMPARISON OF IONIC AND NON-IONIC AGENTS*

*Necla Buyan MD***, *Muhammed Arab MD****, *Enver Hasanoğlu MD*****
*Nahide Gökçora MD******, *Sevim Ercan PhD*******

SUMMARY: Buyan N, Arab M, Hasanoğlu E, Gökçora N, Ercan S. (Nephrology Unit, Department of Pediatrics, and Departments of Nuclear Medicine and Pharmacology, Gazi University Faculty of Medicine, Ankara, Turkey). The effects of contrast media on renal function in children. Comparison of ionic and non-ionic agents. Turk J Pediatr 1995; 37: 305-313.

Nephrotoxicity is a common side effect of intravascular contrast media (CM). Although nephrotoxicity of ionic CM has been widely demonstrated, recent studies suggest that newer and more costly non-ionic agents are no less nephrotoxic.

We studied the hemodynamic, hematologic and nephrotoxic effects of CM prospectively in 38 patients (ages six months-16 years) with or without risk factors predisposing to nephropathy and compared ionic and non-ionic CM. We performed intravenous urography (IU) with an ionic CM, sodium meglumine diatrizoate (n = 18) and a non-ionic CM, iohexol (n = 20). The patients were divided into three groups according to glomerular filtration rate (GFR) [GFR ≤ 50 (n = 9), 50-80 (n = 13), ≥ 80 ml/min/1.73m^2 (n = 26)]. Eleven patients had risk factors for nephropathy. Blood pressure, heart rate, ECG, urine and blood samples were obtained 24 hours and one hour before as well as one, 24, and 48 hours after CM infusion. Although a significant increase was found in urine specific gravity, protein/creatinine ratios and serum Na and creatinine levels, the increased levels were within normal limits. We observed a significant reduction in Hb and Htc and urinary prostaglandin E_1 levels. Many of the changes observed in the urine and serum values after the use of CM were minor, insignificant and transient, later returning to their initial values. The GFR levels, the presence of risk factors and the use of ionic vs. non-ionic CM had no effect on the results. The elevated urinary basal beta-2-microglobulin levels further increased after CM infusion in patients with low GFRs.

It was concluded that non-ionic CM was not superior to ionic CM in patients with GFRs greater than 50 ml/min regardless of predisposing risk factors. One of the non-invasive radiological methods is advised instead of IU in patients with low GFRs.
Key words: contrast nephropathy, ionic contrast media, non-ionic contrast media, beta-2-microglobulin, intravenous urography.

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This study was supported by the Research Foundation of Gazi University.

Contrast nephropathy (CN) is defined as acute toxic nephropathy due to radiographic contrast media (CM)[1].

Recently, it has been shown that CN is not common in patients with normal renal function, but occurs more frequently in patients with renal impairment (RI), especially due to diabetic nephropathy. Although nephrotoxicity of ionic, high-osmolar CM has been widely demonstrated, recent studies suggest that newer and more costly non-ionic, low-osmolar agents are no less nephrotoxic than standard preparations, especially in high-risk patients with RI and/or diabetic nephropathy[2-6].

The aim of this prospective study was to evaluate and compare the hemodynamic, hematologic and nephrotoxic effects of an ionic conventional CM with a non-ionic low-osmolar CM in patients with or without risk factors predisposing to nephropathy, since low-osmolar CM is 10 to 20 times more expensive than high-osmolar CM[1,7].

Material and Methods

Thirty-eight children between the ages of six months and 16 years (mean 7.6 years) who underwent intravenous urography (IU) between August 1991 and November 1992 were studied. They were divided into three groups according to creatinine clearance [Group A: glomerular filtration rate (GFR) $\leq$ 50 (n = 9), Group B: GFR = 50-80 (n = 13), Group C: GFR $\geq$ 80 ml/min/1.73 m^2 (n = 16)] and each group was stratified into either low-risk (n = 27) or high risk (n = 11) groups based on the presence of risk factors reported previously for predisposition to nephropathy. GFR was determined from the creatinine clearance using the formula: creatinine clearance (ml/min per 1.73 m^2) = k x height (cm)/plasma creatinine (mg/dl). "k" was calculated according to the degree of malnutrition in our patients. Patients were placed in the high-risk group if they had azotemia (Cr > 2 mg/dl), hypertension, DIDMOAD syndrome, solitary kidney with RI, or nephrotic syndrome. Eighteen patients were examined with an ionic CM, sodium meglumine diatrizoate (Urografin, 76% Shering AG, Berlin, Germany) while the remaining 20 received a non-ionic CM, iohexol (Omnipaque, Nycomed, Oslo, Norway) (Table I).Each patient received CM at a dose of 1 ml/kg body weight intravenously (i.v) within 10 minutes through a catheter inserted into an antecubital vein. Food was restricted three to 12 hours prior to the CM infusion depending on the patient's age. Patients were given i.v. fluids before IU as a clinical precaution to minimize nephrotoxicity.

IU was necessary in the diagnostic evaluation of all patients for symptoms possibly related to urologic abnormality.

Patients were excluded from the study if they had a history of: 1) adverse reaction to any medicine, 2) coagulopathy, 3) plasma creatinine higher than 3 mg/dl, 4) electrolyte or fluid imbalance, 5) previous contrast agent administration, 6) nephrotoxic antibiotic therapy.

Table I: Primary Diseases of the Patients

GFR ml/min per 1.73 m²			Grokup A (n = 9) ≤ 50	Group B (n = 13) 50-80	Group C (n = 16) ≥ 80
High-Risk Group (n = 11)	Na-meglumine diatrizoate	n = 7	Group = 1 – VUR – Hydronephrosis – Hydronephrosis	Group = 2 – DIDMOAD Syn.	Group = 3 – Hypertension – Hypertension – Hypertension
	Iohexol	n = 4	Group = 4 – Renal agenesis (UL) – Nephrolithiasis	Group = 5 – Nephrotic Syn. – Renal agenesis (UL)	Group = 6
Low-Risk Group (n = 27)	Na-meglumine diatrizoate	n = 11	Group = 7 – Hydronephrosis – Nephrocalcinosis	Group = 8 – Recurrent UTI – Hydronephrosis – Urolithiasis renal agenesis (UL) – Urolithiasis	Group = 9 – Hematuria – Hematuria – Rhabdomyosarcoma – Hematuria – Recurrent UTI
	Iohexol	n = 16	Group = 10 – Urolithiasis – Multiple congenital abnormalities	Group = 11 – Multiple congenital abnormalities – Neuroblastoma – Recurrent (UTI) – Urolithiasis – Urolithiasis – Hematuria	Group = 12 – Horseshoe kidney – Urolithiasis – Recurrent UTI – Urolithiasis – Recurrent UTI – VUR – Hematuria – Hematuria

VUR = Vesico ureteral reflux
UTI = Urinary tract infection
UL = Unilateral

Blood and urine samples were obtained 24 hours and one hour before, as well as one, 24 and 48 hours after CM infusion (Fig. 1). Blood pressure, heart rate and ECG patterns were recorded at set times established according to the pharmacokinetic characteristics of ionic and non-ionic CM (Table II).

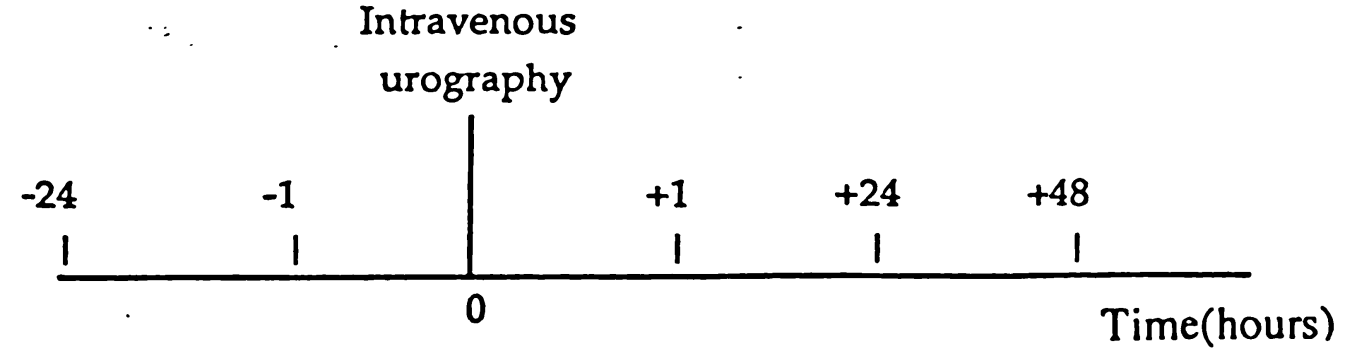

Fig. 1: Time points when plasma and urine samples were obtained.

Table II: Properties of the Selected Contrast Media

Contrast Media	Max.Urinary Excretion Time	Iodine (mg/ml)	Osmolality (mOsm/kg)	Viscosity 20 °C	Viscosity 37 °C	Na+ (mEq/L)	Disodium EDTA
Sodium meglumine	10-20 min	370	2100	13.8	8.4	190	0.4
Diatrizoate Iohexol	1 h.	350	780	23.3	10.6	Negligible	0.1

Urine specimens were analyzed for levels of creatinine, sodium (Na), potassium (K), chloride (Cl), uric acid (ua), protein, beta-2-microglobulin β_2 (M) and prostaglandin E_1 (PGE_1). Blood samples were analyzed for hemoglobin (Hb), hematocrit (Htc), blood urea nitrogen (BUN), ua, creatinine, Na, K and Cl levels.

Proteinuria, hematuria, glucosuria and urine pH were measured with a urine dipstick, urine osmolality was measured with an osmometer and urine specific gravity was measured with refractometer. All urine specimens were analyzed microscopically by a physican. Fractionated excretion of sodium (FENa), fractionated excretion of potassium (FEK), fractionated excretion of chloride (FECl), fractionated excretion of uric acid (FEua) and ratios of urinary protein to creatinine were calculated with standard formulas. Urinary β_2 M samples were alkalinized immediately after voiding with sodium hydroxide to prevent decomposition and were analyzed with an RIA kit (IEMA KIT DSL-6100, Webster, TX). Urine PGE_1 levels was measured by bioassay.

In all cases, the parents were informed and consent obtained.

Data analysis: Data were presented as mean plus or minus standard deviation. The Wilcoxon test on medians was used for statistical analysis, and intergroup significance was calculated by analysis of variance and Student's t-test.

Results

Data obtained at different times and at the same time in different groups were compared. Statistical analysis was performed in only four low-risk groups (Group = 8, 9, 11, 12) because of insufficient numbers of patients in other groups, especially those with low GFRs and high risk factors because of ethical reasons. All the results in the remaining groups were evaluated, but statistical analysis was not performed.

We observed no adverse reaction or side effect on renal function requiring treatment after the use of ionic or non-ionic CM in any group. Many of the changes observed in urine or serum values after the use of CM were minor, insignificant and transient.

No significant change in blood pressure, heart rate, ECG pattern, urinalysis, FENa levels or urine osmolality values was observed at any point in any group, regardless of risk factors or the use of ionic versus non-ionic CM. Although a

statistically significant increase in serum Na and creatinine levels was found one hour after CM infusion (in groups 8 and 9, and groups 9 and 12, respectively), the increased levels were within normal limits (Fig. 2).

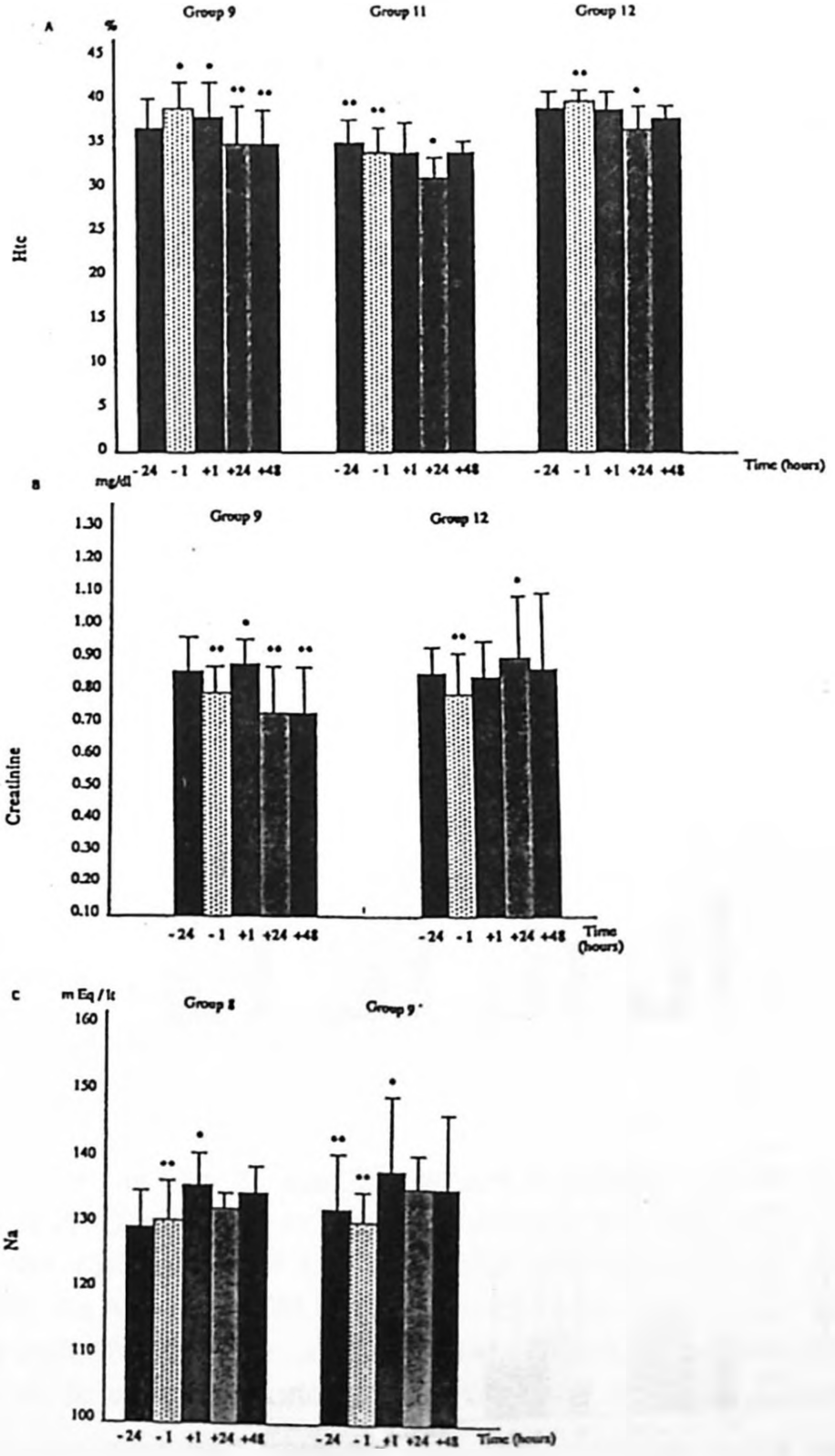

Fig. 2: Changes in hematocrit (A), serum creatinine (B) and serum sodium levels (C) before and after contrast media infusion in different groups. Only the groups with significant differences were included. * < 0.05 vs. ** for each group. Values given as mean ± SD.

We observed a significant reduction in Hb and Htc levels at +24 and +48 hours in group 9 and at +24 hours in groups 11 and 12 ($p < 0.05$) (Fig. 2).

Urine specific gravity increased one hour after CM infusion in all groups and was statistically significant in groups 8, 9, 11 and 12 ($p < 0.05$) (Fig. 3). A decrease in urinary PGE_1 levels was found at different times after CM infusion in all groups ($p < 0.05$ in groups 8, 9, 11 and 12) (Fig. 3) A significant increase was observed in the urine protein / creatinine ratio at +24 hours in group 9 and at + one hour in group 12 ($p < 0.05$) (Fig. 3).

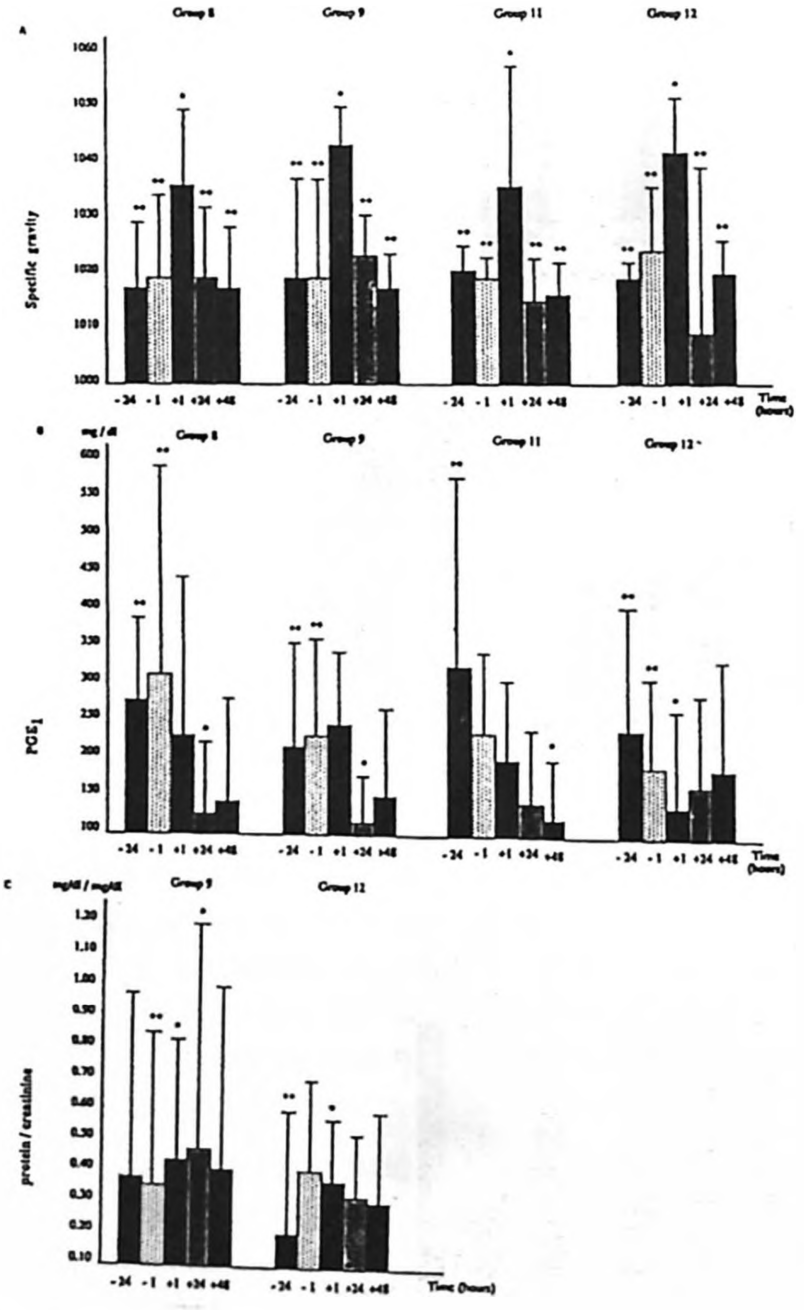

Fig. 3: Changes in urine specific gravity (A), urinary PGE_1 levels (B) and urine protein / creatinine ratios (C) before and after contrast media infusion in different groups. Only the groups with significant differences were included. * < 0.05 vs. ** for each group. Values given as mean ± SD.

We observed insignificant and transient increases in BUN, serum K, Cl, uric acid, FEK, FECl and FEua values, and insignificant decreases in creatinine clearance at some points in different groups after CM infusion, regardless of risk factors and the use of ionic versus non-ionic CM ($p > 0.05$).

Urinary basal β_2 M values were observed at higher than normal levels and fruther increased after CM infusion in patients with low GFRs (Table III). We found no significant difference between the values obtained at the same time in different groups ($p > 0.05$) (Group 8, 9, 11 and 12).

Table III: Urinary β_2 Microglobulin Levels in Patients with Low GFRs

	β_2 Microglobulin (mg/l)				
Time Before or After CM (h)	-24	-1	+1	+24	+48
GFR ≤ 50 ml/min HO, HR (n = 3) (Group 1)	7.92 ± 14.74	8.18 ± 10.86	16.58 ± 9.24	16.49 ± 9.07	7.66 ± 10.13
GFR ≤ 50 ml/min HO, LR (n = 2) (Group 7)	0.78 ± 0.05	2.82 ± 0.6	5.18 ± 5.83	5.72 ± 9.1	2.0 ± 0
GFR ≤ 50 ml/min LO, HR (n = 2) (Group 4)	2.29 ± 2.96	9.61 ± 12.88	13.94 ± 18.82	2.08 ± 2.42	2.6 ± 0.3
GFR ≤ 50 ml/min LO, LR (n = 2) (Group 10)	0.65 ± 0.26	0.37 ± 0.22	3.4 ± 5.11	2.94 ± 3.93	1.62 ± 1.03

HR : High risk.
LR : Low risk.
LO : Low osmolality.
HO : High osmolality.
CM : Contrast media.

Discussion

The incidence of CN after IU was 55 percent in patients with RI (serum creatinine > 2 mg/dl) and 15 percent in patients without existing renal disease. In the literature, the incidence of CN after the use of ionic or non-ionic CM is controversial. As non-ionic CM is 10-20 times more expensive than conventional agents, the cost-effectiveness of CM should be evaluated carefully before making a decision as to which material should be used in which patient[1, 7-9].

In our study we observed transient and mild changes in the majority of urine and serum values after either ionic or non-ionic CM infusion in both the low-risk and high-risk groups.

It is known that an expansion in plasma volume occurs after CM infusion. In our study the reduction observed in Hb and Htc levels may be related to the osmotic effect of CM on plasma volume resulting in a rapid increase[10, 11].

The increase in the urine specific gravity observed in all groups one hour after CM infusion is secondary to the excretion of CM in high concentration in the urine[11].

Injection of CM into the renal artery was shown to cause a biphasic change in renal blood flow (RBF), and a transient vasodilation followed by a more prolonged vasoconstriction phase in experimental studies. It was concluded that the decrease observed in the urinary PGE_1 levels after either ionic or non-ionic CM infusion in all groups may be related to the reduced PGE_1 synthesis in the renal medulla secondary to the decrease in RBF. The role of prostaglandin (PG) inhibitors in clinical CN is unknown. It is recommended that all drugs known to inhibit PG synthesis should be discontinued prior to the administration of CM[12-15].

A significant increase observed in serum NA levels one hour after ionic CM infusion was found to be related to the Na content (190 mEq/L) of Na-meglumine diatrizoate. The increased Na levels were within normal limits and returned to the initial values.

In the literature, CN was defined as an elevation in the serum creatinine level of 30 percent or more over the baseline value[8]. Although we observed a significant increase in the serum creatinine levels in two groups, the increased levels were not greater than 20 percent more than basal values in any patient.

Additionally, urinary excretion of β_2 M is a widely used test of renal proximal tubular function. In the literature, there were some reports that accepted β_2 as a reliable marker for diagnosis of CN. It was concluded that the patients with RI were more sensitive to CN, since the elevated urinary basal β_2 M levels had further increased following either ionic or non-ionic CM infusion in patients with low GFRs in our study[10, 16-19].

Finally, our study showed that expensive and non-ionic CM was not superior to ionic CM in patients with GFRs greater than 50 ml/min./1.73 m^2, regardless of predisposing risk factors, since iv administration of both CM caused similar, mild and transient hematologic and nephrotoxic effects in these patients. One of the non-invasive diagnostic studies is advised instead of IU in patients with low GFRs, because these patients are more sensitive to CN.

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The Turkish Journal of Pediatrics 1995; 37: 315-321

COMPARATIVE EFFICACY OF RICE – ORS AND GLUCOSE – ORS IN MODERATELY DEHYDRATED TURKISH CHILDREN WITH DIARRHEA*

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SUMMARY: Yurdakök K, Yalçın S. (Department of Social Pediatrics, Hacettepe University Institute of Child Health, Ankara, Turkey). Comparative efficacy of rice-ORS and glucose-ORS in moderately dehydrated Turkish children with diarrhea. Turk J Pediatr 1995; 37: 315-321.

The efficacy of precooked rice-based (50 g/L) oral rehydration solution (R-ORS) was compared with standard glucose-based ORS (G-ORS) in a randomized controlled trial in 79 children who were moderately dehydrated due to diarrhea. ORS intake rate and weight gain after rehydration were found to be similar in the two treatment groups ($p > 0.05$). The time necessary for rehydration was significantly lower in the R-ORS-treated group than in the G-ORS-treated group (5.2 ± 2.2 and 7.5 ± 3.4 hours, respectively, $p < 0.05$). Although the mean serum bicarbonate levels were significantly increased in both treatment groups at the end of the treatment, a significant increase in the mean pH value was observed in only the R-ORS treated group ($p < 0.05$). *Key words: diarrhea, treatment, rice-based oral rehydration solution.*

The WHO/UNICEF-recommended glucose-based ORS (G-ORS) has greatly reduced the case-fatality rate for acute diarrhea among children in developing countries. Despite its wide availability, global G-ORS usage is only about 23 percent in all diarrheal episodes[1]. One of the main reasons for its under-use is that G-ORS effectively replaces fluid loss but does not decrease stool volume and frequency, and may even increase it[2,3]. This is of practical concern to both mothers and health workers and leads to increased, unnecessary use of antidiarrheal drugs[1].

Studies are focused on alternate solutions containing starch instead of glucose, mainly rice-based oral rehydration solutions (R-ORS), to increase the co-transport molecules for the coupled transport of sodium without increasing the osmolality[4]. Studies with rice-based solutions containing 30-50 g rice powder for each liter of water have been shown to reduce stool output and diarrhea duration[4]. In Turkey, G-ORS has been used for rehydration treatment since the early 1980s, but its usage is similar to the world average[5]. As far as we know, no clinical experience has been reported on the comparison of R-ORS and G-ORS treatment in Turkish children. Therefore, this study was conducted to evaluate the comparative efficacy of R-ORS and G-ORS on the treatment of diarrheal dehydration by assessing the frequency of watery stool, vomiting, duration of rehydration, amount of ORS consumed for rehydration and improvement in metabolic acidosis among Turkish children.

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Material and Methods

This study was carried out from September 1993 to September 1994 at the Hacettepe University İhsan Doğramacı Children's Hospital Diarrhea Training and Treatment Unit. After initial clinical history-taking, patients were examined to determine the degree of dehydration, nutrition and the presence of associated conditions. Children who were diagnosed as moderately dehydrated due to diarrhea according to standard clinical criteria[6] were enrolled in the study, and those with systemic infections or other diseases requiring specific additional treatments were excluded.

Patients were randomly assigned to two treatment groups. Children in one group were treated with a precooked R-ORS solution prepared by WHO, and the other group received the standard WHO/UNICEF-recommended G-ORS containing citrate as the base. The composition of rice-based ORS was identical to that of glucose-based ORS except that glucose was replaced by 50 g precooked, whole rice powder. Some of the characteristics of G-ORS and R-ORS are summarized in Table I.

Table I: Comparison of the Oral Solutions Used to Treat Infants with Diarrhea

	Rice-ORS	Glucose-ORS
Sodium (mmol/L)	90	90
Potassium (mmol/L)	20	20
Chloride (mmol/L)	80	80
Citrate (mmol/L)	10	10
Glucose (mmol/L)	–	111
Rice powder (g/L)	50	–
Osmolality (mOsm/L)	250	308

All patients were given 100 ml/kg of body weight of the assigned ORS solution during the first four hours of treatment, and then reassessed frequently for signs of dehydration. Patients were discharged when the signs of dehydration disappeared.

If signs were still present at the end of four hours, the calculated deficit was again replaced with the assigned ORS. This procedure was repeated until signs of dehydration disappeared. Treatment failure was defined as deterioration in clinical signs of dehydration after two hours of treatment, or failure to maintain fluid and electrolyte balance with oral fluids because of persistent vomiting or a high purging rate. All patients were weighed on admission and on completion of rehydration.

Blood samples were taken on admission and after complete rehydration for the measurement of serum sodium, potassium, chloride and bicarbonate concentrations as well as blood pH levels by standard methods. Frequency (no. per hr) of vomiting and stool output in the 24 hours before admission and during the treatment were also recorded.

The efficiency of treatment was assessed by the frequency of watery stool and vomiting, the duration of rehydration, the amount of ORS consumed for rehydration and the improvement in metabolic acidosis.

Statistical analyses were done with Epi-info Version 5 software. Chi-square and Student's t tests were used to compare the groups.

Results

On admission, there were no significant differences ($p > 0.05$) in the clinical characteristics between the treatment groups (Table II).

Table II: Characteristics of Patients on Admission

	Rice-ORS (n: 37)	Glucose-ORS (n: 42)
Male/Female	27/10	28/13
Age (months)	12.6 ± 9.3	10.6 ± 7.0
Body weight (kg)	8.2 ± 2.3	7.7 ± 2.2
Duration of diarrhea before admission (days)	7.8 ± 6.9	5.8 ± 4.6

Values denote means ± SD.
No statisticaly significant differences were found between the groups ($p > 0.05$).

Treatment was unsuccessful in five (14%) of 37 infants treated with R-ORS and nine (21%) of the 42 infants treated with G-ORS. Treatment failure was comparable in the two groups (Table III).

Table III: Clinical Outcome of the Patients

	Rice-ORS (n: 37)	Glucose-ORS (n: 42)	Total (n: 79)
Successfully treated (%)	32 (86)	33 (79)	65 (82)
Treatment failures (%)	5 (14)	9 (21)	14 (18)

Yates corrected Chi-Square 0.39, $p = 0.53$

On admission, the treatment groups had similar numbers of patients with vomiting. During rehydration, fewer patients had vomiting in the R-ORS treated group but the difference was not statistically significant ($p > 0.05$). The frequency of vomiting during rehydration remained the same when compared with admission levels within and also between the treatment groups ($p > 0.05$) (Table IV).

The mean frequency of stool output increased significantly during rehydration in both the R-ORS and G-ORS-treated patients (Table IV).

The ORS intake rate (ml/kg/hr) and weight gain after rehydration were similar in the two treatment groups ($p > 0.05$). However, infants treated with R-ORS required significantly less oral rehydration fluid for treatment ($p < 0.05$, Table IV).

Table IV: Clinical and Laboratory Features of Patients Before and During Rehydration Phase

	Rice-ORS (n: 37)	Glucose-ORS (n: 42)
No. of patients with vomiting (%)		
On admission	25 (66)	30 (71)
During rehydration	9 (24)	15 (36)
Frequency of vomiting (No. of vomiting per hour)		
On admission	0.21 ± 0.13	0.27 ± 0.17
During rehydration	0.23 ± 0.12	0.30 ± 0.28
Frequency of stool output (No. of stool per hour)		
On Admission	0.30 ± 0.16	0.34 ± 0.36
During rehydration	0.71 ± 0.42**	0.60 ± 0.31**
ORS intake rate (ml/kg/hr)	18 ± 6	20 ± 7
Net ORS requirement (ml/kg)	108 ± 29*	135 ± 42
Weight gain after rehydration (% of admission weight)	5.6 ± 2.9	6.2 ± 3.1
Duration of rehydration (hr)	5.8 ± 2.2*	7.5 ± 3.4
Blood pH		
On admission	7.30 ± 0.08	7.29 ± 0.06
After rehydration	7.36 ± 0.07***	7.31 ± 0.03
Serum HCO_3^- (mmol/L)		
On admission	14.4 ± 3.4	14.0 ± 2.9
After rehydration	16.1 ± 3.1**	16.2 ± 2.4**
Serum Na^+ (mmol/L)		
On admission	138 ± 5	140 ± 7
After rehydration	140 ± 5	142 ± 6
Serum K^+ (mmol/L)		
On admission	3.7 ± 0.6	4.3 ± 0.7
After rehydration	3.9 ± 0.7	4.0 ± 0.8

Results given as means ± SD

* Significant differences were found between the groups ($p < 0.05$).
** Significantly different from admission levels ($p < 0.05$).

The mean duration of rehydration, measured as the time between the initiation of oral rehydration therapy and the disappearance of signs of dehydration, was significantly lower ($p < 0.05$) in the R-ORS treated group (Table IV).

No significant difference was observed between the treatment groups in the mean serum concentrations of sodium and potassium at the time of admission and after rehydration (Table IV).

On admission, the mean blood pH and serum bicarbonate levels were similar ($p > 0.05$), and the mean blood pH levels revealed mild-moderate metabolic acidosis ($7.20 < pH < 7.35$) in both R-ORS and G-ORS-treated patients. At the end of treatment, the mean serum bicarbonate levels increased significantly in both treatment groups; however, a significant increase in the mean pH value was observed in only the R-ORS-treated group ($p < 0.05$). The mean blood pH level measured after rehydration was also higher in the R-ORS-treated group than in the G-ORS group ($p < 0.05$, Table IV).

Discussion

According to the results of a meta-analysis of 13 randomized clinical trials involving 1367 patients published in 1992, rice-based oral rehydration solutions (R-ORS) containing 50-80 g/L rice-powder decreases the stool volume and treats dehydration more effectively, especially in patients with cholera. However, the effect was found to be substantially less for non-cholera diarrhea in these studies[7]. Later studies were performed to compare the effect of treatment with R-ORS and G-ORS on total stool output and duration of diarrhea in children with acute non-cholera diarrhea and showed no difference between the two treatment groups[1,8]. In particular, G-ORS was found to be as efficacious as R-ORS when patients were given food immediately after the correction of dehydration[8].

There is still uncertainty, however, about the clinical advantage of R-ORS in the treatment of dehydrated children. We had an experience of a 10-month-old, severely dehydrated and severely acidotic (pH = 6.96) infant who improved and became moderately dehydrated with R-ORS treatment in four hours (pH = 7.22), but then deteriorated when treatment continued with G-ORS (pH = 7.11) and again improved and successfully rehydrated when R-ORS was given (pH = 7.30) for the following eight hours of treatment. As we know from previous experience, improvement of a moderate to severe degree of metabolic acidosis is slower and usually takes 11 hours of rehydration treatment with G-ORS[3]. Although the two solutions contained the same amount of base precursor, this study shows the superiority of R-ORS over G-ORS in terms of improving metabolic acidosis, an issue which is not clearly discussed in previous studies, and reducing the necessary time for rehydration.

Contrary to previous reports, we observed increased frequency of stool output during the rehydration period, not only in G-ORS-treated patients but also in the R-ORS-treated group[9, 10]. An increase in the mean frequency of stool output during rehydration treatment with G-ORS has been reported before without affecting the treatment success[3, 4]. This increase is explained with the relatively higher osmolality of G-ORS, which may cause osmotic diarrhea if given in excessive amounts[11, 12].

In this study, despite increased frequency of stool output, successful rehydration and weight gain as well as greater improvement in metabolic acidosis was achieved in a shorter time with R-ORS, suggesting that the volume absorbed with R-ORS is better than that with G-ORS. Because hydrolysis of oligosaccharides by brush border enzymes occurs in close proximity to glucose transport sties, there is a greater local concentration of glucose for absorption than would occur with random diffusion of free glucose[11]. Therefore, the higher carbohydrate content of R-ORS increases the absorption of sodium and water without an osmotic penalty[4, 11]. The R-ORS used in this study had a lower osmolality (250 mOsm/L) than does G-ORS (308 mOsm/L). In another study, hypotonic G-ORS (224 mOsm/L) containing 60 mmol/L sodium and 84 mmol/L glucose was shown to have clinical advantages over istonic (304 mOsm/L) G-ORS in terms of decreasing diarrheal stool, diarrheal duration and hospital stay; this finding suggested that the hypotonicity of the ORS solutions was more important than its glucose type for optimal water absorption[13]. The mean weight gain in hypotonic and isotonic G-ORS-treated groups was found to be less than had been assumed, and was explained by overestimation of initial dehydration. Although the number of diarrheal stools on admission was not recorded in that study, the frequency of stool output with isotonic G-ORS during treatment was similar (0.56 ± 0.50) to that observed in our study. Thus more ORS is needed to overcome increased fluid loss due to increased frequency rather than overestimation of dehydration.

In summary, our findings show that R-ORS shortens the rehydration period and corrects metabolic acidosis better than G-ORS. These clinical advantages are important for many Diarrhea Training and Treatment Units where overnight stays and/or 24 hour follow-up of patients are unavailable.

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SERUM OSTEOCALCIN LEVELS IN TYPE I DIABETES MELLITUS*

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SUMMARY: Paşaoğlu H, Kumandaş S, Keleştimur F. (Departments of Biochemistry, Pediatrics and Internal Medicine, Erciyes University Faculty of Medicine, Kayseri, Turkey). Serum osteocalcin levels in type I diabetes mellitus. Turk J Pediatr 1995; 37: 323-329.

Serum osteocalcin levels are a marker of bone formation. In this study, bone and mineral metabolism in type I diabetes mellitus (DM) were investigated, and the changes related to diabetic microvascular complications were examined. Serum calcium (Ca), inorganic phosphate (P), osteocalcin (OC) and parathyroid hormone (PTH) levels were measured in 42 type I diabetic subjects. Diabetics were subdivided into those with or without complications. Age and sex-matched control subjects were used for comparisons with the diabetic groups. Serum P and PTH levels were not different from those of controls. Serum Ca levels were significantly increased ($p < 0.001$) although the values were within the normal range. OC levels were significantly lower in the complicated (retinopathy and/or protenuria) diabetic group ($p < 0.005$). In Type I diabetes mellitus, the serum OC level is influenced by the presence of microvascular complications. *Key words: osteocalcin, Gla protein, diabetes mellitus.*

Altered bone and mineral metabolism has previously been reported in both experimental and clinical diabetes mellitus (DM)[1-3]. Decreased bone mass as well as disturbed calcium (Ca) and vitamin D homeostasis have been described in DM. However, the effects of diabetes on bone and mineral metabolism in humans is still far from clear, since there are conflicting reports where decreased, normal or increased bone mass have been reported[4-6].

Osteocalcin (OC) or bone g-carboxyglutamic acid (Gla) protein is a small, noncollagenous protein of the bone matrix with three residues of vitamin K-dependent Gla[7,8]. Circulating levels of OC, a specific product of osteoblasts, reflects the rate of bone turnover with high sensitivity and has clear advantages over other parameters of bone metabolism[8,9].

In recent years, serum OC levels in DM and in several metabolic bone diseases have been studied, and the results in diabetic patients have been contraversial[8,10,11]. Also, the effects of type microvascular complications and treatments on bone metabolism in diabetic patients are not yet clear (Fig. 1).

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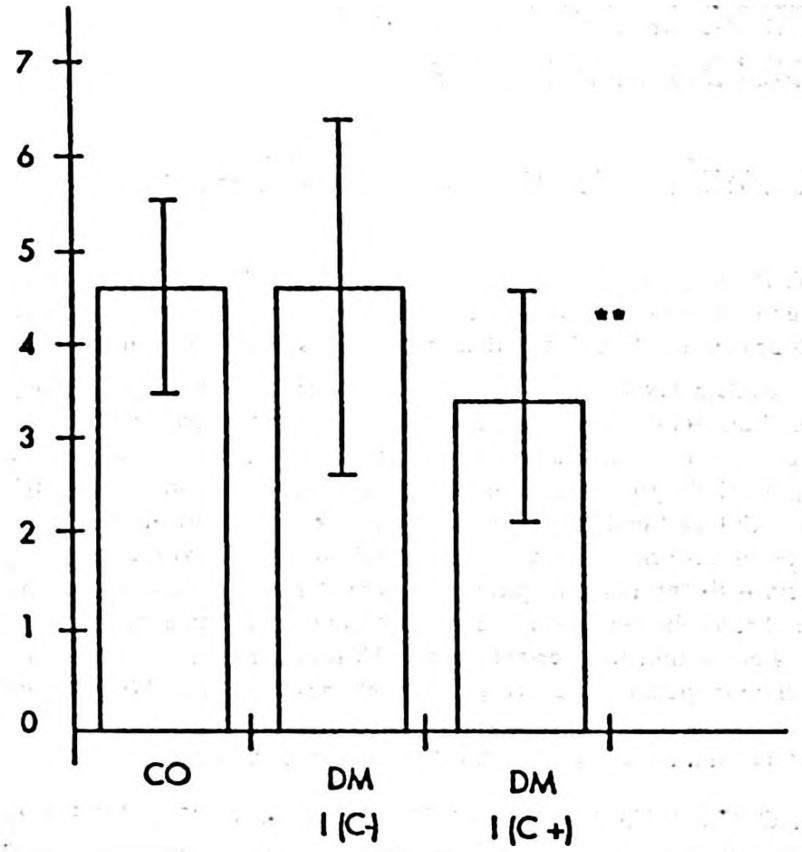

Fig. 1: Mean serum osteocalcin (OC) levels in diabetic patients and in control subjects.
CO : Control subjects.
I (C-) : Type I diabetics without complications.
I (C+): Type I diabetics with complications.
Vertical lines (I) inticate ± SD values **: $p < 0.005$.

In our yprevious study[12], although the serum PTH levels were not significantly changed, 1.25 $(OH)_2$ vitamin D_3 levels were found to be decreased in newly diagnosed type I diabetic patients who had no previous insulin treatment. The present study was undertaken to determine serum OC, Ca and inorganic phosphate (P) levels in type I DM and to investigate whether changes in these values were related to diabetic microvascular cmoplications (retinopathy, nephropathy and neuropathy).

Material and Methods

Subjects

Forty-two patients with type I DM, routinely attending the Diabetic Clinics of the Departments of Pediatrics and Endocrinology at the Faculty Hospital of Erciyes University, were included in this study. The patients were free from diseases other than DM, and no subject was taking any medication known to interfere with bone metabolism. Type I diabetics were then subdivided into those with or without microvascular complications (e.g. retinopathy, neuropathy and

nephropathy). Retinopathy was diagnosed after fundoscopic examination; in doubtful cases fluorescein fundus angiography was performed by ophthalmologists. While diabetic neuropathy was diagnosed following the neurological examination including electromyography, nephropathy was diagnosed with the help of laboratory tests such as blood urea nitrogen (BUN), creatinine, microalbumin and creatinine clearence.

All diabetic subjects had been on insulin replacement therapy since diagnosis. Twenty-six age- and sex-matched control subjects with no clinical or biochemical evidence of bone or metabolic disease were also included in the study. Details of the diabetic and control subjects are given in Table I.

Table I: Details of Diabetic and Control Subjects

	n	Sex (M/F)	Age (yr) mean ± SD	Duration of Diabetes (yrs)	HbA_{1C} (%)	Fasting Glucose (mg/dl)	Serum Creatinine (mg/dl)
Controls	26	12/14	14 ± 3	–	< 7	80 ± 5	0.8 ± 0.04
Diabetics	42	20/22	14 ± 3	1-10	9.9 ± 0.7	169 ± 53	0.9 ± 0.05

Patients' results were compared with those of the control group. Student's test was used for statistical analysis.

Laboratory Methods

As a circadian rhythym of OC in human serum has been reported[13], blood samples were drawn between 8:00 and 9:00 a.m. in the overnight fasting state, before insulin injections. Blood sampling in the patients and controls was equally distributed throughout the year.

Serum was separated from the samples without delay and kept at -20 °C until the time of OC assay.

OC levels were measured by radioimmunoassay using the Incstar^{125}I. RIA Kit. Parathyroid hormone (PTH) levels were measured by DPC (RIA) kit. Serum fasting glucose, total Ca, P and creatinine levels were measured on the same day by Technican RAXT autoanalyser, using routine Biotrol Kits. Also, Hemoglobin (HbA_{1c}) levels in erythrocytes were measured by Biotrol Kit on the same day.

Results

The results obtained in diabetic patients as compared to control subjects are outlined in Tables I and II. The fasting serum glucose and HbA_{1C} levels of diabetics were greater than those of control subjects (Table I).

In type I diabetics, serum Ca levels were significantly increased ($p < 0.05$), although the values were within the normal ranges for age- and sex-matched human serum. Serum inorganic P and PTH levels were not different from those of controls ($p > 0.05$) (Table II).

Table II: Serum OC, Ca, P and PTH levels in Diabetic Patients and Control Subjects

	n	Osteocalcin (ng/ml)	Ca (mg/dl)	P (mg/dl)	PTH (ng/ml)
Control	26	4.64 ± 0.92	9.3 ± 1.1	4.0 ± 0.8	0.46 ± 0.2
Type I (Comp -)	29	4.66 ± 1.96	10.4 ± 0.4 ≠**	3.8 ± 0.9	0.44 ± 0.1
Type I (Comp +)	13	3.37 ± 1.17 Ø***	9.9 ± 0.7 ≠*	4.2 ± 1.0	0.44 ± 0.2

Mean ± SD values are given
(Comp -) = Diabetic patients without complications.
(Comp +) = Diabetic patients with complications.
Ø: Less than control *: $p < 0.05$.
≠: Greater than control **: $p < 0.01$ ***: $p < 0.005$.

Serum levels of OC were significantly lower in diabetic patients with microvascular complications than in controls. Also, serum OC levels of the complicated group decreased more than those of the noncomplicated group ($p < 0.02$).

Discussion

Diabetic children and adults have decreased bone mass as shown by photon absorptiometry and radiometry[1, 3]. This osteopenia is evident not only in the peripheral skeleton but also in the spine of diabetic women[5], and diabetic osteopenia differs from typical osteoporosis in character[6]. The pathogenesis of diabetic osteopenia in humans remains unclear.

Despite normal serum Ca levels, disturbed Ca metabolism has been seen in diabetic patients and is thought to be related to a skeletal defect[14]. Studies on experimental and human diabetes have showed normal[14-16], low[5] and high[10, 17] serum Ca levels, Glachen et al.[11] found that the levels of ionized Ca were not changed in diabetic rats. In the present study, ionized Ca levels could not be measured.

In our study, when we examined the Ca and P levels, serum Ca levels were higher in patients with type I DM than in controls ($p < 0.01$), although these high values were within normal limits for human serum. On the other hand, PTH was not significantly different. Serum P levels are not changed in diabetics. Auwerx et al.[5] found decreased serum Ca (9.3 ± 0.3 mg/dl) and P (3.0 ± 0.6 mg/dl) levels in type I diabetic patients (Age 41.5 ± 13.5 years, disease duration 18.3 ± 7.8 years). Pedrazzoni et al[10]. reported increased Ca (9.6 ± 0.3 mg/dl) and normal P (2.8 ± 0.7 mg/dl) levels in type I diabetics (Age 49.1 ± 1.55 years, disease duration 8.9 ± 5.9 years). Hough et al.[17], who also found high levels of serum Ca in diabetic rats, suggested that this may be due to increased intestinal Ca absorption. These different findings may have resulted from differences in the study groups and their durations of disease.

Serum concentrations of OC have been shown to reflect the synthesis of OC by osteoblast and thus are a parameter of bone formation[7, 18]. The source of OC in

plasma is new osteoblastic synthesis and not a release from resorbed bone; it is cleared mainly by glomerular filtration in the kidneys[19]. Vitamin K1 is essential for OC biosynthesis, and synthesis is stimulated by 1.25 $(OH)_2$ Vitamin D_3[20]. OC may be a valuable marker for decreased bone remodeling in insulinopenic diabetes[11].

In the present study, OC levels were lower in type I diabetics who have complications than in controls. Also, serum OC levels were diminished in complicated diabetics as compared to noncomplicated diabetics. However, in type I diabetics without complications, OC levels were not different from those of controls. This may be partly related to the regular treatment of our patients with insulin. The increasing effect of insulin replacement therapy on serum OC levels has been suggested in a previous report[10]. A direct influence of insulin on in vitro OC synthesis has also been reported[21]. Guarneri et al.[22] showed that serum OC values were lower in newly diagnosed diabetic children than in controls. After 15 days of insulin therapy they found no difference between diabetics and controls. These results support the effect of insulin on OC. Pedrazzoni et al.[10] suggested that the low levels of OC they found in insulin-dependent and non-insulin-dependent diabetics might be due to a reduction in the levels of 1,25-dihydroxyvitamin D_3. They said that the reduction of OC in their diabetic population was related to the type of treatment, with diet-controlled subjects showing greater differences from the expected normal values than those treated with oral hypoglycemic agents or insulin. Our previous study[23] showed serum 1.25 $(OH)_2$ vitamin D_3 levels to be decreased in newly diagnosed type I diabetics who did not have insulin therapy. This result may indicate that diminished serum OC levels were due to decreased 1.25 $(OH)_2$ vitamin D_3.

Verhaeghe et al.[24] showed that plasma OC concentrations were markedly decreased in spontaneously diabetic rats after 3 to 4 weeks of diabetes. The half life of [^{125}I] OC was similar in diabetic and non-diabetic rats, indicating that decreased plasma OC was due to decreased synthesis. They suggested that the number and/or function of osteoblasts are severely suppressed in diabetes, resulting in decreased plasma OC levels. In the literature, only Pietschmann et al.[25] have examined the effects of microvascular complications on serum OC levels in diabetic patients. They found that OC levels were significantly lower in type I diabetics with retinopathy and/or protenuria than in type I diabetics without microangiopathy. In this respect, the results of the present study support their findings. Therefore, bone formation as reflected by serum OC levels seems to be influenced by the presence or absence of microvascular complications in type I DM.

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AGE – SPECIFIC SEROPREVALENCE OF HEPATITIS B VIRUS INFECTION*

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SUMMARY: Kuru Ü, Şenli S, Türel L, Kuru N, Başkent A, Ulucaklı Ö. (Departments of Pediatrics and Microbiology, Bakırköy Social Security Maternity and Children's Hospital, İstanbul, Turkey). Age-specific seroprevalence of hepatitis B virus infection. Turk J Pediatr 1995; 37: 331-338.

In this study, we have tried to determine the age-specific seroprevalence of hepatitis B virus (HBV) infection and to make some conclusions about the mode of transmission and vaccination strategy which should be chosen in Turkey.

Eight hundred and one patients between the ages of six months and 60 years of age were included in this study. According to the HBV serologic markers, (HBsAg, Anti-HBc and Anti-HBs), HBsAg positivity and HBV exposure rates were 6.5% and 32.8%, respectively. HBsAg positivity was 6.6% under one year of age. The highest rate of HBsAg positivity was in the 6-10 year age-group ($p < 0.05$). The prevalence of total hepatitis B virus seropositivity increased with age ($p < 0.05$). The HBV exposure rate was higher in males than in females ($p < 0.05$).

It was concluded that HBV infection is an important infection in Turkey and is acquired very early in life. A mass hepatitis B vaccination strategy should thus be chosen in Turkey.
Key words: seroepidemiology, hepatitis B virus, horizontal transmission, hepatitis B vaccination.

Hepatitis B virus (HBV) infection, with its chronic sequelae of cirrhosis of the liver and hepatocellular carcinoma (HCC), constitutes a major health problem in countries where HBV is hyperendemic[1]. Studies among Turkish adults have established the high prevalence of HBV infection in the general population and the significant contribution by HBV to acute viral hepatitis and chronic liver disease[2,3]. The positivity rates of hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs) are reported to differ by region in Turkey (1.7-13.9% and 26.2-68.8%, respectively)[2,3].

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The availability of safe and efficacious vaccines has led to the feasibility of effective control of HBV infection, especially in areas of high prevalence where most chronic HBV carriers acquire the infection very early in life[4-6]. The immunization strategy for preventing HBV infection may vary from country to country depending on: HBV endemicity; predominant modes of infection (i.e., sexual, vertical perinatal, early horizontal, needle sharing during drug abuse, etc.); age of infection; and health-care resources. An appropriate strategy for preventing HBV infection must be determined by large series seroepidemiologic studies.

Age-specific seroepidemiology of HBV infection gives some clues about the routes of transmission. Therefore, we can make some conclusions about the most cost-effective way of preventing this infection. Studies of this type have been few in Turkey. This study aimed to determine age-specific seroepidemiology of HBV infection and discuss which mode of prevention should be chosen in Turkey.

Material and Methods

Eight hundred and one patients were included in this study, which was carried out between October and December of 1993. The patients' ages ranged from six months to 60 years. The reason for choosing children older than six months was to minimize the possibility of passive immunization of infants from mothers who were previously exposed to HBV infection. Persons included in this study were matched according to the following age groups: six months to five years, 6-10 years, 11-15 years, 16-20 years, 21-25 years, 26-30 years, 31-35 years, 36-40 years and older than 40 years of age. Children who were less than ten years of age were also matched according to the following age groups: six months to one year, 2-3 years, 4-5 years, 6-7 years and 8-10 years of age. The distribution of the age groups and their characteristics are shown in Table I.

Table I: Characteristics of Studied Population

Age Groups (Years)	Number	%	Female (%)	Male (%)
1/2-1	30	3.7	16 (53.3)	14 (46.7)
2-3	32	4	14 (43.8)	18 (56.2)
4-5	29	3.6	13 (44.8)	18 (55.2)
6-7	57	7.1	29 (50.9)	28 (49.1)
8-10	61	7.6	36 (59)	25 (41)
11-15	52	6.5	29 (55.8)	23 (44.2)
16-20	64	8	29 (45.3)	35 (54.7)
21-25	130	16.2	26 (20)	104 (80)
26-30	140	17.5	28 (12.9)	112 (87.1)
31-35	74	9.3	9 (12.2)	65 (87.8)
36-40	49	6.1	5 (10.2)	44 (89.8)
≥ 41	83	10.4	27 (33.7)	56 (66.3)

Patients less than 20 and older than 40 years of age had applied to Bakırköy Maternity and Children's Hospital outpatient clinics for any reason except liver disease, and none had received transfusion of blood or blood products. Patients in the 21-40 years age-group were blood donors who came to the same hospital, and all of them were healthy and non-professional donors. There were more males than females (540 vs. 261) in our study because of a greater number of male blood donors.

Specimens of approximately five ml of blood were taken from all patients. Sera were separated by centrifugation and stored at -30 °C until tested within 15 days. Hepatitis B serologic markers (HBsAg, anti-HBc and anti-HBs) were investigated by ELISA. Using commercially available kits of Pasteur Diagnostics (Pasteur Institute, France).

Chi-square test was used to compare proportions. Statistical analysis was performed by StatView software. A p value of < 0.05 was considered significant.

Results

Among 801 persons studied, the prevalence of HBsAg was 6.5 percent (52/801). The HBV exposure rate was 32.8 percent (264/801) (Table II). As shown

Table II: Seroprevalence of Hepatitis B Virus in Studied Population

	HBsAg		Anti-HBc[a]		Anti-HBs[b]		Anti-HBc/ Anti-HBs		Seropositive[‡]		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Sex											
Male	34	6.3	36	6.7	24	4.4	98	18.1	192	35.6	540
Female	18	6.9	14	5.4	8	3.1	32	12.3	72	27.6	261
Age (Years)											
≤ 1	2	6.6	2	6.6	0		0		4	13.3	30
2-3	1	3.1	2	6.3	0		1	3.1	4	12.5	32
4-5	0		2	6.9	0		1	3.4	3	10.3	29
6-7	5	8.8	3	5.3	0		2	3.5	10	17.5	57
8-10	9	14.8	1	1.6	0		3	4.9	13	21.3	61
11-15	5	9.6	1	1.9	2	3.8	7	13.4	15	28.8	52
16-20	7	10.9	2	3.1	1	1.6	5	7.8	15	23.4	64
21-25	6	4.6	9	6.9	6	4.6	23	17.7	44	33.8	130
26-30	12	8.6	3	2.1	9	6.4	36	25.7	60	42.9	140
31-35	2	2.7	3	4.1	5	6.8	20	27	30	40.5	74
36-40	1	2	3	6.1	5	10.2	12	24.4	21	42.9	44
≥ 41	2	2.4	19	22.9	4	4.8	20	24.1	45	54.2	83
All ages	52	6.5	50	6.2	32	4	130	16.2	264	32.9	801

[a] Anti-HBc positive only.
[b] Anti-HBs positive only.
[‡] Total seropositive includes first four columns.

in Figure 1, the highest rate of HBsAg positivity belonged to the 6-10 years age-group (11.9%). After the 10-year age group, there were approximately steady rates of HBsAg positivity until age 21. Thereafter, there was a decline in the HBsAg positivity rate, except in the 26-30 year age-group. The high HBsAg positivity rate in the 6-10 year age-group was statistically significant when compared to the other age-groups ($p < 0.05$).

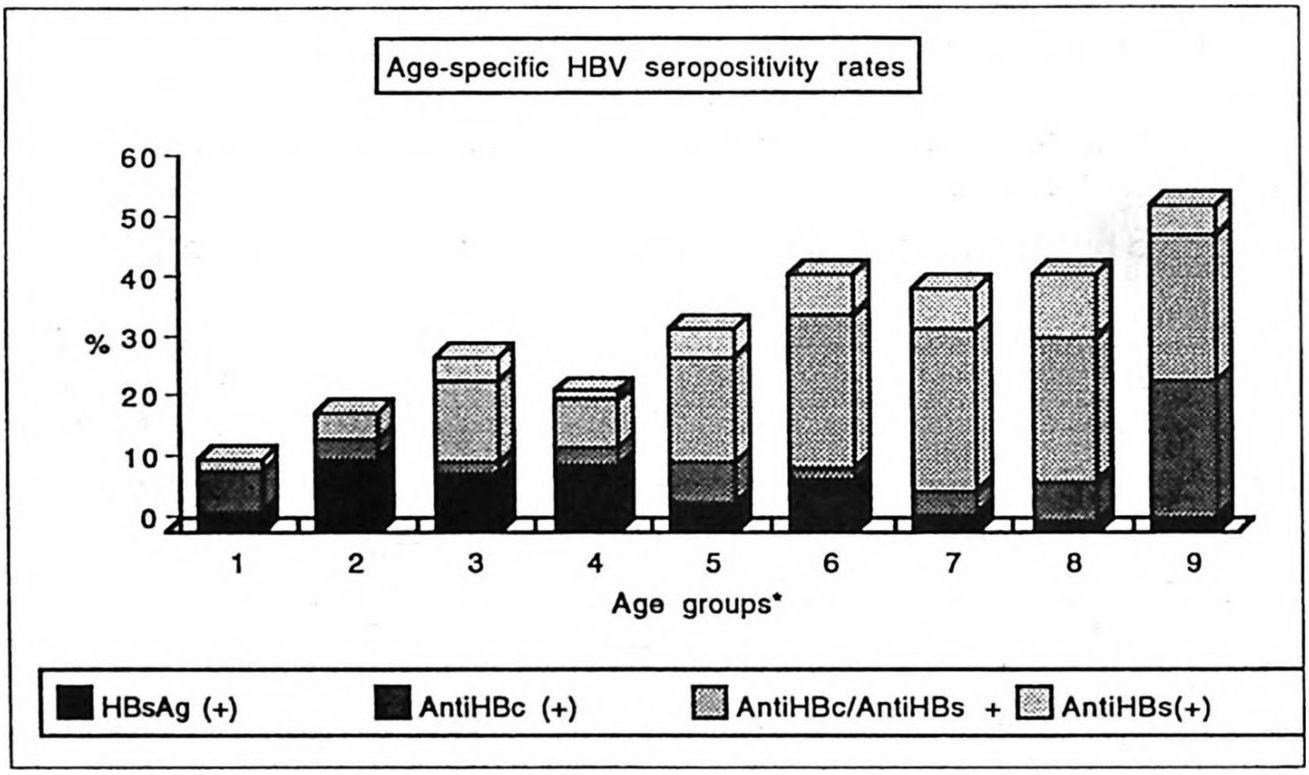

Fig. 1: Age-specific seroprevalence of the studied population.

* 1 = ≤ 5 years of age, 2 = 6-10 years, 3 = 11-15 years, 4 = 16-20 years, 5 = 21-25 years, 6 = 26-30 years, 7 = 31-35 years, 8 = 36-40 years, 9 = > 41 years.

Of 234 patients, 26 HBsAg-positive persons were found in the 6-20 year age-group (11.1%). Of 567, 26 HBsAg-positive persons were determined in the other age groups combined (4.59%) the difference was significant ($p < 0.05$). We concluded that HBV infection was generally acquired very early in the studied population.

The second peak age of HBsAg prevalence was in the 26-30 year age-group, but was not statistically significant when compared to other age groups. Excluding the 6-20 year age-group, the prevalence of HBsAg positivity was 3.29 percent (14/427). When we compare this rate with the prevalence of HBsAg in the 26-30 year age-group (8.57%), then the difference was significant ($p < 0.05$).

We found gradually increasing rates of HBV exposure with increasing age ($p < 0.05$).

When we examined the children between six months and 10 years of age with closer age intervals, we found the results as shown in Figure 2. The

HBsAg-positivity rate was 6.6 percent (2/30) under one year of age. Thereafter there was a decline among children 2-5 years in age. The highest HBsAg positivity rate was in the 8-10 year age group (14.8%). HBsAg positivity was 3.29% under five years of age and 11.8% over five years of age ($p < 0.05$). The difference in HBV exposure rates in children under and over five years of age was not statistically significant (12.1% vs. 19.4%).

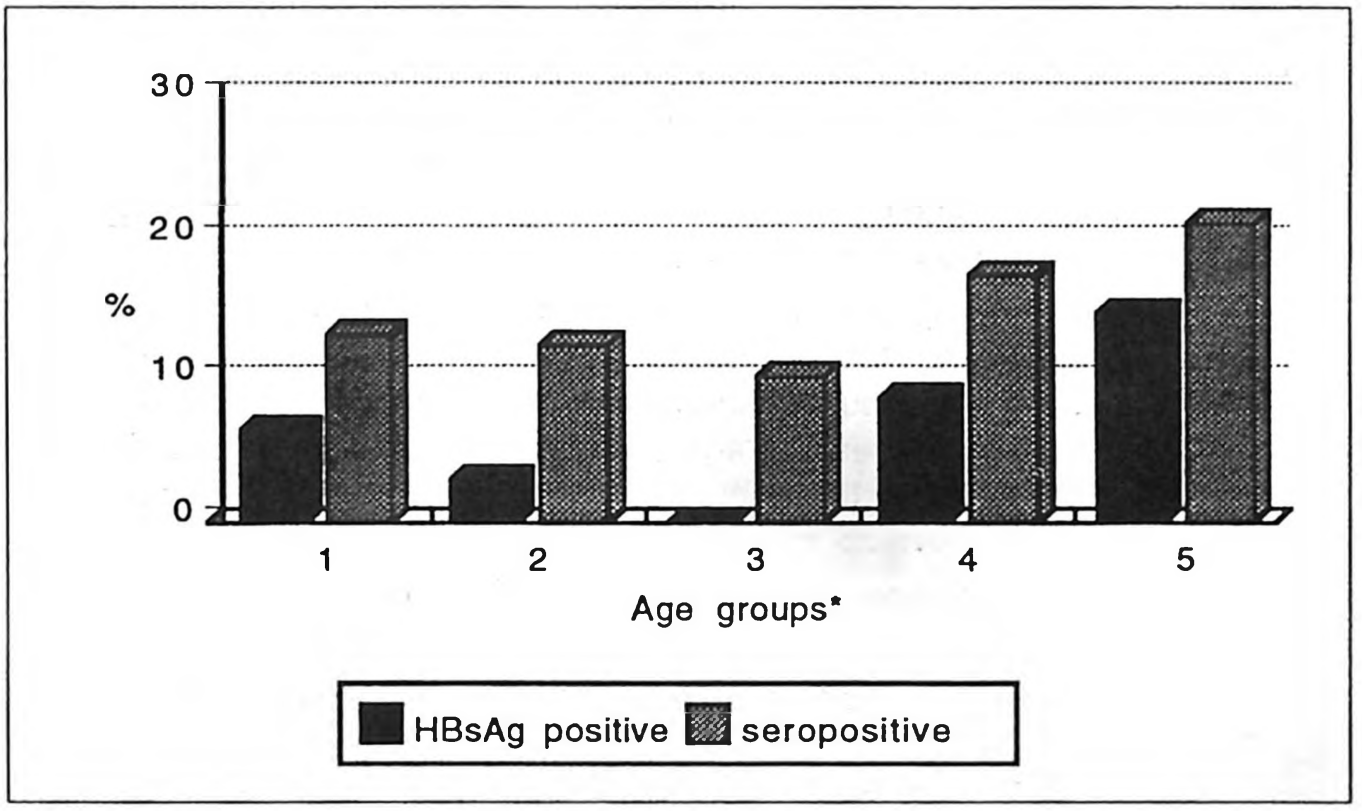

Fig. 2: Detailed age-specific seroprevalence of the children under ten years of age.

* 1 = ≤ 1 year of age, 2 = 2-3 years, 3 = 4-5 years, 4 = 6-7 years, 5 = 8-10 years.

The overall prevalence rate of HBsAg was 6.29% in males and 6.89% in females ($p > 0.05$). The seropositivity rate was higher in males than in females (35.6% vs. 27.6%) ($p < 0.05$).

Discussion

The serious consequences of HBV infection are a result of development of the persistent viral carrier state, which occurs in 70 to 90 percent of acute infections in infancy and declines to six to ten percent of infections which occur after the sixth year of life[7-9]. An estimated 25-30 percent of individuals who become persistent HBV carriers and who have an estimated life expectancy of at least 30 years at the time of infection will die of HBV-induced cirrhosis or hepatocellular carcinoma[7].

Studies have shown that HBV infection is the cause of most cirrhosis and HCC cases in Turkey[10-13], and that the HBeAg-positivity rate in Turkish chronic carriers

of HBsAg is not very high[14]. Therefore vertical transmission is probably not the major mode of transmission in Turkey, and few carriers originate from carrier mothers, most arising from horizontally transmitted infections. This is due to the much lower infectivity and lower HBeAg prevalence of Turkish HBsAg-carrier mothers.

The current study showed that 6.5 percent of people living in İstanbul are HBsAg-positive, and 33 percent have been exposed to HBV infection. The HBsAg prevalence was 6.6 percent in the first year of life, the same as the overall prevalence of HBV infection in the studied population. Both vertical and horizontal transmission must be responsible for the rate of HBsAg positivity in this period of life. The decrease in HBsAg prevalence after the first year and increase in the 6-10 year age-group show the importance of horizontal transmission in our study population. This finding in the pediatric age group has also emerged in other studies from Turkey and other endemic areas of the world[15-19].

The prevalence of HBsAg carriers did not consistently increase after the 6-10 year age-group, unlike the HBV-seropositivity rate. Exposure to the HBV infection increased across the age groups, showing that it continues throughout life; also, persons infected after 6-10 years of age seem to be much less likely to become persistent virus carriers than those infected as neonates or young children, but instead most of them develop immunity to HBV.

In some studies the prevalence of HBsAg has been higher in males than females[19, 20], but in our study it was not. However, the HBV exposure rate was higher in males.

We can make some conclusions about the major mode of transmission of the HBV infection in Turkey, although the numbers in this study are insufficient; moreover, multicenter age-specific seroprevalence studies and cost-benefit analyses including all regions of Turkey must be done. All of the seroepidemiologic studies from Turkey have shown that horizontal transmission was the major mode of transmission and HBV exposure occurred very early in our country[15-18].

Turkey has an intermediate endemicity for HBV infection. In areas of intermediate endemicity, infection occurs in both adults and children, but vertical perinatal transmission is relatively uncommon because most carrier mothers are HBeAg-negative. In intermediate as well as high endemic areas, immunization of all infants may be considered the proper approach for long-term control of hepatitis B[7]. Ideally, a combined program of infant and adolescent immunization together with other individuals at high risk should be applied where economically feasible and where appropriate infrastructure for delivery exists. In Italy, where approximately the same HBV infection prevalence and mode of transmission exists as in Turkey, vaccination of all newborns and 12-year-old adolescents has become compulsory under Italian Law[21]. Although the United States of America has a low endemicity for HBV infection, it is now recommended that all infants receive hepatitis B vaccine as part of their routine immunization schedule[22].

With the high HBsAg prevalence and HBV exposure rates and with horizontal transmission as a major mode of transmission, a mass HBV vaccination which is integrated into the expanded program of immunization (EPI) strategy should be chosen in Turkey. Universal immunization of all infants in Turkey can prevent horizontally transmitted HBV infections. Ideally, extension of HBV vaccination to all pre-school children for the next few years would, reduce the reservoir of HBV infection in these children. Screening and immunization of babies born to carrier mothers would not be an effective strategy, because it would not prevent horizontally transmitted HBV infection later in life to susceptible children who were not vaccinated in infancy due to having seronegative mothers.

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SALMONELLA TYPHI INFECTIONS

A 10-Year Retrospective Study*

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SUMMARY: Seçmeer G, Kanra G, Cemeroğlu AP, Özen H, Ceyhan M, Ecevit Z. (Infectious Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Salmonella typhi infections: a 10-year retrospective study. Turk J Pediatr 1995; 37: 339-344.

Enteric fever is still a common health problem in many countries, especially in children. Thus a ten-year retrospective study was carried out to evaluate the clinical and laboratory properties of enteric fever and the incidence of antimicrobial resistance in children. Throughout the past 10 years, Salmonella was isolated in 105 patients by blood culturing, 27 of which were Salmonella typhi. Most of the patients were above the age of two. Besides the typical symptoms and signs of enteric fever, 29.2% of the patients had some neurologic findings. Besides, 68.5% had elevated liver enzymes while only 44.4% had hepatomegaly with or without splenomegaly. Anemia was present in 44%, leukopenia in 16% and leukocytosis in 11.1% of the cases. The emergence of antimicrobial resistance during the last five years against ampicillin, chloramphenicol and trimetoprim-sulfamethoxazole has created a challenge in treating these infections.
Key words: salmonella typhi, clinical properties.

Enteric fever is caused mainly by S.typi and paratyphi serotypes and is still a great problem, especially in children[1]. In recent years, the extended use of various antibiotics for salmonella infections has caused not only an increased incidence of the carrier state but also the emergence of multiple antibiotic resistance[1-3]. Thus, the management of salmonella infections is very important, both for the patient and the public health point of view.

Here, we present a 10-year retrospective study of patients with Salmonella typhi infections, including the signs and symptoms, clinical pictures, laboratory findings, complications and the incidence of resistance to antimicrobial agents.

Material and Methods

Between August 1982 and September 1992, Salmonella was isolated from the blood cultures of 105 inpatient cases at Hacettepe Children's Hospital. Out of

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105 blood isolates, 74 (70.5%) were S.typhimurium, 27 (25.7%) were S.typhi, three (2.9%) were S.paratyphi B and one was S.choleraesuis. The clinical and laboratory properties of the 27 S.typhi blood isolates were documented retrospectively from the records.

Cultures, serotyping and antibiotic resistance studies were performed by the Microbiology Department of Hacettepe Children's Hospital. Information was obtained from the medical records of each patient. The age and sex distribution, signs and symptoms, clinical pictures, complete blood count (CBC), liver function tests, fatality rate and resistance to antimicrobial agents were evaluated retrospectively.

Results

Salmonella typhi was isolated from the blood cultures of 27 cases. In addition to blood cultures, eight had positive stool and three had positive bone marrow cultures. Out of the 27 blood isolates, 16 (59.3%) were diagnosed in the first five years (1982-1987) and 11 (40.7%) in the second five-year period (1988-1992). There was no seasonal variations in the number of cases.

As shown in Table I, most of the cases were above two years of age (77.8%) and the mean age was 6.35. The youngest patient was 15 days old and the oldest, 13 years. Sixteen cases were males and nine were females.

Table I: Age Distribution of Patients with Salmonella Typhi Infection

Age (months)	Number of Patients
< 1	2
1-6	1
7-12	1
13-24	2
> 24	21
Total	27

Seven of the S.typhi blood isolates had an associated disease (two congenital heart disease, two mental retardation and three malignancy); types of cancer included acute lymphoblastic leukemia (ALL), acute non-lymphoblastic leukemia (ANLL) and non-Hodgkin's lymphoma (NHL).

The symptoms of patients at presentation were fever (23 cases, 85.1%), diarrhea (13 cases, 48.1%), vomiting (10 cases, 37%), malaise (five cases, 18.5%), abdominal pain (three cases, 11.1%), jaundice (two cases, 7.4%), abdominal distention (two cases, 7.4%), headache (two cases, 7.4%), and neurologic symptoms (eight cases, 29.2%). Neurologic symptoms included convulsions (three cases, 11.1%), aphasia (two cases), stupor (one case), ataxia (one case) and behavioral abnormality (one case) (Table II).

Table II: Symptoms of Patients with Salmonella Typhi Infection

Symptoms	No. and Percentage of Patients
Fever	23 (85.1%)
Diarrhea	13 (48.1%)
Vomiting	10 (37.0%)
Malaise	5 (18.5%)
Abdominal pain	3 (11.1%)
Jaundice	2 (7.4%)
Abdominal distension	2 (7.4%)
Headache	2 (7.4%)
Neurologic symptoms	8 (29.2%)
• convulsions	3
• aphasia	2
• stupor	1
• ataxia	1
• behavioral abnormalities	1

On physical examination, seven (25.9%) had hepatosplenomegaly, four (14.8%) had only hepatomegaly, three had encephalopathy, one had ataxia and two had aphasia (Table III). None of the patients had isolated splenomegaly without hepatomegaly.

Table III: Physical Findings of Patients with Salmonella typhi Infections

Physical Findings	No. and Percentage of Patients
Hepatosplenomegaly	7 (29.5%)
Hepatomegaly only	4 (14.8%)
Splenomegaly only	0
Encephalopathy	3 (11.1%)
Aphasia	2 (7.4%)
Ataxia	1 (3.7%)

In the laboratory studies, 13 (48.1%, including one patient with ALL and one with NHL) patients had anemia, three (11.1%) had leukocytosis and five (15.4%, including a patient with ALL) had leukopenia[4]. When the patients with ALL and NHL were excluded, 44% of the patients had anemia, 16% had leukopenia, 11.1% had leukocytosis and 72.9% had normal leukocyte counts (Table IV). In 19 cases, liver enzyme levels were measured and 13 (68.5%) had elevated SGOT. Ten (52.6%) had elevated SGOT and SGPT, while three (15.9%) had only elevated SGOT levels (mean for SGOT: 487.5 IU, range: 12-7455 IU; mean for SGPT: 226.8 IU, range: 16-2682 IU).

Table IV: Laboratory Findings of Patients with Salmonella Typhi Infection

Laboratory Findings	No. and Percentage of Patients
Liver enzymes*	
• increased SGOT	13 (68.5%)
• increased SGOT and SGPT	10 (52.6%)
• increased SGOT only	3 (15.9%)
• increased SGPT only	0
CBC**	
• Anemia	11 (44%)
• Normal Hb	14 (56%)
• Leukopenia	4 (16%)
• Leukocytosis	3 (11.1%)
• Normal WBC count	18 (72.9%)

*: Data on only 19 patients were available.
**: Cases with ALL and NHL are excluded.

Complications included subdural effusion (one case) and hemolytic anemia (one case). A total of four (14.8%) cases died, and the age distribution of the deaths is shown in Table V.

Table V: Distribution of Deaths According to the Age of Patients with Salmonella Typhi Infections

Age in Months	No. of Patients	No. of Deaths
< 1	2	1
1-6	1	0
7-12	1	0
13-24	2	0
> 24	21	3
Total	27	4

The antimicrobial resistance of S.typhi was strikingly different in the first and second five-year period of the study (Table VI). There was no antimicrobial

Table VI: Antimicrobial Resistance of Patients with Salmonella Typhi Infections

	Frequency of Resistance (%)	
Antibiotics	1982 - 1987	1988 - 1992
Ampicillin	–	23.5
Chloramphenicol	–	17.6
Trimetoprim - sulfamethoxazole	–	17.1
Cephaperazone	–	–
Ceftriaxone	–	–

resistance detected during the period between 1982 and 1987. However, between 1988 and 1992, antimicrobial resistance was found to emerge against ampicillin (23.5%), chloramphenicol (17.6%) and trimetoprim-sulfamethoxazole (TMP-SMX) (17.1%), but there was still no resistance against third-generation cephalosporins such as cefoperazone and ceftriaxone.

Discussion

Human Salmonella infections are important at any age, but especially important in children. In our study, most cases were above two years of age, which may be attributed to the protective effect of breastfeeding.

The signs and symptoms of our cases were similar to those in other reported series[2, 5-7]. However, ataxia, aphasia and behavioral abnormalities are not classical findings of enteric fever although reported occasionally[2]. This emphasizes that in patients with unusual neurologic findings in addition to signs of infection such as fever, diarrhea and organomegaly, enteric fever should be considered.

In the laboratory findings, 68.5 percent of patients had increased SGOT and/or SGPT while only 44.3% had hepatomegaly and/or splenomegaly; these findings show that the liver may be involved even in the absence of hepatomegaly. Thus, liver enzyme levels may be a helpful laboratory test in the diagnosis of salmonellosis and should be measured in all suspected cases. On the other hand, anemia was detcted in 44 percent of the cases while 56 percent had normal hemoglobin counts according to age standards. Leukopenia was detected in 16 percent of patients and lekocytosis in 11.1 percent, while 72.9 percent had normal leukocyte counts. Although similar results were reported in a study from Singapore[7], our results are somewhat different from the other reports indicating leukopenia as more common[2, 8]. In another study it has been shown that leukocytosis is as common as leukopenia in children with typhoid fever, but most have normal leukocyte counts in contrast to adult patients[9].

In this study, it has been found that there was no antimicrobial resistance of S.typhi serotype between 1982-1987, while resistance against ampicillin, chloramphenicol and TMP-SMX developed after 1987. On the other hand, resistance against third-generation cephalosporins, being the newly introduced antimicrobial agents, has not yet developed. Thus, third-generation cephalosporins may be good alternatives for resistant cases[10, 11]. In addition to third-generation cephalosporins, response to ciprofloxacin has been very statisfactory[3]. However, wide use of these agents should be avoided, otherwise emergence of resistance will be inevitable in the near future. Since most cases in this study were lost to follow-up, we could not detect the carriers in our series.

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THE EFFECT OF HIGH – DOSE METHYLPREDNISOLONE ON CD34 – POSITIVE BONE MARROW CELLS IN CHILDREN WITH ACUTE MYELOBLASTIC LEUKEMIA*

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SUMMARY: Tuncer AM, Hiçsönmez G, Gümrük F, Albayrak D, Duru F, Güzel E, Şaylı T. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The effect of high-dose methylprednisolone on CD34-positive bone marrow cells in children with acute myeloblastic leukemia. Turk J Pediatr 1995; 37: 345-349.

The expression of CD34 antigen on the surface of bone marrow (BM) cells during remission induction was studied in 20 patients with CD34-negative acute myeloblastic leukemia (AML). The patients were given high-dose methylprednisolone (HDMP) alone for one week, after which time mitoxantrone and low-dose Ara-C were added.

BM cells from all patients were studied one, two and four weeks after initiation of treatment to evaluate CD34 antigen expression using a three-step peroxidase anti-peroxidase staining technique. The mean percentage of CD34-positive BM cells was 5.3% at presentation, increasing to 15.6% in the first week, 12.9% in the second week and 21.7% in the fourth week of therapy. During the same period the mean percentages of the initial BM blasts decreased from 64% to 22%, 7% and 2% in the first, second and fourth weeks of therapy, respectively. The increase in the CD34-positive BM cells one week after HDMP treatment alone suggests that HDMP directly or indirectly stimulates CD34-positive hematopoietic progenitor cells while decreasing BM blasts in patients with AML. *Key words: high-dose methylprednisolone, acute myeloblastic leukemia, CD34.*

All hematopoietic progenitor cells express the CD34 antigen, expression of which decreases during maturation of progenitor cells[1-3]. CD34 membrane glycoprotein expression is restricted to about one to five percent of normal bone marrow (BM) cells. Stimulation of CD34-positive cells in BM and acceleration of the recovery of peripheral blood leukocytes in leukopenic children with acute lymphoblastic leukemia (ALL) by high-dose methylprednisolone (HDMP) treatment have previously been reported by the current authors[4, 5].

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This study was undertaken to evaluate the effect of HDMP and its combination with cytotoxic chemotherapy on the expression of CD34 antigen-positive cells in the BM of CD34-negative acute myeloblastic leukemia (AML) patients during induction therapy.

Material and Methods

Patients: From September 1990 to April 1991, the expression of CD34 antigen of BM cells from 20 patients with CD34 negative AML (one with M1, 12 with M2, three with M3, three with M4, one with M5) was studied. The patients' ages ranged from five to 15 years. Diagnosis was made by morphology according to the French-American-British (FAB) classification, cytochemistry and cell surface marker analysis. Only CD34-negative cases were chosen in order to avoid any confusion of residual leukemic cells in bone marrow in remission. In this study less than 15 percent positivity was considered to be CD34-negative[6].

All patients received HDMP (30 mg/kg/day per orally) alone in the first week. Then mitoxantrone (0.3 mg/kg/week intravenous infusion) and low-dose Ara-C (0.3 mg/kg/twice daily subcutaneously) were combined with HDMP (20 mg/kg/day per orally). This combination was given for four weeks.

Immunoperoxidase Staining: Cells were obtained from heparinized BM aspirates at diagnosis and one, two and four weeks after the initiation of therapy. Mononuclear cells were separated by Ficoll-Hypaque^{R} (density 1.077 g/ml) gradient centrifugation. Air-dried cytospin slides were acetone-fixed and incubated with anti-CD34 monoclonal antibody (MoAb) (Anti HPCA-1, Sera Lab, England) as a primary antibody (diluted 1:10 in Tris-NaCl buffer containing 0.1% BSA, pH 7.4) and washed with tris-NaCl wash buffer[7]. They were incubated with peroxidase-conjugated rabbit anti-mouse IgG (p161, DAKO, Copenhagen, Denmark) and peroxidase-conjugated goat anti-rabbit IgG (Medao, Hamburg, Germany) followed by the addition of the substrate, 3 amino-9 ethylcarbazole (AEC, 30% Merck, Frankfurt, Germany). Hydrogen peroxide was added to the AEC solution to block endogenous peroxidase activity. Two hundred cells were counted to assess the antibody reactivity with CD34 antigen.

Statistical Analysis: Statistical analysis was performed by variance analysis and student's t test.

Results

CD34 reactivities, found to be 5.3 percent at diagnosis, increased to 15.6 percent, 12.9 percent and 21.7 percent one, two and four weeks after the initiation of treatment, respectively (Fig. 1). During the same period the mean percentages of BM blasts decreased from 64 percent to 22, 7 and 2 percent in the first,

second and fourth week of therapy, respectively (Fig. 1). There was significant difference in the percentages of CD34-positive cells at diagnosis and in the first week of treatment ($p < 0.05$). Although there was no significant difference between the first and second week results, the difference in the percentages of CD34-positive cells obtained in the second and fourth weeks of therapy was statistically significant ($p < 0.05$).

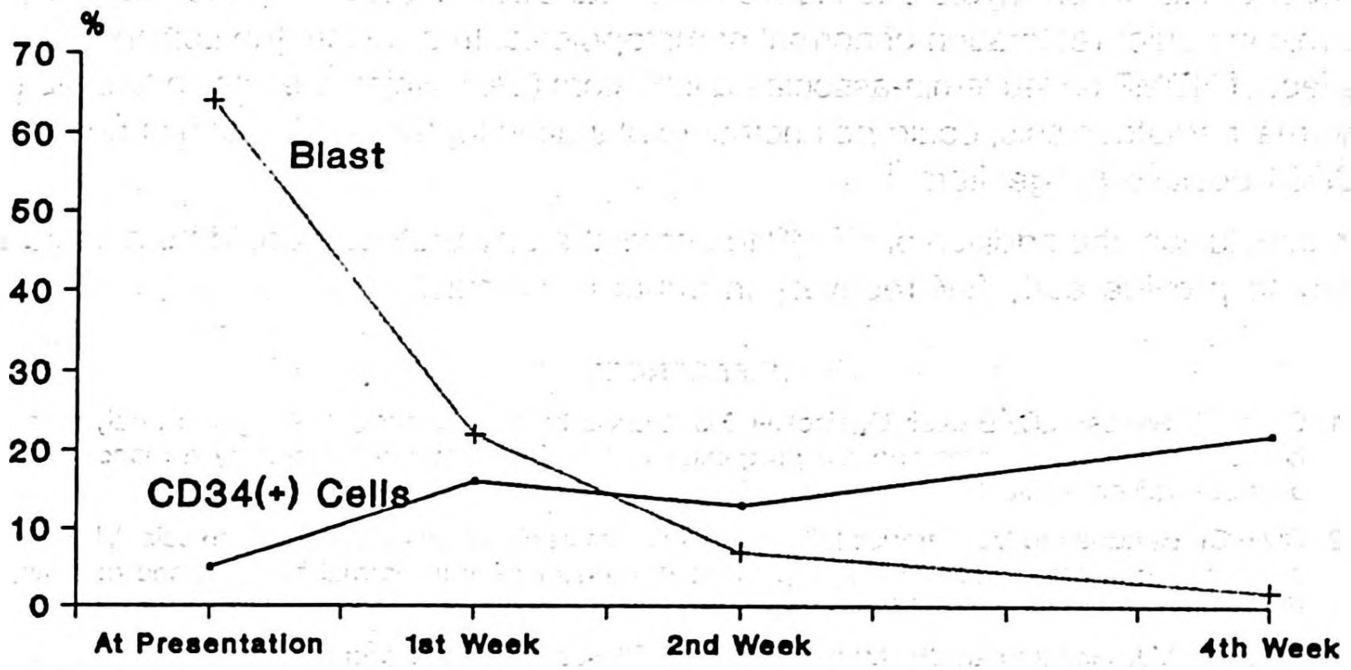

Fig. 1: The percentages of CD34 + cells and blasts in bone marrow.

Discussion

Our data has shown that the proliferation of $CD34^+$ progenitor cells is induced by HDMP treatment in AML during remission induction therapy. In our previous study we demonstrated that BM CD34-positive cells significantly increased during induction therapy in CD34-negative ALL patients who received HDMP treatment. In this study the increase in CD34-positive cells was found significantly higher than that obtained in patients who received conventional dose (2 mg/kg prednisolone) steroid therapy[4].

In the present study, in CD34-negative AML patients who received only HDMP treatment during the first week of therapy, the number of CD34 + cells increased, while BM blasts decreased significantly. The increase in the number of CD34-positive cells indicates the stimulation of normal hematopoietic progenitors.

The acceleration of peripheral blood leukocyte recovery in leukopenic patients with ALL by HDMP treatment was reported previously by Hiçsönmez et al.[5] This result might also be explained by the stimulation effect of HDMP on the proliferation of bone marrow $CD34^+$ hematopoietic cells. Similarly, enhanced

$CD34^+$ cells by intravenous administration of recombinant human granulocyte-macrophage colony stimulating factor (rhGM-CSF) has been shown by Sienna et al.[8] The proliferation of hematopoietic progenitors could also be explained by the stimulatory effect of HDMP on the endogenous production of some growth factors. Stimulation of endogenous production of GM-CSF in patients with ALL and AML has been reported by Tuncer et al.[9] Moreover, the in vivo differentiation effect of HDMP on myeloid leukemia cells has been shown[10-12]. This may play a role in earlier restoration of normal hematopoiesis. In addition, the suppressive effect of HDMP on leukemia-associated inhibitors (LAI), which are known to inhibit normal hematopoiesis, could be another explanation for the proliferation of normal CD34-positive progenitors[13].

In conclusion, the addition of HDMP to chemotherapy protocols could be a useful way to provide early BM recovery in acute leukemias.

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The Turkish Journal of Pediatrics 1995; 37: 351-356

SHOULD AN ECHOCARDIOGRAPHIC SCAN BE DONE ROUTINELY FOR INFANTS OF DIABETIC MOTHERS?*

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SUMMARY: Vural M, Leke L, Mahomedaly H, Maingourd Y, Kremp O, Risbourg B. (2nd Service of Pediatrics and Pediatric Cardiology Unit, Picardie Jules Verne University Faculty of Medicine, Amiens, France). Should an echocardiographic scan be done routinely for infants of diabetic mothers? Turk J Pediatr 1995; 37: 351-356.

Several cardiologic pathologies are seen in infants of diabetic mothers (IDMs). Though asymmetrical septal hypertrophy (ASH) is a frequent pathology in IDMs, it is not routinely searched for with an echocardiographic scan. We have performed an echocardiographic examination for all IDMs (56 neonates) hospitalized between January 1987 and December 1992 in our neonatology and neonatal reanimation units. Of 56 patients, the diagnosis of 17 cases of ASH (30%) was made. The group with ASH (17 neonates) had a greater corporeal index than the group without ASH (39 neonates) ($p < 0.05$). Four of the 17 IDMs (24%) with ASH and one of the 39 IDMs (3%) without ASH presented with a cardiac insufficiency ($p < 0.05$). ASH is a pathology which should be searched for routinely in IDMs. *Key words: infants of diabetic mothers, asymmetrical septal hypertrophy, diabetes mellitus, echocardiography.*

It is well known today that infants of diabetic mothers (IDMs) may present with many complications including macrosomia, poor intrauterine growth, organomegaly, hypocalcemia, hypoglycemia, hypomagnesemia, respiratory distress syndrome, hyperbilirubinemia and congenital malformations in the neonatal period[1-3]. Two types of cardiac pathologies are commonly observed in these infants: cardiac malformations and asymmetrical septal hypertrophy. Asymmetrical septal hypertrophy (ASH), a pathology often ignored in IDMs, was wirst described by Poland et al.[4] and then by Gutgesell et al.[5]

The purpose of this study was to determine the ASH frequency in IDMs and to examine the necessity of performing echocardiographic scan routinely.

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Material and Methods

Fifty-six IDMs hospitalized between January 1987 and December 1992 in the neonatology and neonatal reanimation units of the University Hospital (Amiens, France) were studied. An echocardiographic scan was done routinely regardless of cardiac or respiratory distress syndromes in the first 72 hours of life.

All echocardiograms were obtained with a Hewlett Packard 1000 SONO echograph with a 5 mhz transducer. End diastolic interventricular septal thickness was measured in M-mode at the third or fourth intercostal space and the left sternal border. We paid close attention to differentiating the posterior tricuspid valve leaflet from the ventricular septal endocardium. Septal hypertrophy is defined as +2 standard deviations compared to the gestational age of our reference population.

Infants presenting with blood sugar of less than 2 mmol/L in the total blood specimen were considered hypoglycemic. Bilirubinemia is defined as a serum bilirubin concentration of greater than 150 micromol/L, polycythemia as hematocrit of greater than 60 percent and hypocalcemia as serum calcium concentration of less than 1.75 mmol/L.

The results are expressed as a mean ± standard deviation, and Chi-square test was used for statistical calculations.

Results

Sixteen of 56 mothers had insulin-dependent diabetes mellitus, 37 had non-insulin-dependent diabetes and three had gestational diabetes. Summarized characteristics of our infant population with or without ASH are presented in Table I. The gestational age ranged from 32 to 42 weeks (mean 37.7 ± 2.3) and the birthweight from 1200 to 4970 g (mean 3628 ± 890). Sixteen of 56 infants (29%) were large for gestational age, two (4%) were small for gestational age and 38 (68%) were appropriate for gestational age.

Table I: Characteristics of Our Population, Grouped According to Presence or Absence of ASH

	without ASH (n = 39)	with ASH (n = 17)	p
Gestational age (weeks)	37.5 ± 2.4	37.5 ± 2.3	non significant
Birthweight (g)	3585 ± 920	3842 ± 804	non significant
Birth length (cm)	50 ± 4.1	51 ± 2.4	non significant
Corporeal index	2.79 ± 0.31	3.02 ± 0.23	< 0.05

The diagnosis of 17 cases of ASH was made out of 56 infants (30%) with a routine echocardiographic scan. No cardiac malformation or systolic anterior movement (SAM) was diagnosed.

Of the 56 IDMs, 36 (64%) presented with hypoglycemia and 11 (20%) presented with hypocalcemia, all of which resolved after supplementations. Fourteen (25%) were polycythemic and 34 (61%) were icteric. Fifteen (nine without ASH, six with ASH) of the neonates showed symptoms of respiratory distress syndrome, which led in six (three without ASH, three with ASH) cases to the need for mechanical ventilation (Table II).

Table II: Complications and Their Relations with Presence or Absence of Asymmetric Septal Hypertrophy

	without ASH (n = 39)	with ASH (n = 17)	p
Hypoglycemia	26 (67%)	10 (59%)	non significant
Hyperbilirubinemia	24 (62%)	10 (59%)	non significant
Polycythemia	11 (28%)	3 (17%)	non significant
Respiratory distress syndrome	9 (23%)	6 (35%)	non significant
Hypocalcemia	8 (21%)	3 (18%)	non significant
Cardiac insufficiency	1 (3%)	4 (24%)	< 0.05

Five of the infants required antidiuretic treatment because of cardiac insufficiency. Four of them were in the ASH group and only one did not have cardiomyopathy.

Discussion

The frequency of ASH in this study was 30 percent (17/56). Trowitzsch et al.[6] found ASH in 35 percent of their population of 30 IDMs, and Fenichel et al.[2] discovered 14 cases of ASH in 44 macrosomic IDMs (31%). Lusson et al.[7] reported six cases of this type of cardiomyopathy in 11 neonates. On the other hand, Erdem et al.[8] did not show any statistical difference in the thickness of the left ventricular posterior wall and the interventricular septum between 31 IDMs and 14 control infants.

In our population, there was no statistical difference between ASH and non-ASH groups for birthweight, length and gestational age. However, infants with ASH had a greater corporeal index than neonates without cardiomyopathy (Table I). It is generally agreed that corporeal index better reflects tissue development than a simple measure of weight or length. Insulin causes an increase not only in cell number but also in cell size of the fetus. The same hormone stimulates an increase in myocardial nuclei, cell number and fiber[9-11]. It is not surprising to find a parallel between interventricular septum thickness and corporeal index augmentation, both influenced by fetal hyperinsulinism (Fig. 1).

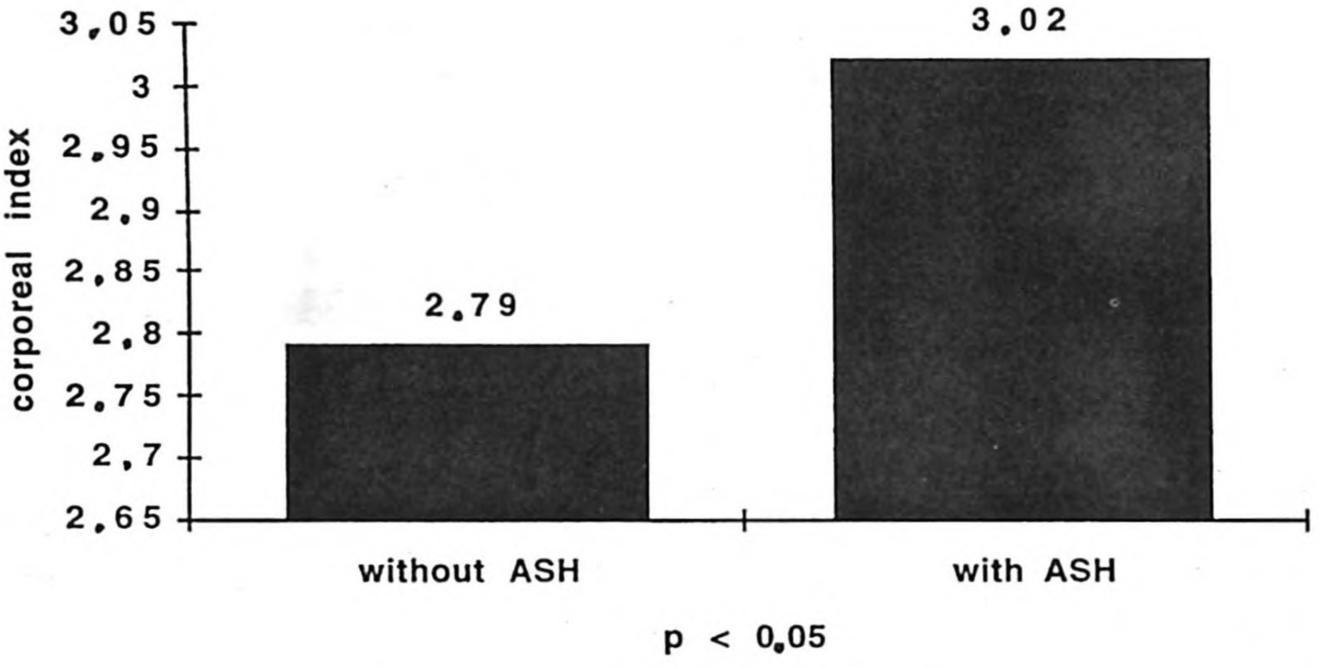

Fig. 1: Mean corporeal values are shown for each group. The difference is statistically significant.

The two groups were not statistically different when compared for bilirubinemia, glycemia, calcemia and hematocrit.

Though other authors found cardiac malformation, we had none in our population. Various studies have examined cardiac pathologies in IDM. Rowland et al.[3] found 19 infants with a congenital heart lesion out of 470 IDMs. Cruveiller[12] and Day[13] found rates of major cardiac malformations to be six percent and 3.6 percent, respectively. The only explanation we can make for the absence of malformation in our population may be better metabolic regulation in the first six to seven weeks of pregnancy.

Another statistically important result of our study was the presence of cardiac insufficiency syndrome in IDMs. This syndrome is seen in 24 percent of neonates presenting with an ASH but in only three percent of neonates without cardiomyopathy. This statistically significant difference shows the importance of an early ASH diagnosis, which may avoid progression towards cardiac insufficiency and sudden infant death syndrome. Diuretics (furosemide) are obligatory, and digoxine is contraindicated in the treatment. All of our neonates in the ASH group (with or without cardiac insufficiency syndrome) were surveyed until the age of six months. Disappearance of cardiomyopathy was observed in all of the 17 infants before six months of age (Fig. 2).

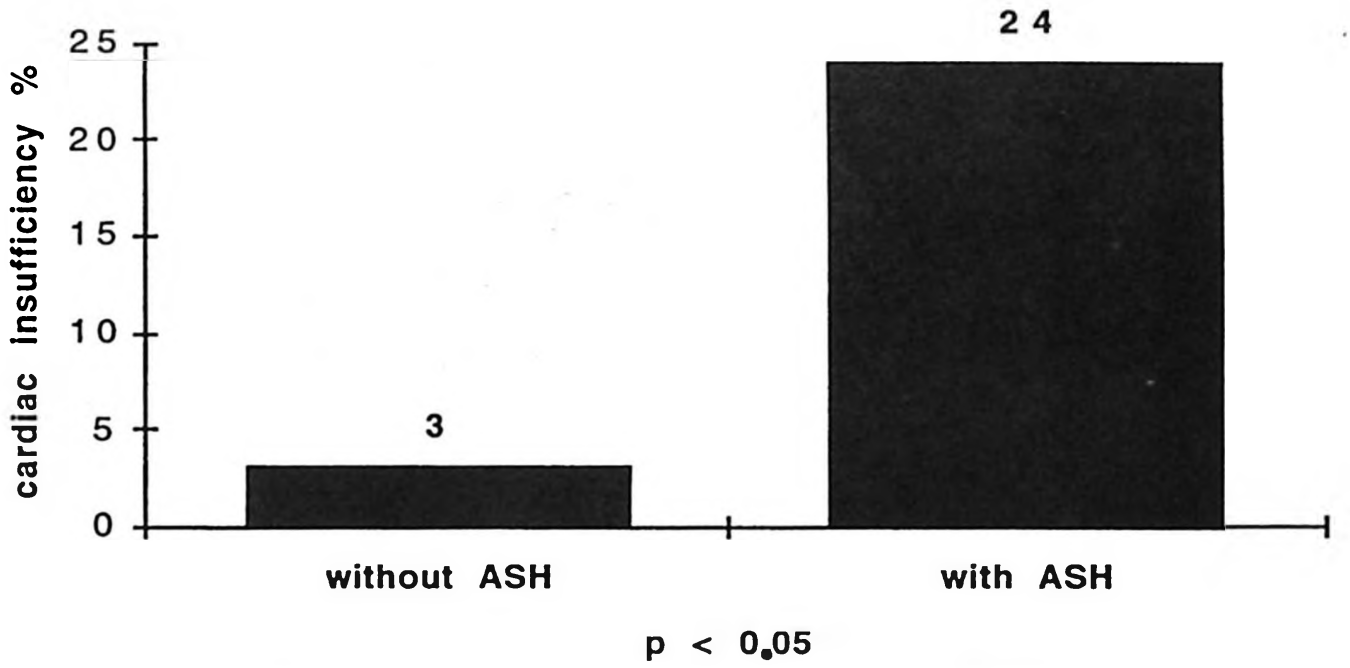

Fig. 2: Presence of cardiac insufficiency in each group.

Respiratory distress syndrome existed in both groups with no statistical difference. Artificial ventilation was indicated in three of four infants presenting with cardiac insuffiency secondary to cardiomyopathy. In the group without cardiomyopathy, artificial ventilation was indicated once secondary to cardiac insufficiency, and twice secondary to hyaline membrane disease.

This study shows the importance of echocardiography for the diagnosis of asymmetric septal hypertrophy (17/56 in our population) in infants of diabetic mothers. The risk of cardiac insufficiency is much more important in IDMs with ASH. ASH is a pathology which should be searched for routinely in each IDM, and its echocardiographic follow-up is obligatory until complete disappearance.

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The Turkish Journal of Pediatrics 1995; 37: 357-373

RENAL AMYLOIDOSIS IN CHILDHOOD*
An Overview of the Topic with 25 Years Experience

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SUMMARY: Tınaztepe K. (Nephropathology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Renal amyloidosis in childhood: an overview of the topic with 25 years experience. Turk J Pediatr 1995; 37: 357-373.

Amyloidosis is a heterogeneous group of diseases characterized by extracellular accumulation of an eosinophilic, hyalin and proteinaceous material containing mucopolysaccharide substance in various tissues and organs. Knowledge about the chemical structure of amyloid fibril proteins has led to the recognition of various forms of amyloidosis including Amyloid-A (AA), Amyloid-L (AL), hereditary, senile, dialysis-related, localized and cerebral amyloidosis. It is now recognized that all types of amyloid contain amyloid P (AP) component which is derived from the serum amyloid P component, a normal circulating glycoprotein and a member of the pentraxin family. A recent classification proposed by WHO-IUIS (Nomenclature Subcommittee) is based on the chemical nature of amyloid fibris rather than their clinical and pathologic features. The kidneys are frequently involved, and renal failure is the major cause of death.

Childhood renal amyloidosis is almost always secondary (reactive, AA type) and usually associated with chronic inflammatory, infectious and heredofamilial diseases. In developed countries, rheumatoid arthritis is the most common cause of renal amyloidosis, while in developing countries patients with familial Mediterranean fever (FMF) (untreated) and chronic suppurative infections constitute a large proportion of renal amyloidosis cases. No specific therapy is currently available for amyloidosis. Once renal amyloidosis develops, progress to end-stage renal failure is almost inevitable within 2-13 years. The aim of treatment is to give effective supportive therapy and to control the underlying diseases by colchicine, alkylating agents and appropriate antibiotics. The prognosis of patients with end-stage renal failure can be improved by maintenance dialysis and renal transplantation. The growing knowledge about the pathogenesis and chemical nature of amyloid fibris may open up further avenues for the discovery of specific therapeutic modalities against amyloidosis. *Key words: renal amyloidosis, childhood, AA amyloidosis, WHO classification, pathogenesis.*

Amyloidosis is a multisystemic disease characterized by deposition of an extracellular eosinophilic substance in various organs[1, 2]. It may be localized or systemically distributed throughout the body, leading to organ damage and failure, and serious morbidity. Although the etiopathogenesis remains unsettled, recent advances in determination of the chemical structure of amyloid proteins has resulted in recognition of various forms of amyloidosis includin Amyloid-A, Amyloid-L, hereditary, senile, dialysis-related, localized and cerebral amyloidosis[3]. In addition, it is now recognized that all types of amyloid contain

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amyloid P (AP) component which is derived from the serum amyloid P component, a normal circulating glycoprotein and a member of the pentraxin family[3,4].

The kidneys are frequently involved in amyloidosis, and renal failure is the major cause of death. Cases of childhood renal amyloidosis are usually secondary to chronic inflammatory and infective disorders and familial conditions[1,2-5]. The incidence of renal amyloidosis as a cause of nephrotic syndrome has been estimated at about four percent in childhood, while its incidence varies from three to 12 percent in renal biopsies[2,5].

In an earlier study from our center (referral) of 170 children with biopsy-proven nephrotic syndrome, 33 cases (19%) were reported to have renal amyloidosis[6]. Additionally, the disease constitutes 11.5 percent of biopsy-requiring pediatric nephrological diseases in our center. The geographic predisposition of our country to familial Mediterranean fever (FMF) and the frequency of consanguineous marriages make renal amyloidosis a common nephrologic problem in childhood in Turkey.

Nomenclature and Classification

Many attempts have been made to classify amyloidosis. Most classifications have been based on the clinicopathological features. However, the methods for isolating and purifying amyloid fibrils and for identifying the chemical nature of the fibril proteins and their precursors have greatly developed, and amyloidosis is now classified on this basis. The most recent is the classification proposed by WHO-IUIS* Nomenclature Sub-committee in 1993 (Table I)[7]. The distinction between systemic and localized (organ or tissue-limited) amyloidosis has been avoided unlike in previous classifications, since some amyloid deposits which are thought to be localized might represent a predilection site of systemic amyloidosis.

Pathogenesis

The amyloid deposit is composed of amyloid fibrils which are rigid, linear, non-branching, 7.5-10 nm wide and of indefinite length. They are insoluble and resistant to proteolytic digestion. These properties are partly related to "β-pleated sheet" conformation revealed by x-ray crystallography[1] (Fig. 1). Although very little is known about the factors involved in the formation and deposition of amyloid fibrils, it is clear that the presence of a protein precursor is necessary. The precursors could be either locally produced or circulating substances which are mainly abnormal in structure or concentration or both. Proteolytic cleavage of the precursor is also important in fibril formation since the subunit of a given fibril is usually a lower molecular weight fragment of the precursor. After cleavage, the fragment can aggregate itself and/or interact with the other fragments, leading

* International Union of immunological Societies.

to polymerization and fibril formation. However, there is now evidence that some intact undegraded variant transthyretin and β-2 macroglobulin molecules can also form fibrils in familial amyloid polyneuropathy and dialysis-related amyloidosis, respectively[3]. It seems clear that the presence of a precursor is necessary; however, the factors which determine the deposition of the amyloid in some individuals but not others, and its distribution throughout the body, are still unknown.

Table I: Neomenclature and Classification of Amyloid and Amyloidosis (WHO-IUIS Neomenclature Sub-Committee 1993)

Amyloid protein[a,b]	Protein Precursor	Protein Type or Variant	Clinical Diagnosis
AA	ApoSAA		Reactive (secondary) amyloidosis Familial Mediterranean Fever Familial amyloid nephropathy with urticaria and deafness (Muckle-Wells syndrome)
AL	κ, λ, e.g.,κIII	Aκ, Aλ, e.g., AκIII	Idiopathic (primary) amyloidosis, associated with myeloma or macroglobulinemia
AH	IgG 1 (γ1)	Aγ1	
ATTR	Transthyretin	e.g., Met 30[c]	Familial amyloid polyneuropathy, (Portuguese)
		e.g., Met 111	Familial amyloid cardiopathy, (Danish)
		TTR or Ile 122	Systemic senile amyloidosis
AApoAI	ApoAI	Arg 26	Familial amyloid polyneuropathy, Iowa
AGel	Gelsolin	Asn 187[d]	Familial amyloidosis, Finnish
Acys	Cystatin C	Gln 68	Hereditary cerebral hemorrhage with amyloidosis, Icelandic
Aβ	β protein precursor e.g., βPP 695[e]	Gln 618	Alzheimer's disease Down syndrome Hereditary cerebral hemorrhage with amyloidosis, Dutch
Aβ2M	β2-microglobulin		Associated with chronic dialysis
AScr	Scrapie protein precursor 33-35[f] cellular form	Scrapie protein 27-30	Creutzfeldt-Jacob disease, etc..
		e.g., Leu 102	Gertsmann-Straüssler-Scheinker syndrome
Acal	(Pro) calcitonin	(pro) calcitonin	In medullary carcinoma of the thyroid
AANF	Atrial natriuretic factor		Isolated atrial amyloid
AIAPP	Islet amyloid polypeptide		In islet cells of Langerhans Diabetes type II, insulinoma
AIns[g]	Insulin		Islet amyloid in the degu (a rodent)
AApoII[g]	ApoAII (murine)	Gln5	Amyloid in senescence, accelerated mice

[a] Non-fibrillar proteins, e.g., protein AP (amyloid P component), excluded.

[b] Abbreviations: AA, amyoid A protein; SAA, serum amyloid A protein; apo, apolipoprotein; L, immunoglobulin light chain; H, immunoglobulin heavy chain.

[c] ATTR Met 30 when used in text.

[d] Aminoacid position in the mature precursor protein. The position in the amyloid fibril protein is given in parentheses.

[e] Number of amino acid residues.

[f] Molecular mass (kilodaltons).

[g] Not found in humans.

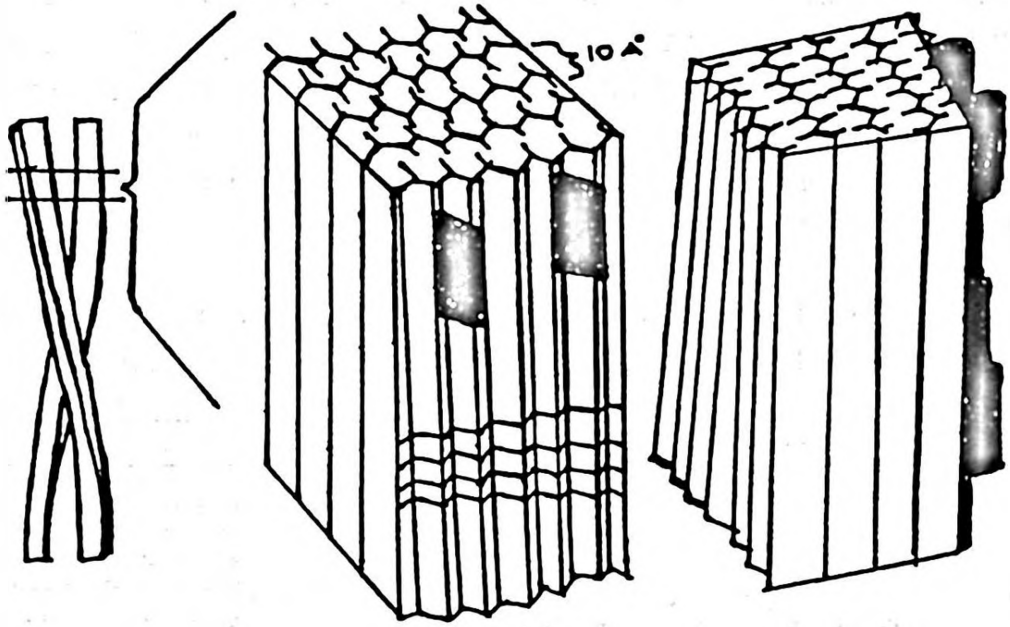


Fig. 1: "β-pleated sheet" structure of AA and AL fibrils. (The black areas represents the places where the molecules of Congo red dye bind to amyloid fibrils).

Amyloid-L protein (AL) is the major component of amyloid fibrils in multiple myeloma, macroglobulinemia and idiopathic (primary) amyloidosis. The AL proteins consist of polypeptide chains derived from immunoglobulins. The amino acid sequence of these chains has been found in some cases to be identical with the variable region of circulating light chains from the same patients. The constant region of the light chain at the C-terminal end is usually deficient, suggesting a cleavage mechanism (Fig. 2). Certain Bence-Jones proteins which were found in the primary type of amyloidosis can form fibrils in vitro showing all the morphologic and staining characteristics of amyloid[1,3].

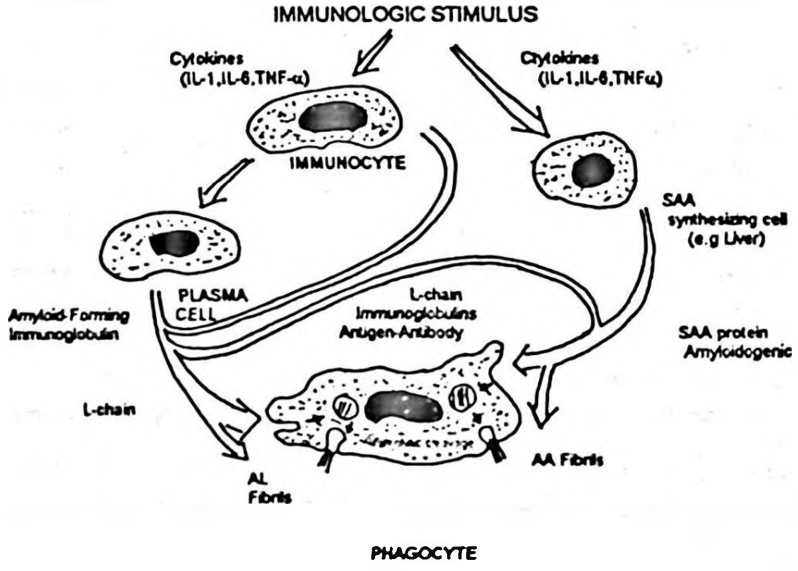


Fig. 2: Schematic representation of amyloidogenesis.

Amyloid-A protein (AA) is found in secondary (reactive) amyloidosis, familial Mediterranean fever and familial amyloid nephropathy with urticaria and deafness (Muckle-Wells' syndrome). It is likely derived from serum amyloid A (SAA), an acute-phase protein synthesized and secreted by the liver in response to interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF). In a few individuals, the cells of the mononuclear phagocyte system are thought to be partially responsible for cleavage of SAA to form a fragment of 8500 kDa which makes amyloid deposits in several organs and systems (Figs. 2, 3). From the murine models it is known that SAA is polymorphic, and only gene products of SAA 2 are amyloidogenic[3, 4]. On the other hand, susceptibility to AA amyloidosis may be related to amyloid enhancing factor (AEF), which accelerates deposition of the amyloid. AEF is likely a product of immunologically competent spleen cells, but its chemical structure is unknown.

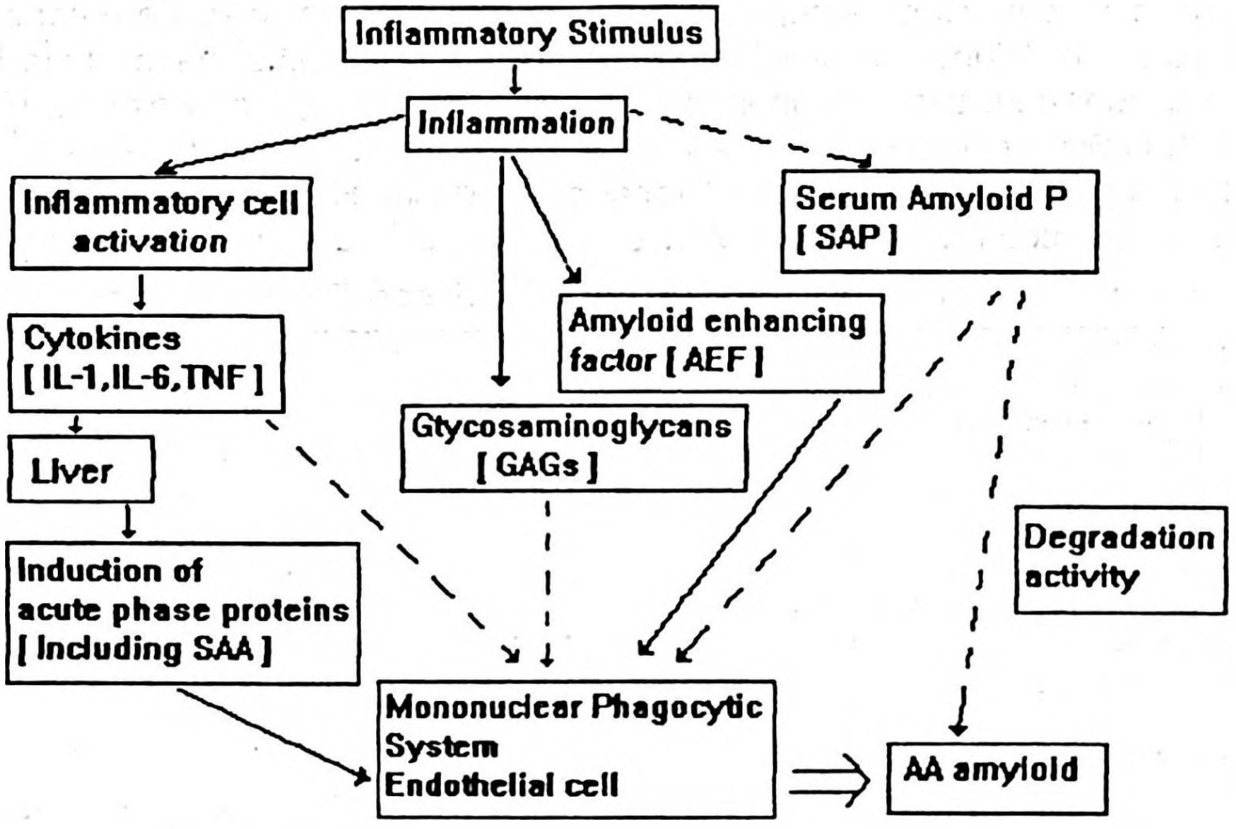


Fig. 3: Pathogenesis of reactive (AA type) amyloidosis.

Amyloid deposits have two additional constituents: sulphated glycoaminoglycans (GAGs) which are mainly heparin or heparansulphate, and amyloid P (AP) component. They are all present in all types of amyloid deposits. GAGs may be important in forming and maintaining β-pleated sheet structure. AP, which comprises 15 percent of the amyloid deposit, is identical and derived from a normal circulating plasma protein, a member of the pentraxin family SAP is also a normal constituent of the glomerular basement membrane and elastic fiber microfibrils throughout the body. The role of SAP in the pathogenesis of

amyloidogenesis is not known, but its function may be related to the binding reactions of amyloid with DNA, chromatin, GAGs and fibronectin and may contribute to the persistence of amyloid deposits by protecting them against proteolytic digestion[3, 8]

Clinical and Laboratory Features

Amyloidosis is rare in childhood. Primary amyloidosis-associated multiple myeloma or plasma cell dyscrasia has not been reported in children. It is uncommon before the age of 50, and the prominent clinical manifestations are cardiomyopathy, nephropathy, carpal-tunnel syndrome, hepatomegaly, subcutaneous nodules, hemorrhagic diathesis, macroglossia and peripheral autonomic neuropathy[1, 2].

Childhood amyloidosis is almost always secondary (AA type), and is usually associated with juvenile rheumatoid arthritis, chronic suppurative infections and familial Mediterranean fever (Table II)[2, 9-11]. Chronic infections such as tuberculosis, chronic pyelonephritis, empyema and brochiectasis are common causes of amyloidosis in developing countries. On the other hand, there has been a significant decrease in infectious causes of AA-type amyloidosis in the majority of Western countries where juvenile rheumatoid arthritis has been reported to be the most common cause of renal amyloidosis. However, this is not the case for our country and other Mediterranean and Middle Eastern countries.

Table II: The Predisposing Causes of Childhood Renal Amyloidosis.

A. Inflammatory
– Juvenile Rheumatoid Arthritis
– Reiter's syndrome
– Psoriatic arthritis
– Dermatomyositis
– Scleroderma
– Behçet's syndrome
– Inflammatory bowel disease
B. Infectious
– Tuberculosis
– Bronchiectasis
– Cystic fibrosis
– Chronic lung and pleural infections
– Chronic bone infections
– Chronic pyelonephritis
– Paraplegia
– Chronically infected burns
– Others (Mucormycosis, schistosomiasis etc.,)
C. Neoplastic
– Hodgkin's disease
– Renal carcinoma
– Others (Lymphomas, carcinomas of the gastrointestinal tract, etc.,)
D. Heredofamilial conditions
– Familial Mediterranean fever (FMF)
– The other familial autosomal dominant forms of amyloidosis

In our center, we studied 174 children (the majority being referrals) with renal amyloidosis whose ages ranged from four to 18 years and found that familial Mediterranean fever (FMF) as an underlying disease accounted for the majority of the cases[10] (47.7%) (Table III). In 46 cases (26.4%), no underlying disease was determined. However, in this undetermined group, the development of AA-reactive type of amyloidosis could be explained as follows: Because of the geographic predisposition and the high rate of consanguineous marriages in our country, 46 cases of the undefined group as seen in Table III could be phenotype II patients

Table III: The Distribution of Associated Conditions in 174 Cases with Renal Amyloidosis

Associated Condition	Number Cases	%
Familial Mediterranean fever (FMF)	83	47.7
Undefined*	46	26.4
Juvenile rheumatoid arthritis (JRA)	15	8.6
Tuberculosis	9	5.1
Chronic suppurative infections**	5	3.0
Unusual associations		
– Hodgkin's lymphoma	3	1.7
– Bronchial asthma	3	1.7
– Henoch-Schönlein syndrome (HSS)	3	1.7
– Cirrhosis	2	1.1
– MPGN***	1	0.6
– Rheumatic Heart Disease	1	0.6
– Alveolar Microlithiasis	1	0.6
– Myelofibrosbis	1	0.6
– Prader-Willi syndrome	1	0.6

* Accepted as possible phenotype II FMF cases. Thus FMF probably accounted for 74.1% of the cases.

** Chronic pyelonephritis, lung abscess, empyema and bronchiectasis.

*** Membranoproliferative glomerulonephritis.

of FMF, in which renal amyloidosis precedes the classical signs and symptoms of FMF. Therefore, FMF probably accounted for nearly three-fourths (74.1%) of the cases with renal amyloidosis. As shown in Table IV, together with the above-mentioned series, we have experienced unusual associated cases in 18 patients out of 254 renal amyloidosis cases over a period of 30 years in our center[12, 13].

Table IV: Unusual Associations in 174 Cases with Amyloidosis

Disorder	Number of Cases
Hodgkin's lymphoma	3
Bronchial asthma	3
Henoch-Schönlein syndrome (HSS)	3
Cirrhosis	2
MPGN*	1
Rheumatic Heart Disease	1
Alveolar Microlithiasis	1
Myelofibrosis	1
Prader-Willi syndrome	1
Hyper-IgM syndrome	1
Mucocutaneous candidiasis	1

* Membranoproliferative glomerulonephritis.

Four characteristic stages are described in amyloid nephropathy associated with FMF[9]. The first stage is the preclinical stage in which there are no clinical signs of amyloidosis, but amyloid deposits could be present in the body for an unknown period and be detected histologically in causal appendectomies, as well as in renal and rectal biopsies of patients with negative urinary findings. The second stage (proteinuric stage) is the longest stage and lasts for two to 10 years (usually 3-5 years). There is first intermittent and later continuous and increasing proteinuria without significant changes in urinary sediment. There is no disturbance in renal functions except for nonselective proteinuria. During the third stage (nephrotic stage), increasing proteinuria eventually results in full-blown nephrotic syndrome in six months to five years (usually 1-2 years). The degree of proteinuria may reach 20-30 g per day, and serum albumin levels may decrease to 1 g/dl. Severe edema develops and the disease course might be complicated by infections or renal vein thrombosis manifested as a sudden increase in proteinuria and acute deterioration of renal functions. The last stage is the uremic stage which lasts for six months to six years (usually 1-1.5 years). During this stage, the serum creatinine level increases and the features of renal failure appear.

Hypertension has been found to occur in 20-50 percent of adult patients, while its highest incidence has been 14 percent in pediatric cases[2, 5, 9, 10]. This wide range depends on the clinical stage and age of the patient with renal amyloidosis. The incidence of hypertension considering all stages was found to be as low as 2.8 percent in Hacettepe's pediatric series, leading to the conclusion that hypertension was a rare complication of childhood renal amyloidosis[10]. Proteinuria and edema may decrease or persist in some cases. The overall period from the first appearance of proteinuria to end-stage renal failure ranges from two to 13

years (mean four years). The amyloidogenic process is accelerated in young children. In our patients with FMF, amyloidosis occurred within approximately 4.7 years after the first attack of FMF.

Rheumatoid arthritis, which has been reported to be the most common cause of AA-type amyloidosis in Western countries, was third in rank of the causes in the Hacettepe series following FMF and chronic infections. Symptoms depend on the tissues involved. When the kidney or heart is affected, functional impairment may cause death. In our study, edema was the most common sign (87.8%), whereas hypertension was present in 2.8 percent of cases. The presenting features are shown in Table V. Proteinuria is the most common presenting feature of secondary amyloidosis and has been observed in 82-100 percent of cases, while nephrotic syndrome has been described in 37-87 percent of cases with amyloidosis[1,2,9]. In our pediatric series, proteinuria of varying degrees was present in all cases (100%) sixty-four percent of patients were nephrotic. Hematuria was noted in 7.2 percent of cases, hypoalbuminemia in 122 (7.3%) and azotemia in 56 (34.3%). Laboratory data are summarized in Table VI.

Table V: Presenting Features of 174 Cases with Renal Amyloidosis

Sign	Number of Cases	%
Edema	154	88.5
Hepatomegaly	30	17.0
Splenomegaly	18	14.3
Hypotension	9	5.1
Hypertension	5	2.8

Table VI Laboratory Data of Cases with Renal Amyloidosis at the Time of Diagnosis

Findings	Number of Cases	%
Anemia	47 (160)*	29.4
Leukocytosis	91 (158)	57.6
Proteinuria	174 (174)	100.0
Hematuria	13 (166)	7.2
Hyposthenuria	25 (145)	17.4
Azotemia	56 (163)	34.1
Hypoalbuminemia	122 (167)	73.0
Hyperlipidemia	105 (155)	67.7
Hypercholesterolemia	116 (148)	78.3
Decreased Clcr**	44 (108)	40.7

* Number of cases so tested in parentheses.
** Creatinine clearance.

The age at onset of renal amyloidosis associated with untreated FMF appears to differ in various ethnic groups[9]. The majority of cases may occur in childhood as early as the first decade of life in our country, other Middle Eastern and some African countries, while renal amyloidosis occurs after the second decade in the majority of cases in some European countries[2, 10]. We found that the majority of our cases presented between the second half of the first decade and the first half of the second decade of life. The variation in onset of development of renal amyloidosis associated with FMF could be explained by possible genetic factors. Our proposal is that different phenotypes can arise due to population-specific mutations, the presence and effect of modulator alleles, and the effect of enviromental factors.

Pathologic Findings

Classically, the kidneys are described as large pale kidneys. However, they may demonstrate prominent contraction with granular cortical surfaces, especially when associated with prolonged hypertension.

A) Light Microscopic Findings: The earliest deposits in glomerular amyloidosis are in the mesangium. Initially, their distribution occurs irregularly (segmental form) (Fig. 4), but as deposition increases the involvement becomes more uniform. It

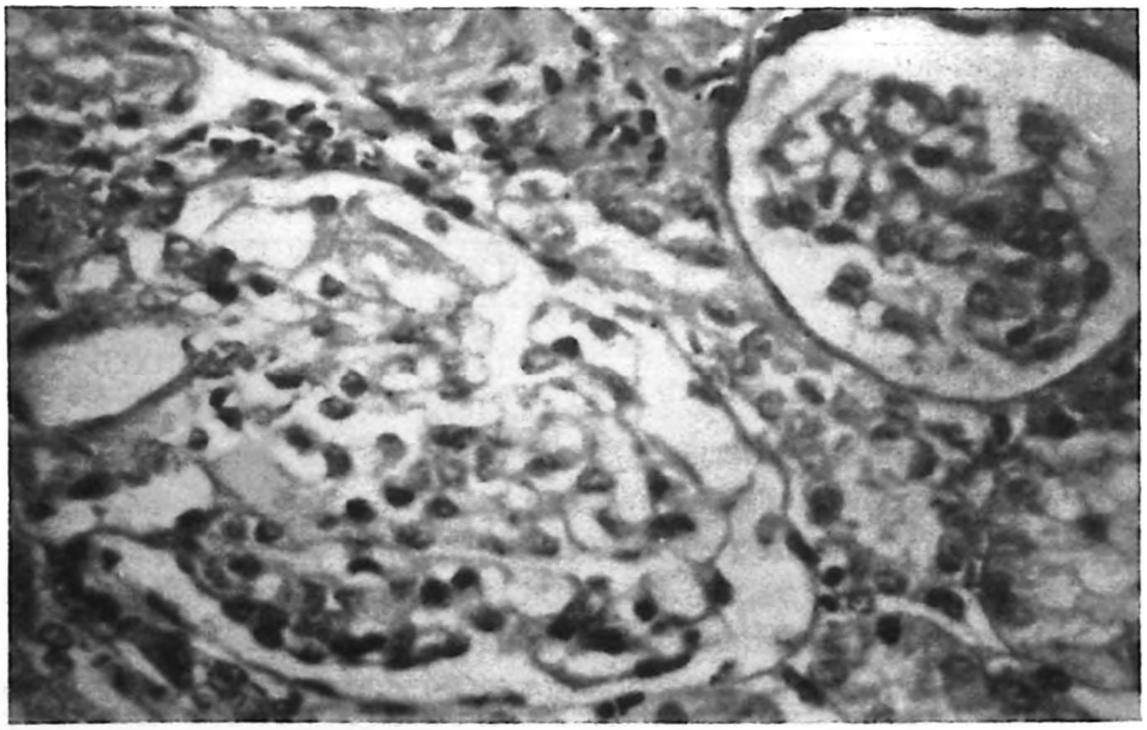


Fig. 4: Segmental amyloid deposition in a glomerulus (Grade I). HE x 450.

may form nodules (nodular form) (Fig. 5) or spread instead along the capillary

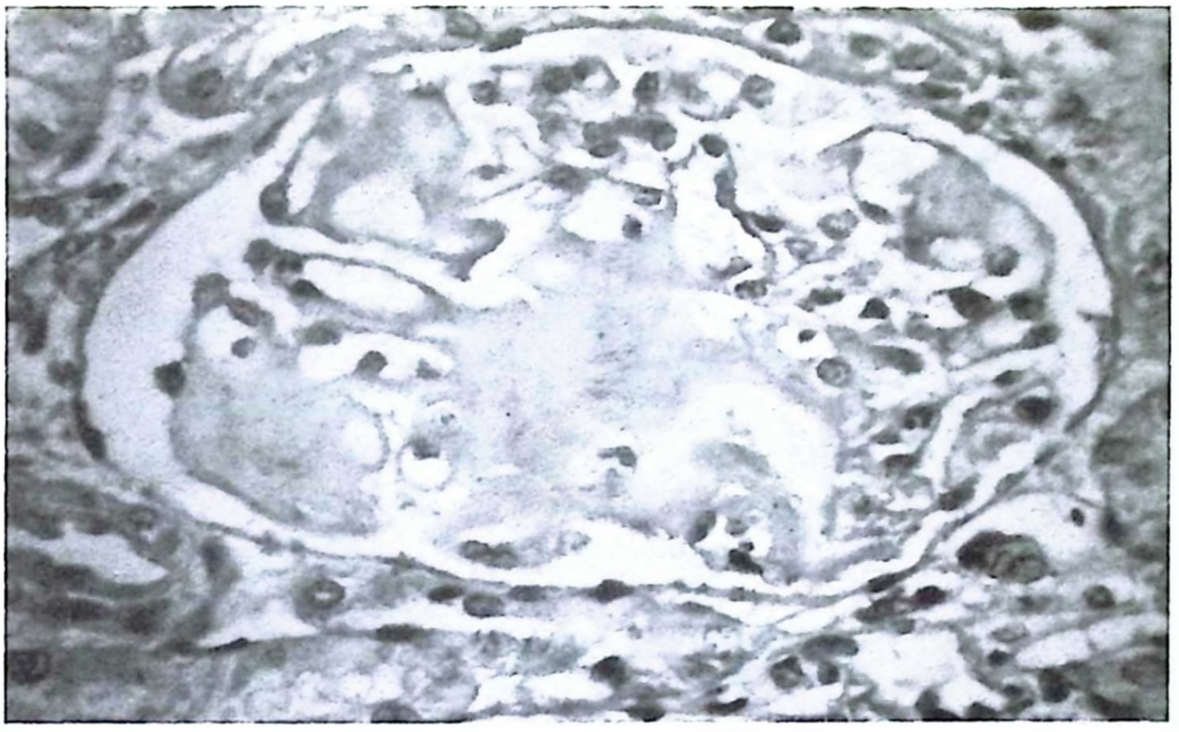


Fig. 5: Nodular type of amyloid deposition (Grade II). HE x 450.

walls (diffuse form) (Fig. 6). In some cases, there may be a combination of nodular

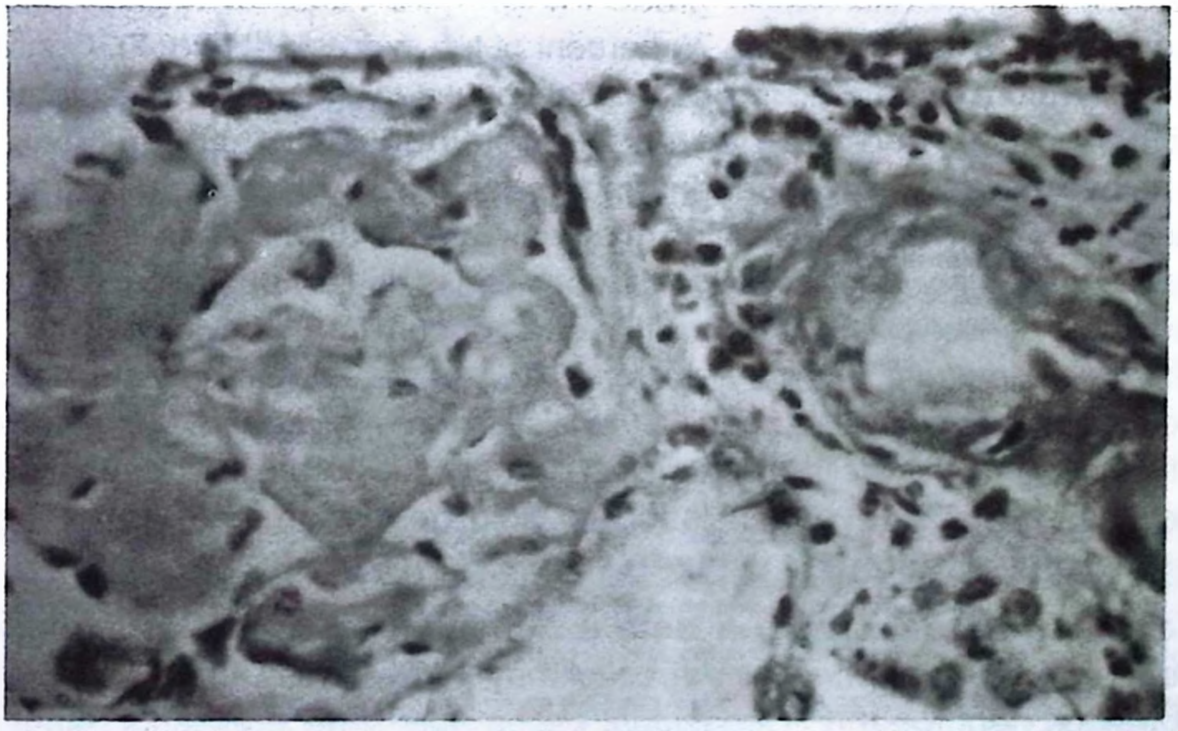


Fig. 6: Diffuse form. Diffuse staining of capillary walls and an adjacent muscular artey is seen (Grade III). Congo red x 450.

and diffuse forms (mixed form) (Fig. 7)[10]. The amount of glomerular amyloid has

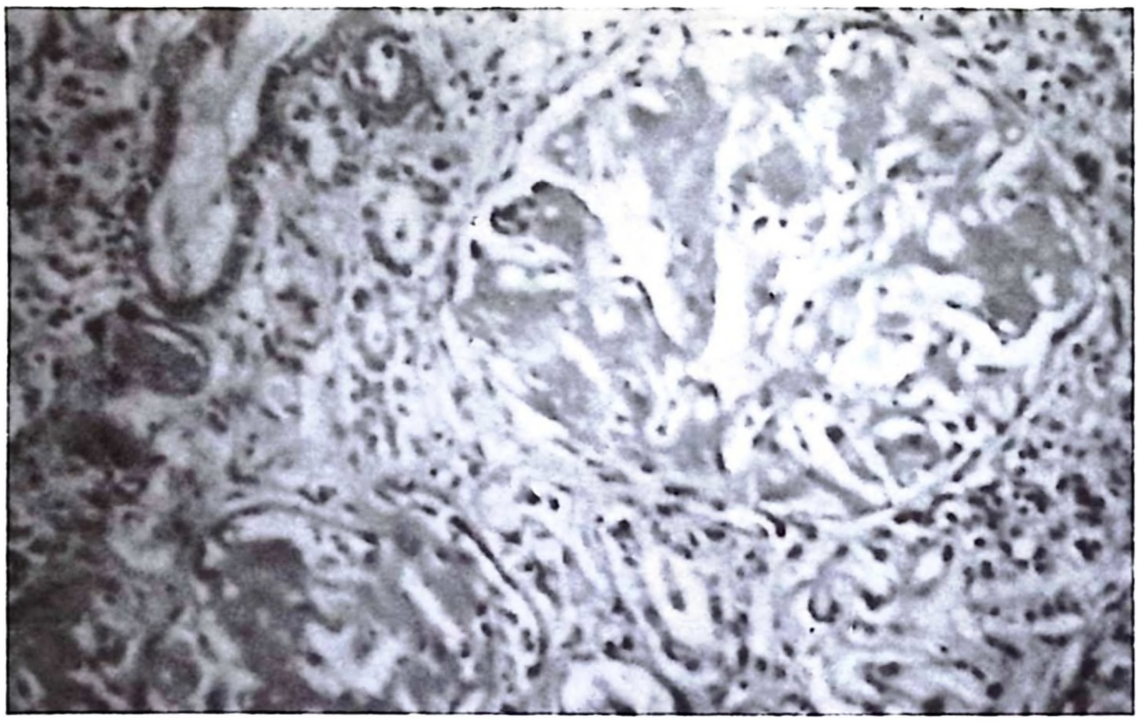


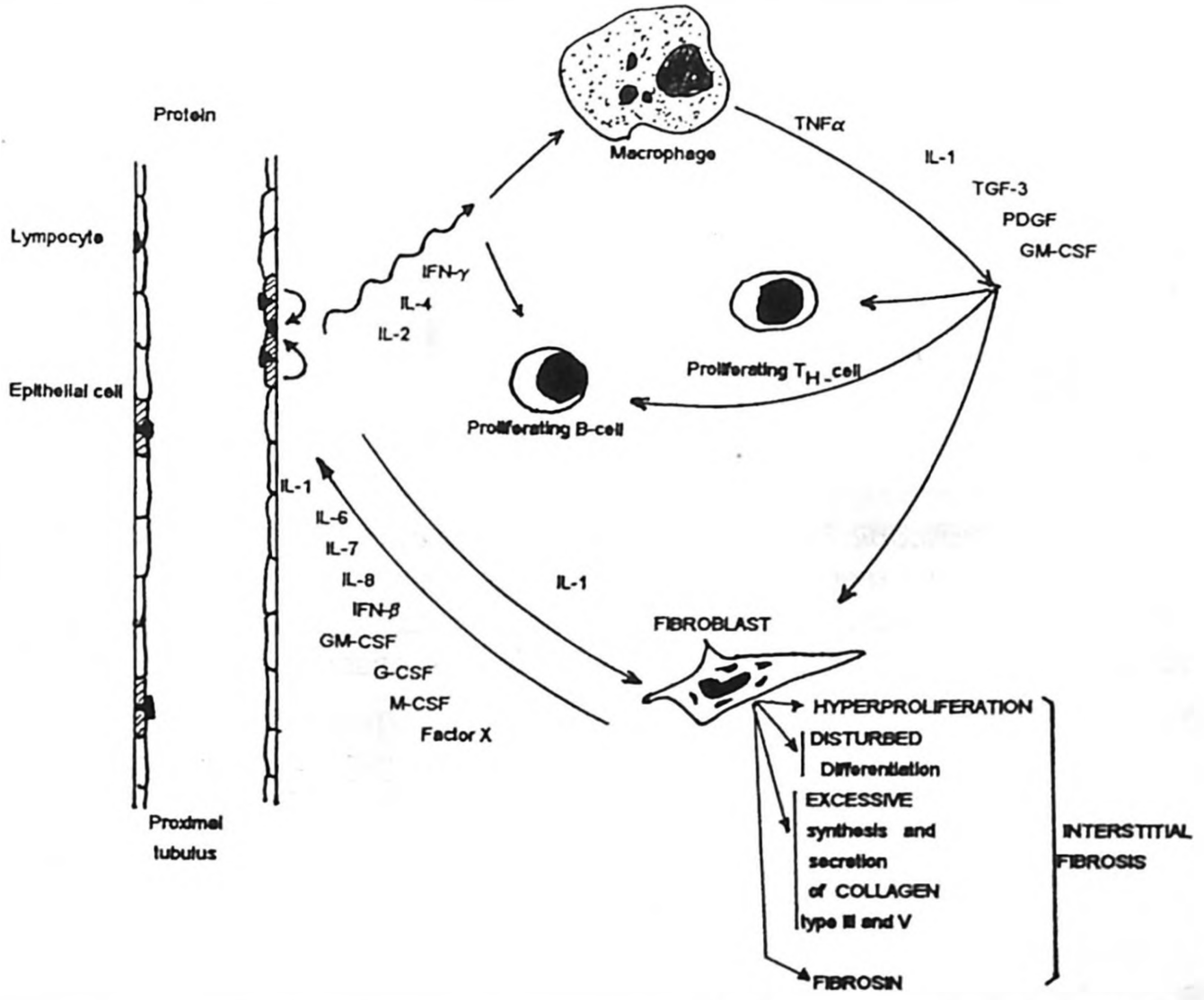
Fig. 7: Mixed form (Grade III). Note both diffuse staining of capillary walls and nodule formation in the mesangium.

been classified as grade I, II or III. Amyloid deposits were found to occupy 25 percent of glomerular tuft in grade I (Fig. 4) 25-75 percent glomerular tuft in grade 2 (Fig. 5) and more than 75 percent of tuft in grade III (Fig. 7). Consistent with the literature, we found no correlation between the amount of glomerular amyloid deposits and the degree of proteinuria. On hematoxylin-eosin (HE)-stained sections, an important finding for amyloidosis is an increment of mesangial matrix with pink-staining material without an increase in mesangial cellularity. In AA amyloidosis, amyloid deposition is usually perireticular, whereas an additional pericollagenous deposition often occurs in AL amyloidosis[1]. In early stages, the glomerular capillary walls are free of detectable amyloid deposits. As the deposits increase, the capillary walls become thickened. It is noteworthy that thickening of the walls of arterioles/arteries due to amyloid deposits does not necessarily cause hypertension[10]. Amyloid deposition tends to involve the whole vessel wall, and may occur in vessels of all sizes.

Amyloid may be deposited in both a subepithelial and a subendothelial distribution. The subepithelial deposits may form diffuse spikes and mimic membranous nephropathy. Occasional cases may show crescents, giant cells and sclerosis in glomeruli. Tubuli show no changes in the early stages. Later on, deposition occurs along the tubular basement membrane. The increased

accumulation of amyloid in glomeruli, tubuli, loops of Henle and interstitium may lead to tubular atrophy. In our series of 174 cases, we found that the creatinine clearance was very low in grade III cases, particularly in those with tubular atrophy.

Interstitial fibrosis may be seen occasionally, and there is a significant negative correlation between the degree of interstitial fibrosis (particularly, in the renal cortex) and the creatinine clearance. Therefore, it is not suprising that even cases with mild amyloidosis accompanied by interstitial fibrosis may have renal failure[10]. The leakage of proteins through the disturbed glomerular basement membranes may cause a series of immunological events leading to renal cortical interstitital fibrosis, the pathogenesis of which is described in detail in Figure 8.



Endogenous proteins pass into urine through the areas of podocyte denudation caused by subepithelial amyloid deposits. These proteins, then reabsorbed by proximal tubulus epithelial cells (PTECs) and processed as antigen. PTECs probably express these antigens in association with MHC-Class II molecules on their surface and present them to intraepithelial lymphocytes which subsequently release several cytokines. These mediators cause activation and proliferation of local macrophages and T-cells. Further release of various cytokines can also activate renal fibroblast cell system and activated renal fibroblasts may respond with hyper proliferation, disturbed differantiation and synthesis of fibrosin and excessive amounts of collagen. These events end up with renal cortical interstitial fibrosis leading chronic renal failure. IL-1: Interleukin 1, IL-2: Interleukin 2, IL-4: Interleukin 4, IL-1: Interleukin 1, INF β: Interferon-β, INFT: Interferon-T, INF, Tumor necrosis factor, TGF-3: T cell growth factor, PDGF: Platelet derived growth factor, GCSF: Granulocyte macrophage colony stimulating factor, MCSF: Macrophage colony stimulating factor, TH: T-Helper cell ICAM 1, intercellular adhesion molecule 1, HLA: Human Leukocyte antigen, ICAM-1: Intercellular adhesion molecule-1.

Fig. 8: Pathogenesis of renal cortical interstitial fibrosis in amyloidosis (modified from Ref. 16).

A well-known complication of amyloidosis is renal vein thrombosis starting in the small vessels of the kidney and spreading to major veins[14]. The interstitial deposition of amyloid and foam cells can be seen in some cases[1, 10, 14].

B) Immunofluorescence Findings: Little systematic data are available in the literature regarding immunofluorescence findings in human renal amyloidosis[1]. If positive, the immunofluorescence staining patterns are homogeneous, non-granular and non-linear, forming round and confluent masses. We demonstrated positive fluorescence in 68.5 percent of 57 cases with tissue-diagnosed renal amyloidosis and observed various combinations of depositions of immunoreactants with the exception of IgE and albumin antisera, which yielded continuously negative reactions (Table VII)[15].

Table VII: Distribution of the Deposits of the Immunoreactants in 57 Patients with Renal Amyloidosis

Immune Reactants	No. of Specimens stained	Positive Staining	
		No.	%
C3	57	31	54.3
IgM	57	25	43.8
IgG	57	11	19.2
IgA	57	10	17.9
Fibrinogen	47	25	53.2

C) Electron Microscopic Findings: Electron microscopic (EM) studies may show amyloid fibrils in the mesangium and basement membranes of capillary walls. In the subepithelial location, spikes can be demonstrated. One may occasionally recognize the fragmentation and double-contour of basement membranes[1, 10].

Diagnosis

Amyloidosis can be suspected clinically in a certain group of patients with particular clinical manifestations (proteinuria, hepatosplenomegaly, etc.) associated with chronic inflammatory conditions, heredofamilial syndromes and neoplastic disorders. However, the diagnosis of amyloidosis should depend on identification of amyloid on biopsy taken from the involved tissue. The amyloid is identified by demonstrating the characteristic apple-green birefringence with polarized light in tissues stained with Congo red (Fig. 9).

In recent years, antibodies against all known amyloid fibril proteins have become available and can be used in both immunofluorescence and immunoperoxidase techniques for the detection and classification of amyloid. Tissue biopsies can be taken from the rectum, subcutanous fat, gastric mucosa, gingiva, liver, sural nerve, bone marrow and kidney. EM studies can show amyloid fibrils which are

rigid, non-branching and 10-15 nm in diameter. However, EM alone is not sufficient for the diagnosis of amyloidosis. In vivo scintigraphy with ^{123}I-labelled human serum amyloid P component allows the amyloid deposits to be visualized and quantified[3]. In heredofamilial conditions, genetic and chromosomal studies must be performed.

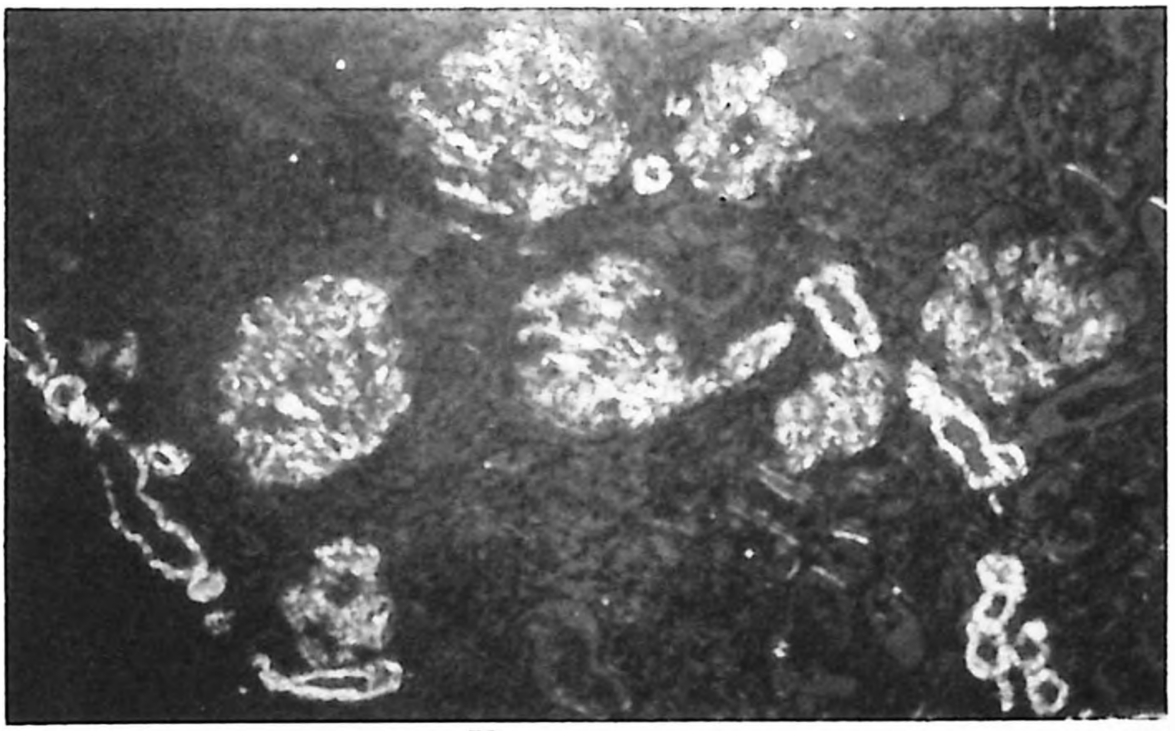


Fig. 9: Apple-green double refractility of glomerular, vascular and tubular (trace) amyloid depositions under polarized light. Congo red Polarized microscopy x 10.

Treatment and Prognosis

There is no specific treatment which can prevent the development of amyloidosis or halt the disease progression. The prognosis of patients with renal amyloidosis is poor when compared with that of other renal diseases[1,2,16]. The aim of therapy in AA amyloidosis is control of the underlying disease, e.g. by colchicine in FMF, cytotoxic agents and dimethyl sulphoxide (DMSO) in juvenile rheumatoid arthritis, and appropriate treatment of chronic infections[2,17]. In dialysis-related amyloid, a successful renal transplant rapidly reduces β_2-microglobulin levels to the normal range. Management of patients with amyloidosis involves supportive therapy. Failure of vital organs should be corrected promptly and aggressively, including allogeneic transplantation whenever possible. It is now clear that patients with renal insufficiency due to renal amyloidosis can be treated by regular hemodialysis or by continuous ambulatory peritoneal dialysis since these therapeutic modalities improve both the quality and duration of life. Renal transplantation has been done for more than 20 years in renal amyloidosis patients with end-stage renal failure.

Though recurrence of amyloid disease has been observed to occur in 13 percent of transplanted kidney cases, renal transplantation is a valuable treatment modality for patients with amyloidosis and end-stage renal failure[18].

In summary, renal amyloidosis is not a rare condition in biopsy-requiring nephrotic syndromes in childhood, and it is practically a secondary (reactive, AA) type of amyloidosis. The age at onset of renal amyloidosis varies in differenet ethnic populations. In our series including 174 children with renal amyloidosis, the onset of renal involvement occurred mainly between the ages of nine and 14. Thus, it is of great importance to consider FMF in the differential diagnosis of childhood nephrotic syndrome in the first two decades of life in our country. On the other hand, before the complication of renal amyloidosis occurs, colchicine therapy must be used in the course of FMF.

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The Turkish Journal of Pediatrics 1995; 37: 375-381

PRIMARY OSTEOSARCOMA PRESENTING IN AXIAL BONES IN CHILDHOOD*

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SUMMARY: Akyüz C, İlhan İ, Kutluk T, Büyükpamukçu M. (Oncology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Primary osteosarcoma presenting in axial bones in childhood. Turk J Pediatr 1995; 37: 375-381.

Six cases of osteosarcoma occurring between 1971 and 1992 and involving the axial bones were reviewed. They constituted 4% of 129 osteosarcomas occurring in the skeleton in childhood during the same period at our center. The patients' ages ranged from eight to seventeen years. Four of the six patients were female. The distribution of axial bones of osteosarcoma was as follows: one case was in the vertebrae, two cases in the craniofacial bones (maxilla and mandible), two cases in the pelvis and one case in the ribs. The prognosis was very poor, with only one case of mandible osteosarcoma still alive. The other five patients died three to sixteen months after first diagnosis. A combination of wide surgical resection and aggressive chemotherapy may offer the best chance for long-term survival. *Key words: osteosarcoma, axial bone, childhood.*

Osteosarcoma constitutes approximately 22 percent of all primary malignant tumors of the bone[1]. More than 80 percent of osteosarcomas occur at the ends of long bones. Involvement of the axial skeleton occurs in 15-20 percent of cases of osteosarcoma in the pediatric age-group[1].

The aim of this report was to present our experience with osteosarcoma as a primary tumor of axial bones in six cases at the Pediatric Oncology Unit of Hacettepe Children's Hospital.

Case Reports

Case 1

A nine-year-old girl was admitted in 1977 with a six-month history of intermittent pain in the neck and head. On physical examination a 3 x 2 cm mass was palpated behind the left sternocleidomastoid muscle. She had weakness in the arms and legs, and a positive Hoffman sign bilaterally. Roentgenograms of the cervical spine revealed dislocation of the second cervical vertebra. Chest radiography was normal. The first cervical vertebra, a hard mass, and the second

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and third cervical laminae were removed. The pathologic diagnosis was osteosarcoma. Postoperatively, vincristine + adriamycine + cyclophosphamide (VAC) chemotherapy was started[2]. Three months later, because of the progressively increasing mass in her neck, a new protocol was planned; however, the patient died due to progressive disease in the third month.

Case 2

A 17-year-old girl was admitted to our center in 1986 because of a swelling of the maxilla for more than six months. On physical examination, a hard mass was found on her right maxilla and extended through the right nasal cavity. Roentgenograms of the craniofacial bones showed a right maxillary tumor with involvement of the medial wall of the maxillary antrum. Chest radiography was normal. The patient had been diagnosed with rhabdomyosarcoma of the face seven years previously in Germany, when she presented with the same complaints. She had received chemotherapy and radiotherapy, the details of which were obscure. Biopsy of the mass in the nasal sinus showed osteosarcoma. After biopsy, she received T-10 A Grade I-II chemotherapy protocol since we could not perform tomography of the lesion to demonstrate it to be expansile with lytic and necrotic area[3]. Although she received two courses of this protocol, no decrease in the mass was noted. The treatment protocol was changed to high-dose methotrexate (6 g/m^2) with rescue four times; however, the tumor did not respond to chemotherapy. The patient was lost to follow-up eight months after first admission.

Case 3

A 17-year-old girl was admitted to our center in 1987 with a two-month history of swelling and pain in the right side of the pelvis. She had been diagnosed with retroperitoneal rhabdomyosarcoma 10 years before in our center, and had received VAC chemotherapy for two years. Also, at the time of diagnosis she received 45 Gy radiotherapy to the abdomino-pelvic anterior and posterior, parallel, opposed fields. Two years later she was considered to be in remission and her treatment was stopped. In 1987, examination revealed a firm mass on her right crista iliaca anterior superior region. A plain film of the pelvis showed a sclerosing lesion with destruction of the anterior right ilium. Chest plain radiography and computerized thoracal tomography were normal. Biopsy of this tumor showed osteosarcoma. The patient received six courses of high-dose methotrexate therapy (10 g/m^2/day/infusion). Despite intensive chemotherapy, she developed pulmonary metastasis. Her treatment was changed to T-10 A Grade I-II chemotherapy protocol, but she died due to progressive disease in the eleventh month.

Case 4

An eight-year-old girl was admitted in 1990 with complaints of swelling and pain in the right side of the pelvis for the previous three months. On examination a firm mass was palpated in her right gluteal region. Plain films of the pelvis showed a sclerosing lesion with permeative destruction of the cortex of the right ilium. Chest plain radiography and computerized thorax tomography were normal. Biopsy of this tumor showed osteosarcoma. The tumor was then resected en bloc. She received one course of T-10 A Grade I-II chemotherapy protocol[3]. The tumor recurred in the same region and right hemipelvectomy was formed. After surgery, she again received two courses of the same protocol, but six months later local recurrence was observed. Following the removal of her sacrum, she received a radiotherapy dose of 45 Gy to the right hemipelvis and 20 Gy to the spine. One month later she developed a third recurrence with involvement of the L5 vertebra. At the 16-month follow-up, she died due to progressive disease.

Case 5

A 14-year-old boy was admitted in 1991 complaining of swelling and pain in front of the right parotis gland for six months. On physical examination, a firm, tumor-like 3 x 3 cm mass in front of the right parotis gland and right facial asymmetry were noted. Plain film of the mandible showed involvement of the posterior part of the horizontal ramus with destruction of the right ramus. Chest plain radiography and computerized thorax tomography were normal. Radical surgical excision of the right corpus of the mandible with soft tissue margins was done. Histopathologic examination showed osteosarcoma. Postoperatively he received T-10 A Grade I-II chemotherapy protocol[3]. After two courses of cisplatin he had 50 percent decrease in creatinine clearance, and chemotherapy was cancelled. Two months after stopping chemotherapy, a right hemimandibulectomy was performed. At this time we found no tumor involvement in the pathologic specimen. This patient was still alive without evidence of disease three years later.

Case 6

A 12-year-old boy was admitted in 1991 with a four-month history of swelling of the left chest wall. On physical examination, a hard, 20 x 20 cm mass was noted between the left axilla and left mamma. Chest plain radiography showed an 8 x 8 cm irregular mass between the second and seventh ribs which was not related to the pulmonary parenchyma. Computerized thorax tomography was normal.

The tumor was excised along with the second, third and fourth ribs. Postoperatively the patient received two courses of cisplatinum (100 mg/m^2 IV) and adriamycin (45 mg/m^2 IV). However, four months after the first diagnosis, pulmonary metastasis was discovered in addition to local recurrence. He died due to progressive disease in the sixth month.

Discussion

Osteosarcoma typically involves long bones, particularly the distal femur and proximal tibia with a predilection for the metaphyses[4]. Although the disease more frequently affects males than females (1.5:1), four of six patients in our study were female. The peak incidence of osteosarcoma occurs in the second decade of life during the adolescent growth spurt[5,6]. Our patients were all in the second decade of life (Table I).

Table I: Selected Clinical Characteristics of Six Patients with Osteosarcoma of the Axial Bones

Patient No.	Age Sex	Tumor Location	Associated Disease	Surgery	Treatment		Survival
					Chemotherapy	Radiotherapy	
1	9 F	Vertebra	–	Radical primary area excision	VAC	–	3 month DwD
2	17 F	Maxilla	RMS	Biopsy	T-10 A Grade I-II protocol High dose Mtx	–	Lost to follow-up
3	17 F	Pelvis	RMS	Radical primary area excision	High dose Mtx T-10 A Grade I-II protocol	–	11 month DwD
4	8 F	Pelvis	–	Hemipelvectomy	T-10 A Grade I-II protocol	45 Gy right hemipelvis 20 Gy spine	16 month DwD
5	14 M	Mandible	–	Right mandibulectomy	T-10 A Grade I-II protocol	–	3 years NED
6	12 M	Rib	–	Radical primary area excision	CDDP+Adriamycin	–	6 month DwD

M : Male
VAC : Vincristine + adriamycin + cyclophosphamide
RMS : Rhabdomyosarcoma
Mod. : Modified
CDDP : Cisdiammine dichloroplatinum
F : Female
DwD : Died with disease
Mtx : Methotraxete
NED : No evidence of disease

Primary osteosarcoma of the axial skeleton is a very rare tumor of young adults. The occurrence in children has merited case reports or small seris in the literature, and has been observed to represent a small percentage of osteosarcoma patients[7-10]. Although there have been many case reports of osteosarcoma in axial bones, no reported study has specifically documented a series of these lesions.

Primary osteosarcoma arising in the vertebral column is rare. The incidence in several reported large series of osteosarcoma of the bone has ranged from 0.85-2.0 percent[11-13]. The distribution is fairly equal between lumbar and thoracic segments of the spine, but cervical involvement is less common[11].

Vertebral osteosarcoma often occurs in irradiated or Pagetic bone[14]; however, there was no history of irradiation or Paget's disease in our first patient. Due to

the early diffusion of this tumor to the medullary canal, patients tend to display neurological involvement associated with pain, as in our first patient. The prognosis of these lesions in the vertebra has been uniformly poor. In Barwick et al's[12] series, only one patient survived for more than two years and most died within a year of diagnosis. According to Shives et al.[15], mean survival is 10 months, but in some rare cases it may reach 2.6 years or even 11 years without pulmonary metastasis. Our patient with vertebral osteosarcoma lived only three months after diagnosis.

Osteosarcoma of the craniofacial bones is again a rare neoplasm, accounting for 6-13 percent of all osteosarcomas[16]. The maxilla is also an uncommon site for osteosarcomas, either post-irradiation or de novo[10]. In two large series, this site accounted for only 3.5 and 2.9 percent of cases[17, 18]. Osteosarcoma of the craniofacial bones tends to affect patients in the third decade, while osteosarcoma of the long bones affects patients in the second decade of life. In our sries, two patients (Cases 2 and 5) had osteosarcoma of the craniofacial bones. One of them had received irradiation due to rhabdomyosarcoma of the cheek seven years previously. Radiation therapy is a risk factor for the development of bone sarcomas, and the relative risk for osteosarcoma increases in doses exceeding 10 Gy[19]. The most common complaints in patients with osteosarcoma of the craniofacial bones are swelling followed by pain, while pain is the initial complaint in patients with osteosarcoma of the peripheral bones[16]. In these two patients, swelling was noted as the first complaint followed by pain. The prognosis in patients with post-irradiation sarcoma has been shown to be very poor, regardless of the location of the primary lesion and the length of survival[15]. Although a predilection for the female sex is noted in mandibular tumors, our patient (Case 5) was a boy[16]. In the case of craniofacial bones, the role of chemotherapy is less clear, mainly because local control is still a major problem and distant metastases are rare[10].

Primary osteosarcomas of the pelvic bones are uncommon. Dahlin and Uni[20] reported an incidence of 9.5 percent in their extensive study of 1274 osteosarcomas at the Mayo Clinic. As mentioned previously, ionizing radiation is known to predispose patients to the development of osteosarcoma. The features in our third case that are typical of post-radiation sarcoma of the bone include the latent period of 10 years between therapy and the occurrence of sarcoma, the rapidly fatal clinical course and the uncommon sites. Because of its rarity and poor prognosis, osteosarcoma of the pelvis has traditionally been grouped with other nonresectable sarcomas for treatment purposes[21, 22]. Thus, relatively little information is available in the literature concerning the response of pelvic osteosarcoma to systemic and regional chemotherapy. In our fourth case, although we performed a mutilating surgical procedure in addition to chemotherapy, the patient died due to progressive disease.

Osteosarcoma of the ribs is a very rare neoplasm, constituting one percent of all osteosarcoma cases[1]. There is relatively little information about treatment for this kind of osteosarcoma.

The poor prognosis of osteosarcoma localized in the axial bones has been discussed frequently in the literature and confirmed by our cases. In the past, treatment was only palliative. It is our belief that even modern chemotherapy, which has considerably improved the prognosis in tumors of the extremities, is not actually efficacious in the treatment of osteosarcoma of the axial bones. The anatomical site also precludes adequate oncologic treatment, which is indispensable to success. We believe that more aggressive surgery, such as total removal of the affected axial bone, together with adjuvant therapy pre- and postoperatively, is currently the most rational treatment. A larger number of cases submitted to this type of surgery with long-term follow-up will tell us if it is possible to improve the short- and long-term prognosis.

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A CASE OF ADENOSINE DEAMINASE – NEGATIVE SEVERE COMBINED IMMUNODEFICIENCY WITH NEUROLOGICAL ABNORMALITIES*

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SUMMARY: Tezcan İ, Ersoy F, Çağlar M, Sanal Ö, Kotiloğlu E, Aysun S. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). A case of adenosine deaminase-negative, severe, combined immunodeficiency with neurological abnormalities. Turk J Pediatr 1995; 37: 383-389.

Presented here is a 17-month-old adenosine deaminase-deficient, severe combined immunodeficient patient with chest symptoms, oral ulcer, neurologic manifestations, head lag, spasticity and developmental delay in motor functions. Antibiotics, systemic antifungal agents, intravenous immunoglobulins and partial exchange transfusions with irradiated fresh red cells were given. No other mode of therapy for adenosine deaminase (ADA) deficiency was available at that time. Amelioration of neurologic manifestations within one month of therapy with irradiated fresh red cell exchange transfusions suggests that these manifestations may have resulted from accumulated toxic metabolites. However, no improvement was seen in the course of infection and oral ulcer, and the patient died of respiratory failure on the 48th day of admission. *Key words: adenosine deaminase deficiency, severe combined immunodeficiency, neurological abnormalities.*

Severe combined immunodeficiency (SCID) is the early-onset clinical syndrome characterized by the absence of both T- and B-cell immunity. Approximately 20 to 25 percent of all cases with SCID occur due to deficiency of adenosine deaminase (ADA), a purine salvage enzyme[1-5]. In ADA deficiency, adenosine, deoxyadenosine and their metabolites accumulate, and their toxic effects appear preferentially in the lymphoid system. Although the clinical phenotype of ADA deficiency demonstrates varying pictures from early-onset SCID to partial ADA deficiency with slight immune function abnormalities, the majority of affected infants cannot be grossly distinguished from patients with classical SCID due to other causes[2, 6]. Patients with ADA deficiency may also have abnormalities in non-lymphoid tissues including costochondral junctions, to a lesser extent the kidney and adrenal gland, and very rarely the central nervous system[1, 2, 7-9].

We present here an ADA-deficient SCID infant with neurological manifestations.

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Case Report

A 17-month-old girl, the first child of non-consanguineous parents, was admitted to Hacettepe Children's Hospital, Immunology Division, because of fever, cough, irritability and spasticity.

The medical history revealed that she was the product of an uncomplicated full-term pergnancy with a birth weight of 3.3 kg. BCG and three doses of DTP-OPV were administered. An axillary lymphadenopathy developed one week after the BCG vaccination.

Her developmental milestones were not appropriate for age. She could not sit without support and had no head control. Spasiticity of the extremities and developmental delay in motor functions were the principal complaints. She developed pneumonia at the age of 15 months and was put on antibiotic treatment at another institution. However, she began to suffer from persistent cough, recurrent fever and oral candidosis until her referral, and antibiotic combinations administered in the hope of ameliorating recurrent bouts of pneumonia were of no benefit.

On admission, her axillary temperature was 36.5 °C, and her weight, height and head circumference were below the 5^{th} percentile. She had respiratory difficulty with perioral cyanosis, tachypnea and intercostal retractions. Oral examination disclosed a mucosal ulcer measuring 2 x 2 cm on the palate, and several monilial patches were found. Neurological evaluation showed that she could follow light and objects with normal eye movements, and the fundi were normal. She had marked head lag, irritability, spasticity in the extremities and increased deep tendon reflexes. She was also retarded in language, motor functions and social performance.

Laboratory examination revealed a leukocyte count of 3800/mm^3 with lymphopenia (980/mm^3), IgG 52.4 mg/dl (N: 605-1430), IgM 19.7 mg/dl (N: 66-228), and IgA 21 mg/dl (N: 30-107). Delayed-type hypersensitivity skin tests to PHA, Candida, tetanus and PPD were negative. Lymphocyte subpopulations were CD_3 16%, CD_4 14% CD_8 5%, CD_{20} 6% and CD_{56} 2%. Lymphocyte proliferation assays showed no response to mitogenic lectins. [Patient: 394 cpm to phytohemagglutinin (PHA); 636 cpm to concanavalin A (Con A); Control: 140202 cpm to PHA, 156967 cpm to Con.A]. ADA activity in red cells was zero and her parents' ADA activities were within heterozygous ranges. Purine nucleoside phosphorylase (PNP) enzyme activities were found to be normal. Chest x-ray showed interstitial infiltration, and thymus shadow was not evident. Roentgenograms of the bones revealed no abnormality, and computerized axial tomography (CT) of the cranium showed cerebral cortical atrophy. Other laboratory findings were within normal ranges. Besides administration of intravenous immunoglobulin, antibacterial and systemic antifungal agents, partial exchange transfusions with irradiated fresh red cells were performed as other specific modes were not available. Within one month

of her hospitalization she gained head control and her muscle tone gradually decreased. However, there was no improvement in either her immunologic laboratory findings or her susceptibility to infections. Despite all therapeutic attempts, the mucosal ulcer on the palate enlarged and respiratory difficulty worsened. Eventually, she died of respiratory failure on the 48th day of admission.

A partial necropsy examination excluding the central nervous system was performed according to the family's wishes. Necropsy findings were as follows: The thymus was not identified grossly. Although all available soft tissues in the expected localizations of the thymus were examined microscopically, no thymic structure was seen. Lymphoid follicles in the cortical regions of the lymph nodes, in the white pulp of the spleen and in the intestinal mucosa were sparse and mostly of primary type without germinal centers (Figs. 1 and 2). There were multiple foci of central coagulative necrosis surrounded by sparse mononuclear inflammatory reaction and parenchymal cells with intranuclear inclusions in the lung, liver, tongue, esophagus, adrenal glands and ovaries (Fig. 3). An immunohistochemical study revealed that these inclusions were Herpes Simplex Virus type I (DPC-Monoclonal antibody; avidin-biotion peroxidase technique). Thin, fibrous bands around parenchymal cell cords in the outer cortex of the adrenal glands, diffuse fatty change in the liver and focal interstitial mononuclear cell infiltrates in the kidney were also observed.

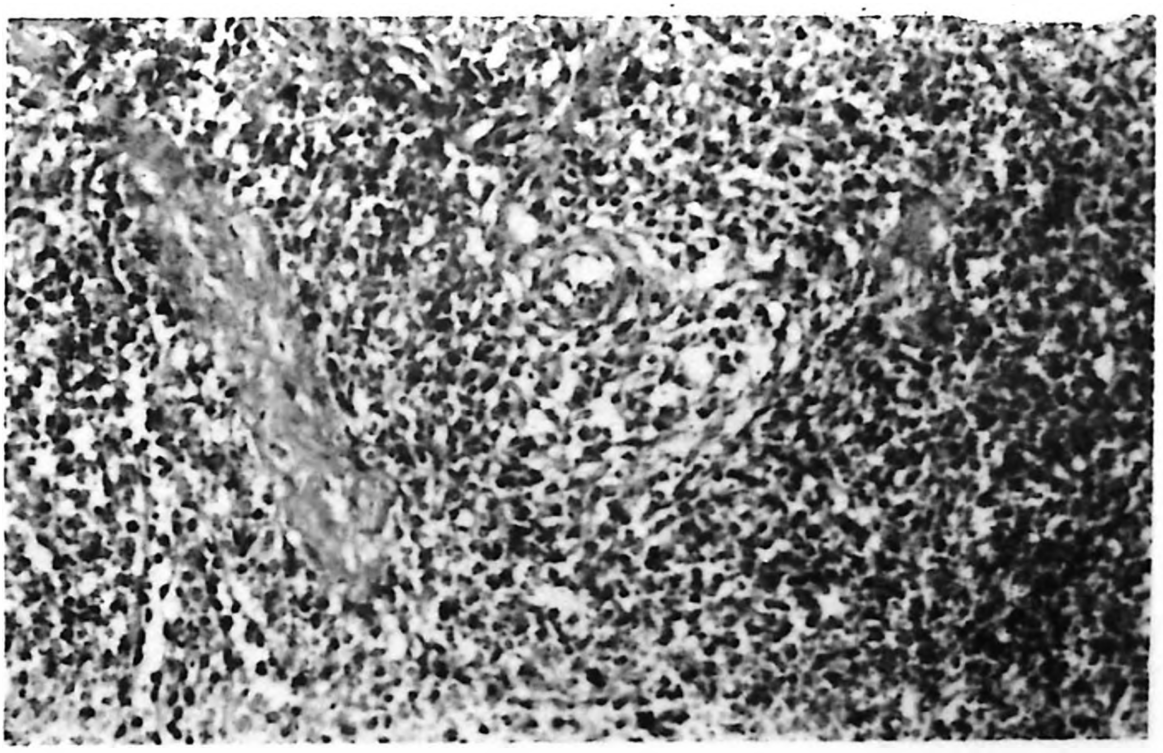

Fig. 1: Sparse lymphoid cells around the central arteriole in the spleen (HE, X 66)

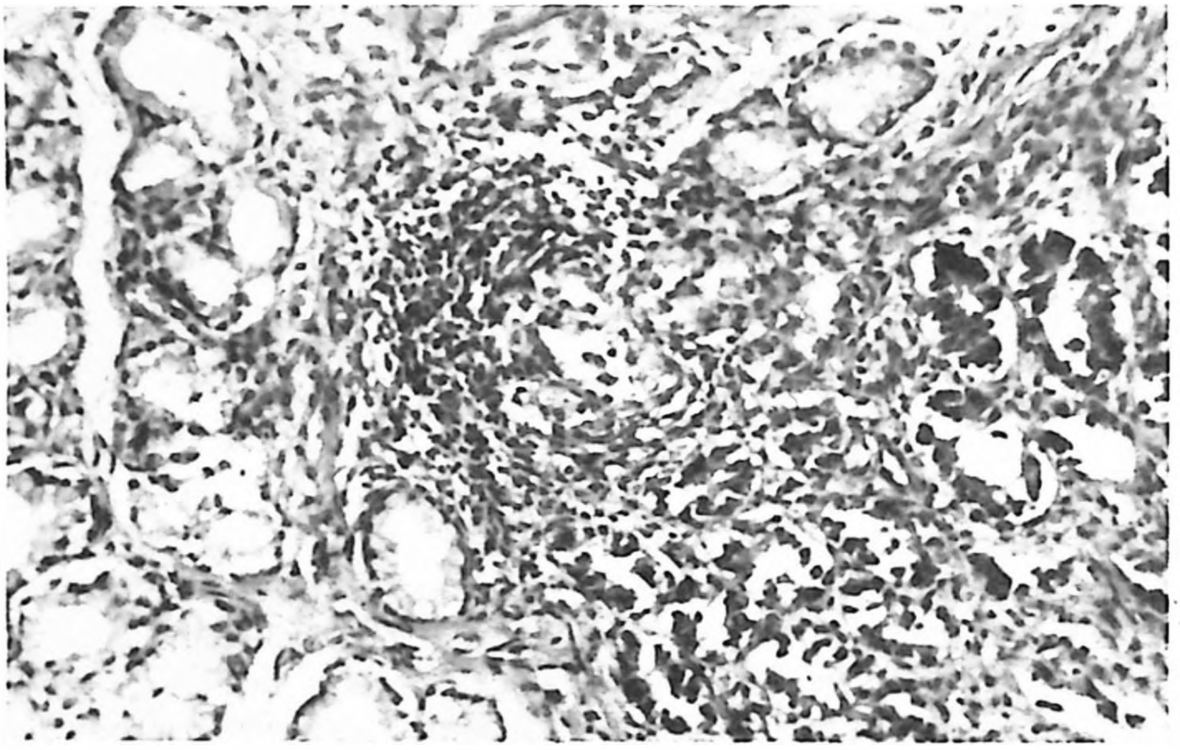

Fig. 2: Small lymphoid follicle in the intestinal mucosa (HE, X 66).

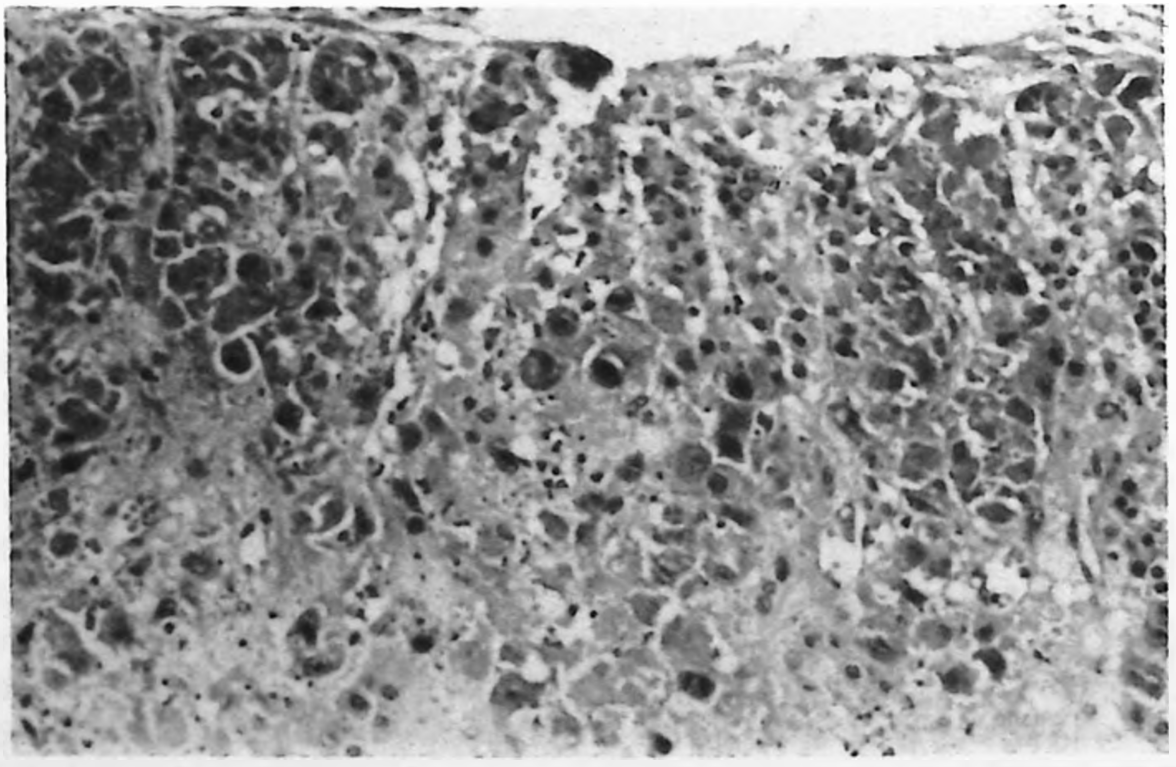

Fig. 3: Cortical cells with intranuclear inclusions in the adrenal gland (HE, X 66).

In the year following the patient's death, prenatal diagnosis was performed by the family. ADA activity determined in the erythrocytes isolated from the fetal blood taken via cordocentesis in the 21st week of pregnancy was very low. (9 µmol uricacid/h/gr Hb). Spontaneous abortion occurred two days after the cordocentesis. Autopsy could not be performed.

Discussion

When admitted to a local health center, the patient was diagnosed with cerebral palsy, and recurrent lung infections were thought to be due to aspirations caused by epiglottic dysfunction. Taking into consideration the history of recurrent lung infections, resistant oral candidosis and laboratory findings, the patient was diagnosed with SCID due to ADA deficiency. She had classical findings of SCID such as recurrent respiratory tract infections, failure to thrive and oral candidosis. Primary abnormalities specific for ADA-deficient SCID belong to the lymphoid system. In the thymus, diverse morphological findings are typically observed. However, sometimes the thymus cannot be observed grossly, as in our case.

Some pathologic alterations have also been reported in non-lymphoid tissues such as kidney, adrenal and chondro-osseous tissues[9]. In our case, we could detect only fibrosis in the adrenal cortex. Our patient also had neurologic manifestations such as head lag, spasticity, irritability and developmental delay. Neurologic abnormalities are uncommon in ADA-deficient SCID infants, but such abnormalities can be seen in mice after the injection of ADA enzyme inhibitor, deoxycoformycin[10]. A few reports have been published about ADA-deficient SCID infants with neurologic manifestations[8-11]. One of the cases described by Hirschhorn et al.[8] had spasticity of the upper extremities and the other had tremors in his hands and intermittent dystonic postures. Another case was reported in 1980[8]. This four-month-old could not follow light and had nystagmus, dystonic posture, athetoid movement, head lag and absent deep-tendon reflexes. These abnormalities improved considerably during the removal period of toxic metabolites by erythrocyte exchange transfusions. In ADA deficiency, toxic substrates such as deoxyadenosine and phosphorylated metabolites accumulate and may have some effects on the central nervous system, probably via purinergic receptors. Treatment with erythrocyte exchange transfusions provides intact enzyme and binding sites for the clearance of metabolites and may lead to improvement of neurologic manifestations.

Treatment of our patient with bone marrow transplantation, polyethylene gycol-modified ADA and somatic gene therapy was not available; therefore, red cell partial exchange transfusions were initiated[11-15]. Improvement of muscle spasticity, irritability and head control was observed after the initiation of transfusions. However, she did not respond with regard to immunologic

parameters, a finding consistent with some of the cases reported previously[2]. These neurologic abnormalities might have been secondary to a previous viral infection of the brain or an undefined event during the perinatal period. Amelioration of neurologic findings with eyrthrocyte transfusions suggests that these abnormalities may result from accumulated toxic metabolites acting via purinergic receptors in the central nervous system. Hirschhorn et al.[8] showed that a decrease in toxic metabolites accompanied the improvement of neurologic manifestations in an infant with ADA-deficient SCID.

It is difficult to explain why most ADA-deficient patients have no neurologic abnormalities. Although environmental factors and genetic heterogeneity may play a role, the main mechanism responsible for involvement of the central nervous system remains to be elucidated.

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UNUSUAL MALFORMATIONS IN OCCULT SPINAL DYSRAPHISM*

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SUMMARY: Gök A, Bayram M, Coşkun Y, Özsaraç C. (Department of Neurosurgery, Gaziantep University Faculty of Medicine, Gaziantep, Turkey). Unusual malformations in occult spinal dysraphism. Turk J Pediatr 1995; 37: 391-397.

Two cases of occult spinal dysraphism with different clinical symptoms, signs and congenital pathologies are presented. One had malformations including scoliosis, dermoid tumor, hydromyelia, diastematomyelia, dermal sinus, low conus, vertebrae anomalies and dextrocardia. The occurrence of dextrocardia in association with occult spinal dysraphism was found to be extremely unusual. The second case is presented in relation to the rarity of teratoma with dermal sinus and tethered cord in the lumbar area. Myelography, computed tomography (CT), Myelo CT and magnetic resonance were used in making a diagnosis. *Key words: spinal dysraphism, dermal sinus, diastematomyelia, teratoma, dextrocardia.*

Occult spinal dysraphism is an entity composed of a variety of malformations of embriological development. It typically causes progressive neurologic deterioration, whether of bladder, bowel or lower extremity sensorimotor function. Tethered cord due to lipoma, lipomyelomeningocele, tight filum terminale and adhesion, dermal sinus with or without tumors, diastematomyelia, skin and spine abnormalities have appeared under the term occult spinal dysraphism[1-4]. More than one type of lesion tends to occur in a single case.

The symptoms of these lesions may arise at any age, mostly occurring in the pediatric group[1, 5, 6] and rarely in adulthood and late life[7, 8]. Myelography, myelo computerized tomography (CT) and particularly magnetic resonance imaging (MRI) have made possible the identification of the exact location and have simplified the surgical procedure of these malformations[2, 9-11].

Case Reports

Case 1

A 13-month-old infant was admitted with the complaint of inability to stand or sit straight. Neurologic examination revealed paraparesis, analgesia under L3

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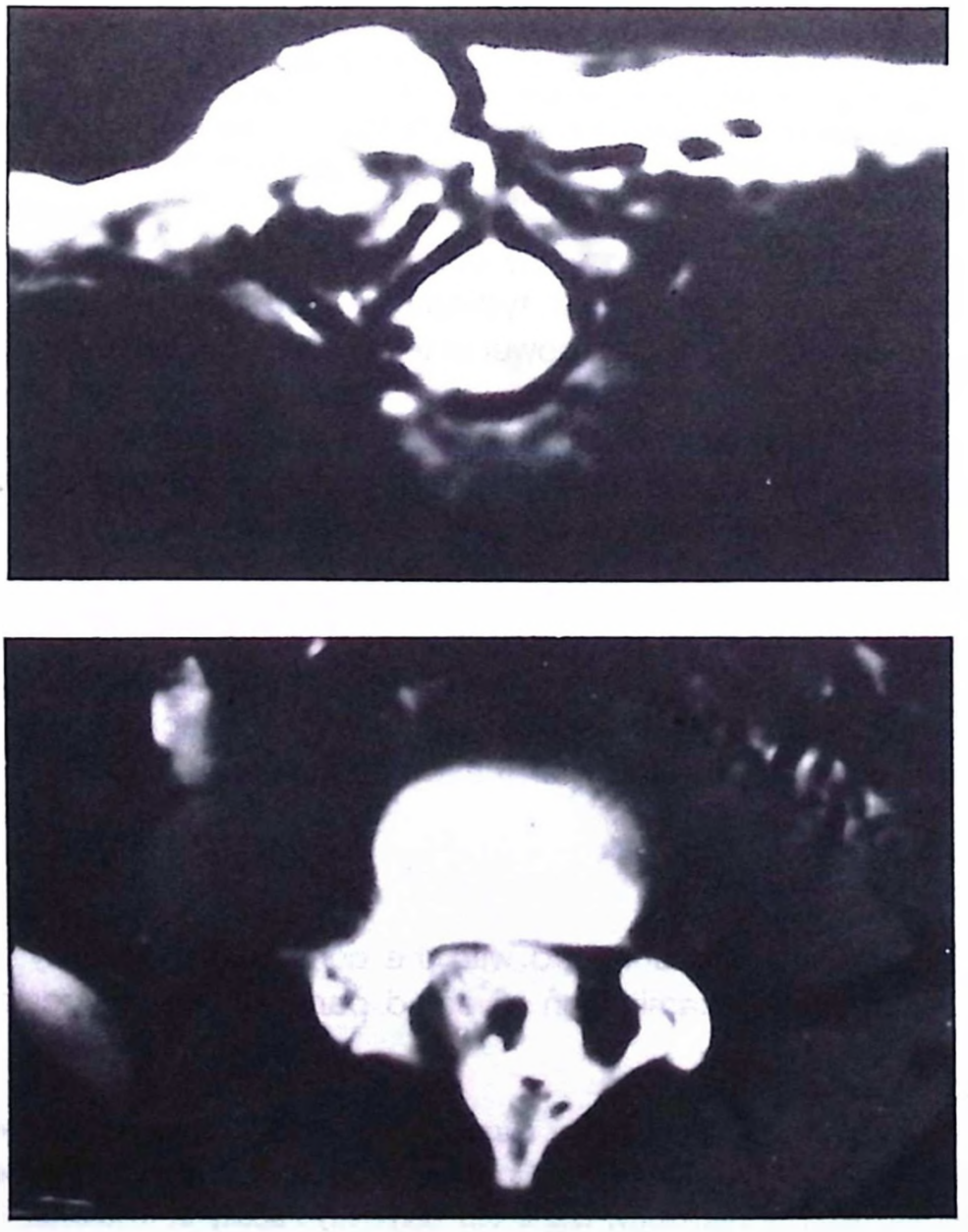
dermatomes, and absent anal and achilles reflexes. In the mid-dorsal area, an outwardly protruding, mobile mass with a diameter of 1 cm was noted. In the mid-sacral region the skin was dark blue and included a dermal sinus.

Plain radiographs demonstrated dextrocardia and vertebrae anomalies between T10 and T12 vertebrae. MR imaging disclosed two masses located in the subarachnoid space and the subcutanous layer and a tract between them at the level of T9-10. The spinal cord lost its normal configuration, had irregular borders and included hydromyelia proximal to the mass. A bony septum at the T11 level and bifid conus at the L5 level were also visualized (Figs. 1a,. b).



Figs. 1a, b: Magnetic Resonance Image of the thoracic and upper lumbar area in the coronal plane. Hydromyelia, tumoral mass and diastematomyelia are clearly visualized.

Complete laminectomy was performed at the T8-12 levels. The masses located in the subcutaneous layer and in the subarachnoid space and the tract between them were removed completely with microtechnique. The bony septum was drilled. At the level of T11, the cord divided in two unequal parts with their own separate pial, arachnoid and dural coverings. The dural tubes reunited below the septum into a single tube, though the split cords continued caudally. While closing the dura, bradycardia and then cardiac arrest occurred. After three hours the patient died. The patient's family refused autopsy.

The tumor had two cystic components and a tract between them. The cysts were composed of matted hair as well as soft, white, cheesy material. Histological sections revealed stratified squamous epithelial cells in the cyst wall and keratinocious lamelles inside. The tract was composed of stratified squamous epithelium in papillary structure with underlying sebaceous glands, hair follicles and capillaries (Fig. 2).

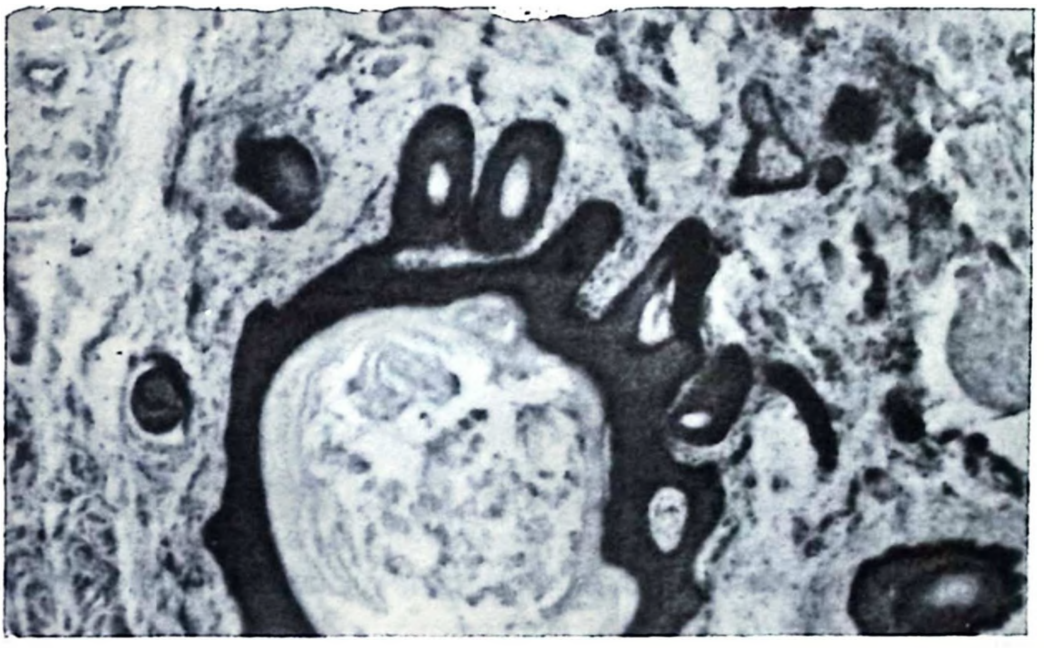


Fig. 2: Histologic section of the dermal tract revealed stratified squamous epithelium in papillary structure with underlying sebaceous glands, hair follicles, capillaries, and keratinocious lamellas inside. H.E X 40.

Case 2

A 13-year-old girl was referred in September 1993 with mild back pain increasing during exercise and with the complaint of serous discharge occurring occasionally in the lumbosacral area. Neurologic examination was normal. The skin 2 cm to the right of the midline was dark bule and included a dermal sinus. Plain radiographs demonstrated posterior fusion defects in the sacral vertebrae, lamina and spinous process anomaly at L5, and a wide interpeduncular space at the L3-5 levels.

Omnipaque myelography disclosed a large caudal sac and filling defect on the posterior surface of the dural sac at the L4-5 disc level. CT delineated a hyperdense mass located intrathecally. Myelo CT demonstrated the attachment of a dermal sinus tract with the mass at L4-5 (Fig. 3) and conus visualization at the L3-4 disc level.

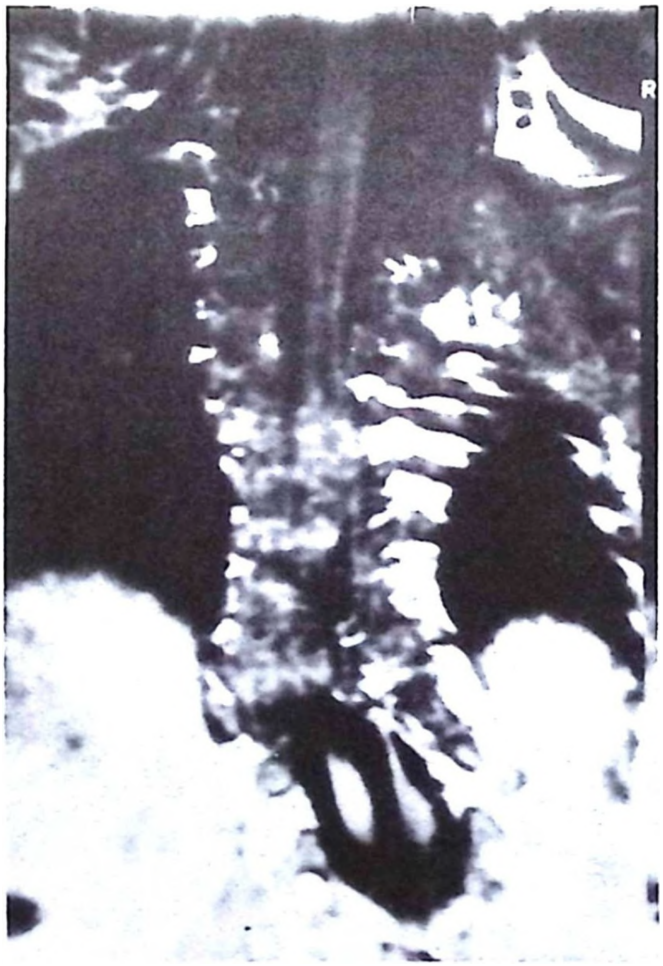


Fig. 3: Myelo CT demonstrates the attachment of dermal sinus tract with the mass at the L5 lavel.

Complete laminectomy was performed on the L4 and L5 vertebrae and partially on the L3. A dermal sinus tract extending obliquely on the right side perforated the L5 lamina and dura and adhered to a tumor in the subarachnoid space. Upon opening the dura, a conus at the L3-4 disc level was revealed. With microsurgery the sinus tract and the mass with a separate peduncle that attached the conus were removed completely. The filum terminale, which was thick and short and ended at the posterior dural surface at the L5 level, was sectioned. The patient's postoperative course was uneventful, and after three months she had no complaint.

Microscopic sections of the tumor showed that the cyst was lined by stratified squamous epithelium, and underlying it connective tissue, fat and muscle tissue, vascular structures, sympathetic ganglia and lymphoid tissue were observed. Inside the cyst there were keratinocious lamelles (Fig. 4).

Fig. 4: Histologic section of the tumor showed connective tissue, muscle and fat tissue and peripheral nerves H.E X 40.

Discussion

Congenital malformations appearing in association with occult spinal dysraphism may occur as separate entities or in a more complex pattern. Various combinations of these malformations have been reported in the literature[2, 6, 11-15].

The manifestations associated with these malformations are caused by traction, compression, myelodysplasia or rarely inflammation[3]. The clinical presentation of a patient with occult spinal dysraphism differs according to the pathological events involved. It can manifest itself with a neuromusculoskeletal syndrome[6, 16], sphincter disturbance[2, 4, 8], spinal curvature[6, 16], cutaneous malformation[2] or back pain[8, 17]. In most cases the neurological impairment of the lower extremities or of bladder function is superimposed on the clinical situation.

The tumor observed in the thoracic region of the first case had two cystic components and a tract between them. The cystic component of the tumor and the structure of the tract included this tumor in the category of dermoids. Although the spinal cord typically reunites below the cleft in most patients with diastematomyelia, extension as split cords through the conus is extremely rare[3, 16]. A second form of occult spinal dysraphism including low conus and dermal sinus in the lumbosacral area and hydromyelia in the thoracic region is rarely seen[3, 14].

Another unusual occurrence is dextrocardia, which is usually observed in a patient with complete situs inversus or with Kartagener's syndrome. When it occurs without situs inversus, associated malformations are the rule[18]. Dextrocardia in association with occult spinal dysraphism was thought to be an extremely unusual finding in our patient, as no report was found related to this association in the literature.

Fifty percent of patients reported in the literature with a dermal sinus had an inclusion tumor. These tumors were classified as epidermoid in 13 percent, dermoid in 83 percent and teratoma in four percent of cases[3]. Teratoma are tumors having various cellular or organized components of normal derivatives from more than one germ layer[19]. Occasionally it has appeared in the spinal canal as a separate case[20], and occurrence with occult spinal dysraphism is extremely rare[21, 22]. The tumor found in the second patient was included in the category of benign teratomas due to its composition, which had components arising from the mesoderm and ectoderm. Congenital spinal dermal sinuses above the sacrococcygeal area are quite rare, and almost all reported cases have occurred along the dorsal midline[23].

Plain roentgenograms are abnormal in the majority of patients[1, 2, 16]. MR imaging is simplifying the investigation of occult spinal dysraphism to a great degree, and it was possible to achieve an accurate diagnosis in most cases[2, 9, 10]. Some difficulty was observed with the MRI scan in differentiating the exact level o the conus from a thickened filum and in solving the diagnostic problem of ruling out a retethered conus[10]. Despite these pitfalls, the MRI scan has become the first investigative technique in evaluation of occult spinal dysraphism[9, 24]. When it is not available or there is high suspicion about the pathology despite normal MRI findings, the patient should be further investigated with water-soluble contrast myelography and Myelo CT[3, 11, 15].

Any child with a cutaneous stigmata, foot deformity, spinal curvature or failure to gain sphincter control at an appropriate age should undergo radiologic investigation regardless of neurologic status. If the initial deficit is due to true myelodysplasia, no improvement can be achieved surgically, but secondary effects due to traction or compression may be prevented or reversed[2, 6, 15, 16]. Thus, early diagnosis and surgical therapy to prevent future or progressive neuronal deficit are mandatory.

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The Turkish Journal of Pediatrics 1995; 37: 399-402

BILIARY ASCARIASIS*

A Case Report

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SUMMARY: Sarıhan H, Gürkök Ş, Sarı A. (Departments of Pediatric Surgery and Radiology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Biliary ascariasis: a case report. Turk J Pediatr 1995; 37: 399-402.

Ascaris lumbricoides is a worldwide intestinal infestation that may cause various complications. Biliary ascariasis, however, is a rare condition. We describe a child with biliary ascariasis. The patient's clinical symptoms were pain, vomiting and abdominal tenderness, and she was thought to have acute appendicitis. However, laboratory examination revealed high serum alkaline phosphatase and amylase levels, and ultrasonography and percutaneous cholangiography demonstrated biliary ascariasis. The patient was successfully treated with mebendazole and antispasmolytic drugs. *Key words: ascaris lumbricoides, biliary ascariasis, cholangiography, ultrasonography, mebendazole.*

Infestation by Ascaris lumbricoides roundworm, which mainly lives in the jejunum, is an almost worldwide phenomenon. The most common clinical presentation involves passage of worms per rectum, vomiting of worms, small bowel obstruction by a bolus of worms, intestinal perforation and peritonitis, and appendicitis due to obstruction of the lumen by the worm[1-3]. Sometimes the worms can enter the common bile duct and cause biliary symptoms[4, 5]. We present a case of ascariasis within the common and intrahepatic bile ducts.

Case Report

A three-year-old girl presented with a one-day history of abdominal pain, nonbilious vomiting and anorexia. The patient had no history of infestation of parasites or urinary tract infection.

Physical examination revealed a body temperature of 37.6 °C and pulse of 120 beats/min. There was upper abdominal tenderness on palpation, no muscular defense and hepatosplenomegaly.

Laboratory values were: hemoglobin 9.8 g/dl, leukocyte count 14.000/mm^3, serum amylase 400 U/L. (N: 25-125 U/L) serum alkaline phosphatase 280 U/L. (N: 71-142 U/L). Bilirubin, SGOT and SGPT levels and urinalysis were normal. Ascaris ova were demonstrated in feces. Plain radiography of the abdomen was unremarkable. Abdominal ultrasonography showed hyperechogenic tubular structures within the dilated intrahepatic and common bile duct. This appearance

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was thought to be due to biliary ascariasis and to represent the "spaghetti sign" (Fig. 1). Intravenous cholangiography was not helpful. Percutaneous hepatic cholangiography showed many linear radiolucencies within the dilated intrahepatic and common bile duct which extended into the duodenum (Fig. 2). The patient was treated with mebendazole 3 x 100 mg/d and hyoscine-N-butyl bromide 3 x 5 mg/d for five days. One week later, abdominal ultrasonography showed the dilated bile ducts but no ascariasis. The medical treatment was repeated and the patient was discharged from the hospital with no clinical symptoms. Six months of follow-up were uneventful.

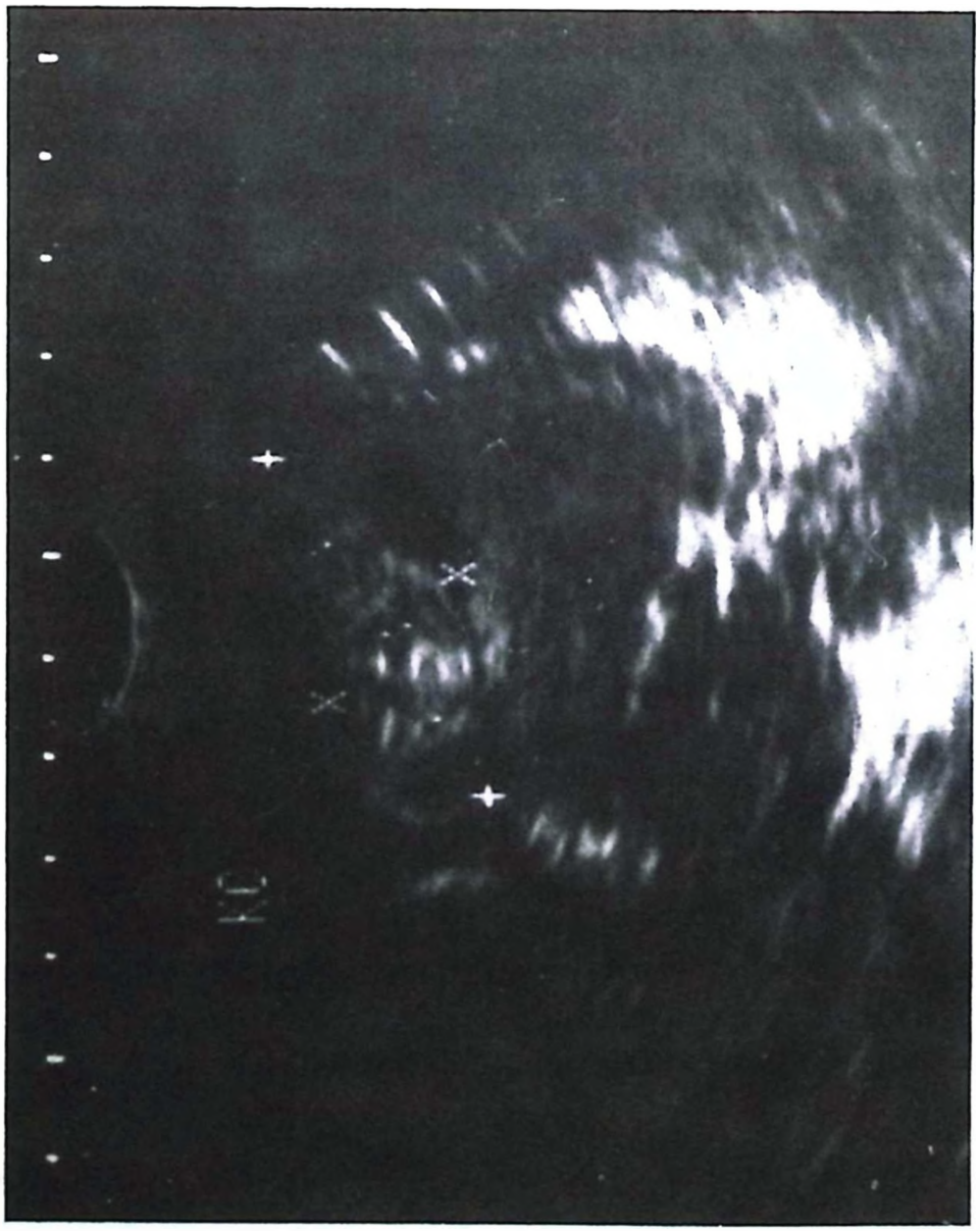

Fig. 1: Ultrasonography of the liver shows hyperechogenic ascaris worm within the intrahepatic bile duct.

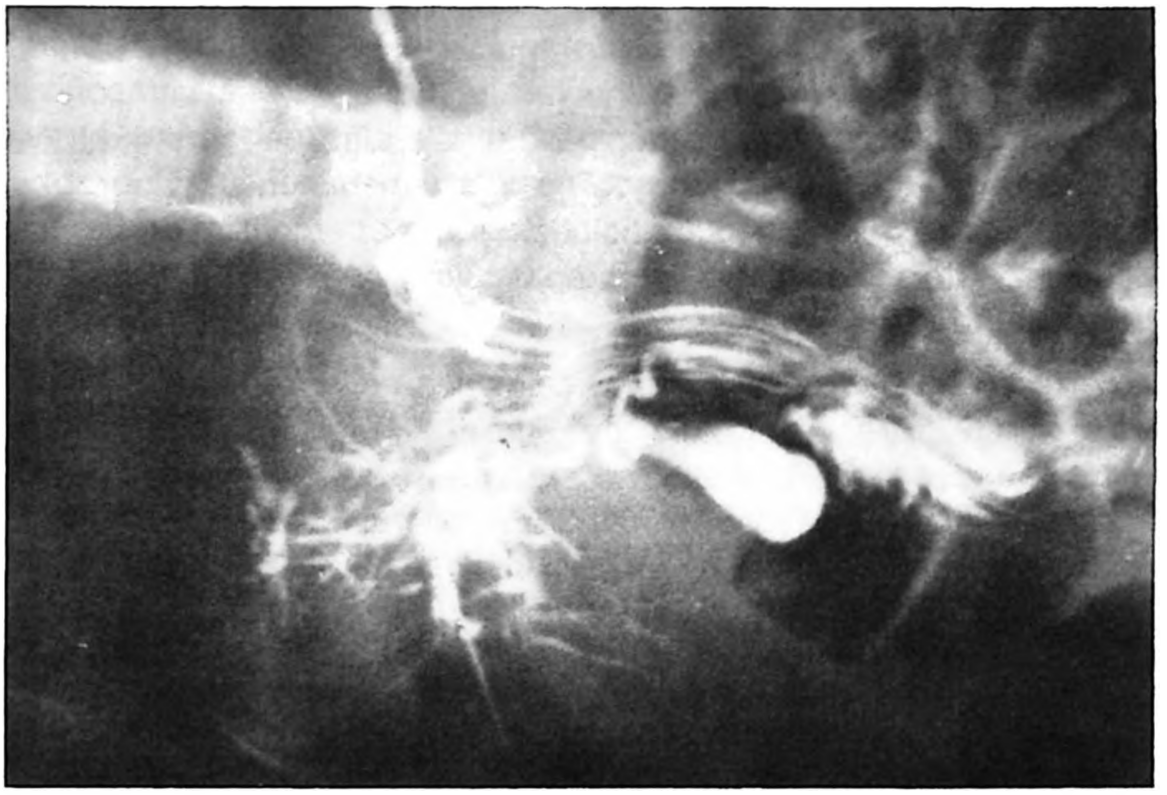

Fig. 2: Percutaneous cholangiography shows linear radiolucencies within the dilated and opacified common bile duct and intrahepatic main bile ducts, indicating worms.

Discussion

Biliary ascariasis is an uncommon manifestation of infestation of ascariasis. The roundworm has a tendency to move up into the common bile duct from the small intestines and enter the gallbladder or intrahepatic bile ducts[4, 5]. Although the infestation may be silent, biliary colic frequently develops and may imitate acute appendicitis. The patients usually have a history of passage of worms per rectum or vomiting of worms. The serum bilirubin level is often normal, but liver and pancreatic enzyme values are often increased. Complications, including cholecystitis, pancreatitis, development of gallbladder stone and obstruction of the common bile duct may result[4-6]. Worm-containing liver abscess or ascending cholangitis is seen less frequently[6, 7]. Our patient had abdominal pain, vomiting and anorexia. Initially we thought that she had acute appendicitis; however, the location of tenderness and increased serum alkaline phosphatase and amylase levels led us away from a dignosis of acute appendicitis.

Ultrasonography is a noninvasive and safe diagnostic method in biliary ascariasis. The intraluminal worms are seen as hyperechogenic, tubular structures. This appearance has been described as the spaghetti, coil or strip sign. The worm, seen as a thick, hyperechogenic strip with a central, longitudinal and anechoic component, is described as the "inner-tube" sign[5]. If ultrasonography is technically

inadequate, intravenous, retrograde or percutaneous cholangiography can be performed to diagnose biliary ascariasis. These methods demonstrate characteristic vermiform defects in the biliary ducts[8, 9]. The ultrasonography findings described were noted in our patient. We also performed intravenous and percutaneous cholangiography. The intravenous cholangiography was inadequate, but the percutaneous cholangiography demonstrated many linear radiolucencies within the dilated intrahepatic and common bile ducts, which extended into the duodenum.

In uncomplicated patients, antihelminthic treatment is preferred in biliary or intestinal ascariasis. If medical treatment is unsuccessful, the worms may be removed with the did of an endoscope[8-10]. If a complication such as perforation, biliary stone or liver abscess develops, surgery is the sole alternative method[4, 6, 7]. We also successfully treated the patient by antihelminthic and antispasmolytic drugs. No complications developed.

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SPLENIC ABSCESS DUE TO BRUCELLA IN CHILDHOOD*

A Case Report

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SUMMARY: Seçmeer G, Ecevit Z, Gülbulak B, Ceyhan M, Kanra G. Anlar Y. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Splenic abscess due to brucella in childhood. A case report. Turk J Pediatr 1995; 37: 403-406.

An eleven-year-old male was diagnosed with multiple splenic abscesses due to brucella. He was treated only with antibiotics. Although splenic abscess is very rare in childhood, in febrile patients with upper quadrant abdominal pain, tendemess and splenomegaly, splenic abscess should be suspected especially in epidemic regions. Diagnosis can be confirmed by ultrasonography and computerized tomography. *Key words: brucella, splenic abscess.*

Splenic abscess is rare in childhood and occurs mostly in the fifth and sixth decade of life in the form of multiple or solid abscesses. As the mortality rate is very high, early diagnosis and treatment is of great importance.

The metastatic infections and predisposing factors generally have an important role in the occurrence of splenic abscess. Among the infectious diseases, typhoid fever, malaria and dysentery infections are the main causes.

In this article, a case of multiple splenic abscesses due to brucella is reported which may be of interest since it was treated only by antimicrobial therapy.

Case Report

An eleven-year-old male was admitted to Hacettepe Children's Hospital with the complaints of fever of four days duration and left upper quadrant abdominal pain. His body temperature increased to 39.5 °C, especially during the night, despite treatment with penicillin procaine for three days.

The physical examination revealed fever (38.5 °C), left upper quadrant tenderness, splenomegaly of 2 cm and muscular rigidity. The white blood cell count was 4600/mm^3 with 36% neutrophils, 52% lymphocytes and 2% monocytes; hemoglobin was 12 g/dl and erythrocyte sedimentation rate was 40 mm/h.

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The chest and plain abdominal radiograms were normal and PPD was negative. Abdominal ultrasonography demonstrated splenomegaly with multiple hypo-echoic lesions 6-8 mm in diameter, and the liver and biliary system was found to be normal. Brucella and Salmonella group agglutination tests were negative. C3, C4, CH_{50}, quantitative immunoglobulins and nitroblue tetrazolium tests were normal. Sickling test was found to be negative. No pathogenic microorganism was cultivated on throat, urine, blood and bone marrow cultures. The bone marrow differential cell count and morphology was normal with no evidence of malignancy. Ampicillin and amikacin therapy was initiated at first with the diagnosis of enteric fever, but the patient did not respond to this therapy.

In the second week, the brucella agglutination test was repeated and found to be positive with a titer of 1/640. Then ampicillin was replaced with tetracycline therapy. The patient's body temperature decreased to normal levels and splenomegaly disappeared. In the sixth week of therapy, the Brucella agglutination test was positive with a titer of 1/80, abdominal ultrasonography and computerized tomography (CT) scan revealed completely normal findings and the patient was discharged. The brucella agglutination test was repeated in the third and sixth months and at the end of the first year and found to be negative. The patient was found to be healthy as well.

Discussion

Splenic abscesses occur only rarely. In a large autopsy series, the incidence of splenic abscess was reported to be between 0.2 and 0.7 percent[1,2]. The etiology of splenic abscess is often one or more of the following: metastatic infection, superinfection, ischemia, hemoglobinopathies, hemolytic anemias, trauma, chronic infections and immunodeficiency[3,4]. None of the above predisposing factors was encountered in our patient.

The symptoms and findings of splenic abscesses are nonspecific; fever and upper left quadrant abdominal pain are the earliest and most frequent symptoms[4-6]. Fever is seen in 80-95 percent, upper left quadrant abdominal pain in 35-60 percent splenomegaly in 25-33 percent tenderness in the upper left quadrant in 40 percent of cases[3,4,6]. If the abscess is located in the upper pole of the spleen, the patient complains of left shoulder pain. If the abscess is deep-seated and does not involve the splenic capsule, diaphragm irritation may not occur[4,7].

The most common etiologic agents of splenic abscesses are streptococci, staphylococci and gram-negative bacilli (especially E.coli)[4,6,8]. Although brucella organisms have an abundance of reticuloendothelial cells, splenic abscess due to brucella is rarely seen and is generally caused by B.melitensis and B.suis[9]. A definite diagnosis of brucellosis can be made by recovering the organism

from blood, body fluids, tissue specimens or serologically. While in 17 percent of cases, diagnosis is made by culture, in 85 percent of cases it is made by serologic tests, especially in endemic areas[10, 11]. The agglutination test was negative in our patient at the beginning, then it increased to a titer of 1/640 the following week. The prognosis of splenic abscess is good with early diagnosis and treatment. However, the diagnosis is difficult to make because the clinical symptoms are insidious. The use of new non-invasive and sensitive imaging techniques, such as ultrasonography and CT, has facilitated the making of a diagnosis to a great extent[12]. The sensitivity of CT and ultrasonography is 96 percent and 76 percent respectively[3]. Also, ultrasonography has a great advantage in that it allows percutaneous drainage[12]. The mortality rate of splenic abscess is 100 percent without therapy[3, 4]. In cases of multiple or large solitary abscess, splenectomy is preferable; the percutaneous drainage with antimicrobial therapy has decreased the necessity of splenectomy in recent years[12]. In our case, only antimicrobial therapy was used against brucella, and remarkable clinical improvement was attained.

Spink[9] reported six adult cases of brucellosis, five of which had splenic abscess and underwent splenectomy. Also, in those five cases B.suis was isolated from the splenic abscess. In another series composed of 173 cases, four adult patients were reported with abscess due to brucella[4].

Interestingly we could not find any other case of splenic abscess due to brucella in childhood in the literature. Thus especially in endemic regions, splenic abscess should be considered in the differential diagnosis.

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ENDOPHTHALMITIS IN A YOUNG CHILD WITH MENINGOCOCCAL MENINGITIS*

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Davut Albayrak MD[**]

SUMMARY: Aydın M, Gürses N, Çetinkaya F, Albayrak D. (Department of Pediatrics, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey). Endophthalmitis in a young child with meningococcal meningitis. Turk J Pediatr 1995; 37: 407-410.

Meningococcic meningitis is still a serious infection with high rates of morbidity and mortality. It is associated with severe complications. In recent years ocular complications have occurred less frequently, and endophthalmitis has been recognized as a rare complication. We present a case of meningococcic meningitis complicated by endophthalmitis. *Key words: endophthalmitis, Neisseria meningitidis, meningococcic meningitis.*

Meningococcal infections remain an important cause of morbidity and mortality in children and adults. Although the incidence of meningococcal infections and complications has decreased markedly with newer chemotherapeutic agents, early diagnosis and therapy are necessary to prevent complications and death. In recent years ocular complications have occurred less frequently, and endophthalmitis has been recognized as an unusual complication of meningococcal meningitis. Here, we report a case with meningococcal meningitis as well as endophthalmitis.

Case Report

A two-year-old girl had been well until ten days before admission to Ondokuz Mayıs University Children's Hospital. The child had fever and weakness for ten days and widespread rash for four days. Her parents noted an opacity in her left eye before admission. The child was observed to be severely ill, irritable and disoriented. Axillary temperature was 39.2 °C, pulse rate 148/min, respiration rate 40/min and blood pressure 90/60 mmHg. There were multiple petechial and purpuric lesions over her forearms, chest and especially thighs. She had a stiff neck in addition to positive Kernig's and Brudzinski's signs. On ophthalmologic examination, the right eye was normal but the anterior chamber of the left eye was found to be hazy with pus-like material in the inferior area (Fig. 1). The left orbital region was red and swollen. Slit-lamp examination revealed a hypopyon 2 mm in thickness. Orbital computerized tomography scan and ultrasonography were normal as were the other systemic findings.

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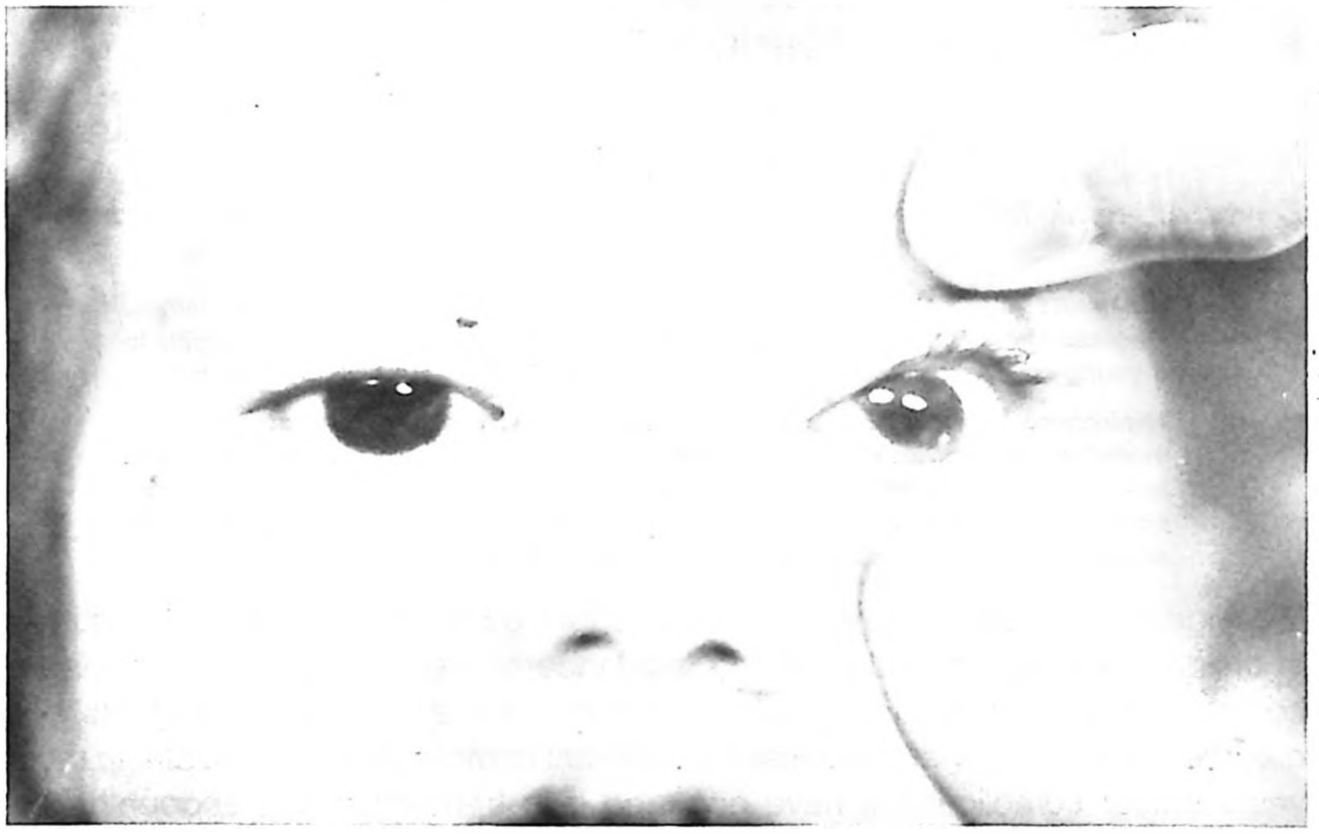

Fig. 1: Two millimeters' thickness hypopyon on the anterior chamber of the left eye of the patient with meningococcic meningitis is seen.

Laboratory studies showed a hemoglobin of 8.8 g/dl, white blood cell (WBC) count of 12,400/mm^3 with 66% polymorphonuclear leukocytes, 28% and 6% band forms. Erythrocyte sedimentation rate was 120 mm/h, while routine urinalysis and other biochemical results were normal. Lumbar puncture was performed immediately. Cerebrospinal fluid was turbid with 14,200 WBCs/mm^3, a protein level of 320 mg/dl and glucose level of 10 mg/dl. Latex agglutination test was positive for Neisseria meningitidis group C, and Gram staining smear revealed Gram (-) diplococci. Cerebrospinal fluid culture confirmed Neisseria meningitidis. No growth was noted in the blood cultures.

Therapy was started with intravenously administered ceftriaxone 100 mg/kg/day and dexamethasone 0.5 mg/kg/day. The hypopyon in the left eye was treated with topically applied ophthalmic gentamycin 0.3% 4 x 1 gtt, cefazoline 3.3% 4 x 1 gtt and atropine 1% 4 x 1 gtt sulfate. Appropriate supportive care was instituted. The patient became afebrile within three days; the hypopyon started to clear five days after the initiation of therapy and disappeared by the seventh day of treatment. Ceftriaxone therapy was continued for seven days, and other topical antibiotics and atropine sulfate were discontinued after 18 days. After being discharged from the hospital, the child was examined ophthalmologically every two weeks, and her eyes were found to be normal, including visual acuity, over a ten-month period.

Discussion

Meningococcal infections are still important causes of morbidity and mortality in all age groups[1]. Although N.meningitidis can be found in the birth canal and attacks the eyes of the neonate, endogenous meningococcal disease has been the most common form of endophthalmitis[2-4]. Endophthalmitis has been reported in about five percent of cases with meningococcal meningitis. Staphylococci, Streptococci, Bacillus species, gram-negative enteric bacilli, Pseudomonas and Haemophilus influenza type b are the other microorganisms which have caused endophthalmitis[5].

Ocular infections of the meningococci have been classified into three groups: 1) those occurring without meningitis; 2) those occurring during or after an attack of meningitis; and 3) meningitis following ocular infection[6]. Our case probably had ocular infection after meningitis. She came to the hospital with both orbital and meningeal involvement.

The incidence of ocular complications of meningococcal infections in the USA has ranged from 0.5 to 5.7 percent of cases[7]. About one-third of these have bilateral ocular involvement. Our case had unilateral endophthalmitis. Koch and Carson[4] reported three cases of uveitis in 128 children with meningococcal infections. In addition to uveitis, conjunctivitis[6], episcleritis[8] and cataracts[9] may also be seen as a result of meningococcal infection.

The only way to determine the cause of bacterial endophthalmitis is by aspirating intraocular fluids and recovering organism from cultures. The experience of the past ten years has demonstrated that in metastatic endophthalmitis, positive cultures from other sites in the body are very reliable indicators of the causative organism[10]. Thus, we did not take any ocular fluid for culture from the patient. Greenwald et al.[10] reported that the same microorganisms had been isolated from ocular fluids and other infected sites of the body in 16 of the 72 cases they reviewed. It has been postulated that in endogenous endophthalmitis as a result of hematogenous spread of infection, there may be a disruption of the blood-ocular barrier, similar to disruption of the blood-brain barrier in meningitis. Thus, systemic antibiotics are effective for both meningitis and endophthalmitis. Only in cases of severe endogenous endophthalmitis which involve most of the posterior chamber or progress to panophthalmitis, invitreal antibiotics must be used[10]. Our case was treated with systemic antibiotics, dexamethasone and local drugs for the eye. The anti-inflammatory activity of the corticosteroids may be important in preventing cicatricial complications secondary to endophthalmitis[7].

The prognosis of meningococcal endophthalmitis is generally good. However, delay in appropriate diagnosis and antibiotic therapy may contribute to poor prognosis[10]. We suggest that ocular involvement be sought in every case with meningococcal meningitis.

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CYCLOSPORIN – INDUCED REMISSION IN AN INFANT WITH ALKYLATING AGENTS – RESISTANT NEPHROTIC SYNDROME*

A Case Report

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SUMMARY: Yılmaz GG, Gür GÜven A. (Nephrology Unit, Department of Pediatrics, Akdeniz University Faculty of Medicine, Antalya, Turkey). Cyclosporin-induced remission in an infant with alkylating agents-resistant nephrotic syndrome: a case report. Turk J Pediatr 1995; 37: 411-414.

The efficacy of cyclosporin-A, a potent immunosuppressive agent, has not been clearly proven in the management of childhood nephrotic syndrome. The occurrence of early relapse as the dose of cyclosporin is tapered or as soon as the drug is stopped and the potential nephrotoxic effects of prolonged treatment have caused it to be used in limited cases. We report an eighteen-month-old boy with steroid toxicity and alkylating agents-resistant nephrotic syndrome, who subsequently went very quickly into remission lasting at least one year after receiving cyclosporin-A for only three months. *Key words: nephrotic syndrome, steroid toxicity, alkylating agents resistance, cyclosporin-A.*

Achieving sustained remission with minimum drug-induced adverse effects is the goal of therapy in the management of idiopathic nephrotic syndrome (INS). When basic corticosteroid treatment fails or symptoms of steroid toxicity appear, immunosuppressive drugs must be used. Traditionally, alkylating agents (AA) have been the first choice. The efficiency of AA in preventing further relapses and inducing prolonged remissions has been proven by prospective and retrospective studies[1-4]. Cyclosporin-A (CyA) is a new drug which has been used in the treatment of INS during the last ten years[5]. Both therapy regimens have numerous side effects. CyA can also cause nephrotoxicity, which can be suspected by abnormal renal functional tests or identified histopathologically. Other side effects of CyA are moderate elevation of blood pressure, hyperkalemia, hypomagnesemia, gum hypertrophy and hypertrichosis[6]. Detailed knowledge about the effectiveness and safety of the drug, as well as precise indications and duration of treatment in various clinical and histological forms of INS have not been clearly described.

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This case report was presented at "X. Ulusal Böbrek Hastalıkları, Dializ ve Transplantasyon Kongresi", Bursa, 1993.

Case Report

An eighteen-month-old boy was admitted with intractable generalized edema. Five months previously he had been diagnosed with INS and treated with corticosteroids (Prednisolone) at a dosage of 2 mg/kg/day for four weeks. Remission was achieved, but when the dose was tapered he relapsed. His clinical nephrotic picture, mainly edema, deteriorated despite taking steroids irregularly for three months. On admission to our unit, prednisolone was readministered at 2 mg/kg/day. Proteinuria decreased to 1+ in ten days, but a relapse occurred when the prednisolone was tapered to 1 mg/kg/day. He was hypertensive, and his serum albumin was 1.3 g/dl. Edema was so prominent on his eyelids that he could not open his eyes. Urinary tract infection, sinusitis and oral moniliasis ensued, and steroids had to be withdrawn. Cyclophosphamide was prescribed at 2.5 mg/kg/day for eight weeks with no benefit. In the meantime, several infusions of human albumin and diuretics were given with no effect. The decision was made to follow him with general supportive treatment and no medication. Renal biopsy was performed, revealing glomerular changes compatible with minimal lesion nephrotic syndrome. His generalized and disturbing edema, hypertension and massive proteinuria did not change despite another course of therapy with the second alkylating agent, chlorambucil, at a dose of 0.2 mg/kg/day for five weeks. Subsequently CyA was started at 7 mg/kg/day. The proteinuria diminished within three days. On the tenth day of therapy the edema and proteinuria dramatically disappeared. The dose of CyA was manipulated between 3-6 mg/kg/day, maintaining the blood level at 43-97 ng/ml (with RIA). Since he was in complete remission, the dose was not increased and was stopped at the end of three months. Serum creatinine levels were 1.1 mg/dl and 0.5 mg/dl before and after CyA therapy, respectively. The patient remained in remission for eleven months after cessation of CyA. No biochemical or clinical side effects were observed during or after CyA therapy.

Discussion

Corticosteroids are introduced as standard therapy when the diagnosis of INS is made, with or without a kidney biopsy[7]. However, at least seven to 15 percent of children with INS are resistant to therapy[8]. Some of them show steroid dependency and/or toxicity related with variable individual components and with the cumulative doses. In many of these patients, a short course of cyclophosphamide or chlorambucil can achieve a stable remission[3,4,6]. But alkylating agents also have cumulative toxicity[8,9].

In our case, the initial therapy with corticosteroids sustained a short remission. Subsequently, the patient presented with steroid dependency, and adverse effects of steroids such as bacterial and fungal infections and hypertension were

observed. We were concerned that this patient would not be a good candidate for alkylating agents. These drugs are known to be more effective in older children, in frequent relapsers, when given in the remission period and combined with full-dose steroids[6].

The poor clinical outcome of our patient despite additional albumin and diuretic infusions, persistent generalized edema, and long-lasting massive proteinuria led us to give cyclophosphamide and chlorambucil, one after the other. When these treatments failed, the new drug, CyA, which has been used in last ten years in the treatment of INS, was introduced to our patient. A dramatically rapid and complete remission was obtained.

A one-year sustained remission following a three-month course of CyA treatment encouraged us to report this experience. The indications and mode of therapy with CyA in various clinical and histopathological forms of INS have not yet been established. Its effect is based on two postulates: first, INS is presumably an immunologically-based disorder; and second, CyA exerts its immunomodulator effect on T-cell immunity. CyA also changes the properties of the glomerular barrier, resulting in increased charge and size selectivity, and diminishes the proteinuria[10, 11].

The first experience in children treating with CyA was reported by Hoyer et al.[12]. Thereafter, Capodicasa et al.,[13] Tejani et al.,[14] Niaudet et al.[15] and others showed that 80 percent of children with NS can be maintained in remission with CyA. CyA is also effective in patients with frequent relapses, as in steroid-dependent nephrotics, but less encouraging results have been reported in steroid-resistant patients and those with focal glomerular sclerosis[13-15]. It has been reported that alkylating agents can be more effective than CyA in steroid-dependent INS[16].

There is some concern over the duration of treatment, since relapses may occur when CyA is tapered or stopped[14, 15, 17, 18]. Relapse can occur immediately or one to ten months after cessation of therapy. Although two months to 5.2 year periods have been reported, a three or four-month course seems to be the preferred duration of therapy[14, 17, 19].

The long-term tolerance of CyA has been investigated[19]. The drug has nephrotoxic and other (hypertension, hypertrichosis, gum hypertrophy, hyperkalemia, hypomagnesemia) side effects, and many factors must be considered for the safe and effective use of the drug[5].

In conclusion, patients with minimal-change nephrotic syndrome can successfully be treated with CyA even after former failure of therapy with steroids and alkylating agents. In our case, remission was achieved in a very short time and sustained at least a year following a relatively short duration of therapy.

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The Turkish Journal of Pediatrics 1995; 37: 415-419

INFANTILE MYOFIBROMATOSIS*

A Case Report

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*Havvanur Turgutalp MD******

SUMMARY: Sarıhan H, Değer O, Önder Ç, Turgutalp H. (Departments of Pediatric Surgery, Biochemistry, Orthopedics and Pathology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Infantile myofibromatosis: a case report. Turk J Pediatr 1995; 37: 415-419.

Infantile myofibromatosis is a rare mesenchymal disorder of infancy characterized by the formation of tumors in the skin, muscle, viscera, bone and subcutaneous tissue. The etiology of the disorder is unknown. We describe here a newborn with multiple infantile myofibromatosis, peritonitis and intestinal perforation. Surgery revealed multiple intestinal obstructions and jejunal perforation due to intestinal tumors; consequently, a jejunostomy was performed. The patient was maintained on total parenteral nutrition and oral semiliquid infant formula for two months, however he died due to multiple attacks of diarrhea and septicemia. *Key words: infantile myofibromatosis, newborn intestinal obstruction, intestinal perforation.*

Infantile myofibromatosis (IM) is a rare mesenchymal disorder in newborns and infants, and is characterized by the formation of tumors involving the skin, skeletal muscle, viscera, bone and subcutaneous tissues[1,2]. It was first documented in 1954 and called "congenital generalized fibromatosis"[2,3]. It is also known as generalized hamartomatosis, multiple congenital mesenchymal tumor, diffuse congenital fibromatosis, and multiple vascular leiomyomas of the newborn[1,2]. Chung and Enzinger[4] named the entity "infantile myofibromatosis" in 1981.

We describe here a newborn with multiple infantile myofibromatosis involving the gastrointestinal tract, which was perforated as a result.

Case Report

A four-day-old boy was admitted to the Department of Pediatric Surgery, Faculty of Medicine, Trabzon, with bilious vomiting, abdominal distension and multiple subcutaneous nodules. The infant was the product of a full-term pregnancy ending in spontaneous delivery with no apparent complication. The mother had no prenatal care and there was no family history of disease.

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On physical examination, the infant was found to have multiple subcutaneous nodules, abdominal distension, dehydration and angulation of the right thigh. The subcutaneous nodules were firm, mobile and 0.5 to 4.0 cm in diameter in the scalp, thoracal wall and extremities (Fig. 1). Abdominal plain films showed free air and air fluid levels. Plain films of the body demonstrated osteolytic lesions of the extremities and a fracture of the right femur (Fig. 2).

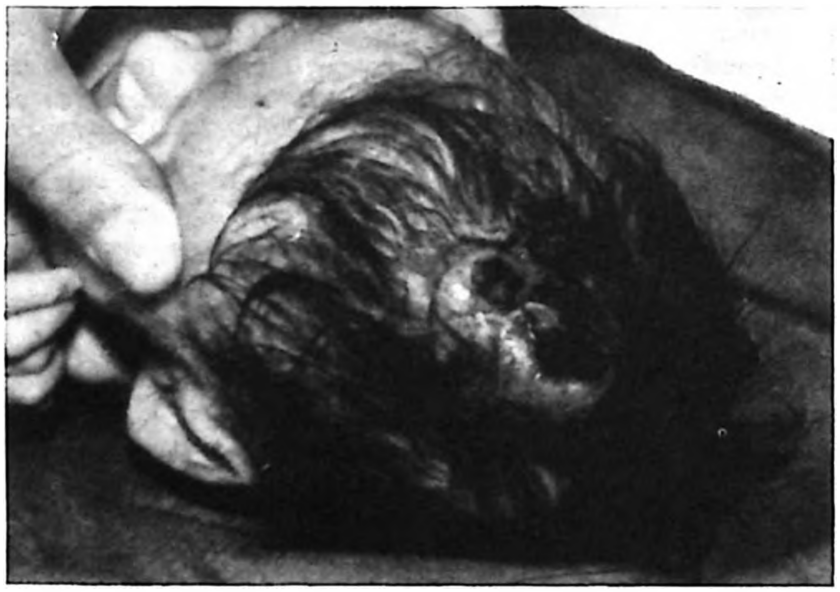

Fig. 1: The mass in the parietal region is 4 cm in diameter. The overlying skin was ulcerated.

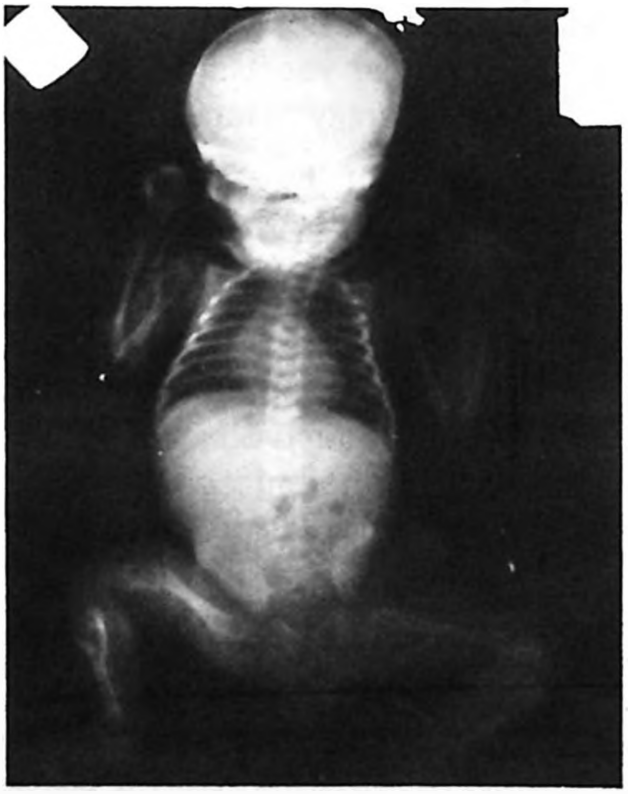

Fig. 2: Whole-body, post-operative x-ray showing osteolytic lesions of the extremities and fracture of the right femur.

After resuscitation with intravenous fluid, injection of vitamin K, nasogastric suction and antibiotics, an emergency laparotomy was performed through a right, transverse, supraumbilical incision. Peritonitis, multiple nodules from the stomach to the sigmoid colon and parietal peritoneum, and jejunal perforation 40 cm distal to the ligament of Trietz in the intact intestine were found. In addition, there were multiple intestinal obstructions in the jejunum, ileum and colon due to tumors. After washing the peritoneal cavity with hot saline, a biopsy specimen from the jejunal segment was obtained for pathological examination, a jejunostomy was performed and the abdominal wound was closed in a single layer. A subcutaneous nodule was excised for pathologic examination. Subsequently, traction of the right leg was performed for the femur fracture.

Parenteral nutrition was started postoperatively, and following the removal of the nasogastric tube on the fifth day, liquid oral nutrient was started. Histologic examination of subcutaneous and intestinal nodules indicated features of infantile myofibromatosis (Fig. 3). On the ninth postoperative day, semiliquid infant formula and colestyramine were permitted.

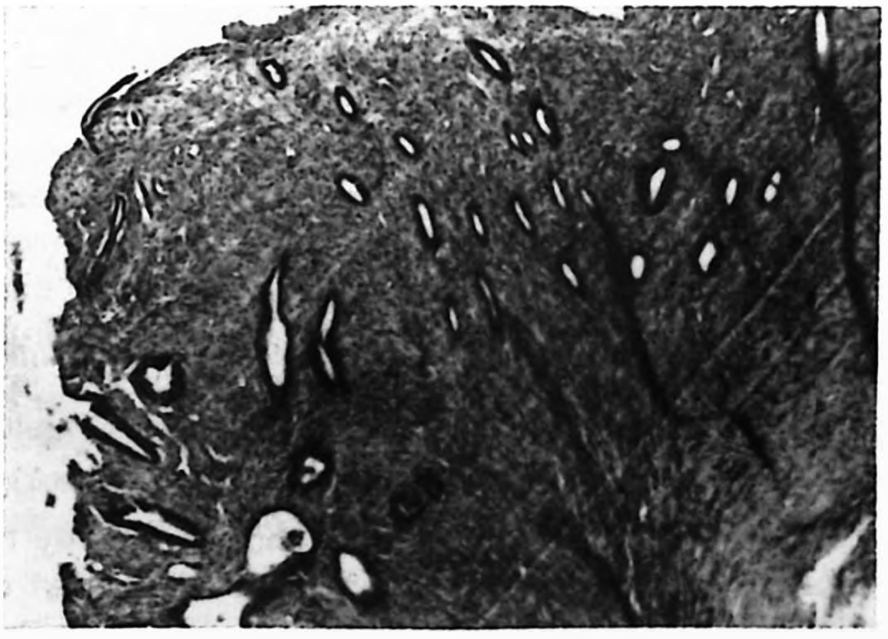

Fig. 3: Photomicrograph from the intestinal lesion demonstrating the characteristic appearance of infantile myofibromatosis.

In the postoperative period, the patient developed multiple attacks of severe diarrhea. Two months later, the infant's general status deteriorated and respiratory distress developed. After two days the infant died due to septicemia. The blood culture grew Pseudomonas aeruginosa resistant to all antibiotics.

Discussion

Infantile myofibromatosis is a rare mesenchymal disorder manifested by the formation of tumors in the skin, muscle, viscera, bone and subcutaneous tissues. The etiology of the disorder is uncertain. There is evidence to support that infantile myofibromatosis is a heritable condition[3-5]. It has also been suggested that IM lesions are hamartomatous in nature[6], and that IM results from in utero stimulation by estrogenic hormones[2, 6, 7].

It has been well established that there are two types of IM: i) the solitary lesion, and ii) the multiple lesion[1, 2]. The solitary lesion usually involves the skin, muscles, subcutaneous tissue and sometimes the viscera, and is present at the time of birth or shortly thereafter. The multiple-lesion type, which is more common, involves either subcutaneous tissue or the viscera together with subcutaneous tissue and the musculoskeletal system. There is a male predominance (1.7:1) in both forms of the disorder[1, 2].

The clinical manifestations and clinical course of IM depend on the number and localization of the tumor lesions[1-3]. A single, large tumor with multiple smaller lesions may be mistaken for a primary malignancy with metastases. Due to prominent tumor vascularity, skin lesions may resemble hemangiomas.

In cases of pulmonary involvement, the lesion may be seen as a solitary mass or diffuse intestinal inflammation in the chest x-ray[1]. Bone lesions are osteolytic and usually solitary, or as seen in our case, multiple bone lesions may also be present[8]. In addition, it may be thought that the right femoral fracture in our case had occurred during delivery. Neurologic symptoms usually develop because of compression of neural structures by the nodules present in the dura mater, soft tissue or bones[3]. Although diarrhea and intestinal obstruction due to involvement of the gastrointestinal tract have been reported[9, 10], in our case, as a consequence of multiple intestinal obstructions, a distinct feature of jejunal perforation was evident.

Evaluation of an infant with IM must include a thorough family history, chest x-ray, skeletal survey, computerized tomographic (CT) scan of the body, echocardiography and tumor biopsies. Contrast studies of gastrointestinal or genitourinary tracts should be performed if relevant signs or symptoms are present. Differential diagnosis should be made with soft tissue sarcoma in soft tissue tumors, and in bony lesions with Langerhans cell histiocytosis.

The histology of IM is quite characteristic and usually shows a distinct zoning phenomenon[1, 3]. The peripheral areas consist of spindle-shaped cells arranged in short bundles and fascicles. These cells demonstrate staining of both myoblastic and fibroblastic character. There is often a considerable amount of

fibroblastic character and frequently a large quantity of collagen within the surrounding matrix. The central portions usually consist of less-differentiated cells arranged around prominent vascular spaces in a hemangiopericytoma-like pattern. In addition, using immunohistochemical technique it has been possible to distinguish IM from the adult form[3].

The prognosis of IM is variable. Solitary or multiple lesions without visceral involvement generally have a benign course and spontaneous regression. However, in a patient with multiple lesions and visceral involvement, the mortality and local recurrence rates are high. Surgical excision should be reserved for cases in which vital structures are affected. Death from IM only results from complications related to visceral lesions in the multiple form of the disorder. Pulmonary involvement seems to carry the most grave prognosis[7].

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NEONATAL FORM OF HYPOPHOSPHATASIA*

A Case Report

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SUMMARY: Tekinalp G, Gürakan B, Yalçın S, Çağlar M, Ergin H. (Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neonatal form of hypophosphatasia. A case report. Turk J Pediatr 1995; 37: 421-424.

Hypophosphatasia is a rare (1/100,000), inherited inborn error of metabolism characterized by low serum and tissue alkaline phosphatase activities resulting in skeletal abnormalities. Four clinical forms are recognized depending on the age of diagnosis. Since treatment is not available and the prognosis is always lethal, detection of index cases and prenatal diagnosis in subsequent pregnancies is very important. Here we report a case with the most severe form of hypophosphatasia associated with lung hypoplasia. *Key words: neonatal, hypophosphatasia.*

Hypophosphatasia is an inherited disorder of bone mineralization characterized by decreased alkaline phosphatase (ALP) enzyme activity. A wide range of presentations has been described, however the disorder can be classified into four forms according to the age of onset of clinical manifestations. This classification as neonatal, infantile, childhood and adult forms of the disease, also has prognostic implications. Infants affected with the severe congenital form cannot survive beyond the neonatal period[1].

Here we report a case with neonatal hypophosphatasia who died from early respiratory insufficiency.

Case Report

The patient was the third child of consanguineous parents who were first cousins. Their first child had been healthy and the second child had been delivered stillborn with multiple anomalies. There was no definite information about the existence of hypophosphatasia in that fetus. The family history revealed no other cases with skeletal abnormalities.

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A female infant was delivered at 35 weeks gestation by cesarean section because of fetal distress. Birth weight was 1900 g, length 32 cm and head circumference 30 cm. Abnormalities apparent at birth included short and bowed extremities, dimples on the extensor surfaces, generalized hypotonia, small chest, very manifest craniotabes, and a large anterior fontanel (Fig. 1). The serum alkaline phosphatase activity was measured at birth and six hours later. Both measurements revealed very low levels of 7 and 10 IU/L, respectively (normal 185-340). The serum calcium and phosphorus concentrations were 10.9 mg/dl and 11 mg/dl, respectively. Radiographs showed hypomineralization of all bones, especially the long bones and ribs, consistent with hypophosphatasia (Fig. 2).

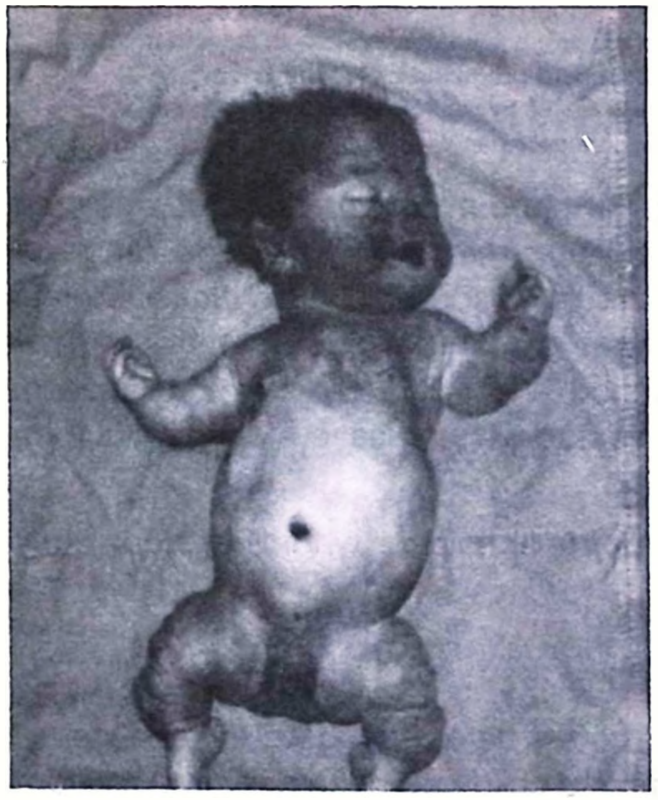

Fig. 1: Lethal neonatal form of hypophosphatasia. Note the curved and shortened limbs.

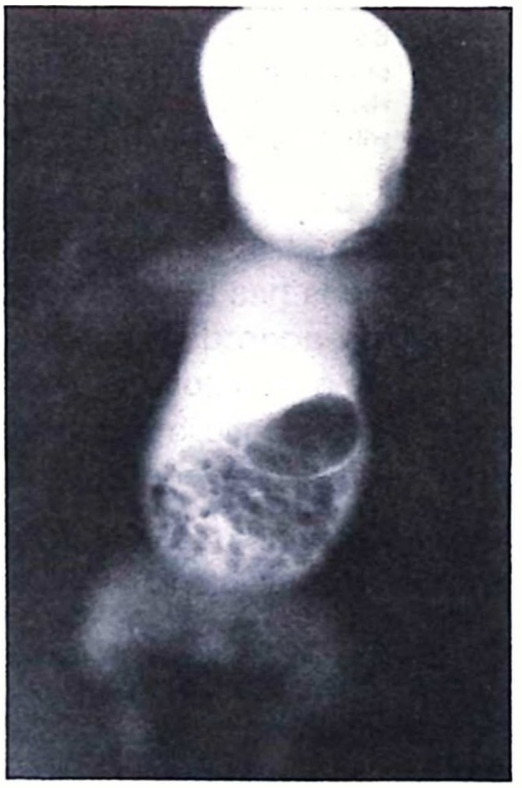

Fig. 2: Radiograph of the case. Note severe hypomineralization.

The infant was in respiratory distress. She was ventilated mechanically, but unfortunately lived only nine hours. The postmortem examination revealed pulmonary hypoplasia. A widened and flattened endochondral zone with pronounced disorganization of the chondrocytes was noted.

Discussion

Human ALPs are glycoproteins, and four isoenzyme forms have been identified. The placental, intestinal and placental-like isoenzymes are expressed in the

placenta, intestinal mucosa and neoplastic tissue, respectively. The liver/bone/kidney isoenzyme, however, is expressed in all tissues and localized particularly in hepatic, skeletal and renal tissue[2]. Only the latter form, which is also called tissue nonspecific (TNS) ALP, has a known biological function. The studies concerning hypophosphatasia indicate that TNS-ALP is necessary for normal bone mineralization, and its deficiency causes well-known deformities of the skeleton[2, 3]. The blood or urine levels of substrates for ALP including, phosphoetanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal-5' phosphate (PLP), are found to be increased in subjects with hypophosphatasia.

Hypophosphatasia varies widely in its clinical expression and has four main forms. Cases with the infantile form have early failure to thrive, hypotonia, renal compromise from hypercalcemia and severe skeletal deformities. This form presents in the first six months and is lethal in approximately 50 percent of cases. The childhood and adult forms are milder conditions, causing premature loss of deciduous teeth. Pathologic fractures in adulthood may be the first findings[1, 4].

Neonatal hypophosphatasia can be diagnosed easily at birth with its characteristic appearance. The short and deformed extremities, cutaneous dimples, small thorax with short ribs, shortness of stature and manifest craniotabes are the prominent findings. In our case, similar findings including abnormally soft cranial bones, severely shortened limbs and respiratory distress strongly suggested hypophosphatasia (Fig. 1).

Radiographs of these infants reveal small, sclerotic bones at the base of the skull and a membranous calvaria. The ribs are small, thin and deformed. Sclerotic patches are also observed in the ribs and other tubular bones. In accordance with these findings, long bones and ribs were not visible in the radiographs of our case due to generalized hypomineralization (Fig. 2). In addition to the clinical and radiographic findings, the diagnosis was confirmed by deficient levels of ALP. Unfortunately, we had no urine sample from which to make a PEA analysis.

Infants with this form of disease die within a few days from respiratory insufficiency due to reduced thoracic volume. In fact, the respiratory distress of our case deteriorated in spite of mechanic ventilation, and the lungs were found to be hypoplastic on autopsy.

The frequency of consanguinity and the recurrence rates indicate an autosomal recessive transmission mode in the neonatal and infantile forms. Since no effective treatment is currently available and the prognosis is always lethal, prenatal diagnosis is very important in these forms. Measurement of the ALP activities in amniotic fluid, cultured amniotic fluid cells or chorionic villi has been reported as a diagnostic method[5, 6]. However, the reliability of these tests is not yet fully established. More reliable results have been noted with DNA analysis[7, 8].

Since impaired mineralization occurs in utero, ultrasonographic diagnosis is possible in neonatal hypophosphatasia. The diagnosis may be considered in the presence of polyhydramnios, very low echogenicity of all bones and the sign of the prominent falx cerebri, skeletal deformities, abnormal measurements of the bones and small thorax[9]. Currently, ultrasound scanning seems informative and more available than enzymatic and molecular studies in our country.

In conclusion, this fatal disorder, although very rare, is one that should be taken into consideration in the newborn when manifest craniotabes, respiratory distress, or short and bowed limbs are present. Radiographic changes and low ALP levels confirm the diagnosis. The presence of an index case indicates the need for more careful prenatal diagnostic evaluation of subsequent pregnancies.

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BERNARD – SOULIER – LIKE FUNCTIONAL PLATELET DEFECT IN MYELODYSPLASTIC SYNDROME AND IN ACUTE MYELOBLASTIC LEUKEMIA ASSOCIATED WITH TRILINEAGE MYELODYSPLASIA*

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SUMMARY: Hiçsönmez G, Gümrük F, Çetin M, Özbek N, Tuncer M, Gürsel T. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Bernard-Soulier-like functional platelet defect in myelodysplastic syndrome and in acute myeloblastic leukemia associated with trilineage myelodysplasia. Turk J Pediatr 1995; 37: 425-429.

Platelet function was studied in a child with myelodysplastic syndrome (MDS: refractory anemia with an excess of blasts) and a child with acute myeloblastic leukemia (AML-M6) associated with trilineage myelodysplasia (TMDS). An acquired Bernard-Soulier-like platelet defect was considered in both patients with the findings of prolonged bleeding time and abnormally large platelets that failed to aggregate in response to ristocetin. In contrast to findings in von Willebrand's disease, the abnormal response of platelets to ristocetin could not be corrected by the addition of normal fresh plasma. The detection of abnormal platelet aggregation response to ristocetin may be a useful diagnostic finding for clonal disorders causing impaired platelet function in MDS and coexistent TMDS associated with AML. Further studies of ristocetin-induced platelet aggregation in a large number of these patients are required. *Key words: myelodysplastic syndrome, acute myeloblastic leukemia, Bernard-Soulier-like platelet defect.*

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hemopoietic disorders in which defective maturation involves one or more of the hematopoietic cell lines. Although morphologic abnormalities of platelets are the most common findings, functional defects of platelets have been described in MDS in a limited number of studies[1-5]. Here we report Bernard-Soulier-like functional platelet abnormality in a child with MDS and a child with acute myeloblastic leukemia-M6 (AML-M6) associated with trilineage myelodysplasia (TMDS).

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Case Reports

Case 1

A 13-year-old girl presented with a two-year history of weakness, pallor and abdominal distention. There was no history of bleeding or exposure to cytotoxic drugs or radiotherapy.

Physical examination revealed an enlarged liver and spleen, which extended 6 and 15 cm below the costal margins, respectively.

A blood count showed a Hb of 6.58 g/dl, MCV 87 fl, WBC 4 x 10^9/L, neutrophils 60%, lymphocytes 26%, monocytes 8%, myelocytes 3% and blasts 3%. The platelet count was normal, but the peripheral blood smear revealed predominantly morphologically abnormal giant platelets and marked anisocytosis, poikilocytosis, hypogranular and Pelgeroid polymorphs. The bleeding time (Ivy) was greater than 15 minutes. Prothrombin and activated partial thromboplastin times were within the normal ranges.

The bone marrow aspirate was hypercellular and showed dyserythropoiesis and dysmyelopoiesis with eight percent myeloblasts and dysmegakaryopoiesis. Iron stores were increased with ring sideroblasts (15%). Cytogenetic analysis revealed a normal karyotype. A diagnosis of MDS (refractory anemia with an excess of blasts) was made according to the French-American-British (FAB) classification[6].

Case 2

A five-year-old girl was examined for weakness and abdominal distention which began six months prior to admission. The patient had no current bleeding problems or history of bleeding.

Physical examination revealed an enlarged liver and spleen, which extented 7 and 5 cm below the costal margins, respectively.

A blood count showed a Hb of 12.2 g/dl, MCV 72 fl, reticulocyte 3.2%, and WBC 40.2 x 10^9/L with 61% blasts, 3% myelocytes, 4% metamyelocytes, 11% neutrophils, 13% lymphocytes and 8% nucleated red blood cells. The platelet count was normal. Examination of peripheral blood showed numerous giant platelets and occasional micromegakaryocytes, anisopoikilocytosis, hypogranular and Pelgeroid neutrophils. The bone marrow aspirate was hypercellular with erythroid hyperplasia (55%) and showed dyserythropoiesis. Dysmyelopoiesis with 67% blasts (expressed as a percentage of the non-erythroid bone marrow cells) and dysmegakaryopoiesis were also noted. Bone marrow cytogenetic analysis revealed hypodiploidy, hyperdiploidy and tetraploidy in 36 evaluable metaphases. The HbF was abnormally high (46%). A diagnosis of AML-M6 was made, and trilineage myelodysplasia was considered based on the peripheral blood and

bone marrow morphology defined by the FAB group[6]. The patient's bleeding time (Ivy) was greater than 15 minutes. The prothrombin and activated partial thromboplastin times were normal.

Platelet Aggregation Studies

The patients had not taken any medications known to interfere with platelet function prior to this study. Venous blood was collected in a 0.1 M disodium citrate solution (9:1 blood to anticoagulant ratio). Platelet-rich plasma (PRP) was prepared by centrifugation at 150 x g for 10 minutes at room temperature and diluted with freshly prepared platelet-poor plasma (PPP) from the same subject to a final platelet concentration of 200×10^9/L. Platelet aggregation studies were performed on a aggregometer (chronolog Broomally, Pa, USA) at 37 °C. Aggregation was observed in 1 ml aliqouts under continuous stirring after the addition of adenosine diphosphate (ADP, Sigma 10^{-5} M final concentration), bovine tendon collagen (Sigma, 20 µl of standardized suspension) and ristocetin (Lundbeck, Copenhagen 1.2 mg/ml final concentration). The degree of aggregation was evaluated according to the percent aggregation (Tmax), which indicates the maximum percent change in light transmission of PRP after the addition of ADP, collagen and ristocetin.

The responses to ADP were normal; however, no ristocetin or collagen-induced platelet response was observed in either patient. The absence of platelet aggregation by ristocetin could not be corrected with the addition of normal fresh plasma. The patient data are presented in Table I.

Tablo I: Characteristics of Patients

Case No.	Age (yrs)/Sex	Diagnosis	Previous Bleeding History	Bleeding Time	Platelet Aggregation (T max %)		
					Ristocetin	Collagen	ADP
1	13/F	RAEB	No	> 15 min	NR	NR	N
2	5/F	AML-M6/TMDS	No	> 15 min	NR	NR	N

RAEB : Refractory Anemia Excess Blast.
AML-M6: Acute myeloid leukemia-M6.
N : Normal.
TMDS: Trilineage Myelodysplasia.
NR : No response.

Discussion

While thrombocytopenia is a common finding in MDS, functional platelet disorders have also been described in these patients. Prolonged bleeding time and poor response to ADP, epinephrine and collagen are the abnormalities that have been most frequently reported[2, 4, 7]. Furthermore, various degrees of decreased platelet aggregation rates by ristocetin have been reported in a few patients with MDS[2, 3, 5]. In addition, an acquired Bernard-Soulier-like platelet defect has been described in a child with coexisting primary MDS and monosomy 7[8]. A deficiency of platelet

membrane glycoprotein (GP) Ib-IX complex, and a weak agglutination response to ristocetin were documented in this case. In our patients, the platelet aggregation by ristocetin was absent. Although platelet membrane GP analysis of our patients was not available, an acquired Bernard-Soulier-like platelet defect was considered in light of the prolonged bleeding time and unusually large platelets that failed to aggregate in response to ristocetin. The abnormal ristocetin response could not be corrected with the addition of normal fresh plasma, which is also characteristic of the platelets of patients with Bernard-Soulier disease[9, 10]. These platelet abnormalities presented with no clinical bleeding in our patients, similar to that reported previously[5]. Although morphologic abnormalities of platelets are the most common striking feature in MDS, the ultrastructural observations of platelets are consistent with the possible presence of both normal and abnormal platelets in the peripheral blood[11]. The reason that variable degrees of abnormal or even normal ristocetin-induced platelet response could be detected in MDS is not clear[2, 4]. However, one explanation may be the variation in the number of abnormal platelets in the circulation, as was observed in a heterozygous state of Bernard-Soulier disease[12].

Although various defects in platelet function have also been described in leukemia[11], the abnormal platelet response to ristocetin in our patient with AML-M6/TMDS may indicate the possibility of an additional platelet defect in patients with AML coexistent with features of TMDS. Studies of ristocetin-induced platelet aggregation in a large number of these patients are needed. The detection of an abnormal aggregation response to ristocetin may facilitate earlier diagnosis of clonal disorders causing impaired platelet function in patients with MDS and patients with AML who have evidence of coexistent TMDS.

Acknowledgements

We thank the Department of Genetics for performing cytogenetic analysis of our patients.

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The Turkish Journal of Pediatrics 1995; 37: 431-434

A CASE OF CHILDHOOD SHIGELLOSIS WITH MUTISM*

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SUMMARY: Selimoğlu M, Akdağ R, Kırpınar İ. (Department of Pediatrics, Atatürk University Faculty of Medicine, Erzurum, Turkey). A case of childhood shigellosis with mutism. Turk J Pediatr 1995; 37: 431-434.

Bacillary dysentery, an acute infection caused by various strains of Shigella, is characterized by abdominal pain, tenesmus, and diarrhea with mucus, pus and blood. Neurologic manifestations including meningismus, delirium and convulsions may accompany the infection. We describe a thirteen-year-old girl who presented with headache, convulsion and loss of consciousness at the onset and developed diarrhea with blood and pus after hospitalization. The diagnosis of shigellosis was based on clinical data and isolation of the microorganism in the stool specimen. After improved physical functions, the patient developed mutism that continued for two days in the course of her illness, despite having no history of neurologic or psychological problems. She was diagnosed by a psychiatrist with organic mental syndrome NOS (Not Otherwise Specified) according to DSM-III-R criteria. None of the conditions that may cause mutism could be confirmed. This is the first reported case of mutism accompanying shigellosis.
Key words: childhood shigellosis, mutism.

Bacillary dysentery is an acute infection caused by various strains of Shigella. The classical clinical picture is one characterized by severe abdominal pain, tenesmus and constitutional symptoms with frequent stools containing mucus, pus and blood[1]. Neurologic manifestations including meningismus, delirium and convulsions may accompany Shigella dysentery. Convulsions are the most frequent and prominent symptom among them[1,2].

Some rare neurologic symptoms such as hallucinations have been reported in childhood shigellosis. In this report we describe a child with shigellosis who had convulsions, postictal coma and organic mental syndrome with mutism, the inability or unwillingness to speak resulting in absence or marked paucity of verbal output, in the course of her illness[3,4].

Case Report

A 13-year-old girl was admitted to the hospital because of severe headache, convulsions and loss of consciousness. The child had no history of neurologic or psychological problems. On the day of admission, she had had a febrile,

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generalized convulsion of five minutes' duration and lost consciousness. She had been taken to the hospital within a few hours after her seizure.

Physical examination revealed a critically ill girl in a coma. Her body temperature was 36.5 °C, pulse rate 100 beats/min and blood pressure 110/60 mm Hg. She had no signs of meningeal irritation except nuchal rigidity. No pathological reflex was detected. The EEG revealed a normal pattern.

The white blood cell count was 19.7 x 10^9/L (24% neutrophils, 2% band forms, 2% monocytes, 72% lymphocytes), and hemoglobin level 15.5 g/dl. Serum electrolyte, glucose, calcium and liver function values were within normal limits. Serum creatinine was 0.8 mg/dl and blood urea nitrogen was 22 mg/dl. Urine analysis was normal. Lumbar puncture revealed a nonpathologic screen with no organism on Gram stain and a negative culture.

Approximately 12 hours later she began to respond to mechanical stimulation. During this period she developed diarrhea containing blood and mucus. Polymorphonuclear leukocytes were detected in stool, and the culture specimen showed Shigella flexneri; for this reason ampicillin administration was initiated. Approximately 24 hours later she regained consciousness and was fed by her mother within four hours. Approximately 12 hours later the watery diarrhea disappeared. Despite improved physical functions, she demonstrated mutism during the waking state. She was not confused or disoriented and she was indicating what she wanted with her hands. For two days she had no hallucinations, agitation, anxiety or mood disturbances. She ate her meals, slept well and obeyed other suggestions. However, she did not speak, and she refused to write and read. General physical and neurological examination, EEG and other laboratory assessments including parathyroid hormone (PTH), thyroid stimulating hormone (TSH), thyroxine (T_4), serum glucose, calcium, liver function tests and blood pH were repeated to rule out the conditions which might cause mutism, and none revealed an abnormality. After two days she began to speak, and despite of all our efforts she did not tell us why she had refused to speak.

A psychiatric evaluation was performed by an experienced psychiatrist. The patient was diagnosed with organic mental syndrome NOS (Not Otherwise Specified) according to DSM-III-R criteria[5]. No psychotropic medication was started. On the sixth day of her hospitalization, she was discharged with complete recovery.

Discussion

Neurologic symptoms are among the most frequent extra-intestinal manifestations of shigellosis. Convulsions have been described in 12-45 percent of hospitalized patients with culture-proven shigellosis[2]. Other neurologic symptoms, including lethargy, confusion and severe headache, are usually considered manifestations

of encephalopathy and occur in approximately 49 percent of patients with shigellosis[6]. Both seizures and transient encephalopathy are considered benign and rarely recur or have permanent sequelae, although fatal cases have been reported[3, 7].

Our case exhibited mutism accompanying shigellosis. The literature reveals that a myriad of psychiatric and non-psychiatric illnesses can present with mutism, and that patients with non-psychiatric disorders who are mute are frequently misdiagnosed. Of the cases reported in the literature, only three gave sufficient information to assess the prevalence of various disease states that may present with mutism. According to these reports, 39 percent of patients presenting with mutism are likely to have an affective disorder, 29 percent to have some form of schizophrenia, 17 percent to have organic brain syndrome, nine percent to have character disorders, and six percent to have an uncertain diagnosis[4].

Mutism in childhood is usually of the non-catatonic type. Mutism without catatonia may also be a symptom of conversion hysteria. The features considered helpful in making this diagnosis include an abrupt onset, a recent stressful event, an indifferent attitude (la bella indifference) and the absence of identifiable organic disease[4]. In our case the child had culture-proven shigellosis, and the syndrome did not meet the criteria for any other organic mental syndromes. She also had no history of a psychiatric problem.

The known toxic and metabolic conditions that cause mutism are hypoparathyroidism, Addison's disease, myxedema, diabetic ketoacidosis, hypercalcemia, acute intermittent prophyria, hepatic encephalopathy, glutethamide withdrawal and organic fluoride toxicity[4]. Our clinical and laboratory assessment confirmed none of these conditions. Petit mal status epilepticus closely resembles elective mutism and must be considered in the differential diagnosis[4], however the EEG of the patient was normal.

The mechanism involved in the development of convulsions and encephalopathy in shigellosis is poorly understood. There is a little evidence to support the shiga toxin hypothesis. The mechanism of the toxin and its relationship to other cytotoxins are still unclear if one or more toxins are involved[3].

Other pathologic mechanisms may contribute to the development of neurologic manifestations in shigellosis. Direct invasion of the central nervous system by shigella strains is rare and does not explain the frequent neurologic findings. Fever has been implicated as the cause of the neurologic manifestations; however, children may develop seizures during shigellosis even if they do not experience seizures during other febrile infections, and shigella-associated convulsions occur in children older than the usual age for febrile seizures. It has been suggested that the rate of temperature increase is especially rapid in shigellosis and accounts for the high incidence of seizures and other neurologic symptoms, but the clinical

assessment is difficult and this assumption has not been proven. In addition, host factors may play a role in defining individuals who are most susceptible to developing neurologic disturbances during shigellosis[2, 3, 6].

This case of shigellois with mutism should alert physicians that mutism can be a neurologic symptom of shigellosis, and that shigellosis should be considered in the differential diagnosis of mutism.

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The Turkish Journal of Pediatrics 1995; 37: 435-438

UNILATERAL AGENESIS OF THE STERNOCLEIDOMASTOID MUSCLE*

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SUMMARY: Koçak G, Aysun S, Akhan O. (Departments of Pediatrics and Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Unilateral agenesis of the sternocleidomastoid muscle. Turk J Pediatr 1995; 37: 435-438.

An eight-year-old girl with an asymmetrical appearance of the neck is presented. Physical examination and ultrasonographic (USG) findings revealed the absence of the patient's right sternocleidomastoid muscle. *Key words: sternocleidomastoid muscle, congenital absence, ultrasonography.*

Congenital agenesis of some muscles has been described, but the descriptions have been based primarily on anatomical dissections. Of individual muscle defects, the pectoralis is the most common and best known, followed by the trapezius, serratus anterior and quadratus femoris, but many other muscles may be affected either singly or in combination[1]. Here we describe a patient with congenital agenesis of the right sternocleidomastoid muscle. We used ultrasonography (USG) in this case to demonstrate the agenesis.

Case Report

An eight-year-old girl was admitted to the Department of Pediatric Neurology, Hacettepe University, because of the asymmetrical appearance of her neck. The girl's parents had noticed a depression in front of her right lower neck. She was born after a normal gestation and delivery. Her developmental milestones, both motor and cognitive, appeared normal. She had one older sibling, alive, in good health, and without any known musculoskeletal defect. The family history was unremarkable. During infancy the patient had suffered from congenital stridor. She had been admitted to the same hospital at that time, but there had been no abnormal findings in her physical examination and laboratory tests. The direct laryngoscopy was normal. On examination, nothing was noted in relation to the asymmetrical appearance of her neck at that time. The stridor dissapeared spontaneously when she was 1.5 years old.

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The latest physical examination of the patient revealed a healthy child with an asymmetrical appearance in her neck (Fig. 1). There was no facial asymmetry. The right supraclavicular area appeared to be deeper than normal and bulged when she breathed. The overlying skin was normal in appearance. She was found to have full motion of her neck. The results of the neurologic examination were within normal limits. The right sternocleidomastoid muscle could not be palpated either at rest or when isometrically contracted.

Laboratory investigations revealed normal muscle enzymes, liver and kidney functions. The roentgenography of the neck showed no abnormality, while USG of the neck revealed that there was no sternocleidomastoid muscle on the right side. A representative section is illustrated in Figure 2.

Fig. 1: Photograph showing right supraclavicular depression.

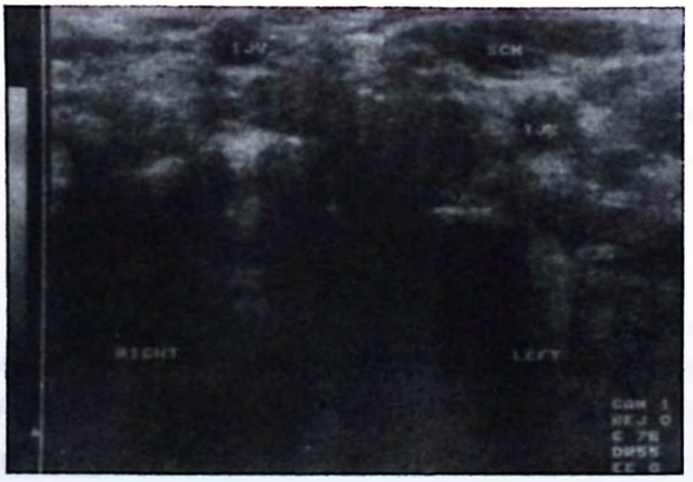

Fig. 2: Ultrasound of the neck shows absence of the right sternocleidomastoid muscle.

Discussion

The sternocleidomastoid muscle is one of the muscles of the neck. It originates from the upper part of the manibrium sterni and the medial third of the upper surface of the clavicle. The heads join and are inserted into the mastoid process and the superior nuchal line of the occipital bone. The contraction of one muscle pulls the ear down to the shoulder on the same side and rotates the head to the opposite side. In addition, the muscle can act as an accessory inspiration muscle[2].

The congenital absence of muscles is extremely rare, with an incidence of approximately one in 11,000 births[1]. Of these, the absence of the sternocleidomastoid muscle is particularly rare, representing three of the 185 cases described in the literature[3]. Congenital abnormalities of muscles tend to be unilateral and are often limited to a single muscle or a related group of muscles[1].

Although the diagnosis is not based on anatomical dissection, we believe the findings obtained by USG to be quite convincing. In some reports, magnetic resonance imaging and computerized tomography techniques are used to demonstrate muscle agenesis or anomalies without dissection[4-6].

The etiology is unknown. Some studies have revealed abnormalities and variations of muscles, vessels and peripheral nerves in trisomies, especially in trisomies 13, 18 and 21[7]. A few familial cases have been reported[8-11]. There is nothing in the history of this patient or in the clinical and roentgenographic findings to suggest a possible cause for the anomaly. Nothing can be said about the functional disability that this patient may suffer in the future.

We believe that our patient's stridor during infancy may have resulted from agenesis of the sternocleidomastoid muscle, which is an accessory muscle in respiration. During infancy the anomaly could not be found because of the shortness and increased fat tissue of the neck. The defect must be compensated by adaptive hypertrophy of the local muscular structures, which is why the stridor disappeared and we could not find any deficit on neuromuscular examination. We suggest than in cases of infantile stridor, investigations be performed to show whether any muscular anomaly is present, if routine investigations show no etiologic factor.

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ERRATA

The following is a correction to the article entitled, "Serum Ferritin and Hemoglobin Levels of Mothers and their Newborns" that appeared in the October-December 1994 issue of Turkish Journal of Pediatrics (1994; 36: 289-293). Table II should have read:

Table II: Hemoglobin, Serum Ferritin Values and Other Parameters of Mothers Whose Iron Stores are Depleted (Group II A), of Their Newborns (Group II B), and of Mothers Who Have Adequate Iron Stores (Group I A) and of Their Newbrons (Group I B).

	Group I A (n: 18)	Group I B (n: 18)	Group II A (n: 34)	Group II B (n: 34)	Group I B vs II B	
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	t	p
Hb (g/dl)	13.1 ± 0.7	16.1 ± 1.3	11.6 ± 1.4	15.9 ± 1.6 ± 0.1	> 0.5	
S.Ferritin (ng/ml)	20.2 ± 12.1	153.2 ± 56.8	9.1 ± 1.7	76.5 ± 27.7	5.7	< 0.001
S.Transferrin (mg/dl)	279.0 ± 33.6	208.8 ± 30.4	281.8 ± 30.2	203.2 ± 41.2	0.2	> 0.05
Transferrin Sat (%)	14.4 ± 1.1	44.8 ± 8.1	11.3 ± 2.0	45.0 ± 11.7	0.1	> 0.05
Serum Iron (µg/dl)	49.2 ± 5.2	111.2 ± 11.3	39.2 ± 5.1	110.0 ± 10.4	0.2	> 0.05
T.I.B. Capacity (µg/dl)	348.3 ± 33.4	256.3 ± 38.4	348.1 ± 58.3	257.7 ± 60.6	0.3	> 0.05

In addition, in the article entitled "Vitamin A Status of Healthy Children in Ankara, Turkey" that appeared in the July-September issue of Turkish Journal of Pediatrics (1995; 37: 187-192), Table I should be changed to the following:

Table I: Vitamin A Status of the Children According to Various Parameters

	Serum Retinol Level (µg/dl)	P*	No. with Retinol < 20 µg/dl	P*	No. with Retinol < 10 µg/dl	P*
Male (n: 44)	23.15 ± 6.63	NS	15 (34.1%)	NS	0	NS
Female (n: 36)	23.98 ± 7.11		9 (25%)		1 (2.8%)	
Shanty areas (n: 36)	22.67 ± 6.71	NS	12 (33.3%)	NS	1 (2.8%)	NS
Residential areas (n: 44)	24.22 ± 6.94		12 (27.2%)		0	
Infections during the last three months (n: 30)	22.57 ± 7.56	NS	10 (33.3%)	NS	1 (3.3%)	NS
No infections during the last three months (n: 50)	24.10 ± 6.35		14 (28.0%)		0	
Those receiving vitamin support (n: 32)	26.20 ± 7.12	0.004	6 (18.7%)	0.07	0	NS
Those not receiving vitamin support (n: 48)	21.75 ± 6.05		18 (37.5%)		1 (2.0%)	
Total (n: 80)	23.54 ± 6.68		24 (30%)		1 (1.3%)	

P < 0.05 was considered significant; NS: not significant.

ANNOUNCEMENTS

A NEW BOOK: 40 YEARS WITH İHSAN DOĞRAMACI

Written by Şinasi Özsoylu, MD, retired Professor of Pediatrics.

This short biography describes the achievements of the "Monumental Man" (as described by Süleyman Demirel, President of Turkey), the founder of İhsan Doğramacı Children's Hospital, the Institute of Child Health, Hacettepe Medical School and Hacettepe University in addition to five other universities and eight medical schools. Several chapters of the book reflect accomplishments on medical education and training during İhsan Doğramacı's Children's Hospital era and the reforms accomplished in this hospital, medical school and university in a very short period of time. These national and international achievements have been crowned by more than 260 awards, medallions, fellowships and memberships. Most recently he received UNICEF's Maurice Pate Award on May 22, 1995 in New York, making us proud of him once more. The book is written in Turkish in honor of his 80th birthday and is available in large book stores and all medical school libraries.

MEETINGS

CAEN, 19-21 OCTOBER 1995

THE FRAGILE X SYNDROME AND INHERITED MENTAL HANDICAPS
To Understand In Order to Help

Inquiries to: French Fragile X Syndrome Foundation
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Inquiries to: Halil G. Karabulut, MD
Ankara University
Medical Faculty
Medical Biology Dept., Genetics
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BASEL , 22-24 OCTOBER 1995

GENE THERAPY

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The First Turkish - Russian Meeting

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Selçuk University
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Biology and Genetics
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Inquiries to: Dr. Balvir S. Tomar
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