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ORIGINAL ARTICLE

CASE REPORTS

The Turkish Journal of Pediatrics 1999; 41: 287-297 *Original*

RESULTS OF THE TURKISH CONGENITAL MALFORMATION SURVEY*

*Ergül Tunçbilek MD**, Koray Boduroğlu MD***, Mehmet Alikaşifoğlu MD, PhD*****

SUMMARY: Tunçbilek E, Boduroğlu K, Alikaşifoğlu M. (Clinical Genetics Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Results of the Turkish congenital malformation survey. Turk J Pediatr 1999; 41: 287-297.

In order to acquire data about the incidence of congenital malformations in the Turkish population, we recorded all livebirths and stillbirths at 22 university hospitals between July 1993-July 1994. Congenital malformation incidence was 3.65 percent. Incidence of individual malformations were compatible with that reported from other populations, with the exception of neural tube defects and cleft palate which were found to be significantly frequent. Abnormal ultrasonographic findings and disorders such as hypertension, diabetes mellitus and vaginal bleeding during pregnancy were found to be valuable indicators for the presence of congenital malformations in the fetus. Incidence of congenital malformations was lower in the western Anatolian region. Variables such as maternal age, education and employment were found to be risk factors for congenital malformations. *Key words: congenital malformations, ultrasonography, prenatal diagnosis, neural tube defects, abnormal pregnancy.*

Congenital malformations are important causes of mortality and morbidity in infancy and childhood. Once detected no satisfactory treatment methods are available for some of these malformations. Both genetic and environmental factors are implicated in the etiology, leading to a variation in incidence of congenital malformations in different populations. A common congenital malformation in a given population is not necessarily frequent in another one.

Programs for prevention of congenital malformations have been launched in different countries in recent years. Naturally, priority is given to the most common malformation in each country. Congenital malformation surveillance studies that have been ongoing since the early 1980's in Europe have disclosed the most frequent malformations in each registry[1]. Results gave inspiration for the establishment of preventive programs.

No data is available on the incidence of congenital malformations in Turkey since the 1969 study by Say et al.[2] in a maternity hospital. Many factors contributing to the incidence of congenital malformations may have changed since then.

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We report the results of a congenital malformation survey conducted at 22 centers from different regions of Turkey between July 1993-June 1994.

Material and Methods

The study began on 1 July 1993. During the preceding two months a pilot study was done to assess the suitability and clarity of the questionnaire and ability of interviewers to collect accurate information from the mothers. This pilot study showed that the interviewers at Hacettepe University could successfully gather data using the questionnaire. Consequently, one interviewer from each center was invited to the registry center for a one-day course on how to collect data, including criteria for exclusion from the study group. The query form was prepared to obtain data about the following topics: a) social and cultural status of the mother, b) history and outcomes of previous pregnancies, c) history of the current pregnancy, d) family history and e) product of the current pregnancy. The interviewer was the pediatrician of each center who attended the training course. Records for each case were transmitted on a standard form to the registry center at Hacettepe University for processing.

All births in obstetrics and gynecology departments at all (22) university hospitals in Turkey between 1 July 1993-31 June 1994 were recorded. Each hospital was from one of five geographical regions (north, east, south, west and central) of Turkey. Distribution of cases by geographical region was made on the basis of the mother's residence, not according to the region in which the hospital of birth was located. Thus, this study was a hospital-based study analyzed according to mother's residence.

Stillbirths and abortions weighing less than 500 g or of less than 20 weeks of gestational age were excluded. Each newborn was examined by a pediatrician for identification of birth defects. A routine physical examination was performed, and weight, height and head circumference measurements were obtained for all newborns. All participating registries used the common coding system of the 10th revision of the International Classification of Diseases (ICD-10)[3] for definition of congenital anomalies. Malformations were classified by organ system according to the ICD-10.

Results

Of 21,907 babies included in the study 11,238 (51.3%) were male and 10,669 (48.7%) female. Stillbirths were recorded at 2.18 percent. Of these, 96.2 percent were singletons and 3.8 percent were multiple.

In the study population, 84 percent of mothers were between 20-35 years of age. Only seven percent were below 20 and nine percent above 35. Distribution

of newborns by maternal education and maternal employment showed that most were born to unemployed but well educated women. Only 5.7 percent of mothers were illiterate, and 72 percent were housewives (Table I).

Table I: Distribution of Cases by Maternal Education and Employment

Education of Mother	%	n
Illiterate	5.7	1208
Primary incomplete	2.1	447
Primary graduate	39.7	8477
Secondary graduate	34.6	7393
High school graduate	17.9	3835
Employment		
Housewife	72.4	15339
Working without salary	1.2	256
Working with salary	26.4	5592

Estimation of infant, child and under-five mortality rates using the preceding birth history revealed that the mothers in the study group had higher risks than those in the general Turkish population (Table II). Estimated infant mortality rate was 89.6 percent. According to the results of the "Turkish Demographic and Health Survey (1993)", the infant mortality rate was 53 per 1,000 in Turkey[4].

Table II: Predicted Rates of Infant, Child and Under-five Mortality Using the Preceding Birth History (per thousand)

Sex	Infant Mortality Rate	Child Mortality Rate	Under-Five Mortality Rate
Male	101.8	29.7	128.5
Female	74.5	23.3	96.1
Total	89.6	27.5	114.6

All mothers were asked regarding complications during pregnancy, with special emphasis on hypertension, diabetes mellitus, vaginal bleeding, abortus imminens or incipiens, anemia, eclampsia or preeclampsia. Mothers with any one of these diseases were included in the group of "pregnancy with an abnormal finding". The frequency of congenital malformations in the "abnormal pregnancy" group was 3.8 percent versus only 1.5 percent in the group without abnormal findings (Table III).

Mothers were also asked if an obstetrical ultrasonography (USG) was performed in the course of this pregnancy. Of the 18,144 mothers who had an ultrasonographic examination, 885 (4.8%) were found to have an abnormal ultrasonographic finding; the remainder were normal. Among the babies born

to a mother with an abnormal obstetric USG, 10.5 percent had a congenital malformation. Only 1.4 percent of women with a normal obstetric USG had a baby with a congenital malformation (Table IV).

Table III: Frequency of Congenital Malformations in Babies of Women With and Without Abnormal Findings During Pregnancy (by Region)

	Congenital Malformation Frequency in Pregnancies with Findings			
	Abnormal		Normal	
Region	N	%	N	%
West	24	*4.0	47	1.0
South	10	**3.8	32	1.9
Central	45	*3.1	118	1.8
North	11	4.3	15	2.2
East	27	*5.3	52	1.4
Total	117	*3.8	264	1.5

The difference between congenital malformation frequency in pregnancies with and without abnormal findings was found to be statistically significant, (*) $p < 0.001$ and (**) $p < 0.05$, in all geographic regions with the exception of the northern region.

Table IV: Frequency of Congenital Malformations in Babies of Women With Abnormal and Normal Ultrasonographic (USG) Findings During Pregnancy

	Congenital Malformation Frequency in Pregnancies with			
	USG Abnormal		USG Normal	
Region	N	%	N	%
West	17	*8.6	49	1.0
South	6	*9.0	31	1.9
Central	45	*11.1	105	1.5
North	10	*16.4	15	1.9
East	15	*9.8	47	1.6
Total	93	*10.5	247	1.4

The difference between congenital malformation frequency in pregnancies with and without abnormal ultrasonographic findings was found to be statistically significant, (*) $p < 0.001$, in all geographic regions.

Incidence of congenital malformations was 3.65 percent in this study. A male preponderance was observed among malformed newborns, with 54 percent of malformations in boys. Distribution of congenital malformations according to organ system is listed in Table V. Comparison of the results with those of the previous Turkish study and with medical literature is also provided.

Table V: Distribution of Malformations by Organ System

ICD10 Code	Malformation	No. Case	Incidence %0.	Literature %0.	Prev. Study %0.
81.0	Epidermolysis bullosa	6	0.27		
18.0	Hemangioma	13	0.59	62	
	Others	5			
	Total Skin	24	1.09		
00.0	Anencephaly	24			
0.1	Encephalocele	6			
			3.0	1.0	1.2
01.1	Nasal encephalocele	7			
05.0	Spina bifida (meningocele, myelocele, meningomyelocele)	29			
03.0	Congenital hydrocephaly	22	1.0	0.4	0.87
	Others	11			
	Total Central Nervous System	99	4.51		
02.0	Microcephaly	21			
75.3	Macrocephaly	26			
	Others	50			
	Total Head-Neck	97	4.42		
11.2	Microphthalmia	5			
12.0	Congenital cataract	1			
13.3	Congenital corneal opacity	3			
	Others	49			
	Total Eye	58	2.64		
16.1	Congenital absence/atresia of the external auditory canal	1			
17.1	Macrotia	1			
17.2	Microtia	5			
30.0	Choanal atresia	1			
35.0	Cleft palate	17	0.77	0.4	0.3
36.0	Cleft lip	17	0.77	1	0.4
37.0	Cleft lip and palate	21	0.95	1	0.4
	Others	70			
	Total Otorhinolaryngeal	133	6.07		
39.1	Tracheoesophageal fistula and esophagus atresia	3	0.13	0.3	0.1
42.3	Imperforate anus	8	0.3	0.2	1.1
79.2	Omphalocele	5	0.22	0.2	
79.3	Gastroschisis	2	0.09	0.1	
	Others	17			
	Total Gastrointestinal System	35	1.59		
21.0	Ventricular septal defect	14			
21.1	Atrial septal defect	12			
	Others	15			
	Total Cardiovascular System	41	1.87	8	1.7
67.6	Pectus excavatum	6			
67.7	Pectus carinatum	8			
83.3	Accessory nipple	1			
	Others	3			
	Total Respiratory System	18	0.82		
52.5	Labial fusion	2			
53.1	Cryptorchidism (unilateral)	9			
			1.9	30	4.2
53.2	Cryptorchidism (bilateral)	33			

Table V: Distribution of Malformation by Organ System (Continued)

ICD10 Code	Malformation	No. Case	Incidence %0.	Literature %0.	Prev. Study %0.
54.0	Hypospadias	37	1.6	0.8-8	2.6
64.0	Epispadias	3			
56.4	Genital ambiguity	13	0.5		0.2
	Others	25			
	Total Genitourinary	122	5.56		
65.0	Congenital hip dislocation (unilateral)	6			
			0.5	1	1.4
65.1	Congenital hip dislocation (bilateral)	6			
66.7	Pes cavus	5			
66.8	Pes equinovarus	43	1.9		2
67.5	Congenital scoliosis	2			
69.0	Polydactyly	17	0.77	0.3-1.5	2.6
70.0	Syndactyly	10	0.45	0.3	1.3
70.4	Polysyndactyly	6	0.27		
	Others	29			
	Total Skeleton-Musde	124	5.66		
	Total Unclassified	20	0.91		
90.0	Down syndrome	27	1.2	1.2-1.6	0.7
91.0	Trisomy 18	1			
96.4	Turner syndrome	1			
	Total Chromosomal Abnormality	29	1.32		
	Total	800	36.5	20-32	

Incidence of congenital malformations was significantly lower in the western Anatolian region, the most developed part of the country. There was no statistically significant difference between the other geographic regions. Regional distribution of malformations is shown in Table VI.

Table VI: Distribution of Malformations by Regions

	Malformation				
	+		-		
Region	n	%	n	%	Total
West	154	2.7	5507	97.3	5661
South	70	3.6	1855	96.4	1925
Central	313	3.7	8069	96.3	8382
North	38	4.0	909	96.0	947
East	176	3.8	4503	96.2	4679
Subtotal	751	3.5	20843	96.5	21594
Not recorded*	49	15.7	264	84.3	313
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference of incidence in the west is significant, ($p < 0.001$); that between the other regions is not significant.

Malformation incidence was significantly higher in the babies of mothers older than 35 years of age ($p < 0.001$). The group of those less than 18 years had the lowest congenital malformation incidence ($p < 0.05$). Table VII shows the distribution of malformations by maternal age.

Table VII: Distribution of Malformations by Maternal Age

	Malformation				
	+		−		
Maternal Age	n	%	n	%	Total
< 19	14	1.9	735	98.1	749
19-34	625	3.3	18357	96.7	18982
35+	132	7.0	1777	93.0	1909
Total	**771**	**3.6**	**20869**	**96.4**	**21640**
Not recorded*	29	10.9	238	89.1	267
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference of 35+ group is statistically significant, ($p < 0.001$). When this group is excluded, the difference between the other two groups is also significant, ($p < 0.05$).

Illiteracy of the mother was closely related with malformations (Table VIII): 9.3 percent of illiterate mothers had a malformed child ($p < 0.001$). Congenital malformation incidence was found to be highest in babies born by operational delivery (forceps, vacuum extraction, etc.) or cesarean section. We observed that fetuses with congenital malformation were more likely to have a presentation other than vertex. Babies with vertex presentation and breech presentation had significantly different incidences of congenital malformations, at 3.1 and 8 percent, respectively.

Table VIII: Distribution of Malformations by Maternal Education

	Malformation				
	+		−		
Education of Mother	n	%	n	%	Total
Illiterate	112	9.3	1096	90.7	1208
Primary incomplete	16	3.6	431	96.4	447
Primary graduate	321	3.8	8167	96.2	8488
Secondary graduate	215	2.9	7200	97.1	7415
High school graduate	89	2.3	3754	97.7	3843
Total	**753**	**3.5**	**20648**	**96.5**	**21401**
Not recorded*	47	9.3	459	90.7	506
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference between the groups is statistically significant ($p < 0.001$). The illiterate mothers' group is different. When this group is excluded, the primary in complete and graduate groups are also found to be different, ($p < 0.05$).

As expected, congenital malformations were significantly frequent in the stillbirth and perinatal death groups in comparison to livebirths (Table IX).

Table IX: Distribution of Malformations by the Outcome of the Pregnancy

	Malformation				
	+		−		
Outcome	n	%	n	%	Total
Livebirth	567	2.7	20477	97.3	21044
Stillbirth	123	25.9	355	74.1	478
Perinatal death	72	40.7	105	59.3	177
Total	762	3.5	20937	96.5	21699
Not recorded*	38	18.3	170	81.7	208
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference between the groups is statistically significant, ($p < 0.001$). The perinatal death group is different. When this group is excluded, the stillbirth group is also found to be different, ($p < 0.001$).

Discussion

The present study was based on a study population defined by the residence of the mother who delivered a child in one of the 22 university hospitals between July 1993-July 1994. Thus, this is a hospital-based study analyzed according to mother's residence. While results of this study may not be comparable with the previous Turkish studies because of different ascertainment methods, we believe they give a better idea about the prevalence of congenital malformations in the different geographical regions of Turkey. In contrast to the previous surveys[2,5] which were based on the registration of congenital malformations at a single hospital, our study included all malformed babies from 22 centers dispersed throughout the country.

Evaluation of the mothers in the study population showed that they had a higher social and cultural level than those in the general Turkish population. This might lead to a bias and an incorrect estimation of a low prevalence of congenital malformations, since it is known that environmental factors related to poor social and cultural status impact the occurrence of birth defects. However, these women also had higher infant, child and under-five mortality rates than Turkish women in the general population, which might have led them to choose university hospitals for prenatal care and delivery of their baby. Higher mortality rates estimated with the preceding birth history make the mothers in the study a high risk population for congenital anomalies, again leading to another bias. Induced abortions after prenatal diagnosis were impossible to ascertain for lack of data and were not registered in this study.

Actually, if therapeutic abortions had been recorded, the prevalence of congenital malformations in this study would have been higher. Despite all the mentioned methodological issues, we believe that this is the best possible study that can be done in Turkey, if one keeps in mind that only 60 percent of all births take place in a health department and still a great majority of them are not registered[4]. We compared the incidence of certain malformations with the results of the previous Turkish study[2] and those provided in the medical literature. While many of them had similar incidences, some showed significant differences. One obvious difference is in the frequency of neural tube defects (NTDs) in Turkey and in Europe. When compared with the EUROCAT registries, Turkey has a very high prevalence rate of NTD (30/10,000). Within Europe, diversity in the epidemiology of NTDs was observed. The prevalence was much higher in the British Isles than in continental Europe in the early 1980's[6]. Periconceptional use of folic acid by women of childbearing age lowered the prevalence of NTDs significantly in England and Ireland. The decreasing trend in the prevalence rate of NTDs confirms the impact of environmental factors, especially folic acid, on the etiology of neural tube defects. In Turkey, prevalence of NTDs is very high when compared to Europe. Maternal illiteracy, maternal advanced age and residence in either the northern or eastern regions of Turkey are shown to be risk factors for having a baby with a NTD. Women who live in western Anatolia, have graduated from a high school or university, and are below 35 years of age are less likely to have an offspring with a NTD. Lower social and economic status may correlate with the lesser consumption of folic acid and other environmental factors. We believe that this is the more likely explanation for the high frequency of NTDs in Turkey.

Cleft palate incidence was two times higher in our study than in the previous Turkish study and medical literature, but cleft lip with/without cleft palate was not significantly different. We know that cleft palate is related to maternal smoking habits and folate intake[7]. Folate intake is also closely related with the prevalence of neural tube defects as mentioned previously.

Incidence of gastrointestinal malformations such as imperforate anus, omphalocele and gastroschisis in our study was very close to that reported in the literature[8]. Tracheoesophageal fistula was three times lower in both the current and previous Turkish studies, probably due to the difficulty of identifying the malformation in the early neonatal period.

Cardiovascular system (CVS) malformations, congenital hip dislocation and cryptorchidism were found to be less frequent in our study than in medical literature[1,9]. Hemangiomas were also very rare[8].

We think that the malformations found to be infrequent in this study were not easy to identify on the physical examination just after birth (e.g. CVS malformations). We believe that some other malformations are undiagnosed by the physician, incorrectly appearing to be infrequent in our study.

In this study, incidence for all malformations was 36.5 per 1,000. Previously, congenital malformation incidence has been reported as 20-32 per 1,000 in various studies[1,9]. Since we did not know which malformations were included in the literature available, we decided to take all detected malformations into consideration in this study. However, comparison of the incidence of every single malformation with, that reported in literature showed no significant differences except concerning incidence of neural tube defects and cleft palate. Thus, the difference of the included malformations might account for the difference between the incidences observed in the current study and those found in the literature. Analysis of the data showed that congenital malformations were more frequent in the babies of mothers who were illiterate and older than 35 years of age. In a Utah study[10], congenital malformations were also found to be more frequent in babies born to illiterate mothers.

Babies who presented other than vertex and were born by operational delivery or cesarean section had a higher incidence of congenital malformations. High incidence in operational delivery may be explained by the fact that obstetricians preferred interfering with the normal process of labor when they observed that the fetus was malformed.

In this study, congenital malformation incidence was significantly higher among those pregnancies in which an ultrasonographic abnormality was observed. This indicates that ultrasonography is a very valuable tool for the prenatal diagnosis of malformations. However, many babies with ultrasonographically recognizable malformations were born even though an ultrasonography had been performed early in those pregnancies. While ultrasonography is a valuable diagnostic tool for prenatal detection of congenital malformations, it may fail unless done by an expert. It can be concluded that a considerable amount of ultrasonographic examinations in this study were done by inexperienced medical staff.

High frequency of congenital malformations in babies of mothers with diabetes mellitus, eclampsia, preeclampsia or vaginal bleeding showed that these abnormalities might be indicators of birth defects during pregnancy.

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NEURAL TUBE DEFECTS IN TURKEY: PREVALENCE, DISTRIBUTION AND RISK FACTORS*

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SUMMARY: Tunçbilek E, Boduroğlu K, Alikaşifoğlu M. (Clinical Genetics Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neural tube defects in Turkey: prevalence, distribution and risk factors. Turk J Pediatr 1999; 41: 299-305.

The aim of the study was to determine the prevalence rate and risk factors relevant to neural tube defects (NTDs) in Turkey. All livebirths and stillbirths recorded at the university hospitals throughout Turkey between July 1993-June 1994 were evaluated with respect to congenital anomalies. For each birth, information was recorded about the child, the mother, the pregnancy and risk factors. A total of 66 cases with a NTD were recorded in 21,907 births. Prevalence rate of NTDs was 30.1 per 10,000 births. Of these 66 cases, 29 (43.9%) were male and 37 (56.1%) female. Female/male ratio was 1.27. The ratio of spina bifida/anencephaly is 1.20 for Turkey. Maternal illiteracy, maternal advanced age and residence in northern or eastern regions of Turkey are shown to be risk factors for having a baby with a NTD. The prevalence rate of NTDs is very high for Turkey. Geographical distribution of NTDs in this country confirms a relationship between the socioeconomic status and environmental factors for the development of a NTD. The results of this study point to the importance establishing a health policy to prevent neural tube defects in Turkey. *Key words: neural tube defects, prevalence, risk factors, Turkey.*

Neural tube defects (NTDs) are one of the most severe of all congenital anomalies. Epidemiological data have shown that NTDs have regional variations in prevalence rate[1]. Unfortunately, Turkey is one of the countries for which data about the prevalence of this severe congenital malformation is missing. Since there is no registry system for births in Turkey, and only 60 percent of all births occur at a health center[2], registration of congenital anomalies has not been possible thus far.

As a part of a program to register congenital anomalies in Turkey (The Turkish Congenital Malformatilon Survey)[3] 66 cases of NTDs were recorded among 21,907 births between July 1993-June 1994. Regional variation in the prevalence rates and risk factors of NTD have been evaluated.

Material and Methods

The study began on 1 July 1993. During the preceding two months, a pilot study was done to assess the suitability and clarity of the questionnaire and ability of interviewers to collect accurate information from the mothers. This pilot study

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showed that the interviewers at Hacettepe University could ensure accurate recording of data on the questionnaire. Consequently, one interviewer from each center was invited to the registry center for a one-day course on presenting the questionnaire, including criteria for exclusion from the study group. The query form was prepared to obtain data on the following topics: a) social and cultural status of the mother, b) history and outcomes of previous pregnancies, c) history of the current pregnancy, d) family history and, e) product of the current pregnancy. The interviewer at each center was the pediatrician who had been trained at the course previously. Records for each case were transmitted on a standard form to the registry center at Hacettepe University for processing.

All births in obstetrics and gynecology departments at all (22) university hospitals in Turkey between 1 July 1993-31 June 1994 were recorded. Each hospital was from one of five geographical regions (north, east, south, west and central) of Turkey. Distribution of cases by geographical region was made on the basis of the mother's residence, not according to the region in which the hospital of birth was located. Thus, this study was a hospital-based study analyzed according to mothers residence.

Stillbirths and abortions weighing less than 500 g or of less than 20 weeks of gestational age were excluded. Each newborn was examined by a pediatrician for identification of birth defects. A routine physical examination was also performed with weight, height and head circumference measurements obtained for all newborns. All participating registries used the common coding system of the 10th revision of the International Classification of Diseases (ICD-10)[4] for definition of congenital anomalies. Malformations were classified by the organ systems according to the ICD-10.

Neural tube defects include anencephaly, encephalocele and spina bifida. The spina bifida group did not include spina bifida occulta or cases associated with anencephaly or encephalocele. Cases with the syndromic forms of NTDs, such as Meckel-Gruber syndrome, were also excluded.

Results

We observed that 84 percent of mothers in the study population were between 20-35 years of age, 50 percent graduated from secondary school or had a higher level of education, and 98 percent married after the age of 20. All these parameters show these mothers with a better social and cultural situation in comparison to the general Turkish population. However, estimated values of the infant mortality rate (89.6 per 1,000), childmortality rate (27.5 per 1,000) and under-five mortality rate (114.6 per 1,000) using preceding birth history demonstrate significantly higher rates for these mothers when compared with the rates of the Turkish population, which are 53, 9, and 61 per 1,000, respectively[2].

A total of 21,907 livebirths and stillbirths were examined, and 66 cases with neural tube defects were recorded. Prevalence rate of NTDs was 30.1 per 10,000 births. Of these 66 cases, 29 (43.9%) were male and 37 (56.1%) female. Female/male ratio was 1.27 for NTDs, 1.5 for anencephaly and 0.81 for spina bifida.

Distribution of the different types of NTDs was as follows: 29 (43.9%) cases with spina bifida, 24 (36.4%) cases with anencephaly and 13 (19.7 percent) cases with encephalocele. The ratio of spina bifida/anencephaly is 1.20 for Turkey, as it is in countries where the prevalence rate of NTDs is very high. Distribution of NTDs by geographical region is shown in Table I. Prevalence rate of NTD was higher in northern and eastern regions of Turkey, with the western region having the lowest prevalence rate. A Z-test was performed for all possible pairs. Differences between geographical regions were found to be significant when p value was < 0.01, except for the difference between prevalence rates for the northern and eastern regions, which was found to be statistically insignificant.

Table I: Distribution of NTDs in Turkey by Geographical Region

Region	Anencephaly	Spina Bifida	Encephalocele	NTD Total	Number of Cases Examined	Prevalence Rate (per 10,000) of NTDs
North	1	2	1	4	926	43.2
East	6	9	4	19	4179	45.4
South	1	2	2	5	1908	26.2
West	6	6	0	12	5523	21.7
Central	10	10	6	26	8141	31.9
Total	24	29	13	66	20677*	

* Data about the residence of the mother was not available for 1,230 cases.

Children born to mothers with a lower educational level are more likely to have NTDs than children of mothers with a higher education. Distribution of NTDs by maternal education is shown in Table II. Differences between all maternal education levels were found to be significant when p value was < 0.01 (Z-test). A child of an illiterate mother has a seven-times higher risk of having a NTD than a child of a mother with a high school education. The number of cases not completing primary school was small, which may explain the rather low prevalence rate in that group. When this group is excluded from the results, a steady decline is observed in the prevalence rate from the illiterate group to the high school graduate group.

None of the mothers of the NTD cases were older than 39. Below this age, increased maternal age is associated with a higher risk of having a child with a NTD. Distribution of NTDs is shown in Table III. Differences between all maternal age groups were found to be significant when p value was < 0.01 (Z-test).

Table II: Distribution of NTDs in Turkey by Maternal Education Geographical Region

Education of Mother	Anencephaly	Spina Bifida	Encephalocele	NTD Total	Number of Cases Examined	Prevalence Rate (per 10,000) of NTDs
Illiterate	5	5	1	11	1208	91.05
Primary incomplete	0	1	0	1	447	22.37
Primary graduate	13	10	6	29	8477	34.21
Secondary graduate	2	9	3	14	7393	18.92
High school graduate	2	1	2	5	3835	13.03
Total	22	26	12	60*	21360*	

* Data about maternal education was not available for 547 cases and 6 NTD patients.

Table III: Distribution of NTDs in Turkey by Maternal Age

Maternal Age	Anencephaly	Spina Bifida	Encephalocele	NTD Total	Number of Cases Examined	Prevalence Rate (per 10,000) of NTDs
19	0	2	0	2	1424	14.04
20-24	8	6	4	18	6623	27.17
25-29	9	11	4	24	7309	32.83
30-34	2	6	5	13	4373	29.27
35-39	5	4	0	9	1588	56.67
40-44	0	0	0	0	291	
45-49	0	0	0	0	30	
Total	24	29	13	66	21638*	

* Data about maternal age was not available for 269 cases.

Discussion

A few reports concerning neural tube defects have been published previously from Turkey[5-8]. All of them covered a population defined by the place of birth (hospital-based) and found a high prevalence of NTDs in their region. In some of these studies, assessment of the effects of the Chernobyl accident indicated a significant increase in the prevalence rate of NTDs after May 1986[5,6], whereas some others denied an increase due to this event[7,8].

The present study is also a hospital-based one, but it covers all five geographical regions of Turkey. Results of this study cannot really be compared with the previous Turkish studies because of the different methods used, but the study does provide a chance for comparison between the regions.

Evaluation of the mothers in the study population demonstrated a better social and cultural situation than found in the general Turkish population[2]. This might lead to a bias, and an estimation of a incorrect low prevalence rate of NTDs, since it is recognized that environmental factors related to poor social and cultural status impact the occurrence of this anomaly[9]. However, these women also had

higher infant, child and under-five mortality rates than Turkish women in the general population, causing them to choose university hospitals for prenatal care and delivery of their baby. Higher mortality rates estimated with the preceding birth history for the mothers in the study reveal a high risk population for congenital anomalies, again leading to a bias, although in the opposite direction. We assumed that the biases in opposite directions would minimize the deviating effect of both.

Induced abortions after prenatal diagnosis were not registered in this study. The rate of prenatal diagnosis might vary between different geographic populations, leading to a bias in the calculation of prevalence rates in different regions when livebirths and stillbirths are registered alone. However, prenatal diagnostic services were not in routine use in any regions of Turkey in 1993. Thus, we assumed that the lack of registration of induced abortions did not result in a difference of prevalence rates of NTDs between geographical regions.

When compared with the EUROCAT registries[10], Turkey has a very high prevalence rate of NTDs. Within Europe, contrasts in the epidemiology of NTDs are observed. The prevalence was much higher in the British Isles than in continental Europe in the early 1980's[1,10]. Periconceptional use of folic acid by women of childbearing age lowered the prevalence of NTDs significantly in England and Ireland[1]. The trend in the prevalence rate of NTDs confirms the impact of environmental factors, especially folic acid, on the etiology of neural tube defects. In Turkey, prevalence of NTDs is found to be very high when compared even with rates in the British Isles in the 1980's. The spina bifida/anencephaly ratio is low due to an increase of anencephaly cases when the prevalence rate of total NTDs is high in a geographical region[11]. An inverse relationship between the male preponderance and the prevalence of NTDs has also been suggested in different ethnic groups[11]. In this study, the spina bifida/anencephaly ratio was 1.20, very low when compared with the ratio (1.41) of 16 EUROCAT registries for 1990-1994[10]. The average male preponderance is 44 percent for all NTD cases, 33.3 percent for anencephaly cases and 55 percent for spina bifida cases. Consistency of our results with those of the EUROCAT study, particularly with the centers where the NTD prevalence is high, confirms the accuracy of this study. Each of the biases presumed to have effects on the results of this study is more likely to have a lowering impact on the prevalence rate of NTDs.

Recent studies have shown that periconceptional folic acid supplementation reduces a woman's risk of having a baby with neural tube defects[12]. It has been demonstrated that mothers of infants with a NTD have increased homocysteine levels[13,14]. Persons with a thermolabile form of the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) have reduced enzyme activity and increased plasma homocysteine which can be lowered by supplemental folic acid[15]. Thermolability of the enzyme has recently been shown to be caused by a common mutation (677C→T) in the MTHFR gene[15,16]. This is the first mutation shown in the etiology of NTDs.

One explanation for the high prevalence rate of NTDs in Turkey might be the high frequency of the mutated allele in the Turkish population. But, our recent studies on the role of the 677C→T mutation in the 5, 10 MTHFR gene did not show an increased frequency of the TT genotype in NTD cases when compared with the control group[17,18]. Variation in the distribution of NTDs by regions indicates contributing environmental factors.

Maternal illiteracy, maternal advanced age and residence in northern or eastern regions of Turkey are shown to be risk factors for having a baby with a NTD. Women living in western Anatolia who graduated from a high school or university and are below 35 years of age are less likely to have an offspring with a NTD. Lower socioeconomic status may correlate with a lesser consumption of folic acid and other environmental factors. We believe that this explanation for the high frequency of NTDs in Turkey is more likely. The eastern Anatolian region actually has the worst social, cultural and economic situation among the five geographic regions of Turkey[2]. The western region is the best. The geographical distribution of NTDs in Turkey confirms a relationship between the socioeconomic status and environmental factors for development of the NTD. The results of this study point to the importance of establishing a health policy in at least in two steps to avoid neural tube defects. First, establish a system to supply women of childbearing age with a 0.4 mg daily supplement of folic acid. Second, achieve use of prenatal diagnostic procedures nationwide for early diagnosis of NTDs in order to have the chance of managing the pregnancy properly. The trend in the prevalence rate of NTDs after establishment of this policy may indicate the need to discriminate between other environmental factors in Turkey.

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PSYCHIATRIC SYMPTOMS AMONG TURKISH ADOLESCENTS

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SUMMARY: Çuhadaroğlu F, Yazıcı KM. Psychiatric symptoms among Turkish Adolescents. Turk J Pediatr 1999; 41: 307-313.

This research was planned to investigate psychiatric symptoms in a normal adolescent population. Four hundred and thirty-four students were selected randomly from three schools of different socioeconomic status. Symptom Check List 90-R was used to evaluate the psychiatric symptoms. The results were analyzed considering the effects of age, gender and socioeconomic status. It was concluded that being female, 15-16 years of age and having a lower socioeconomic status are risk factors for developing psychiatric symptoms. *Key words: adolescence, psychiatry.*

Adolescence is a period of rapid changes in the psychological world of the individual which leads to frequent mood swings. These characteristics make adolescents more vulnerable and increase the risk of their developing psychiatric symptoms. This period has been a subject of interest for quite a number of researchers[1-9]. In Turkey, studies investigating normal adolescents and the psychopathologies of this period have been increasing in number. Some investigated the adaptational and social problems related to adolescents[10-15], while others studied the psychiatric symptoms seen in this period[16-23]. Most of these studies were done among university students. Studies related to younger adolescents covered either youngsters living in orphanages[22,23] or those who applied to cilincs with psychiatric symptoms[16]. One of the studies evaluating normal adolescents included only female high school students[17] and another was done in a high school where most of the children were from families of upper socioeconomic class[17]. To what extent these sample groups represent normal adolescents in the Turkish population is open to discussion. This research was planned to study the psychiatric symptoms in normal adolescent populations of three different socioeconomic status (upper, middle and lower) to obtain more valid results which could be generalized for Turkish adolescents. This paper presents the data related to the psychiatric symptoms seen among high school students and is a part of a larger project planned to investigate normal adolescents in the Turkish population.

Material and Methods

In order to study the psychiatric symptoms seen among normal adolescents, three high schools from different socioeconomic regions (lower, middle and upper) in the city of Ankara were chosen randomly from a list published

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by the Ministry of Education which classifies schools according to the socieconomic status of the attending children. Eighth, ninth, tenth and eleventh grade classes (one of each) were selected randomly in each school. The number of adolescents screened in this study was 434 (239 female and 195 male). The distribution of the students according to socioeconomic groups and gender is shown in Table I. Age range for all groups is 13-21 years, with a mean age of 16.

Table I: Distribution of Students by Gender and Socio-Economic Status (SES)

SES	Females	Males	Total
Upper	58	66	124
Middle	95	54	149
Lower	86	75	161

Symptom Check List (SCL-90-R) was used to get a profile of the psychiatric symptoms. This self-rating screening instrument was developed by Derogatis et al.[24] and contains 90 items describing psychiatric symptoms which are evaluated in ten groups of psychopathologies: somatization, obsessive-compulsive symptoms, interpersonal vulnerability, depression, anxiety, hostility phobia, paranoid ideation, psychoticism, and other. The higher the scores, the more intense the symptoms. This instrument has been used in various studies[17,19-21] and has been shown to be valid and reliable for Turkish adolescents[25]. SCL-90 has three indices showing the level of psychopathology: General Symptom Index (GSI), Total Positive Symptoms (TPS) and Positive Symptom Index (PSI). GSI was used for evaluation in this research. The cut-off point for a pathological level of symptoms on GSI was 1.57 for Turkish adolescents[25].

Statistical analysis was done using one way analysis of variance and t-tests.

Results

The distribution of the mean scores for all subscales of SCL-90 and GSI according to the socioeconomic class and gender is given in Table II. GSI values for all groups were under the cut-off point showing that psychiatric symptoms are not at a pathological level.

The results were evaluated considering the effects of gender, socioeconomic level, and age.

The mean scores and the results of the analysis of the scores for all males and females in the group are given in Table III. ANOVA results show that all symptom groups except hostility were found more in females; GSI (psychopathology index) was also significantly higher in females.

Table II: Mean Scores of SCL-90 Among Groups and Genders

	Upper SES		Middle SES		Lower SES	
SCL-90	Females	Males	Females	Males	Females	Males
Somatization	0.80	0.82	0.72	0.52	0.80	0.74
Obsessive-Compulsive	1.32	0.82	1.02	0.75	1.25	0.99
Interpersonal Vulnerability	1.12	0.82	1.19	0.74	1.43	0.96
Depression	0.89	0.82	0.94	0.53	1.13	0.74
Anxiety	0.70	0.82	0.78	0.46	0.88	0.70
Hostility	0.83	0.82	0.97	0.62	1.00	0.84
Phobia	0.43	0.82	0.55	0.36	0.65	0.50
Paranoid Ideation	0.93	0.82	0.92	0.57	1.08	0.80
Psychoticism	0.66	0.82	0.73	0.44	0.88	0.62
Other	0.88	0.82	0.83	0.50	0.94	0.73
GSI	0.82	0.82	0.86	0.54	1.00	0.70

SES: Socioeconomic status; GSI: General Symptom Index.

Table III: Difference of SCL-90 Scores Between Females and Males

SCL-90	Total	Females	Males	t
Somatization	0.71	0.77	0.64	1.82*
Obsessive-Compulsive	1.01	1.11	0.88	3.82***
Interpersonal Vulnerability	1.08	1.26	0.87	3.96***
Depression	0.83	1.00	0.64	4.02***
Anxiety	0.72	0.80	0.61	2.13**
Hostility	0.88	0.95	0.81	1.66
Phobia	0.51	0.56	0.44	1.80*
Paranoid Ideation	0.86	0.98	0.72	3.54***
Psychoticism	0.64	0.76	0.61	2.14**
Other	0.78	0.88	0.65	3.20***
GSI	0.80	0.90	0.69	3.18***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, GSI: General Symptom Index.

When the adolescents were evaluated according to socioeconomic class groups (Table IV), significant differences were found on obsessive-compulsive symptoms ($F = 4.89$, $p < 0.01$), interpersonal vulnerability ($F = 3.81$, $p < 0.05$), depression ($F = 4.67$, $p < 0.01$) and GSI ($F = 3.11$, $p < 0.05$). T-tests revealed that higher scores for the lower socioeconomic status group caused the differences (Table IV.i).

SCL-90 scores were also analyzed in terms of age factor (Tables V and V.i). ANOVA and t-test showed that the 15-16 years of age had significantly higher scores than the other age groups for GSI ($F = 3.46$, $p < 0.05$), interpersonal vulnerability ($F = 3.73$, $p < 0.05$), depression ($F = 5,73$, $p < 0.01$) and paranoid ideation ($F = 6.18$, $p < 0.01$).

Table IV: SCL-90 Scores of the Three SES Groups and ANOVA Results

SCL-90	Upper SES	Middle SES	Lower SES	F
Somatization	0.70	0.65	0.68	1.93
Obsessive-Compulsive	0.95	0.92	1.13	4.89**
Interpersonal Vulnerability	0.99	1.02	1.21	3.81*
Depression	0.74	0.79	0.95	4.67**
Anxiety	0.67	0.67	0.79	2.25
Hostility	0.88	0.84	0.93	0.51
Phobia	0.44	0.48	0.58	2.34
Paranoid Ideation	0.84	0.80	0.95	1.90
Psychoticism	0.70	0.62	0.76	1.97
Other	0.78	0.71	0.84	1.78
GSI	0.77	0.74	0.88	3.11*

* $p < 0.05$, ** $p < 0.01$, SES: socioeconomic status; GSI: General Symptom Index.

Table IV.i: T-test Results of the Differences Between the SES Groups

SCL-90	Upper-Middle SES	Middle-Lower SES	Upper-Lower SES
Obsessive-Compulsive	0.34	-2.87**	-2.44**
Interpersonal Vulnerability	-0.39	-2.13**	-1.68
Depression	-0.66	2.24*	-2.95**
GSI	0.38	-2.28*	-1.94*

* $p < 0.05$, ** $p < 0.01$, SES: socioeconomic status; GSI: General Symptom Index.

Table V: SCL-90 Scores of the Three Age Groups and ANOVA Results

SCL-90	13-14 Years	15-16 Years	17-21 Years	F
Somatization	0.65	0.77	0.66	1.97
Obsessive-Compulsive	0.92	1.08	0.95	2.76
Interpersonal Vulnerability	1.07	1.18	0.96	3.73*
Depression	0.75	0.94	0.73	5.73**
Anxiety	0.61	0.78	0.67	2.71
Hostility	0.86	0.95	0.81	1.41
Phobia	0.53	0.56	0.42	2.96
Paranoid Ideation	0.83	0.98	0.73	6.18**
Psychoticism	0.70	0.75	0.62	1.94
Other	0.70	0.85	0.72	2.82
GSI	0.77	0.87	0.73	3.46*

* $p < 0.05$, ** $p < 0.01$, GSI: General Symptom Index.

Table V.i: T-test for Differences Between the Age Groups

SCL-90	13-14 Years/ 15-16 Years	15-16 Years/ 17-21 Years	13-14 Years/ 17-21 Years
Interpersonal Vulnerability	-1.03	2.78**	1.03
Depression	-2.25*	3.18***	0.19
Paranoid Ideation	-1.66*	3.54***	1.25
GSI	-1.45	2.58**	0.75

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, GSI: General Symptom Index.

Discussion

Normal adolescents demonstrated a mean score of 0.80 for GSI which was lower than the psychopathological cut-off point of 1.57 for Turkish adolescents as determined by Dağ[25]. Neither males nor females showed psychiatric symptoms at pathological levels. However, the mean scores of females on all scales except hostility were significantly higher than those of males. This result points to the possibility that females have more difficulties during adolescence and are more inclined to develop psychiatric symptoms, which is in parallel with the results of other studies on normal adolescents[12,19,26]. Casper et al.[27] studied gender differences in self-reported psychiatric symptoms in adolescents using SCL-90 and found that female adolescents, regardless of race, reported significantly higher levels of depression and anxiety than did male adolescents. Our results regarding gender differences were also similar to those obtained in studies with Ethiopian and Hawaiian adolescents[28,29].

When the students were evaluated according to socioeconomic status, those from the lower status school showed significantly higher scores on several subscales and GSI of SCL-90 compared to the students of the other two schools. This result shows that adolescents from lower socioeconomic classes are at greater risk for developing psychiatric symptoms. This result is similar to the result found in The Great Smoky Mountains Study of Youth, which states that poverty is the strongest demographic correlate of psychopathology, in both urban and rural children[30]. It was shown that the lower the socioeconomic status of adolescents, the lower is their self-esteem[31] and that low self-esteem is one of the major risk factors for developing psychiatric symptoms in teenagers[32].

Age is found to be another factor affecting the development of psychiatric symptoms in adolescents. Interpersonal vulnerability, depression and paranoid ideation increase at the age of 15-16 years and then decrease. This is also reflected on GSI scores. This result shows that adolescents at 15-16 years of age are at greater risk of developing psychiatric symptoms, and is similar to the results of another study done with Hawaiian youth which found that ninth graders reported more aggressive symptoms that did twelfth graders[29].

Increased interpersonal vulnerability is related to difficulties in coping with interpersonal relations, and these difficulties may lead to the development of depression and paranoid ideation symptoms. This result also confirms the results of another study showing that depression increases at the age of 15-16 and decreases afterwards[28]. It can be speculated that adolescents in Turkish society are suffering mostly from the turmoil of this period between the ages of 15-16.

Our results demonstrate that being female, coming from a lower socioeconomic class and being between 15-16 years of age are risk factors for developing psychiatric symptoms. This data is important in leading the preventive studies for adolescents. Fifteen-sixteen-years-old youngsters, especially females and those from economically lower groups, need more preventive work and support because they are psychologically at greater risk of developing psychiatric symptoms and perhaps some disorders.

This study is also of importance to pediatricians, especially those working with adolescents. Studies done with Turkish youth show that they usually express their psychological stresses by somatic symptoms. Thus, while treating adolescent patients having somatic complaints, consideration of the risk factors mentioned above may help the pediatrician to make a better differential diagnosis.

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THE IMPACT OF THE SEXUAL MATURATION STAGE ON BODY MASS INDEX IN ADOLESCENT GIRLS*

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SUMMARY: Yalçın SS, Kınık E. (Department of Social Pediatrics, Hacettepe University Institute of Child Health, Ankara, Turkey). The impact of the sexual maturation stage on body mass index in adolescent girls. Turk J Pediatr 1999; 41: 315-321.

Body mass index (BMI) is used in the clinical assessment of adiposity in children and adolescents. Population-based, race-specific and age-specific curves of BMI for children and adolescents exist, but there are noknown sexual maturation-based BMI curves. The aim of this study was to investigate the effects of pubertal development (assessed according to the Tanner breast stage) on BMI in adolescent girls in a cross-sectional study. The study group comprised 167 healthy girls, between the ages of nine and 16 years, attending school near a hospital in Gerede, Bolu. A significant positive correlation was found between the Tanner stage of breast development and BMI ($r = 0.79$, $p < 0.001$). Age also had a significant influence on BMI ($r = 0.69$, $p < 0.001$). After controlling the effects of age, BMI was highly correlated with weight ($r = 0.82$, $p < 0.001$) and the Tanner breast stage ($r = 0.49$, $p < 0.001$), but not with height. The correlation between BMI and the sexual stage was also found to increase with increasing age. But when breast development was taken as a control parameter, BMI was not statistically associated with age or height. As a result, there was a significant variation in BMI with the Tanner breast stage in addition to the well known change with increasing age in adolescent girls. Developmental differences occurring in the same age may require that BMI be evaluated only within the same sexual stages in adolescence. This study indicates that the curves of BMI need to take into account the sexual maturation stage of adolescents.

Key words: body mass index, Tanner breast stage, adolescent girls.

The exact chronologic timing of the initiation, progression and completion of puberty, as well as the degree of linear growth, weight gain and secondary sexual development are variable from individual to individual and between the sexes. Normally, about 50 percent of adult weight and 20-25 percent of final adult height are gained during puberty[1]. So clinical assessment of weight status is difficult in adolescence. Body mass index (BMI) is the most useful criteria for screening adolescent obesity because it correlates significantly with both subcutaneous and total body fat in adolescents, particularly those with the greatest proportion of body fat[2,3]. There are standards of BMI defined by age, sex and race, since adiposity is known to vary with these factors[4-7]. Garn et al.[8] also attributed the relationship of BMI to stature, lean body mass, and body frame or proportion as three limiting factors of BMI. However, there may be other fundamental factors that have not been identified which may limit the

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accuracy of BMI in adolescence. BMI has a normal low point between four and eight years and then it increases until 19 years of age[4]. Accordingly, the fat component of body weight increases from the childhood baseline of 14.3 percent body fat to 23.7 percent by the end of puberty in girls[9]. This raises the possibility that puberty and the associated changes have been linked to an increase in adiposity during puberty. Thus, one limitation of BMI may be the normal variability of physical growth and development during puberty. Given that adolescence is a time of dynamic biologic change, it would seem useful to incorporate sexual stages into the curves of BMI.

The hypothesis is that pubertal development is a factor for changes in BMI. The goal of this article was to investigate the effects of pubertal development (assessed according to the Tanner breast stage) on BMI in adolescent girls.

Material and Methods

A cross-sectional study of 167 healthy schoolgirls (aged 9-16 years) was carried out in January 1991 to examine the effects of pubertal development on BMI among this group of girls. The study group was chosen from primary and high schools near a hospital in Gerede, Bolu. Students were not included in the study if they had any abnormalities of body proportions or history of chronic illness. Informed conset was obtained from both children and parents.

Ages were calculated from each child's date of birth to the date on which the anthropometric measurement was taken during the physical examination. After an overnight fast, body weight was determined to the nearest 0.1 kg using a digital scale, with the subjects wearing light indoor clothing without shoes or coats. Height was measured to the nearest milimeter using a portable, direct reading stadiometer, with subjects standing with shoes removed, with back, buttocks and heels (together) pressed to a wall. In measuring sitting height, girls were asked to sit as far back as possible on the measuring table so that the back of the knee joints were at the front edge of the table. Sexual maturation was assessed according to the Tanner breast stage by examination[10].

Body mass index was calculated as weight per height^2 with weight in kilograms and height in meters. Relative sitting height was calculated as sitting height per height.

Statistical analyses were performed by SPSS (version 6.0 for Windows; SPSS Inc, Chicago, IL). Pearson and Spearman correlation coefficients were used to assess the relationships between BMI and other parameters (Tanner breast stage, age, and measurement of body sizes such as weight, height, and sitting height). After adjusting for age or Tanner breast stage we calculated partial correlations. Changes in BMI by Tanner breast stage or age were assessed by analysis of

variance (one way ANOVA) with pairwise contrasts using the Duncan test. Stepwise multiple linear regression was used to determine which factors among age, Tanner breast stage and sitting height best predicted an individual's BMI. Multiple linear regression included neither weight nor height as a parameter since both were used in calculation of BMI.

Results

The characteristics of the study population are shown in Table I. The mean age for girls was 13.0 (SD, 2.1) years. As shown in Table II, BMIs for girls aged 13-16 years were higher than those of younger girls. The mean BMI varied significantly among girls with different Tanner breast stages ($p < 0.001$, Table II). The percentile values of BMI by Tanner breast stage are presented in Fig. 1, The percentile values of BMI for adolescent girls increased from Tanner stage I to V.

Table I: Clinical Characteristics of Adolescent Girls

Age (yr)	13.0 ± 2.1
Weight (kg)	43.6 ± 11.8
Height (cm)	149.4 ± 12.0
Sitting height (cm)	76.0 ± 5.5
Relative sitting height (%)	50.90 ± 2.1
Body mass index (kg/m^2)	19.2 ± 3.1

Values are mean ± SD.

Table II: Mean Body Mass Index (BMI) of Adolescent Girls by Age and Tanner Stage

	n	BMI
Age range*		
9.0-10.9	25	15.8 ± 1.8^a
11.0-12.9	44	17.3 ± 1.9^a
13.0-14.9	48	20.3 ± 2.7^b
15.0-16.9	50	21.4 ± 2.4^b
Tanner stage**		
I	28	15.7 ± 1.4^a
II	34	17.3 ± 2.0^b
III	37	18.7 ± 1.7^c
IV	42	20.9 ± 2.3^d
V	26	23.0 ± 2.3^e
Total	167	19.2 ± 3.1

Values are mean ± SD, * $F = 47.7$ $p < 0.01$, ** $F = 60.7$ $p < 0.001$.
All comparisons between the groups marked with different lower case letters are statistically significant.

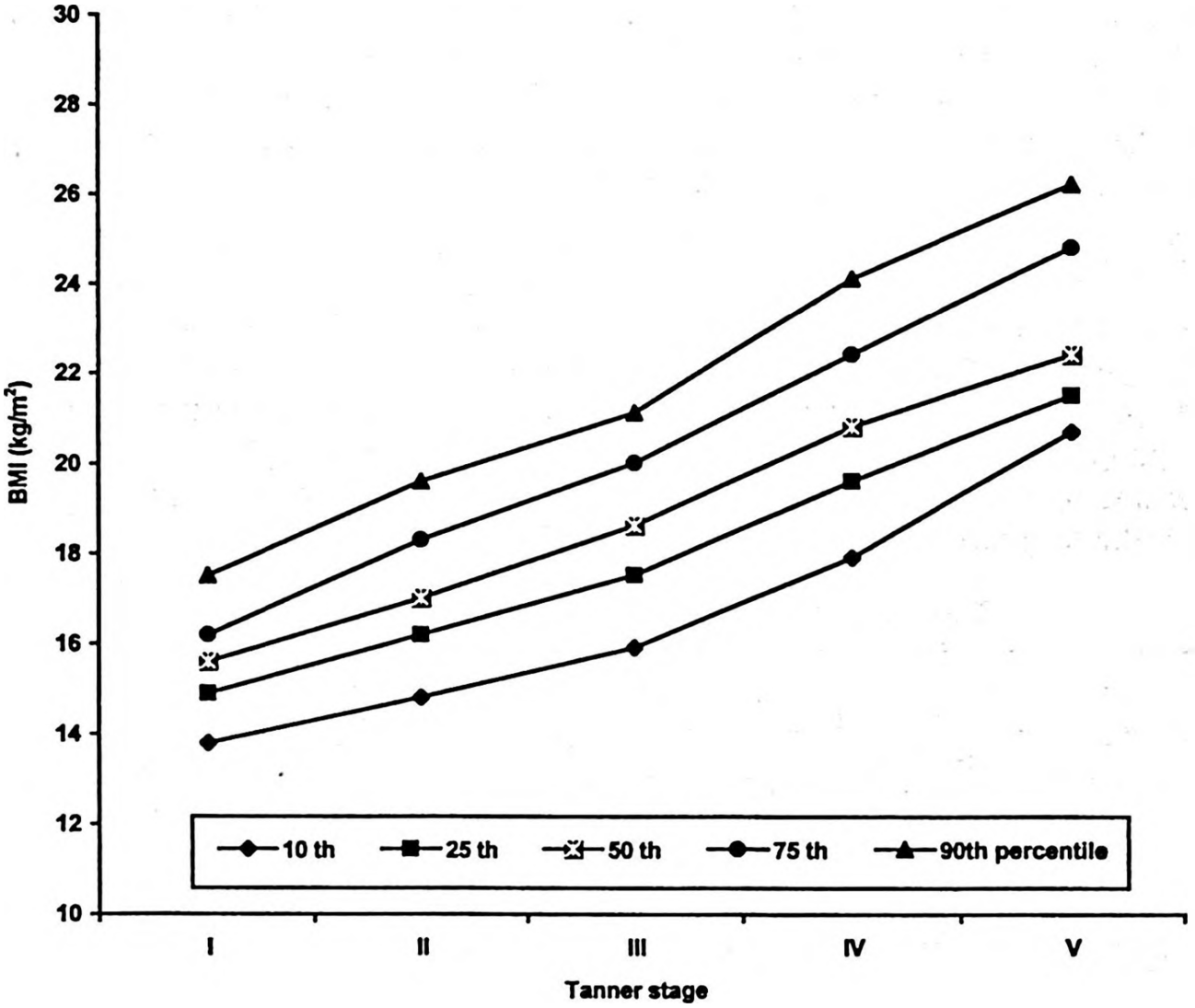

Fig. 1: The percentile values of body mass index (BMI) by Tanner stage.

Body mass index was significantly and positively correlated with Tanner stage ($r = 0.79$ $p < 0.001$), age ($r = 0.68$ $p < 0.001$), weight ($r = 0.90$ $p < 0.001$), height ($r = 0.57$ $p < 0.001$), and sitting height ($r = 0.61$ $p < 0.001$), but not with relative sitting height ($r = -0.08$ $p > 0.05$) (Tabe III). After adjusting for age, BMI was highly correlated with weight ($r = 0.82$ $p < 0.001$), Tanner breast stage ($r = 0.49$ $p < 0.001$) and relative sitting height ($r = 0.20$ $p = 0.011$), but not with height ($r = 0.05$ $p > 0.05$). For girls 9.0-10.9 years of age, there was no significant correlation between Tanner stage and BMI (Table IV). On the other hand, the correlation between BMI and sexual stage was found to increase with age (for girls aged 11.0-12.9, 13.0-14.9 and 15-16.9 years, $r = 0.32$, 0.57 and 0.58 respectively). After adjusting for Tanner breast stage, a significant positive relationship was found between BMI and weight ($r = 0.73$ $p < 0.001$), whereas no statistical correlation was found with age, height or sitting height (Table III). When divided into pubertal stage, there was no correlation between BMI and age in any stages (Table IV).

Table III: Correlations between Body mass Index (BMI) and Age, Weight, Height, Sitting Height, Relative Sitting Height, and Tanner Breast Stage in Adolescent Girls

	BMI	Partial Correlations Adjusting for Age	Partial Correlations Adjusting for Tanner Stage
Age	0.68**	–	0.09
Weight	0.90**	0.82**	0.73**
Height	0.57**	0.05	-0.07
Sitting height	0.61**	0.18*	0.07
Relative sitting height	-0.08	0.20*	0.16*
Tanner stage	0.79**	0.49**	–

* $p < 0.05$, ** $p < 0.001$.

Table IV: Correlations Between Age and Body Mass Index (BMI) by Tanner Stage and Between Tanner Stage and BMI by Age in Adolescent Girls

	Correlation Between Age and BMI by Tanner Stage			Correlation Between Tanner Stage and BMI by Age			
Stage	n	r	p	Age	n	r	p
I	28	0.23	> 0.05	9.0-10.9	25	0.30	> 0.05
II	34	0.18	> 0.05	11.0-12.9	44	0.32	0.03
III	37	0.26	> 0.05	13.0-14.9	48	0.57	< 0.001
IV	42	0.08	> 0.05	15.0-16.9	50	0.58	< 0.001
V	26	-0.18	> 0.05				

To explore possible causal relationships between BMI and other parameters, stepwise multiple linear regression was performed using BMI as the independent variable, and age, Tanner breast stage and sitting height as the dependent variables. Tanner breast stage, but neither age nor sitting height, was found to be a significant predictor of BMI (adjusted $r^2 = 0.59$, $p < 0.001$).

Discussion

Body mass index has been proposed as a practical measure of weight status although it has some well-known limitations in adolescents. To some extent BMI is influenced by age, sex, race, genetic and socioeconomic status[4-7,11-14]. It is known that BMI increases concomitantly with increasing age. Interestingly, we found a significant variation in BMI with Tanner breast stage in both univariate and multivariate analyses. There was a positive significant correlation between BMI and sexual maturation after controlling for age. Differences in development between children of the same age suggest that age- and sex-specific curves of BMI will be misleading for at least some children. Developmental differences

occurring in the same age may require that BMI be evaluated only within the same sexual stages in adolescents. Furthermore, the correlation between Tanner breast stage and BMI in the older adolescent girls was more noticeable than that in the younger ones. The absence of a correlation between age and BMI within the same Tanner breast stage supports our hypothesis. There are sex- and age-specific, population-based curves of BMI for children and adolescents[4-7]. Currently there is no known sexual maturation-specific BMI curves for adolescents. It has been reported that the mean levels of BMI in Mexican-American children were higher than those of white children and black children[7,13]. Roche et al.[7] suggested that differences in growth between Mexican-American and white children could have been due, in part, to differences between these groups in the rates of sexual maturation. Our results confirm this hypothesis.

Recently, the World Health Organization Expert Committee recommended that maturational status be taken into account for interpreting anthropometric data based on chronological age. The Committee reported that age-specific means or medians for anthropometry might be adjusted for rates of maturation of a population that differ from the reference data[2]. Furthermore, the age of sexual maturation of a population should be known for use of this age-specific data. In our study, the significant relationship between BMI and Tanner breast stage which was independent of age implies that care must be taken when assessing different sexual stages using existing BMI curves. Alternatively, BMI reference data from different sexual stages is needed to appropriately evaluate weight status using BMI. If sexual maturation-based curves of BMI are created, adolescent girls can be compared with reference data for that sexual stage without any need of adjustment. Thus, we suggest that BMI data classified according to the pubertal stage could be more applicable to most population groups.

Previous studies reported that BMI is positively correlated with height in adolescents[8]. This was also observed in the present study. On the other hand, after controlling for Tanner breast stage, the effect of height on BMI disappeared. Thus, height would not affect the evaluation of adolescent girls by sex-specific BMI curves.

In conclusion, there was a significant variation in BMI with Tanner breast stage in addition to the well-known change with increasing age in adolescent girls. These factors may be responsible for the instability of BMI to indicate weight status with greater accuracy in adolescents. In general, our data suggest that the existing BMI curves will be of limited value in the evaluation of weight status among adolescents. This study indicates that the BMI curves need to be created considering the sexual maturation stage of adolescents. Other studies are required to detect the presence of a relationship between BMI and the sexual stage in adolescent boys. Additional studies are also necessary to deal with

the important issue of appropriate reference data for defining weight status of adolescents, taking into account that cut-off limits probably differ depending on age, sex, race and also sexual maturation stage.

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CHANGES OF HEMOSTATIC FACTORS IN PATIENTS WITH HEMOGLOBINOPATHIES*

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SUMMARY: Öner AF, Gürgey A, Okur H, Kirazlı Ş, Gümrük F, Altay Ç. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Changes of hemostatic factors in patients with hemoglobinopathies. Turk J Pediatr 1999; 41: 323-327.

In this study, protein C (PC), protein S (PS), heparin cofactor II (HCFII), prothrombin fragment 1+2 (PF1,2), thrombin-antithrombin III complex (TAT), von Willebrand factor (vWF) and thrombomodulin (TM) were investigated in 13 patients with beta thalassemia intermedia (TI) not requiring transfusion, six patients with sickle cell disease (SCD), and seven patients with HbS-beta thalassemia (S-BT) who were not in crisis. These hemostatic parameters were also studied in 12 healthy children assigned as a control group.

Protein C and Protein S (PC-PS) were found to be decreased in TI patients and normal in S-BT patients. PC was decreased in SCD patients. In the patients with TI and SCD, the mean PF1,2 level was elevated, whereas the TAT level was not statistically different from that of the control group. These results suggested that in patients with hemoglobinopathies: a) decreased natural anticoagulants and b) enhanced procoagulant activation have been encountered. Other unexpected and interesting results of this study are the decreased vWF and elevated HCFII levels in all three patient groups. *Key words: thalassemia, sickle cell disease, coagulation inhibitors, activation in coagulation.*

In thalassemic patients, many ischemic strokes, peripheral arterial or venous thrombosis, pulmonary emboli and renal infarcts have been reported[1,2]. These observations indicate that thrombosis is the one of the important life threatening complications in hemoglobinopathies. Thrombosis is observed in these patients especially after splenectomy[2]. Recently, several studies concerning hemostatic disturbance and their influences on the development of thrombosis have been reported in thalassemic patients[3,4]. In sickle cell disease (SCD), it has been generally suggested that the sickling phenomenon and its interaction with the vascular endothelium provoke sickle cell crisis; however, the role of hemostatic changes in the pathogenesis of vaso-occlusion has been encountered only

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recently[5,6]. At present, although studies have yielded controversial results, it is thought that vascular occlusion in sickle cell patients is a multifactorial event rather than merely a sickling phenomenon[5,6]. Hemoglobinopathies are frequent in Turkey and in other Mediterranean countries[7]. It has therefore been possible in this study to investigate several parameters of different hemostatic compartments in quite a high number of patients with hemoglobinopathies, in an effort to shed light on the mechanisms leading to thrombophilia in this group of disorders.

Material and Methods

The subjects of this study were 26 patients (mean age 14.5 ± 1.9 years) whose cases were followed at Hacettepe University Children's Hospital between 1996-1997 [13 patients with thalassemia intermedia (TI) not requiring blood transfusion, 7 patients with HbS-thalassemia syndrome (S-BT) and 6 patients with SCD]. No S-BT or SCD patients were in crisis. These hemostatic parameters were also studied in 12 healthy children assigned as a control group (mean age 8.4 ± 3.1 years). Following separation from the whole blood, plasma samples were stored at -70 °C until the study was performed. The plasma antigenic levels of protein C (PC), total protein S (PS), von Willebrand factor (vWF), thrombomodulin (TM) (asserochrome protein C, protein S, von Willebrand factor, thrombomodulin, Diagnostica Stago, Paris, France), thrombin-antithrombin III complex (TAT) and prothrombin fragment 1-2 (PF1,2) (Anzygnost TAT, PF1,2 micro, Behring, France) were measured by enzyme-linked immunoabsorbent assay (ELISA). The heparin cofactor II (HCFII) level (stachrome HCFII; Diagnostica Stago, Paris, France) was measured by colorimetric assay. Statistical analyses were performed using the Mann-Whitney U, Wilcoxon and Pearson tests.

Results

The results of all three groups are presented in Table I.

TI Group: Plasma PC, PS and vWF levels were found to be decreased, while PF1,2 and HCFII levels were increased, as compared to those of the control group ($p < 0.01$ for all five tests); TAT and TM levels were not different from the control levels. A positive correlation was found between the PF1,2 and TAT levels (r: 0.85, $p < 0.01$).

S-BT Group: vWF level was decreased, while PF1,2 and TAT levels were increased, as compared to those of the control group ($p< 0.01$, < 0.01, < 0.01 respectively). The mean plasma levels of PC, PS, HCFII and TM were normal.

SCD Group: PC and vWF levels were decreased (p:0.01 and < 0.01, respectively) and the HCFII level was increased ($p < 0.01$); TAT and TM levels in this group were normal.

Table I: Results of the Plasma Levels of Hemostatic Parameters in Three Groups Compared to the Control Group

Hemostatic Parameters		β-Thalassemia Intermedia (n:13) (1)*	S-β Thalassemia Group (n:7) (2)*	Sickle Cell Disease Group (n:6) (3)*	Control Group (n:12) (4)*	P**
PC	(mg/L)	69.3 ± 3.9	97.4 ± 11.5	81.5 ± 8.2	113.5 ± 8.8	1-4:<0.001 3-4:<0.01
PS	(mg/L)	48.3 ± 2.6	60.7 ± 6.7		100.1 ± 6.4	1-4:<0.001
PF1,2	(µg/L)	5.8 ± 2.4	6.6 ± 2.1	40.8 ± 10.1	1.6 ± 0.1	1-4:<0.01 2-4:<0.01
TAT	(µg/L)	80.8 ± 25.9	133.2 ± 32.4	61.0 ± 5	40.8 ± 10.1	2-4:<0.01 3-4:<0.01
HCFII	(U/ml)	88.6 ± 6.5	88.7 ± 2.2	105.0 ± 6.1	61.0 ± 5	1-4:<0.001 3-4:<0.01
vWF	(%)	52.6 ± 8.2	67.8 ± 12.9	17.9 ± 2.5	105.0 ± 6.1	1-4:<0.001 2-4:<0.01 3-4:<0.01
TM	(ng/ml)	18.6 ± 2.8	19.4 ± 2.3		17.9 ± 2.5	

* The groups are numbered as 1, 2, 3 and 4 for statistical analysis.
** Only significant "p" values are showed in the table.
PC: protein C, PS: protein S, PF1,2: prothrombin fragment 1+2, TAT: thrombin-antithrombin III complex, HCFII: heparin cofactor II, vWF: von Willebrand Factor, TM: thrombomodulin.

Discussion

Hemoglobinopathies complicated with hemostatic disorders showing bleeding or thrombosis have been reported in several studies[1,2,4]. However, in the majority of studies only one component of the hemostatic system is evaluated. In this study, the three different components of hemostasis have been studied.

Protein C PC and PS, important natural anticoagulants, inhibit active FV and FVIII. HCFII, together with dermatan sulfate, inhibits thrombin as well. PFI,2 is a secondary product during the conversion of prothrombin to thrombin. TAT is a stable substrate which is required for the inactivation of thrombin. PF1,2 and TAT have been accepted as sensitive indicators of activation in coagulation, while vWF and TM are the most important indicators of vascular injury, in addition to functioning in hemostasis[8].

In this study, PC and PS levels were found to be decreased in the TI group. In the SCD group, PC was also found to be decreased (PS was not studied in this group). These findings are in accordance with the results of previous studies which interpreted these levels as due to either impaired protein production in the liver or as secondary to increased thrombin generation[3,8]. In the S-BT group, an increase in PF1,2 indicated that the coagulation system was activated, whereas normal PC and PS levels suggested that the production of these proteins by the liver was not diminished in this group.

Phospholipids, leaking from the erythrocyte membranes following hemolysis, have been shown to activate coagulation cascade probably causing an elevation in PF1,2 and TAT levels[6,9]. It was therefore suggested that the activation of coagulation cascade seen in TI and SCD is probably seconday to hemolysis, which enhances thrombotic risks in these patients. The elevation in the HCFII level found in this study but not in previous publications needs to be evaluated in further studies[10,11].

von Willebrand Factor levels were found to be decreased in all three groups ($p < 0.01$ in all three groups). Acquired vWF deficiency was described in some conditions, such as hematological malignancies, and in patients to whom some drugs were administered. The low vWF levels could be explained by the presence of an antibody to the vWF, proteolysis of vWF directly, and/or absorption of vWF by malignant cells[12]. However, we could not interpret the statistically significant low vWF levels found in all three patient groups ($p < 0.01$) by these mechanisms.

There was no decrease in the TM levels in any of the patient groups, indicating that endothelial injury does not seem to contribute to thrombotic complications in these patients. However, measurement of this parameter in S-BT and SCD during crisis could be useful in the evaluation of endothelial injury that may occur in vaso-occlusive crisis in these patients.

In conclusion, our study indicated that some natural inhibitors such as PC and PS are decreased in hemoglobinopathies. These low levels may be secondary to increased thrombin generation or due to the impaired hepatic production of these proteins. Elevated levels of PF1,2 and TAT indicated that a subclinical thrombotic process occurs in hemolytic anemia. However, since thrombosis a multifactorial process, thrombotic tendency in patients with hemoglobinopathies may be enhanced by other factors.

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PROFILE OF BONE MARROW IRON STORES IN CHILDHOOD IRON DEFICIENCY ANEMIA*

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SUMMARY: Çetin M, Gönül A, Kara A, Kara ŞP, Yetgin S. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Profile of bone marrow iron stores in childhood iron deficiency anemia. Turk J Pediatr 1999; 41: 329-334.

To demonstrate the importance of bone marrow iron stores, we examined the complete hemogram, serum iron (SI), serum iron-binding capacity (SIBC), transferrin saturation (TS), serum ferritin and bone-marrow-stored iron in 31 children with iron deficiency (ID). The ages of the patients ranged from one to 14 years (mean 3.7 ± 3.9). Laboratory findings of the 31 patients were as follows: hemoglobin (Hb) 8.5 ± 2.4 g/dl, hematocrit (Hct) 27.8 ± 6.3 percent, mean corpuscular volume (MCV) 58.6 ± 8.6 fl, red blood cell count (RBC) 4 ± 0.8 10^{12}/L, red cell distribution width (RDW) 19.3 ± 4.9, SI 17.2 ± 9.3 µg/dl, SIBC 311 ± 50.5 µg/dl, TS 5.5 ± 2.8 percent and ferritin 6.7 ± 7.3 ng/dl. In the bone marrow smears with iron stains, all patients' scores were zero for iron stores, which shows that bone-marrow-stored iron in childhood is easily affected. Because of the traumatic effect of bone marrow aspiration, it is recommended that it not be done routinely. The diagnosis of ID could be especially difficult in patients with low SI levels but normal SIBC levels and in patients with chronic inflammatory diseases. In those conditions, illustration of bone marrow stores could be of particular assistance for diagnosis of iron deficiency. *Key words: iron deficiency anemia, bone-marrow-stored iron, children.*

Iron deficiency anemia (IDA) is still a common problem in childhood in both underdeveloped and developed countries. The most common etiologies are inadequate intake even in developed countries because of fast-food diets, rapid growth, abnormal iron absorption and blood loss[1]. In the early stage of iron deficiency (ID), despite a decrease of iron stores in the liver, spleen and bone marrow (BM), including ferritin levels, hemoglobin (Hb) levels could be within normal limits. Therefore, measurements of serum ferritin concentration, a so-called acute phase protein, is often recommended as a useful estimate of iron status[2] or of a decreased red blood cell catalase level[3]. The amount of stainable iron in the marrow is also used to assess iron stores in the accessory system[4,5].

In this study, to demonstrate the importance of bone marrow iron stores, we analyzed the complete hemogram, serum iron (SI), serum iron-binding capacity (SIBC), transferrin saturation (TS), serum ferritin and bone-marrow-stored iron in 31 children with iron deficiency.

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Material and Methods

This study included 36 subjects, aged between one and 14 years (mean age of 3.7 ± 3.9 years). Thirty-one of the patients were diagnosed as ID (25 patients with and 6 patients without anemia) and five control cases with acute idiopathic thrombocytopenic purpura (ITP) with normal hemoglobin values, all seen at Hacettepe University, İhsan Doğramacı Children's Hospital, Hematology Unit between April 1993 and May 1994. Ten patients (31%) were girls and 21 were boys (69%). Patients with suspected or documented infections were excluded from the study since iron metabolism changes can accompany acute viral infections[6].

The medical histories of all patients were reviewed in detail. Diagnosis of IDA was based on a Hb level and a mean corpuscular volume (MCV) lower than their age-matched controls; SI[7], SIBC[8] and TS less than 10 percent[9]; and a serum ferritin (Ferritin Kit, Amersham) level below 12 µg/L[1]. Coulter-Counter S was used for analysis of Hb, hematocrit (Hct), MCV, and red cell distribution with (RDW) measurements. Peripheral smears were stained with Wright's stain. Iron stores in BM of 31 ID patients and five control subjects were evaluated by examination of Prussian blue stained bone marrow from posterior iliac crests, as described previously[10].

Fifteen (60%) of 25 patients with anemia were seen for complaints other than anemia. In seven (23%) patients, pica was present according to their medical histories. Eighteen (60%) of the 31 patients had insufficient dietary intake history. Twenty-five (83%) patients were less than three years of age; 14 (56%) of those were consuming large amounts (more than 0.75 litre/day) of cow's milk in their diet.

Two patients (6%) were found below the third percentile for weight, and six patients (19%) were below the third percentile for height on physical examination. The other 23 (75%) were within normal limits for weight and height.

The etiological investigations in four patients between seven and 14 years of age indicated chronic ITP, gastrointestinal bleeding due to a gastric ulcer, a history of pica and a parasite (Giardia) (one case of each).

Correlation coefficient studies and Student's t test were used in the statistical analysis.

Results

The mean values of the hematological studies of the patients with ID and IDA are shown in Table I. None of those patients had any sign of infection. Bone marrow BM iron staining was absent in all patients, whereas the control group stained positive. In eight of 31 patients (26%) with low ferritin and SI levels without an elevated SIBC, favorable response to oral iron therapy was observed.

Table I: Selected Hematological Findings in Children with Iron Deficiency and Iron Deficiency Anemia

	Age (yr)	Hb (g/dl)	Hct (%)	MCV (fl)	SI (µg/dl)	SIBC (µg/dl)	TS (%)	Ferritin (ng/ml)	RBC ($x10^{12}$/L)	RDW
Patients with IDA n = 25	3.9 ± 4.2*	8.1 ± 2.2	26.8 ± 6.3	57.0 ± 7.8	17.4 ± 9.9	311 ± 50	5.6 ± 2.9	6.5 ± 7.9	4.0 ± 0.9	20.0 ± 3.8
	1-14**	2.9-10.7	9-33	48.0-70.0	10-32	207-400	2.5-10.0	0.3-11	1.7-4.7	15.0-28.7
Patients with ID n = 6	2.3 ± 0.9	11.9 ± 0.6	35.5 ± 2.1	66.0 ± 9.8	26.5 ± 13.6	345 ± 46	7.8 ± 4.1	7.2 ± 2.1	4.3 ± 0.4	18.0 ± 3.6
	1.5-4	11.4-12.7	35-38	50-76	10-45	271-389	2.7-10	4.8-12.2	3.8-5.0	13.0-28.7
p	0.2	0.0001	0.001	0.01	0.05	0.06	0.06	0.4	0.2	0.06

* Mean ± SD

** Minimum and maximum values

IDA: iron deficiency anemia, ID: iron deficiency, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, SI: serum iron, SIBC: serum iron-binding capacity, TS: transferrin, RBC: red blood cells, RDW: red cell distribution width.

A positive correlation was shown between Hb and SI (r = 0.55), Hb and TS (r = 0.53), Hb and ferritin (r = 0.58), SI and ferritin (r = 0.54), ferritin and TS (r = 0.59) and ferritin and RBC count (r = 0.53), while a negative correlation was demonstrated between Hb and RDW (r = -0.5), and RDW and MCV (r = -0.64). There was no correlation between ferritin and MCV or RDW or between Hb and MCV.

Discussion

Most patients (69%) with IDA in this study were initially seen for complaints, other than pallor, requiring medical attention. In healthy infants and children the most common cause of ID is insufficient dietary intake, which was present in 60 percent of our patients[11]. High intake of cow's milk is often seen in the dietary history of children with ID, due to its lower iron content and chronic blood loss from the gastrointestinal tract[11,12]. Occult blood in the feces, fat malabsorption and mucosal histological changes have been described in patients with IDA[13]. However, in some patients these abnormalities are not the primary result of iron deficiency, but are instead related to intake of cow's milk[12]. By history, 56 percent of our patients under the age of three consumed a large amount (more than 0.75 litre/day) of cow's milk in their diet.

Iron deficiency anemia IDA is rare in school-aged children due to the intake of a wider variety of foods. However, gastrointestinal blood loss due to parasites and gastric ulcers is an important cause of IDA in this age group[14]. One out of four patients was positive for a parasite (Giardia) in the feces, and one had gastrointestinal bleeding due to a gastric ulcer.

Pica is a behavioral change characterized by compulsive ingestion of non-nutritive substances and is thought to be related to iron deficiency, though the true underlying mechanism is not clear[15]. The incidence of pica in ID patients was reported to be as high as 50 percent by Crosby[16]. In the present study, only 22 percent of patients had a positive history of pica.

Iron staining in the bone marrow is an indicator of the level of iron stores in the accessory system. Demonstration of a decrease of iron stores in the BM is one of the methods of diagnosing ID. In the first stage, iron deposition is deficient, but the erythrocyte morphology remains normal. Transferrin saturation TS may decrease by 25-50 percent and serum ferritin may also decrease. In the second stage, iron stores are completely depleted but the erythrocyte morphology and count still remain normal, while TS is less than 10 percent[1]. In six of the patients studied, hemoglobin levels were 11.4-12.7 g/dl, SI and SIBC were compatible with ID, and iron stores in the bone marrow were decreased, as is characteristic of the second stage. In the third stage, iron levels deficient for hemoglobin synthesis cause anemia, the erythrocyte protoporphyrin level increases,

transferrin saturation is lower than 10 percent, and the erythrocyte count decreases. Twenty-five of our cases were in this stage. It is pointed out that BM iron stores in infants and adolescents are not as valuable as in adults[1], because of the borderline level of iron storage. In adults with IDA, BM iron stains may be trace, while in our study in children the absence shows that iron stores can decrease more steadily.

The measurement of serum ferritin facilitates the estimation of iron stores by noninvasive means in ID patients[17]. A positive correlation was found between ferritin and Hb, SI, TS and RBC in our study. Often a low SI level and SIBC may accompany chronic disease. In chronic disease, measurement of ferritin is not reliable for estimating BM ID or overload[18,19]. Furthermore, liver cell damage and some malignancies may also increase the ferritin concentration. Thus, evaluation of bone marrow iron stores in childhood may be a better method on some occasions, especially in patients who are believed to have ID but who have normal serum ferritin levels. In the present study, SIB was found to be normal in 26 percent of the patients with ID. In spite of the traumatic effect of bone marrow aspiration, bone marrow iron staining for iron may be helpful for the diagnosis of iron deficiency on some occasions, especially in patients with conflicting values of SI and SIBC and/or chronic diseases.

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INCREASED GASTRIC JUICE LEUKOTRIENE B_4, C_4 AND E_4 CONCENTRATIONS IN CHILDREN WITH HELICOBACTER PYLORI COLONIZATION*

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SUMMARY: Kasırga E, Çoker I, Aydoğdu S, Yağcı RV, Taneli B, Gousseinov A. (Division of Gastroenterology, Department of Pediatrics, Ege University Faculty of Medicine, İzmir, Turkey). Increased gastric juice leukotriene B_4, C_4 and E_4 concentrations in children with Helicobacter pylori colonization. Turk J Pediatr 1999; 41: 335-339.

During recent years, the role of inflammatory lipid mediators in the pathophysiology of Helicobacter pylori (H. pylori) infections has been investigated in several studies. The concentrations of leukotrienes (LTs) in gastric juice from H. pylori positive (n = 13) and negative (n = 18) children with recurrent abdominal pain were studies in order to determine whether these lipid inflammatory mediators are involved in local and systemic biological actions. Gastric juice samples and biopsy specimens of mucosa were obtained endoscopically from 31 patients with recurrent abdominal pain for assessment of LTs and histopathological examination. In this study, all children with recurrent abdominal pain were investigated by rapid urease test and histological assessment for H. pylori colonization. Leukotriene levels were measured by high performence liquid chromatography (HPLC) and raioimmunoassay (RIA) in gastric juice samples. Gastric juice LTB_4, LTC_4, and LT_4 levels were significantly higher in patients with H. pylori colonization than in children without H. pylori colonization. These results indicate that increased gastric content of proinflammatory mediators (LTB_4, LTC_4, and LT_4) may be related to the pathogenesis of H. pylori-associated gastritis. *Key words: Helicobacter pylori, antral gastritis, leukotrienes, lipid mediators, gastric juice.*

Helicobacter pylori (H. pylori) is the most prevalent agent of chronic gastritis and duodenal ulcer disease in adults as well as in children[1,2]. It is known that H. pylori initates an inflammatory cascade that leads to self injury[3]. During recent years, the role of inflammatory lipid mediators in the pathophysiology of H. pylori infections has been investigated in several studies[4-6]. Leukotrienes (LTs) are synthesized from arachidonic acid which derived from lipid layers of the cell membrane by phospholipase A_2 through the lipoxygenase pathway by immunologic and nonimmunologic stimulation[7]. LTs are well known proinflammatory mediators[8]. LTB_4 is a potent chemoattractant of polymorphonuclear cells and causes degranulation

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and a relase of lysosomal enzymes. Peptide LTs (LTC_4, LTD_4 and LTE_4) could mediate gastric mucosal damage both by their vasoconstrictive actions and effects on vascular permeability, promoting vascular stasis and subsequent reduction in tissue perfusion[9,10]. Increases of both LTB_4 and LTC_4 have also been reported with gastritis associated with H. pylori[11-13].

The aim of this study was therefore to investigate the relation between H. pylori colonization and synthesis of eicosanoids by gastric mucosa, as detected by LT concentrations in gastric juice from H. pylori positive and negative children with recurrent abdominal pain (RAP).

Material and Methods

Thirty-one patients (16 girls, 15 boys; mean age ± SD: 12.7 ± 3.6 years) with RAP underwent diagnostic upper gastrointestinal endoscopy. All patients had normal laboratory values and radiological findings. At endoscopy, three biopsies were taken from the antrum. One sample was placed in a quick urease test for assessment of H. pylori colonization. Two samples were fixed in 10 percent formalin for histopathological examination. Gastric juice was obtained endoscopically. Gastric juice sample from all children with RAP was placed in a filtered tube containing a 5 ml mixture of methanol: water: acetic acid (70:30:0.01 v/v) for LTs analysis and was stored at -70 °Ç until assayed. Before assessment, cold PBS was added to the contents of the tube and this mixture was centrifuged at 6,000 rpm for 10 min for precipitating proteins and other deposits. The supernatant was filled into Sep. Pak C18 cartridges which were activated previously by 10 ml each of methanol and water both at the flow rate of 1.5 ml/min. The flow rate of the supernatant was 2.5 ml/min. These cartridges were rinsed twice with 5 ml of water and then with 5 ml of 20 percent methanol; the rinse solution was discarded. The LTs which were separated from other small molecule-sized, nonpolar lipids were extracted from the columns by 3 ml of methanol and then collected into a tube by passing through a 0.45 µ pore membrane filter and evaporated to dryness by speed vacuum concentrator. Dried samples were dissolved in 20 µl of solvent and kept at -70 °C.

Separation of LTs was performed by high performance liquid chromatography (HPLC) (Waters 625 LC System). The system was composed of a multisolvent delivery pump system, powerline system controller, water 486 tunable absorbance UV detector, Rheodyne 7012 injector, column areas and Baseline 810 HPLC software program. Separon SGX C18 super (250 x 2.0 mm 1.0) analytical column and precolumn (100 x 2-0.10) containing the same filling material were used with methanol: water:acetic acid gradient for separations of LTs. LTs were sequenced at 280 mm and 235 mm wavelengths and 1.0 ml/min and 1.5 ml/min flow rates, respectively. The LTs were collected from HPLC UV detector output according

to their retention times and were dried again in a vacuum speed evaporator. The retention time for LTE_4 was 7 min, LTB_4 min, 11 LTD_4 13 min, and LTC_4 15 min. The amounts of LTB_4, LTC_4 and LTE_4 were quantitatively measured using LTB_4 (^3H), LTC_4 (^3H) and LTE_4 (^3H) assay systems (Amersham Life Science, UK). The procedure was performed according to kit instructions, LTB_4, LTC_4 and LTE_4 concentrations were measured by Beta-liquid scintillation counter (TRI-CRAB-1600 TR, LSA-Packard, Canberra Company).

Results of LTs were expressed as ng/ml in gastric juice samples.

Statistics: Data on leukotriene concentrations are expressed as mean and standard error. Student's t test was used for comparisons between H. pylori positive and negative groups. A p value of less than 0.05 was considered significant.

Results

In gastric juice, LTB_4 concentrations in patilents with H. pylori colonization (mean ± SEM: 1.6 ± 0.29, range: 0.36-3.2) were significantly higher than in children without H. pylori colonization (mean ± SEM: 0.28 ± 0.09, range: 0-1.2) ($p < 0.001$). The values for LTC_4 in those with colonized H. pylori (mean ± SEM: 0.80 ± 0.16, range: 0.3-2.1) were higher than in those not colonized (mean ± SEM: non-detectable). LT_4 levels in children with H. pylori colonization (mean ± SEM: 2.75 ± 0.67, range: 0-0.67) were found to be significantly elevated when compared to H. pylori negative patients (mean ± SEM: 0.88 ± 0.31, range: 0-5.2) ($p < 0.05$).

In gastric juice, LTB_4, LTC_4 and LTE_4 were non-detectable in 55.5 percent (10/18), 100 percent (18/18) and 55.5 percent (10/18) respectively, of children without H. pylori colonization. On the other hand, LTE_4 was also non-detectable in 7.6 percent (1/13) of patients with H. pylori colonization.

Discussion

In this study we have shown that H. pylori colonization in children is associated with an increased gastric juice LTB_4 level as compared with children not colonized. Our study also shows that H. pylori colonization of gastric mucosa results in increased concentrations of gastric juice peptide LTs (LTC_4 and LTE_4). It has been reported that patients have higher LT concentrations in gastric mucosa if they are colonized by H. pylori than if they are not[4,11-13]. On the other hand, in the gastric juice of children without H. pylori colonization, LTs (LTB_4 and LTE_4) were also assessed in detectable concentrations but significantly less than the levels measured in children with H. pylori colonization. In H. pylori negative children, the source of these LTs are gastric epithelial cells and resident peripheral blood leukocytes in normal gastric mucosa. Increased concentration of these mediators in children with H. pylori colonization may be explained by increased mononuclear

cells and neutrophil infiltration in the gastric mucosa. LTB_4 is a potent chemotactic facor, as it attracts neutrophils, monocytes and lymphocytes to the inflammation area[4,8]. LTC4 causes local ischemia by vasoconstriction in gastric mucosa, and infiltration of inflammatory cells to this ischemic area leads to a release of secondary mediators[13]. Previous studies in humans have shown that synthesis of LTs correlates with mucosal histological injury[11-13]. However, the mechanisms of inflammation reaction in H. pylori infections are often complex and multiple[14,15]. The ammonia produced by H. pylori has been reported to have a cytotoxic effect on the gastric mucosa[16-19]. The pathogenesis of H. pylori-associated gastritis is also related to other factors such as free oxygen radicals, cytotoxins and cytokines[19-21]. Basso et al's[22] results supported the role of increased synthesis of several cytokines in the pathogenesis of H. pylori-associated gastritis. In addition, phospholipases produced by H. pylori induce the synthesis and relase of LTs from cytoplasmic membrane phospholids[23]. In conclusion, we investigated the influence of H. pylori colonizatilon on gastric juice LT concentrations in children with recurrent abdominal pain, and showed that H. pylori seemed to enhance the synthesis of LTs by promoting mucosal inflammatory cell infiltration. These results suggest that antileukotrienes will probably become effective agents in H. pylori-associated antral gastritis treatment.

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PERCUTANEOUS TRANSVENOUS BALLOON MITRAL VALVULOPLASTY: MID – TERM RESULTS IN ADOLESCENTS*

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SUMMARY: Ünal N, Meşe T, Hüdaoğlu S, Çelikkol B, Yunus Ş, Saylam GS, Akçoral A. (Department of Pediatric Cardiology, Dokuz eylül University Faculty of Medicine, İzmir, Turkey). Percutaneous transvenous balloon mitral valvuloplasty: mid-term results in adolescents. Turk J Pediatr 1999; 41: 341-348.

Six patients with mitral valve stenosis underwent percutaneous balloon mitral valvuloplasty (PBMV) in our department between November 1992 and December 1997. Five patients had rheumatic mitral valve stenosis and one had congenital mitral valve stenosis and Eisenmenger's syndrome with patent ductus arteriosus (PDA). Functional status before PBMV was class IV in two patients, class III in two patients, and class II-III in two patients, as classified by the New York Heart Association (NYHA).

The mean diastolic pressure gradient across the mitral valve measured during heart catheterization before and immediately after PBMV was 18.8 ± 10.42 and 9.4 ± 7.7 mmHg, respectively ($p < 0.01$). The patients were followed for a mean period of 36.6 ± 8.5 months (range 12 to 72 months) after the procedure. During follow-up, post PBMV mean diastolic transmitral gradient measured by color Doppler echocardiography decreased from 19.3 ± 11.16 to 7.43 ± 7.3 mmHg ($p < 0.01$) and the mitral valve area increased from 1.09 ± 0.7 to 3.1 ± 0.9 cm² ($p < 0.002$). Functional capacity showed improvement to NYHA class I in four patients, to class II-III in the paient with congenital mitral valve stenosis and Eisenmenger's syndrome with PDA and to class II in one patient with severe mitral valve calcification in whom restenosis occurred three years after PBMV.

Percutaneous balloon mitral valvuloplasty PBMV can achieve very good short- and mid-term results in relieving symptomatic rheumatic mitral valve stenosis.
Key words: mitral stenosis, percutaneous balloon mitral valvuloplasty.

Stenotic mitral valve diseases are relatively uncommon in childhood. Congenital mitral valve stenosis accounts for 0.2 percent of all congenital heart diseases. Mitral stenosis is mostly secondary to deformity of mitral valve leaflets and chordae tendineae following recovery from rheumatic pancarditis. The most common finding is commissural union with increased fibrosis in leaflets.

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Calcifications may be found together with fusion and fibrosis. Not uncommonly, mitral insufficiency may accompany these valvular degenerative changes. Although mitral valve stenosis may occur as early as two or three years after an attack of acute rheumatic fever, a patient usually lives 10-20 asymptomatic years after the first rheumatic attack. Sometimes patients with severe mitral valve stenosis develop early symptoms[1-3].

After the appearance of symptoms related to mitral valve stenosis (New York Heart Association [NYHA] functional capacity class II), the disease follows a rapid downhill course. Symptomatic rheumatic mitral stenosis requires various interventions. Basically, two different approaches are available for palliation of mitral stenosis: surgical mitral commissurotomy using either cardiopulmonary bypass (open) or transvalvar dilation (closed), or percutaneous catheter balloon mitral valvuloplasty (PBMV)[2]. Percutaneous mitral valvuloplasty is of particular importance. PBMV is increasingly being performed more often for the treatment of acquired isolated mitral valve stenosis as an altrenative to surgical closed mitral commissurotomy[4-7]. Previous studies have demonstrated marked immediate improvement in hemodynamic measures and symptoms after PBMV[8-10], even in patients with calcification of the mitral valve[8,11] or severe pulmonary hypertension[8,11,12]. Although most of these studies are from elderly patients, PBMV has also emerged as a viable option in childhood, especially in adolescents. In this study, we present the short- and mid-term results of the first six patients in our department who underwent PBMV for mitral stenosis.

Material and Methods

Between November 1992 and December 1997, six patients (3 girls and 3 boys) aged 14 ± 2.8 years (range 10 to 17 years) underwent PBMV in our department. PBMV candidates were selected based on history, physical examination, ECG, chest x-ray and echocardiographic findings. Five patients had rheumatic mitral valve stenosis, one patient (Case 5) had congenital mitral valve stenosis (hypoplastic mitral valve with asymmetric papillary muscle) with patent ductus arteriosus (PDA) and Eisenmenger's syndrome (Table I). Two patients were in NYHA functional class I-III, two were in class III and two in class IV (Table II). Echocardiographic evaluations were done with Acuson 128 XP with 3-5 MHz transducers. Two-dimensional (2-D) and color Doppler echocardiography were performed 24 hours before valvuloplasty to exclude the presence of left atrial thrombus, to determine the degree of mitral regurgitation and mitral valve area, and to evaluate valvular structure. Echo score of each paient was determined with 2-D echocardiography considering valve thickness, calcification, mobility, and subvalvular apparatus[13]. Patients were selected according to the following criteria[12]: i) severe symptomatic mitral valve stenosis (NYHA clases ≥ II), mitral

valve area ≤ 1 cm^2; ii) no previous history of thromboembolic complications; iii) having sinus rhythm; iv) mitral regurgitation ≤ 1st degree; v) no detectable left atrial thrombi on 2-D echocardiography; and vi) an echo score < 8. Cardiac catheterization and PBMV were performed simultaneously during the same study.

Table I: Demographic Features of Patients and Etiologies of Mitral Valve Stenosis

N	Age (Years)	Sex	Etiology
1	17	F	RF*
2	14	M	RF
3	12	F	RF
4	17	M	RF
5	10	F	Congenital
6	14	M	RF
Mean ± SD	14 ± 2.8		

* RF: Rheumatic fever.

Table II: Functional and Hemodynamic Status Before and After PBMV[1]

	Before PBMV					After PBMV				
N	FS[2]	MVA[3]	MG[4]	LAP[5]	PVR[6]	FS	MVA	MG	LAP	PVR
1	IV	2.0	12.2	26	4.66	I	3	2.7	17	2.09
2	II-III	0.5	7.4	25	23.64	I	3.8	7.3	17	18.22
3	II-III	0.5	25	20	7.73	I	2.06	3.7	12	4.63
4	III	1.7	10	15	2.35	I	3.7	0.9	8	1.65
5	IV	0.25	36	28	14.62	II-III	1.53	21.2	15	14.15
6	III	1.6	25	35	2.79	II	3.7	8.4	20	2.79
Mean±SD		1.09±0.7	19.3±11.16	24.8±6.8	9.30±8.35		3.17±0.97	7.43±7.3	14.83±4.26	7.26±7.11
						p	.002	.001	.001	.06

[1] PBMV : Percutaneous balloon mitral valvuloplasty.
[2] FS : Functional status (NYHA class)
[3] MVA : Mitral valve area (cm^2)
[4] MG : Transmitral valve mean gradient (mmHg)
[5] LAP : Left atrial mean pressure (mmHg)
[6] PVR : Pulmonary vascular resistance (Wood unit)

After premedication with lytic cocktail (demerol, Phenergan, Thorazine), or after sedation with ketamine and midazolam, diagnostic catheterization was performed. Serial oxygen and hemodynamic measurements and left and right ventricular angiograms were obtained before and after the valvuloplasty procedure. All patients were anticoagulated with heparin during catheterization. Dilation of the mitral valve was performed by the transvenous transseptal approach using properly sized monofoil or trefoil single balloon. After the diagnostic study, a Mullins sheath was inserted over the guide wire to the right atrium, and a Brockenbrough needle was used to make a transseptal puncture in the interatrial

septum. After introducing the needle to the left atrium, confirmation was done by monitoring high pressure in the left atrium, and a back-up guide wire was then inserted in the left atrium. The interatrial septum was dilated with a 5-6 mm single balloon and the Mullins sheath was safely placed in the left atirum. A flow-directed balloon-tipped catheter was sent to the left ventricle through the mitral valve. A 260 cm x 1.10 cm J guide wire was placed at the apex of the left ventricle. The balloon-tipped catheter and Mullins sheath were then removed. A mitral valvuloplasty balloon of appropriate size for body surface area was positioned in the valve and inflated with diluted contrast media either by means of an indeflator at 4-6 atmosphere pressure or manually until the impression of the commissures disappeared (or for a maximum of 30 seconds). This procedure was repeated three times. Post procedure pressure tracings and left ventricular contrast injection for mitral regurgitation were obtained.

The clinical and echocardiographic findings were evaluated one day, two weeks and six months after PBMV (Figs. 1, 2). NYHA functional class was assessed

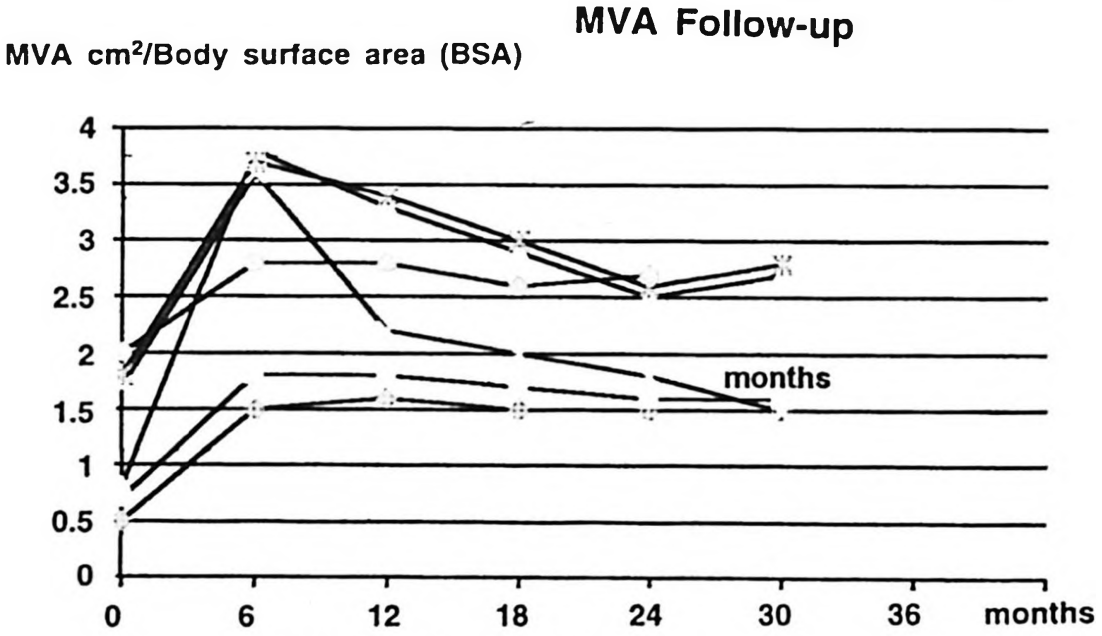


Fig. 1: Mitral valve area follow-up.

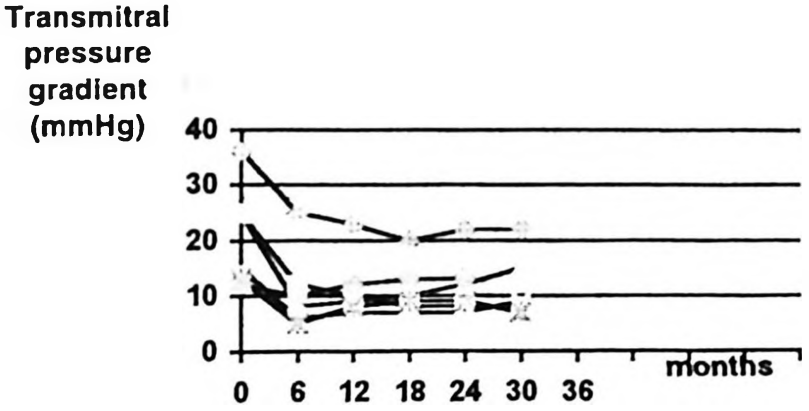
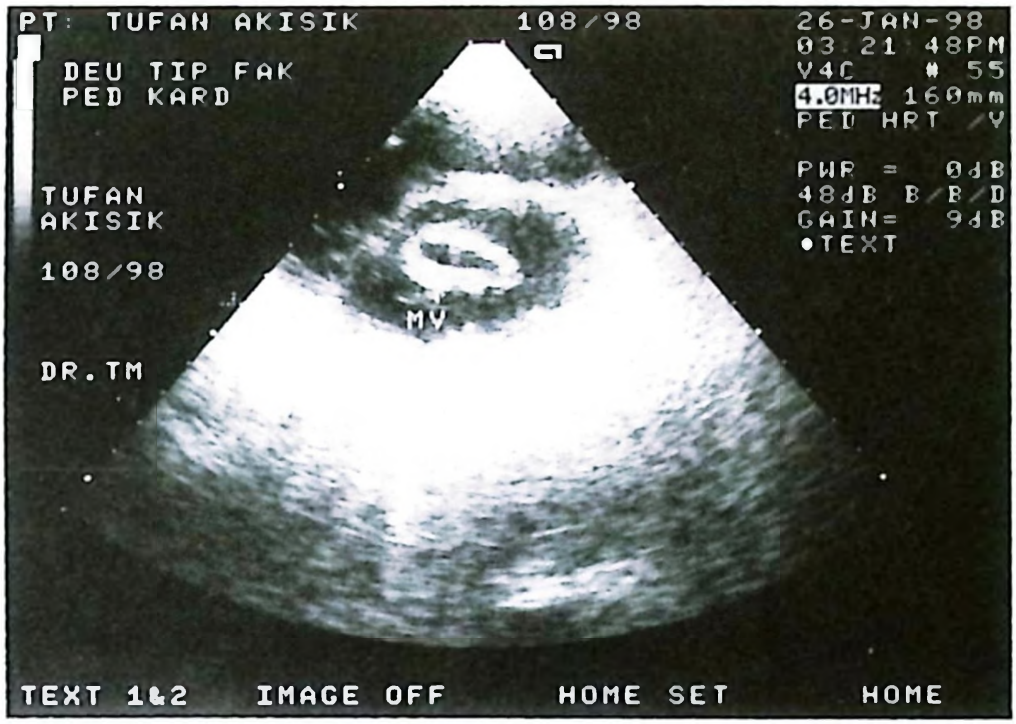
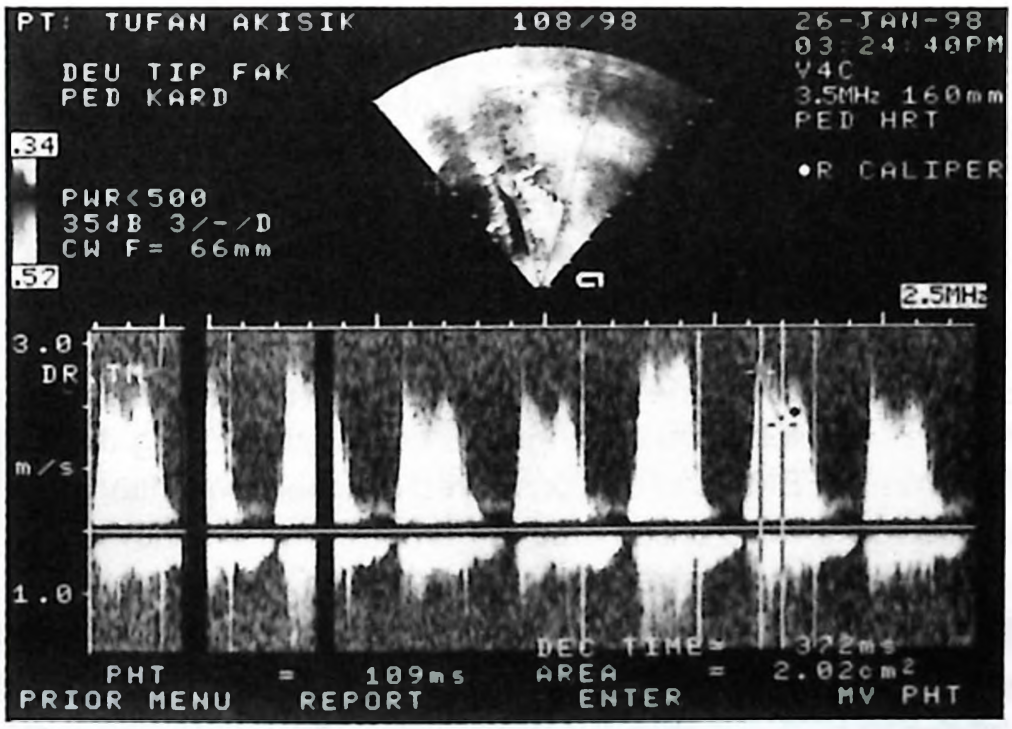


Fig. 2: Transmitral gradients measured by echocardiography.

and a complete echocardiographic study was carried out, including mitral valve area calculations using planimetric and pressure half time (PHT) methods (Fig. 3 a, b), presence and degree of mitral valve regurgitation, subvalvar and mitral valve abnormalities and left atrial thrombus formation.



(a)



(b)

Fig. 3 a, b: Mitral valve area calculations using planimetric and pressure half time (PHT) methods.

Wilcoxon rank sum test in SPSS software was used for statistical analysis. All data were expressed as mean ± 2 SD.

Results

Before PBMV, four of the patients with rheumatic mitral stenosis had mobile, pilable mitral valves. In one patient (Case 6), the mitral valve showed severe calcification (Fig. 3a). None of our patients had mitral valve regurgitation or atrial fibrilation. PBMV was performed without complications in all candidates and the patients were discharged 48 hours following the procedure.

After PBMV, cardiac catheterization findings revealed a decrease in the mean transmitral pressure gradient from 18.8 ± 10.42 mmHg to 9.4 ± 7.7 mmHg ($p < 0.01$), and the left atrial mean pressure decreased from 24.8 ± 6.8 mmHg to 14.8 ± 4.3 mmHg ($p < 0.001$). Pulmonary vascular resistance decreased from 9.3 ± 8.35 Wood units to 7.26 ± 7.11 Wood units ($p < 0.06$). The mitral valve orifice area measured by echocardiography increased from 1.09 ± 0.8 cm^2 to 3.1 ± 0.9 cm^2 ($p < 0.02$) (Table II). The patients were followed for 12-72 months (mean follow-up duration 36.6 ± 8.5 months). In Case 6 with the calcified mitral valve, restenosis developed. Although his functional status did not deteriorate (NYHA class II), a repeat PMBV was performed 36 months later. Functional status in Case 5 with congenital mitral stenosis with PDA and Eisenmenger's syndrome improved from class IV to II-III after PMBV. The remaining four patients (Cases 1-4) who were in NYHA class II-IV before PBMV showed good progress and are currently in NYHA class I.

Discussion

Percutaneous balloon mitral valvuloplasty PBMV was originally performed in 1984 by Inoue et al.[4] Following the first attempts, many other institutions used different techniques for mitral valvuloplasty with single or double balloon[4,11,12,14,15]. These techniques used either the retrograde route from the femoral artery[8,16] or the antegrade route from the femoral vein with transseptal puncture[4-7,17,18]. Insertion of the balloon catheter into the valve without the need for transseptal puncture has also been described[8]. There is no significant superiority of these techniques[8-10,12,15]. We preferred the monofoil or trefoil single balloon method using the transvenous transseptal approach. PBMV can be considered in patients with functional capacity NYHA class-II, a mitral valve orifice area ≤ 1 cm^2/m^2, mitral transvalvular pressure gradient ≥ 10 mmHg, and mitral regurgitation grade 1. Patients with higher degrees of mitral regurgitation are candidates for mitral valve replacement surgery.

Body surface area (BSA) is the main domain in choosing the right balloon. Balloon area/BSA ratio must be 3.5-4. With ratios lower than 3.5 successful results cannot be achieved, and with ratios greater than 4.5 complications are more frequent. Criteria for classification of a successful procedure are complete separation of

both commisures (very well), complete separation of one commissure and partial separation of the other (well) complete separation of one commissure with the other still fused (good), both comissure partially separated or still fused (unsuccessful)[19]. According to these criteria, all of our patients were classified very well after PBMV except for the patient with congenital mitral stenosis. PBMV for congenital mitral valve stenosis is a matter of conflict, since the results are often suboptimal. Yet, some authors suggest a PBMV trial in certain forms of congenital mitral valve stenosis[20,21]. The rationale of this opproach in congenital mitral valve stenosis is to provide symptomatic relief and postponement of valve replacement. Because our patient was not eligible for open heart surgery due to Eisenmenger's syndrome with PDA, we performed PBMV.

After PBMV, complications such as restenosis, mitral regurgitation, iatrogenic secundum atrial septal defect (ASD), thromboembolic phenomena, cardiac perforation and tamponade, dysrhythmias, bleeding, vasoocclusion in the femoral artery or vein, cardiac arrest and death have been reported[8,9,12,14,16-19,22,23]. Ventricular dysrhythmias (ventricular premature beats, non-sustained ventricular tachycardia) were recorded in all our patients while the exchange guide wire was being positioned in the left ventricle, but none required treatment. Reported complication rate for mitral regurgitation is 20 percent and for iatrogenic ASD is 63 percent in short-term 20 percent after six months and four percent after one year[8,12,14,19]. All our patients developed minimal mitral regurgitation after PBMV. Four patients had interatrial left-to-right shunt on echocardiography soon after the procedure, but as of three months following PBMV, none has interatrial shunting Christodoulos et al.[8] reported 15.4 percent restenosis at two years follow-up. Should restenosis occur, it is easier, safer and less expensive to redilate with a percutaneously introduced balloon than it is to operate[8]. Only one of our patients, with heavy calcifications, developed restenosis 30 months after PBMV, and a second PBMV was performed successfuly.

Rheumatic mitral stenosis during childhood and adolescence is still not uncommon in developing countries. Adolescents with pure mitral valve stenosis are suitable candidates for PBMV as an alternative for surgery. PBMV should be considered the procedure of first choice for most patients with mitral stenosis, particularly for those whose mitral valve is mobile, pliable and not heavily calcified. PBMV can achieve very good short-term and mid-term results in relieving symptomatic rheumatic mitral stenosis.

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THE ACCURACY OF ANTENATAL FETAL ECHOCARDIOGRAPHY*

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SUMMARY: Özkutlu S, Saraçlar M. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The accuracy of antenatal fetal echocardiography. Turk J Pediatr 1999; 41: 349-352.

The purpose of this study was to evaluate our experience with a group of patients who were either selected by us or referred by an obstetrician or geneticist with the indication of fetal echocardiography.

This prospective study was done on 128 cases between 1996-1998. Maternal age range was between 16 and 41 years (mean: 28.79). Gestational age range was between 15 and 37 weeks (mean: 26). In the postnatal period the newborn babies were reevaluated for cardiovascular system abnormalities by physical examination, ECG, telecardiogram and, if it was necessary, by echocardiography, cardiac catheterization and angiography. By comparing prenatal and postnatal findings, sensitivity and specificity of fetal echocardiographic diagnosis were determined. Among the total cases studied, nine had major congenital heart disease in postnatal evaluation. Two cases had false negative; there were no false positive prenatal diagnoses. Sensitivity of echocardiographic diagnosis was 100 percent and specificity 78 percent. Three patients had paroxysmal atrial tachycardia and two atrioventricular block. We concluded that the fetal echocardiography is a very useful technique in the evaluation of the fetal cardiovascular system. However, awkward fetal position, severe maternal obesity, and technologic insufficiency of the echo machine may result in unfavorable scanning conditions. Minuteness of anomaly may also result in a false negative prenatal evaluation. *Key words: echocardiography, fetal echocardiography, fetus, congenital heart disease, dysrhythmia.*

Anatomic and functional evaluation of the fetal cardiovascular system has been possible by fetal echocardiography. However, the method may have some limitations pereventing the echocardiographer from detecting some detail. The purpose of this study was to evaluate our experience with a group of pregnant mothers having a child with congenital heart disease or who were referred by an obstetrician or geneticist with the indication of fetal echocardiography.

Material and Methods

This prospective study was done on 128 cases in the Pediatric Cardiology Unit of Hacettepe University. All pregnant mothers were either selected by us or were referred by the Obstetrics and Genetics Departments of the same University with the indication of fetal echocardiography. Standard methods were applied for prenatal cardiovascular system evaluation (I) using a Toshiba Sonolayer SSH-160 A machine. In the postnatal period the newborn babies were reevaluated for cardiovascular system abnormalities by physical examination, ECG,

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telecardiogram and, if it was necessary, by echocardiography. Cases without postnatal evaluation were excluded from the study. Newborn babies with congenital heart disease were further evaluated by cardiac catheterization and angiography, if needed. Maternal age range was between 16 and 41 years (mean 28.79). Gestational age range was between 15 and 37 weeks (mean 26). By comparing prenatal and postnatal findings, sensitivity and speificity of fetal echocardiographic diagnosis were determined.

Results

Among the 128 cases included in this study nine had major congenital cardiac anomalies in the postnatal evaluation (Table I). One tetralogy of Fallot, two pulmonary atresia, one atrioventricular (A-V) canal, one transposition of the great arteries (TGA), two single atrium, one large ventricular septal defect (VSD), and one tricuspid atresia were diagnosed. Of those nine patients, two had a false negative evaluation in the prenatal examination: one with pulmonary atresia and one with A-V discordance. None of the cases had a false positive diagnosis. For major lesions, sensitivity of prenatal echocardiographic diagnosis was calculated as 78 percent and specificity 100 percent (Table II).

Table I: Major Cardiac Anomalies

Tetralogy of Fallot	1
Pulmonary atresia	2*
Atrioventricular (A-V) canal	1
Transposition of the great arteries (TGA)	1*
Single atrium	2
Large ventricular septal defect (VSD)	1
Tricuspid atresia	1
Total	9

* one patient with false negative diagnosis.

Table II: Results I

Major cardiac anomalies	9
False negative	2
False positive	0
Sensitivity	78%
Specificity	100%
Dysrhythmias	
Paroxysmal atrial tachycardia (PAT)	3
Atrioventricular (A-V) block	2

The total number of individual cardiac lesions was 19 (Table III). Five patients had VSD. Another five cases of atrial septal defect (ASD) or single atrium, three cases of pulmonary stenosis, and two of pulmonary atresia were diagnosed. The other individual lesions were tricuspid atresia, A-V discordance, A-V canal, and TGA. Among the total 19 individual lesions, four had false negative evaluation (Table IV). No false positive diagnosis was made. The sensitivity of fetal echocardiographic diagnosis was 79 percent and the specificity was 100 percent.

Table III: Individual Cardiac Lesions

Tricuspid atresia	1
Atrial Septal defect (ASD) or single atrium	5
Large ventricular septal defect (VSD)	5
Pulmonary stenosis defect	3*
Pulmonary atresia	2*
Atrioventricular (AV) discordance	1*
Atrioventricular (AV) canal	1
Transposition of the great arteries (TGA)	1*
Total	19

* one patient with false negative diagnosis.

Table IV: Results II

Total individual lesions	19
False positive	0
False negative	4
Sensitivity	79%
Specificity	100%

In five cases, major rhythm abnormalities were diagnosed (Table II). Three patients had paroxysmal atrial tachycardia which was controlled with maternal digoxin administration. In two patients, atrioventricular block was diagnosed. Following birth a pacemaker was implanted in both cases.

Discussion

There is a wide range of accuracy reported in the medicalliterature for fetal echocardiography[2] (Table V). For specificity, it was between 57 and 92 percent for high risk patients. Buskens et al.[3] reported sensitivity as 43 percent and specificity as 95 percent. However, Allan et al.[4] reported sensitivity as 93 percent and specificity as 99.8 percent in their study.

Table V: Results of Various Studies

Ott WJ, 1995[2]	Sensitivity	62%
Buskens et al., 1996[3]	Sensitivity	43%
	Specificity	95%
Allan et al., 1989[4]	Sensitivity	93%
	Specificity	99.8%
Özkutlu-Saraçlar, 1998		
For Major Anomalies		
	Sensitivity	78%
	Specificity	100%
For Individual Lesions		
	Sensitivity	79%
	Specificity	100%

Our experience with detailed fetal echocardiography showed results similar to those listed in the literature (sensitivity 78%, specificity 100%) (Tables II, V).

In conclusion, fetal echocardiography is a very useful technique in the evaluation of the fetal cardiovascular system. However, awkward fetal position, severe maternal obesity, and technical insufficiency of the echo machine may result in unfavorable scanning conditions. Minuteness of anomaly may also result in false negative prenatal evaluation. Small ASD, mild coarctation of the aorta, and mild A-V or semilunar valve abnormalities may be missed during fetal echocardiography. By experience and with the development of computer imaging technology better results will be obtained.

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ULTRASTRUCTURAL FINDINGS OF BONE MARROW IN A CASE WITH MALIGNANT OSTEOPETROSIS FOLLOWING SUCCESSFUL ALLOGENEIC BONE MARROW TRANSPLANTATION*

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SUMMARY: Korkusuz P, Aşan E, Çetin M, Tuncer M, Tezcan İ. (Department of Histology and Embryology, and Hematology and Immunology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Ultrastructural findings of bone marrow in a case with malignant osteopetrosis following successful allogeneic bone marrow transplantation. Turk J Pediatr 1999; 41: 353-360.

A nine-month-old female patient suffering from malignant osteopetrosis was evaluated by light and transmission electron microscopic study before and following allogeneic bone marrow transplantation (BMT). Bone marrow specimens were obtained from iliac crest biopsies. Before BMT, the bone marrow had an irregular appearance and was filled with bridging bony trabeculae devoid of cells. Following BMT, the marrow had an almost normal appearance with no myelofibrosis and a relatively regular distribution of hematopoietic cells. The osteocytes were visible in their lacunae in the bone matrix. Presence of bone resorbing and bone forming cell together demonstrated that the bone was beginning to gain its normal dynamic structure. These findings were in accordance with the clinical, laboratory and radiological data which showed the beneficial effect of the therapy. *Key words: malignant-infantile osteopetrosis, allogeneic bone marrow transplantation, ultrastructure.*

Osteopetrosis is an extremely rare disease characterized by skeletal sclerosis due to failure of osteoclast-mediated resorption and remodeling of bone. Two types of genetic transmission have been described[1,2]. The autosomal dominant pattern is relatively benign and diagnosed in adulthood. Most patients are asymptomatic and have normal life spans[3]. The classic form of infantile-malignant osteopetrosis is autosomal recessive (AR). Patients with the AR form of osteopetrosis have severe symptoms, including abnormal bone remodeling due to defective osteoclast function, deficient hematopoiesis and neurological impairments such as blindness and auditory nerve damage. Children affected by AR osteopetrosis have poor prognosis and usually die during the first decade of life[1,2,4].

Histologically, bone marrow spaces are narrow and usually contain fibrous tissue with very few elements of hematopoiesis. Bone trabeculae consist of a cartilage

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surrounded by an immature or woven bone[5,6]. The histology of the bone tissue, however, shows a considerable variation, with regard to number and activity of both the bone forming and resorbing cells[7,8].

A number of therapeutical approaches have been used in malignant osteopetrosis, including steroids, parathyroid hormones and cytokine therapies (M-CSF, IFN-ψ); however, response has been minimal and transient[9,10]. Because the cell origin of the osteoclast is the pluripotent hemapoietic stem cell, allogeneic bone marrow transplantation (BMT) has been applied successfully since 1911 (following animal experiments) for the correction of AR osteopetrosis[11-15].

In this report, we present ultrastructural findings of bone in a case with malignant osteopetrosis after a successful allogeneic bone marrow transplantation.

Material and Methods

Bone marrow specimens were obtained from the iliac crest of a nine-month-old female patient suffering from malignant osteopetrosis. Biopsies were taken before and three months after allogeneic BMT. Tissue specimens were fixed in 2.5 percent glutaraldehyde in Sorensons' phosphate buffer, and decalcified in sodium 0.1 M EDTA (EDTA disodium salt, Sigma) solution. After washing in PBS, they were postfixed in one percent osmium tetroxide in PBS at 4 °C for one hour. Specimens were then dehydrated in a graded series of ethanol to absolute ethanol in preparation for embedding in araldite Cy 212 (agar). Semi-thin sections were stained with methylene blue azure II, and thin sections with uranyl acetate and lead citrate, before being examined and photographed.

Results

Semi-thin sections were examined to study the bone matrix, the marrow cavity, the osteoblasts and the osteoclasts in terms of size, number, nucleation and relationship to the persistent matrices.

The light microscopic observations on the semi-thin sections before BMT revealed irregularly shaped bone trabeculae consisting of large cartilage cores surrounded by an immature (woven) bone material occupying most of the sections so that intervening marrow spaces were very narrow. Hematopoietic elements were nearly absent in the marrow cavities. Bone matrix was irregular in density. Neither bone forming (osteblast) nor bone resorbing (osteoclast) cells were seen in the semi-thin sections, indicating that bone formation and resorption were affected. Furthermore, there was no clear evidence of main bone cells (osteocytes) embedded in the bone matrix (Fig. 1).

Three months after BMT, semi-thin sections revealedmany large osteoclasts located within the resorption cavities they produce. Some osteocytes were embedded in the matrix, whereas highly active osteoblasts are usually found

in the bone surfaces. Osteoclast number, size and nucleation varied from normal to increased levels. The marrow tended to have an almost normal appearance with no myelofibrosis and a relatively regular distribution of hematopoietic cells. The presence of bone resorbing and bone forming cells together demonstrated that the bone was beginning to gain its normal dynamic structure. Collagen synthesized by the osteoblasts was apparent. In the semi-thin and thin sections, osteoblasts appeared to be highly active (Figs. 2, 3, 4).

Fig. 1: Light micrograph before bone marrow transplantation (BMT) showing large cartilage cores (arrow) and woven bone (double arrow), (x 10, methylene blue azure II).

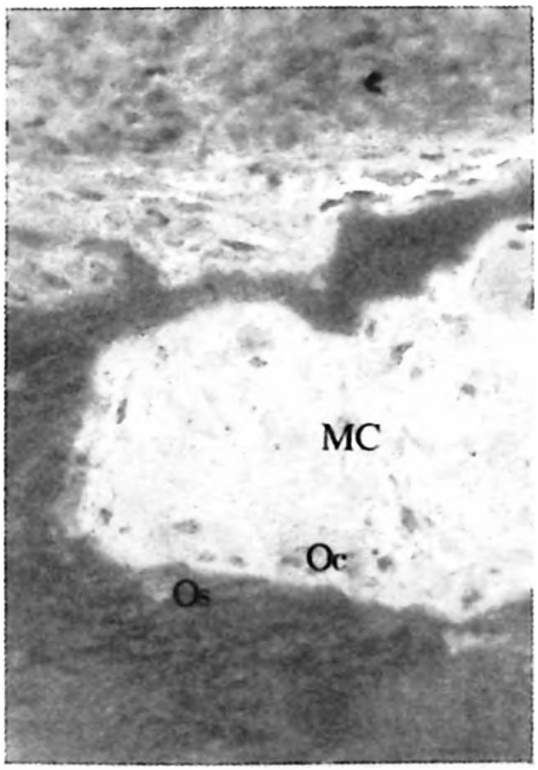

Fig. 2: Light microscopic appearance of bone and bone marrow after bone marrow transplantation (BMT). Osteocytes (Os), osteoclasts (Oc) and the cellular elements in the marrow cavity (MC) are observed, (x 40, methylene blue azure II).

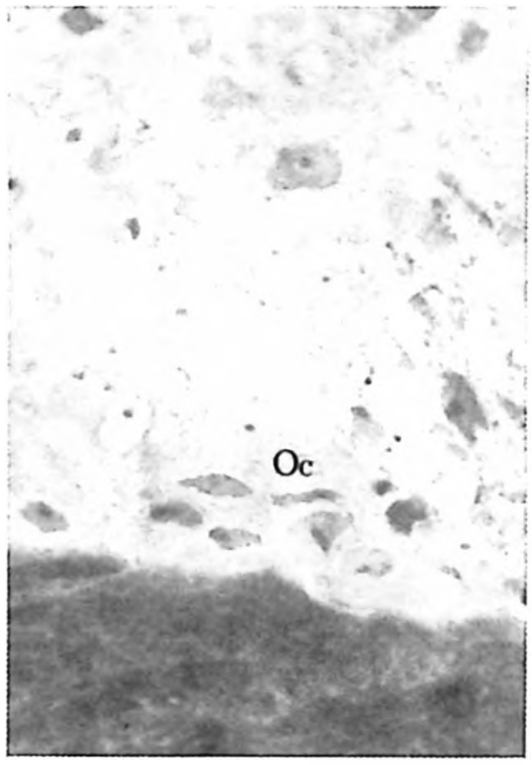

Fig. 3: A large multinucleated osteoclast (Oc) on the surface of a bone trabecula, (x 100, methylene blue azure II).

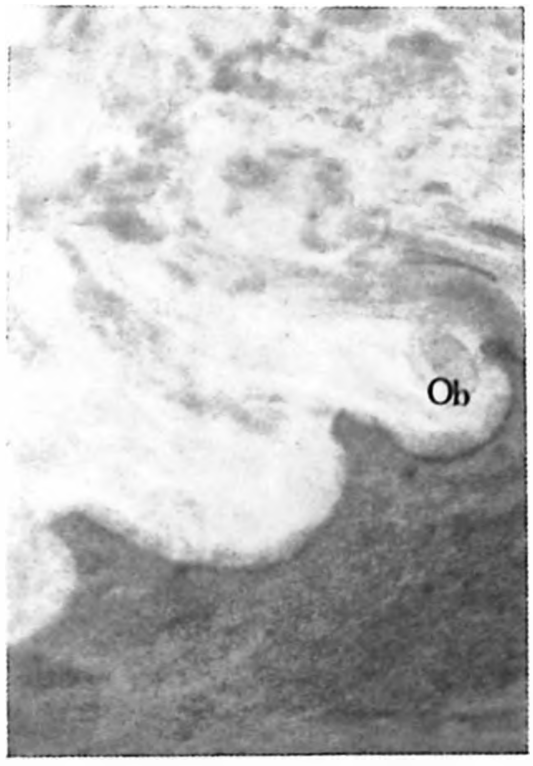

Fig. 4: Resorption cavities in he margin of the bone trabeculae, and an osteoblast (Ob) forming the collagenous matrix, (x 40, methylene blue azure II).

Electron microscopic observations on the thin sections three months after BMT revealed that the osteoblasts were numerous and active (synthesizing the collagen component of the matrix). They had a normal appearance, with a well developed rough endoplasmic reticulum, euchromatic nucleus, and prominent nucleolus. The collagen fibers were normal in terms of periodicity, size, and shape (Fig. 5). The osteocytes in their lacunae had a normal mature and inactive appearance. Osteoclasts were infrequently observed. They were large, rich in cytoplasmic vesicles and vacuoles, and had active and prominent irregularly shaped nucleoli (Fig. 6). The ruffled border and the clear zone complexes, however, were not evident.

Fig. 5: Electron micrograph showing the many active bone forming cells (osteoblast). Cytoplasm contains many rough endoplasmic reticulum cisternae. Section of collagen matrix is seen arround the cells. Dark areas (arrow) represent the onset of calcification in the osteoid matrix, (x 13,500, uranyl acetate-lead citrate).

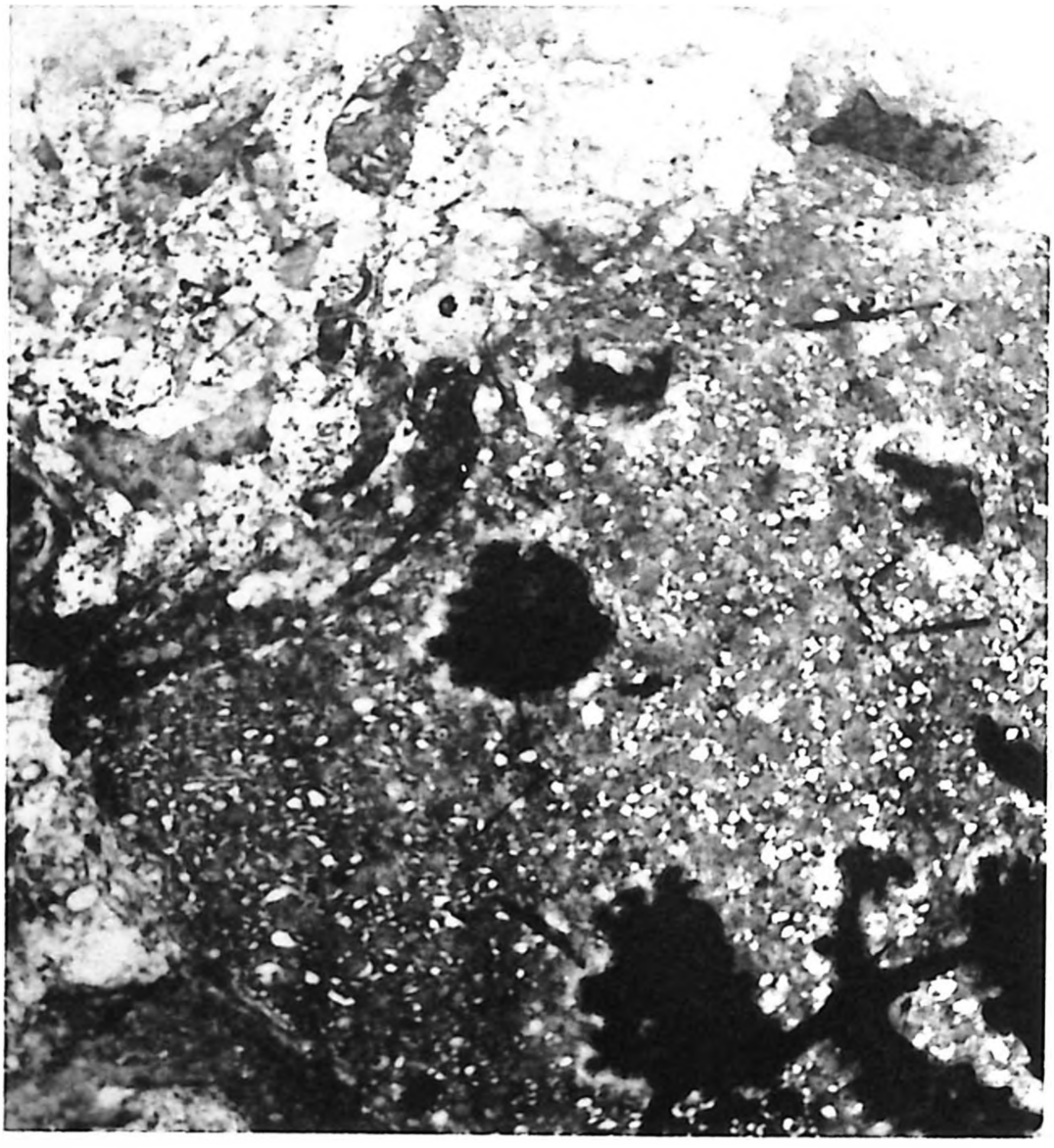

Fig. 6: Electron micrograph of an osteoclast after bone marrow transplantation (BMT). The cytoplasm is filled with vacuoles, (x 25,500, uranyl acetate-lead citrate).

Discussion

Our case had the symptomatology of malignant osteopetrosis including optic atrophy, nistagmus, bone fractures, hepatosplenomegaly, anemia, and thrombocytopenia. The patient had a history of sibling death with the same disorder. We performed bone marrow transplantation from her HLA-matched healthy sibling, and the patient showed clinical and laboratory improvement and was cured. Before BMT, the osteopetrotic bone consisted of an amorphous organic material with an acellular appearance. Following BMT, a new and healthy bone formation was beginning. Active bone formation together with bone resorption demonstrated physiological remodeling. The specific plasticity of bone is provided by a sufficient number of osteocytes. In thin sections the osteoclasts

did not show ruffled border-clear zone complexes, but they were present and active in the resorption cavities. The bone marrow appeared relatively normal compared to the period prior to transplantation.

We still do not know definitively whether the failure of effective bone resorption is due to intrinsic osteoclast abnormalities or to extrinsic factors such as matrix abnormalities. The extrinsic factors may make osteoclasts ineffective; however, it has been suggested that a strong reduction in the number of osteoblasts in an osteopetrotic patient may have a negative influence on the functioning of the osteoclasts and even on hematopoiesis[6]. On the other hand, it is also conceivable that the opposite occurs: that an osteoclastic abnormality influences osteoblastic activity leading to an abnormal bone deposition (woven bone). Our electron microscopic observations after BMT showed that osteoblastic activity was very prominent, indicating that both apparently normal endochondral bone formation and bone resorption had already begun.

Ultrastructural studies document the heterogeneity of the bone marrow in AR osteopetrosis[6,7]. Although diminished, the absent ruffled border-clear zone complexes of osteoclasts can be observed in the majority of osteopetrotic biopsies; extensive complexes are even noted in some cases[7]. The profiles of normal controls indicate that not all osteoclast membranes adjacent to bone and cartilage are thrown into a ruffled border conformation. Thus, it is not correct to note an area of non-ruffling by ultrastructure and assume that all the cells are inactive or, in reverse, to indicate that all areas of ruffling imply effective activity[7]. In this case report, active appearance of the osteoclasts within the resorption cavities in the presence of a healthy bone matrix and osteoblastic cells were found in association with an improvement of clinical, laboratory and radiological parameters. The patient engrafted rapidly and the new bone formation was of the same density as the original bone.

Careful morphological bone biopsies after BMT in combination with more delicate cell biological studies, related to the function of bone forming and resorbing cells, are needed to clarify the pathogenesis and treatment of the disease.

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FATAL ACIDOSIS IN A NEONATE WITH PEARSON SYNDROME*

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SUMMARY: Gürakan B, Özbek N, Varan B, Demirhan B. (Departments of Pediatrics and Pathology, Başkent University Faculty of Medicine, Ankara, Turkey). Fatal acidosis in a neonate with Pearson syndrome. Turk J Pediatr 1999; 41: 361-364.

We report a neonate who presented with hypotonia, hypoglycemia, and severe lactic acidosis. The patient's acidosis did not respond to bicarbonate replacement and dialysis. Postmortem liver samples revealed portal dilatation, fibrosis, canalicular proliferation, cholestasis, and hepatocellular hemosiderosis. Vacuolization of bone marrow precursors suggested a diagnosis of Pearson syndrome. A common mitochondrial DNA deletion of 4,978 bp was found. We emphasize that Pearson syndrome should be considered in neonates with lactic acidosis despite absence of anemia. *Key words: lactic acidosis, neonate, Pearson syndrome.*

Pearson syndrome is a fatal disorder involving the hematopoietic system, exocrine pancreas, liver, and kidneys[1]. In most previously reported patients, diagnosis of this syndrome has been based on the presence of anemia and vacuolization of marrow precursors[1-4]. However, diagnosis by demonstrating mutations in mitochondrial DNA (mtDNA) is possible today.

Metabolic acidosis in neonates has been reported in only a few cases[3,5-7]. Here we report a neonate with Pearson syndrome who presented in the first days of her life with severe acidosis and hypoglycemia.

Case Report

A 2,100 g girl was born after a normal pregnancy and delivery. She was the third child of consanguineous parents. The other siblings were alive and healthy. Physical findings at birth were reported to be normal, apart from a wasting of the buttocks and thighs, compatible with intrauterine growth retardation. She was referred to our hospital due to vomiting, poor sucking ability and grunting on the first postnatal day.

On admission the baby was hypoactive, hypotonic and was experiencing mild respiratory difficulty. Her length and head circumference were 48 cm and 33 cm, respectively. The liver was 3 cm palpable under the right costal margin on the midclavicular line.

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Laboratory studies were as follows: hemoglobin 16.4 g/dl, white blood cell count 27.9 x 10^9/L, blood glucose 9 mg/dl, blood urea nitrogen 12 mg/dl, aspartate aminotransferase 310 U/L, alanine aminotransferase 200 U/L, total bilirubin 3 mg/dl, direct bilirubin 0.5 mg/dl, arterial pH 7.02, HCO_3 4 mEq/L, base excess-24, lactic acid (LA) 39 mg/dl (normal 10-14), and pyruvic acid (PA) 0.85 mg/dl (lactic acid/pyruvic acid = 45). Urinalysis and chest x-ray findings were normal. The infant was suspected to have sepsis, and antibiotic treatment, glucose infusion, and bicarbonate replacement were initiated. Since severe acidosis persisted, peritoneal dialysis was performed. Despite intensive treatment the patient's condition deteriorated and she died on the eighth postnatal day. Histopathological examination of the liver necropsy revealed portal dilatation, fibrosis, canalicular proliferation, cholestasis and hepatocellular hemosiderosis (Fig. 1). A bone marrow smear was normocellular with vacuolization of precursor cells of the erythroid and myeloid series (Fig. 2). The mtDNA analysis of a liver necropsy sample revealed the deletion of 4,978 bp (nt8469-13447) between the ATPase 8 gene and the ND5 gene.

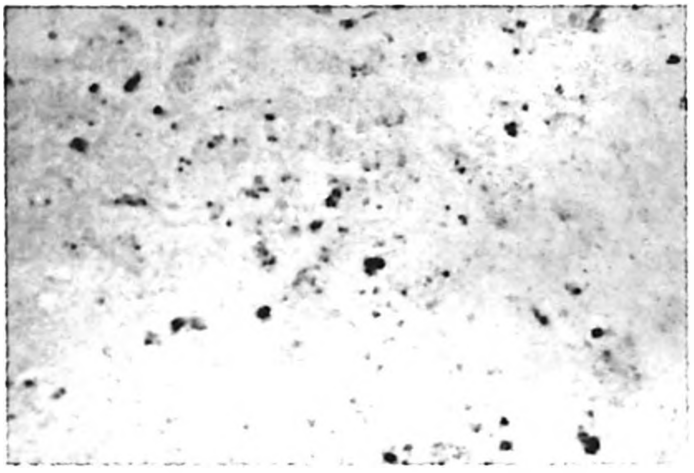

Fig. 1: Iron deposition in the patilent's liver (Perls' stain, x 230).

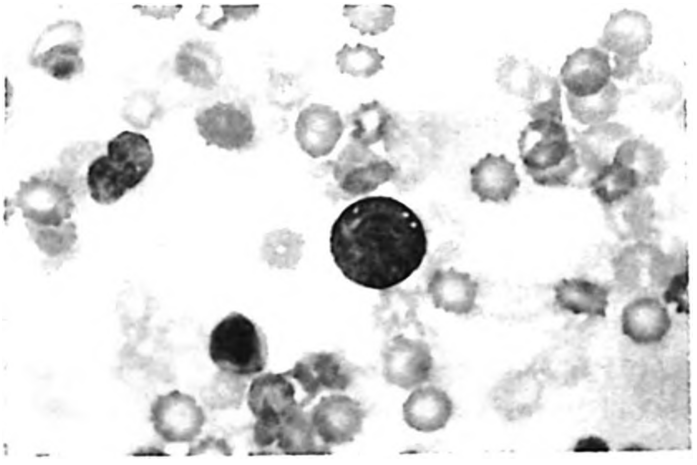

Fig. 2: Vacuolization of bone marrow cells (Wright's stain, x 1000).

Discussion

Pearson et al.[1] described a fatal syndrome in 1979 which involved severe anemia, vacuolization of marrow precursors, and pancreatic dysfunction. In the following years, case reports similar to this syndrome indicated that the disease was not limited to the bone marrow and pancreas the liver, kidneys, and other systems were involved[3-9]. In addition to multisystemic involvement, acidosis was another common finding. Evaluation of acidosis and hyperlactatemia in these patients resulted in the identification of this syndrome as the first mitochondrial disorder without neuromuscular expression[3]. Subsequently, deletions of mtDNA were found between 8 and 13 bp directly repeated sequences[10].

The patient reported here presented with hyhpotonia, hypoglycemia, and acidosis. Her liver was slightly enlarged and transaminases levels were high. An inborn error of metabolism or a mitochondrial disorder was considered after her refractory acidosis was identified as lactic acidosis (LA/PA > 40). Blood samples were obtained for further metabolic investigations. The diagnosis of Pearson syndrome was strongly suggested based on postmortem bone marrow aspiration and liver necropsy, and was confirmed with the demonstration of mtDNA deletion. The identification of this syndrome has important implications for clinical management and genetic counselling. Bone marrow transplantation seems difficult because of the multisystemic nature of the disease. A carbohydrate-rich diet which can precipitate hepatic failure should be avoided. Pearson syndrome results from de novo mutations and, due to random partitioning of mitochondria during embryogenesis, chorionic villi or amniotic fluid samples would give unreliable results. Thus, prenatal diagnosis is not available.

Gürgey et al.[6] reported a newborn patient with similar findings who had a 3.5 kb mitochondrial deletion which mapped to the ND5 region.Furthermore, postmortem examination revealed that their patient had multiple renal cysts. Since we could not obtain consent for an autopsy, we do not know whether our patient had other organ anomalies. Our case is one of few in which patients present with severe acidosis in the newborn period due to Pearson syndrome. Involvement of liver mtDNA may be responsible for the early appearance of the disease. We conclude that Pearson syndrome should be considered in the differential diagnosis of acidotic neonates prior to the development of anemia and pancreatic dysfunction.

Acknowledgements

The authors would like to thank Dr. Agnes Rötig for the mitochondrial DNA analysis.

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BENIGN RHEUMATOID NODULES OF CHILDHOOD*

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SUMMARY: Kabukçuoğlu S, Tel N, Paşaoğlu Ö, İlhan H. (Departments of Pathology and Pediatric Surgery, Osmangazi University Faculty of Medicine, Eskişehir, Turkey). Benign rheumatoid nodules of childhood. Turk J Pediatr 1999; 41: 365-368.

The nodules associated with rheumatoid arthritis and rheumatic fever appear with other signs of active rheumatic disease. Rheumatoid nodule-like lesions irrelevant to rheumatoid disease occasionally occur in children who are well and have no complaints associated with rheumatoid diseases. Laboratory tests are normal. Children with benign rheumatoid nodule are not at increased risk for rheumatic disease. No therapy or prophylaxis is required. We present a two-year-old girl with a subcutaneous nodule on the right pretibial region who was diagnosed with clinical and histological findings. *Key words: benign rheumatoid nodule.*

The rheumatoid nodule is the most characteristic histopathological lesion of rheumatoid arthritis[1]. Nodules occur particularly over extensor surfaces and the metacarpophalangeal and interphalangeal joints. They may also involve pericardial, pleural, peritoneal, and endocardial tissues, lungs, gastrointestinal system, central nervous system and kidneys. Subcutaneous rheumatoid nodules are found in about 25 percent of rheumatoid arthritis cases. These nodules are generally accompanied by positive test result for rheumatoid factor and symptoms of rheumatoid arthritis[2-6]. Subcutaneous nodules with the histopathological features of rheumatoid nodules can occur in both rheumatic and non-rheumatic diseases[1,7-10].

The terms benign rheumatoid nodule and pseudorheumatoid nodule are used for nodules localized in the subcutis that mimic rheumatoid nodules histologically but develop in the absence of rheumatoid arthritis or systemic disease. These nodules have also been considered a subcutaneous variant of granuloma annulare. The subsequent development of rheumatoid arthritis occurs infrequently in adults but rarely in children[11].

In this report, we describe a benign rheumatoid nodule in a two-year-old girl without rheumatoid disease.

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Case Report

A two-year-old girl was admitted to hospital because of a two-month enduration on her right pretibial region. There was no pain or limitation of motion. There was no history of trauma in this area. Physical examination was normal. Complete blood count, sedimentation rate, ASO, C-reactive protein (C-RP), latex, antinuclear antibodies (ANA), anti-DNA and immunglobulin values were in normal limits. A provisional differential diagnosis of soft tissue tumor/leiomyoma was considered. The lesion was totally excised without skin. Biopsy specimen was 2.5 x 1.5 x 1 cm. It was fixed in 10 percent formalin and tissue sections were stained with hematoxylin-eosin, Masson's trichrome and alcian blue. Microscopic examination showed that the central fibrinoid necrosis was surrounded by radially oriented mononuclear cells, and a marginal zone of vascular connective tissue was seen around these cells (Fig. 1). The fibrinoid necrosis was stained red-blue with Masson's trichrome and was stained dark blue in some areas with alcian blue (Fig. 2). Special stains were negative for fungi and mycobacteria. Benign rheumatoid nodule was diagnosed with clinical and histological findings. The patilent was healthy and without complaint after one year.

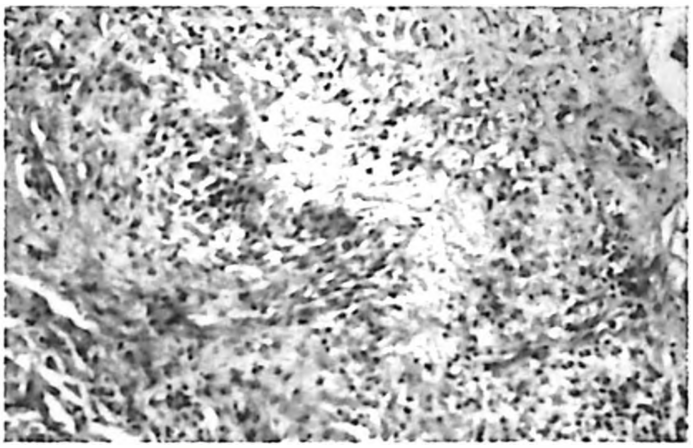

Fig. 2: Fibrinoid necrosis staining red-blue (Masson's trichrome x 80).

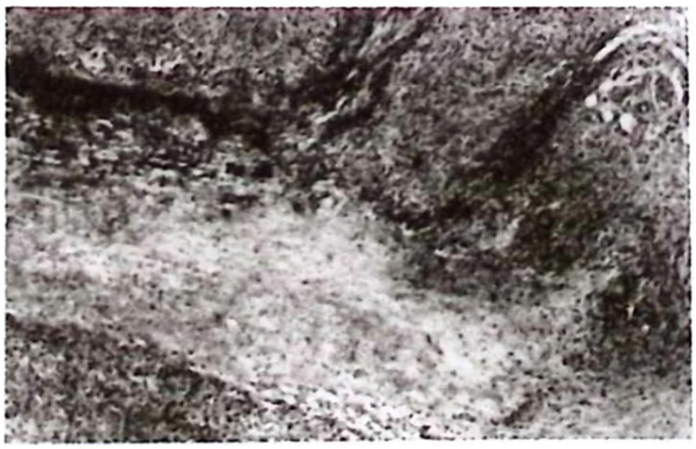

Fig. 1: Rheumatoid nodule (hematoxylin-eosin x 80).

Discussion

The etiology of benign rheumatoid nodule is unknown. Single or multiple lesions may be present over various sites, including pretibial areas, dorsa of the feet, hands, scalp and elbows. They may appear over pressure points or after trauma as do true rheumatoid nodules.

Affected children are well and have no associated rheumatic complaints. Laboratory tests of active rheumatic disease are normal. Tests for rheumatoid factor and ANA are negative[9,12]. "Hidden" rheumatoid factor has been found with higher titers than in controls. The nodular lesions may recur, but recurrences eventually cease, although it could be after months or years[8,11].

Subcutaneous nodules are characterized by foci of fibrinoid necrosis surrounded by palisading histiocytes and fibroblasts and a marginal zone of vascular connective tissue usually having chronic inflammatory cells[1]. Patterson[13] studied more closely the histology of subcutaneous granuloma annulare and rheumatoid nodules. He was able to differentiate these lesions by alcian blue and Masson's trichrome staining. Alcian blue, which stains mucin in degenerated collagen, was the most helpful diagnostic histochemical method. Patterson suggested that positive alcian blue staining shows the benign nature of the disease. He demonstrated that rheumatoid nodules stain homogeneous red with Masson's trichrome, whereas the central zone of granuloma annulare stains blue-red[13]. A similar staining pattern was demonstrated in our case.

Rheumatoid nodules can occur in association with rheumatoid arthritis, juvenile rheumatoid arthritis, rheumatic fever and systemic lupus erythematosus. Single or multiple subcutaneous nodules are a major criterion for the diagnosis of rheumatic fever; however, they are very infrequent. They are most commonly observed with severe carditis. Histologically, central, homogeneous fibrinoid necrosis and palisading of histiocytes usually do not develop well in rheumatic fever nodules, and fibrosis is minimal or absent[1,11,12,14]. The clinical and histopathological features and the age of our patient were not compatible with rheumatic fever.

Other subcutaneous nodules that might be considered in the clinical differential diagnosis include erythema nodosum, sarcoid, bone and soft tissue tumors, mycobacterial or fungal infections and the occasional nodules of scleroderma and periarteritis nodosa[8,11]. The clinical features associated with these diseases are usually sufficient to distinguish them.

Children with benign rheumatoid nodule do not have increased risk for rheumatic disease. No therapy or prophylaxis is required[12].

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GASTRIC ANTRAL STRICTURE IN A PATIENT WITH CHRONIC GRANULOMATOUS DISEASE*

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SUMMARY: Metin A, Sanal Ö, Tezcan İ, Ersoy F, Berkel Aİ. (Immunology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Gastric antral stricture in a patient with chronic granulomatous disease. Turk J Pediatr 1999; 41: 369-373.

Chronic granulomatous disease (CGD) is a rare disorder of phagocytic cell oxidative metabolism. Patients have recurrent infections with catalase-positive organisms and granulomatous lesions throughout the body. Gastric antrum can be an occult site of involvement. We describe a four-year old boy with chronic granulomatous disease who was admitted with the complaints of persistent vomiting and weight loss. Gastric antral narrowing was diagnosed according to radiological findings. Treatment with steroid and antibiotics yielded a good clinical response in 15 days with a relief of the obstruction. This case report emphasizes the beneficial effect of this form of therapy in preventing life-threatening obstruction of vital organs in CGD. *Key words: chronic granulomatous disease, complications.*

Chronic granulomatous disease (CGD) is a rare disease affecting about 1 in 500,000 individuals. It is characterized by recurrent, life-threatening infections with catalase-positive microorganisms and excessive inflammatory reactions that lead to granuloma formation. Neutrophils do not respond to various stimuli with respiratory burst, therefore failing to reduce molecular oxygen to superoxide which is required for the generation of other toxic metabolites such as hydrogen peroxide and hydroxyl radicals. Several different mutations of NADPH-oxidase are associated with this disorder[1]. In addition to recurrent and severe pulmonary and skin infections, CGD patients have inflammatory disease of the gastrointestinal and urinary systems which leads to luminal narowing[2-8]. The general management of CGD includes prophylactic antimicrobial agents in order to prevent infection and immunomodulatory therapy with interferon-gamma[9]. Here we present a CGD patient with granulomatous narrowing of the gastric antrum who was treated successfully with corticosteroid and antibiotic.

Case Report

A four-year-old boy diagnosed as having CGD at the age of two months was admitted to Hacettepe Children's Hospital with persistent vomiting and weight loss. There was a medical history of a recent cranial trauma, the complaints of

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which had been evaluated at a local hospital. His cranial computed tomography was (CT) normal, and he was treated for the diagnosis of peptic ulcerative disease because of an antral abnormality shown by roentgenograms. His first admission to our hospital was at two months of age. He was the fourth child of parents who are first-degree relatives. The first and second children were healthy boys, but the older sister of the patient had also been admitted to our hospital for generalized lymphadenopathy two months after BCG vaccination. Culture of the left axillary discharge grew M. bovis (BCG strain). She was diagnosed with CGD by slide NBT test and died at eight months of age after developing pneumonia at home.

On the first admittance to our hospital at two months of age, our patient's physical examination revealed generalized pustular rash; a liver and spleen palpable 3 and 2 cm below the costal margins, respectively, and a suppurative lymphadenitis on the left inguinal region. Cultures were positive for coagulase-positive staphylococci, and the patient was diagnosed as his sister with CGD. Medical management from infancy included administration of trimethoprim-sulfamethoxazole (TMP-SMX) and itraconazole. Over a three-year period he was admitted regularly for controls and treatment of occasional upper and lower respiratory tract infections, and he was hospitalized for a deep neck infection at three years of age. He achieved age-appropriate developmental milestones between the 3^{rd}-10^{th} percentile. Hepatosplenomegaly disappeared. He was initially maintained on prophylactic TMP-SMX and itraconazole but for the previous 13 months, his parents were unsuccessful in administering the medication due to the child's resistance.

On this admission at the age of four years with persistent emesis of one-month duration, findings remained unchanged. He had several small, mobile, non-tender cervical and inguinal lymph nodes and scars which were fully healed. There was no hepatosplenomegaly or pulmonary symptoms. He was midly dehydrated. His complete blood count showed a hemoglobin level of 12 g/dl, a leukocyte count of 10,000/µl with 55 percent neutrophils, 3 percent banded neutrophils, 36 percent lymphocytes, 6 percent monocytes and a platelet count of 385,000/µl.

Esophagus, stomach, and duodenum radiograms with barium swallow taken to investigate a gastric outlet obstruction showed antral narrowing (Fig. 1). Treatment with oral methylprednisolone (2 mg/kg/day, bid) and clindamycin (25 mg/kg/day, qid) decreased the frequency of emesis in a week and the patient began tolerating oral feeding. After 14 days, the methylprednisolone dose was slowly tapered over two months and stopped. He has been doing well four about eight months without recurrence of symptoms, and control radiographic studies are normal (Fig. 2). Daily prophylactic TMP-SMX and itraconazole therapies were started again and have been continued to date.

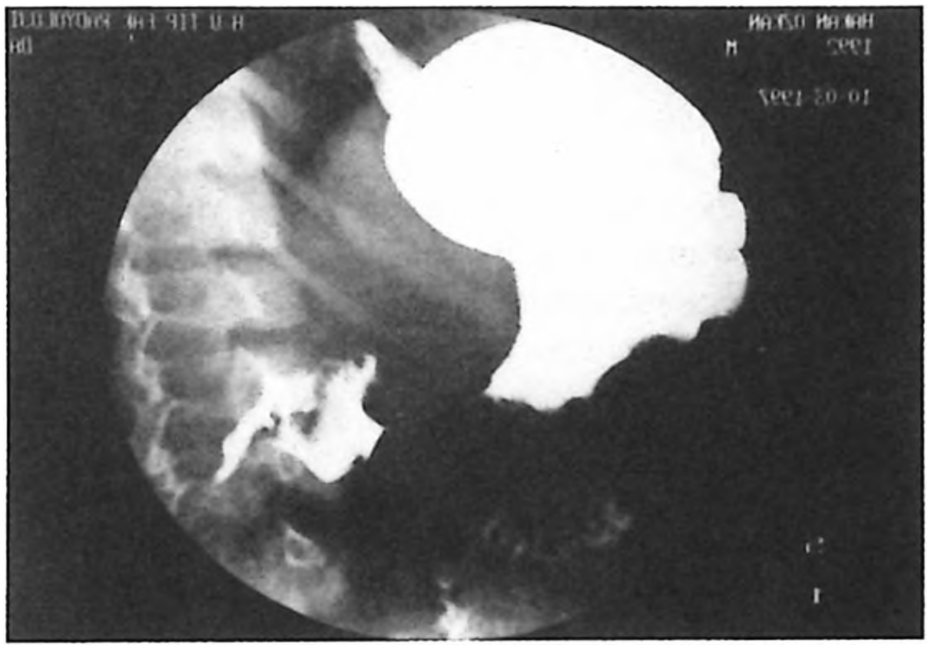

Fig. 1: Upper gastrointestinal radiography shows nearly complete gastric outlet obstruction.

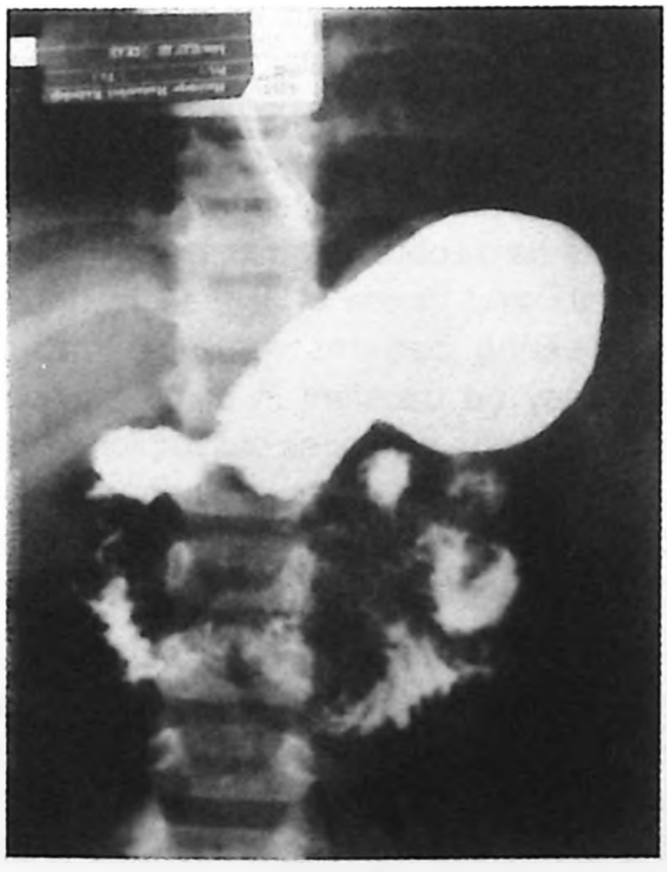

Fig. 2: Appearance of antrum after steroid therapy.

Discussion

Gastrointestinal manifestations of CGD include persistent diarrhea, vitamin B_{12} malabsorption, steatorrhea, and diffuse or localized granulomatous and obstructive lesions in the esophagus, gastric outlet or entire intestine due to incomplete resolution of the inflammatory response[10]. Involvement of the terminal ileum and colon results in enteritis and colitis similar to that of Crohn's disease. Gastric antral narrowing or obstruction may lead to vomiting, delayed gastric emptying and malnutrition. Genitourinary tract may also be an occult site of involvement. A retrospective chart review revealed that seven of 60 CGD patients (10%) had ureteral strictures[6]. Histopathological changes leading to obstruction in luminous organs are the same as in other parts of the body, characterized by sterile non-caseating granulomas with an accumulation of phagocytes and giant histiocytes and focal necrosis in the muscle layers.

Griscom et al.[2] first reported gastrointestinal obstruction as a major complication in CGD in 1974. Since this initial report, 20 patients with CGD and gastric outlet obstruction have been reported.

Surgery must be considered in the treatment of certain obstructions in CGD patients. However, because of the possibility of postoperative complications due to excessive granuloma formation in the site of operation, defective wound healing and fistulization, corticosteroid and antibiotic treatment is preferred. Indeed, this protocol has been effectively used in many patients to reverse the excessive inflammatory process in CGD[2,3,5,6]. In our patient, symptomatic relief occurred within two weeks and allowed outpatient management, as in the patient described by Chin et al.[3] and we thus avoided surgical intervention. However, responses of different patients or of the same patient at different episodes may vary. Patients described by Bowen et al.[7] and Varma et al.[8] received therapy for five to six months before normal eating patterns returned. Improvement with this combination of therapy may be transient in some patients for variable time periods. Some patients showed recurrences of symptoms[2,3]. On the other hand, most of the patients described to date showed urinary system involvement as well (granulomatous cystitis, bladder outlet obstruction or ureteral obstruction[2,3,6]. Therefore, therapy for these complications has been difficult.

Differential diagnosis of gastic antral narrowing in a child should include Crohn's disease, peptic ulcerative disease and eosinophilic gastritis, but these conditions seldom produce the abrupt annular narrowing of the antrum usually seen in CGD patients. Annular narrowing may occasionally be the presenting symptom of CGD[8]. Therefore, when an antral stenosis is discovered, an NBT test should be done to exclude CGD.

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TUMORAL CALCINOSIS*
A Case Report

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SUMMARY: Özkan İ, Türeli C, Çullu E, Karaman C, Şendur F, Alparslan B. (Department of Orthopedics and Traumatology, Adnan Menderes University Faculty of Medicine, Aydın, Turkey). Tumoral calcinosis: a case report. Turk J Pediatr 1999; 41: 375-379.

Tumoral calcinosis is a rare disorder with the calcified masses in subcutaneous tissues. We report herein a nine-year-old girl, in whom the calcified lesions bilaterally involved the soft tissues in the anterior part of the knee joint. Serum calcium and phosphorus levels were in normal ranges and there was no family history. Surgical excision was performed and recurrence was not observed in early follow-up. Review of the literature shows that only clinical and radiological appearance of tumoral calcinosis are generally agreed while its epidemiology, etiology and treatment are still under discussion. *Key words: tumoral calcinosis, ectopic calcification syndrome.*

Tumoral calcinosis is an uncommon disease of uncertain origin, which is rarely seen in Europe but is much more common among black Africans[1]. This ectopic calcification syndrome is characterized clinically by para-articular soft tissue calcifications. Various locations and types of calcium deposits have been defined. Irregular and painless calcifying masses were previously reported arround the shoulder, hip, elbow, temporomandibular joint, paraspinal soft tissues and eye[2-6]. Cases of tumoral calcinosis in association with hyperphosphatemia have been reported, and it seems likely that hyperphosphatemia may play a role in the pathogenesis[4,7,8]. However, numerous underlying factors are thought to increase susceptibility to this disease. Genetical disorders, recurrent soft tissue microtrauma and terminal renal failure have been cited as causes of tumoral calcinosis[7,9]. In most cases, local factors are probably involved as well.

Histologically, there are fibrous walled cystic spaces containing structureless calcific debris in association with a variable inflammatory reaction.

We report herein a case of a nine-year-old girl with idiopathic tumoral calcinosis on the anterior part of both knees.

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Case Report

A nine-year-old girl was admitted suffering from multiple, painless masses on the anterior part of both knees since 10 months of age. The masses were irregular in shape and located on the anterior part of the patella and patellar tendon (Fig. 1). Radiographs revealed several calcific subcutaneous masses around the knee joint (Fig. 2).

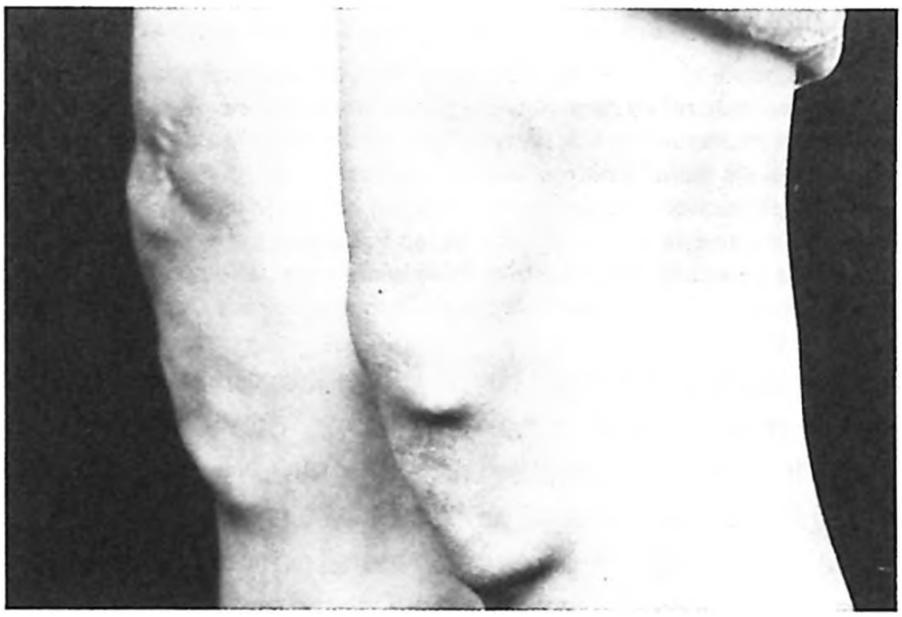

Fig. 1: The appearance of the patient's knees.

Fig. 2a: Lateral radiography of the right knee.

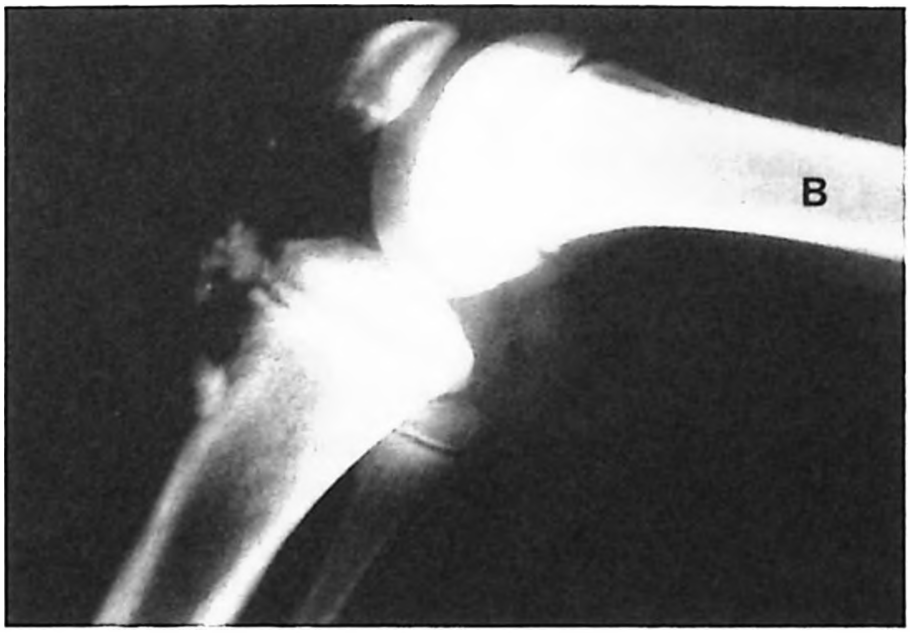

Fig. 2b: Lateral radiography of the left knee.

Serum calcium was 9.5 mg/dl and serum phosphate 4.0 mg/dl. Urea, creatinine, alkaline phosphatase, sodium, potassium, magnesium, parathormone, free and total T3 and T4, testosterone and cortisone values were in normal limits. Excretions of calcium and phosphate in 24-hour urine were also normal. Laboratory examinations for serum calcium and phosphate were repeated at monthly intervals three times, each time revealing normocalcemia and normophosphatemia.

The masses on the right knee were removed under general anesthesia. During surgery, a chalky semifluid material extruding through the masses was observed. Histological examination revealed fibrous walled cystic spaces containing calcific debris and various inflammatory reactions (Fig. 3).

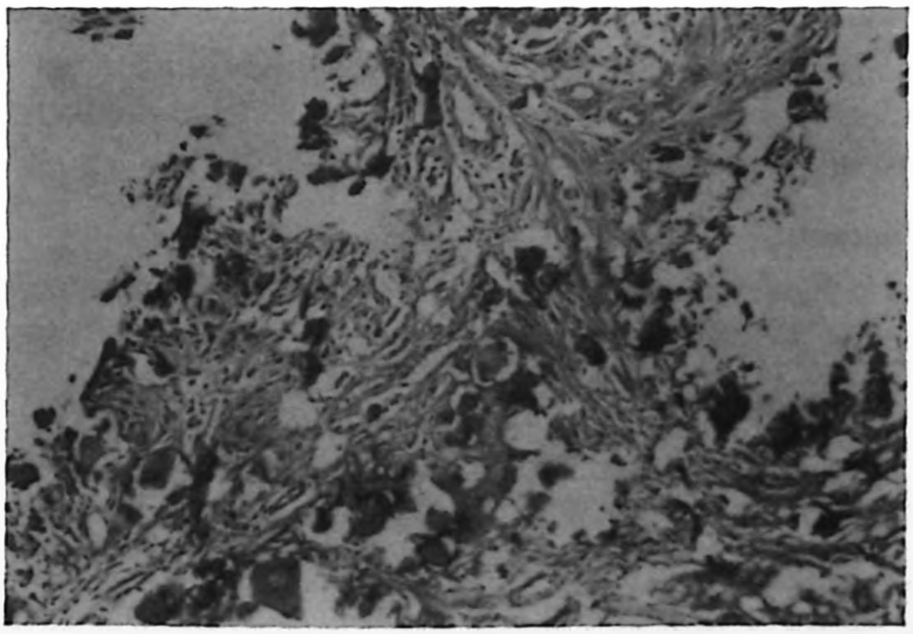

Fig. 3: Photomicrograph of calcifying masses (hematoxylin eosin x 200).

Discussion

Idiopathic tumoral calcinosis should be diagnosed by eliminating the other diseases in which similar calcifying masses are seen. Idiopathic synovial chondromatosis must be differentiated, especially when the lesions in tumoral calcinosis are seen around big joints as in the case reported here. Tumoral calcinosis may be confused with synovial sarcomas when the synovial sarcomas present with dense and conglomerate calcifications. Malignancies such as extraskeletal osteogenic sarcoma, extraskeletal chondrosarcoma and mesenchymal chondrosarcoma must also be considered in the differential diagnosis[10].

Pathogenesis-based classification of tumoral calcinosis was made by Smack et al.[11]. They suggested three pathogenically distinct subtypes of tumoral calcinosis: 1) primary normophosphatemic tumoral calcinosis, 2) primary hyperphosphatemic tumoral calcinosis, and 3) secondary tumoral calcinosis. The presented case is a group 1 tumoral calcinosis with normal serum phosphate level and no family history. Soft tissue calcifications are a frequent complication in patients with chronic renal failure[7]. These patients are accepted as secondary tumoral calcinosis. Familial cases of tumoral calcinosis have also been reported[9]. Some authors suggest that tumoral calcinosis should be included among the clinical presentations of calcium pyrophosphate dehydrate crystal deposition disease[12]. However, we believe that is difficult to explain this with normal serum calcium and phosphorus levels as in the presented case.

The medical treatment of tumoral calcinosis is symptomatic. At present the valid medical treatments are surgical excision and/or a low-phosphorus, low-calcium diet with phosphate-binding antacids[8,13]. Acetozolamide appears useful in treatment of tumoral calcinosis, which is resistant to phosphorus deprivation by aluminum hydroxide alone[8]. Complete surgical excision of lesions has been recommended[13,14], but recurrence is common[16,14]. Although there has been only eight months of follow-up in the present case, there has been no early recurrence of the lesions around the knee.

Review of the literature shows that only clinical and radiological appearance of tumoral calcinosis are generally agreed while its epidemiology, etiology and treatment are still under discussion.

Acknowledgement

We would like to thank Associate Professor Emel Dikicioğlu, Department of Pathology, Adnan Menderes University Faculty of Medicine, for her histopathological evaluation.

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EOSINOPHILIC FASCIITIS – PROGRESSION TO LINEAR SCLERODERMA*

A Case Report

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SUMMARY: Balat A, Akıncı A, Turgut M, Mızrak B, Aydın A. (Departments of Pediatrics and Pathology, İnönü University Faculty of Medicine, Turgut Özal Medical Center, Malatya, Turkey). Eosinophilic fasciitis-progression to linear scleroderma: a case report. Turk J Pediatr 1999; 41: 381-385.

Eosinophilic fasciitis is a rare disease in children. Although changes similar to linear scleroderma have been reported, the outcome is usually good. In this report, a 10-year-old boy who developed eosinophilic fasciitis without a good response to steroids is presented. He progressed to linear scleroderma within months. Our case reinforces the hypothesis that eosinophilic fasciitis may be an early manifestation or a variant of localized scleroderma similar to the other cases in the literature. *Key words: eosinophilic fasciitis, childhood scleroderma.*

Eosinophilic fasciitis (EF) is a connective tissue disease characterized by rapid development of thickening and induration of the skin in the extremities with pain, swelling and stiffness, but there is no internal organ involvement. A peripheral and cutaneous eosinophilia is present[1,2]. It is a rare disease in children. The outcome is usually good, although changes similar to linear scleroderma have been reported[3,4]. In this article, we present a 10-year-old boy who was diagnosed with eosinophilic fasciitis and who progressed to linear scleroderma within months.

Case Report

This 10-year-old boy was otherwise healthy when swelling of his left hand occurred after physical stress. Within a month, there was swelling of the left leg below the knee, and he was reluctant to use his left arm or leg due to pain.

Physical examination revealed diffuse swelling without pitting in his left forearm and distal leg. The skin was indurated and had mild erythema (Fig. 1a, b). The subcutaneous tissue felt thickened. His head, neck, and trunk were normal. These

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was full passive range of motion of his joints, but with pain in the left. The joint appeared normal and no definite muscle weakness was apparent. No facial swelling or heliotrope skin rash was present. His white blood cell count was 8,500/mm^3 with 10 percent eosinophils. The serum IgG level was 1,126 mg/dl (normal: 748-20,001 mg/dl). Antinuclear antibody titer (ANA) was positive. His erythrocyte sedimentation rate (ESR), blood hemoglobin and hematocrit, complement levels, serum creatine kinase, T3 and T4, serum chemistry profile, urine and stool analysis, chest and limb roentgenograms, barium swallow examination, and abdominal ultrasonography were normal. Skin biopsy of the indurated left forearm showed intense eosinophilic, leukocytic, and lymphocytic fasciitis with edema (Fig. 2).

A diagnosis of EF was made on the basis of the clinical and histological findings, and prednisone 2 mg/kg was prescribed, but his response to the steroid was not good. The lesion was active and involved the joints. Penicillamine 2 mg/kg/d was initiated in combination with prednisone for the first three months, followed by penicillamine alone. The swelling of the extremities decreased. The skin in these areas became tight and hard over the joints and range of movement was limited. These skin changes were identical to those of localized scleroderma (Fig. 1c). Physical therapy was initiated to preserve joint range of motion. The disease was in remission with penicillamine therapy.

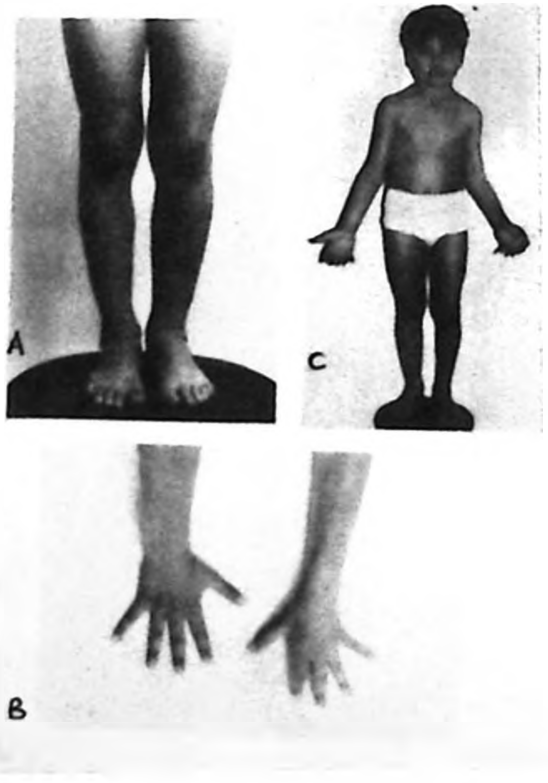

Fig. 1: Left distal leg (a) and forearm (b) of the patient depicting diffuse swelling without pitting at the beginning of the disease. Note the indurated and mild erythematous skin. After remission of the lesions, note the sclerotic areas of skin (c) in a linear, bandlike distribution crossing joint lines and leading to joint contractures on left.

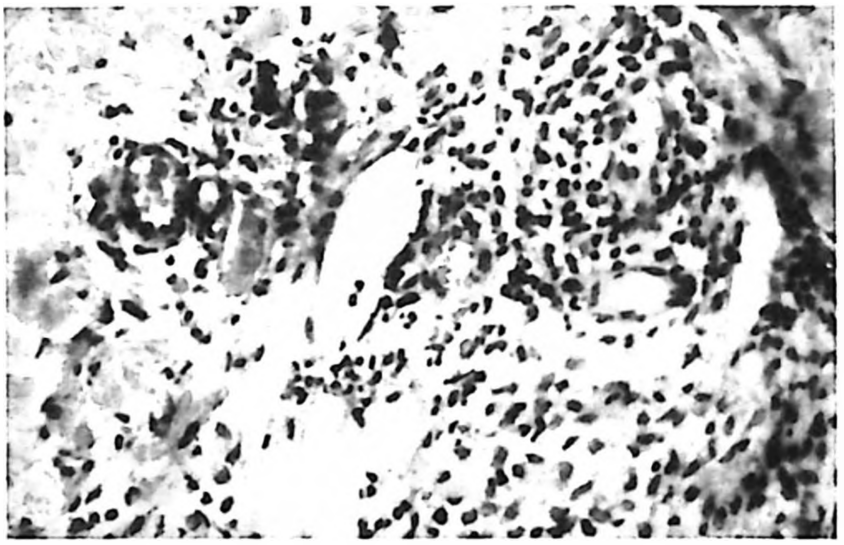

Fig. 2: Subcutaneous tissue in biopsy obtained from patient about a month after onset of symptoms. An intensive fasciitis with edema is evident. The inflammatory infiltrate was predominantly composed of eosinophils, lymphocytes and leukocytes. Patient was under no therapy at the time of biopsy (HE x 400).

Discussion

Eosinophilic fasciitis is a connective tissue disease characterized by painful induration and thickening of the skin and soft tissues, predominantly of the extremities[5]. Biopsy of involved tissue reveals diffuse inflammation of the fascia, often with eosinophilia.

Eosinophilic fasciitis (EF) in adults was originally described as a corticosteroid responsive disease which often completely resolves[3]. More recent reports of adult and pediatric cases describe initial resolution of soft tissue induration and correction of laboratory abnormalities with prednisone therapy; however, gradual progression to thickened skin occurs[6-8]. Some hemotological complications, such as aplastic anemia, thrombocytopenic purpura and others, which occur in adults, have not been reported in children[9]. These differences suggest that the pediatric form of EF may be a distinct clinical entity.

Pediatric EF predominantly affects girls and frequently involves the hands; associated arthritis is found in only 25 percent of case[1]. The outcome of adult eosinophilic fasciitis is generally favorable, and the majority of cases respond to steroid therapy. However, complications due to residual fibrosis occur in a substantial number of patients. These include flexion contractures secondary to fascial involvement, localized morphea which develops in up to one-third of cases, and carpal tunnel syndrome which is seen in about 20 percent[3,4]. However, the outcome of pediatric EF has not been well studied. Recently, Farrington et al.[2] evaluated long-term outcome in 21 pediatric patients with biopsy-proven EF. It was shown that two-thirds of pediatric EF cases eventually progress to a form of residual cutaneous fibrosis, while one-third enjoyed

complete resolution of disease. Progression to cutaneous fibrosis may occur over one or more years, indicating that a substantial period of follow-up is required to fully assess the outcome in pediatric EF[2]. In our patient, this progression occurred within months. According to results of Farrington's series[2], two possible risk factors that are associated with the likelihood of progression to cutaneous fibrosis were identified: age under seven years and more extensive initial disease at the time of diagnosis. Although our patient was over seven, he had extensive initial disease. Farrington et al.[2] detected no association between progression to cutaneous fibrosis and the sex of the patient, duration of symptoms prior to therapy, type of therapy, history of prior physical stress, or laboratory variables at diagnosis. Transition to scleroderma has been reported but is considered a rare event[1,2,10,11]. In Farrington's series[2], one-fourth of pedilatric patients with EF progressed to some form of scleroderma-like cutaneous fibrosis. Ten of 17 reported pediatric patients with EF also developed residual skin lesions consistent with cutaneous fibrosis.

Laboratory findings in EF show peripheral eosinophilia, hypergammaglobulinemia, elevated ESR and variable presence of rheumatoid factor, ANA, anti-DNA antibody and hypocomplementemia[3]. No clear correlation between clinical features and a particular ANA titer or pattern exists. Usually these serologic abnormalities are present during periods of disease activity and disappear during remission[12,13]. Our patient had peripheral eosinophilia and ANA positivity during the period of disease activity. Peripheral eosinophilia disappeared in remission, but he still had ANA positivity.

In summary, our patient had the characteristic clinical picture of EF but no good response to prednisone. The other disturbing feature was the presence and gradual worsening of the skin changes: there is now a puckered, brown, hidebound sclerodermatous appearance. These dermatological developments reinforce the notion that EF may be an early manifestation or a variant of localized scleroderma[8,14,15]. A younger age and more extensive disease should alert the clinician to the probable eventual progression of the disease to residual skin fibrosis.

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SACROILIITIS IN FAMILIAL MEDITERRANEAN FEVER*
An Unusual Presentation in Childhood

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SUMMARY: Beşbaş N, Özdemir S, Saatçi I, Bakkaloğlu A, Özen S, Saatçi Ü. (Nephrology and Rheumatology Unit, Department of Pediatrics, and Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Sacroiliitis in familial Mediterranean fever: an unusual presentation in childhood. Turk J Pediatr 1999; 41: 387-390.

Familial Mediterranean fever (FMF) is an autosomal recessively transmitted disease characterized by attacks of fever and serositis. The course of arthritis, which is a common manifestation of FMF, is generally benign. Sacroiliitis due to FMF has been reported by several authors, but all the patients described so far had roentgenographic abnormalities, and most of them were adult cases. Here we report the youngest FMF patient with sacroiliitis without any abnormality on sacroiliac x-ray. She is also the first FMF patient in whom sacroiliac involvement was diagnosed by computed tomography (CT) in childhood. It is concluded that CT is a useful technique for the early diagnosis of destructive arthritis in FMF patients even in early childhood.
Key words: familial Mediterranean fever, sacroiliitis, childhood, computed tomography.

Familial Mediterranean fever (FMF) is an autosomal recessive disease of unknown origin characterized by recurrent and self-limited episodes of fever accompanied by peritonitis, pleuritis and arthritis[1,2]. FMF attacks are usually short in duration, typically lasting 12-72 hours, but protracted episodes of arthritis lasting approximately one year, mainly affecting the large joints of the lower extremities, are also seen[3]. The course of arthritis is typically benign without any destruction or incapacity, but cases with destructive arthritis have also been reported in the literature[4,5].

In 25 percent of FMF patients, arthritis is the initial symptom. HLA-B27-negative sacroiliitis has been reported in the literature[6-8], but the diagnosis of destructive sacroiliitis has been based on roentgenographic findings in all the patients previously reported[4,6,7,9]. Destructive sacroiliitis presents a considerable problem, sometimes requiring surgical treatment[5]. The diagnosis may be difficult and, in cases presenting with arthritis only, this may cause a delay in the specific therapy of FMF.

We report an FMF patient with HLA-B27-negative destructive sacroiliitis without any abnormality on conventional x-ray studies.

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Case Report

A $5^1/_2$ year-old Turkish girl was admitted to Hacettepe Children's Hospital in January 1994 for evaluation of hip pain and intermittent fever with attacks of abdominal, chest and lower extremity joint pain At $1^1/_2$ years of age, her left ankle became swollen and painful together with systemic fever lasting two days. Subsequently, she suffered from intermittent attacks of fever with severe abdominal and chest pain, sometimes with arthritis that ceased spontaneously in two or three dyas. Duration of symptom-free intervals were between three weeks and six months. The patient was also complaining of continuous right hip pain for approximately three years, which was aggravated during the attack periods. Family history revealed similar complaints in a female cousin on her father's side, and her father's uncle was diagnosed as end stage renal failure due to amyloidosis at the age of 44.

On examination, she was at the 25^{th} percentile for weight and 50^{th} percentile for height; her blood pressure was 100/65 mmHg. Minimal atrophy of the right leg was observed; otherwise, physical examination including ophthalmological evaluation was normal.

Complete blood cell count and the results of urinalysis, electrolytes, blood urea nitrogen, creatinine concentrations, erythrocyte sedimentation rate and fibrinogen were all normal. Antinuclear antibodies, C-reactive protein and rheumatoid factor tests were negative. Repeated values of erythrocyte sedimentation rate, fibrinogen (normal: 200-400 mg/dl) and C-reactive protein (normal: < 2 mg/dl) levels during an attack were: 80 mm/hr, 518 mg/dl and 8.3 mg/dl, respectively. Although there was no abnormality on her sacroiliac joint roentgenogram (Fig. 1), a computed

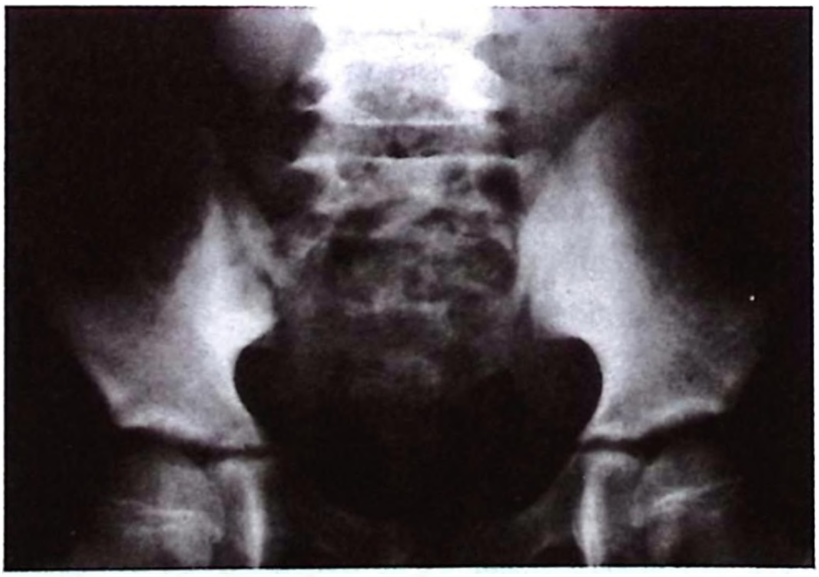

Fig. 1: Anteroposterior radiogram of pelvis is unremarkable except for the incidental spina bifida noted at the L-5 vertebrae.

tomography (CT) of the sacroiliac joints was performed since the patient had severe hip pain. Irregularity in the iliac aspects of the sacroiliac joints, more pronounced in the right, was demonstrated, indicating bilateral sacroiliitis (Fig. 2). HLA-B27 was not present. Colchicine therapy (1 mg/day orally) was started, and responded well to the therapy. The patient has been free of symptoms, including continuous hip pain, since July 1994.

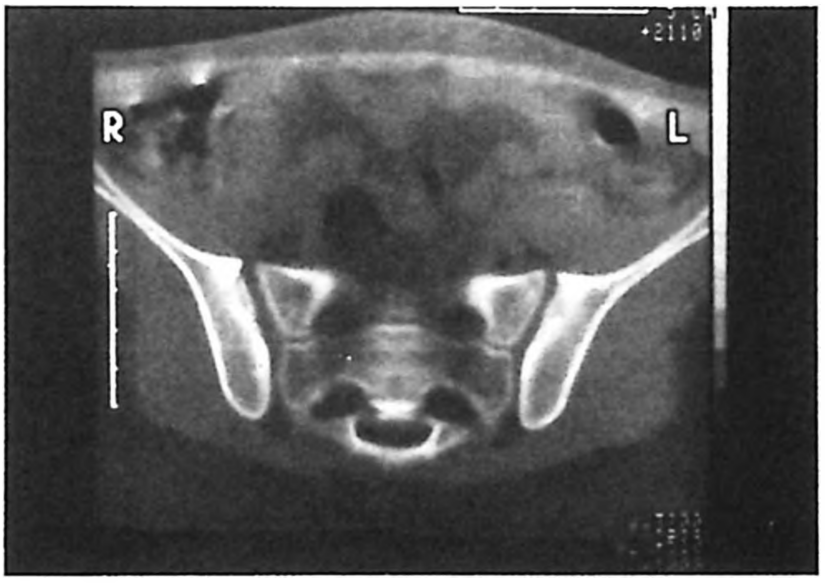

Fig. 2: Axial tomography section through the sacroiliac joints demonstrates the widening of the joint space on the right. Irregularity in the iliac aspect of the sacroiliac joints, more pronounced on the right, indicates destruction of the articular surfaces.

Discussion

Familial Mediterranean fever is a lifelong disease, usually appearing after the first two years of life. The diagnosis is mainly based on clinical findings together with a positive family history and exclusion of any other disorder that may cause similar attacks[1,8]. Arthritis of FMF manifests itself as an episodic monoarthritis or oligoarthritis of large joints that appears in childhood or adolescence, and may precede other manifestations of the disease. Although the episodes are short and self-limited (days to weeks) in nature, five percent may occasionally last for several months and even up to one year[3,4]. Permanent joint damage is a rare finding, but transient osteoporotic periarticular changes are reported[3,9]. Sacroiliac joint involvement due to FMF has been reported, especially in adult patients, with the diagnosis based on roentgenographic abnormalities[4,10]. There are only two reports of sacroiliitis associated with childhood FMF in the literature, with the youngest case reported so far being ten years old[6,7].

Sacroiliitis is commonly seen in Reiter's syndrome, ankylosing spondylitis, Crohn's disease, ulcerative colitis, Whipple's disease and psoriatic arthritis. In these disorders, HLA-B27 positivity is higher than in the normal population[11]. However,

HLA-B27 is not present in FMF patients with sacroiliitis, as was the case with our patient. She complained of a continuous hip pain aggravated during the periods of fever and abdominal pain. The roentgenographic appearance of the sacroiliac joints was unremarkable. A CT examination was performed in order to explain the atypical complaints of the patient, and destructive changes were observed which confirmed the diagnosis of sacroiliitis. The patient was diagnosed as FMF with sacroiliac joint involvement based on the clinical course of her disease: recurrent fever accompanied by abdominal and joint pain history with elevated acute phase reactants during the attacks, together with a positive family history and her ethnic origin. All complaints, including continuous hip pain, resolved after colchicine treatment.

This is the youngest FMF patient with sacroiliitis reported so far. All previously reported cases were diagnosed by x-rays. Our patient is the first case diagnosed by CT as sacroiliitis due to FMF in the absence of pathologic findings on x-ray. We conclude that CT is a useful technique for the early diagnosis of destructive arthritis in FMF patients with long-standing joint involvement.

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RESPIRATORY DISTRESS DUE TO ESOPHAGEAL PERFORATION CAUSED BY BALL POINT INGESTION*

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SUMMARY: Türken A, Tanyel FC, Hiçsönmez A. (Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Respiratory distress due to esophageal perforation caused by ball point ingestion. Turk J Pediatr 1999; 41: 391-393.

A 15-month-old girl who developed respiratory distress which persisted for three days prior to admission demonstrated pleural effusion on the chest x-ray which was determined to be due to esophageal perforation caused by the ingestion of a ball point. A gastrotomy was performed to extract the ball point. A gastrostomy was performed and a chest tube was inserted. The esophagus was normal radiologically within one month. Foreign body ingestion may cause esophageal perforation in childhood. If it goes unnoticed and a diagnosis is delayed, there is danger of the more hazardous development of mediastinitis. It is important that a child with respiratory distress also be evaluated for esophageal foreign body ingestion.
Key words: esophageal perforation, respiratory distress.

Respiratory distress is a frequent cause of emergency admission of young children[1]. Among the numerous causes of respiratory distress, esophageal perforation resulting from unwitnessed foreign body ingestion accounts for a small percentage. Although foreign body perforation of the esophagus has a favorable prognosis, a delay in diagnosis and treatment can lead to a fatal outcome[2-3].

A 15-month-old infant who was in respiratory distress due to esophageal perforation is presented to stress the possibility of esophageal perforation as a cause of respiratory distress in childhood.

Case Report

A 15-month-old girl was admitted with respiratory distress. Her complaints had begun three days prior to admission with coughing and vomiting. The characteristics of the vomitus had changed from the ingesta to bilious, and respiratory distress had become the predominant symptom.

On physical examination, tachypnea together with substernal, suprasternal and intercostal retractions were observed. Her pulse rate was 120/min, blood pressure 100/70 mmHg and axillary temperature was 38.2 °C. Auscultatilon revealed absence of respiratory sounds on the right hemithorax. A pencil-like substance of 6 cm was palpated in the epigastric area beneath the xyphoid directed to the umbilicus. When this was brought to the attention of the parents, they recalled seeing the baby playing with a ball point three days previously.

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Routine investigations including complete blood count, urinalysis and biochemistry were in normal limits. Chest x-rays obtained in posteroanterior and lateral directions revealed pleural effusion in the right hemithorax, and the radiopaque tip of the ball point at the level of the 5th thoracic vertebra (Figs. 1-2).

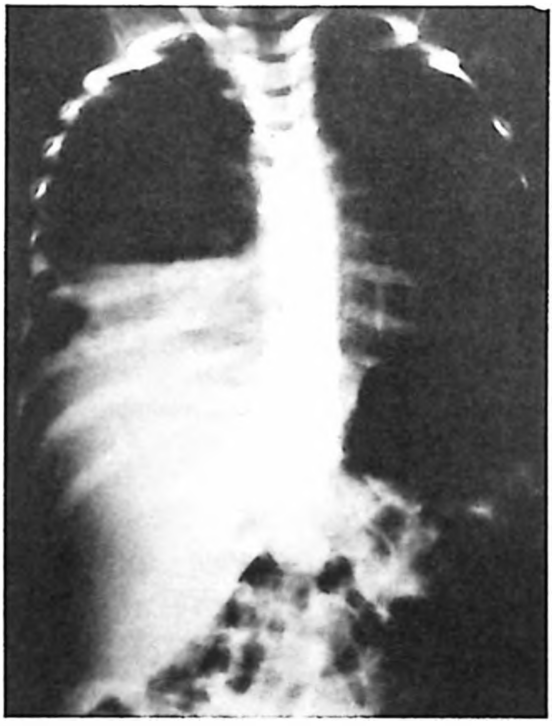

Fig. 1: Posteroanterior projection showing pleural effusion and the radiopaque tip of the ball point.

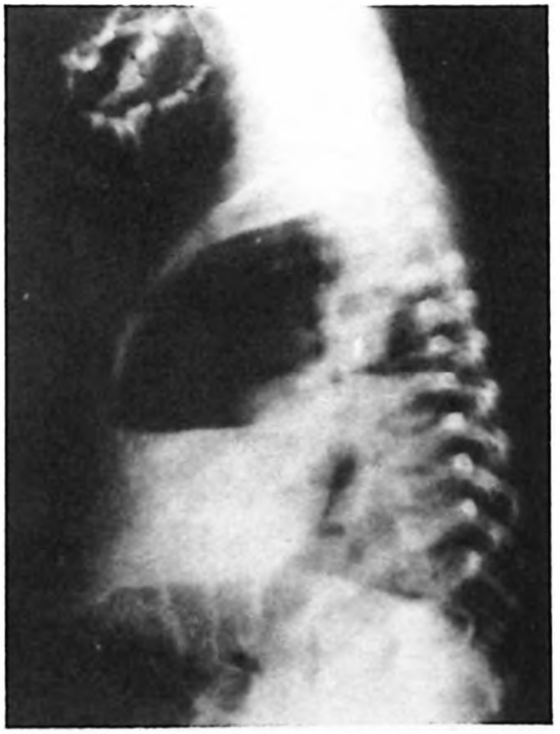

Fig. 2: Lateral projection showing the same findings.

Following initial resuscitation she was taken into the operating room with the diagnosis of esophageal perforation from ball point ingestion. Initial attempts of esophagoscopic removal unfortunately failed. Due to cranial direction of the perforating tip, removal by gastrotomy was decided. Through a midline laparatomy and gastrotomy the ball point was easily extracted. A Stamm gastrostomy was performed through the same incision. A chest tube was inserted through the right 6th intercostal space for underwater drainage and remained until the drainage ceased. Feeding through the gastrostomy was initiated afterwards.

The esophagogram was normal one month after operation. The patient has been free of symptoms and findings for two years.

Discussion

Foreign body ingestion is a frequent reason for emergency admission of young children around the world[1]. Seven to 14 percent of ingestions result in esophageal perforations, with the intrathoracic portion the most common site of involvement[2-3].

The most common symptoms of esophageal perforation are refusal to take foods, increased salivation, pain on swallowing and vomiting[4].

Radiological findings of esophageal perforations are dependent upon the time interval between perforation and radiological examination, site of perforation and integrity of mediastinal pleura[5]. If the ingestion is unwitnessed and symptoms unrelated to the esophagus predominate, consideration of a diagnosis of esophageal perforation becomes more difficult. Respiratory distress, without any complaints related to swallowing initially directed us toward the common causes of respiratory distress among infants. Palpation of a pencil-like object led to careful examination of the chest x-rays which revealed the radiopaque tip of the ball point with pleural effusion on the right hemithorax, making the diagnosis of esophageal perforation easy.

Foreign body perforation of the esophagus usually has a favorable outcome; however, it depends on the time interval between injury and initiation of the treatment. A delay in diagnosis worsens the outcome[2-3].

In conclusion, esophageal perforation complicating unwitnessed foreign body ingestion should be considered in the differential diagnosis among infants with respiratory distress, even in the absence of signs and symptoms related to swallowing.

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TORSADE DE POINTES ASSOCIATED WITH ENCEPHALITIS*

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SUMMARY: Alehan D, Ceviz N, Çeliker A. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Torsade de pointes associated with encephalitis. Turk J Pediatr 1999; 41: 395-398.

Torsade de pointes is a polymorphic ventricular tachycardia. Causes of torsade de pointes are well described. Although intracranial disease can produce dramatic electrocardiographic (ECG) changes, we are not aware of previous cases with torsade de pointes and encephalitis. We report a case with encephalitis who developed torsade de pointes, and was treated with temporary ventricular pacing and magnesium infusion.

Key words: torsade de pointes, encephalitis.

Torsade de pointes is a polymorphic ventricular tachycardia, characterized by a continuous twisting of the QRS axis around an imaginary baseline on the electrocardiogram (ECG)[1]. Causes of torsade de pointes are well described[1,2]. Although we know that intracranial disease can produce dramatic ECG changes[3], we are not aware of the concurrence of torsade de pointes and encephalitis in a previous case. We report herein a case with encephalitis who developed torsade de pointes in the absence of a known cause, and was treated with temporary ventricular pacing and magnesium infusion.

Case Report

A two-year-old girl was admitted to the Pediatric Emergency Unit with fever, diarrhea, vomiting and decreased consciousness over the previous two days. Physical examination revealed an unconscious child with hyperactive deep tendon reflexes, bilateral positive Babinski reflex, signs of severe dehydration, and normal funduscopic findings. During physical examination the patient developed a generalized seizure which terminated after intravenous diazepam infusion. In view of the state of unconsciousness, positive meningeal irritation signs and the seizure, a computed brain tomography was obtained and a lumbar puncture was performed. Computed tomography revealed minimal brain edema. No view consistent with mass or hemorrhagic lesion was determined. Cerebrospinal fluid (CSF) was clear. Biochemical examination of CSF was in normal limits, and 22 lymphocytes per mm^3 were detected on microscopic

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examination. Bacterial and fungal cultures did not reveal an agent, and the culture for tuberculosis was also negative. We could not perform any diagnostic study for viruses, but considering CSF findings and gastroenteritis, we assumed that encephalitis was probably viral in origin. ECG showed a sinus rhythm with a heart rate of 160 beats per minute, normal QRS axis, and no signs of ventricular enlargement. PR and QT intervals were in normal limits according to the age and heart rate. Echocardiographic findings were normal. Serum sodium, potassium and calcium levels were in normal limits. Blood pH was 7.20 and HCO_3 was 5 mEq/L. After the proper $NaHCO_3$ infusion, pH reached normal limits. For the following six days, the patient was clinically stable and there were no additional problems except those relevant to meningoencephalitis. On the 7^{th} day of admisison, arrhythmia was detected during monitorization and ECG revealed torsade de pointes (Fig. 1). During the episode, serum K^+ was 3.2 mEq/L, Ca^{++} 9 mEq/L and Mg^{++} 2 mEq/L. A temporary ventricular pacemaker, with a rate of 100 beats per minute, was inserted and ventricular tachycardia stopped. Propafenone (300 mg/m^2) was started for prevention of recurrences. Despite temporary ventricular pacemaker and propafenone, torsade de pointes episodes recurred but for shorter durations than previous ones. Thus, intravenous magnesium sulfate injection at a bolus of 2 g, followed by a continuous infusion of 10 mg/min was performed. Following the magnesium sulfate infusion, no new episode was observed. The pacemaker was removed on the 13^{th} day of the insertion but oral propafenone was continued. Two months after discharge, the patient had sequelae of encephalitis but no episode of torsade de pointes was observed on 24-hour Holter monitoring.

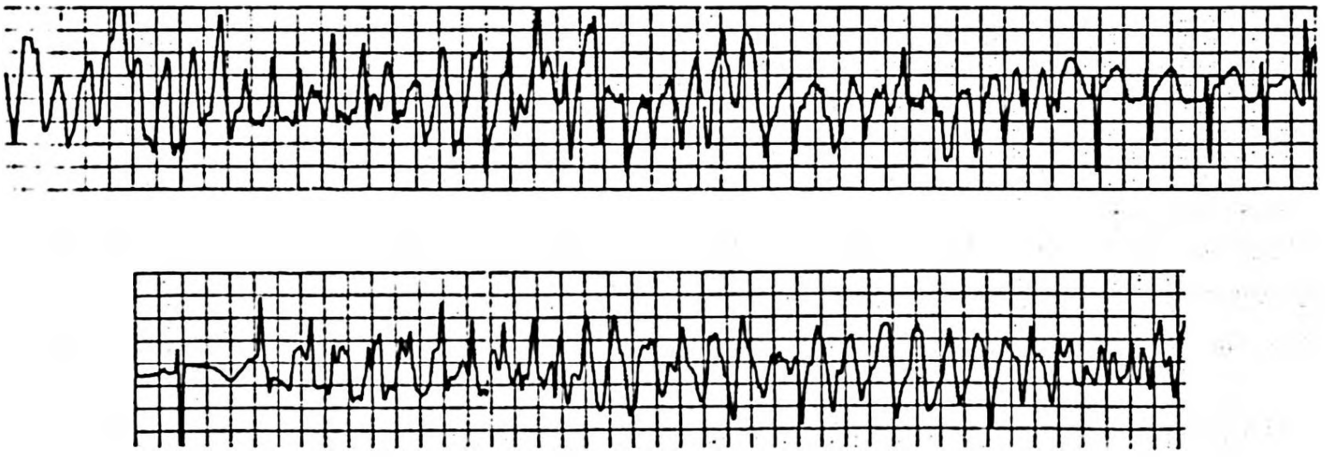

Fig. 1: Electrocardiographic tracings from two separate attacks showing the torsade de pointes.

Discussion

Prolongation of ventricular repolarization associated with the development of torsade de pointes can be observed in many clinical conditions, commonly referred to as prolonged QT syndromes. These syndromes are divided into two

groups: 1. idiopathic long QT syndrome and adrenergic-dependent torsade de pointes, and 2. acquired prolonged QT syndromes and pause-dependent torsade de pointes[1,2]. Jackman et al.[3] gives a detailed classification of this clinical condition. Since we could not demonstrate a known cause for torsade de pointes in our patient, we thought it might be due to encephalitis.

Intracranial diseases, most notably subarachnoid hemorrhage, but also intracerebral hemorrhage, cerebrovascular occlusive disease, trauma, and infection, can produce dramatic ECG changes. Hersch[4] determined electrocardiographic changes in adult patients with subarachnoid hemorrhage, pyococcal meningitis, intracranial space-occupying lesions, labor pneumonia, and in normal adults. QT prolongation was present in nine (45%) patients with subarachnoid hemorrhage, but not in patients with meningitis. It has been suggested that QT prolongation in patients with intracranial hemorrhage may be associated with severe ventricular arrhythmias, based on the observation of torsade de pointes in two of 72 consecutive patients with intracranial hemorrhage[3]. Although there are several reports about torsade de pointes that has developed during the course of intracranial hemorrhage, especially subarachnoid hemorrhage, we have no information about the concurrence of intracranial infections and torsade de pointes. And, to our knowledge, this is the first report of torsade de pointes associated with encephalitis. In the previous reports of torsade de pointes associated with subarachnoid hemorrhage, treatment consisted of either propranolol or pharmacologic blockade of the stellate ganglion with lidocaine. As a result, adrenergic pathways may play a role in torsade de pointes in association with intracranial diseases[3]. The most effective treatment in torsade de pointes related to acquired long QT syndromes is rapid electrical pacing of the heart (90-100 beats/min). In addition, magnesium sulfate, as a safe, rapid, and easily applied treatment, may be effective in suppressing recurrence of torsade de pointes, regardless of plasma magnesium levels[1,5,6].

We were able to treat the torsade de pointes in our patient with temporary ventricular pacing and intravenous magnesium sulfate infusion. After discontinuation of pacing and magnesium infusion, the episodes did not recur and the patient was discharged with the sequelae of encephalitis.

In conclusion, torsade de pointes may develop during the course of encephalitis, a clinical picture which has not been described before.

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SCIMITAR SYNDROME WITH ABSENCE OF THE RIGHT PULMONARY ARTERY*

A Case Report

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SUMMARY: Saltık İL,Eroğlu AG, Öztunç F, Sarıoğlu A. (Division of Pediatric Cardiology, İstanbul University Institute of Cardiology, İstanbul, Turkey). Scimitar syndrome with absence of the right pulmonary artery: a case report. Turk J Pediatr 1999; 41: 399-402.

We report a two-year-old female child with scimitar syndrome associated with absent pulmonary artery but with normal pulmonary artery pressure although several collaterals originated from the abdominal aorta to the right lung. To our knowledge, this is the fifth case with an absent pulmonary artery. Our case also had microphthalmia, an association not previously described in scimitar syndrome.

Key words: scimitar syndrome, right pulmonary artery.

Scimitar syndrome is a congenital anomaly that consists mainly of total or partial anomalous venous drainage of the right lung to the inferior vena cava. It is often associated with hypoplasia of the right lung, dextroposition of the heart, anomalous systemic vascular supply of the right lung from the aorta and bronchial anomalies. The name "scimitar" is derived from the radiological shadow of the abnormal right-sided pulmonary vein along the right border of the heart, resembling a Turkish sword. In about half of the cases, the size of the right pulmonary artery is minimally reduced, but in some cases the reduction can be severe. Only four cases have as yet been described in which the right pulmonary artery is absent[1-3]. All these patients had pulmonary hypertension.

Additional forms of cardiovascular abnormalities have been described in approximately 25 percent of cases with scimitar syndrome. A variety of extracardiac abnormalities have been frequently associated with the syndrome.

We present a case in which the right pulmonary artery was absent, but in whom there was a normal pulmonary artery pressure although several collaterals originated from the abdominal aorta to the right lung. Our case also had microphthalmia, an association not previously described in scimitar syndrome.

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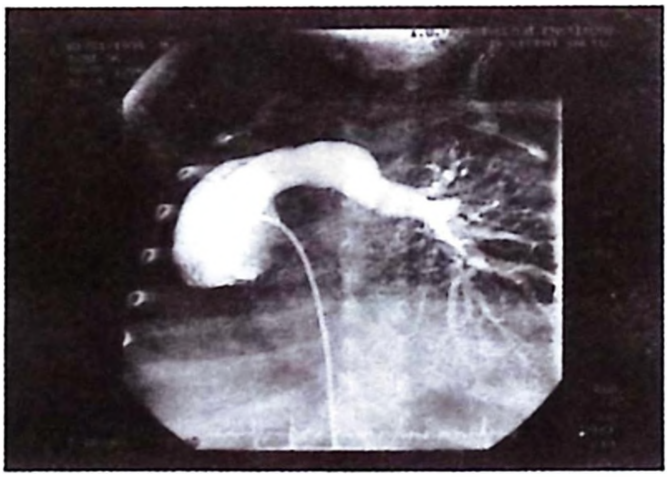
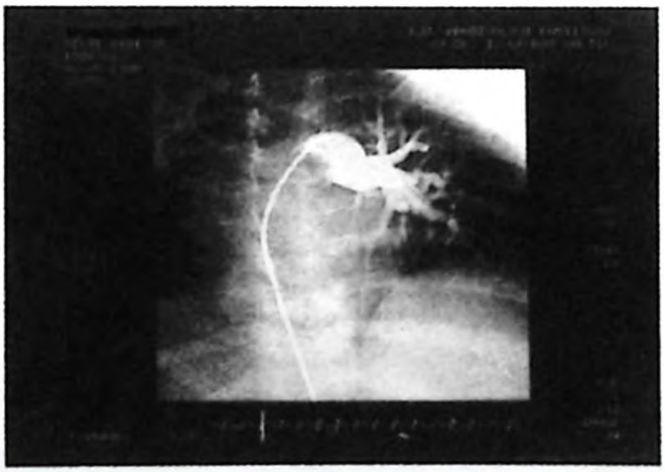
Case Report

A two-year-old girl presented with a past history of frequent respiratory infections. The physical examination was normal except for microphthalmia of the left eye and palpable cardiac activity which could be felt best over the right chest. Chest roentgenogram showed hypoplasia of the right lung with dextroposition of the heart and mediastinal shift to the right. The electrocardiogram was normal. The echocardiogram was normal except for an undetectable right pulmonary artery and dextroposition of the heart. Computerized tomography scans showed dextroposition of the heart, hypoplasia of the right lung and absence of the right pulmonary artery. Cardiac catheterization revealed dextroposition of the heart and normal right ventricular and pulmonary arterial pressures (30/0 mmHg and 30/10 mmHg, respectively). There was no right pulmonary artery (Fig. 1) and arterial supply to the right lung was via several collateral vessels from the abdominal aorta (Fig. 2). Venous drainage of the right lung was to the inferior vena cava.



(a)



(b)

Fig. 1a: Anteroposterior projection of right ventricle angiogram and b: 30° left anterior oblique and 20° cranial projection of pulmonary angiogram demonstrate large main and left pulmonary arteries and absent right pulmonary atery.

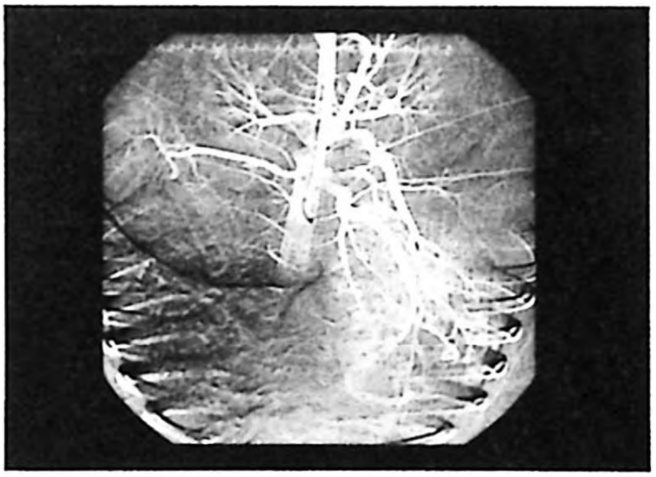


Fig. 2: Anteroposterior projection of aortogram demonstrates systemic arteries supplying the right lung.

Because of the relative well-being and young age of the child, surgical intervention was not planned for the near future. Medical treatment consisted of daily chest physiotherapy and early oral antibiotic therapy at the first signs of respiratory infections. At follow-up 36 months later, the child remained asymptomatic.

Discussion

Patients with scimitar syndrome are typically asymptomatic and thus, the actual prevalence of this rare syndrome is difficult to determine. The diagnosis is usually suspected as a result of incidental discovery of the scimitar vein on chest radiograph. Symptoms, when present, most often include the following: recurrent pulmonary infection secondary to alteration of the tracheobronchial architecture, congestive heart failure due to left-to-right shunt and associated cardiac malformations[1,4-6]. A small subset of patients, however, present with cardiac failure early in infancy[1,5,6]. All of them have extreme hypoplasia of the right pulmonary artery and a large left-to-right shunt from systemic collaterals via the right lung to the right atrium. Cardiac catheterization demonstrates pulmonary hypertension in most of them. Absence of the right pulmonary artery in scimitar syndrome has previously been described in only four cases[1-3]. All these patients had pulmonary hypertension and were critically ill.

The mechanisms for pulmonary hypertension in patients with scimitar syndrome have not been clearly delineated; there are several hypotheses[1,5-7]. It has been proposed that, in scimitar syndrome with extreme hypoplastic or even absent pulmonary arteries and large systemic collaterals, the left lung has to handle both systemic venous return and shunt volume and probably reacts abnormally to this increased volume load[1]. Absence of the right pulmonary artery without pulmonary hypertension despite several collaterals from the abdominal aorta,

as in our case, does not support tihs hypothesis. Another theory is that a reduction of the pumonary vascular bed may induce a persistence of fetal circulation[1]. More studies will be needed in order to detect the true origin of pulmonary hypertension.

Cardiovascular abnormalities, most commonly atrial septal defect, ventricular septal defect, coarctation of the aorta, patent ductus arteriosus, tetralogy of Fallot, atrioventricular septal defect, double outlet right ventricle, hypoplastic left heart syndrome and pulmonary valvular stenosis, may be present as well. Additional extracardiac anomalies that may coexist include accessory or eventrated diaphragm[5], horseshoe lung[5,8], hemivertebrae[8], scoliosis[6,8], meningomyelocele[5], double ureter[8], duplication of the uterus[2], Hirschsprung's disease[8], cleft palate[8] and hypospadias[8]. Our case had microphthalmia, an association not previously decribed in scimitar syndrome.

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VASCULAR RING FORMED BY RIGHT AORTIC ARCH WITH ABERRANT LEFT SUBCLAVIAN ARTERY AND LEFT LIGAMENTUM ARTERIOSUM*

A Rare Cause of Respiratory Distress in Newborn Infants

*Naci Ceviz MD**, Sema Özer MD***, Coşkun İkizler MD*****

SUMMARY: Ceviz N, Özer S, İkizler C. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Vascular ring formed by right aortic arch with aberrant left subclavian artery and left ligamentum arteriosum: a rare cause of respiratory distress in newborn infants. Turk J Pediatr 1999; 41: 403-407.

Vascular ring, in which the trachea and esophagus are completely surrounded by vascular structures, is one of the causes of respiratory distress in children. Right aortic arch with aberrant left subclavian artery is a common aortic arch anomaly; however, respiratory distress due to vascular ring is seldom associated with this anomaly. We report herein a newborn infant treated surgically because of severe respiratory distress caused by vascular ring formed by right aortic arch with aberrant left subclavian artery and left ligamentum arteriosum. As laryngomalacia was first thought to be the reason for respiratory distress, we suggest that patients with respiratory distress diagnosed with laryngomalacia be evaluated for possible vascular ring. *Key words: respiratory distress, right aortic arch, vascular ring, laryngomalacia.*

The causes of respiratory distress in children are diverse. Some of them, like vascular rings, may be silent. Several aortic arch anomalies can form a vascular ring and, when sufficient compression of the trachea and/or esophagus exists, symptoms are present[1-3]. When the compression is mild, however, there may be no symptoms[4]. Aberrant subclavian arteries, either right or left, are the most common aortic arch anomalies. However, most of the cases do not have respiratory symptoms; they are rarely associated with respiratory distress.

In this paper, a newborn infant who had been previously diagnosed with laryngomalacia was later found to have a vascular ring. The case is reported to emphasize that patients with respiratory distress and the diagnosis of laryngomalacia must be evaluated for vascular ring. Our patient had right aortic arch with abberrant left subclavian artery and left ligamentum arteriosum, which is an uncommon form of vascular ring.

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Case Report

A five-day-old newborn infant was admitted to the Neonatology Unit with severe respiratory distress. There was no physical finding related to the cardiovascular system. Chest x-ray showed mild cardiomegaly. Echocardiographic study did not reveal any congenital cardiac abnormalities. Laryngoscopic and fluoroscopic examination of the trachea and larynx suggested laryngomalacia. Barium esophagography revealed a posterior indentation at the first 1/3 proximal part of the esophagus (Fig. 1). Cardiac catheterization was performed. Aortic angiography showed a right aortic arcus and an aberrant retroesophageal left subclavian artery (Fig. 2). Ductus arteriosus was not patent. Since a vascular ring most likely completed by aberrant subclavian artery and ligamentum arteriosum could not be excluded, the patient underwent surgery. The left subclavian artery was the last artery leaving the aortic arch. Left ligamentum arteriosum extending between the left subclavian artery and left pulmonary artery was completing the ring and compressing the trachea. Ligamentum arteriosum was excised and the trachea was released. Although the patient was previously dependent on a ventilator, by

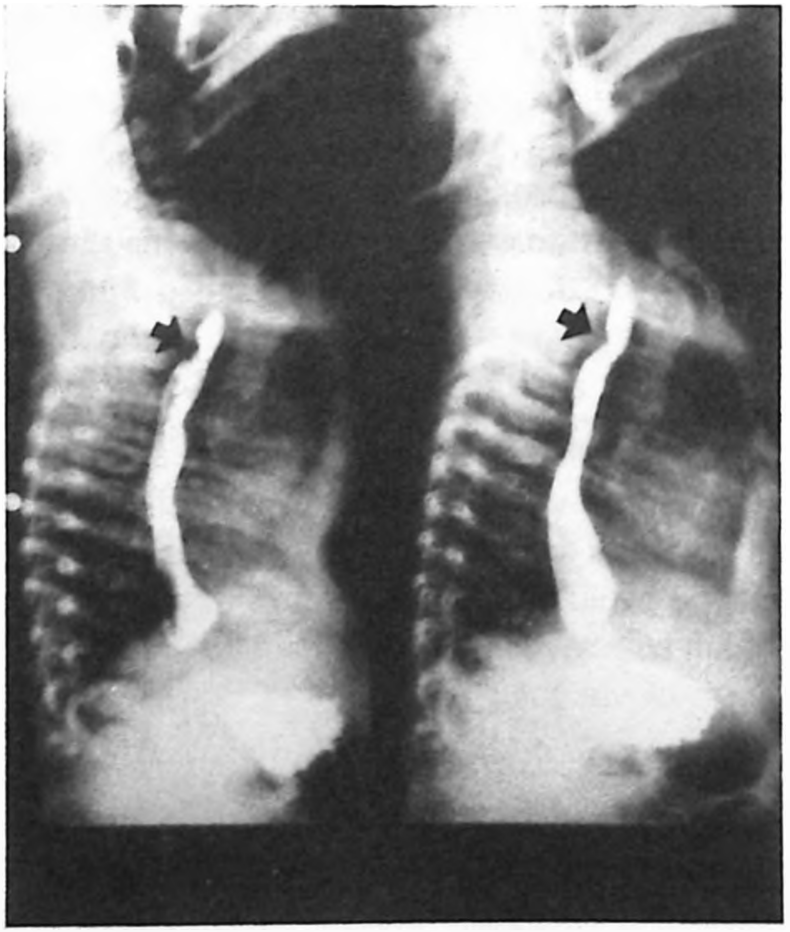
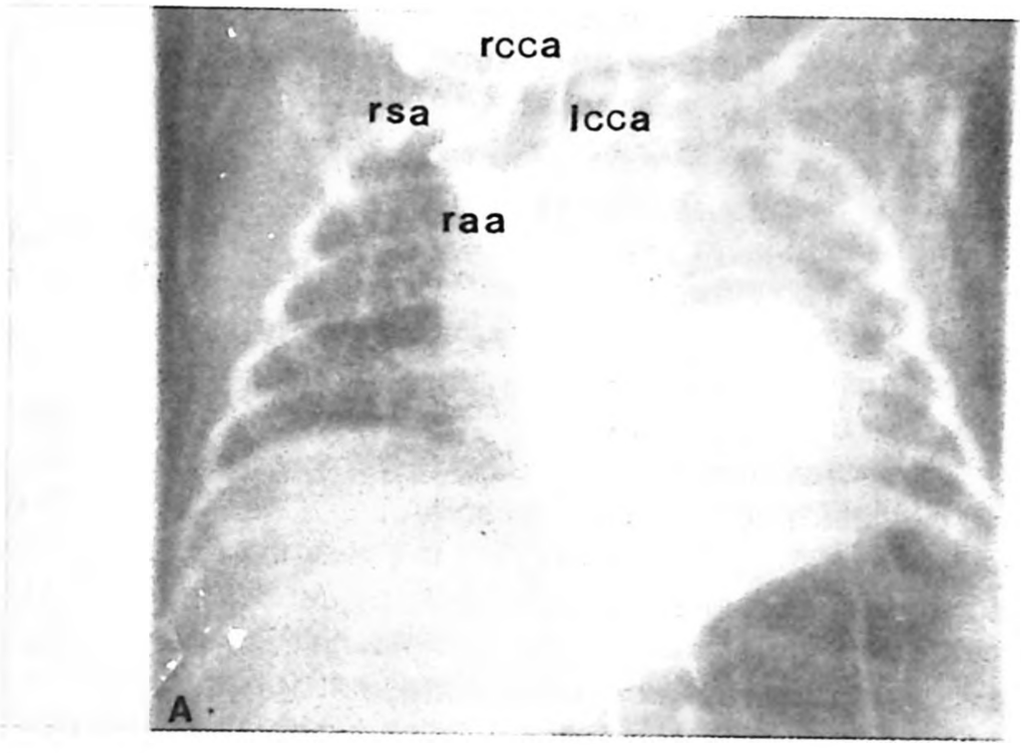
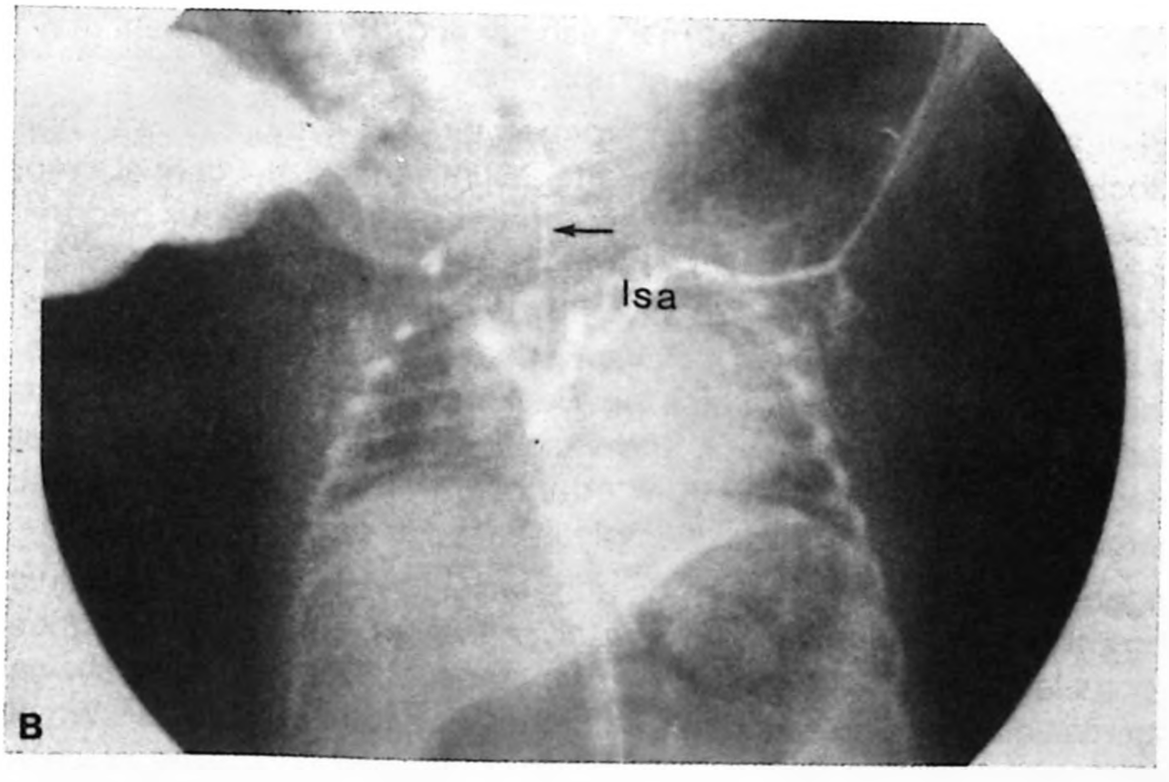


Fig. 1: Barium esophagography depicting the posterior indentation (arrow) at the proximal esophagus.



(a)



(b)

Fig. 2: Aortic angiography at postero anterior projection shows a) right aortic arch (raa), right subclavian artery (rsa), right common carotid artery (rcca), and left common carotid artery (lcca), and b) aberrant retroesophageal left subclavian artery (lsa) stemming from the descending aorta. The arrow indicates the feeding tube placed into the esophagus.

the 48th hour of operation there was no need for artificial ventilation. In the postoperative second week respiratory distress disappeared but pulmonary infection developed; the patient was discharged by the family during treatment.

Discussion

Vascular ring comprises one to two percent of congenital heart diseases. Although numerous variations from normal aortic arch development have been reported, only a few distinct patterns can produce extrinsic tracheal obstructions. The most likely types that compromise the trachea and esophagus are a) right aortic arch c) anomalous innominate or left carotid artery, d) aberrant right subclavian artery, and e) pulmonary artery sling[5]. The most common aortic arch anomaly causing vascular ring is double aortic arch[1,3]. Cases with right aortic arch are divided into five subgroups according to the branching pattern of the vessels: a) circumflex retroesophageal aortic arch, b) cervical right aortic arch, c) right aortic arch with abnormal origin of left subclavian artery and patent ductus arteriosus, d) right aortic arch with isolated left subclavian artery, and e) right aortic arch with absence of unilateral pulmonary artery. Although aberrant left subclavian artery is the most frequent vascular anomaly seen with right aortic arch, these cases are commonly asymptomatic[3]. Sometimes, as in our patient, a ductus arteriosus or a ligamentum arteriosum may be associated with aberrant left subclavian artery, and may form a vascular ring. Thus, the patient may have symptoms of tracheo esophageal compression.

Reported prevalence of vascular ring formed by right aortic arch with aberrant left subclavian artery and ligamentum arteriosum varies. Lincoln et al.[6] reported 29 patients with vascular anomalies compressing the esophagus and trachea, but none of them had a vascular ring as in our case. Among the 19 children with five types of vascular ring reported by Wychulis et al.[7], only one had right aortic arch with aberrant left subclavian artery and left ductus arteriosus. This patient had respiratory symptoms. In Backer et al's.[8] report, 65 percent of 52 patients with right aortic arch and vascular ring had a retroesophageal left subclavian artery and ligamentum arteriosum. These patients formed the 29 percent of the patients with complete vascular ring.

Laryngomalacia is the most common congenital laryngeal anomaly of unknown etiology that causes inspiratory stridor. Although the clinical diagnosis of laryngomalacia can be confirmed by laryngoscopy, it has been shown that laryngomalacia may be associated with other respiratory disorders[9]. Wu et al.[10] reported seven children with variable types of vascular anomalies, of whom five were previously diagnosed as having laryngomalacia. In Nussbaum et al's study[9], one percent of children diagnosed with laryngomalacia also had vascular ring. Our patient was also first diagnosed as having laryngomalacia. However, after the barium esophagography and angiography, the structural anomaly that was the true reason for respiratory distress was revealed.

In newborn infants with severe respiratory distress, vascular ring must be considered in the differential diagnosis, even if there is a previous diagnosis of laryngomalacia. In these patients, if one detects a right aortic arch with aberrant left subclavian artery, the presence of a vascular ring completed by left ligamentum arteriosum must be considered. These patients may be successfully treated with surgery.

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The Turkish Journal of Pediatrics 1998; 40: 409-411

Errata

Kanra T. Rh blood group system in Turkey. Turk J Pediatr 1998; 40: 525-531.

Table I is reprinted below with a correction under the section entitled "Positivity in Basques %" (in bold).

Table I: Major Rh Antigen Frequencies

Antigens	Positivity in Turks %	*Positivity in Caucasians %	**Positivity in Basques %	**Positivity in Orientals %
D	85.3	85	60-80	99-100
C	69.6	70		
E	29.7	30		
c	79.05	80		
e	95.63	98		

* Issit et al.[6]

** Mourant et al.[7]

Table II is reprinted below, with three corrections (in bold).

Table II: Frequencies of Some Rh Genes in Turkey (5,600 people)

Wiener	Fisher-Race	Frequencies %
Allele	Gene Combination	
R_1	**CDe**	0.42
r	cde	0.385
R_2	cDE	0.16
R_0	cDe	0.0115
R^w_1	**C^wDe**	0.01
r'	Cde	0.0055
r"	cdE	0.0055
Rz	CDE	0.0025

Table III is reprinted below, with two corrections under the column entitled, "Fisher Race" (in bold).

Table III: Comparison of Some Gene Frequencies in Different Countries

					USA***			
Wiener	Fisher-Race	Turkey	England*	Sweden**	Whites	Blacks	Orientals	Indians
R_1	**CDe**	0.42	0.4076	0.40356	0.42	0.17	0.7	0.44
r	cde	0.385	0.3886	0.38205	0.37	0.26	0.03	0.11
R_2	cDE	0.16	0.1411	0.16701	0.14	0.11	0.21	0.34
R_0	cDe	0.0115	0.0257	0.01855	0.04	0.44	0.03	0.02
R_1^w	C^wDe	0.01	0.0129	0.011983	—	—	—	—
r'	Cde	0.0055	9.0098	0.00498	0.02	0.02	0.02	0.02
r"	cdE	0.0055	0.0119	0.00295	0.01	0	0	0.01
R_2	**cDE**	0.0025	0.0024	0.00082	0	0.01	0.01	0.06
r'^w	C^wde	—	—	0.00034	—	—	—	—

* Race et al.[8]
** Heiken and Rasmuson[9]
*** Mourant et al.[7]

Table IV is reprinted below, with one change in the column entitled, "Wiener" (in bold).

Table IV: Frequencies of Rh Genotypes (Phenotypes) in 5,600 Turkish People

Reactions with anti-								
D	C	E	c	e	Cw	Fisher-Race	Wiener	Frequencies %
+	+	o	+	+	o	CDe/cde	R_1 r	34.48
+	+	o	o	+	o	CDe/CDe	R_1 R_1	17.7
o	o	o	+	+	o	cde/cde	r r	14.7
+	+	+	+	+	o	CDe/cDE	R_1 R_2	14.06
+	o	+	+	+	o	cDE/cde	R_2 r	11.96
+	o	+	+	o	o	cDE/cDE	R_2 R_2	3.45
+	o	o	+	+	o	cDe/cde	R_0 r	0.85
+	o	o	+	+	+	C^wDe/cde	R_1^w r	1.17
o	+	o	+	+	o	Cde/cde	r' r	0.28
o	o	+	+	+	o	cdE/cde	r" r	0.14
+	+	+	+	o	o	CDE/cDE	**R_z R_2**	0.14

On page 530, the first sentence of the 5th complete paragraph, beginning "In our study...", should read as follows:

"In our study, due to the inadequate number of fully screened people for Rh genotypes (phenotypes), rare Rh deleted red cells, such as -D-, cD- and Rh null, were not encountered".

The second sentence of the same paragraph begins, "Since the D^u phenotypes...".

Line two of the 7th full paragraph on the same page, originally printed as "The cDE/cde...", should read as "The cDe/cde...".

In the 8th full paragraph on the same page, reference number 15 cited at the end of the paragraph should read as number 16.

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