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SPUTUM BACTERIOLOGY AND ITS ANTIBIOTIC SUSCEPTIBILITIES IN TURKISH CYSTIC FIBROSIS PATIENTS*

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SUMMARY: Özçelik U, Şener B, Göçmen A, Kiper N, Ergin A, Dilber E. (Chest Diseases Unit, Department of Pediatrics, and Department of Microbiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Sputum bacteriology and its antibiotic susceptibilities in Turkish cystic fibrosis patients. Turk J Pediatr 1996; 38: 281-288.

To identify lower respiratory tract pathogens and their in-vitro antibiotic susceptibilities in Turkish cystic fibrosis (CF) patients, a total of 383 sputum cultures were evaluated from 45 CF children in 168 symptomatic and 215 control periods over 25 months. Microorganisms were isolated in 252 of the cultures. The isolation rate was 82 percent for symptomatic periods and 53 percent for control periods. The most common microorganism was P. aeruginosa in the symptomatic period and S. aureus in the control period. Other microbiological species included E. coli, H. influenzae, K. pneumoniae, S. epidermidis, β-hemolytic streptococcus, H. parainfluenzae, K. oxytoca, E. aerogenes and E. aglomerans. P. cepacia was not found. In 20 cultures more than one microorganism was isolated at the same time. In in-vitro conditions, high susceptibility rates were detected to amikacin, ciprofloxacin and ceftazidim for P. aeruginosa; cefuroxime, ceftriaxone, amikacin, cephalothin, chloramphenicol and erythromycin for S. aureus; amikacin and ceftriaxone for E. coli; ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime, ceftazidime, ceftriaxone and aztreonam for H. influeanzae; and aztreonam and amikacin for K. pneumoniae. Lower respiratory tract pathogens and their antibiotic susceptibilities in Turkish CF children were not significantly different from those indicated previously in the literature. *Key words: cystic fibrosis, sputum bacteriology, antibiotic susceptibility.*

Chronic pulmonary disease and its complications of recurrent pulmonary infections determine the quality of life and survival of cystic fibrosis (CF) patients. Since the early description of CF, various efforts have been made to identify and eliminate the microorganisms in the lungs of CF patients. The aim of this study was to detect microbiological flora in the respiratory system and antibiotic susceptibility in CF patients in our country.

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Material and Methods

The study group comprised 45 CF children, 22 female and 23 male, who were being followed at Hacettepe Children's Hospital between January 1991 and February 1993. Their ages ranged from two months to 16 years. They were diagnosed with CF by obtaining at least two sweat chloride values higher than 60 mEq/L with the method of pilocarpin iontopheresis[1], and typical clinical and laboratory findings. Sputum cultures were taken from the patients at routine monthly check-ups and during lower respiratory system infections. Sputum brought to the oropharynx by coughing in children, and by stimulating the coughing reflex in infants, was removed with cotton-tipped swabs. Samples were immediately sent to the laboratory in Stuarts transport medium and inoculated onto appropriate media by the same microbiologist who was working with the subject. All the samples were streaked directly onto two five-percent sheep blood agar (Oxoid); one eosin-methylene blue agar (EMB) (Oxoid); one chocolate agar with 10 percent horse blood containing 300 µg/ml bacitracin. 5 µg/ml vancomycine, 1 µg/ml clindamycine (CHOC-BVC) which was selective for Haemophilus species[2]; one cetrimide agar for Pseudomonas aeruginosa; and one OFPBL (oxidation fermentation medium supplemented with 300,000 U/L polymyxcin B sulfate, 200 U/L bacitrain and lactose) for Pseudomonas cepacia[3]. One sheep blood agar and CHOC-BVC were incubated in five to 10 percent CO_2 at 35 °C for 18-24 hours. One sheep blood agar, EMB agar, cetrimide agar and OFPBL agar were incubated in normal atmosphere at 35 °C for 18-24 hours. If there was no bacterial growth on CHOC-BVC agar at the end of 24 hours, the plates were reincubated for an additional 24 hours. Standard microbiological techniques were used to identify the microorganisms[4]. Antibiotic susceptibilities of detected microorganisms were evaluated by the Bauer-Kirby disk diffusion method according to NCCLS standards[5].

Antibiotic disks used for gram-negative microorganisms included ampicillin-sulbactam (10/10 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), chloramphenicol (30 µg), amikacin (30 µg), ceftazidime (30 µg), cefuroxime (30 µg), cefoxitin (30 µg), ceftriaxone (30 µg), aztreonam (30 µg) and ciprofloxacin (5 µg). Antibiotics disks used for gram-positive microorganisms included ampicillin (10 µg), ampicillin-sulbactam (10/10 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), amikacin (30 µg), erythromycin (15 µg), cephalothin (30 µg), cefuroxime (30 µg), ceftriaxone (30 µg) and chloramphenicol (30 µg). Antibiotic disks used for Haemophilus species were ampicillin (10 µg), ampicillin-sulbactam (10/10 µg), amoxicillin-clavulanate (20-10 µg), aztreonam (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), ceftazidime (30 µg), cefuroxime (30 µg) and chloramphenicol (30 µg).

Results

During the study period a total of 383 cultures were taken from CF children (215 in control and 168 was in symptomatic periods), and microorganisms were isolated in 252 of them (114 in control, 138 in symptomatic periods). The isolation rate was 82 percent during symptomatic periods and 53 percent for control periods.

The most frequently isolated microorganism was Pseudomonas aeruginosa (23%) in symptomatic periods and Staphylococcus aureus (19%) in control periods. All cultivated microbiological species are shown in Table I. In 20 sputum cultures, more than one microorganism was isolated at the same time-frequently in the symptomatic period (Table II). The in-vitro antibiotic susceptibilities of the main isolated microorganisms are shown in Table III. In in-vitro conditions, high susceptibility rates were detected to amikacin, ciprofloxacin and ceftazidime for P. aeruginosa; cefuroxime, ceftriaxone, amikacin, cephalothin, chloramphenicol and erythromycin for S. aureus; amikacin and ceftriaxone for E. coli; ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime, ceftazidime, ceftriaxone and aztreonam for H. influeanzae; and aztreonam and amikacin for K. pneumoniae.

Table I: Microbial Species in 252 Sputum Specimens of 46 CF Children and Distribution According to Age as well as Symptomatic and Control Periods

P. aeruginosa	S	6	6	9	7	4	32 (23)
	C	–	3	3	8	5	19 (17)
S. aureus	S	2	2	7	2	4	17 (12)
	C	–	2	7	2	11	22 (19)
E. coli	S	3	1	11	1	–	16 (12)
	C	4	3	6	1	2	16 (14)
H. influenzae	S	4	2	11	3	2	22 (16)
	K	1	3	–	2	–	6 (5)
K. pnemoniae	S	7	1	2	–	1	11 (8)
	C	7	6	2	1	–	16 (14)
S. pneumoniae	S	3	0	1	4	2	10 (7)
	C	2	2	6	4	–	14 (12)
β Hemolytic streptococcus	S	1	–	8	3	2	14 (10)
	C	–	–	5	2	–	7 (6)
H. parainfluenzae	S	1	1	8	1	2	13 (9)
	C	–	2	2	–	1	5 (4)
S. epidermidis	S	–	–	2	–	–	2 (1.4)
	C	–	1	–	–	–	1 (0.9)
K. oxytoca	S	–	–	–	–	–	–
	C	–	1	–	–	–	1 (0.9)
E. aerogenes	S	–	–	–	1	–	1 (0.7)
	C	–	–	–	–	–	–
E. agglomerans	S	–	–	–	–	–	–
	C	1	–	–	–	–	1 (0.9)
Total	S						138 (100)
	C						144 (100)

S: Symplomatic period C: Control period.

Table II: Pattern of Combination of Microorganisms in 252 Sputum Specimens

Microorganisms	Symptomatic Period	Control Period
H. influenzae + S. aureus	3	–
H. influenzae + H. parainfluenzae	1	–
H. influenzae + B. hemolytic streptococcus	2	–
H. influenzae + S. pneumoniae	2	–
H. influenzae + H. parainfluenzae + β hemolytic streptococcus	1	1
E. coli + H. parainfluenzae	2	1
E. coli + S. pneumoniae	–	1
S. aureus + H. parainfluenzae	–	1
S. aureus + K. oxytoca	–	1
S. aureus + E. coli	1	–
S. aureus + K. pneumoniae	2	–
S. epidermidis + H. parainfluenzae	1	–

Table III: Antibiotic Susceptibility of Microorganisms

	Pseudomonas Aeruginosa (t: 51)				Escherichia Coli (t: 32)				Klebsiella Pneumoniae (t: 27)			
Antibiotic	n	S (%)	S.S (%)	R (%)	n	S (%)	S.S (%)	R (%)	n	S (%)	S.S (%)	R (%)
Ampicillin	–	–	–	–	(32)	–	–	32 (100)	(27)	–	–	27 (100)
Ampicillin-sulbactam	(51)	3 (5)	–	48 (95)	(32)	12 (38)	2 (6)	18 (56)	(27)	6 (22)	6 (22)	15 (56)
TMP-SMX	(51)	5 (10)	1 (2)	45 (88)	(32)	9 (28)	–	23 (72)	(27)	18 (67)	–	9 (33)
Chloramphenicol	(51)	2 (4)	4 (8)	45 (88)	(15)	8 (53)	–	7 (47)	(10)	3 (30)	–	7 (70)
Amikacin	(51)	51 (100)	–	–	(32)	30 (94)	2 (6)	–	(27)	23 (85)	3 (11)	1 (4)
Cefuroxime	(28)	–	3 (11)	25 (89)	(32)	18 (56)	6 (19)	8 (25)	(27)	14 (52)	9 (33)	4 (15)
Cephalothin	–	–	–	–	(18)	5 (28)	5 (28)	8 (44)	(27)	3 (11)	3 (11)	21 (78)
Cefoxitin	(7)	–	–	7 (100)	(–)	–	–	–	(–)	–	–	–
Ceftazidime	(51)	48 (94)	3 (6)	–	(9)	4 (44)	–	5 (56)	(11)	–	–	11 (100)
Ceftriaxone	(51)	11 (22)	18 (33)	23 (45)	(32)	29 (91)	3 (9)	–	(27)	18 (67)	7 (26)	2 (7)
Aztreonam	(20)	11 (55)	4 (20)	5 (25)	(32)	26 (81)	–	6 (19)	(27)	25 (93)	2 (7)	–
Ciprofloxacin	(6)	6 (100)	–	–	(–)	–	–	–	(–)	–	–	–

	Staphylococcus aureus (t: 39)			
Antibiotic	n	S (%)	S.S (%)	R (%)
Ampicillin	(39)	2 (5)	–	37 (95)
Ampicillin-sulbactam	(39)	28 (72)	6 (15)	5 (13)
TMP-SMX	(39)	26 (67)	1 (2)	12 (31)
Chloramphenicol	(27)	23 (85)	–	4 (15)
Amikasin	(39)	34 (87)	3 (8)	2 (5)
Erythromycin	(39)	33 (85)	–	6 (15)
Cephalotin	(39)	33 (65)	1 (2)	5 (13)
Cefuroxime	(4)	4 (100)	–	–
Ceftriaxone	(39)	35 (90)	3 (8)	1 (2)

	Staphylococcus aureus (t: 39)			
Antibiotic	n	S (%)	S.S (%)	R (%)
Ampicillin	(28)	13 (46)	8 (29)	7 (25)
Ampicillin-sulbactam	(28)	28 (100)	–	–
Amoxcillin-clavulanate	(28)	28 (100)	–	–
TM-SMX	(28)	21 (75)	4 (14)	3 (11)
Chloramphenicol	(20)	17 (85)	–	–
Cefuroxime	(28)	28 (100)	–	–
Ceftazidime	(17)	17 (100)	–	–
Ceftriaxone	(28)	28 (100)	–	–
Aztreonam	(28)	28 (100)	–	–

S: Sensitive
S S. Semi-sensitive
R: Resistant

t: Total number of microorganisms isolated from sputum cultures
n: Number of cultures to which antibiotic was applied.
TM-SMX: Trimethoprim-sulfamethoxazole

Discussion

Despite the importance of evaluating the sputum cultures of CF patients, it is often difficult to obtain these cultures in infants and young children. The most appropriate methods for obtaining sputum samples are probably by the transtracheal approach or broncho-alveolar lavage, but it is quite difficult to use these routinely. As shown in previous comparative studies, samples taken from the oropharynx in CF patients give information about lower respiratory tract flora, although this method is less valid for some microorganisms in the normal flora of the oropharynx[6,7].

Pseudomonas aeruginosa was the most common of the isolated microorganisms found during symptomatic periods. According to studies from various countries, there has been a gradual increase in the isolation of P. aeruginosa and the other pseudomonas species over the years[8,9]. The cause of this increases could be linked to patients' common activities, such as summer camps, as well as to the use of selective media for isolation[10,11]. In our study we did not detect P. cepacia in any culture despite selective media. The fact that such activities are rare in Turkey may explain the lack of P. cepacia in our CF patients.

Staphylococcus aureus was reported to be the most commonly isolated microorganism in the early years of CF. In the 1962 study by Iacoca et al.[6] in which they evaluated the sputum cultures of 34 CF children. S. aureus was isolated in 85 percent of cultures. On the other hand, in the study by Mearns et al.[12] it was shown that S. aureus infections were decreasing gradually over the years.

Haemophilus influenzae is an important microorganism that is particularly common in CF patients. Corey et al.[9] showed that the role of H. influenzae infections is gradually increasing in CF patients. In the literature, the incidence of H. influenzae infections in CF patients has been described as 10 to 20 percent[6,7,13,14]; the same incidence was noted in our patients. Two H. influenzae strains which were isolated in control periods were serotype b, but no serotype b isolate was detected during smptomatic periods.

It has recently been proposed that E. coli strains forming mucoidal colonies play a role in lower respiratory tract infections of CF patients[15]. In the same study E. coli ranked fourth and third in symptomatic and control periods, respectively. The isolation rate for Klebsiella pneumoniae was eight percent in symptomatic periods, and 14 percent in control periods. In the study by Bauernfeind et al.[14], however, E. coli and K. pneumoniae were isolated in 0.9 and 0.4 percent of cases, respectively. These percentages were much lower than our findings.

Streptococcus pneumoniae was detected in seven percent of cultures taken in symptomatic periods, and 12 percent in control periods. This high rate may be

related to the use of oropharyngeal cultures in the current study. Although S. pneumoniae has not frequently been detected in the suputum cultures of CF patients. It was detected in 11.8 percent of the specimens in our study, similar to the findings of Bauernfeind et al.[14]. Beta-hemolytic streptococcus was also isolated frequently, especially during smyptomatic periods. In this study, although P. aeruginosa, S. aureus, H. influenzae and E. coli infections were seen in all age-groups. K. pneumoniae was generally seen in the first six months of life. Some reports regarding serum antibacterial precipitins have shown that S. aureus precipitins were gradually increasing. P. aeruginosa precipitins which were high in young age-groups were gradually decreasing and H. influenzae precipitins were increasing with age[16]. Mearns et al.[12] reported that P. aeruginosa precipitins were high in all age-groups and S. aureus and H. influenzae precipitins were low in young children but gradually incerased with age.

H. influenzae was observed to be the microorganism most commonly isolated together with other bacteria in the specimens.

The standard regimens of treatment for P. aeruginosa in CF patients have previously consisted of a combination of a antipseudomonal penicillin and an aminoglycoside. However, increasing resistance to antipseudomonal penicillins and adverse drug reactions to aminoglycosides have created the need for other treatment regimens. Ceftazidime or imipenem plus aminoglycosides have been recommended as new antibiotic regimens for P. aeruginosa infections in CF patients[17-24]. Aminoglycosides are known to be very effective in CF patients[25,26], and in our study a high susceptibility to amikacin (100%) was detected in all of the P. aeruginosa isolates in in-vitro conditions. Ciprofloxacin, which has gained importance because of its oral antipseudomonal effect[27,28], was used in only six patients considering their young age, and the P. aeruginosa strains isolated from these patients were found to be susceptible to ciprofloxacin (100%). In-vitro response to ceftazidime was also high (94%). Aztreonam seems to be a valid antibiotic, as the results showed 55 percent susceptibility and 20 percent moderate susceptibility. In-vitro resistance was detected in most of the P. aeruginosa strains against ceftriaxone, trimethoprim-sulfamethoxazole, chloramphenicol, cefuroxime and cefoxitin.

In S. aureus infections high susceptibility rates were detected to cefuroxime, ceftriaxone, amikacin, chloramphenicol and erythromycin. Ampicillin resistance was found in 95 percent of the S. aureus isolates.

Haemophilus influenzae was found susceptible in in-vitro conditions to ampicillin-sulbactam, amoxicillin-clavulanate, aztreonam, cefuroxime, ceftriaxone and ceftazidime. On the other hand, susceptibility to ampicillin, which is recommended in classical H. influenzae treatment, was determined to be only 46 percent. It

is known that H. influenzae resistance to ampicillin has gradually increased in recent years[29,30]. One might think that the widespread use of ampicillin in our country would play an important role in these results. Trimethoprim-sulfamethoxazole and chloramphenicol were other recommended antibiotics in the classical treatment of H. influenzae infections, and susceptibilities to these two agents were 75 and 85 percent respectively.

In the current study, high in-vitro susceptibility was found to amikacin and aztreonam in K. pneumoniae and to amikacin, aztreonam and ceftriaxone in E. coli.

Although advanced microbiological methods were not used in this study, it is the first on this subject in Turkey, and the results were similar to those obtained from studies in Europe and North America.

P. aeruginosa was the most commonly isolated microorganism, especially in symptomatic periods. S. aureus infections are still important for CF children in our country, and P. cepacia is not. The in-vitro antibiotic susceptibility results obtained in our study were not significantly different from those of similar studies in the literature.

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INCIDENCE OF H. INFLUENZAE IN A DAY-CARE CENTER*

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SUMMARY: Akçakaya N, Torun MM, Söylemez Y, Sevme R, Çokuğraş H, Ergin S, Pinçe O, Eşkazan G. (Department of Pediatrics, Istanbul University Cerrahpaşa Faculty of Medicine, Istanbul Turkey). Incidence of H. influenzae in a day-care center. Turk J Pediatr 1996; 38: 289-293.

In this study nasopharyngeal haemophilus influenzae flora of healthy children in a day-care center in Istanbul were analyzed. Nasopharyngeal cultures of 168 children between two and five years of age were obtained between December 1, 1992 and April 1, 1993 and investigated. H. influenzae was isolated in 104 cultures. H. influenzae type b (Hib), type f and H. parainfluenzae were found 87 children (51.8%), 15 children (8.9%) and one child (0.6%), respectively, while non-typable H. influenzae was discovered in one child (0.6%). Hib, which is the cause of invasive H. influenzae infection in childhood, was evaluated with respect to age; its incidence was found to be highest in two and three-year-old children, and reduced in children older than four years of age. Although Hib was seen in 518 percent of normal children in the day-care center, invasive Hib disease was not seen in any of those children. Therefore, these children have considered carrier of Hib without clinical manifestations. *Key words: H. influenzae, childhood, incidence.*

H. influenzae type b (Hib) is an important cause of severe bacterial infections in children between the ages of one month and three years and is associated with appreciable mortality. Meningitis and epiglottitis are the most common and serious manifestations of invasive H. influenzae type b infection. Non-typable H. influenzae is the major etiologic agent of otitis media, sinusitis and conjunctivitis[1-4]. Socioeconomic factors such as crowded families as well as overcrowding of day-care centers and schools may lead to an increased risk of exposure to H. influenzae type b infections. The relative risk for day-care attendees has also been shown to be much greater than that for the general population[5-13].

Due to insufficient routine laboratory evaluations, there are virtually no studies available on the incidence of H. influenzae type b in children in Turkey. The aim

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of the present study was to evaluate the importance of H. influenzae type b infections in a day-care center.

Material and Methods

A total of 168 healthy children (71 girls, 97 boys) of medical staff in a day-care center of Cerrahpaşa Medical Faculty were included in the study. The age distribution ranged between two and five years. Children in a day-care center were selected because they provide a defined group at the appropriate age. There was no ongoing systemic H. influenzae type b illness in that day-care center.

One nasopharyngeal specimen was obtained from each child between December 1, 1992 and April 1, 1993. Nasopharyngeal specimens were plated onto chocolate agar medium containing fish extract and prepared by adding 18.9 U/mml bacitracin. Furthermore a special disk consisting of X and V factors were also used to provide the requirements for these factors [X factor DD3-V factor DD4 (oxoid)]. After identification of H. influenzae, encapsulated strains were classified by the polysaccharides of the capsular substance (Wellcome Diagnostic) and designated as types a through f[14-15].

Results

H. influenzae type b was isolated from nasopharyngeal cultures of 87 (51.8%) children (37 girls, 50 boys). H. influenzae type f was recovered from 15 (8.9%) children (10 girls, 5 boys). In addition, non-typable Hemophilus in one girl (0.6%) and H.parainfluenzae in one boy (0.6%) were identified. H. influenzae was isolated from 104 (61.9) of 168 cultures, and 64 (38.1%) cultures were negative (Table I).

Table I: Characteristics of H. influenzae Strains Cultured from the Nasopharynges of Children in a Day-Care Center (n: 168)

	H. influenzae	Hib	Type f	Non-typable	H. parainfluenzae	Not isolated
Total (n)	104	87	15	1	1	64
Female		37	10	1		23
Male		50	5		1	41
Total (%)	61.9	51.8	8.9	0.6	0.6	38.1

Table II: The Age Distribution of H. influenzae Strains

Age (years)	Total n: 168	Hib n	Hib %	Type f	Non-typable	H. para-influenzae	Not isolated
2	41	25	15	4			12
3	54	30	18	3		1	20
4	53	21	13	5	1		26
5	20	11	7	2			7

Hib was evaluated with respect to age its incidence being highest in two- and three-year-old children, and reduced in children older than four years of age (Table II).

Discussion

Haemophilus influenzae type b (Hib) was identified in 51.8 percent of children between the ages of two and five years in a day-care center (Table I). This stdy represent the first analysis of the nasopharyngeal H. influenzae flora of normal children in day care.

In a previous study, Hemophilus influenzae was isolated in 48 throat or nasopharyngeal specimens of 100 children with upper respiratory tract infections who attended our outpatient clinic[16]. Among these 48 children, H. influenzae type b was recovered in 37 (77%), H. influenzae type c in five (10.4%), H. influenzae type e in one (9%), influenzae f in 2 (4%) and non-typable strains in three children (6.2%). Sixteen patients (33.3%) with upper respiratory tract infections concurrently had other pathogenic agents such as beta hemolytic streptococci, S.pneumonia, S.aureus, E.coli, P.aeruginosa and C.albicans[16]. The distribution of Hib incidence in the day-care center varied with age 15 percent in two-year-old, 18 percent in three-year-old, 13 percent in four-year-old and seven percent in five-year-old children. The peak incidence of Hib was observed at three years of age (Table II). Although invasive Hib disease was not observed in any of those children, these children were considered to be carriers of Hib without clinical manifestations.

Incidence rates were 1.3 times higher in boys than in girls. Although the risk of invasive Hib disease was most marked among children less than one year of age, in a study by Istre et al.[5] the risk was found to increase with age[4]. It has been suggested that day-care centers are the source of repeated experiences with infections due to H. influenzae. Prophylaxis with rifampin has proved useful in children more than two years of age[6-8]. Rifampicin administered to the contacts

eradicates the organism from 96 percent of cases and is also effective in reducing the risk of secondary disease[7,17-19]. It must be considered that infants and children in early childhood are at risk for H. influenzae infection, therefore feeding with breast milk[4,5] and active immunization with Hib vaccine are recommended[1-6].

The incidence of non-typable H. influenzae was found to be 39 percent in a longitudinal survey of infants followed for four winter months in nurseries in Sweden[8]. Several reports have documented that the rate of the carrier state of Hib without clinical manifestations was 10 percent and may increase to 50 percent in preschool children[8,20-23]. Children less than seven years of age have the highest nasopharyngeal carriage rate of Hib. Children who are close in age are also more likely to have close contact with each other[10].

The incidence of Hib has 51.8 percent in healthy children in the day-care center, which is not as negligible a rate as it was previously thought to be. This ratio shows that the incidence may be similar to that in western countries, as long as we have the opportunity to use proper and advanced techniques in our routine microbiology laboratories.

In conclusion, this study has revealed a remarkably high incidence of Hib (51.8%) with a peak incidence at three years of age in children in a day-care center in metropolitan Istanbul. Invasive Hib infections were not seen in the children in this day-care center during our one-year investigation period. This suggests that these children are in carrier state of Hib without clinical manifestations.

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EFFECTS OF ORAL AND INTRAMUSCULAR VITAMIN K PROPHYLAXIS ON PIVKA-II ASSAY PARAMETERS IN BREASTFED INFANTS IN TURKEY*

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SUMMARY: Uluşahin N, Arsan S, Ertogan F. (Neonatal Intensive Care Unit, Department of Pediatrics, Ankara University Faculty of Medicine, Ankara, Turkey). Effects of oral and intramuscular vitamin K prophylaxis on PIVKA-II assay parameters in breastfed infants in Turkey. Turk J Pediatr 1996; 38: 295-300.

Protein induced by vitamin K absence (PIVKA-II) has been used for the evaluation of vitamin K deficiency in the newborn. Differing PIVKA-II detection rates in various studies on hemorrhagic disease of the newborn have not been explained satisfactorily. In this study we investigated the PIVKA-II values of 44 healthy breastfed infants, of whom 29 recevied vitamin K1 either orally (N=13) or intramuscularly (n=16), and the remaining 15 constituted the control group. PIVKA-II was detected in 15.3 percent (2/13) of the oral and 25 percent of the (4/16) intramuscular group on the third day of life. The detection rate was 93.3 percent (14/15) in the control group. However, at the one-month follow-up, there were no PIVKA-II positive infants. In conclusion, PIVKA-II positivity among breastfed Turkish infants on the third day of life was high compared to that in other studies, perhaps due to a delay in enzyme maturation related to racial, environmental and nutritional factors. *Key words: vitamin K1, neonate, PIVKA-II, hemorrhagic disease.*

"Hemorrhagic disease of the newborn" was first designed as a term in 1894, and its relation to vitamin K was discovered later[1]. Although considerable progress has been made in understanding the biological role of vitamin K in this disease, hemorrhagic disease of the newborn still remains a cause of infant morbidity and mortality[2-10]. It has also been documented that hemorrhagic disease of the newborn occurs more frequently in infants who are breastfed; thus, routine administration of vitamin K or requirements for fortification of all infant formulas with vitamin K has been proposed[10-12].

In order to assess the disease a method of detection of the protein induced by vitamin K absence (PIVKA-II) has been developed[13-15]. PIVKA-II is an abnormal protein (prothrombin) that is mainly induced in the absence of vitamin K. Various studies have been conducted for the detection of PIVKA prothrombin, though with some limitations, for the evaluation of vitamin K deficiency in the newborn.

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Since the first attempt to detect PIVKA-II in the cord blood of newborn infants[16], various reports have shown different detection rates depending on the method used; the differences in the reported incidences have not been explained satisfactorily[13]. In this small preliminary study, we investigated the effects of oral and intramuscular vitamin K1 on Turkish newborns by the PIVKA-II detection method.

Material and Methods

This study was conducted on newborn infants born at the Ankara University Obstetrics Department. Infants were enrolled in the study only if they were full-term and healthy at birth, had APGAR scores greater than six at five minutes and had mothers fully intending to breastfeed. Written informed consents were obtained prior to enrollment. The mothers had had uneventful pregnancies and were not on vitamin K1, anticoagulant, antiepileptic or antituberculosis treatment.

This two-phase study involved three groups of newborns (n=44), who were randomly allocated to one of the groups. These three groups consisted of infants given either oral (n=13) or intramuscular (n=16) treatment, the remainder (n=15) comprising the control group (Table I). Infants in the oral treatment group were given 2 mg vitamin K1 in the form of 1 mg/ml phytomenadione (Konakion, Hoffman-LaRoche) and the intramuscular treatment group received 1 mg vitamin K1 intramuscularly within six hours of birth. The control group was not treated after birth but received 1 mg vitamin K intramuscularly at the age of one month, just after the second blood samples were drawn.

In the first phase of the study a venous sample was drawn 68.8±19.9 hours after birth in all 44 subjects. In the second phase, venous samples were drawn again one month later. Unfortunately only nine subjects in the oral group, eight in the intramuscular group and eight in the control group came for this follow-up visit.

Venous blood samples for PIVKA-II assay were collected in citrated tubes (3.8% sodium citrate) and immediately centrifuged at 3000 g for 10 minutes. Supernatant plasma samples were stored at –30°C until PIVKA-II detection. PIVKA-II was

Table I: Demographic Comparison of the Three Study Groups

	Oral	Intramuscular	Control
Number of infants	13	16	15
Sex (F/M)	6 / 7	5 / 11	5 /1 0

Table II: Comparison of Gestational Age, Apgar Scores and Age at Vitamin K Administration for Orally and Intramuscularly Treated and Control Groups (Results given as mean ± SD).

	Oral	Intramuscular	Control	p
Gestational weeks	39.92 ± 1.04	39.19 ± 1.05	39.13 ± 1.13	0.79
Apgar Score (5 minutes)	9.23 ± 0.44	9.75 ± 0.45	9.27 ± 0.59	0.01
Age at Vitamin K administration (hours)	8.92 ± 13.6	12.13 ± 9.4		0.48

assayed by an enzyme-linked immunosorbent assay, implementing a monoclonal antibody method (Asserachrom PIVKA-II, Diagnostica Stago, France). With this methodology, PIVKA-II values were expressed in arbitrary units as AU/ml, where one AU was one microgram purified prothrombin per ml.

The normal detection limit was 0.13 AU/ml, which defined PIVKA-II concentrations as positive or negative when greater or less than this limit, respectively. The statistical evaluation of data was performed with the Statistical Package for Social Sciences Program (SPSS-PC, Version 4.01). For inter-group comparisons, analysis of variance, and for intra-group comparisons the student's t test was employed. Pearson's correlation coefficient was implemented for regression analyses.

Results

Selected patient characteristics are displayed in Tables I and II. No feature other then sex was found to be statistically different between the groups in either phase of the study.

All infants remained healthy during follow-up and no side effects were reported related to vitamin K administration. There were also no reports of bleeding diathesis during the study.

The presence of PIVKA-II was evaluated in all infants. Follow-up screening was performed no later than at the end of the first month. Patients' results are displayed in Table III.

Table III: Presence of PIVKA-II (Protein Induced by Vitamin K Absence) in Breastfed Infants at Different Ages In Controls and After Oral or Intramuscular Vitamin K Prophylaxis at Birth

	Time after birth	
	3 Days	1 Month
Oral group	2/13 (15.3%)	0/9
Intramuscular group	4/16 (25.0%)	0/8
Control group	14/15 (93.3%)	0/8

In the group treated orally, 15.3 percent of the infants were positive for PIVKA-II, while 25 percent of infants treated intramuscularly were positive. A much higher percentage of infants (93.3%) who had no vitamin K treatment had high PIVKA-II values. Although the number of infants who followed up at one month was much lower, none of them was PIVKA-II-positive.

The difference in percentages of PIVKA-II positive samples among orally treated patients compared with those treated intramuscularly was not statistically significant ($p=0.05$). However, there was a statistically significant difference between the control and treatment groups ($p=0.001$).

Discussion

In this preliminary study the detection of PIVKA-II was taken as an indication of vitamin K status in breastfed newborns in Turkey. Although further investigation is necessary before a possible correlation between PIVKA-II findings and early or late hemorrhagic disease of the newborn can be made our results show that PIVKA-II values were highly positive (93.3%) in control group infants who had not received vitamin K at birth. On the contrary, infants who were either orally or intramuscularly treated with vitamin K and breastfed had low PIVKA-II values.

To our knowledge, the PIVKA-II positivity rate found in this study is the highest reported. Motahara et al.[16] found levels of PIVKA-II in 21.5 percent of cord blood samples of 51 newborns; however, on the third and fifth days of his study these values had increased to 50 and 60 percent PIVKA-II positive, respectively. Hathaway et al.[7] also reported similar (27/51, 53%) PIVKA-II positivity on the fourth and fifth days of life without vitamin K supplementation.

There have also been controversial results from other studies. In the Widdershoven study[18], PIVKA-II was only found to be present in the cord blood of five newborns out of 16 (31.3%). However, on the fourth day of life, PIVKA was detected in the plasma of 12.9 percent of cases (12/93 cases).

A similar result was reported by Anai et al.[1], in whose study PIVKA II-positive infants represented only seven percent of cases (13/186) on the fifth day of life. According to Widdershoven[20], this difference in PIVKA-II values could only be attributed to the detectability of vitamin K in the breast milk of Japanese and Dutch women.

As the PIVKA-II results of several studies contradict each other, the cause of hemorrhagic disease of the newborn has not yet been explained clearly. In light of Widdershoven's attribution for the vitamin K content of breast milk in different races, limited transport of the vitamin to the fetus through the placenta or minute amounts of vitamin K production by the intestinal flora of newborns could be postulated. Although the data are inconclusive, the response to vitamin K administration is claimed to be limited by the immature liver's incapability to synthesize and carboxylate precursor proteins. Also, the difference in the capabilities of premature and full-term babies is unknown[20].

The PIVKA-II, which is considered an indicator of vitamin K levels, has no clinical consequences but indicates whether enough vitamin K has been available for carboxylation of vitamin K-dependent proteins[13]. High levels of PIVKA-II may be caused by a dysfunctioning liver or by environmental factors that may have an inhibitory effect on hepatic utilization of vitamin K.

The results of our preliminary study showed PIVKA-II positivity at levels higher than previously reported. These elevated levels of PIVKA-II may be evidence of a high prevalence of vitamin K deficiency among our breastfed infant population.

Another controversial finding of our study was the absence of PIVKA-II at the end of one month in all breastfed infants, whether or not they had vitamin K treatment. This inconclusive finding may be result of the limited number of follow-up infants. A prevalence study on hemorrhagic disease of the newborn in Turkey has not yet been performed. Our group is currently planning such a study as we believe that some racial factors may play an important role in the high incidence of elevated PIVKA-II levels we detected. Similarly, there is a high incidence of unexplained unconjugated jaundice among Turkish newborns. In conclusion, it would be worthwhile to conduct another study on Turkish mothers and newborns to detect the vitamin K content of breastmilk and the degree of immature reutilization of vitamin K epoxide by newborns, two possible etiological factors for the disease concerned.

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IMMUNE GLOBULIN TREATMENT IN INTRACTABLE EPILEPSY OF CHILDHOOD*

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SUMMARY: Türkay S, Baskın E, Dener Ş, Gültekin A, Tanzer F, Sekreter E. (Departments of Pediatrics and Neurology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Immune globulin treatment in intractable epilepsy of childhood. Turk J Pediatr 1996; 38: 301-305.

Six children suffering from epilepsy refractory to conventional anti-convulsive therapy were treated with high-dose intravenous immune globulin (IVIG) (200 mg/kg three times per week, repeated after three weeks). In four children clinical and EEG findings markedly improved, while a partial response was noted in the other cases. These results suggest that high-dose intravenous immune globulin may have a beneficial effect in the treatment of intractable epilepsy. *Key words: intractable epilepsy, intravenous immune globulin (IVIG).*

High-dose intravenous immune globulin (IVIG) has been used successfully in the treatment of various immune-mediated diseases[1-3]. Intractable childhood epilepsy is characterized by convulsions which are resistant to treatment with adequate dosages of appropriate anticonvulsant drugs[4-6]. IVIG therapy has also been tried by several groups in so-called intractable childhood epilepsy on the hypothesis that the immune mechanism may play a role in triggering or maintaining this severe form of epilepsy[5-10]. We too decided to treat six patients with intractable epilepsy with high-dose IVIG.

Material and Methods

The study group consisted of six children between the ages of five and 13 years. Two of them were male. All children suffered from frequent daily seizures. All patients had been treated with a variety of anti-convulsant drugs (valproic acid, carbamazepine, phenobarbital, clonazepam) in various combinations. In all cases the epilepsy was accepted to be resistant to these drugs. These patients had had seizures for a long time, as seen in Table I.

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Table I:
Clinical Features of Patients

Patient No.	Age (years)	Neurological findings	Mental status	Etiology	Age at onset of seizures	Type of seizure	Cranial tomography
1	8	Normal	Moderate retardation	Idiopathic	4 months	Left partial generalized tonic-clonic	Normal
2	13	Normal	Profound retardation	Idiopathic	3 months	Generalized tonic-clonic	Cortical Atrophy
3	5	Microcephaly, spasticity quadriparesis	Profound retardation	Idiopathic	3 weeks	Myoclonic generalized tonic-clonic	Cortical Atrophy
4	7	Spasticity, quadriplegia	Moderate retardation	Neonatal sepsis	2 weeks	Myoclonic jerks	Cortical atrophy
5	9	Normal	Borderline	Neonatal asphyxia	1 week	Generalized tonic-clonic	Normal
6	12	Normal	Moderate retardation	Idiopathic	1 year	Myoclonic jerks, atonic akinetic	Normal

Table II: Effect of Immune Globulin Treatment on EEG and Seizures of Patients

Patient No.	Therapy of admission	EEG before treatment	No. of seizures before treatment	EEG after treatment	No. of after treatment	Duration of follow-up
1	Valproic acid, carbamazepine	Normal	2-3/day, tonic-clonic	Normal	1-2/week, tonic-clonic	4months
2	Phenobarbital, valproic acid	Generalized slowing, generalized bursts of high slow waves	3-4/day, general tonic-clonic	Generalized slowing	1-2/day, clonic	6 months
3	Clonazepam, phenobarbital	Slow, irregular, generalized bursts of high slow waves and polyspike activity (Lennox-Gastaut)	10-15/day myoclonic jerks	Slow activity, single spike	3-4/week, akinetic, atonic	9 months
4	Phenobarbital, valproic acid, clonazepam	General slowing	7-8/day myoclonic jerks	No change	2-3/week, tonic-clonic	1 year
5	Valproic acid, carbamazepine	Normal	9-10/week, general tonic-clonic	Normal	2-3/week, atonic-akinetic	18 months
6	Phenobarbital, valproic acid, clonazepam carbamazepine	low, irregular polyspike activity (Lennox-Gestaut)	2-7/day, atonic-akinetic	No change	1-2 day, atonic-akinetic	8 months

Clinical and laboratory investigations (EEG evaluations and serum IgG, A and M levels) were performed before and three weeks after immune globulin administration. IVIG (Sandoglobulin) was administered at a dose of 200 mg/kg over a period of six hours. This was repeated twice at 48-hour intervals for a total of three doses (600 mg/kg). No adverse reactions were observed. This procedure was performed again three weeks later. None of the patients became seizure free. The patients were followed up for a period of four to 16 months.

Results

In our of six patients the number of attacks decreased dramatically and a marked improvement in EEG findings was noted. The others showed partial improvement (Table II). Serum immunoglobulin G, A and M levels were within normal limits in all children, but other immunological tests could not be studied.

Discussion

The etiology of intractable epilepsy is still unknown, but a disregulation of the immune system may play a role. Several studies have proposed an immunological basis for intractable epilepsy[1,3,7]. While some researchers have been able to document underlying immune defects in these patients, others did not determine any immunological abnormalities even in cases with an observed beneficial effect of IVIG[4,7,10-12]. In previous studies the efficacy of IVIG was found to be approximately 50 percent[5-10]. However, in one study[13], IVIG treatment was associated with minimal improvement. The number of our cases is very limited, but four patients markedly improved. All children had some evidence of mental retardation. In four of six children, decreased frequency of seizures as well as improved behavior and psychologic performance were observed. We were unable to show any immune dysfunction in our patients.

Reported laboratory investigations in favor of an immunological component in human epilepsy include: impaired humoral immunity (predominantly IgA and IgG_2 deficencies)[13,14], lower kappa/lambda ratios of serum IgG and serum IgM[14], an increased incidence of antibodies against the frontal cortex[15], an increased percentage of B-cells[16], decreased percentage of T-cells[17], and differences in HLA class II antigen frequencies compared with the general population[18]. The IgA deficiency found in five to 10 percent of patients with epilepsy is usually drug-induced, but such patients can have subnormal IgA levels before treatment[19]. Disturbances of the IgA immune system have been described in association with a variety of drugs, such as certain gold preparations, d-penicillamine benoxaprofen[20], and long-term anticonvulsant administration[21,22]. One report concluded that at present epileptics do not seem to require special immunological or clinical monitoring[19].

In humans, IVIG has been reported to be beneficial for more than 35 diseases that may be produced by immunopathology[23]. The mechanism of action of IVIG in intractable epilepsy remains unclear. Two main theories have been proposed. The first suggests that the correction of some undiagnosed immunological abberration by IVIG my influence the convulsive activity[1,12]. The second theory for the mode of action of IVIG is the occurrence of an idiotype-anti-idiotype interaction[1,4,24]. IVIG may be effective in the treatment of an auto-immune disease by providing a source of anti-idiotypic antibodies. This possibility is based on the observation that cross-reactive idiotypes can be suppressed by administering anti-idiotypic antibodies. By selective reduction of the concentration of pathogenic antibodies, auto-immune disease may be effectively treated[1,2]. The main component of the IVIG preparation (the IgG molecule) crosses the blood cerebrospinal fluid (CSF) barrier, significantly increases the CSF IgG concentration, and is likely to reach the brain and act centrally[25].

We concluded that although the mechanism is still obscure, high doses of immune globulin may be useful in the treatment of selected children with intractable epilepsy unresponsive to anticonvulsants. However, there is a need for multicenter controlled studies to evaluate the pathogenesis and the possible effect of this therapy, and to clarify the exact indication and dosage of IVIG in therapeutically refractory epilepsy.

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CARDIORESPIRATORY FUNCTION IN DUCHENNE AND BECKER MUSCULAR DYSTROPHY*

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The purpose of this study was to investigate the cardiorespiratory function in Duchenne (DMD) and Becker muscular dystrophy (BMO) patients and to determine whether there is a correlation between these functions and muscular strength. The study involved 32 patients with progressive muscular dystrophy (28 DMD and four BMD). The mean age of the patients was 9.6±3.5 years. Cardiac investigations were performed in all of the patients, and pulmonary function tests were obtained in 16 cases. In five cases (31%), vital capacity (VC) was less than 80 percent of the predicted value. There was a good correlation between VC and muscular strength. There were various cardiologic findings in 50 percent of the cases with DMD. Electrocardiographic changes were present in 43 percent of the patients. Left ventricular systolic function in the patients who could not walk was significantly lower than that of the patients who could walk. There may be some unknown mechanisms that preserve left ventricular function relatively in the normal range in spite of cardiac involvement. *Key words: Duchenne muscular dystrophy, Becker muscular dystrophy, cardiomyopathy, echocardiography.*

Patients with Duchenne (DMD) or Becker muscular dystrophy (BMD) have a spectrum of clinical phenotypes that include skeletal myopathy, cardiomyopathy and mental retardation. They have been characterized by absent or diminished expression of the protein dystrophin in skeletal muscle, the heart and brain[1,2]. The abnormal gene is on the X-chromosome at the Xp21 locus which produces the protein dystrophin. The absence of dystrophin or the presence of structurally

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abnormal dystrophin results in degeneration and necrosis of muscle fibers and eventually in muscular weakness[1-3].

One of the most important problems in BMD and DMD patients is cardiorespiratory complications. Severe weakness of respiratory muscles produces a restrictive ventilatory defect due to inability to inflate the lungs sufficiently[4]. The combination of inadequate defense against infection and reduced pulmonary reserves may predispose patients to frequent and prolonged respiratory infections[5]. Similarly, cardiac involvement in DMD and BMD patients has been reported[6-11]. Left ventricular function has also been well investigated, however its relation to total point of muscle strength (TPMS), which demonstrates the clinical severity of cases, was not investigated. Therefore, the purpose of this study was to investigate the cardiorespiratory function in DMD and BMD patients and to determine whether there is a correlation between these functions and muscular strength.

Material and Methods

The study involved 32 patients with progressive muscular dystrophy (28 DMD and 4 BMD) ranging in age from three to 18 years. The diagnosis was assessed by the patient and family histories, physical examination, serum creatine kinase, electromyography, muscle biopsies and DNA analysis for Xp21 deletion by polymerase chain reaction (PCR).

The total muscular strength of the major muscle groups was evaluated on a point scale between 0 and 5 according to the "modified MRC muscle strength evaluation method" in half of the body with patients sitting, lying on one side, in the supine or prone position. The maximum "total point of muscular strength" (TPMS) was is 85 in a healthy person.

The following pulmonary function tests were obtained in 16 patients: vital capacity (VC), maximum voluntary ventilation (MVV), forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), peak expiratory flow (PEF), and maximal expiratory flow (MEF_{50}). When the VCs were less than 80 percent of the predicted value (% pred.), the subjects were considered to have respiratory impairment.

All children were examined by a pediatric cardiologist. Electrocardiographic and telecardiographic data were also available to the pediatric cardiologist. Echocardiography was performed with a Toshiba SSH 60-A Echocardiograph and 2.5-5 mHz transducers. The complete cardiac anatomy was examined for defects, valvar stenosis or insufficiency, and mitral valvar prolapsus. For all measurements, three consecutive cardiac cycles were evaluated and the mean was taken for further calculations.

M-mode echocardiographic studies: The images of the heart were obtained in parasternal long-axis views. Left ventricle chamber ($LVID_4$, $LVID_4$) and wall

dimensions (thicknesses of interventricular septum and posterior wall) were measured according to standard methods of the American Society of Echocardiography[12] over three cardiac cycles. Left ventricular ejection (LVEF) and shortening fraction (LVSF) were calculated. LVEF less than 55 percent and LVSF less than 28 percent were considered to be abnormal[8,9].

The patients were classified into five groups as follows: DMD patients able to walk, TPMS>62 was classified as Group I a and TPMS<62 as Group Ib; among DMD patients unable to walk, TPMS>40 as Group IIa, and TPMS<40 as Group IIb; and BMD patients who were able to walk as group III.

Relationships were analyzed for statistical significance by the use of chi-square and Student's t tests. For testing correlations, Pearson's or Spearman's correlation analyses were performed. Statistical significance was accepted as $p<0.05$.

Results

The study group consisted of 32 male patients. Twenty-eight of them had DMD, and the other four had BMD. The mean age for DMD patients was 9.6 ± 3.5 years (range 3-18 years) and for BMD patients was 11.2±2.2 years (range 8.5-13.5 years).

Pulmonary function tests were performed in 16 patients, and in all of them the FEV/FVC rate was greater than 70. However, the predicted value of VC was less than 80 in five patients (31%). In the groups based on VC, other tests were investigated (Table I). In the groups based on TPMS, the pulmonary function test results are shown in Table II. In this table, the predicted values of VC and FVC of the patients who could walk were significantly higher than those of the other groups. The other pulmonary function test results were similar in all groups. A good correlation between VC and TPMS was demonstrated (p: 0.04, r: 0.5541). However, there was only a mild correlation between FVS and TPMS (p: 0.07, r: 0.4851). There was no correlation between TPMS and other tests.

There were various cardiac findings in 14 of the DMD patients (50%) (Table III). In the four patients with BMD, the cardiac investigations were all normal. Some electrocardiographic changes including conduction defects were present in 12 patients (43%) with DMD. Left ventricular systolic function was investigated in all groups (Table IV). The LVEF and LVSF data in the group whose clinical status was worst according to TPMS (Group IIb) were significantly lower than those of the other groups (Table IV). Left ventricular systolic function was abnormal in two patients in Group IIb. There was no correlation between left ventricular systolic function and age, TPMS or VC. In addition, there was no relation between the localization or length of the deletion in Xp21 locus and cardiac or respiratory functions.

Table I: Summary of Pulmonary Function Tests

	Groups (VC: % of Predicted value)			
	VC > 80	VC: 65-80	VC: 50-65	VC < 50
VC* (mean)	97**			
Range	83.134	66	53-55	14-28
MVV (L/m) (mean)	70			
Range	56-99	46	28	22-23
FVC* (mean)	93			
Range	67-129	64	55-56	14-27
FEV_1*	(Mean)	96		
Range	72-131	70	56-61	17-30
PEF* (mean)	72			
Range	42-96	50	38-58	19-24
MEF_5* (mean)				
Range	42-155	85	49-90	31-36
FEV1/FVC (%) (mean)	93			
Range	81-100	97	92-100	100-100
No. of cases (%)	11 (69)	1 (6)	2 (12.5)	2 (12.5)

* Percent of predicted values.

** The mean is not displayed for groups consisting of one or two patients.
FEV1: Forced Expiratory Volume at one second; FVC: Forced Vital Capacity; MEF_{50}: Maximal Expiratory Flow; MVV: Maximum Voluntary Ventilation; No: Number; PEF: Peak Expiratory Flow; VC: Vital Capacity.

Table II: Pulmonary Function Tests Related to the Clinical Groups

	Pts. able to walk	Pts. not able to walk	
	TPMS ≥ 54	TPMS ≥ 30	TPMS < 30
Number of cases	5	6	5
VC (% Pred)	109±15*	76±13	57±38
MVV (L/M)	66±21	62±25	43±26
FVC (% Pred)	104±18*	74±13	55±36
PEF (% Pred)	104±22	79±16	60±38
MEF50	94±37	82±41	76±46

* $p < 0.05$
% Pred: % of the predicted value; Pts: Patients; TPMS: Total Point of Muscle Strength; VC: Vital Capacity; MVV: Maximum Voluntary Ventilation; FVC: Forced Vital Capacity; PEF: Peak Expiratory Flow; MEF_{50}: Maximal Expiratory Flow.

Table III: Cardiologic Data of the Patients with Duchenne Muscular Dystrophy

	Pts who could walk		Pts who could not walk		Total	
	No.	%	No.	%	No.	%
Preclinical CM	3	11	2	7	5	18
Congestive CM	1	4	2	7	3	11
Hypertrophic CM	–	–	2	7	2	7
Conduction defect in EKG	8	29	4	14	12	43
Normal	8	29	6	21	14	50

CM: Cardiomyopathy, Pts: Patients
Total number of patients was greater than 28 because of the association of cardiomyopathy and electrocardiographic findings in some cases.

Table IV: Echocardiographic Left Ventricular Systolic Function of Clinical Groups

	No.	LVEF	LVSF
Pts who could walk TPMS ³ 62 (Ia)	7	66±9	37±7
Pts who could walk TPMS < 62 (Ib)	8	67±5	36±4
Pts who could not walk TPMS ≥ 40 (IIa)	6	65±4	38±6
Pts who could not walk TPMS < 40 (IIb)	7	58±7*	30±4*

LVEF: Left Ventricular Ejection Fraction; LVSF: Left Ventricular Shortening Fraction; No: Number; Pts: patients; TPMS: Total Point of Muscle Strength.
* $p<0.05$

Discussion

The most frequent cause of death in patients with myopathy is respiratory infection[13]. While the clinical presentation of the respiratory problem may be acute, it is almost always superimposed on chronic respiratory insufficiency, and irreversible pathophysiologic changes frequently underlie the acute presentation. Muscle weakness eventually results in the following changes: decreased ventilatory reserve, low lung volumes, inadequate handling of secretions, and late development of pulmonary fibrosis and pulmonary arterial hypertension[14]. One of the earliest changes is reduction in vital capacity due to weakness of the muscles of the chest wall and/or diaphragm[15]. The respiratory problem is exacerbated by the developing scoliosis[16,17].

Of the 16 patients (14 DMD, 2 BMD) who were suitable for the pulmonary function tests, 11 (69%) had normal VC levels (>80% pred.); however, in the remaining five patients (31%), VC was abnormal (<80% pred.). There was an obvious correlation between VC and TPMS, but there was no correlation between TPMS and other pulmonary function tests. Similarly, a large number of reports showed that VC was the most reliable test for monitoring pulmonary function tests in DMD or BMD patients[5,13,17,18]. In addition, this study also demonstrated that VC decreased with the inability to walk that is, VC is related to muscle weakness. There were two cases with scoliosis in the present study. One of them had normal pulmonary function tests, while the other was abnormal. Because of the low number of cases with scoliosis, the impact of scoliosis on the pulmonary function tests could not be investigated.

In the present study, 14 patients with DMD (505) had cardiac involvement. Nigro et al.[9] reported that the rate of cardiac involvement was 78% percent in DMD. The cause of this difference is the age range of the study subjects. In the study of Nigro et al.[9], one-third of the patients were greater than 14 years in age, while in the present study this rate was one-eighth. Nigro et al.[9] also showed that clinically detected cardiac involvement had an onset after the age of 10 years and gradually increased in incidence with age. This comment supports our thoughts. In progressive muscular dystrophy the heart is always affected and presents characteristic histological lesions: irregular, diffuse and intense rearrangements predominantly in the left ventricle, the septum, and conductive tissue, consisting of wide, poorly vascularized fibrous bands that are destructive but without an inflammatory aspect[19]. Roberds et al.[20] reported that dystrophin-associated proteins are decreased in abundance in the cardiomyopathic hamster heart; for this reason they proposed that the cardiomyopathy was more severe than the myopathy.

D'orsogna et al.[8] reported that all cases in their study had electrocardiographic abnormalities. We doubted this data because there is no other report supporting their findings. In the present study, 12 patients (43%) had some electrocardiographic abnormalities. The cause of the difference between these data may be the difference in the ages of the patients. The mean age in the present study was 9.6 years, whereas it was 15.7 years in the study of D'orsogna et al[8].

There was no correlation between TPMS and left ventricular systolic function such as LVEF or LVSF. The left ventricular systolic function data were similar in the three groups comprising patients who were able to walk; however in the patients who were unable to walk, LVEF and LVSF values were significantly lower than those of the other groups. Nevertheless, the left ventricular systolic function in the patients who were unable to walk was not less than the normal range.

Nowadays it is believed that the failure of cardiac function is due to the presence of abnormal dystrophin in the cardiac structures[1-3]. If so, there must be a positive correlation between the TPMS and left ventricular systolic function such as LVEF and LVSF; however, in the present study there was no correlation between these parameters. In conclusion, we propose that there may be some unknown mechanisms that preserve left ventricular function relatively in the normal range despite cardiac involvement.

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MEASLES ANTIBODY RESPONSE IN VACCINATED CHILDREN*

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The incidence of measles has declined in our country since the routine administration of measles vaccination was initiated. However, measles outbreaks have been observed even among previously vaccinated children. The objective of this study was to evaluate the measles antibody response of children vaccinated at nine months of age. Measles-specific IgG antibodies were determined by enzyme-linked immunosorbent assay. Of 345 children tested, 20.3 percent were immunologically measles-susceptible. When measles-specific antibody titers were analyzed with respect to the elapsed time since prior vaccination, the result was found to be insignificant ($p>0.05$). These data suggest that the underestimated seropositivity rate of measles antibody may be related to both primary vaccine failure and inappropriate vaccination age. *Key words: enzyme-linked immunosorbent assay, measles antibodies, measles vaccine, vaccine failure.*

Although preventable, measles remains a disease with the potential to cause serious morbidity and mortality. It continues to be a significant public health problem in the world. WHO estimates that approximately 1.4 million children die of measles every year[1]. The measles vaccine prevented an estimated 52 million cases of measles during the first 20 years of its use and measles complications declined more than 99 percent from the prevaccine era[2].

By 1978, it was believed that measles could be eliminated from the United States in the near future[3]; however, continued measles outbreaks have induced public

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health authorities to review measles vaccination strategies. In Turkey, a single-dose vaccination at nine month of age is being administered, as recommended by WHO[1]. The incidence of measles has declined in our country since 1985 when measles immunization campaigns were initiated. Nevertheless, measles outbreaks have continued in recent years. In 1991, 22,521 measles cases were reported in our country[1]. In the 1990s, measles outbreaks have usually been observed among preschool and school-age children who were previously vaccinated. In Adana, vaccine coverage for children between the ages of one and nine years was recently found to be 80 percent as compared to 85% percent in 1992[4]. Thus, we planned this pilot study to determine the measles antibody response of children vaccinated at nine months of age.

Material and Methods

Study population

All children from four health departments who had been vaccinated at nine months of age with live measles vaccine were eligible for participation in this study. A total of 345 children (181 boys, 164 girls) between the ages of one and 10 were included in the study. Birth date, sex and date of measles vaccination were ascertained from each subject. Children were excluded from the study if they had 1) received more than one measles vaccine; 2) had had any disease known by their family as measles or compatible with it.

The study population was grouped according to the interval since measles vaccination (0-2; 3-4; 5-6; 7-8; 9-10 years). The number of children in each group was 65, 80, 69, 74 and 57, respectively.

Specimen collection

Serum samples were collected by venipuncture, centrifuged and stored at –20°C.

Antibody titers

Measles-specific IgG antibodies were detected by a direct binding enzyme-linked immunosorbent assay (ELISA), which is both sensitive and specific (100%) for the detection of measles-specific antibodies. Clin-ELISA (Incstar Corporation, Stillwater, Minnesota, USA) commercial test kits were used for the detection of anti-rubeola antibodies. Absorbances of the serum samples were read at 405 nm and converted to ELISA values using a test-fit linear regression program. If an ELISA value was equal to or greater than 110, it was considered to be positive. Alls samples for which ELISA values were between 101 and 108 were repeated. If an ELISA value was 100 or less, it was considered to be negative.

Statistical analysis

Comparisons were evaluated using chi-square and t test with corresponding p values. Hypothesis tests for population proportions were made by calculating the z-statistics. The significance level was defined as $p<0.05$.

Results

Subjects

Serum samples were obtained from 345 children, 181 (52.5%) male and 164 (47.5%) female. There were no significant differences with regard to sex ($p>0.05$).

IgG Titers

The distribution of ELISA test results is shown in Table I. Although the highest positivity rate for anti-rubeola IgG antibody was found in the fifth group, there was no statistically significant difference between the groups ($X^2=6.49$, $p>0.05$).

Table I: ELISA Test Results in the Study Groups

Study groups	Interval (years)	No. of samples			IgG results		Mean ELISA value of positive samples
		Male	Female	Total	No. of positive (%)	No. of negative (%)	
I	0-2	36	29	65	55 (84.6)	10 (15.4)	247
II	3-4	41	39	80	60 (75.0)	20 (25.0)	224
III	5-6	32	37	69	52 (75.4)	17 (24.6)	234
IV	7-8	38	36	74	59 (79.7)	15 (20.3)	229
V	9-10	34	23	57	49 (85.9)	8 (14.1)	242
Total	0-10	164	181	345	275 (79.7)	70 (20.3)	

ELISA values of the anti-rubeola IgG-antibody-positive samples in the study groups can be seen in Fig. 1. The highest ELISA value was 580, and it was found in a 16-month-old girl who had been vaccinated seven months previously. The mean ELISA values of the positive samples are shown in Table I. Group I included children vaccinated recently (within past 24 months) who had the highest mean ELISA values. No statistically significant difference was found between the groups.

Among 345 children, 55 (84.6%) of the 65, 60 (75.0%) of the 80, 52 (75.4%) of the 69, 59 (79.7%) of the 74 and 49 (86.0%) of the 57 in the study groups, respectively, were seropositive. While a total of 275 (79.7%) of the 345 children

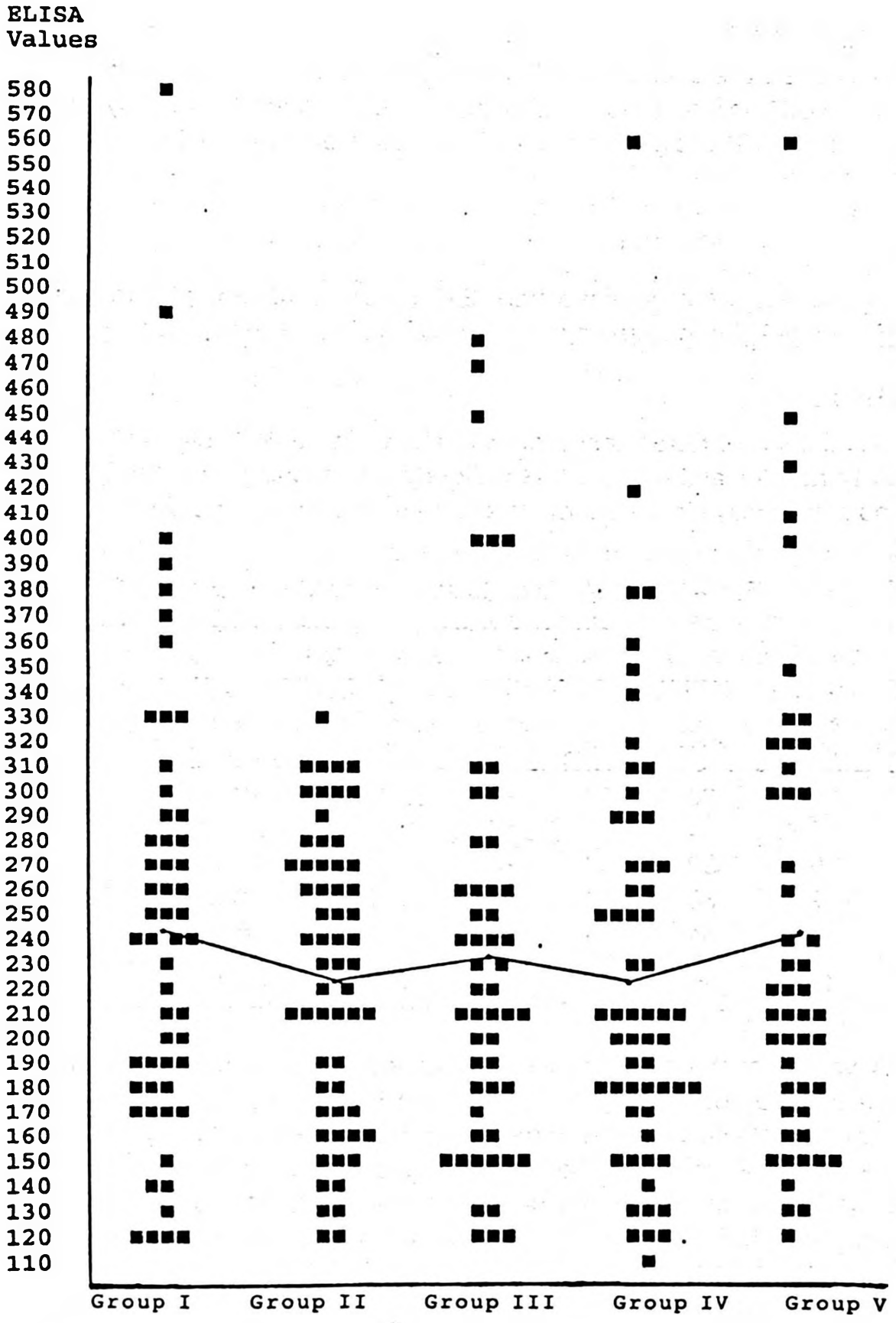

Fig. 1: ELISA values in positive samples.
(*): Mean ELISA values of the groups.

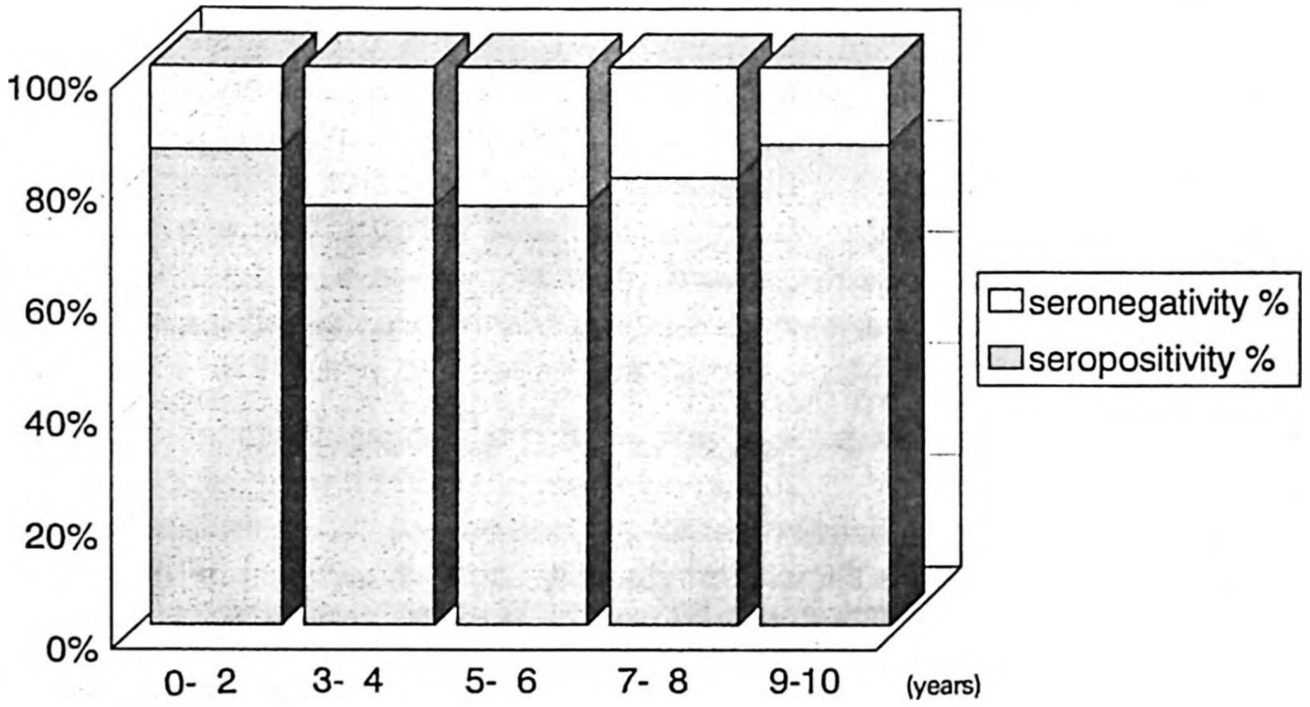

Fig. 2: Distribution of results.

were seropositive, 70 (20.3%) children who were known to have been vaccinated previously proved to have no detectable ELISA antibody. The ratios of serologic tests are shown in Fig. 2.

The vaccine seropositivity rate (78.7%) in our study when compared with a similar study in Adana in 1992 was found to be significant according to z test ($t=7.5$, $p<0.05$).

Discussion

Although a very effective measles vaccine is being used, measles has not yet been eliminated. The major problem of measles elimination is vaccine failure, which can be primary or secondary. Secondary vaccine failure occurs when immunity is lost after initial seroconversion. Though secondary vaccine failure has been reported most frequently in recipients of killed-measles vaccine, it may also occur in recipients of live measles vaccine[3,5]. Waning immunity may be responsible for the increased number of cases in school-age children[8].

In our study, by comparing the immunologically measles-susceptible subjects who were grouped according to two-year intervals since vaccination, we could not find statistically significant differences. We suggest that immunity to measles remained the same for nine years in our vaccinated children. Weibel et al.[7] concluded that the patterns of antibody persistence 7.5 years after administration of combined measles-mumps-rubella were the same and that there was no alteration in the retention of immunity. In Krugman's[8] prospective study of immunologic response of 47 children who had natural measles and 70 children immunized with live measles vaccine it was revealed that immunity persisted 16 years after immunization as well as after natural measles infection. In other investigations, vaccine failure was not associated with the time elapsed since vaccination[9,10]. On the contrary, several other studies have suggested that the duration of immunity derived from vaccination may not be as long-lasting as that from natural infection[11,12]. More studies are needed to prove this suggestion.

The principal cause for the measles epidemic in previously vaccinated persons is primary vaccine failure[13,14]. The known reasons for primary vaccine failure include residual transplacental maternal antibodies which inhibit vaccine virus replication and resulting sufficient antigenicity, and vaccine virus inactivation caused by inappropriate vaccine storage or handling.

Serological surveys have demonstrated rates of postvaccination seroconversion as high as 95 percent in several studies[3,15,18]. Orenstein et al.[17], seroprevalence was 98.6% percent for measles antibodies in high school students who had been immunized after 14 months of age with a single dose of measles.

We found 79.7 percent seroconversion in 345 children vaccinated at nine months of age. This result was statistically higher than that of the 1992 study in Adana[4]. Though our vaccine failure rate seems to be lower than that reported in 1992, it is actually a higher rate, since the estimated rate was only two to 10 percent[18]. We believe that the vaccination age may alter this result, because the inhibitory effect of maternal antibodies persists until nine to 12 months[18-21]. Vaccination before the age of 12 months may be a risk factor for vaccine failure.

The results of this study suggest the need for some new precautions and further studies:

1. In order to increase measles vaccine coverage and efficacy, all children at the recommended age should be vaccinated, and the persons and associations who administer the vaccination should be educated.

2. The exact elimination time of maternal antibodies in children must be determined so that the appropriate age for measles vaccination in Turkey can be established.

3. To prevent measles outbreaks in school-age children, revaccination policy should be reevaluated.

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INTRACEREBRAL TUBERCULOMA IN CHILDREN WITH TUBERCULOUS MENINGITIS*

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SUMMARY: Altunbaşak Ş, Alhan E, Baytok V, Aksaray N, Önenli N. (Departments of Pediatric Neurology and Infectious Disease, Çukurova University Faculty of Medicine, Adana, Turkey). Intracerebral tuberculoma in children with tuberculous meningitis. Turk J Pediatr 1996; 38: 323-327.

Not all patients with tuberculosis develop tuberculoma during the disease or anti-tuberculous therapy. Therefore, we compared various parameters in patients with and without tuberculoma and presented the results. We formed two groups from the patients with tuberculous meningitis: Group I consisted of 18 patients with tuberculoma, and Group II consisted of 18 randomly selected patients without tuberculoma. Significant difference between the groups was found with respect to level of consciousness and CSF-glucose level ($p<0.05$). The consciousness level was more depressed and the CSF-glucose level more decreased in the group without tuberculoma. These findings were discussed. *Key words: tuberculous meningitis, tuberculoma.*

In developing countries, five to eight percent of space-occupying lesions of the central nervous system (CNS) are tuberculomas[1]. Intracranial tuberculoma can develop or enlarge in patients treated for tuberculosis during supervised anti-tuberculous chemotherapy[2-4]. Most of them resolve, however, if adequately treated with anti-tuberculous therapy and a course of corticosteroids[3].

Not all patients with tuberculosis develop tuberculoma during the course of the disease or anti-tuberculous therapy. Therefore, we compared various parameters in patients with and without tuberculoma and presented the results.

Material and Methods

Between May 1988 and 1992, 52 patients with tuberculous meningitis (TBM) were treated in the Clinic of Pediatric Infectious Disease, Medical Faculty of Çukurova University. We formed two groups from these patients: Group I consisted of 18 patients with tuberculoma, and Group II consisted of 18 randomly selected

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patients without tuberculoma. Lymphocytic meningitis accompanying at least one of the criteria below was accepted as the minimal diagnostic criteria for TBM[5]. These criteria were: 1) positive cerebrospinal fluid (CSF) or gastric fluid culture; 2) positive acid-fast bacilli on CSF or gastric fluid smear; 3) 10 mm or more induration on Mantoux test; and 4) family history of tuberculosis. Patients were divided into three clinical stages according to the classification of Lincoln et al.[6] with respect to their clinical status on admission: stage I: nonspecific fever with no neurological sign; stage II: signs of meningeal irritation and neurological findings with no alteration of consciousness; stage III: major neurological findings with unconsciousness extending to coma.

Multiple computed tomographic (CT) examinations with and without contrast were obtained while patients were hospitalized. Hydrocephalus determined on CT scans was categorized as mild and moderate to severe.

After a follow-up period of two to 40 months, patients were categorized according to the prognostic criteria defined by Smith[7]. Category I included patients who were totally cured or patients with psychic abnormalities that did not affect their daily lives. Patients with slight mental retardation, hemiparesis, slight deafness, epilepsy or emotional disorders were included in Category II. Category III involved patients with severe mental retardation or hydrocephalus associated with severe neurological sequelae such as hemiplegia. Patients who died were included in Category IV.

Chi-square test within the SPSS-X program package[8] was used for data analysis.

Results

There were no significant differences between the groups with and without tuberculoma with respect to age, sex, family history of tuberculosis, time before onset of therapy, symptoms before admission, clinical stage and neurological findings on admission, Mantoux test, convulsion within the first15 days of therapy, peripheral blood leukocyte count, blood sedimentation rate, serum sodium and glucose concentrations, CSF-protein level, cell count and lymphocyte ratio, radiological findings on chest x-ray, basal arachnoiditis, the degree of hydrocephalus on CT scan of the brain or prognosis ($p>0.05$).

A significant difference between groups was noted with respect to level of consciousness and CSF-glucose level ($p<0.05$). The consciousness level was more depressed and the CSF-glucose level more decreased (27.9±12.9 vs 46.4±30.8 mg/dl) in the group without tuberculoma (Table I).

Tuberculomas were located within the cerebral hemispheres in eight cases, within the cerebellum in five, within the thalamus in five, within the cisternas in five and in the suprasellar region in five and had multiple localizations in seven cases.

Table I: Distribution of Patients According to Level of Consciousness

	Group I		Group II	
Consciousness	No	%	No	%
Normal	4	27.2	3	16.7
Lethargy or irritability	10	55.6	3	10.7
Stupor	1	5.6	3	16.7
Coma	3	16.7	9	50.0
Total	18	100	18	100

* $p<0.05$

The images of the tuberculomas on CT scan were dics-like, ring-like or irregular in shape. The irregular masses consisted of multiple discs or rings coalescing to produce such irregular contours. All had some perilesional edema (Fig. 1).

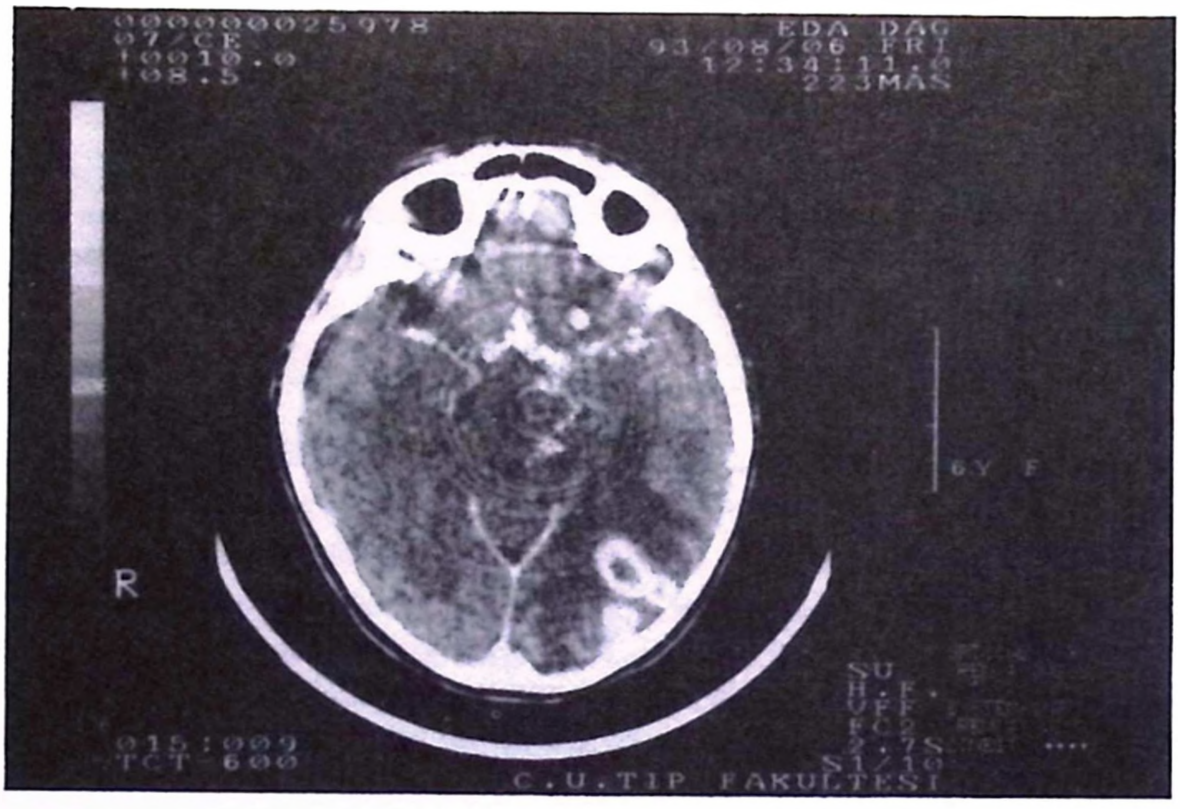
Discussion

Intracranial tubercuoloma is one of the most serious complications of tuberculosis, and generally accompanies tuberculous meningitis. It may be single or multiple and develops before or during the specific therapy. The pathogenesis of developing or enlarging tuberculoma in succssfully treated tuberculosis is unknown[9]. An exaggerated host reaction against tuberculous protein is thought to play an important role[10].

Tuberculomas are generally located within the cerebral hemispheres. Gupta et al.[10] reported that 41 of 44 tuberculomas in their patients were located within the hemispheres. Some authors have reported disc-like or ring-like tuberculomas, as well as varied sized masses with irregular contours, as in our case. Also, the ring-shaped hypodense area within the tuberculomas is interpreted as a caseification necrosis[9,11].

There was no difference between the two groups with respect to most parameters. Only three of our cases had tuberculoma on admission. This can account for our groups' similarity in terms of neurologial findings and clinical stages on admission.

We found a significant relationship between the clinical stages on admission, hydrocephalus and prognosis in our previous extensive study[12]. However, there was no significant relationship between these two groups regarding prognosis.



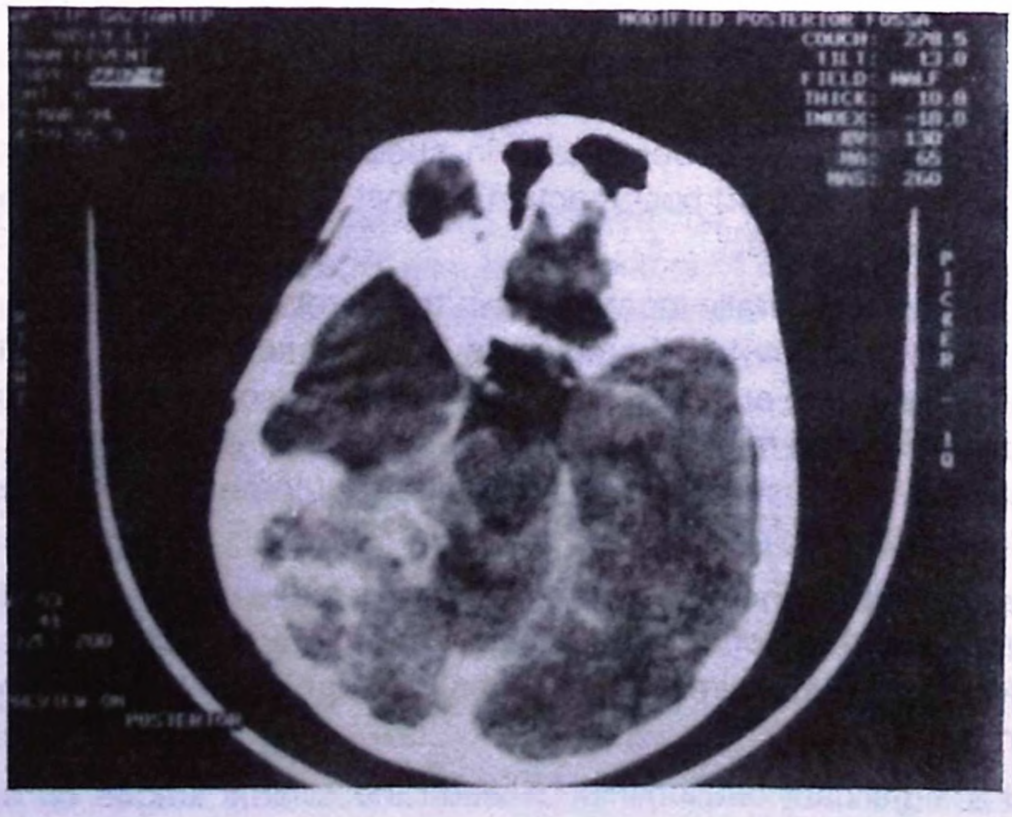


Figure 1. Enhanced CT scans of the brain from two patients in Group I showing multiple ring- and disk-shaped tuberculomas located in various regions of the brain.

The consciousness level of the patient with TBM during admission is affected by two factors. One of these is the degree of hydrocephalus, and the other is the degree and extent of inflammatory pathological changes within the cerebral tissue. We found no significant difference between the groups in terms of the degree of hydrocephalus, but the level of consciousness was more depressed in the group without tuberculoma. This finding suggested that the pathological changes within the cerebral tissue were more severe in this group.

The CSF-glucose level is known to be related to the consumption of glucose by bacteria in either bacterial or tuberculous meningitis. The decreased CSF-glucose level in the group without tuberculoma suggested greater bacteria invasion into the CNS in this group. This also implies a higher level of tuberculoprotein.

We found more bacteria and therefore more pathological changes within the cerebral tissue of Group II than Group I. Tuberculomas would be expected to form in Group II, but appeared in Group I. As a result, we can say that immunity, especially cell-mediated immunity, of the patients in the two group must be investigated separately.

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HELICOBACTER PYLORI SEROLOGY IN CHILDHOOD*

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SUMMARY: Gürakan F, Koçak N, Yüce A. (Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Helicobacter pylori serology in childhood. Turk J Pediatr 1996; 38: 329-334.

Serology is now generally accepted as a valid noninvasive screening method for the detection of Helicobacter pylori (Hp) infection. We determined the frequency of serum Hp IgG antibodies in 59 children with dyspeptic complaints and 48 age-matched controls by ELISA. Positive Hp antibodies were found in 52.5 percent of patients and 41.7 percent of controls. The difference was not statistically significant. The percentage of positivity increased with age for both patients (50% in 5-9, 51.7% in 10-14 and 72.7% in 15-17 year age-groups) and controls (36.8% in 5-9, 50% in 10-14, 68.4% in 15-17 year age-groups). These results suggest that Hp infection has a relatively high prevalance among children in our region, and increase with age. A large proportion of asymptomatic children also demonstrate signs of past or present exposure. *Key words: Helicobacter pylori, children, serology.*

Nowadays there is little doubt about the relationship between Helicobacter pylori and the presence of active chronic gastritis, duodenitis and peptic ulcer in both adults[1,2] and children[3,4]. Very recently it has been suggested that this microorganism might play a role as a cofactor in the evolution of gastric cancer[5,6]. Asymptomatic carriers of Hp have been demonstrated[7]. The prevalence of Hp infection has been reported to increase with age[8]. The main reservoir of Hp seems to be the human stomach[9], and the main infection route person-to-person transmission[10].

As for any bacterial infection, culture is the preferred method of diagnosis of Hp infection[11]. An upper digestive tract endoscopy must be performed to collect a sample for culture, histological examination or rapid urease test, those being the other diagnostic methods for Hp. However, this invasive technique is difficult to use in children, have and cannot be proposed as a screening method. Recent articles have reported the reliability of serologic tests for the detection of Hp infection[12,13].

We determined Hp anibodies by means of an enzyme-linked immunosorbent assay (ELISA) to assess the prevalence of Hp serum antibodies in dyspeptic and asymptomatic children.

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Material and Methods

Over a six-month period (November 1993 - May 1994) we prospectively studied 59 patients referred to the Pediatric Gastroenterology Unit for evaluation of dyspepsia. None of these patients had received nonsteroidal antiinflammatory agents, antibiotics, H2 receptor antagonists or bismuth salts for one month prior to serologic examination. The patient group consisted of 31 boys and 28 girls, mean age 11.1 ± 3.4 years (range 5-17), who had had epigastric or periumbilical pain and/or nausea, vomiting and regurgitation for at least one month. They were subjected to a standard protocol consisting of routine laboratory investigations of blood and stool as well as radiological examination of the upper gastrointestinal system.

The control group consisted of 48 children, 24 boys and 24 girls, with a mean age of 10.73 ± 3.63 years (range 5 - 17 years), who were seen in the outpatient clinics for nongastrointestinal complaints. None of them had abdominal pain or vomiting. All patients and controls were grouped according to age.

Two ml of whole blood was obtained, and the serum was frozen at –20°C. Sera were coded and examined blindly by Hp-specific ELISA (Pyloriset EIA -G- Orion Diagnostica, Finland), which allows detection of IgG antibodies to Hp in human sera. The cut-off value (positive result) was defined as an IgG level greater then two standard deviations above the mean of all negative titers (in optical density units at 450 nanomicrons).

Statistical significance was determined utilizing chi square analysis and two-tailed Student's t test.

Results

Serology for Hp was positive in 31 of 59 patients (52.5%) and 20 of 48 controls (41.7%). The difference between the prevalence of Hp antibodies among the dyspeptic group compared to the control group was not statistically significant ($p>0.05$). Among the dyspeptic group, 15 were diagnosed with dudodenal ulcer. Seven of 15 peptic ulcer (46.7%) and 24 of 44 (52.5%) other dyspeptic patients were positive for anti-Hp IgG antibodies. There was no difference in the prevalence of Hp antibody between the two patient groups ($p>0.05$). The percentage of positivity increased with age for both patient and control groups (Fig. 1). In the patient group, Hp antibody positivity increased from 50 percent (8 of 19) in 5-9-year-old children to 51.7% (15 of 29) in the 10-14-year-old group, and to 72.7 percent (8 of 11) in the 15-17 years group. While Hp antibody positivity was 36.8 percent (6 of 20) for 5-9-years control group, it increased to 50 percent (9 of 19) in the 10-14-year-old and to 68.4% percent (5 of 9) in 15-17-year-old children. Although the positivity was higher for every age-group among dyspeptic patients

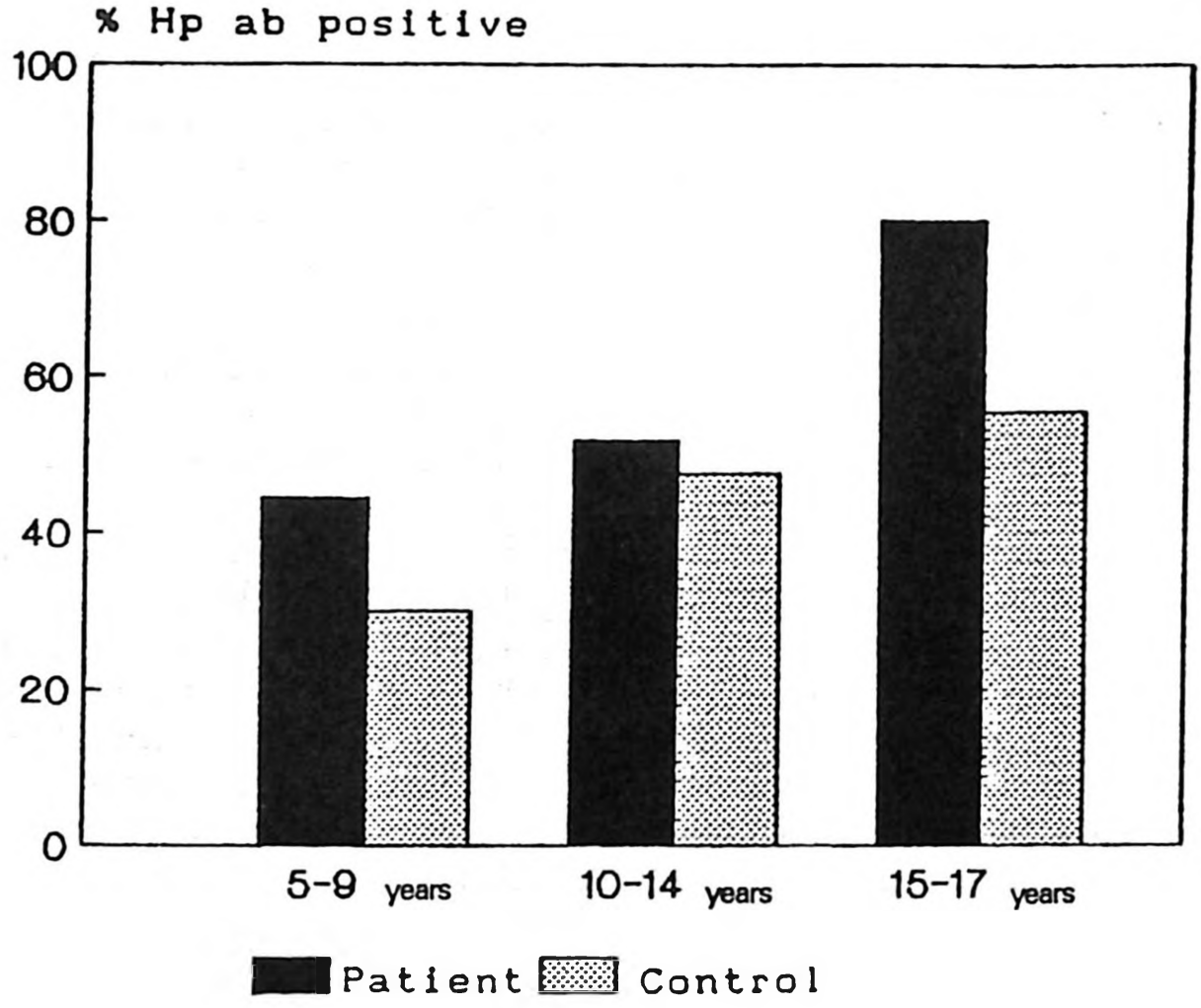

Fig. 1: Hp antibody positivity according to age-groups.

compared to the control group, these differences were not statistically significant at any age ($p > 0.05$ for all).

In the patient group, the mean age of Hp antibody-positive children was greater than that of negative ones (mean age 11.96 m 3.15 years for Hp positive, 10.19 m 3.39 years for Hp negative, $p<0.05$). This difference was not statistically significant in the control group (mean age 11.42 m 3.48 years for Hp positive, 10.25 m 3.73 years for Hp negative, $p>0.05$). The difference between the mean ages of Hp antibody-positive children in the two groups was not statistically significant ($p>0.05$).

The difference betwen the prevalence of Hp antibodies among boys (40%) and girls (55.7%) was not significant overall, nor was there a significant difference within the patient (boys 45.2%, girls 60.7%) and control (boys 30%, girls 50%) groups ($p>0.05$).

Discussion

Infection with Hp increases an individual's risk of peptic ulcer and gastric cancer. Difference have been noted in the prevalence of Hp infection in various countries. In the developed world, prevalence increases with age and varies with social class[14]. In underdeveloped parts of the world. Hp infection appears to occur a decade of more earlier, with high rates even in young children[15]. In such countries, most people acquire the infection by late childhood[16].

Epidemiological studies using serological tests have shown that a large proportion of healthy people have antibodies to Hp. Musgrave et al.[17] reported that eight of 39 patients without gastritis and Hp colonization, had high anti Hp titers. Laffeld et al.[18] found that six of 22 patients without Hp had Hp antibodies in the range found in actively infected patients. Meyer et al.[19] showed that 49 percent of healthy blood donors had anti Hp, but only 24 percent had active infection. It is uncertain whether the presence of anti Hp indicate active infection or only past exposure to the microorganism. These studies suggest that a considerable number of healthy people previously infected with Hp have spontaneously eliminated the microorganism. That means that Hp colonization is a dynamic process with an active phase of infection and subsequent elimination in at least a proportion of infected people. Avşar et al.[20] found positive serology in 85.8 percent of asymptomatic adults in our country.

The prevalance of Hp in children with different gastrointestinal disorders is reported to range from six to 30 percent[21]. As in adults suffering from nonulcer dyspepsia, Hp can be responsible for the abdominal complaints in some children with recurrent abdominal pain (RAP). Meer et al.[22] however have shown no significant difference between the Hp antibodies in children with RAP and the control group. Our study also showed no difference in the Hp seropositivity rate between symptomatic and asymptomatic children. Blecker et al.[23] found seven percent seropositivity in asymptomatic children of all ages. While our antibody rate was 41.7 percent, another study from Turkey revealed 25 percent[24] seropositivity in a childhood control group. The higher rate from developed countries is an expected finding.

In both the patient and control groups, the Hp antibody rate increased with increasing age, in accordance with other studies[8,25]. Similarly no sex difference was found in this study.

Serologic tests are easy to perform, relatively inexpensive, devoid of radioactivity, and very acceptable to patients, including children. However, a solely serological diagnosis might negatively affect the actual prevalence of Hp. As there was no difference in antibody rate between dyspeptic and nondyspeptic children in our study, the diagnostic role of Hp antibodies in the gastrointestinal diseases of

pediatric patients should not be overestimated. Titers of antibody to Hp are known to fall with eradication of bacteria[26]. Therefore, serological testing might be a suitable method for monitoring treatment and probably for diagnosing recurrent but not primary infection.

Although some authors have proposed serological screening of dyspeptic patients for cancellation of endoscopy if negative[27], our findings do not support this recommendation. Eight of our fifteen duodenal ulcer patients (53.3%) were seronegative for Hp. Other diagnostic methods, such as endoscopic biopsy, urease test and culture, are necessary for accurate diagnosis of Hp infection.

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REPRODUCTIVE EFFECTS OF MATERNAL METABOLIC DISORDERS: IMPLICATIONS FOR PEDIATRICS AND OBSTETRICS*

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SUMMARY: Levy H. [Division of Genetics (Biochemical Genetics),Children's Hospital, The New England Newborn Screening Program, State Laboratory Institute, and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA]. Reproductive effects of maternal metabolic disorders: Implications for pediatrics and obstetrics. Turk J Pediatr 1996; 38: 335-344.

The reproductive effects of metabolic disorders in women can be divided into four categories. The first of these is infertility. Galactosemia with its complication of ovarian failure is the disorder in this category. This complication may be prenatal in origin but whether this is so and its cause are unknown. The second category includes pregnancy effects of maternal metabolic disorders. The urea cycle disorder ornithine transcarbamylase (OTC) deficiency, maternal maple syrup urine disease and maternal homocystinuria are in this category. In the first two disorders, postpartum life-threatening illness due to metabolic crisis has occurred. Maternal homocystinuria is associated with a high risk for postpartum thromboembolic complications. The third category is the pregnancy effect of a fetal metabolic disorder. Pregnancies in which the fetus had long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) have been complicated by the life-threatening (HELLP) syndrome during the third trimester. Rapid recovery of the mothers followed delivery, on occasion by emergency cesarean section. The fourth category is the fetal effects (teratogenicity) from a maternal metabolic disorder. The best-known example of this is maternal phenylketonuria (PKU), which produces microcephaly, mental retardation, congenital heart disease and intrauterine growth retardation. Treatment with a low phenylalanine diet begun before conception or no later than the earliest weeks of the first trimester markedly reduces the risk to the fetus and can result in normal offspring. Other examples of teratogenicity may include maternal homocystinuria and maternal hypothyroidism. *Key words: maternal metabolic disorder, fetus, reproduction, maternal PKU.*

In 1956 Professor Charles Dent commented that he knew of a mentally retarded woman with phenylketonuria (PKU) who had three retarded children, all without PKU. He thought that perhaps the PKU in the woman during pregnancy caused the retardation in the children[1]. We now know that this was the first published reference to maternal PKU and that Dent was correct in his assumption that maternal PKU is teratogenic[2,3].

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Maternal PKU is a major problem in PKU, perhaps the most important of several serious problems. Our recognition of its seriousness, however, has produced a focus on the teratogenic aspects of maternal metabolic disorders and endangered our overlooking other reproductive complications of metabolic disorders. Indeed, there are several areas in which reproduction or reproductive potential may be complicated by a metabolic disorder. These areas may be divided into four categories.

I. Infertility

The fact that women with PKU could become pregnant and bear children led us to believe that metabolic disorders do not affect fertility. Therefore, it was surprising to learn that females with galactosemia are infertile. In fact, despite even the earliest and most compliant treatment, galactosemia produces ovarian failure[4].

This complication of galactosemia was first reported by Kaufman et al.[5], although there was previous indication of streak ovaries in galactosemic women[6]. The first hint of an ovarian problem in these girls is hypergonadotrophism. Within even the first few months of age, the serum concentration of follicle stimulating hormone (FSH) is very high (Table I). At pubescence, these girls usually either do not menstruate or will experience only an initial menstrual period followed by amenorrhea. Occasionally, girls will menstruate but will be oligomenorrheic. In addition, secondary sexual changes do not appear. On the basis of pelvic ultrasonography, the ovaries are usually very small or cannot be visualized[8]. When directly examined, the ovaries are usually only streaks of stroma completely or almost completely devoid of follicles and oocytes[7]. An international survey of galactosemia reported the complication of ovarian failure in over 70 percent of girls with galactosemia[8].

Table I: Serum Follicle Stimulating Hormone (FSH) Levels in Females with Galactosemia

Age (yrs)	FSH (mIU/ml)*
1/12	29
7/12	40
8/12	13
2	54
13	65

* Normal FSH value is < 4 mIU/ml

The origin of the ovarian failure in galactosemia is unknown. We have reported morphologically normal ovaries in a neonate with galactosemia[9] and have found this to be so in a second galactosemic neonate. This suggests that the damage could be postnatal. On the other hand, Chen et al.[10] have found that rats exposed to galactose prenatally have markedly reduced numbers of oocytes. Moreover, as seen in Table I, serum FSH is markedly increased in galactosemic females as early as the first few weeks of life, virtually identical to Turner syndrome. Moreover, even with the strictest dietary treatment, the complication occurs. These observations suggest that a prenatal factor is either solely responsible for the ovarian failure or is a major cause of the problem. One theory as to its cause was that of reduced uridine diphosphate galactose (UDPGal)[11], a product of the galactose-1-phosphate uridyltransferase reaction that is blocked in galactosemia (Fig. 1). Presumably, reduced UDPGal would be present in the fetus as well as in the infant after birth. As shown in Table II, the Los Angeles group has found that classic galactosemics with ovarian failure have reduced UDPGal, while females with variant galactosemia who have some residual transferase activity have normal UDPGal levels and normal ovarian function[4]. However, supplementation of these girls with uridine, which raises the UDPGal levels to normal, does not prevent ovarian failure[12].

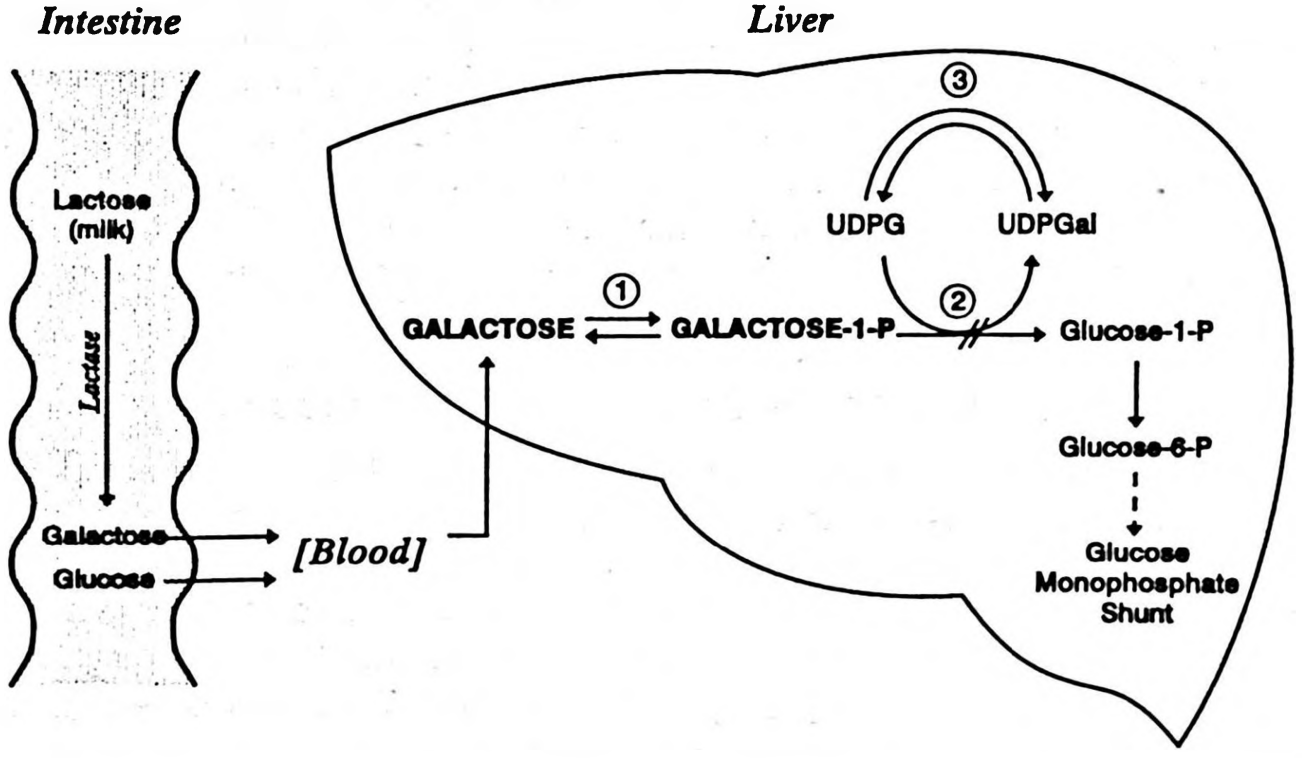

Fig. 1: Galactose metabolism from its liberation from lactose in the intestine through its metabolism. The enzymes required for galactose metabolism are (1) galactokinase; (2) galactose-1-phosphate uridyltransferase (GALT); (3) uridine diphosphate-4-epimerase. In galactosemia, the defective enzyme is GALT, resulting in accumulations of galactose-1-phosphate and galactose and reduced UDPGAL.

Table II: RBC Uridine Diphosphate Galactose (UDPGal) and Ovarian Function in Classic and Variant galactosemia

Classification	RBC UDPGal (umol/100 gm Hgb)	FSH	Ovarian function
Classic galactosemia	3.9	38	Failure
Variant galactosemia	9.4	6	Normal
Normal individuals	10.3	<9	Normal

So far, galactosemia is the only inborn error known to have direct effect on gonadal function. Even in galactosemia, this effect seems to target ovaries and to spare the male gonad[5,13]. Nevertheless, as children with other early treated inborn errors survive to adolescence and adulthood, it will be important to study them carefully for sexual maturation and fertility.

What are the implications for treatment in galactosemia? First, parents of newly diagnosed female infants must be fully informed about the probability that they will develop this problem despite early treatment. Second, gonadotrophins, particularly FSH, should be measured within the first year of life so that ovarian unresponsiveness can be detected. Finally, girls with ovarian failure should be evaluated by pediatric endocrinologists at or before pubescence and, if secondary sexual characteristics are not appearing, given normal therapy to stimulate their appearance. Otherwise, these girls will suffer not only from infertility but also the psychosocial problems that occur from lacking the appearance of sexual maturation.

PREGNANCY EFFECTS OF MATERNAL METABOLIC DISORDERS

Maternal PKU once again lulled us into complacency, this time regarding the safety of pregnancy itself when the woman has a metabolic disorder. After all, women with PKU have withstood pregnancy well. That has also been true of women with histidinemia and several other maternal inborn errors that have come to our attention. Recently, however, we have learned that for women with still other maternal disorders, pregnancy can be a threat. The threat seems to be greatest during the postpartum period. For instance, three women heterozygous for X-linked ornithine transcarbamylase (OTC) deficiency are known to have developed hyperammonemia with coma or other severe symptoms three to eight days following delivery. Two of these women died[14]. A woman with maple syrup urine disease became dizzy and lethargic nine days postpartum with a very

increased blood leucine level; she recovered after her carbohydrate intake was increased[15]. At least three women with homocystinuria have had major thrombotic episodes postpartum[16-18]; one of the women died. The postpartum complications in OTC deficiency and maple syrup urine disease were clearly linked to exacerbation of the biochemical abnormalities. This was not studied in the women with homocystinuria, but could also be true for that disorder. We have noted huge postpartum increases in plasma histidine and phenylalanine in maternal histidinemia and maternal PKU, respectively. These biochemical exacerbations are probably secondary to postpartum catabolism and proteolysis and represent a major threat in childbearing to women with certain metabolic disorders.

PREGNANCY EFFECT OF A FETAL METABOLIC DISORDER

Wilcken and her colleagues have reported severe liver disease and other features of the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome during the third trimester of pregnancy in otherwise healthy women carrying fetuses with the fatty acid disorder known as long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency[19]. The women rapidly recovered following delivery, in some cases by emergency cesarean section. It seems likely that one or more of the biochemical abnormalities, perhaps the hydroxydicarboxylic acids, in these affected fetuses crossed the placenta and were toxic to the maternal liver. So here, the fetus damages the mother, a fascinating converse to the final and most frequent of the reproducive problems in which the mother with a metabolic disorder damages the fetus. The fetus-damages-the-mother problem could occur more frequently in women carrying fetuses affected with disorders than we realize. This might be especially so for those fetuses with inborn errors of organic and fatty acids.

FETAL (TERATOGENIC) EFFECTS OF MATERNAL METABOLIC DISORDERS

The major reproductive problem among the metabolic disorders is that of fetal effects from a maternal metabolic disorder. The most frequent and dramatic of these is maternal PKU.

Maternal PKU is a fetopathy syndrome that produces microcephaly, mental retardation, congenital heart disease and intrauterine growth retardation. In fact, this can be a devastating condition with frequencies of birth defects perhaps the highest known in medicine from a single cause. For instance, when the mother has classic PKU, the frequency of mental retardation in the offspring may be as high as an astounding 92 percent, and that of frank microcephaly as high as 73 percent[3]. This has become a major problem in PKU, perhaps the major current problem in PKU. If mental retardation from maternal PKU cannot be prevented, we are in danger of replacing in the next generation the number of retarded individuals who are being removed from the current generation by

newborn screening and early treatment of PKU[20]. Ironically, this is a potential problem born of success – the success that has virtually eliminated mental retardation in girls with PKU and now allows them to be in the social position of reproducing.

Can this potential tragedy be prevented? We do not yet know. However, there is hope. Evidence from case reports and, most recently, from the Maternal PKU Collaborative Study as shown in Table III, indicates that low phenylalanine dietary treatment when begun prior to conception or within the first 10 weeks following conception might prevent the fetal damage[21]. This table, however, does not answer the question of whether even the best treatment of maternal PKU results in children who are completely normal. Only long-term follow-up of these and other study children will answer this important question.

Table III: Outcome of Offspring from Treated Maternal PKU Pregnancies in the Maternal PKU Collaborative Study

Onset of treatment (gest. wks)	Birth measurement (median centile)			IQ (mean)
	Weight	Length	Head Circumference	
Before conception	70	78	49	107*
0-10	56	78	43	107*
10-20	49	56	31	87
> 20	21	26	10	69

* IQ score refers to treatment onset before conception and to 10 wks gestation.

If favourable results in the treatment of maternal PKU are to be achieved, an understanding of pathogenesis is critical. Perhaps this can be illustrated by another facet of the maternal PKU fetopathy, the dysmorphic facies first reported by Bovier-Lapierre and colleagues[22]. The features of this facies include midface hypoplasia, short palpebral fissures, epicanthal fold, anteverted nares, and elongated philtrum. Interestingly, this facies and that in the fetal alcohol syndrome are virtually identical. In fact, there is a striking similarity between maternal PKU and fetal alcohol syndrome, as listed in Table IV. This similarity suggests that these two syndromes share a common pathogenesis. Perhaps phenylalanine and alcohol, both micromolecules that readily cross the placenta, act at the same control points of development. If so, to understand one syndrome could allow us to understand the other.

Tablo IV: Fetopathies of the Maternal PKU and Fetal Alcohol Syndromes

Fetopathy	Maternal PKU	Fetal Alcohol
Microcephaly	Yes	Yes
Mental retardation	Yes	Yes
Hyperactive behavior	Yes	Yes
Congenital heart disease	Yes	Yes
Dysmorphic facies	Yes	Yes
Intrauterine growth retardation	Yes	Yes

The focus has usually been exclusively on maternal PKU. But what about non-PKU mild hyperphenylalaninemia? There are almost as many girls and young women with mild hyperphenylalaninemia (MHP) known to clinics and newborn screening programs as those with PKU. For years it has been clear that maternal MHP with blood phenylalanine levels between 180 and 720 umol/L (3-12 mg/dl) is less damaging to the fetus than maternal PKU with its higher phenylalanine levels and, in some cases, seemed not to cause damage at all[23]. The question is whether MHP in the pregnant woman is at all teratogenic. From an international survey of untreated maternal mild hyperphenylalaninemic pregnancies, we have found that when the maternal blood phenylalanine level in MHP is less than 400 µmol/L (6.5 mg/dl), birth measurements are not appreciably altered from normal expectation and the median offspring IQ is 108, whereas when the maternal phenylalanine level exceeds 400 µmol/L, birth weight and birth head circumference are significantly lower and the median offspring IQ drops to 100[24]. The relevant data are shown in Table V.

Are these reductions sufficient to justify identifying and treating women with MHP through their pregnancies, many of whom have never been on the diet or perhaps were never even informed that they have a phenylalanine "problem"? This is a

Table V: Offspring Outcome in Survey of Untreated Maternal Mild Hyperphenylalaninemia

Maternal blood phenylalanine (µmol/L)	Birth measurement (Median Z-Score)			IQ (median)
	Weight	Length	Head Circumference	
< 400	.08	.38	-.30	108
> 400	-.36	.16	-.76	100

major current and future question. Our current policy is to recommend dietary treatment when the blood phenylalanine level is consistently greater than 400 µmol/L (6.5 mg/dl).

What are the implications of maternal PKU and maternal non-PKU MHP for newborn screening programs? Is follow-up from newborn screening identification sufficient to guarantee that these young women will be known and will be given the proper advice when they reach childbearing age? What about women with PKU born before newborn screening or in countries without universal newborn screening? Is routine premarital and/or prenatal screening for PKU required? If routine screening at these times is necessary, is it logistically possible? Is newborn screening in most programs sufficiently sensitive to identify infants with non-PKU MHP as well as those with PKU? Or do we miss many or most of the infants with MHP? Is this important in the consideration of maternal MHP? These and many other questions face us. The answers to these questions depend on the answers to the many questions about maternal PKU and maternal MHP that we still have not answered.

Finally, is PKU the only inborn error with maternal implications for the fetus, or are there other inborn errors in the same category? So far, no other maternal inborn error has been found to have the implications of maternal PKU. In fact, a surprisingly large number of maternal inborn errors seem to be benign to the fetus. These include histidinemia[25], hyperprolinemia[26], the HHH syndrome (hyperornithinemia-hyperammonemia-homocitrullinuria)[27], tryptophanemia[28], maple syrup urine disease[15], organic acid disorders such as isovaleric acidemia[29] and propionic acidemia[15], the urea cycle disorder, argininosuccinic acidemia[30], cystinosis[31], Hartnup disorder[32], galactosemia, in the few pregnancies that have occurred[33], and even tyrosinemia[34], which is strange since tyrosine is chemically so similar to phenylalanine. It is possible that maternal homocystinuria, particularly the B_6-unresponsive form, produces mental retardation and congenital anomalies in the offspring, but this is based on only a couple of cases[35]. Notably, maternal hypothyroidism could have major implications for the cognitive development of the offspring[36]. If so, girls with congenital hypothyroidism prevented from becoming mentally retarded by newborn screening and early treatment could in future years form a cohort in danger of having damaged children that might even be considerably larger than the cohort of maternal PKU.

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ADVANCES IN THE CLINICAL MANAGEMENT OF PEDIATRIC KIDNEY TRANSPLANTATION*

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SUMMARY: Saatçi Ü. (Nephrology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Advances in the clinical management of pediatric kidney transplantation. Turk J Pediatr 1996; 38: 345-348.

Renal transplantation is the best form of renal replacement therapy for children reaching end-stage renal failure. The first human transplantation was performed by Dr. Voronoy from a cadaver donor in 1933; however, because of the lack of immunological laboratory assessments, this transplantation resulted in rejection. Progress in immunological evaluation and new immunosuppressive drugs have improved survival in renal transplantation.

The first renal transplantation in Turkey was performed by Dr. Haberal et al. on November 3, 1975. This child was one of five siblings with juvenile nephronophytisis, and the mother was the donor. Dr. Haberal has thus pioneered renal transplantation in Turkey. In the following years Dr. Haberal initiated cadavral transplantation in our country in collaboration with Eurotransplant. He has also contributed to the law concerning transplantation in Turkey. Subsequently many transplantation centers have been developed in the country. In spite of marked progress in transplantation technology, pediatric transplantation has not improved as fast as adult transplantation. This is due to several factors, such as the difference in the etiological factors leading to chronic renal failure, technical factors, growth and sexual development, factors relevant to infections and vaccinations, and psychological problems. *Key words: renal transplantation, children.*

Renal transplantation is the best mode of renal replacement therapy. The first renal transplant in humans was performed in 1933 by Dr. Voronoy from a cadaver donor[1]. However, because of the lack of immunological laboratory assessments, this graft resulted in rejection. Improvement in histocompatibility matching, immunosuppressive therapy, improved peri- and post-operative care as well as the diagnosis and treatment of rejection have all contributed to better patient survival and graft outcome in renal transplantation. The first transplantation in Turkey was performed in 1975 by Dr. Haberal at Hacettepe University Faculty of Medicine. The first cadavral transplantation was done in collaboration with Eurotransplant, again by Dr. Haberal[2,3]. There are now more than 25 years of accumulated experience with renal transplantation in children, but the survival rates have not reached those of adults. According to the registry of United Network

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for Organ Sharing Scientific Renal Transplantation, the one-year graft survival rate is poorer in recipients under the age of 16[4]. Recipient age less than two, donor age less than six, prior transplantation, lack of anti-thymocyte globulin (ATG)/anti-lymphocyte globulin (ALG)/OKT3 therapy, a history of greater than five transfusions, HLA-DR mismatches, and low cyclosporine-A (cys) levels are the reported factors for graft failure in children[5].

However, the survival rate of transplanted children is greater than for those on dialysis programs. Psychological and physiological rehabilitation in particular is better in transplanted patients.

Congenital urinary system defects constitute one of the major causes of renal failure in children, whereas in adults diabetic nephropathy and glomerulopathies are the leading causes. Congenital urinary tract malformations were the cause in 42 percent of end-stage renal disease (ESRD) patients in one study[6]. Vesico-ureteral reflux (VUR) and posterior urethral valves are the most frequent abnormalities. In our department these were found to be the etiology in 47 percent of the population with end-stage renal disease. In the past, children with abnormal lower urinary tracts were not considered suitable candidates for a renal transplant. However, bladder reconstructions are now being performed in preparation for subsequent renal transplantation[7,8].

Growth failure is prominent in children due to multisystem dysfunctions introduced by the uremic state. Although quality of life has been much improved in these children, growth retardation remains a problem. Growth is indirectly correlated with the age of transplantation, whereas it is directly correlated with glomerular filtration rate (GFR). Rejection episodes delay the growth process. Growth is affected by corticosteroids alone, despite normal renal function. Lower doses and alternate day schedules lessen the effect. However, supra-physiological doses of growth hormone (GH) serum to be effective in promoting growth. A marked increase in growth velocity has been established by the use of this hormone in transplanted children[9]. However, there are controversies regarding the deleterious effect of growth hormone on renal function. It has been suggested that it causes glomerulosclerosis by hyperfiltration. GH also affects the immunological system and interferes with other immunosuppressive treatments, enhancing allograft rejection[9].

Infections remain a major cause of morbidity and mortality in transplant patients; however, many infections can be successfully prevented by immunization. The Committee on Infectious Diseases recommends that live attenuated vaccines not be given until three months after immunosuppressive therapy has been terminated[10]. Cytomegalovirus (CMV) is a herpes virus, and OKT3 and ALG have increased the risk of CMV disease. Vaccination provides only poor seroconversion

and incomplete protection. Live attenuated CMV vaccine is given about eight weeks prior to transplantation[11]. Although CMV infection is not prevented by vaccination, the infections that occur in a CMV-seropositive donor are modified. While this vaccine has been successful in adults, studies in children are lacking[10]. Other medical measures in dealing with CMV infection include acyclovir, interferon, ganciclovir and CMV hyperimmunoglobulin.

Varicella is a well-recognised problem for children who are immunocompromised[12]. Seronegative children who are to be transplanted must be vaccinated by attenuated varicella vaccine[13].

Hepatitis C in renal transplant patients is an increasing problem in the pediatric population. To prevent hepatitis C virus (HCV) infection, several measures can be useful, such as avoiding blood transfusions, isolation of anti-HCV (+) patients and performing liver biopsies in patients who are (+) for HCV RNA. Transplantation from HCV-positive donors to negative recipients should be avoided. Patients with evidence of chronic liver disease and detectable HCV RNA can be treated with ribavirin or interferon[14].

Renal transplantation of patients with hepatitis B infection has been tempered by a concern that immunosuppression may lead to viral replication and progressive liver damage. HBsAg positive patients treated with Cys have a better outcome than those treated with azathiopyrine. Post Cys-era HBsAg positivity is not a contra-indication to renal transplantation[15]. Children who do not have HBsAg and antibodies should be immunized prior to transplantation.

Malignancies are increased in transplanted patients due to immunosuppressives. Non-Hodgkin's lymphoma, Kaposi sarcoma and skin cancers are associated with this therapy[16].

Conditions known to be associated with recurrence of disease in transplanted kidneys can be responsible for graft failure[17]. FK506 and cyclosporine regimens are equally effective in maintaining excellent graft function in pediatric renal transplant recipients. Advantages of the FK506 regimen include less hirsutism and gingival hypertrophy. It also reduces the risk of hypertension more than steroids do. FK506 monotherapy may alleviate the persistent growth failure by the avoidance of steroids; its steroid-sparing effects may be of particular importance in the pediatric population[18]. Recently Cys G (OG 37-324) has been reported to be an efficacious immunosuppressant with less nephrotoxicity than Cys A. Cys A and G appear to have similar efficacy; however, objective parameters of renal function demonstrated less nephrotoxicity with the use of Cys G[19]. The available data show that it is possible to use Cys A as monotherapy for maintenance immunosuppression of renal transplantation patients. However, the data also indicate that caution must be exercised and that doubts remain

which must be clarified. Further controlled and randomized trials must be done to answer the questions about this therapy[20].

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SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IN ADRENOLEUKODYSTROPHY*

A Case Report

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SUMMARY: Dirik E, Durak H, Eroğlu Y, Sayıt E, Büyükgebiz B. (Departments of Pediatrics and Nuclear Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Single photon emission computed tomography in adrenoleukodystrophy: A case report. Turk J Pediatr 1996; 38: 349-353.

Adrenoleukodystrophy (ALD) is a genetic disorder leading to progressive dysfunction of the adrenal cortex and nervous system white matter. Accumulation of fatty acids in cerebral white matter results in some anatomical and functional changes which are detectable by imaging studies. Lately, single photon emission computed tomography (SPECT) has been suggested for evaluation of cerebral perfusion changes. In this report, magnetic resonance imaging (MRI) and SPECT neuroimaging of an eight-year-old boy with ALD are presented. SPECT revealed more extensive involvement than that demonstrated by MRI. Its role in early prediction of the extention of disease is stressed.

Key words: adrenoleukodystrophy, magnetic resonance imaging, SPECT neuroimaging.

Adrenoleukodystrophy (ALD) is an X-linked genetic disorder associated with the accumulation of saturated very long chain fatty acids (VLCFA) and progressive dysfunction of the adrenal cortex and nervous system white matter[1]. This accumulation of fatty acids is due to both impaired capacity to degrade them in peroxisomes, possibly related to a defective β oxidation system, and overproduction in microsomes[2,3]. Clinically, ALD is characterized by demyelination of the central nervous system and adrenal insufficiency. In ALD, deposition of fatty acids in cerebral white matter leads to some anatomical and functional changes which are detectable by imaging studies. While computed tomography (CT) and magnetic resonance imaging (MRI) studies domonstrate the anatomical changes, functional brain imaging techniques, positron emission tomography (PET) and signle photon emission computed tomography (SPECT) are gaining widespread use in revealing the characteristic images in childhood neurodegenerative diseases and inborn errors of metabolism[4].

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This report presents the anatomic and functional brain changes of an eight-year-old boy with ALD.

Case Report

An eight-year-old boy was admitted to our clinic for strabismus. His history revealed that he had difficulty with reading and writing during the previous month. Nervousness and some memory defects had also been noted. His parents were unrelated. One of his mother's brothers had died at the age of two years, cause unknown.

On physical examination he had nystagmus and reduced vision. Mild ataxia and positive Babinski sign on the right side were also noted. Contrast-enhanced CT demonstrated symmetrical, hypodense, inactive zones revealing involvement of the periventricular white matter in the posterior parietal and occipital lobes. MRI study showed symmetric increased signal intensity in the white matter of the parieto-occipital region (Fig. 1).

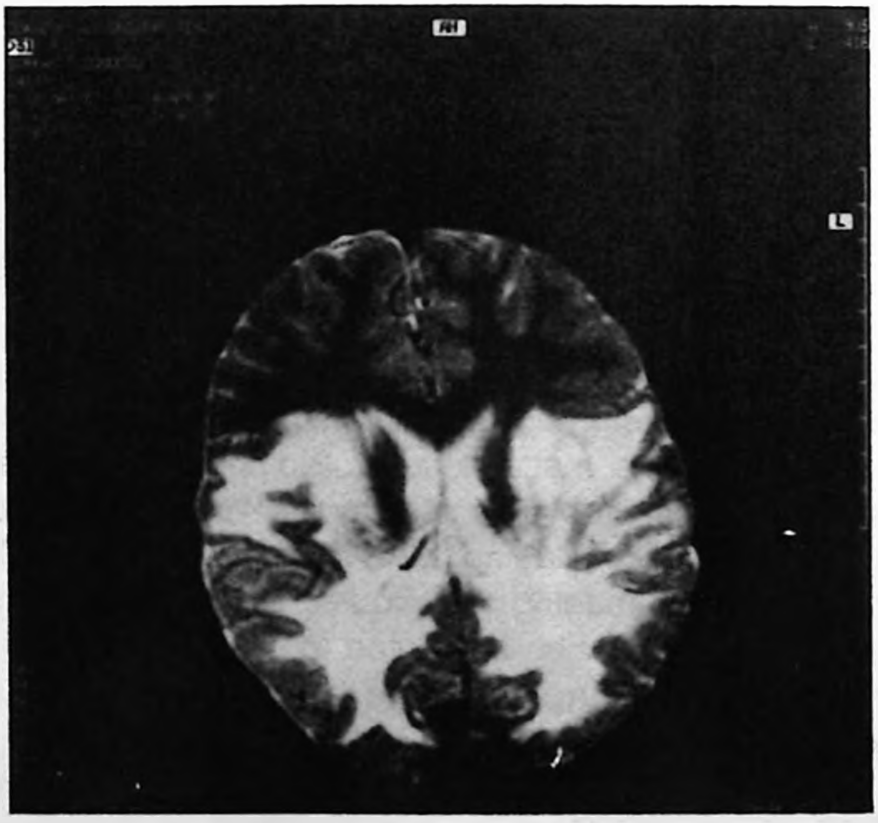

Fig. 1: High-intensity symmetrical signal of parieto-occipital white matter on MRI. The lateral and medial geniculate bodies, corpus callosum splenicum and lateral lemniscus were involved.

Baseline cortisol and ACTH values were 14 mg/dl and 94 pg/ml, respectively. After ACTH stimulation, the cortisol level (11 mg/dl) did not increase. Serum fatty acid analysis indicated a raised VLCFA level, with a ratio of C26:C22 = 0.065 and 0.074.

Four months after MRI imaging, SPECT was performed with intravenous injection of 6 mCi Tc99m HMPAO (Ceretec, Amersham International, UK). The radiopharmaceutical agent was administered to the child in a quiet and dimmed room, and 10 minutes later, 10 mg diazepam was injected intravenously for sedation. With high-resolution collimators, a three-headed gamma camera (GE/CGR neurocom, Horsholm, Denmark) was used for imaging. 128 images of 35 seconds duration in a 64 x 64 matrix were obtained over 360 degrees. Two pixel thick tomographic slices were reconstructed in the transaxial, coronal and sagittal planes. In the superior temporal and parietal cortices, the right occipital cortex, the right cerebellum and the left frontal cortex, markedly decreased blood flow was detected (Fig. 2).

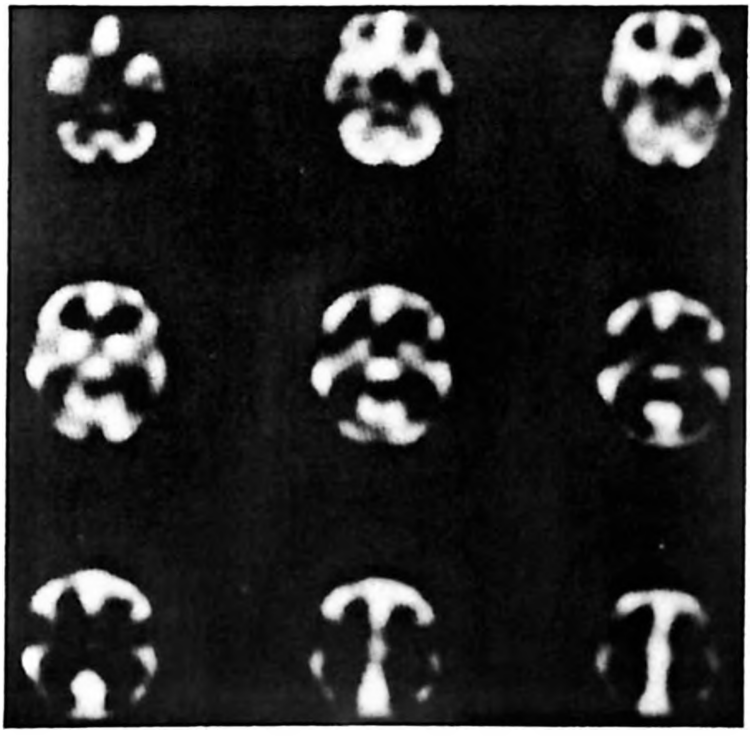

Fig. 2: Markedly decreased blood flow in superior temporal and parietal cortices, right occipital cortex, right cerebellum and left frontal cortex in SPECT.

During the following weeks, the patient's neurologic status rapidly deteriorated, and as of this writing he had great difficulty in swallowing and walking.

Discussion

Clinical and laboratory findings and imaging studies led to the diagnosis of ALD. Serum fatty acid analysis also confirm this neurodegenerative disorder. Although adrenal insufficiency was not apparent clinically, test results indicated the failure of increase in the baseline cortisol value in response to ACTH stimulation.

In ALD patients, characteristic changes have been described in imaging studies. Mostly symmetric lesions involving the periventricular white matter in the posterior parietal and occipital lobes and then advancing to the temporal and frontal lobes

are detectable with CT and MRI studies. Noncontrast CT scans show hypodensities in these regions. After the injection of contrast material, it accumulates adjacent and anterior to the hypodense lesions. This zone corresponds to the zones of intense perivascular lymphocytic infiltration where the blood-brain barrier breaks down. MRI identifies the normal and abnormal white matter more clearly than CT and may even demonstrate abnormalities missed by CT[5].

Lately, SPECT neuroimaging has had an important and expanding role in evaluating physiologic changes in regional cerebral perfusion[6]. In the literature, the number of SPECT studies in ALD is limited. A previous case report of a PET study in ALD showed decreased cerebral blood flow and glucose uptake in the gray matter at the occipital, temporal and posterior parietal cortex[7]. In another report, Tc99m HMPAO SPECT revealed the same regional distribution of decreased blood flow in the posterior cerebral areas as in the PET study, and one recent report showed that brain blood flow was remarkably decreased[8,9]. The demyelinating process of the nerve fibers decreases the neuronal output from the related cortical areas. Decreased cortical metabolism results in decreased perfusion due to the metabolic coupling of glucose utilization and blood flow[10]. In our case, though on MRI the lesions were confined to the parietooccipital region, SPECT demonstrated more extensive cortical hypoperfusion. Additionally, the right cerebellum and left frontal cortices showed decreased perfusion, which may be due to corticocerebellar diaschisis. The lesions in SPECT were more extended than those in MRI. Scattered neuronal loss and mild gliosis in the gray matter has been reported by histopathology in ALD[9]. MRI and CT showed no gray matter involvement, and no histopathologic examination of gray matter is present in our case. SPECT might have revealed a true gray-matter abnormality as well. Our patient's ataxia could be explained by cerebellar hypoperfusion. The degree of functional impairment seemed to correlate better with the SPECT results. Deterioration of the patient's status in the following weeks, provided a clue for possibility of predicting the disease progression by SPECT, when perfusion defects were more extensive than shown on MRI. It may be concluded that SPECT abnormalities precede MRI changes and symptoms, and this may give the earliest indication of the presence of cerebral involvement.

Treatment with glyceryl trierucate and glyceryl trioleate oils combined with dietary restriction of VLCFA leads to a reduction in plasma VLCFA levels, though very limited evidence exists regarding its clinical benefit[11,12]. Dietaray restrictions are recommended for patients with rapidly progressive ALD. Patients who show early cerebral involvement or early signs of progression are considered candidates for bone marrow transplantation[13]. Since therapeutic approaches are based on the extent of the disease, SPECT seems to be of great importance in selecting therapeutic options and follow-up.

This report stresses the indications for SPECT neuroimaging in ALD. Utilization of SPECT in making an early diagnosis, prediciting the prognosis and selecting the therapy, which itself is under intensive investigation, should be encouraged by other studies.

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McARDLE'S DISEASE*
A Case Report

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SUMMARY: Dirik E, Taşkın F, Eroğlu Y, Büyükgebiz B, Selamzade M, Çevik NT. (Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). McArdle's disease: a case report. Turk J Pediatr 1996; 38: 355-359.

McArdle's disease is a hereditary, metabolic myopathy characterized by weakness and muscle cramps after exercise, appearing mostly in the second or third decade of life. Due to myophosphorylase deficiency in skeletal muscle, glycogen cannot be used and deposited in the sarcolemmal spaces, leading to lack of endurance to sustained work. The ischemic exercise test is a screening procedure for muscle energy disorders, and the diagnosis is confirmed by reduced enzyme activity in muscle biopsy.

In this report, a family with one child having enzyme assay-proven McArdle's disease and two other children demonstrating a positive ischemic exercise test is presented.
Key words: McArdle's disease, ischemic exercise test.

McArdle's disease (glycogenosis type V) is an autosomal-recessive disorder characterized by exercise-induced weakness and muscle cramps, and sometimes by myoglobinuria as well. Due to deficiency of the enzyme myophosphorylase, energy production by glycolysis is reduced in skeletal muscle, and intolerance after moderate or heavy work ensues. Raised serum levels of creatine phosphokinase (CK) and a positive ischemic exercise test are rapid screening methods for this metabolic myopathy.

The disorder was first described by McArdle in 1951[1] in a 30-year-old man with a life-long intolerance to exercise. Although several cases with late-onset deficiency of myophosphorylase have been published, patients typically experience symptoms during their teenage years[2-4].

In this report, we describe a 17-year-old boy with McArdle's disease and his family members with positive clinical and laboratory features.

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Case Report

A 17-year-old boy was referred to our clinic for weakness and lack of endurance after exercise since childhood. He suffered from muscle pain, cramps and stiffness after moderate to heavy work. He had never experienced darkening of his urine after exercise. His past history was unremarkable. His parents had second-degree consanguinity and were asymptomatic. The propositus was the second child of the family and had three sisters and one brother. One sister and brother had similar symptoms, though milder than his. This sister, who was 15 years old, had experienced weakness since five years of age, but only after a long-distance walk or heavy exercise. His three-year-old brother's symptoms had appeared recently; he complained of tiring easily.

On examination, these three children's physical and electromyographic findings, including neurological examination, did not reveal any abnormality. The patient's serum creatine phosphokinase (CK) level was extremely high (27,960 U/L). During the ischemic exercise test he developed cramps and could not complete the exercise; his serum lactate concentration increased by only 1 mg/dl, while it would normally be expected to increase by more than 20 mg/dl. The serum CK levels and the results of the forearm exercise test of the patient and his family members are shown in Table I. The exercise test was performed as follows: after a resting period of 30 minutes, venous blood samples were collected for baseline ammonia (NH_3) and lactic acid levels. Following five minutes of exercise with rapid flexion and extension of the forearm, blood samples were obtained again for post-exercise NH_3 and lactic acid levels.

Table I: Laboratory Findings and Exercise Test Results of Patient and Family Members

			NH_3 (mg/dL)		Lactic acid (mg/dL)	
	Age (years)	CK* (U/L)	Before Test	After Test	Before Test	After Test
Propositus	17	27,960	82	155	20.6	21.6
Mother	38	111	98.4	120	9.6	28.3
Father	38	90	63.8	104.6	20.8	46.9
Sister	19	156	109	187	8	13.3
Sister	15	1,262	160	218	8.1	8.9
Sister	9	98	137	174	8.7	8.9
Brother	3	243	73.8	150.7	12.1	8.8

* Creatine kinase (range: 5-130).

The patient had severe pain and contracture after a very brief period of exercise and could not complete the test. His mother had slight weakness during the exercise but completed the test. No other family members reported pain or cramping during the test.

Muscle biopsy was performed in the propositus. The muscle glycogen content was increased (patient 4.4 g/100 g muscle, control $\bar{X}$: 1.1, range: 0.7-2). Muscle phosphorylase activity was diminished (patient 1.4 E/g muscle, control $\bar{X}$: 89.3, range: 69.0-121.5).

Discussion

McArdle's disease is a glycogen storage disease. These diseases result from deficiency or absence of specific enzyme activity in glycogen's metabolic pathway. Patients with McArdle's syndrome have deficiency of muscle phosphorylase. McArdle's disease has a wide clinical spectrum varying from asymptomatic cases to recurrent myoglobinuria with attacks of rhabdomyolysis and unremitting muscle pain with exercise. There have also been a few reports of acute renal failure secondary to intense myoglobinuria[5,6]. The majority of patients present with symptoms during the second or third decade of life. However, the past history usually reveals muscle weakness and lack of endurance since childhood. The severity of symptoms varies with the percentage of enzyme activity. The propositus complained of weakness, exercise-induced cramps and pain since childhood. He had no pigmenturia.

Brief exercise of great intensity or less intense but sustained activity produces symptoms in patients. Because muscle depends almost exclusively on endogenous glycogen for intense exercise, pain and cramping are experienced. Many patients experience a second wind, that is, when they rest briefly after the cramps first appear, they can continue without further symptoms. For moderate exercises with long duration, the fatty acids seem to be the most important source of energy. This may explain the tolerance in patients to moderate exercise[7]. In patients with suspected muscle energy disorders, the ischemic exercise test is the first step and should be performed when cramps develop on exercise. In most normal individuals, serum lactate concentrations increase by more than 20 mg/dl and serum ammonia concentrations increase by more than 100 µg/dl over baseline. Failure to raise the serum lactate level more than 5 mg/dl along with a normal rise in ammonia concentration is diagnostic of a glycogen storage disease[8]. The abnormal increase in the concentration of serum creatine kinase and the exercise test reslts in our patient led us to perform a muscle biopsy. The findings of increased muscle glycogen content and low phophorylase activity confirmed the diagnosis of McArdle's disease. Electromyographic (EMG) findings demonstrate myopathic units in late-onset forms of McArdle's disease; however, this feature has been noted rarely in the early-onset disorder. Our patient's EMG findings were also normal.

In McArdle's disease, myophosphorylase is only deficient in skeletal muscle; the activity in liver and smooth muscle is normal. The glycogen concentration is increased by up to four percent, and excess glycogen is deposited in

subsarcolemmal and intermyofibrillar spaces with disruption of the myofibrillar structure at the level of the I band[9]. Due to insufficient ATP production and accelerating recycling of muscle purine nucleotides, blood ammonia, inosine, hypoxanthine and uric acid level increase[10, 11]. Though infrequent, muscle phosphofructokinase deficiency, muscle phosphoglycerate kinase deficiency, muscle phosphoglycerate mutase deficiency and lactate dehydrogenase deficiency produce symptoms and glycogen deposition similar to that in McArdle's disease; thus, a definitive diagnosis can only be reached by enzyme assays[8].

Being mildly symptomatic, the three-year-old brother and 15-year-old sister of the propositus had serum CK and lactate levels consistent with the disease. The patient's nine-year-old sister had a normal CK concentration but her lactate levels also did not increase normally during the test; she needs further evaluation for the enzyme activity. The mother, feeling weakness during the test, had normal results. The father was completely asymptomatic. These findings are consistent with the autosomal-recessive transmission of the disease. Although biochemical studies have failed to show any differences in the severity of the enzyme defect or in the concentration of muscle glycogen, some rare clinical variants of the disease have been described[12, 13]. There have been reports of late-onset disease with no symptoms until the age of 74 years, and of a fatal presentation before four months of age[3, 4, 14, 15]. Though the enzyme level of the propositus was extremely low, he was able to maintain his daily activites; the symptoms appeared only after heavy exercise.

For carrier studies, evaluation of enzyme activity in muscle biopsy or phosphorus magnetic resonance imaging (^{31}P MRI) is recommended. ^{31}P MRI is a noninvasive diagnostic procedure demonstrating pH, ATP and reduction in phosphocreatinine concentration in response to both aerobic and ischemic exercise[17, 18]. The gene for muscle phosphorylase has been cloned and mapped to chromosome 11q 13-q ter[19]. The most common mutation is the C to T transition at codon 49 in exon 1 of the gene, changing an encoded arginine to a stop codon[7]. Genetic counseling in this disorder is possible by chromosomal analysis and MRI.

McArdle's disease is a relatively benign metabolic disorder. There is no need for specific therapy, as avoidance of vigorous exercise prevents the symptoms. A high-protein diet was found to increase exercise tolerance[19]. Oral intake of glucose or fructose can also augment tolerance to heavy work.

In conclusion, patients having weakness, pain or cramps after exercise should be evaluated for muscle energy disorders. A positive ischemic exercise test along with increased CK levels help to establish the defect in carbonhydrate utilization and indicates the need for biochemical analysis of muscle biopsy for definitive diagnosis.

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CASTLEMAN'S DISEASE*

A Case Report

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SUMMARY: Arslan D, Öztürk F, Patıroğlu T, Küçükaydın M, Gündüz Z. (Departments of Pediatrics, Pathology and Pediatric Surgery, Kayseri, Turkey). Castleman's disease: a case report. Turk J Pediatr 1996; 38: 361-366.

Angiofollicular lymph node hyperplasia or Castleman's Disease (CD) is a rare lymphoproliferative disorder that manifests itself as a local or generalized tumor-like condition affecting both lymph nodes and non-nodal tissues, usually in the chest and abdomen. Hyaline vascular and plasma cell types have been identified histologically. A new clinical form of CD with multisystemic involvement has been defined as multicentric Castleman's disease. It is very rare in childhoed. In this paper we present an eight-year-old boy with multicentric Castleman's disease. *Key words: angiofollicular lymph node hyperplasia, immunglobulin light chain, immunohistochemistry.*

Angiofollicular lymph node hyperplasia or Castleman's Disease (CD) was first described by Castleman and colleagues[1] in 1956. Keller et al.[2] classified the lesions into two types based on clinical and pathological criteria. The more common one, the hyaline vascular type, is characterized by small, hyalinized follicle centers with radially penetrating vessels and prominent interfollicular vascular proliferation. Patients with this type are usually asymptomatic, but occasionally it can give rise to symptoms due to the mass effect. The plasma cell type is characterized by large hyperplastic follicles with intervening sheets of plasma cells. More recently a lymphoproliferative disorder with similar histologic features but more generalized or extensive lymph node involvement has been reported as multicentric CD. Identification of systemic or multicentric CD is based on not only histology but also a combination of clinicopathologic criteria[3]. Although CD can be encountered at any age, most patients are between the ages of 30 and 40 years at presentation, and the disease is very rare in the pediatric age-group, especially the multicentric variant[4,5]. In this paper we present an eight-year-old boy who was diagnosed with multicentric CD.

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Case Report

An eight-year-old boy was admitted to Erciyes University hospital for mediastinal enlargement and hepatosplenomegaly. He had been diagnosed with hepatitis two months earlier, with elevated serum transaminase and bilirubin levels, but the serologic markers for hepatitis A, B, C and D had been negative. He had been fainting for a month and EEG findings were consistent with epilepsy, carbamazepine therapy was initiated.

On examination he had pertibial edema, uveitis and hepatosplenomegaly. Laboratory data revealed a urinalysis of (++++) proteinuria, a urinary protein loss of 108 mg/m^2/h, a hemoglobin of 11.6 g/dl, a white cell count of 12,200/mm^3, and an erythrocyte sedimentation rate (ESR) of 105 mm/h. The tuberculin skin test was negative, C-RP 31 mg/dl (N: < 10), rheumatoid factor 55 IU/ml (N: < 25), ANA (-). Bone marrow aspiration was normal.

Serum BUN, creatinine, sodium, potassium, calcium, phosphorus, alkaline phosphatase, AST and ALT were within normal limits. Serum total protein was 5.2 g/dl, albumin 2.1 g/dl, triglyceride 149 mg/dl, and cholesterol 259 mg/dl. Serum IgG was 1670 mg/dl (N: 700-1630), IgA 187 mg/dl (N: 73-186) and IgM 132 mg/dl (N: 65-206). Chest x-ray showed mediastinal enlargement (Fig. 1). Abdominal

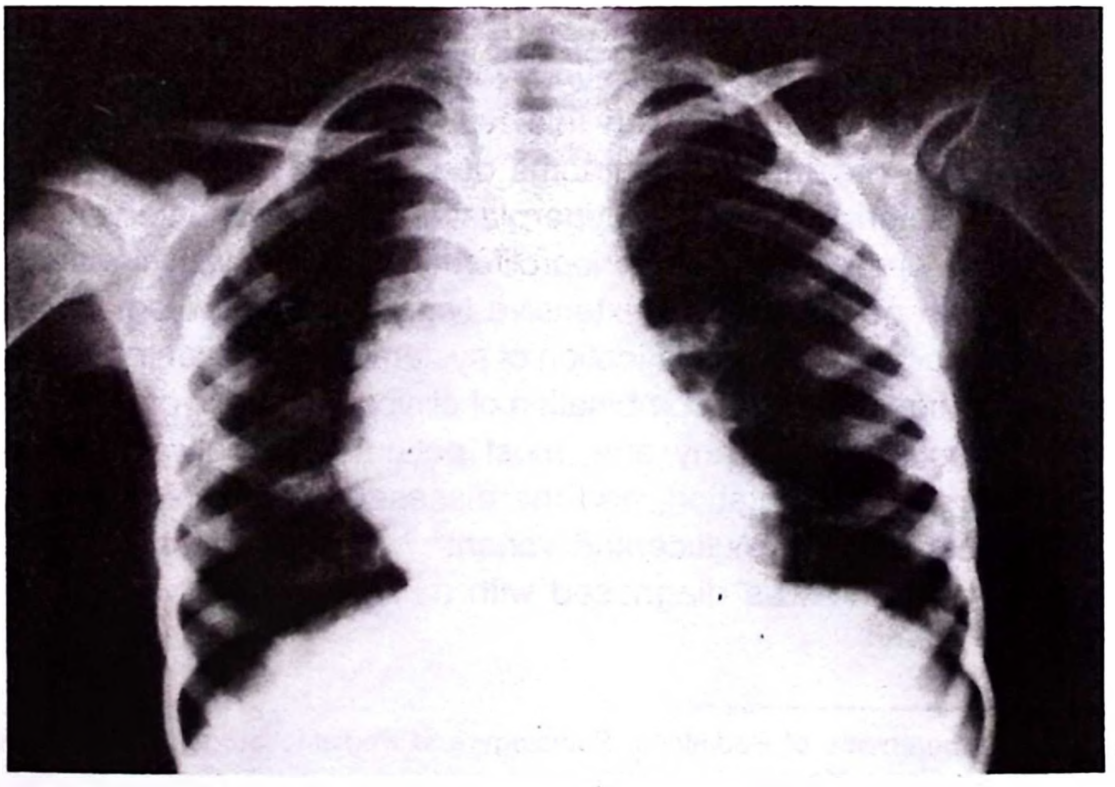

Fig. 1: Postero-anterior chest x-ray showing mediastinal enlargement.

ultrasonography (USG) revealed hepatosplenomegaly and hepatic and splenic hilar lymphadenopathy. Thoracal computed tomography (CT) showed right paratracheal and right inferior mediobasal lymphadenopathy. The findings of the mediastinal

lymph node biopsy were as follows: macroscopically the involved lymph node was firm, encapsulated and 4 x 2 x 1 cm in dimensions, while the cross-section was solid and gray-yellow in color; microscopic examination revealed that the nodal architecture was altered by an increased number of large, lymphoid follicles. In the germinal centers of the follicles were proliferating capillaries and deposits of hyaline material. Surrounding the germinal centers were multiple concentric layers of small and mature lymphocytes (onion-skin appearance). There were scattered histiocytes and some large Reed-Sternberg-like cells between the lymphocytes. The diagnosis was made as angiofollicular lymph-node hyperplasia, hyaline vascular type (Fig .2). Immune histochemical staining resulted as positive staining with λ and κ light chains (Fig. 3).

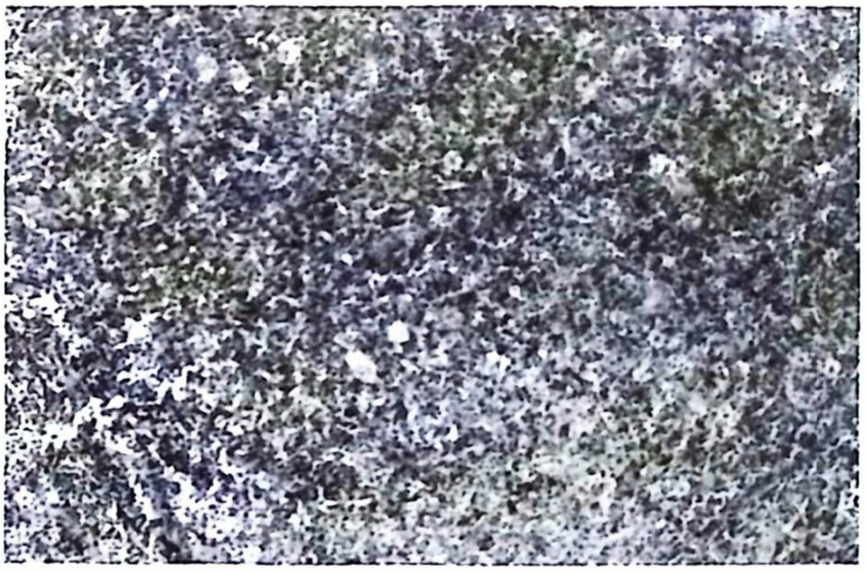

Fig. 2: Histologic appearance of lymph node. Note hyalinized follicle centers (H.E. x 100).

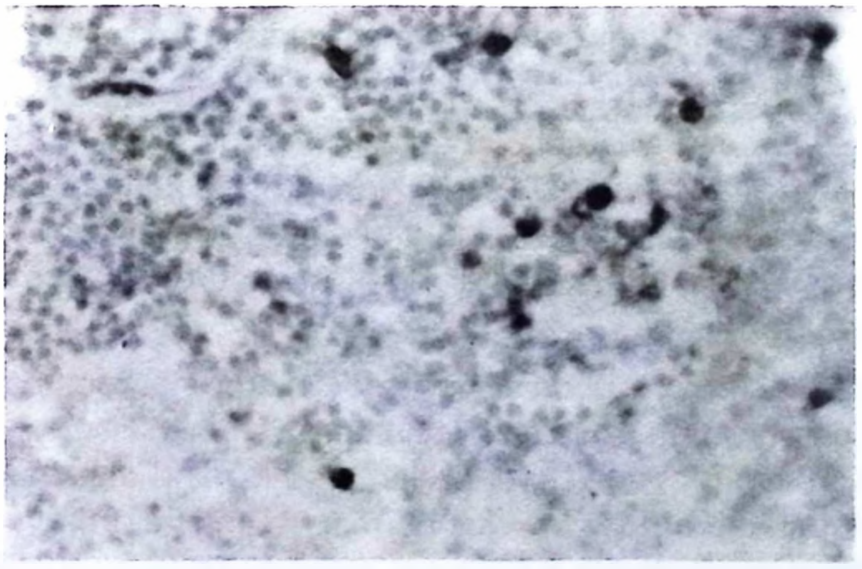

Fig. 3: Positive immunohistochemical staining with λ light chain (x 400).

After a follow-up period of five months the patient was asymptomatic, but in the sixth month the disease relapsed with mediastinal lymphadenopathy, fever and elevated acute-phase reactants.

Discussion

Castleman's disease, especially the multicentric variant, is rarely seen in children. To date approximately 80 cases have been reported in children and adolescents (up to and including 18 years of age). The majority of cases have been 14 years or older at presentation. Only 13 cases of children less than 14 years in age at presentation have been published[4]. None of them had multisystemic involvement as in our case.

The etiology of CD is unclear. The hyaline vascular type seems to be a chronic reactive lymphoid hyperplasia, although the causal agent(s) remains undiscovered. An abnormal immune reaction or immune dysregulation, or an endothelial proliferation or proliferation of autoantibody producing B cells has been suggested in the etiology. Even though the etiologic agent remains unclear, it has recently been proposed that the stimulus for the B-cell proliferation is intervening production of interleukin 6 (IL-6), a B cell growth factor, being secreted by germinal centers. The symptoms, signs and abnormal laboratory findings of CD resolve with monoclonal anti IL-6 antibody treatment[6,7].

The clinical presentation may suggest infection, malignancy or autoimmune or collagen vascular disease[4,5]. Initially our patient was diagnosed with lymphoma.

Lymphadenopathy is universal. In general, the lymph nodes are modestly increased in size, occasionally larger and surgically unresectable. The most common sites are the abdomen, the mediastinum, the hila of the lungs and the neck[3-5]. The majority of pediatric cases have the localized form, but our case had the multisystemic or multicentric form, given the multisystemic involvement and laboratory findings.

As in our case, hepatic and splenic enlargement is present in the majority of cases[3]. Skin rashes are common, ranging from maculopapular to nodular or lichenoid eruptions, and histopathologic changes similar to CD may be found in skin lesions[8]. Our patient had a maculopapular eruption over the torso during hospital follow-up.

Neurologic manifestations, such as sensory motor neuropathy, seizures and pseudotumor cerebri as well as central nervous system masses or leptomeningeal infiltration have been reported[9]. Our patient had fainting attacks with some EEG changes, although the cranial CT was normal. It remained unproven whether or not the patient's neurological symptoms were secondary to the neurological involvement of CD.

A wide variety of rheumatologic symptoms and signs including arthralgia effusion, myalgia, keratoconjunctivitis sicca, xerostomia and Reyn phenomenon have accompanied multicentric CD[5]. We did not observe a these findings in our patient. Renal dysfunction may be manifested by protei hematuria and renal insufficiency. Proteinuria as in the presented case ca significant and could be a major cause of the development of hypoalbumir and thus nephrotic syndrome. Different forms of renal involvement have reported[10]. Our patient did not have a renal biopsy but had proteir hypoalbuminemia, hypertriglyceridemia and hypercholesterolemia. Nepl syndrome resolved spontaneously within a week.

Most patients have mild to moderate anemia at the time of diagnosis. The cell count is generally normal, but both thrombocytopenia and thrombocy have been reported. Bone marrow examination may show a modest plasmocy without distinguishing features. The ESR is usually elevated, the median b approximately 80 mm/h. Almost all patients have a polyclonal increas gammaglobulin levels, frequently in IgG and IgA. Antinuclear antibody, rheum factor, positive VDRL, cryoglobulins and inhibitors of factor VII and VIII been reported in some cases[3, 5]. The patient had moderate anemia, elev ESR, IgG and IgA, and the rheumatoid factor was positive.

Most cases of CD, including multicentric CD, are polyclonal as determine immunohistochemical staining for immunoglobulin light chains, but some c are not[4]. Our case was also positive for λ and κ light chain.

To our knowledge no case of CD with uveitis has been reported so far. Our had bilateral active uveitis and all other possibilities ruled out; the uveitis resc with medical treatment and did not recur during follow-up. This may be the case of CD with uveitis reported in the literature. In adults the course of multice CD is unpredictable, but a high mortality rate has been reported in the litera Higher survival rates have been reported in childhood[3, 4]. Intervening infect are a common cause of death in the systemic form[5].

Patients with multicentric CD are at increased risk of developing malignanc especially malignant lymphoma and Kaposi's sarcoma. On the other hand, r patients with CD are at an age group at which cancers are not uncommo

In the differential diagnosis, especially in multicentric types, Hodgkin's lymphc mixed cellularity type, must be ruled out. This entity includes eosinophils, Re Sternberg cells and fibrosis but lacks hyalinized germinal centres. Follicular lymph may be confused with CD. In follicular lymphoma evenly distributed nodules of sir sizes and shapes can be seen; the nuclei are also atypical. In addition, immunobl lymphadenopathy, toxoplasmosis lymphadenitis, thymoma and plasmocytoma n be ruled out in the differential diagnosis of angiofollicular lymph node hyperpla

Localized variants of CD respond well to surgical excision. Different therapeutic regimens including radiotherapy, steroids and some antineoplastic drugs have been used in adults. Massey et al.[11] used steroid therapy in an unresectable CD patient, but the patient did not respond to therapy. The same patient was treated successfully with radiotherapy. We did not use any therapeutic regimen except for the uveitis, and the patient had a good outcome during follow-up. However, in the sixth month of follow-up, the disease relapsed with mediastinal enlargement, fever, hepatosplenomegaly and elevated acute phase reactants.

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SUPERIOR MESENTERIC ARTERY SYNDROME*

A Case Report

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SUMMARY: Tatar G, Coşkun T, Şimşek H. (Division of Gastroenterology, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey). Superior mesenteric artery syndrome: a case report. Turk J Pediatr 1996; 38: 367-370.

A case of superior mesenteric artery syndrome is reported. A 16-year-old boy with bilious vomiting for six months and weight loss within the previous year is presented. In this symptomatic period, he was fed many dietary formulations. This conservative management failed. Physical examination revealed that he was malnourished. The diagnosis was made by means of an upper gastrointestinal barium study performed through a tube. Gastrojejunostomy was preferred over duodenal mobilization because he had a markedly dilated stomach and enlarged pylorus. The postoperative course was satisfactory. *Key words: superior mesenteric artery syndrome, vascular compression, duodenal obstruction.*

Superior mesenteric artery syndrome (SMAS) results from extrinsic compression of the duodenum by the superior mesenteric artery (SMA) due to a narrow aortomesenteric angle and distance[1]. The site of obstruction is usually the third part of the duodenum. It may present either acutely or chronically with mild abdominal pain, anorexia, nausea and voluminous but infrequent bilious vomiting[2]. Since SMAS is an uncommon condition, the diagnosis can only be made if a high index of suspicion exists.

We recently encountered a 16-year-old boy referred because of bilious vomiting, abdominal fullness, weight loss and early satiety for the previous six months. The diagnosis of SMAS was made on the basis of an upper gastrointestinal contrast study (by inserting a large cannula into the duodenum) that showed almost total obstruction in the third part of the duodenum.

Case Report

A 16-year-old boy, weighing 38 kg (< 5th percentile) and measuring 1.67 m in height (10th - 25th percentile). presented with bilious vomiting and a six-month history of abdominal fullness. The patient had lost a remarkable amount of weight

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within a year prior to the start of his complaints. He was found be malnourished (body weight 60 percent of standard according to weight-for-height criteria) on physical examination. There was no abdominal distension or mass.

His hematological indices and results of biochemical and malabsorption tests were all within normal limits. A plain x-ray of the abdomen showed a dilated stomach and proximal duodenum. An upper gastrointestinal barium study displayed an excessively enlarged stomach and distension of the proximal duodenum with an external obstruction in its third part and antiperistaltic waves from the duodenum towards the stomach (Fig. 1). On the basis of these radiological findings, compression of the duodenum by the SMA was suspected. The stomach was decompressed by a nasogastric tube, and the patient was given total parenteral nutrition. A preoperative gastroduodenoscopy revealed no intrinsic duodenal obstruction but a continuously enlarged, open pylorus. There was no histopathological abnormality on the duodenal biopsy specimen except for giardiasis. At laparotomy, a markedly enlarged stomach and an extrinsically compressed third part of the duodenum by the SMA was found. Gastrojejunostomy was performed and a gastrostomy tube was placed. Following surgery, all symptoms disappeared and the patient began to gain weight. His gastrostomy tube was later removed, and he was discharged home when symptom-free.

Fig. 1: Upper gastrointestinal contrast radiography of patient. Note almost total obstruction in the third part of the duodenum.

Discussion

In the absence of an intestinal mass or anomalies such as malrotation, webs and atresias, vascular compression should be considered as a cause of obstruction. There have been previous case reports of duodenal obstruction due to SMA compression in the literature[2-7].

SMAS is also called Wilkie's syndrome, cast syndrome, chronic duonenal ileus, and arterio-mesenteric duodenal compression syndrome. It was first described by Von Rokitansky in 1861[8] and then reported as a distinct clinical entity by Wilkie in 1921[9]. It may be either congenital or acquired. The acquired form of the syndrome may result from a) accelerated linear growth with no associated weight gain, b) rapid weight loss due to chronic illness or bed rest, or c) hyperextension of the vertebral column in a cast or spica[10].

The third part of the duodenum crosses the spinal column and abdominal aorta at the level of the second lumbar vertebra. This position is caudal to the origin of the SMA, which normally forms an angle of approximately 45° with the aorta. The SMA is normally embedded in mesenteric fat and lymphatic tissue and does not compress the duodenum. If a patient loses weight rapidly, grows rapidly in height without associated weight gain or his vertebral column hyperextends in a cast, the tension in the root of the mesentery increases and/or the fatty cushion around the SMA diminishes. All these conditions result in a decreased aorta-superior mesenteric artery angle to approximately 15° and thus compression of the third part of the duodenum, leading to SMAS[2]. Among the other predisposing factors are peritoneal adhesions, incomplete duodenal rotation and abnormally high position of the ligament of Trietz with an upward displacement of the duodenum, rendering the aortomesenteric angle narrow. Our patient's body weight was not appropriate for his height; thus rapid weight loss within one year prior to his admission to the hospital may be the predisposing factor leading to SMAS.

Patients with SMAS may present either acutely or with a chronic history. The main symptoms are bilious vomiting, epigastric fullness and pain. The chronic cases presenting with intermittent vomiting, early satiety and anorexia may remain undiagnosed for many years or be misdagnosed as having anorexia nervosa. The presented case had a chronic syndrome characterized by bilious vomiting, abdominal fullness, weight loss and early satiety.

The diagnosis of SMAS can be confirmed radiologically by duodenography and/or angiography[4]. To demonstrate compression of the duodenum in our case, we used an upper gastrointestinal barium study performed through a tube. In one study of approximately 6,000 upper gastrointestinal contrast studies over a 10-year period, Anderson et al.[3] reported 12 cases (0.2%) with SMAS, indicating that the syndrome is uncommon.

Conservative therapeutic measures include alteration in diet and feeding habits, such as giving frequent feedings of pureed or blenderized foods and nursing in the prone position or while the patient is lying on his left side. Alimentation of the patient may result in weight gain, deposition of fat within the mesentery and around the SMA and, finally, relief of the duodenal compression. In the acute presentation of the syndrome or if conservative management fails, surgical intervention is necessary. During surgery may be necessary to insufflate the duodenum with air to confirm the diagnosis using the maneuver advocated by Wilkie and popularized by Jones[11], as was done in this case. In children, the most effective method is the one described by Louw et al.,[12] Burrington[13], and Wayne et al.[14] This method consists of mobilizing the entire duodenum and lysing the Treitz ligament through a small, transverse right-upper-quadrant incision. Since there was a markedly dilated stomach with an enlarged pylorus in our patient, gastrojejunostomy along with placement of a gastrostomy tube was performed, resulting in complete relief of symptoms and weight gain.

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UMBILICAL POLYP ORIGINATING FROM URACHAL REMNANTS*

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SUMMARY: Oğuzkurt P, Kotiloğlu E, Tanyel FC, Hiçsönmez A. (Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). An umbilical polyp originating from urachal remnants. Turk J Pediatr 1996; 38: 371-374.

Umbilical polyp is a rare disorder of the umbilical region in childhood. It is said to be the result of incomplete closure of the omphalomesenteric duct and presents as a red, moist umbilical mass after separation of the umbilical cord. Umbilical polyp originating from the urachus has not previously been reported. A 10-year-old boy with an umbilical polyp related to the urachus is presented to stress the possibility that umbilical polyps can originate not only from the omphalomesenteric duct but also from urachal remnants.
Key words: umbilical polyp, urachus remnant, omphalomesenteric duct.

In general surgical practice, umbilical pathologies such as umbilical granuloma and hernia are frequently encountered among children. Contrary to other umbilical pathologies, umbilical polyp, which is the result of incomplete closure of the omphalomesenteric duct (OMD), is rare in childhood[1, 2]. A patient with an umbilical polyp proven to be related to the urachus is reported to stress the possibility that other umbilical-related remnants may also cause umbilical polyps.

Case Report

A 10-year-old boy was admitted because of an umbilical mass which was first noticed three years before admission. There were no additional and/or preceding complaints such as discharge or pain.

Physical examination revealed a sessile mass one centimeter in diameter lined by slightly vascular, smooth skin protruding from the lower edge of the umbilicus.

The results of routine laboratory investigations including complete blood count, urinalysis and blood chemistry were within normal limits.

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The patient underwent an operation through a circular incision around the neck of the polyp. A tract running from the base of the polyp towards the urinary bladder close to the peritoneum was noticed. The polypoid mass and the tract were totally excised, including the connection to the bladder (Fig. 1). There was no relation to the intraperitoneal structures. Histological examination of the polypoid mass revealed a cystic structure lined by stratified squamous epithelium and containing keratinous material (Fig. 2). The tract was lined by a layer of cuboidal epithelium surrounded by a muscular layer that corresponded to the urachus (Fig. 3). The patient's postoperative course was uneventful, and he was free of signs and symptoms a year after surgical intervention.

Fi.g 1: Surgical specimen of the umbilical polyp with its extension to the urinary bladder.

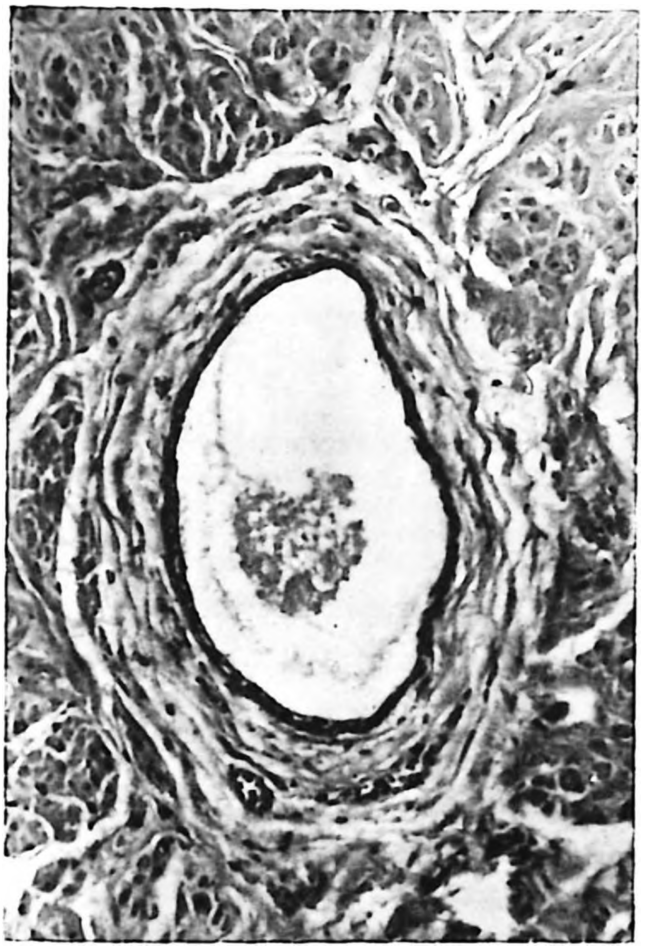

Fig. 2: The polyp was lined by stratified squamous epithelium containing keratinous material (original magnification x 20).

Fig 3: The cuboidal epithelium with a muscular layer around it lining the tract (original magnification x 10).

Discussion

By definition, a polyp is a protruding mass of swollen and hypertrophied mucous membrane caused by chronic inflammation or neoplastic growth. Umbilical polyps are reported to be a remnant of the OMD and may contain small bowel mucosa, gastric or colonic mucosa or, rarely, pancreatic tissue with or without connections to intraabdominal organs[1-5]. They are to be differentiated from exuberant proliferation of granulation tissue which represents granuloma pyogenicum[5]. If a red, moist lesion at the umbilicus persists after several applications of silver nitrate, it is likely to be an umbilical polyp[1, 2, 4].

Despite the classical definition of umbilical polyp, the polypoid mass in the presented case was covered by skin.

Two embryological vestiges may be related to cyst formation in the umbilical cord-the allantoic diverticulum and the OMD, although in most instances these structures can be identified only by microscopic examination. The allantoic diverticulum or duct is frequently identified if the umbilical cord is sectioned close

to its fetal attachment. It may or may not have an identifiable lumen and is lined with flattened, cuboidal transitional epithelium[6].

To the best of our knowledge, no umbilical polyp related to the urachus has previously been reported in the English language literature. It is apparent from the reported case that incomplete closure of the urachus, similar to incomplete closure of the OMD, may cause umbilical polyp. Therefore, umbilical polyp should be evaluated not only for OMD but also for urachal relations.

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BERNARD – SOULIER SYNDROME: A FLOW CYTOMETRIC ANALYSIS OF MEMBRANE GP – Ib EXPRESSION*

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SUMMARY: Yeşilipek MA, Karadoğan İ, Ündar L. (Departments of Pediatrics and Internal Medicine, Akdeniz University Faculty of Medicine, Antalya, Turkey). Bernard-Soulier syndrome: a flow cytometric analysis of membrane GP-Ib expression. Turk J Pediatr 1996; 38: 375-379.

A case of Bernard-Soulier syndrome in a five-year-old female is presented. The diagnosis was confirmed by flow cytometric analysis of glycoprotein Ib (CD 42b) in addition to the patient's classic laboratory findings such as prolonged bleeding time, mild thrombocytopenia, large platelets and failure of platelet aggregation with ristocetin. Her parents and sibling had normal coagulation tests and CD 42b levels. It is emphasized that flow cytometric analysis is useful in the confirmation of congenital platelet function defects. *Key words: platelet function disorders, Bernard-Soulier syndrome, flow cytometric analysis.*

Bernard-Soulier syndrome is a rare autosomal-recessive bleeding disorder characterized by mild thrombocytopenia, large platelets and prolonged bleeding time[1]. The underlying molecular defect is deficiency of membrane glycoprotein Ib/IX complex (CD42). This complex is the receptor for von Willebrand factor (vWF) and is necessary for normal platelet adhesion to the subendothelium[2].

We present a five-year-old girl diagnosed with Bernard-Soulier syndrome with classical laboratory abnormalities. Flow cytometric analysis of the patient's platelets showed a lack of membrane glycoprotein Ib (CD42b) expression.

Case Report

A five-year-old female was admitted to Akdeniz University's Pediatric Hematology Department with epistaxis. She had a history of a hematemesis attack two years previously, following recurrent epistaxis episodes. She had also suffered from oral mucosal bleeding and severe post-traumatic ecchymosis. There was second-degree consanguinity between her parents.

Her physical examination was normal except for a few ecchymoses on the lower extremities. Laboratory studies revealed a hemoglobin level of 11.3 g/dl, WBC

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6 x 10^9/L and platelets 65x 10^9/L. Large platelets were seen on the peripheral smear (Fig. 1). Prothrombin and partial thromboplastin times were normal. The bleeding time (Ivy method) was 13 minutes.

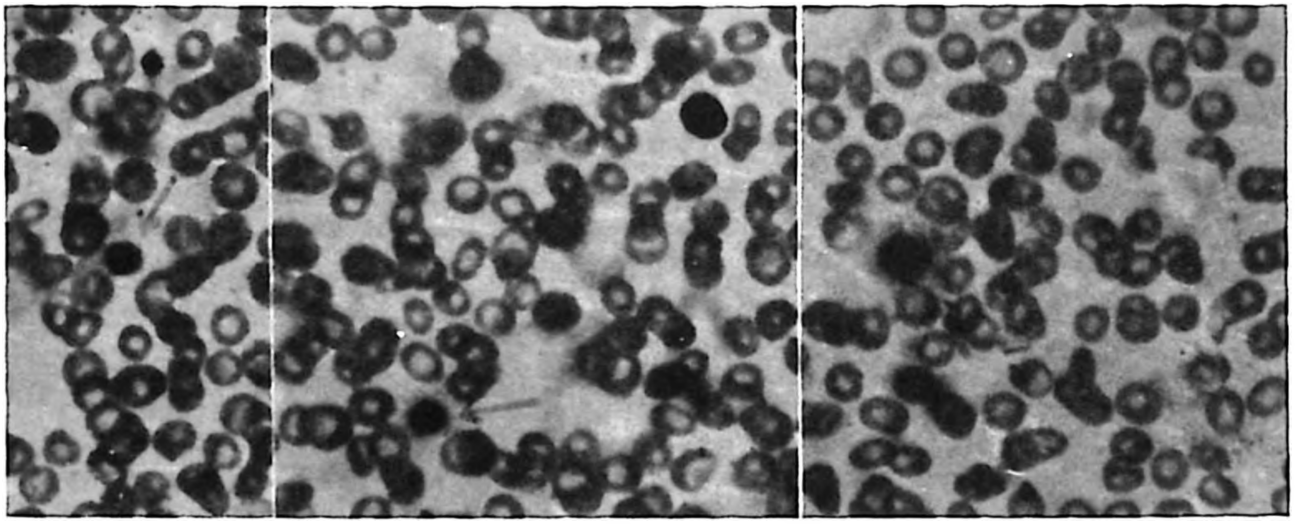

Fig. 1: Large platelets on peripheral smear of the patient.

With a presumptive diagnosis of Bernard-Soulier syndrome, platelet aggregation studies were performed. Because of the absence of ristocetin-induced platelet aggregation, a flow cytometric analysis for platelet membrane glycoprotein Ib expression was done.

Her epistaxis was controlled with local compression. She was discharged without any platelet transfusions, as she had no serious bleeding problems.

Material and Methods

Platelet Aggregation Studies: Adenosine diphosphate, collagen and ristocetin were used as aggregation-inducers (Chrono-Par reagents, Chrono-Log Corp., PA, USA). Platelet aggregation was studied using the whole-blood method (Chrono-Log Whole-Blood Aggro-Meter, model number 530-VS, Chrono-Log Corp., PA, USA).

Platelet Preparation for Flow Cytometric Analysis: Platelet-rich plasmas of the patient, her parents and sibling were prepared, and platelet counts were adjusted to 50 x 10^9/L with phosphate-buffered saline ethilene diamine tetra-acetate (PBS-EDTA).

Flow Cytometric Analysis: The samples were analyzed in a Coulter EPICS Profile II flow cytometer (Coulter Electronics Ltd, Florida, USA). The setting of a platelet gate was based on light scatter data (forward vs. side scatter).

Mouse monoclonal antibody to human platelet glycoprotein IIIa (CD61-FITC) (Serotec, UK) was used to confirm the identification of platelets. At least 100,000 events were acquired in this gate. A positive event, i.e., expression of glycoprotein

Ib (CD42b-FITC) (Immunotech S.A., France), was defined as one exhibiting a fluorescence intensity greater than the isotypic control. The negative marker was set and held at this level for each individual subject. The percentage of CD42b-positive platelets was defined as the percentage of gated events with a fluorescence intensity greater than the negative marker.

Results

ADP- and collagen-induced platelet aggregations were normal, while ristocetin-induced platelet aggregation was absent. This defect could not be corrected by the addition of normal plasma, indicating that the defect was in the platelets themselves. Her parents and sibling had normal ristocetin-induced platelet aggregation. Events within the acquisition gate were more than 95 percent for anti-glycoprotein IIIa binding for all members of the family, including the patient.

Her parents and sibling had normal CD42b expression (93%, 93.5% and 92.7%). In contrast, the patient's platelets showed lack of CD42b expression.

Discussion

Bernard-Soulier syndrome is a rare, autosomal bleeding disorder clinically characterized by prolonged bleeding time, normal clotting retraction and mild thrombocytopenia with large and morphologically abnormal platelets, and the absence of platelet membrane glycoprotein Ib/IX complex (CD42)[1]. Glycoprotein Ib is a major platelet receptor protein concerned with vWF binding, platelet aggregation, and platelet adhesion, and it is required for normal hemostasis. Therefore, deficiency of this vWF receptor on the surface of Bernard-Soulier platelets prevents the formation of an initial layer of adherent platelets on the subendothelial matrix, and leads directly to the hemorrhagic manifestations of the syndrome[3].

Platelets provide for primary hemostasis by forming a hemostatic plug at sites of vascular damage. Normal platelet function can be divided into four phases: adhesion, aggregation, secretion and expression of procoagulant activity. Platelet adhesion initiates plug formation as platelets adhere to the connective tissue at the edges of a wound within seconds after vascular damage. Platelet adhesion requires the presence of subendothelial von Willebrand factor and a specific platelet receptor, the glycoprotein Ib/IX complex. Following initial adhesion, platelets aggregate to complete the formation of a hemostatic plug[2].

The platelet count is usually mildly depressed in these patients[1,3]. We had consistently determined platelet counts as low as 65,000-80,000/mm^3, but fortunately the patient did not need a platelet transfusion. The peripheral blood film revealed the presence of giant platelet forms with mean diameters of 5 to 6 micrometers[1]. Our patient had some platelets with large diameters (Fig. 1).

The key to the diagnosis of Bernard-Soulier syndrome is detection of the failure of platelets to agglutinate in response to the antibiotic ristocetin. In contrast to von Willebrand disease, this abnormality cannot be corrected by the addition of normal plasma, indicating that the defect is in the platelets themselves. Aggregation of Bernard-Soulier platelets induced by agonists such as ADP, collagen, thrombin, and epinephrine is normal[1].

Confirmation of a suspected diagnosis of Bernard-Soulier syndrome may be accomplished by confirming that glycoprotein Ib is absent from the platelet membrane, by using immunocytochemical or immunofluorescence methods[4-7]. We used flow cytometric analysis to detect this defect and confirmed the absence of glycoprotein Ib (CD42b). Some authors reported that heterozygous parents and offspring of patients with Bernard-Soulier syndrome have approximately half of the normal levels of glycoprotein Ib/IX and normal platelet function[1,8]. However we found normal CD42b levels in our patient's parents and sibling, and they did not have any sign of platelet dysfunction. Glanzmann thrombasthenia is an another platelet function disorder with similar clinical findings. Congenital absence of glycoprotein IIb/IIIa leads to fibrinogen-mediated aggregation abnormalities in these patients. It may differ from Bernard-Soulier syndrome by demonstrating the absence of glycoprotein IIIb/IIIa, and a lack of platelets to aggregate with ADP or collagen[1]. In our patient, in addition to normal aggregation of platelets with ADP and collagen, normal platelet membrane expression of glycoprotein IIIa (CD61) ruled out Glanzmann thrombasthenia.

A patient with Bernard-Soulier syndrome may be misdiagnosed with chronic immune thrombocytopenia. This defect has generally been noticed when thrombocytopenia persists in spite of steroid therapy. Moreover, antibodies to glycoprotein Ib have been observed in a small number of patients with idiopathic thrombocytopenic purpura[1]. However, large platelets, such as those seen in Bernard-Soulier syndrome, have not been observed in these cases.

In conclusion, flow cytometric analysis is very useful for studying platelet-associated immunoglobulin and platelet activation. It has also been a promising tool in the diagnosis or confirmation of congenital platelet defects via the demonstration of glycoprotein Ib/IX and glycoprotein IIb/IIIa complexes.

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SPONDYLOCOSTAL DYSPLASIA AND CARDIAC ANOMALIES IN ONE DIZYGOTIC TWIN*

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SUMMARY: Özkınay F, Akısü M,Oral R, Tansuğ N, Özyürek R, Kültürsay N. (Department of Pediatrics, Ege University Faculty of Medicine, Bornova-İzmir, Turkey). Spondylocostal dysplasia and cardiac anomalies in one dizygotic twin. Turk J Pediatr 1986; 38: 381-384.

A 13-day-old, preterm, male infant was referred for respiratory distress syndrome (RDS) and jaundice. His twin sister had died of RDS on the second day of life in another hospital. The patient had typical features of spondylocostal dysplasia. Ventricular septal defect (VSD) and patent ductus arteriosus (PDA) were also diagnosed by echocardiographic evaluation. Parental consanguinity was not reported. There were no other similar cases in the family, and his twin sister and five-year-old living sister were free of deformities. Therefore, autosomal-recessive transmission may be considered first; however, because the patient was the only affected individual in this family, second denovo autosomal-dominant mutation should also be considered. This is the first reported case of spondylocostal dysplasia with VSD and PDA to our knowledge. *Key words: bones, dysostoses.*

Spondylocostal dysplasia was first described by Jarcho and Levin[1] in two brothers. The disease consists of an unusual association of multiple costal and vertebral deformities, including block vertebrae, hemivertebrae, anterior and posterior clefts of the vertebral column, and bizarre costal features such as variations in the size and thickness of the ribs and partial fusion or bifurcation. In the majority of cases there is a reduction in the number of ribs.

Spondylocostal dysplasia is a good example of genetic heterogeneity since there are two clinically similar forms, one dominant[2,3] and the other recessive[4,5]. We report here a case of spondylocostal dysplasia with cardiac anomalies.

Case Report

A 13-day-old male infant of a 23-year-old gravida 2, para 1 mother had been born following a 34-week twin gestation. No gestational problems, such as maternal disease, bleeding or known teratogenic exposure, were reported.

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The patient's twin sister had died of respiratory distress syndrome. There was no parental consanguinity or family history of congenital abnormalities. His twin sister and five-year-old sister were normal.

The patient's weight and length were 1450 g (3rd percentile) and 42 cm (10th percentile), respectively. Physical examination revealed a markedly short neck and flail chest due to absent ribs. Severe respiratory distress and cyanosis were observed. On cardiac auscultation a systolic murmur was heard.

Radiological findings included multiple vertebral deformities with hemivertebrae, crushed and fused vertebrae and scoliosis with convexity to the left in the dorsal column. The ribs showed marked deformities especially near their vertebral attachments. There were only nine ribs on the right side and ten on the left as well as irregularity in the spacing of the ribs on the right side. In addition, chest radiogram showed external herniation of the right lung and increased pulmonary circulation (Fig. 1). The karyotype was 46 XY.

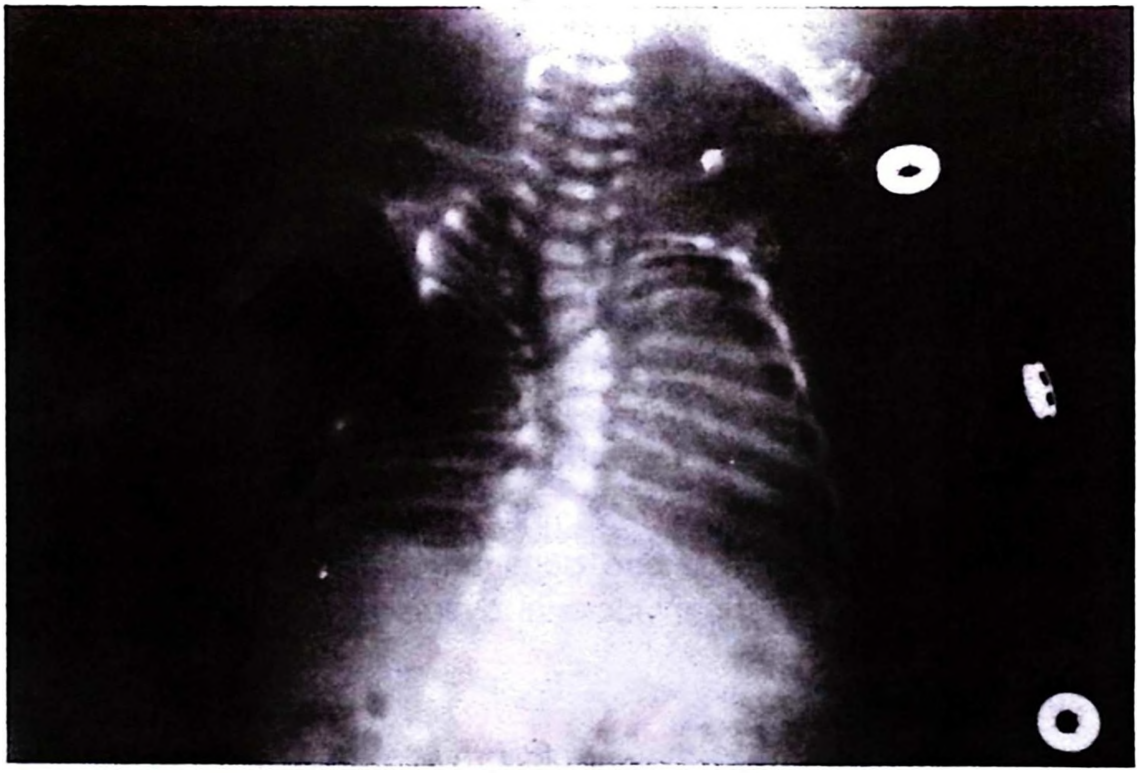

Fig. 1: X-ray of the spine and thorax showing malformed vertebral bodies (hemivertebrae, vertebral fusions), scoliosis and marked costal anomalies with absent ribs.

Echocardiography revealed a patent ductus arteriosus (PDA) of 2 mm, ventricular septal defect (VSD) of 3 mm and pulmonary hypertension.

Severe congestive heart failure developed on the 15th day of life, for which the patient was put on diuretic and digitalis treatment. This therapy was not satisfactory since the patient had pulmonary hypertension due to increased

pulmonary circulation. Three doses of indomethacin, a cyclo-oxigenase inhibitor, were administered perorally at a dose of 0.2 mg/kg in order to close the ductus arteriosus. Ductal closure was achieved after 36 hours, and the clinical findings of congestive heart failure subsequently disappeared.

Discussion

Spondylocostal dysplasia is a disorder with clearly defined clinical and radiological characteristics. The clinical picture is always apparent at birth. The patients show dwarfism because of cervico-dorsal scoliosis or kyphoscoliosis; torticollis, with a general decrease in the motility of the neck; pigeon chest and/or flail chest; and a reduction in the length of the thorax[4, 5].

From the radiological point of view, the disease is characterised by a series of structural changes that affect the vertebral body and ribs, and is associated with significant morphological and functional derangements in the vertebral column and thorax[5, 6]. Several types of malformations may be found in the vertebrae and ribs. The vertebral column may be affected from the atlas to the coccyx. The vertebral malformations include hemivertebrae, block vertebrae, fused vertebrae and spina bifida. The deformities of the ribs are closely related to those found in the spine and seem to be secondary to them. These deformities include symmetrically or asymmetrically absent ribs, and bifid or fused ribs especially near vertebral attachments[5, 6]. A primary failure in the development of chondrification centers takes place between the third and sixth weeks of gestation, subsequently leading to the aforesaid vertebral and rib abnormalities[6].

Both autosomal dominant and recessive inheritance have been reported in this disorder. Dominant inheritance has been demonstrated in the cases of Van der Sar[2] Peralta et al[7] and Caffey[8], and these patients were less severely affected than the patients who had autosomal-recessive inheritance[1, 9, 10]. Surviving children show severe respiratory complications in infancy, such as pulmonary atelectasis, upper respiratory tract infections, bronchitis and bronchopneumonia, which may be lethal[5, 6].

Both autosomal dominant and recessive transmission are possible in our patient. Autosomal recessive transmission may be considered first because of normal parents. However, denovo autosomal dominant mutation should also be considered because the patient is the only affected individidual in this family.

Only Franceschini et al.[5] have described an associated cardiac abnormality in the form of Fallot's tetralogy in a patient with spondylocostal dysplasia. This patient died of bronchopneumonia at the age of six years. A case of dizygotic twins with only one twin affected with spondylocostal dysplasia has not been reported before to the best of our knowledge; neither has the presence of these specific cardiac anomalies.

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CHILDHOOD ACHALASIA*

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SUMMARY: İçağasıoğlu D, Tanzer F, Gültekin A, Bayram G, Sekreter E. (Department of Pediatrics, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Childhood achalasia. Turk J Pediatr 1986; 38: 385-388.

Achalasia is a motility disorder of the esophagus characterized by absence of normal peristalsis and failure of relaxation of the lower esophageal sphincter. Among the most common clinical findings are vomiting and weight loss. Roentgenographically, a narrowed gastroesophageal junction and dilated esophagus are observed. This condition is uncommon in children. Here a seven-year old female patient with achalasia is reported. *Key words: achalasia, childhood.*

Achalasia is a motor abnormality of the esophagus characterized by inability of the lower esophageal sphincter (LES) to relax[1]. The condition affects primarily adolescents and adults; children under the age of four years comprise less than five percent of patients[2-4]. This seven-year-old female patient is presented because achalasia is very infrequently observed in childhood.

Case Report

A seven-year-old girl was admitted to our hospital with persistent vomiting just after eating, sometimes in the form of saliva, in the previous few months. She was also suffering from weight loss. She had no history of corrosive agent ingestion. She displayed no hematemesis or melena.

Physical examination on admission revealed an exhausted child with bilateral ronflan rales in the respiratory system. The neurological examination was normal. Her weight and height were in the 50th percentile.

Complete blood count, urine and stool analyses were normal. Biochemical analysis of the blood was also normal. Water's x-ray showed right maxillary sinusitis, and the chest x-ray showed bilateral infiltrations in the paracardial area.

The esophagus x-ray showed a narrowed gastroesophageal junction and absence of the propulsive peristaltic wave. There was also a massive esophageal dilatation (Fig. 1, 2). No stricture was noted, and hiatal hernia was not observed. There was no evidence of gastroesophageal reflux on endoscopy.

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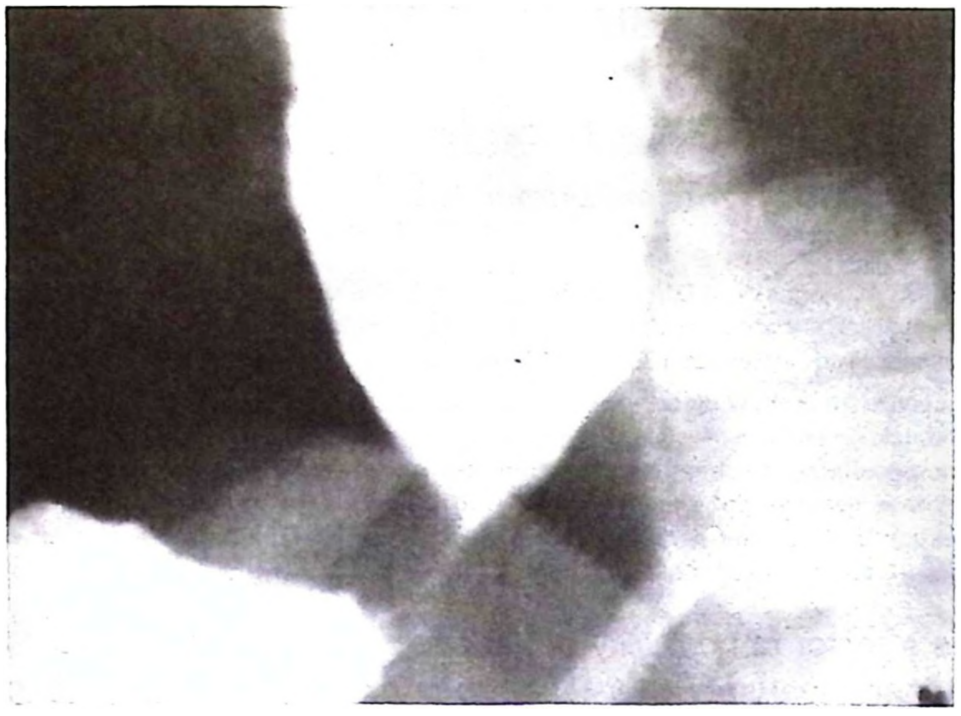

Fig. 1: The typical conical narrowing of the lower end of the esophagus.

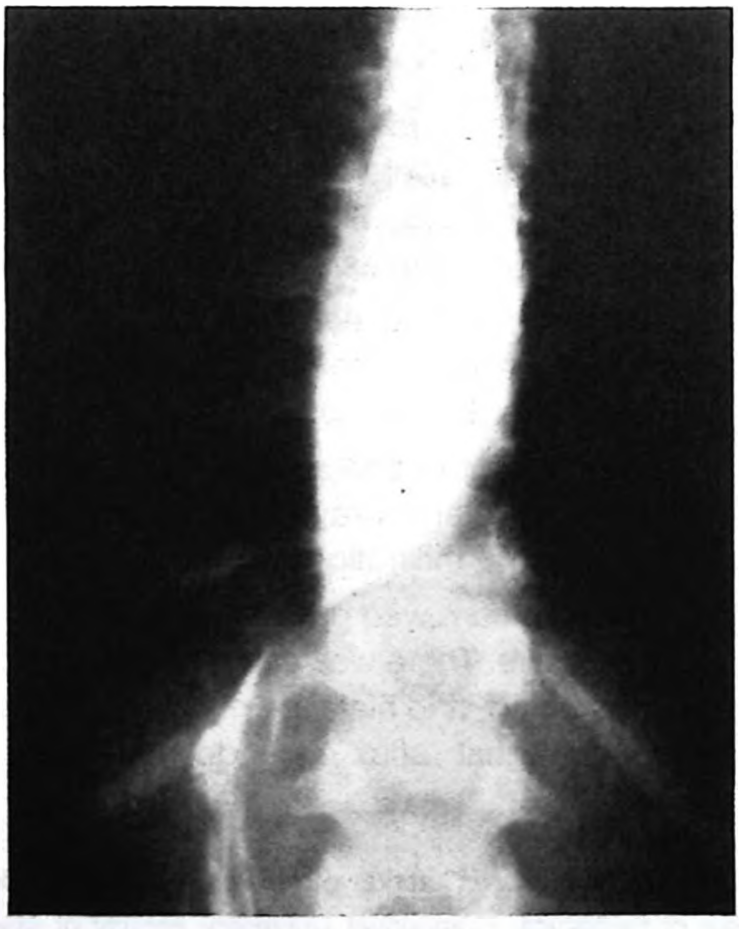

Fig. 2: A barium swallow demonstrating the typical radiological appearance of the esophagus in achalasia.

During her hospitalization, antibiotics were administered for pneumonia and sinusitis. On the seventh day of her hospitalization, the pneumonia resolved and she was referred to the Department of Pediatric Surgery.

Cardiomyotomy combined with a floppy Nissen fundoplication was performed, dramatically relieving the patient's symptoms.

Discussion

Achalasia is usually characterised by loss of peristaltic contractions in the body of the esophagus, and the LES often has increased pressure. As the disease progresses, the esophagus becomes dilated[1], as in our patient.

The incidence of achalasia is estimated to be 0.5-1 per 100,000, with less than five percent of cases presenting in childhood[2,5]. The etiology of the condition is unknown, but selective impairment of the non-adrenergic non-cholinergic inhibitory nerves near the lower esophageal sphincter appears to play a role[6-8]. Ganglion cells are absent from the myenteric plexus in some patients. total absence of ganglion cells in the distal esophagus has been reported in more than 90 percent of patients with achalasia, and denervation of the proximal stomach in half[9].

Familial glucocorticoid deficiency associated with achalasia of the cardia and deficient tear production were described in 1978 by Allogrove et al[10]. This state has been termed "3 A syndrome". Since then there have been a number of reports, including a series of 35 children with achalasia of the cardia by Nihoul-Fekete et al[11]. They determined alacrima and cortisol deficiency in only one child, indicating that most children with achalasia have normal adrenal functions.

It has been reported that if achalasia is associated with absent tear secretion or any other neurological features, cortisol secretion should be tested. Our patient's neurological examination was normal, and there was no evidence of alacrima[12]; consequently, 3 A syndrome was ruled out. Two cases of achalasia secondary to encephalitis have been reported in Turkey[13].

Usually the onset of symptoms is gradual. The diagnosis should be considered in any child with difficulty in swallowing. Often dysphagia of solids occurs before that of liquids, and symptoms such as weight loss, vomiting, and aspiration pneumonia may not be present in the early stages of the disease[9]. Our patient suffered from vomiting at first, and had complaints of weight loss and aspiration pneumonia.

The diagnosis is usually made roentgenographically[2]. The use of barium is diagnostic in all patients, demonstrating the typical features of achalasia: dilated body of the esophagus, absence of normal peristalsis and the typical narrowing at the esophagogastric junction[1,2]. As seen in Figs. 1 and 2, all of the evidence was present in our patient's radiography.

Treatment of this disorder consists of disrupting the failure to relax by the LES[1,2]. Drugs such as nitrates or calcium antagonists, particularly nifedipine, cause a significant decrease in sphincter pressure and may produce immediate relief of symptoms. However, the effect is most often short-lived and rarely avoids the need for surgery[14,15].

In adults, pneumatic dilatation is the recommended initial treatment, while in children this technique has been less successful and surgery is the preferred option[11,16]. Our patient, whose general condition was good, was subjected to cardiomyotomy combined with a floppy Nissen fundoplication.

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FALSE ANEURYSM OF THE BRACHIAL ARTERY IN AN INFANT FOLLOWING ATTEMPTED VENIPUNCTURE*

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*Hasan Özen MD******

SUMMARY: Demircin M, Peker O, Tok M, Özen H. (Department of Thoracic and Cardiovascular Surgery, and Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). False aneurysm of the brachial artery in an infant following attempted venipuncture. Turk J Pediatr 1996; 38: 389-391.

False aneurysms have rarely been described in the pediatric age-group. Here a case of false aneurysm of the brachial artery following accidental arterial puncture at the site of attempted venipuncture is reported. Having obtained vascular control with digital compression, the arterial repair was performed by direct suture technique. The characteristics and differential diagnosis of false aneurysms are described. The majority of false aneurysms occur as complications of percutaneous catheterization. *Key words: false aneurysm, brachial artery, venipuncture, infant.*

An aneurysm is classified as "true" or "false" according to its cause and the composition of its surrounding wall. A false or pseudoaneurysm is bounded only by fibrous tissue and lacks muscular layers[1-4]. False aneurysms are most frequently the result of penetrating or blunt trauma. They are usually at the site of puncture as a complication of percutaneous arterial catheterization. A pulsating, encapsulated hematoma is in communication with a ruptured artery in a false aneurysm[1,2].

False aneurysms have rarely been described in infants. We report here a case of false aneurysm involving the brachial artery of an infant following accidental puncture during attempted venipuncture.

Case Report

A two-month-old male infant was first sent to the pediatric gastroenterology department with jaundice, ascites, a mass in the left antecubital fossa, and hepatosplenomegaly. At the site of venipuncture performed at another hospital,

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there were signs of prolonged bleeding. Probably due to iatrogenic arterial puncture at that time, a pulsatile mass had developed over a three-week period. The prothrombin time was 17 seconds and continuing bleeding was observed at the site of bone marrow aspiration. The patient was diagnosed with Niemann-Pick disease.

Examination revealed a pulsatile mass, 5 cm in diameter, in the left antecubital fossa. No bruit was present. A diagnosis of false aneurysm of the brachial artery was considered (Fig. 1).

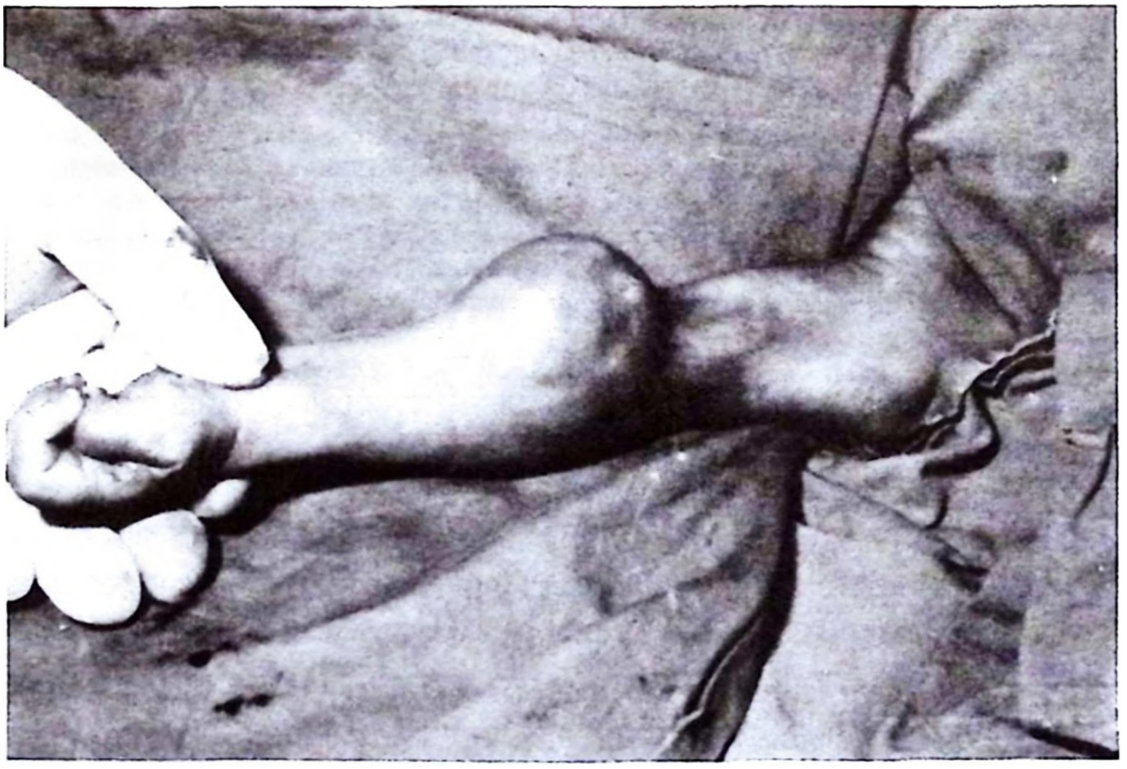

Fig. 1: False aneurysm of the left brachial artery.

Exploration was performed under general anesthesia. Vascular control was obtained with digital compression. The false aneurysm sac was evacuated, and a 1.5 mm defect in the arterial wall was repaired by three interrupted direct sutures with 7-0 prolene. Culture of the clot was sterile, and the postoperative course was uncomplicated. The radial pulse remained palpable. The wound healed satisfactorily and the patient was discharged on the third postoperative day.

Discussion

Arterial false aneurysm is a rare complication of iatrogenic arterial puncture and is manifested most frequently as a rapidly growing pulsatile mass[1,2]. The majority of false aneurysms requiring surgery occur as complications of percutaneous catheterization, and faulty technique has been blamed. Peripheral arteries are more commonly injured than truncal arteries because they are more superficial.

False aneurysms typically present weeks to months after blunt or penetrating trauma[1-3, 5]. In our patient, false aneurysm developed approximately three weeks after prolonged bleeding from the vascular puncture site.

False aneurysms complicate 0.6 percent of diagnostic cardiac catheterizations and 11.5 percent of intra-aortic balloon placements[2]. A review of the literature revealed very few cases of false aneurysms in the pediatric age-range[1]. Our case is the youngest patient with a false aneurysm according to previously reported literature findings.

The presenting signs and symptoms of false aneurysms may include neuropathy from pressure on an adjacent nerve, rupture and hemorrhage, and distal vascular insufficiency[1]. Other causes of a mass in an area of previous trauma include a retained foreign body, abscess formation, or an infected hematoma[1, 2]. The diagnosis of brachial artery false aneurysm is suggested by a history of vascular puncture followed by pain and the appearance of a mass with poorly defined borders.

Attempted drainage or biopsy is strongly contraindicated. Preoperative arteriography may confirm the diagnosis and localizes the lesion. Ultrasonography also demonstrates these lesions accurately.

The risk of pressure to adjacent structures and that of external rupture necessitates an urgent surgical approach to false aneurysms of the brachial artery. Having obtained vascular control, the false aneurysm sac is evacuated and arterial repair is performed by direct suture, end-to-end anastomosis or insertion of a patch or tubular graft of autologous vein, depending on the size of the defect. We performed direct suture technique in our patient[1, 4, 6].

Exploration for a retained foreign body must be done at the time of repair of a false aneurysm caused by a penetrating injury. An abscess or infected hematoma produces a slow-growing, warm, tender but nonpulsatile mass[1]. Although unusual in children, a false aneurysm must be considered when a pulsatile mass develops in an area of recent trauma.

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SIRENOMELIA IN AN INFANT OF A DIABETIC MOTHER*

A Case Report

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SUMMARY: Gürakan B, Karaaslan E, Balcı S. (Social Security Maternity Hospital, Ankara, Turkey). Sirenomelia in an infant of a diabetic mother: a case report. Turk J Pediatr 1986; 38: 393-397.

Sirenomelia is a rare fatal condition characterized by fusion of the lower limbs. Its etiology is unknown. It is believed that there is a connection between sirenomelia and maternal diabetes but this association has not been firmly established. Here a case of a sirenomeliform infant born to a diabetic mother is reported. *Key words: diabetic mother, sirenomelia.*

The characteristic feature of sirenomelia is fusion of the lower extremities. The most common associated anomalies are the absence of the sacrum and other defects of the vertabrae; imperforate anus and absence of the rectum; absence of external and internal genitalia; and renal agenesis and absence of the bladder[1].

Sirenomelia is a rare congenital malformation with an estimated incidence of one in 60,000 births[2]. This defect is also accepted to be the most severe form of caudal regression syndrome (CRS), which is known to be frequently associated with maternal diabetes. As a result, the association between maternal diabetes and sirenomelia may be expected; however, there are only a few reported cases of sirenomelia as the product of a diabetic pregnancy. Here an additional case is detailed to emphasize the connection between sirenomelia and maternal diabetes.

Case Report

This investigation focused on the seventh pregnancy of a 31-year-old woman who had an eight-year history of diabetes mellitus (para 3, abortus 4). Her diabetes had reportedly been controlled satisfactorily by oral antidiabetics. During her pregnancies, however, she had been treated with insulin. Her father was also diabetic, but there was no family history of neonatal deaths or anomalies of the limbs.

Her first child, who was apparently normal, died because of gastroenteritis when he was three months old. Among the remaining pregnancies, the only surviving child, born from her fourth pregnancy, was seven years old as of this writing and had club foot deformity.

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In the fifth month of her last pregnancy, the mother was informed by her doctor that oligohydramnios was present and the fetus was likely to be anomalous. Termination of pregnancy was recommended, but the patient refused. Three months later she was admitted to our hospital, and in the 38th week of gestation a sirenomeliform infant was delivered by cesarean section because of fetal distress. Oligohydramnios was confirmed.

The infant was 2400 g in weight and 46 cm in length. The lower extremities were fused to the level of the heels (Fig. 1). The feet were separated and rotated laterally. Each foot had five toes. There were no external genitalia or urinary tract orifice, and the anus was imperforate. The upper limbs, chest and abdomen showed no evidence of malformation. Low-set ears, a flat nose and prominent epicanthal folds compatible with "Potter's facies" were present.

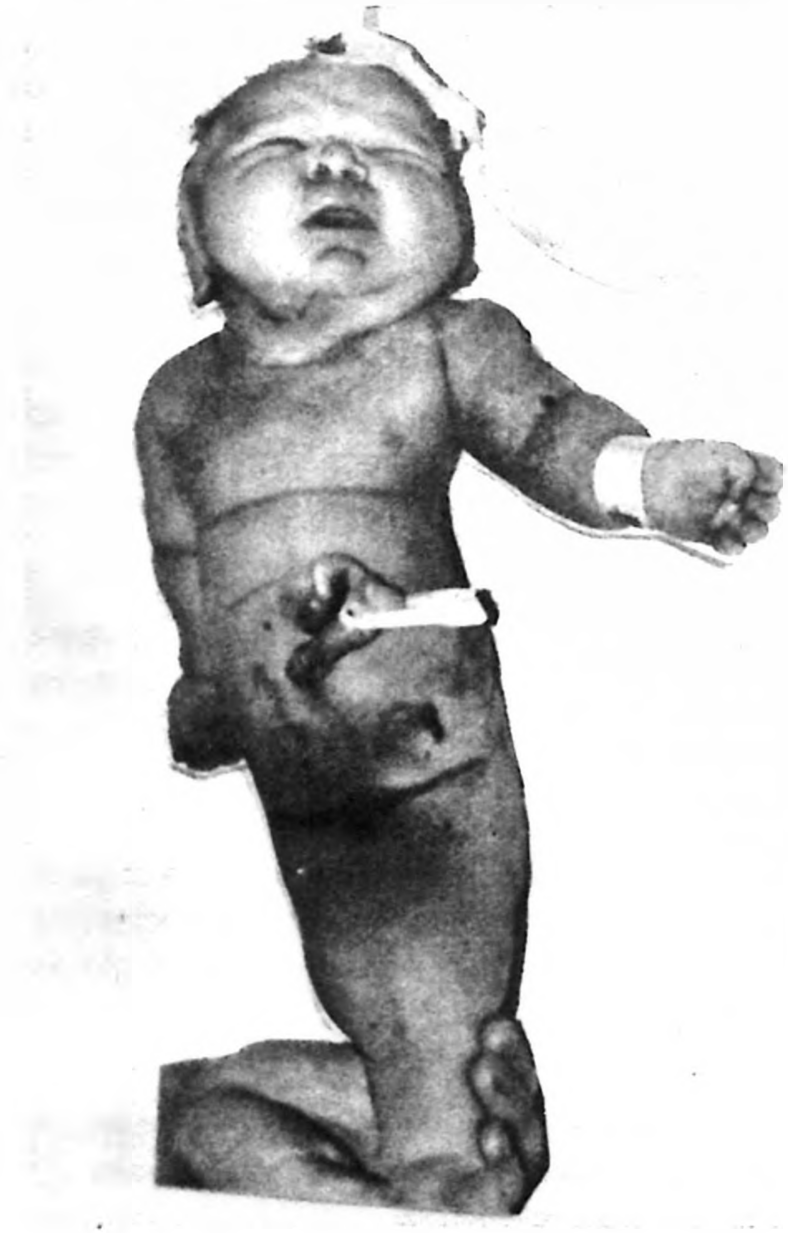

Fig. 1: Anterior aspect of the sirenomelic infant. No external genitalia are present.

X-ray studies demonstrated no abnormalities in the upper limbs, head or trunk. In the caudal region, the sacrum was absent and the pubis was represented by a fused midline bone. Both femurs and tibias were present, but there was only one fibula in the midline between the tibias (Fig. 2).

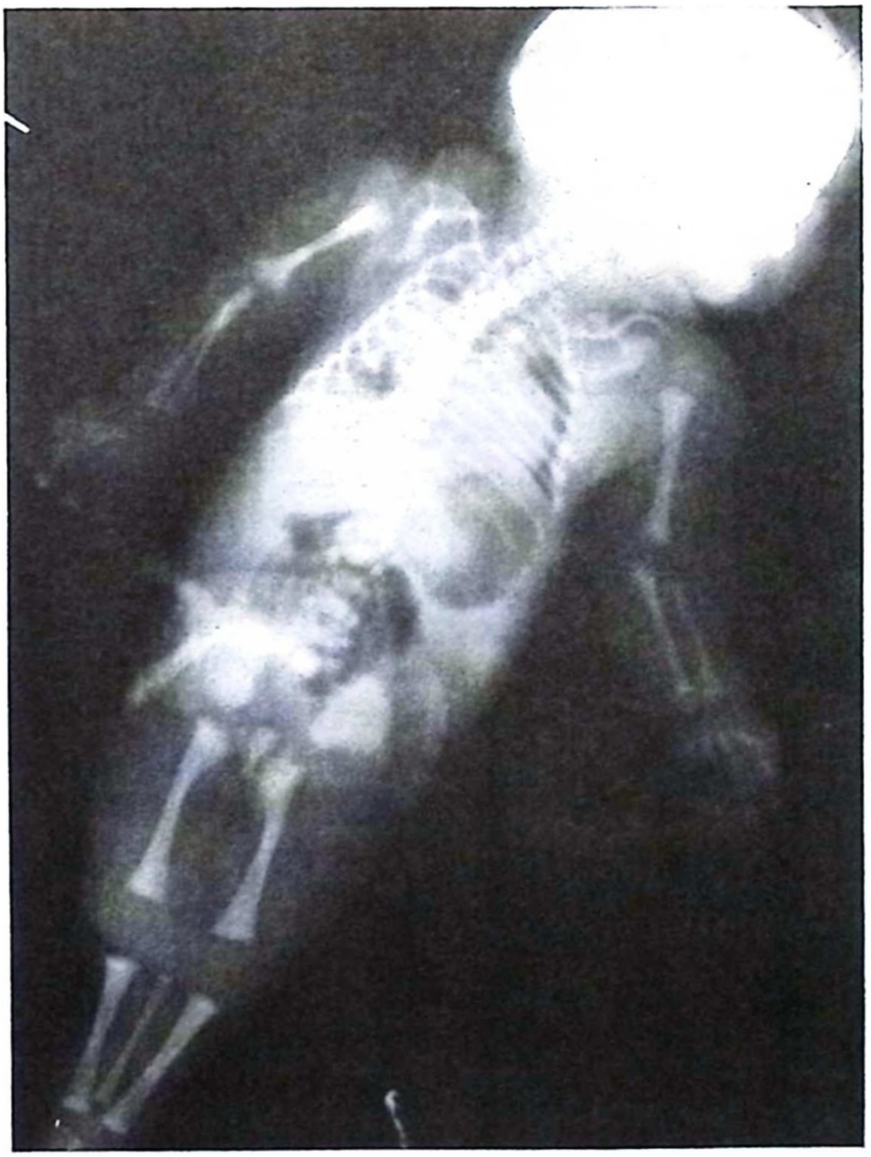

Fig. 2: Antero-posterior radiograph of the infant.

The baby was in respiratory distress and survived only six hours. Unfortunately, the parents refused postmortem examination.

Discussion

The precise cause of sirenomelia is still unclear. Associated conditions have led to speculation regarding its etiology. Intrauterine forces causing pressure on the tail end of the embryo, primary failure of development of the caudal somites, and nutritional deficiency of the lower part of the body have been suggested as pathogenetic mechanisms.

The nutritional deficiency theory, supported by Kampmeimer[3] and later by Stevenson, et al.[4] has been most widely accepted. According to Stevenson, et al.[4] defects found in sirenomelia can be explained by a vascular steal produced by a single, anomalous umbilical artery, Whether this vascular morphology is the consequence or the casuse of the caudal maldevelopment remains unproven[5].

Various combinations of cranial abnormalities and sirenomelia have been reported. Russel et al.[6] tried to explain the association between cephalic defects and caudal regression anomalad, by a generalized disturbance in cell migration from the primitive streak with secondary damage to the cranial and caudal mesodermal masses. Chondebois and Brunet[7] hypothesized that the speeding-up of autonomous differentiation in the notochord anlage caused malformations in both regions.

An additional and significant factor providing insight into the etiology has been the increased incidence of sirenomelia in twins. In eight to 15 percent of cases, sirenomelic births have been reported as the products of monozygotic twin pregnancies[8]. This association led to the suggestion that the process of monozygotic twinning can cause sirenomelia by interfering with the determination or differentiation of caudal embryonic structures[8, 9].

Sirenomelia is generally accepted as constituting the most severe end of the spectrum of CRS[2, 10]. The frequent observation of CRS among the offspring of diabetic mothers strongly suggests that maternal diabetes plays an important role in the pathogenesis of these malformations[11]. This relationship, however, has not been established in sirenomeliform infants. maternal diabetes was associated with only two of the 80 cases of sirenomelia reviewed in a 1987 study[12]. The low incidence of sirenomelia among pregnancies of diabetics may be explained by the effects of separate nondiabetogenic genes, as hypothesized for CRS. From another point of view, the teratogenic effect of diabetes differs from that of other known teratogens, in that it has no specific phenotypic expression. Many of the defects that are common in the general population occur at increased rates in infants of diabetic mothers. Although anomalies such as sacral dysgenesis carry a high risk in diabetic pregnancies, their actual incidence may be very low as they are extremely rare in the general population[13]. Indeed, among more than 50.000 births that took place in this maternity hospital during the last four years, sirenomelia was observed only once, and this was in the infant of a diabetic mother.

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