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Prevalence of asthma - associated symptoms in Turkish children

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SUMMARY : Türktaş İ, Selçuk ZT, Kalyoncu AF. Prevalence of asthma-associated symptoms in Turkish children. Turk J Pediatr 2001; 43: 1-11.

The aim of the first national cross-sectional survey was to determine the prevalence of asthma-like respiratory symptoms and the associated risk factors among children aged 0-17 via interview with the parents by primary care physicians. They were selected through stratified two-stage cluster probability sampling in urban and rural parts of randomly selected 27 of 81 administrative districts in Turkey.

Data was collected for 46,813 children (23,512 males and 23,301 females) of whom 66 percent resided in urban areas. The prevalence of physician-diagnosed asthma was 0.7 percent. The lifetime and current (last 12 months) prevalences were 14.7 percent and 2.8 percent for asthma, and 15.1 percent and 3.4 percent for wheezing respectively. The presence of personal atopy and history of family atopy were the most significant risk factors for current prevalences of wheezing, and asthma [adjusted Odds ratios (OR) and 95% confidence intervals (CI) were 6.2 (CI=4.0-9.5) and 1.8 (CI=1.3-2.4) for wheezing, and 8.5 (CI=5.6-12.9) and 1.9 (CI=1.4-2.5) for asthma, respectively]. Though there were no significant differences among those residing in urban versus rural areas regarding the current prevalences of asthma and wheezing, those living in coastal areas had considerably higher current prevalences than those inland (OR=2.6, CI=1.9-3.5 for wheezing, and OR=2.3, CI=1.7-3.1 for asthma). Residence in northern Turkey appeared to be a significant risk factor for wheezing (OR=1.9, CI=1.4-2.5), and children resident in southern Turkey exhibited the highest risk for occurrence of asthma (OR=1.5, CI= 1.1-2.0) compared with eastern Turkey.

In conclusion, the respiratory symptoms associated with asthma were an important cause of morbidity in childhood in Turkey. The discrepancy between prevalence of physician-diagnosed asthma and lifetime and/or current asthma prevalence figures may reflect the reluctancy of both physicians and parents to diagnose this condition. Besides strongest associations with personal atopy and atopic heredity, there were significant differences in prevalence rates between children residing in different regions, supporting the role of environmental factors.

Key words: childhood asthma, Turkey, ISAAC, epidemiology.

Bronchial asthma is among the most common chronic diseases of childhood. Recent surveys indicate a significant increase in the prevalence of asthma and other allergic diseases worldwide. Despite advances in both the diagnosis and treatment of bronchial asthma in the last decades, the rise in its morbidity and mortality is rather disappointing. Given these facts, intensive research on the pathogenesis and augmented emphasis on preventive measures for allergic diseases appear justified. Epidemiological studies in children from different parts of the world have served well to discriminate the associated risk factors for asthma.

Profound variations in prevalence figures for bronchial asthma exist between populations in different countries and even in regions within the same country. The criteria of the International Study of Asthma and Allergies in Childhood (ISAAC) have been proposed for questionnaire surveys to allow international comparison of prevalence figures[1]. A video version of the questionnaire was also developed to overcome translation problems and cultural background differences present even among those speaking English in different countries or locations[2]. The surveys among children in western countries

show a trend of increased prevalence, up to 20 percent, yet the figures are much lower in east European and Asian countries[3].

Several epidemiological studies on bronchial asthma have been conducted recently in various parts of Turkey via different methodologies (Table I)[4-18]. The ISAAC questionnaire was also successfully employed in a number of these surveys[13-18]. The reported figures for childhood asthma prevalence generally fall somewhere in between those seen in eastern and western populations. Though there are evident differences in the prevalence figures, it is rather inconvenient to draw conclusions due to disparate methodologies and ages of the study groups.

Table I. Prevalence of Asthma in Children in Different Provinces in Turkey

Province	n	Year	Age	Cumulative (%)	Current (%)	Questionnaire type	Reference no.
Ankara	3024	1991	6-13	6.9	–	ATS[a]	6
İzmir	3512	1992	6-13	4.9	–	ATS[a]	7
Bursa	3055	1993	6-12	7.8	–	ATS[a]	8
Samsun	3118	1993	6-14	8.2	–	ATS[a]	9
Ankara	1036	1992	6-12	17.4	8.3	N.Aberg[b]	10
Edirne	5412	1994	7-12	16.4	5.6	N.Aberg[b]	11
Ankara	738	1997	6-13	16.8	9.8	N.Aberg[b]	12
İstanbul	2232	1995	6-12	9.8	–	ISAAC[c]	13
Ankara	2784	1996	7-14	8.1	–	ISAAC[c]	14
Germany	470	1996	9-13	6.4	–	ISAAC[c]	15
Samsun	3090	1996	6-13	14.5	–	ISAAC[c]	16
Adana	4114	1997	12-17	2.8	–	ISAAC[c]	17
Northern Cyprus	2529	1997	6-14	11.4	–	ISAAC[c]	18

a) ATS: American Thoracic Society questionnaire (Ref. 4).
b) Aberg N (Ref. 5).
c) ISAAC: International Study of Asthma and Allergies in Childhood (Ref. 1).

A nationwide survey of children in different parts of the country to investigate the prevalence figures of bronchial asthma, associated respiratory symptoms, and also risk factors was conducted in 1996. In order to permit international and national comparison of figures for the same age groups, a questionnaire based on the ISAAC protocol was employed. This report summarizes the results of this first national survey on childhood bronchial asthma and wheezing.

Material and Methods

Study Population

The first nationwide survey of chronic childhood diseases among those aged 0 to 17 was conducted in 1996. A stratified two-stage cluster probability sample design was used in this epidemiological study[1]. Five strata were determined on the basis of the region, median income and other social and demographic characteristics. After stratification by five major geographical regions (MGRs) of Turkey (east, west, north, south and central), the two stages of sample selection were primary districts (PDs) and residence units (RUs), in hierarchical order. PDs are cities composed of both rural and urban subdistricts.

Since the variance of the estimate of prevalence was expected to be influenced when complex designs (particularly cluster sampling) were used in surveys, a design effect value of 2.0 was decided for this survey while calculating the effective sample size. The total sample size was determined in order to estimate the lowest assumed prevalence of 0.015 percent[19]. The estimated child population aged 0 to 16 in 1996 was 24,773,569 based on the National Census in 1985 and 1990[20,21]. Among the 81 administrative districts, 27 were selected, including the five most populated districts and 22 randomly selected ones (Fig. 1). Thus, one-third of the total 81 districts were included in the study. The estimated total population of children in the same age group was 15,332,748 in these 27 districts. In regard to type I and II errors of 0.05 and 0.10, respectively, a power of 90 percent and effect size of 2, the optimum sample size for this survey was calculated as 50,000.

The total sample size for each MGR was proportionately allocated to selected PDs and then further stratified into the rural and urban subdistricts. The address list obtained from the

1990 National Census was used as the sampling frame to determine the RUs, i.e. street names for urban and village names for rural areas. Cluster size was planned as 20 children.

and Zonguldak in June 1996. The questionnaire was considered appropriate and valid after these pilot studies and revisions.

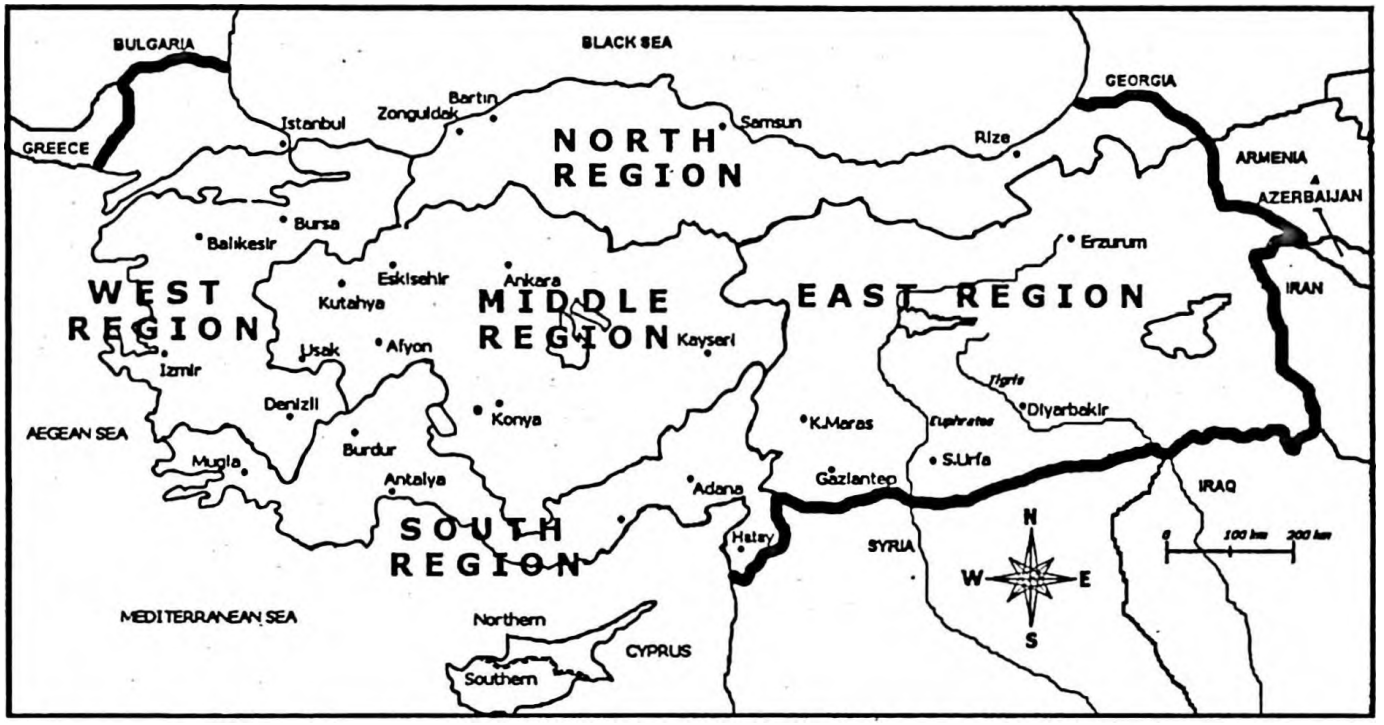

Fig. 1. Map of Turkey showing the locations in which the survey was conducted.

Data Collection

The major questionnaire on chronic diseases of childhood included 60 pages with different modules in Turkish. The questions employed to determine the prevalence rates of asthma and wheezing were derived from the ISAAC protocol in English; minor modifications were made in order to increase the comprehension and clarify questions that might arise from translation problems and cultural differences. Though there is no exact equivalent of "wheezing" in Turkish, phrases successfully employed in previous questionnaire surveys were used[10,11]. The questions employed are included in the Appendix. Apart from those questions regarding the presence of asthma and wheezing in children, a number of other questions about atopic heredity, and social and economical status of the family were included in the general questionnaire. The draft questionnaire underwent a pilot study on 300 children in 10 randomly selected streets of metropolitan Ankara, and also on 40 in- and outpatients of some health institutions. The questionnaire was modified, and underwent a second trial including 300 children randomly selected in Antalya, Bursa, İstanbul, Diyarbakır

One hundred and forty-six primary care physicians from different regions in the country were specially trained for a total of 10 weeks for administration of the questionnaire prior to its use in the survey. Another eight primary care physicians were also employed as supervisors in the field. After validation of the questionnaire and approval of the supervisors for the physicians, the survey began in July 1996 and was completed in October 1996. The questionnaire modules were applied and completed by the trained physicians under supervision at different times and locations during the whole course of the survey. After collection of the first 10,000 questionnaires, 1. in every 20 questionnaires was selected, and a phone call was made to the responders to confirm that the home visit was made and that the questionnaire was completed as required. They were questioned as to the date of the visit, whether there were children at home on that date, and whether they had been examined. The responses of the parents to some 10 to 15 randomly selected questions in the modules were compared with the written responses in the filled form.

Definition of Outcomes

The subjects were grouped as residing in either inland or coastal regions, and in rural or urban areas according to their place of habitation. The place of habitation was also divided into five geographical regions (east, west, north, south and central). The prevalence figures were calculated both for the administrative districts and for the five geographical regions.

The lifetime and current occurrences of wheezing and asthma was defined according to the questionnaire responses by the parents as follows (see Appendix) The presence of wheezing or asthma were determined in regard to combinations of responses to different questions rather than from single ones. If a wheezing or asthma attack had occurred in the past, if the child had become wheezy after exercise or during a cold or bronchitis, or if his speech was limited or sleep disturbed by wheezing, it was regarded as the occurrence of wheezing any time in the past (lifetime wheezing) (Questions 1, 3-6 and 13). If any of these wheezing episodes was observed during the last 12 months, the child was regarded as having current wheezing (Questions No. 3-6). If the parents had responded positively to at least two of the first 14 questions, excluding morning phlegm (Question 8), the child was considered to have asthma any time in the past (lifetime asthma). Since most of the pediatric patients with bronchial asthma were given the diagnosis of either "bronchitis" or "allergic bronchitis", a past history of bronchitis (Question 12) was also included for definition of lifetime asthma. If the parents answered positively to at least two of the questions, inquiring about respiratory symptoms, use of bronchodilator drugs or presence of recurrent/ persistent cough during the last 12 months (Questions 3-10 and Question 14 were included, and Question 8 was excluded), then the child was regarded as having asthma in the last 12 months (current asthma). Those children diagnosed with possible bronchial asthma were referred to the nearest health center for further evaluation.

Statistical Analysis

Prior to analysis, the data entry (responses to the questionnaires) was checked by double entry. Comparisons were made by chi-square test. Statistical analysis was performed via statistical software package SPSS for Windows version 7.5. Adjusted odd ratios (ORs) and 95% confidence limits (95% CI) for risk factors were obtained from multiple logistic regression models for asthma and wheezing. P values below 0.05 were considered statistically significant.

Results

A total of 46,813 children were surveyed during the study (93.6 % of the aimed 50,000 population). The study group included 23,512 boys (50.2%) and 23,301 girls (49.8%), of whom 66 percent resided in urban and 34 percent in rural areas. The majority of the study group were living inland (56.6%). The demographic characteristics of the study group are presented in Table II.

Table II. Demographic Characteristics of the Study Group

Age (years)	Boys n (%)	Girls n (%)	Total n (% of total)
<1	1500 (6.4)	1420 (6.1)	2920 (6.2)
1	1508 (6.4)	1410 (6.1)	2918 (6.2)
2	1452 (6.2)	1357 (5.8)	2809 (6.0)
3	1572 (6.3)	1374 (5.9)	2846 (6.1)
4	1537 (6.5)	1462 (6.3)	2999 (6.4)
5	1529 (6.5)	1484 (6.4)	3013 (6.4)
6	1544 (6.6)	1509 (6.5)	3053 (6.5)
7	1505 (6.4)	1504 (6.5)	3009 (6.4)
8	1408 (6.0)	1533 (6.6)	2941 (6.3)
9	1518 (6.5)	1491 (6.4)	3009 (6.4)
10	1463 (6.2)	1385 (5.9)	2848 (6.1)
11	1428 (6.1)	1498 (6.4)	2926 (6.3)
12	1353 (5.8)	1379 (5.9)	2732 (5.8)
13	1228 (5.2)	1304 (5.6)	2532 (5.4)
14	1116 (4.7)	1206 (5.2)	2322 (5.0)
15	1210 (5.1)	1202 (5.2)	2412 (5.2)
16	662 (2.8)	701 (3.0)	1363 (2.9)
17	63 (0.3)	62 (0.3)	125 (0.3)
Unknown	16 (0.1)	20 (0.1)	36 (0.1)
Place of habitation			
Rural	8048 (34.2)	7875 (33.8)	15923 (34.0)
Urban	15464 (65.8)	15426 (66.2)	30890 (66.0)
Region			
West	6067 (28.8)	6595 (28.3)	13362 (28.5)
South	3173 (13.5)	3209 (13.8)	6382 (13.6)
Central	5145 (21.9)	5188 (22.3)	10333 (22.1)
North	2008 (8.5)	2084 (8.9)	4092 (8.1)
East	6419 (27.3)	6225 (26.7)	12644 (27.0)
Inland	13387 (56.9)	13105 (56.2)	26492 (56.6)
Coastal	10125 (43.1)	10196 (43.8)	20321 (43.4)
Total	23512 (50.2)	23301 (49.8)	46813 (100)
Personal atopy	81 (0.3)	99 (0.4)	180 (0.4)
Family atopy	542 (2.3)	508 (2.2)	1050 (2.2)
Smoking at home	16318 (86.5)	16174 (86.3)	32492 (86.4)
Socioeconomic status			
low	8699 (38.2)	8506 (37.8)	17205 (38.2)
moderate	46666 (20.5)	4683 (20.8)	9349 (20.7)
high	9394 (41.3)	9318 (41.4)	18712 (41.3)

The prevalences of respiratory symptoms, risk factors and use of bronchodilators are depicted in Table III. All respiratory symptoms as well as "ever wheezing" and "physician-diagnosed asthma" were significantly more frequent among males than females in the overall group. There were no differences between sexes for personal or family history of atopy, exposure to cigarette smoke at home and socioeconomic status. Information about smoking at home was obtained for 37,600 children (80.3 %). There was at least one smoker at home for 32,492 children (86.4%). There was only one smoker at home for 22,925 children (61.0 %), two smokers for 7,400 (19.7%), three smokers for 1,442 (3.8 %) and four or more smokers four 725 children (1.9 %).

Table III. Respiratory Symptoms

	Boys (%)	Girls (%)	Total (%)
Ever wheezing*	1968 (8.4)	1546 (6.7)	3514 (7.6)
Physician-diagnosed asthma*	222 (1.0)	115 (0.5)	337 (0.7)
SYMPTOMS DURING THE LAST 12 MONTHS			
Wheezing or asthma attack*	561 (24)	416 (1.8)	977 (2.1)
Waking with cough/wheezing*	515 (2.2)	368 (1.6)	883 (1.9)
Attack of wheezing limiting speech*	178 (0.8)	107 (0.5)	285 (0.6)
Wheezing after exercise*	359 (1.5)	223 (1.0)	582 (1.2)
Coughing at night*	660 (2.8)	550 (2.4)	1210 (2.6)
Morning phlegm*	558 (2.4)	419 (1.8)	977 (2.1)
Morning chest tightness*	203 (0.9)	137 (0.6)	340 (0.7)
Chest tightness and/or shortness of breath after exposure to allergens*	197 (0.8)	140 (0.6)	337 (0.7)
Use of bronchodilators*	384 (1.6)	256 (1.1)	640 (1.4)
Ever bronchitis*	4993 (21.3)	4149 (17.9)	9142 (19.6)
Wheezing with cold/bronchitis*	3546 (15.2)	2829 (12.2)	6375 (13.7)
Recurrent or persistant cough for at least 12 months**	238 (1.1)	193 (0.9)	431 (1.0)

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

Prevalences of both asthma and wheezing according to either single questions or combined responses to various questions in regard to age and place of habitation are presented in Table IV and V. Parents of 3,514 children (7.6 %) stated they had observed their children with wheezing in the past (Appendix, Question 1). However,

Table IV. Prevalences of Lifetime and Current Wheezing and Asthma According to Age Groups in Children

	Wheezing			Asthma		
Age (years)	Ever[1]	Lifetime[2]	Current[3]	Physician-diagnosed[4]	Lifetime[5]	Current[6]
<1	193 (6.7)	332 (11.4)	127 (4.3)	10 (0.3)	324 (11.1)	66 (2.3)
1	341 (11.8)	605 (20.7)	206 (7.1)	23 (0.8)	583 (20.0)	158 (5.4)
2	281 (10.1)	518 (18.4)	152 (5.4)	23 (0.8)	500 (17.8)	125 (4.4)
3	258 (9.1)	504 (17.7)	127 (4.5)	24 (0.8)	500 (17.6)	111 (3.9)
4	289 (9.7)	548 (18.3)	129 (4.3)	30 (1.0)	536 (17.9)	102 (3.4)
5	256 (8.6)	498 (16.5)	107 (3.6)	24 (0.8)	480 (15.9)	93 (3.1)
6	254 (8.4)	501 (16.4)	110 (3.6)	27 (0.9)	495 (16.2)	89 (2.9)
7	240 (8.0)	500 (16.6)	105 (3.5)	22 (0.7)	470 (15.6)	82 (2.7)
8	225 (7.7)	450 (15.3)	84 (2.9)	20 (0.7)	433 (14.7)	81 (2.8)
9	195 (6.5)	433 (14.4)	90 (3.0)	24 (0.8)	423 (14.1)	77 (2.6)
10	196 (6.9)	397 (13.9)	74 (2.6)	24 (0.9)	394 (13.8)	58 (2.0)
11	154 (5.3)	368 (12.6)	53 (1.8)	16 (0.6)	360 (12.3)	47 (1.6)
12	162 (6.0)	354 (13.0)	64 (2.3)	16 (0.6)	349 (12.8)	53 (1.9)
13	130 (5.2)	294 (11.6)	40 (1.6)	23 (0.9)	280 (11.1)	39 (1.5)
14	130 (5.6)	305 (13.1)	39 (1.7)	14 (0.6)	294 (12.7)	46 (2.0)
15	121 (5.1)	275 (11.4)	45 (1.9)	11 (0.5)	266 (11.0)	36 (1.5)
16	81 (6.0)	174 (12.8)	23 (1.7)	5 (0.4)	176 (12.9)	24 (1.8)
17	8 (6.4)	11 (8.8)	2 (1.6)	1 (0.8)	11 (8.8)	4 (3.2)
Total	7069 (7.6)	1577 (15.1)	337 (3.4)	6876 (0.7)	1291 (14.7)	(2.8)

1. Positive response to Question no. 1 (Appendix).
2. A positive answer to any of Questions 1, 3, 4, 5, 6 and/or 13 was regarded as wheezing any time in the past (lifetime wheezing).
3. If the parents had answered positively to any the Questions 3, 4, 5 or 6, the child was regarded as having wheezing during the last 12 months (current wheezing).
4. Positive response to Question 2. (Appendix).
5. If any two of the answers to the first 14 Questions, except Question 8, in the questionnaire were positive, the child was considered to have asthma in the past (lifetime asthma).
6. If two or more of the answers to Questions 3, 4, 5, 6, 7, 9, 10, 11 or 14, were positive, the child was considered to have current asthma.

Table V. Prevalences of Cumulative and Current Wheezing and Asthma in Children According to the Place of Habitation

Region and Cities	Wheezing			Asthma		
	Ever	Lifetime	Current	Physician-diagnosed	Lifetime	Current
Inland	1510 (5.7)	3284 (12.4)	752 (2.8)	105 (0.4)	3275 (12.4)	571 (2.2)
Coastal	2004 (10.0)	3785 (18.6)	825 (4.1)	232 (1.2)	3601 (17.7)	720 (3.5)
Urban	2568 (8.4)	5037 (16.3)	1118 (3.6)	257 (0.8)	4910 (15.9)	938 (3.0)
Rural	946 (6.0)	2032 (12.8)	459 (2.9)	80 (0.5)	1966 (12.3)	353 (2.2)
NORTH						
Bartın	89 (23.7)	94 (24.9)	51 (13.5)	4 (1.1)	91 (24.1)	40 (10.6)
Zonguldak	92 (9.8)	180 (18.7)	58 (6.0)	9 (1.0)	124 (12.9)	43 (4.5)
Samsun	316 (14.0)	500 (22.0)	156 (6.9)	31 (1.4)	467 (20.6)	100 (4.4)
Rize	46 (9.6)	70 (14.5)	11 (2.3)	7 (1.5)	72 (14.9)	11 (2.3)
Regional	543 (13.4)	844 (20.6)	276 (6.7)	51 (1.3)	754 (18.4)	194 (4.7)
WEST						
İstanbul	983 (13.7)	1622 (22.4)	397 (5.5)	117 (1.6)	1556 (21.5)	377 (5.2)
Balıkesir	57 (7.0)	75 (9.2)	31 (3.8)	10 (1.2)	77 (9.4)	33 (4.0)
İzmir	301 (10.8)	435 (15.6)	71 (2.5)	22 (0.8)	415 (14.9)	70 (2.5)
Denizli	20 (2.4)	97 (11.6)	13 (1.5)	2 (0.2)	110 (13.1)	14 (1.7)
Bursa	30 (1.8)	141 (8.4)	14 (0.8)	6 (0.4)	145 (8.7)	12 (0.7)
Regional	1391 (10.5)	2370 (17.7)	526 (3.9)	157 (1.2)	2303 (17.2)	506 (3.8)
EAST						
K. Maraş	167 (9.2)	208 (11.4)	78 (4.3)	6 (0.3)	223 (12.2)	69 (3.8)
Ş. Urfa	187 (6.4)	283 (9.6)	145 (4.9)	17 (0.6)	317 (10.7)	100 (3.4)
Diyarbakır	97 (3.0)	295 (9.0)	80 (2.4)	9 (0.3)	323 (9.9)	89 (2.7)
Erzurum	89 (6.4)	135 (9.7)	31 (2.2)	3 (0.2)	127 (9.1)	25 (1.8)
G. Antep	22 (0.8)	349 (13.4)	26 (1.0)	4 (0.2)	339 (13.0)	20 (0.8)
Sivas	31 (5.2)	60 (10.0)	6 (1.0)	2 (0.3)	62 (10.4)	1 (0.2)
Regional	593 (4.7)	1330 (10.5)	366 (2.9)	41 (0.3)	1391 (11.0)	304 (2.4)
CENTRAL						
Ankara	366 (9.4)	717 (18.3)	206 (5.3)	20 (0.5)	640 (16.3)	119 (3.0)
Konya	223 (7.9)	381 (13.4)	69 (2.4)	12 (0.4)	377 (13.3)	52 (1.8)
Kütahya	15 (2.1)	206 (28.7)	7 (1.0)	5 (0.7)	204 (28.4)	7 (1.0)
Uşak	6 (1.5)	32 (7.9)	4 (1.0)	3 (0.7)	32 (7.9)	4 (1.0)
Kayseri	30 (2.4)	118 (9.2)	15 (1.2)	1 (0.1)	119 (9.3)	12 (0.9)
CENTRAL						
Afyon	142 (13.1)	145 (13.1)	21 (1.9)	4 (0.4)	140 (12.9)	9 (0.8)
Regional	790 (7.7)	1607 (15.6)	322 (3.1)	45 (0.4)	1520 (14.7)	203 (2.0)
SOUTH						
Antaly	58 (5.4)	195 (18.0)	34 (3.1)	8 (0.7)	189 (17.4)	28 (2.6)
Burdur	20 (10.5)	34 (17.9)	6 (3.2)	1 (0.5)	32 (16.8)	5 (2.6)
İçel	32 (2.5)	150 (11.4)	22 (1.7)	12 (0.9)	143 (10.9)	20 (1.5)
Hatay	11 (0.9)	58 (4.7)	10 (0.8)	7 (0.6)	56 (4.5)	11 (0.9)
Muğla	7 (1.5)	28 (6.0)	3 (0.6)	2 (0.4)	26 (5.5)	4 (0.9)
Adana	69 (3.4)	453 (21.6)	12 (0.6)	13 (0.6)	462 (22.1)	16 (0.8)
Regional	197 (3.1)	918 (14.4)	87 (14.4)	43 (0.7)	908 (14.2)	84 (1.3)

when responses to whether the child had experienced wheezing associated with physical exercise, or with a bronchitis or whether they had cold episode, or ever been disturbed by wheezing during speech or sleep were considered together with the response to the first question (combined definition for lifetime wheezing), the positive response rate increased two fold (7,069 children, 15.1%). The prevalence of current wheezing (occurrence of a wheezing attack, disturbance of sleep or speech by wheezing or wheezing associated with exercise during the last 12 months) was 3.4 percent. Asthma was previously diagnosed by physicians in 337 children (0.7%). However, the prevalence figure increased to 14.7 percent (6,876 children) provided lifetime asthma was diagnosed when there were at least two positive responses for the asthma associated symptoms (excluding phlegm production) or use of bronchodilator drugs. The prevalence of current asthma (presence of at least 2 asthma-associated symptoms during the last 12 months) was 2.8 percent (1,291 children). Prevalences of asthma and wheezing were higher in coastal and urban areas. The regional prevalences of both conditions were lowest in eastern Turkey, followed by the central region, and figures were highest in northern Turkey.

Presence of personal atopic history followed by family atopic history were the most prominent risk factors for both lifetime and current (last 12

months) occurrences of wheezing or asthma (Table VI). The risk became more apparent for the occurrences of these conditions during the last 12 months. Male gender and habitation in coastal areas were also risk factors for both asthma and wheezing. Living in urban areas rather than in rural areas was not a significant risk factor for current occurrences of either wheezing or asthma. Age had a minimal effect on the prevalences of these conditions. Indoor exposure to cigarette smoke was also a significant risk factor for both lifetime and current (last 12 months) occurrences of asthma and wheezing. Its presence did not affect the prevalence of physician-diagnosed asthma. Socioeconomic status did not appear as a significant risk factor for asthma and wheezing in childhood.

Discussion

This report summarizes the results on the prevalences of the respiratory symptoms associated with asthma incorporated within the nationwide chronic childhood diseases questionnaire survey in Turkey in 1996. Though several studies have been conducted previously in the urban areas of different cities in the country, comparison of the prevalence figures was not possible due to different methodologies (6-14, 16-18) (Table I). However, these reported prevalences are generally lower than those in most western countries. The results of the present survey provide prevalence figures for comparison between different communities in separate locations (rural vs urban, coastal vs inland, different regions and cities), and allow

Table VI. Adjusted Odds Ratios (OR) with 95% Confidence Intervals of Potential Risk Factors for Childhood Wheezing and Asthma*

	Wheezing			Asthma		
	Ever	Lifetime	Current	Physician-diagnosed	Lifetime	Current
Age	0.98 (0.97-0.98)	0.99 (0.98-0.99)	0.96 (0.95-0.96)	1.00 (0.98-1.02)	0.99 (0.99-099)	0.97 (0.96-0.98)
Sex (male)	1.25 (1.16-1.35)	1.25 (1.18-1.33)	1.32 (1.18-1.48)	2.00 (1.55-2.58)	1.26 (1.19-1.34)	1.39 (1.23-1.58)
Place of Habitation						
Urban	1.02 (0.91-1.14)	1.10 (1.02-1.20)	1.04 (0.89-1.23)	1.04 (0.72-1.49)	1.14 (1.04-1.23)	1.06 (0.89-1.28)
Coastal	3.95 (3.20-4.88)	2.38 (2.08-2.73)	2.59 (1.92-3.49)	2.24 (1.31-3.84)	2.11 (1.85-2.42)	2.31 (1.72-3.12)
Region						
West	1.21 (1.06-1.38)	1.19 (1.07-1.32)	1.67 (1.39-2.00)	1.29 (0.89-1.88)	1.08 (0.97-1.21)	1.26 (1.03-1.55)
South	1.56 (1.25-1.95)	1.28 (1.11-1.47)	1.83 (1.35-2.49)	0.64 (0.34-1.21)	1.23 (1.07-1.42)	1.50 (1.10-2.04)
Central	0.25 (0.21-0.30)	0.69 (0.62-0.77)	0.33 (0.26-0.44)	0.64 (0.43-0.96)	0.72 (0.65-0.80)	0.35 (0.26-0.46)
North	2.26 (1.83-2.81)	1.87 (1.62-2.14)	1.85 (1.36-2.50)	0.86 (0.47-1.56)	1.62 (1.42-1.86)	1.10 (0.80-1.50)
Smoking at Home	1.31 (1.16-1.48)	1.18 (1.08-1.29)	1.18 (1.00-1.40)	0.86 (0.61-1.19)	1.19 (1.09-1.30)	1.24 (1.02-1.50)
Personal Atopy	4.15 (2.83-6.08)	3.62 (2.57-5.11)	6.16 (4.00-9.49)	10.20 (5.54-18.80)	3.78 (2.69-5.33)	8.52 (5.62-12.92)
Family atopy	1.61 (1.29-2.02)	1.66 (1.39-1.97)	1.78 (1.32-2.40)	3.02 (1.87-4.88)	1.66 (1.40-1.98)	1.85 (1.35-2.53)
Socioeconomic Status						
High	0.87 (0.78-0.97)	0.96 (0.88-1.03)	0.94 (0.80-1.10)	0.67 (0.46-0.98)	0.99 (0.91-1.07)	0.85 (0.71-1.02)
Moderate	0.85 (0.76-0.94)	0.92 (0.85-0.99)	0.79 (0.68-0.92)	0.65 (0.46-0.92)	0.93 (0.86-1.01)	0.76 (0.64-0.90)

* The reference groups were female; habitation in rural or inland areas, or in the eastern region; absence of smoking at home; absence of personal or family atopy; and low socioeconomic status. Age was considered a numeric variable.

comparison of these figures with studies in other countries that used similar questions.

Bronchial asthma is a clinical diagnosis and does not have a universal definition[1]. Lacking a gold standard, it is rather difficult to determine the presence of bronchial asthma in epidemiological studies. Thus, surveys have usually inquired about respiratory symptoms, including wheezing, cough, etc., as well as about a previous diagnosis of asthma by a physician. Some studies have used objective markers of asthma such as bronchial hyperreactivity testing, exercise challenge, skin prick or RAST testing, monitorization of peak flow, inflammatory markers (eosinophilic cationic protein, etc.), or evaluation of previous medical records. European Community Respiratory Health Survey (ECRHS) in adults and International Study of Asthma and Allergies in Childhood (ISAAC) protocols have been developed in order to provide a standardized approach to respiratory symptoms and to allow for international comparison[1,2,22]. Further improvements are being implanted to the protocol are being implemented, including a video questionnaire to overcome cultural and translational differences[2]. Though the video questionnaire may provide more accurate evaluation of the prevalences of respiratory symptoms, the technical facilities and differences in cultural comprehension may hamper its use in some countries.

Though the questions in the present survey, about respiratory symptoms were derived from the ISAAC protocol, it is not quite identical with this protocol in its design and questionnaire format. The present study has incorporated ISAAC-based questions within a nationwide survey of chronic childhood diseases. However, the sampling method is different from the ISAAC protocol: the children included have a wider age range (0 to 17 years), and questions were not self-administered. The source of information was parents' responses (mostly mothers) to the questionnaire, and the survey was conducted via face-to-face interview by specially trained general practitioners. Besides evaluation of responses to standard questions on wheezing and physician-diagnosed asthma, new case definitions for lifetime and current (last 12 months) occurrences of wheezing and asthma have been employed. Despite these differences with the ISAAC protocol, we believe that a valuable set of epidemiological data on the prevalence of asthma-associated respiratory symptoms has been provided among children aged 0 to 17 by this survey. Epidemiological studies are difficult to conduct in Turkey, and collection of the data via face-to-face interview was considered necessary to achieve a better participation rate[23,24]. In this study, of the goal of 50,000 children in the study population, 46,813 children were surveyed (93.6 %).

The personal atopy and atopic heredity rates obtained from the present questionnaire were 0.4 percent and 2.2 percent, respectively, apparently lower than those reported in other countries and in previous studies (atopic heredity 12.7-20.5%) in urban areas of Turkey (Edirne, Bursa, Ankara)[8,10,11,14]. Recall bias and lack of adequate information among the responders on these disorders might have played a role in these low figures despite face-to-face interviews with the subjects. The 60-page questionnaire is quite long, despite filter questions, and the parents might not have provided responses with the same enthusiasm. Information obtained by further questions about allergic manifestations in the subject and also about first-degree relatives might have yielded more realistic responses about the atopy rates. The positive response rates for the presence of atopic heredity were not related to the socioeconomic status. Comparison of the responses among those with different socioeconomic levels suggested that the association between atopic heredity and various definitions of asthma used in the present study did not significantly change with socioeconomic level [ORs and (95% CIs) for lifetime wheezing and atopic heredity were 1.5 (1.2-1.9), 2.1 (1.6-2.9), and 1.9 (1.4-2.4), for high, moderate and low socioeconomic levels, respectively; chi-square for interaction: 3.28, $p=0.19$]. As one would expect comprehension of the questions to be better in higher socioeconomic levels, these findings suggested that comprehension by the subjects did not significantly affect the positive response rate for atopic heredity. This single question used to assess atopic heredity appears to have a low sensitivity. There may also be a bias produced by subjects from atopic families to answer more appropriately questions about atopic family history. However, the mis-classification is likely to be non-differential and thus would not lead to an overestimation of the association between atopic heredity and asthma.

Assessment of presence of ever (lifetime) wheezing or asthma by single questions also appears to result in lower prevalence rates than those determined by combined responses to other questions with these specific ones. As an example, the prevalence of lifetime wheezing obtained via combined responses was at least two times higher than that assessed by asking whether the child had ever wheezed (Table V). A similar situation was observed in the case of lifetime asthma. Besides translational challenges and cultural differences among people residing in different parts of the country, a previous diagnosis of "asthma" by a physician might have been interpreted alternatively by the parents. A recent study demonstrated that primary care physicians and pediatricians had a tendency to overlook the diagnosis of asthma in children and failed to prescribe appropriate therapy[25]. Parents would also deny this specific diagnosis and rather report bronchitis in their children. The significantly higher prevalence rate of bronchitis than that of asthma also supports this hypothesis (Table III). Thus, determination of "ever presence" of asthma through combined responses to questions seems more appropriate than assessment via inquiry of physician-diagnosis asthma. Since there is no exact equivalent of "wheezing" in Turkish, the question was translated as "whistling in the chest". As suggested in another study, even children in English-speaking countries may understand the term "wheezing" differently[2]. Further questioning about factors that provoke an asthma attack may yield a better assessment of the status of asthma in the past. In summary, we assume that combined responses to different questions on respiratory symptoms provide a more realistic picture for the occurrences of wheezing and bronchial asthma in Turkish children. This is also evidenced by the fact that the use of bronchodilator drugs was higher than the prevalence of physician diagnosed asthma among children (1.4 % vs 0.7 %, Table III).

There were notable differences in the prevalences reported from different urban parts of Turkey in previous studies. These differences also persisted between studies which used similar methodologies. The lifetime and current prevalences of asthma were reported as 2.8 to 17.4 percent and 5.6 to 9.8 percent respectively (Table I). Only one study (in Edirne) had evaluated childhood asthma and allergic disorders between populations in urban and rural areas, and reported no significant difference[11]. There is a great variation in the climate, geographical conditions, and cultural background between different regions of the country. Air pollution in urban areas, changing dietary habits, low rate of indoor contact with pet animals, and enlarging migration to metropolises might be partially responsible for the different prevalence rates reported in various studies. The house dust mite fauna is also variable in different regions, with the highest rate reported in samples from northern Turkey, and may play a role in promoting bronchial asthma[26]. A multicenter nationwide survey among adult asthmatics revealed that mite sensitivity with skin prick testing was almost two-fold higher in patients residing in coastal areas than in those residing inland [27]. A previous study has also revealed significant differences in dietary intake between preschool and primary school children as well as among those residing in different regions[28]. The consumption of poultry, fish, fresh vegetables and fruits increases with older age. Fish is consumed most frequently by those in the northern region, whereas fresh fruits and vegetables, fish and olive oil are consumed much less in eastern Turkey. The decline in the prevalence of asthma with increasing age might be affected by changes in dietary habits. However, it is unlikely that differences in dietary intake help to explain the prevalence differences between regions, and further studies to clarify this issue are required. In this study, the prevalence rate of physician-diagnosed asthma was almost twice as high among boys compared to girls, whereas the prevalence rate of wheezing was not different to the same extent (Table VI). This may indicate a sex bias in the referral of a wheezing boy rather than a girl to a physician (Yentl syndrome)[29].

Regarding the prevalence rates of lifetime wheezing and physician-diagnosed asthma in childhood in Turkey (5.4% and 0.7%, respectively, for children aged 13-14), the figures are considerably lower than those of neighboring countries such as Iran (10.9% for wheezing and 2.7% for asthma in children aged 13-14) and Greece (3.7% for wheezing and 4.5% for asthma in children aged 13-14), and also the mean figures of Europe and the world (16.7% and 13.8% for wheezing and 13.0 % and 11.3%

for asthma, respectively, among children aged 13-14)[3]. A recent study abroad confirmed the lower prevalence of asthma among children of Turkish immigrants aged 9-11 years than their German peers[30]. Though the rate of physician-diagnosed asthma in the past is very low in Turkey, the prevalence of asthma assessed by combined responses is close to the global figure of asthma prevalence (11.3 %) in the 13-14 years of age group.

In conclusion, the first nationwide ISAAC-based questionnaire survey conducted in 1996 used a physician-administered questionnaire applied to the parents of children aged 0 to 17. The study findings showed that respiratory symptoms associated with asthma were causing important morbidity in childhood. The diagnosis of asthma by physicians was made in a minority of the children having these respiratory symptoms. The prevalence of asthma symptoms were more frequent among boys, those residing in coastal areas and northern Turkey, and among those children exposed to cigarette smoke at home than in the corresponding comparison groups. The strongest associations were with personal atopy and atopic heredity. We believe that inquiry about wheezing and asthma is better accomplished with combined responses to different questions rather than with single ones, as recognition of asthma in childhood is not very good in the general population and even among the primary care physicians in Turkey.

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Appendix Asthma Module of The Questionnaire for Chronic Diseases in Childhood

1. Have you ever observed / heard your children having wheezing or whistling in the past?
2. Have your children ever been diagnosed with asthma?
3. Has your child had a wheezing or asthma attack during the last 12 months?

If the answer is "Yes" to the above question, please indicate the number of attacks:

4. *In the last 12 months*, has your child ever awakened up with wheezing or cough?
5. *In the last 12 months*, has wheezing ever been severe enough to limit his/her speech to one or two words at a time between breaths?
6. *In the last 12 months*, has your child ever had wheezing during or after exercise (running or other sports, crying)?
7. *In the last 12 months*, has your child ever had cough without sputum at night, apart from a cough associated with a cold or chest infection?
8. *In the last 12 months*, has your child ever produced or phlegm mucus in the morning?
9. *In the last 12 months*, has your child ever woken up with chest tightness?
10. *In the last 12 months*, has your child ever experienced chest tightness and/or shortness of breath after contact with animals, feathers or dust?
11. *In the last 12 months*, has your child ever used any bronchodilator drugs?
12. Has your child had bronchitis at any time in the past?
13. Has your child had wheezing during bronchitis or a cold at any time in the past?
14. Has your child ever experienced recurrent or persistent cough for at least 12 months?

Filter Questions From Dermatological Section

15. Does your child have any allergic disease such as eczema, urticaria or atopic dermatitis?
16. Has your child ever experienced allergic rhinitis, bronchial asthma and/or eczema?
17. Has any other family member ever had allergic rhinitis, bronchial asthma and/or eczema?
18. How many family members smoke at home?

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Transcatheter closure of secundum atrial septal defects, a ventricular septal defect, and a patent arterial duct

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We report our clinical experience with the newly developed Amplatzer device in transcatheter closure of nine atrial septal defects (ASDs), one ventricular septal defect (VSD), and one patent arterial duct (PDA).

Eleven patients with ASD (age range 2.5-18 years) selected according to the location and size of the defect by transesophageal echocardiography (TEE), a five-year-old patient with muscular VSD and a one-year-old patient with PDA were considered for transcatheter closure with Amplatzer devices. All procedures were performed under general anesthesia with fluoroscopic and TEE guidance, following a routine hemodynamic evaluation in the catheter laboratory. The optimal device size was selected after the balloon sizing of the ASDs. The sizes of the VSD and PDA were measured on TEE and angiography. The patients were discharged at 24 hours, after an evaluation with x-ray, electrocardiogram (ECG), and echocardiography; they were on 3-5 mg/kg/day aspirin and infective endocarditis prophylaxis for six months after the procedure. They were reassessed at six to eight weeks and Holter monitoring was done in addition.

Devices were used for nine ASD patients, and for the VSD and the PDA patients. Mean ASD size was 14.3 ± 5.3 mm at TEE and 18.3 ± 4.3 mm at balloon sizing ($p=0.02$). The mean size of the device was 18.7 ± 4.2 mm. The procedure time and the fluoroscopy time were 46.1 ± 12.3 and 12.9 ± 1.6 minutes, respectively. Immediately after the procedure, four patients (44%) had trivial shunts (TS). TS remained in only two during discharge, and no shunt was observed at second evaluation. The devices were similarly applied to VSD (12-7 mm) and PDA (8-6 mm) patients. Both cases had TS immediately, which disappeared at 24 hours. None of the patients had major complications. Junctional rhythm developed in one patient, and another patient had frequent supraventricular extrasystoles.

Amplatzer is an effective and safe device for transcatheter closure of ASD, VSD, or PDA, especially in pediatric patients.

Key words: Amplatzer septal occluder, transcatheter closure, atrial septal defect, ventricular septal defect, patent ductus arteriosus.

Surgical repair of interatrial communications has negligible mortality, and is widely accepted as a safe procedure; however, it is associated with morbidity, discomfort after thoracotomy, and a longer stay in hospital[1]. Therefore, transcatheter closure of atrial septal defects (ASD) has been developed as an alternative to surgery. William Rashkind[3] did the first studies about transcatheter closure of intracardiac defects in the late 1960's. "Single hooked umbrella" was the initial device created for this purpose (Fig. 1). This device was implanted in the dog heart (left ventricular posterior wall) via thoracotomy, and the endothelization of the device was observed with serial autopsies. In 1970, in Philadelphia Children's Hospital, Bilgiç used this device, which was produced in the catheter laboratory using transatrial needle,

basket and balloon catheters, on 15 dogs with ASDs (unpublished data) (Figs. 2 and 3). The first reports of transcatheter device closure of secundum ASDs in humans were published in 1976 by King and Mills[2]; and in 1983 by Rashkind[3]. Since then, a variety of devices have been developed, but none has gained wide acceptance[4]. Previous techniques had some limitations like large delivery sheaths, difficult implantation techniques, inability to recapture, structural failure causing damage to neighboring structures, dislodgment, and embolization[5-13]. In 1997, Sharafuddin et al.[14] reported an animal study using a different approach to defect occlusion by stenting the inter-atrial communication with a Nitinol prosthesis, tightly woven into two flat buttons with a short connecting waist[15]. There is clinical evidence that the Amplatzer is a preferable choice among the other devices. It produces significantly higher occlusion rates and is much easier to apply[16,17]. The Amplatzer ventricular septal occluder and ductal occluder are new devices especially designed for transcatheter closure of muscular ventricular septal defects (VSDs), and patent arterial ductus (PDAs), an they have been successfully tested in animal and in vivo experimental studies[18,19]. We report our clinical experience with the Amplatzer device in transcatheter closure of nine ASDs, one VSD, and one PDA.

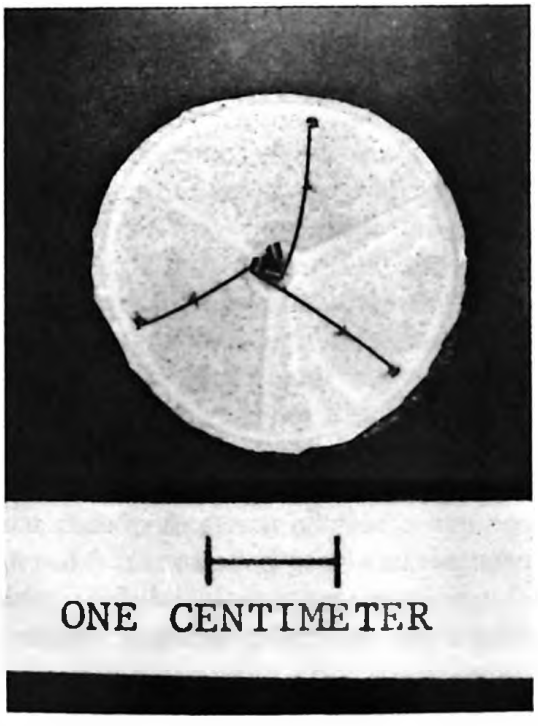

Fig. 1. Single hooked umbrella device (courtesy of Arman Bilgiç, MD).

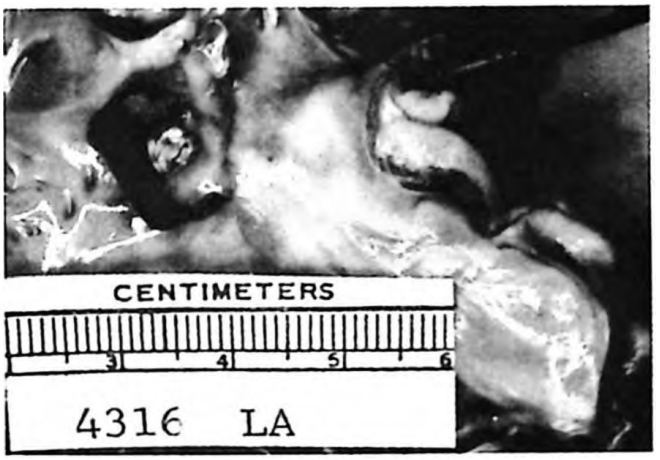

Fig. 2. Transcatheter device closure of atrial septal defects in dogs: two weeks after the procedure (courtesy of Arman Bilgç, MD).

Fig. 3. Transcatheter device closure of atrial septal defects in dogs: six months after the procedure (courtesy of Arman Bilgiç, MD).

Material and Methods

Patients

Eleven patients between 2½-18 years of age (mean 7.8 years) with secundum ASD, a five-year-old patient with mid-muscular VSD, and a one-year-old patient with PDA met echocardiographic criteria for transcatheter closure with Amplatzer device (AGA Medical Corporation, Golden Valley, MN). All patients were evaluated at our institution with two-dimensional and color Doppler echocardiography with multiple subxyphoid and precordial windows. All patients with ASD were further evaluated with biplane transesophageal echocardiography (TEE). Patient inclusion criteria were 1) the presence of an ostium secundum ASD with left to right shunt across the ASD, 2) a distance of >4 mm from margins of the defect to the mitral and tricuspid valves, superior vena

cava, right upper pulmonary vein, and coronary sinus, and 3) dilation of right atrium and right ventricle indicating right ventricular overload. One of the patients with ASD had reentrant ventricular tachycardia originating from the right ventricle, which was successfully ablated one month before the procedure. Another patient had dilated cardiomyopathy complicating a past viral myocarditis. Transcatheter closure was preferred for this patient due to the relative safety of this procedure over open-heart surgery.

The echocardiographic examination revealed a 3 mm mid-muscular VSD and 70 mmHg pressure gradient across the defect with continuous wave Doppler in a five-year-old patient, and a 3 mm PDA in a one-year-old patient. These two patients were also included in the group.

Routine examination before the procedure included electrocardiography (ECG), chest x-ray, and transthoracic echocardiography. Informed parental consent was obtained for each patient. All were discharged the next day. Before discharge, ECG, a biplane chest x-ray, and transthoracic echocardiography were repeated. Six to eight weeks later a follow-up transthoracic echocardiography and a Holter monitoring were done, and six months later a TEE was planned. The patients received prophylactic antibiotics to cover the implant procedure and any intervention for six months following the implantation. They also received 3-5 mg/kg/day acetylsalicylic acid after the procedure for six months.

Devices

The Amplatzer Septal Occluder (Fig. 4) is a self-expanding, self-centering, retractable, and repositionable double disk device constructed of a dense mesh of Nitinol wires. A 3-4 mm short, cylindrical waist connects the two disks. The left atrial disk extends 7 mm and the right disk 5 mm radially around the connecting waist. The left disk is slightly larger than the right, because of the higher left atrial pressure. The prosthesis is filled with Dacron fabric to facilitate thrombosis. The waist of the device is designed to stent the ASD. In order to stent, the diameter of the waist has to correspond to the stretched diameter of the defect. Currently, devices with waist diameters from 4-26 mm are available. The device is connected to a delivery cable by a microscrew fixed to the right atrial disk and loaded into a 6-7 French (F) long sheath[4,15].

Fig. 4. (From right to left) Amplatzer septal occluder, ductal occluder, and ventricular septal defect occluder.

The VSD device (Fig. 4) is similar to the ASD device. The length of the central stent has been increased from 3 to 7 mm to allow for the thicker interventricular septum compared to the interatrial septum. The retention disks are smaller and project only 4 mm on each side of the device. A microscrew is fixed to the right ventricular disk[20].

The Amplatzer ductal occluder (Fig. 4) is a self-expanding mushroom-shaped device with a thin aortic retention disk designed to secure positioning in the aortic ampulla[21].

Procedure

ASD : All procedures were performed under general anesthesia to allow continuous biplane TEE imaging of the atrial septum and neighboring structures. A 7F sheath was placed in the right femoral vein and a 4F sheath in the left femoral artery for pressure monitoring. Right and left heart catheterization was performed to measure the pulmonary artery pressure and to compute the amount of the left-right shunt through the ASD. A left atriogram in a 45° left anterior oblique position and a 35° cranial angulation, with the catheter pointing towards the right upper pulmonary vein, was done to illustrate the angiographic morphology of the left to right shunt. A sizing balloon catheter (AGA Medical, Golden Valley, MN) was passed over an exchange length guidewire and was inflated at the level of the defect until the waist in the middle of the balloon was seen. The waist was measured on the sine-angiographic frame and was calibrated using the radiopaque markers on the shaft of the catheter. The waist of the sizing balloon was used as the stretched diameter of the defect and an occluding device of similar diameter was chosen. A 7F long sheath and a dilator were passed over the exchange guidewire. The selected device was screwed on to the delivery system and was loaded under water. The dilator and the

exchange guidewire were then withdrawn, replaced by the device and the delivery system. The left atrial disk and the waist of the device were deployed under fluoroscopic and TEE guidance. The device was pulled against the septum to enable self-centering and, then the right atrial disk was deployed. At this instant special care was given to detect the residual shunt, or any obstruction of the caval veins, right pulmonary veins, or the atrioventricular valves by TEE. In addition, gentle pulling and pushing of the delivery cable (Minnesota Wiggle) was done to ensure a stable position. If the device was satisfactorily well positioned and no or only a trivial shunt was observed through the stented defect, the device was unscrewed from the cable. A right atriogram was performed to demonstrate the position of the device and any residual shunts.

PDA : The procedure was done under general anesthesia. A multipurpose catheter and an exchange guidewire were placed in the pulmonary artery via the right femoral vein, right atrium and ventricle and were then advanced into the aorta. A 8-6 mm ductal occluder was used. After preparing the device in a similar way to the septal occluder, it was placed across the PDA. The retention disk was deployed at the aortic edge of the ductus. Any residual shunt was detected with repeated contrast injection in the arcus aortae, which is reached via the left femoral artery.

VSD : The procedure was done under general anesthesia and transesophageal guidance. After confirming the place and distance of the defect to the atrioventricular valves and aorta by left ventriculogram, a cobra catheter and an exchange guidewire were advanced to left ventricle via the right femoral artery and arcus aortae. With repeated hand injection of a small amount of contrast through a second catheter introduced from the opposite femoral artery, the catheter and the guide were passed through the ventricular septal defect to the right ventricle and the pulmonary artery. The guidewire was then snared from a percutaneous jugular vein approach. The long sheath was advanced over the guidewire from the jugular vein to the left ventricle. The size of the VSD was measured as 10 mm with TEE. A 12-7 mm ventricular septal occluder was deployed in a manner similar to that used for the septal occluder.

Results

Transcatheter closure was attempted for ASDs in 11 patients aged 2.5 to 18 years old (mean: 7.8 years). Body weight ranged from 14-64 kg (mean: 26.9 kg). The mean ASD diameter determined by TEE was 14.2 ± 5.3 (range 6 to 25) which was significantly smaller (mean: -4.93 ± 3.2; p=0.02) than the stretched diameter of ASD measured by balloon sizing, 18.3 ± 4.3 (range 11 to 26). The pulmonary/systemic flow ratio (Qp/Qs) varied between 1.4 and 3.9 (mean: 2.3 ± 0.8), and the mean pulmonary artery pressure varied between 13 and 24 mmHg (mean: 17.8 ± 3.3). Nine of them were successfully treated with this method. The mean device diameter was 18.7 ± 4.2 (range 12 to 26) and the interatrial septum/device ratio was 1.7 ± 0.4 (range 1.1-2.3).

The procedure was not carried out in two patients. The ASD distance to the superior vena cava was initially measured as 4.3 mm with TEE in one patient; however, on the day of the procedure the repeated measurement was 1 mm. The other patient had 4 mm of superior rim and 26 mm stretched ASD diameter. The superior rim of the ASD was to small in both patients to carry out this procedure. The latter patient, had a large ASD as well. In another patient whose stretched ASD diameter was 20 mm, a 19 mm device was initially used to occlude the defect; however, an obvious residual shunt was observed with TEE. This device was successfully retrieved and replaced with a 24 mm device; only a trivial shunt was then observed with TEE.

The mean total procedure time was 46.1 ± 12.3 (range 27-65 minutes) and the mean fluoroscopy time was 12.9±1.6 (range 11.9-17 minutes). Immediately following the procedure the TEE, and at the time of discharge, the transthoracic echocardiography, revealed no obstruction of superior or inferior vena cava, coronary sinus, or of the right upper pulmonary vein. There was also no atrioventricular valve regurgitation. Immediately after release of the device, four of the patients (44%) had residual trivial shunt with TEE; at the time of discharge this rate was reduced to 22 percent (2 patients). Figure 5 demonstrates the echocardiographic image of the Amplatzer atrial septal occluder.

There were no major complications. Only one patient had a very short duration of junctional rhythm, which returned to normal immediately

after the procedure. Follow-up echocardiographic data revealed no evidence of residual shunt in any of the patients. In one of the patients, frequent isolated supraventricular extrasystoles were present in the follow-up Holter record and there were complaints of palpitation. Because of previously experienced ventricular tachycardia and the radiofrequency ablation procedure, the sense of palpitation caused panic attacks in this patient. Therefore this patient was treated with propranolol. Another patient had junctional rhythm with two short asymptomatic junctional ectopic tachycardia runs (maximum heart rate 170/min). This patient has been followed clinically without medication. All the other Holter records were normal.

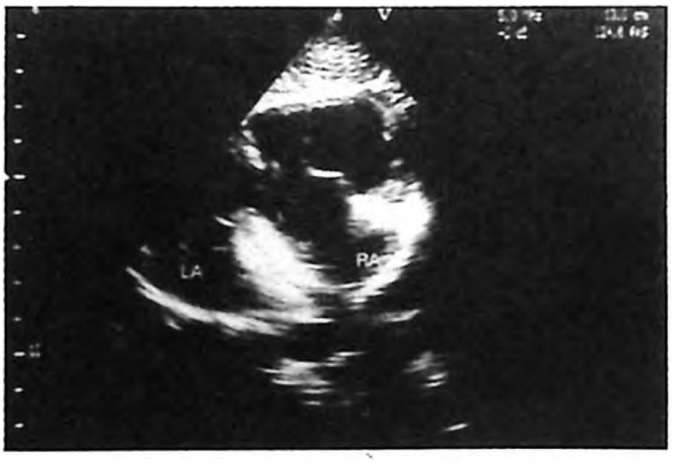

Fig. 5. Echocardiographic image of the Amplatzer septal occluder device (indicated with arrows).

The patients with VSD and PDA were successfully treated with transcatheter closure of the defect. Although both patients had trivial shunt with TEE immediately after the procedure, the shunt had disappeared by discharge the next day. The total procedure time and the fluoroscopy time, respectively, were 150 minutes and, 61 minutes for VSD closure, and 50 minutes and, 15 minutes for PDA closure. A 12-7 mm device was used for closure of VSD, and a 8-6 mm device for PDA. The mean pulmonary artery pressure and the Qp/Qs ratios for these patients with VSD and PDA were 17 mmHg/1.5, and 18 mmHg/1.8, respectively. The patient with VSD had a coil embolization for his PDA a year before the present procedure. No complications, including no arrhythmias, were observed during short-term follow-up. Figure 6 demonstrates the echocardiographic image of the Amplatzer ventricular septal occluder.

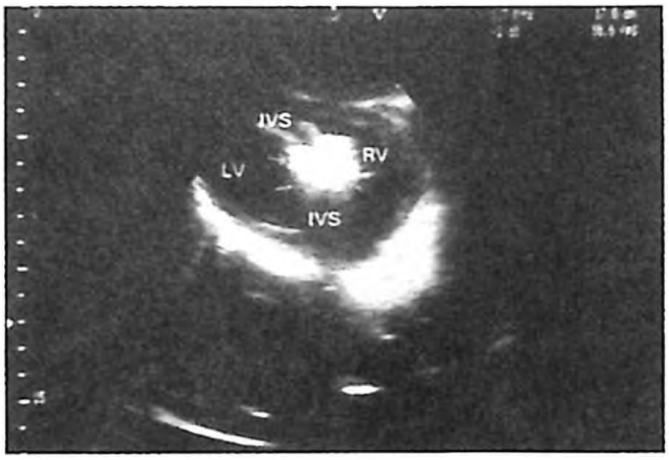

Fig. 6. Echocardiographic image of the Amplatzer ventricular septal defect occluder device (indicated with arrows).

Discussion

Several reports of successful transcatheter closure of secundum ASD's have come into sight in literature in the past 20 years. However, this procedure still has not achieved widespread use, and new devices are being produced or improved every day. The Amplatzer septal occluder seems to overcome many of the disadvantages of previously used devices, namely, requisite large introducer sheaths, a large overall device for complete closure of the defect, difficult application procedures, inability to recapture, structural failure causing damage to neighboring structures, dislodgment, embolization, and higher rates of residual shunts[5-13]. The high success rate of the present device, which has also been reported by other investigators[4, 15-17, 22], is due to its functional design: the self-centering mechanism stenting the potential ASD and forcing blood through a highly thrombogenic Dacron network. Because the potential defect is stented, there was transient trivial left-right shunt seen in 44 percent of our cases, but this immediately decreased to 22 percent the next day, before discharge. In follow-up echocardiographic study, no residual shunt was observed in any of the patients. This is the highest closure rate compared to other reports (100%)[4, 15-17, 23]. The precise measurement of the defect is very important for appropriate selection of the Amplatzer device. If the device is too bulky, the disks may protrude into the atria, if it is too small the risk of residual shunt and embolization increases[4,24]. The selected device was 2 mm smaller than the measured ASD in

two patients, exactly the same size in one, 1 mm larger in two, and 2, 3, 4, and 5 mm larger in each of the remaining patients. Prominent protrusion into the atria was not observed in the latter group of patients. Three of the residual shunts were observed where a smaller or the same-sized device was used for occlusion. However, only one of these patients had shunt at the time of discharge. We believe the identical sized device with the stretched ASD or 1-2 mm larger devices will maximize effect without causing any bulky protrusions.

The design and the method of fixation make it possible to close larger defects with smaller rims[15]. In our study group the largest ASD closed was 21 mm (stretched diameter), and the smallest inferior rim was 5.2 mm. The procedure was not performed in two of our patients because of small ASD rims. One patient had dilated cardiomyopathy complicating a past viral myocarditis. Transcatheter closure of her ASD was thought to be less dangerous; however, the procedure was not performed because she had a large ASD with small rims. This patient and another one with small ASD rims now await surgery.

The Amplatzer's loading, technical deployment and recapturing are simple, which significantly reduces the total procedure and fluoroscopy time[4,11,23]. We assume the longer procedure and fluoroscopy times for VSD closure are because of the relatively more complex procedure; these should improve along the learning curve as better-designed devices are available.

There were no major complications such as device fracture, embolization, migration, or mitral regurgitation. One patient had a very short duration of junctional rhythm during the procedure, which returned to normal right after the procedure. The Holter records of two patients at six to eight weeks after the implantation revealed dysrhythmia. One of these patients was the one with reentrant ventricular tachycardia originating from the right ventricle, which was successfully ablated one month before the procedure. This patient had frequent supraventricular extrasystoles. The other patient had no history of dysrhythmia and had sinus rhythm prior to ASD closure. This patient has asymptomatic junctional ectopic tachycardias. The asymptomatic nature of the dysrhythmia in this patient emphasizes the usefulness of routine Holter monitoring in the follow-up of these patients.

Unlike some other authors, we did not heparinize our patients, but administered low-dose (3-5 mg/kg) aspirin for six months in order to prevent excessive thrombus formation on the device. We believe heparinization is not necessary and may prolong the disappearance of small residual shunts.

The Amplatzer septal, ductal and ventricular septal occluders in their current configuration are easy to implant, and provide an effective alternative for surgery, especially for those at high risk of open-heart surgery. The device can be safely used in children since it requires smaller introducer sheaths, which can be easily removed or repositioned should an undesired implantation occur.

Acknowledgement

We would like to express special thanks to Ziyad M. Hijazi, MD, for his help in establishing this procedure in İhsan Doğramacı Children's Hospital.

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Why hypothermia in neonatal hypoxic ischemic encephalopathy?

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SUMMARY: Gücüyener K, Ergenekon E. Why hypothermia in neonatal hypoxic ischemic encephalopathy? Turk J Pediatr 2001; 43: 19-23.

The incidence of asphyxiated full-term infants is still high in both high income and developing countries. In up to 80 percent of infants, moderate to severe birth asphyxia results in long-term neurological sequelae. Many years of experimental work and a limited data on hypoxic-ischemic neonates have supported the hypothesis that hypothermia after the primary insult induces permanent neuroprotection. In this mini overview, we attempt to update pediatricians in this aspect and raise the following: Will the future treatment include hypothermia along with the conventional and or other promising drugs affecting different aspects of the hypoxia-ischemia?

Key words: brain cooling, neonatal hypoxic-ischemic encephalopathy, hypothermia.

Introduction

Hypoxic injury, in the fetal and newborn brain results in long term sequelea as mental retardation, epilepsy, cerebral palsy and learning disabilities as well as neonatal morbidity and mortality[1]. The origin and timing of injury often are less clear in the clinical settings than observed in animal models. This is why the potential future therapies are in their premature stage; are not put into reality before indepth understanding of the underlying mechanisms. Previous experimental and clinical data showed that hypoxic ischemic injury is a continuing process. There are two phases; first the primary energy failure during which the cerebral metabolism may initially recover but deteriorates in a latent secondary phase after 6-15 hours later[2,3]. It is very ikely that the prominent damage occurs in this secondary phase. In infants with hypoxic ischemic encephalopathy (HIE), a clear cut correlation between the secondary energy failure and neurodevelopmental outcome at 1 and 4 years of age exists[4]. Recent studies hav eled to the idea that modifying yhe post-ischemic cerebral temperature can effectively modulate encephalopathic process occuring both in the primary and secondary phases of cerebral injury[5]. Thus the idea of the neuroprotective effects of cerebral hypothermia during or after cerebral ischemia or asphyxia alone or in combination with other therapy modalities have gained enormous attention.

This review will primarily and briefly focuses on the main factors why this encouriging ttherapy could be promising for the hypoxia susceptible developing brain.

Why is the Developing Brain Prone to Hypoxia

In terms of neonatal brain the developmental status, the interplay of anatomic, structural and functional maturational processes and the response of the potential mechanisms to hypoxia of the cellular components determines the final winner in HIE (Fig. 1).

Brain is rich in polyunsaturated fatty acids that is highly susceptible to oxidative reactions[6]. Previous studies showed that the rate of lipid peroxidation as measured by thiobarbituric acid reactive substances (TBA) was higher in term brain than preterm probably due to the presence of this higher level of polyunsaturated fatty acids[7]. When the brain homogenates of normoxic and hypoxic term fetuses were compared; the TBA reactive substances in the hypoxic group were 3 times, the lipid peroxidation were 5 time shigher than the normoxic controls[8]. T hus during the developmental period a comparable amount of lipid peroxidation occurs in the term babies making them more prone to hypoxia than the pretem. This is one of the reasons why HIE is mostly seen in term neonates.

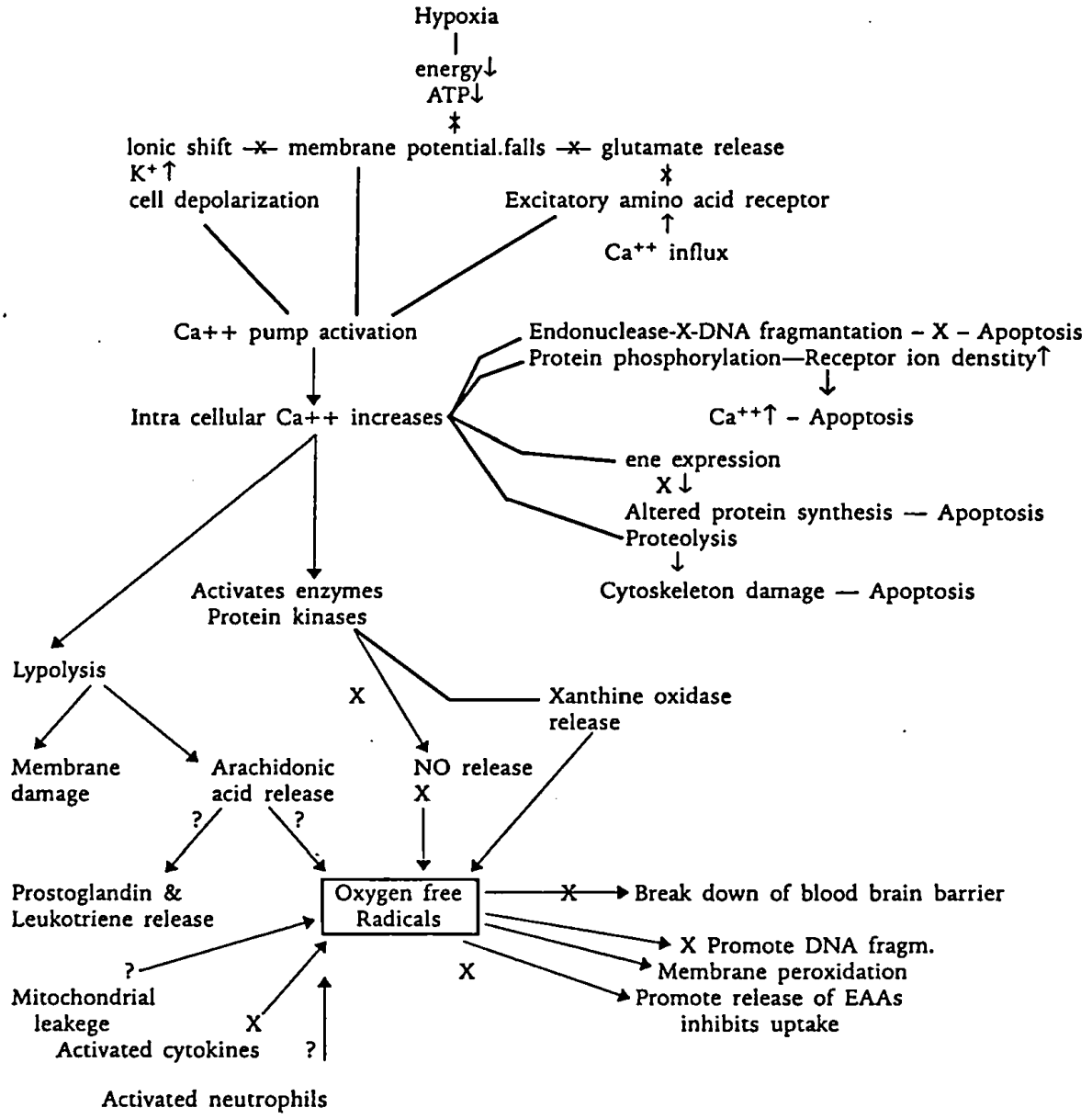

Fig. 1. Where hypothermia definitely (X) and indefinitely (?) interferes in HIE.

Excitatory amino acids is important in neuronal damage in hypoxia and ischemia[8]. As well the N-methyl-D aspartate (NMDA) glutamate receptor plays a pivotal role in the maturational process[9]. The density of glutamate receptors in areas of active development exeeds that in the mature brain The immature glutamate receptor has an increased agonist binding[10], an enhanced response to glycine[11], weaker magnesium blockade and less dependence on membrane depolarisation[11]. Thus ion channel opening is increased and a greater influx of calcium is seen. Mishra et al; showed that an increase in number and activation of NMDA receptor by glutamate and glycine during brain development could probably increase the vulnerability of the fetal brain to NMDA induced excitotocicity near term. This indicates that, the sensitivity of the developing brain to hypoxic injury via NMDA receptor augments with brain maturation. Furthermore hpoxia modifies the NMDA receptor-ion channel complex[12].

In addition during hypoxia the increased concentrations of free fatty acids, by impairing the mitochondrial function decrease its calcium buffering capacity[13]. An increased peroxidation of brain cell membrane lipids during hypoxia in the newborn piglets has been reported[14]. During hypoxia; due to the increased intra cellular calcium, activation of cyclooxygenase, lipooxygenase pathways, nitric oxide sythase occurs, and additionally conversion of xanthine dehydrogenase to xanthine oxidase results in free radical generation. In a study concerning neonatal hypoxic-

ischemic brain damage; the asphyxiated neonates had higher malondialdehyde levels and prostoglandin activity than the controls[15].

How Cooling is Effective

As explained above luckly,most of the main pathophysiologic mechanisms operating in asphyxiated neonates, are more or less effected by hypothermia. Cooling can either be systemic; total body, selective cerebral or both.Hypothermia produces a stepwise increase in cerebral metabolism of about 5-7% for each degree of temperature reduction[16]. Reduces the depletion of high energy phophates thus delays neuronal depolarization that seems toinitiate both apoptotic and necrotic cell death[17]. It also reduces the release of excitotoxins. By intraischemic hypothermia, the delayed neuronal depolarization was shown to reduce the accumulation of excitotoxic neurotransmitters[16]. Post depolarization decrease of release is also reported[18].

Hypothermia also decreases nitric oxide release. In newborn pilets; hypothermia starting immediately after hypoxic-ischemia had reduced NO efflux in the brain along with reduced levels of excitatory amino acids[19]. Cooling during the reperfusion period, by reducing oxygen metabolism hypothermia supresses oxygen free radical bursts abd lipid peroxidation[20]. Hypothermia extends secondary hypoperfusion. Cooling started at 1.5 and 5.5 hr after ischemia was shown to prevent later development of hyperperfusion during secondary phase and improved neuronal outcome[21]. It prevents intracelluler ion and water entery and final osmotic cell swelling even if the ATP dependent Na+/K+pump is inhibited, and prevents secondary cytotoxic oedema[21]. Hypothermia was suggested to prevent delayed cell degeneration via apoptotic mechanism in the cerebral cortex of the piglet withput effecting necrotic cell death[22]. In another study, they showed that the hypothermia had delayed rather than preventing apoptosis in cell cukture systems[23]. Further more, in the newborn rat hippocampus, hypothermia induced reduced apoptotic and necrotic cell death was reported[24*]. It also decreases inflammatory second messangers. IL1β receptor antagonists were proved to be protective in the 7 day old rat model of hypoxia and hypothermia supresses post traumatic release of IL1β in the adult rat[25].

As seen with most of its action mechanisms, hypothermia may be a promising neuroprotective method in hypoxic ischemic injury.

Brief or Prolonged Hypothermia

Hypothermia could be brief or prolonged in duration. The brief hypothermia due to the data in the literature suggests modest neuroprotection in the neonatal rat and piglet[26,16]. Thus brief cooling could be highly effective after relatively mild insults and the protection seems to be decreased if brief hypothermia is delayed, such as; from 15 to 45 minutes after the primary insult[27,28]. When prolonged hypothermia is applied; it was seen that extended period of cooling ranging between 5 and 72 hr post asphyxia was more effective[29]. In unanaesthesided infant rats after amoderate hypoxia-ischemia, a mild cerebral hypothermia applied for 72 hours immediately after hypoxia had prevented the cortical infarction, while 6 hours of cooling had non significant results[29]. As well, in the anaesthtised hypoxia induced piglet, with bilateral carotid ligation 12 hours of mild hypothermia applied just after hypoxia had prevented energy failure and had reduced neuronal loss as indicated before[27]. However when the post ischemic initiation of hypothermia in the fetal sheep was delayed to 5.5 hour just before the secondary sizures a still existing but reduced neuroprotection in intensity had been observed[27]. Gluckmann et al, showed that a delay of 90 minutes in commencing moderate selective cerebral cooling, if continued until 72 hours after ischemia in the fetal sheep had prevented secondary cytotoxic oedema and had improved electroencephalographic recovery[30]. All these observations indicate that optimal benefit is obtained by extending the duration of post ischemic cooling periods bet up to 72 hours.

How Far Cooling

Optimal neuroprotection obtained varies between the animal models used. In the fetal sheep and dog the best result was seen when the temperature was below 34 °C. In the adult humans, whole body cooling to 33.5 °C for 24 hours had improved outcome without profound adverse effects[31].

Newborn Studies

Gunn et al; showed that selective head cooling with mild systemic hypothermia at 34.5-35 °C,in 12 term infants with HIE for 72 hr following

perinatal asphyxia were safe[32]. Ballın et al found no late adverse effects in infants at the age of 18 months who had received selective head cooling[33]. The normal neurodevelopmental outcome of these children reassured us about the safetiness of the method as well. Simbruner had recently retrospectively analysed the records of 21 asphyxiated newborns head-cooled for an avarege of 3.5 days to a temperature between 34-35 °C and found that 4 of 21 infants in the hypothermia and 5 of 15 in the comparison group had died. The advers effects seen during and after induced long term hypothermia in the surviving neonates were not significant. Lately, Asano et al had succesfully treated a case of very low birth weighted of 31 weeks' gestation with intracranial hemorrage and severe asphyxia due to a traffic accident with selective head cooling with minimal hypothermia[34].

Adverse Effects

The two human studies with neonates, as mentioned above; first by Gunn et al, where combined head and body cooling in 12 asphyxiated infants wre applied had no advers effects[32]. Due to the second report by Simbruer et al; 22 asphyxiated infant had mild selective head and systemic cooling for an avare of 3.5 days. Mild hypothermia had reduced their heart and respiratory rates by 13 and 16% respectively. No episodes of bradycardia and dysrhythmias and apnea were observed. They neither reported increased coagulopathy or pulmonary hemorrage and hematuria. Only hypoglycemia incidence was increased[35].

Comments

Taken together all these animal work and human studies, phase I trials in asphyxiated neonates; the take home message is; extending the duration of post asphyxiated moderate hypothermia starting within the first 6 hours and lasting for 72 hours will seem to be promising. Hypothermic treatment effects several of the mechanisms of damage operating in the vulnerable brain of the neonate with HIE. Combining it with the future's planned drugs acting on mechanismas of HIE will give the best results. This millenium's neonatal order sheet for the baby with HIE along with the forthcoming future interventions, (antiapoptotic drugs, some growth factors, free radical scavengers, etc.) will also have ICE CAP therapy for 3 days for selective head cooling. Starting at the possible earliest time post partum, may be at the delivery room if the baby has documented intra uterine fetal distress.

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HLAs in children with minimal change disease and other types of nephrotic syndrome in the southern part of Turkey

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The aim of this study was to investigate the human leukocyte antigen (HLA) profile of children with nephrotic syndrome in the southern part of Turkey. Seventy-eight children with nephrotic syndrome were studied for the frequency of class I and class II human leukocyte antigens. Forty-seven of them were steroid sensitive nephrotic syndrome (minimal change disease-MCD) and 31 were other types of nephrotic syndrome. The results were compared with 133 healthy subjects for HLA groups. HLA B13, Cw5, Cw7, DR4, DR7, DRw10, Drw15(2) and DQ2 in the MCD group and HLA A31, B8, B13, B17, Cw2, Cw6, Cw7, DRw10 and DRw12 in the non-MCD group were found significantly increased when compared to healthy controls. MCD patients with frequent relapses had higher frequencies of both Cw6 and DR1 ($p < 0.005$) and MCD patients with infrequent relapses had a higher frequency of Cw7 ($p < 0.05$). In conclusion, HLA groups may help in the early diagnosis of these variants.

Key words: HLA, nephrotic syndrome, Turkish children.

Nephrotic syndrome (NS), one of the common renal diseases in childhood, is characterized by proteinuria, hypoalbuminemia, hypercholesterolemia, and edema. Minimal change disease (MCD) is the most frequent cause of childhood nephrotic syndrome, accounting for 80 to 85 percent of all cases. Other various subtypes of chronic glomerulonephritis (CGN) result in severe proteinuria and represent an important cause of nephrotic syndrome in children. Of these subtypes, focal segmental glomerulosclerosis (FSGS) is the most frequent one, followed by mesangial proliferation (MesPGN), membranous (MGN) and membranoproliferative glomerulonephritis (MPGN)[1]. The cause of idiopathic nephrotic syndrome remains unknown. Treatment of NS with "immunosuppresive" drugs suggested that the disease was mediated by an immunologic mechanism. Some diseases with immunologic bases are known to be associated with human leukocyte antigen (HLA) system[2]. Also, strong associations with certain HLAs in children with MCD have been shown in several studies. In this study, we investigated HLAs in patients from the southern part of Turkey with MCD and other types of nephrotic syndrome diagnosed by biopsy. We compared our findings in patients and controls to determine the associations with HLAs.

Material and Methods

Of all patients with NS followed at the Department of Pediatric Nephrology, Çukurova University, School of Medicine, 47 children with MCD (the criteria of the International Study of Kidney Disease in Children were used for the diagnosis) and 31 with non-MCD (7 MPGN, 2 FSGS, 19 MesPGN, 3 diffuse proliferative glomerulonephritis) diagnosed by biopsy were included in the study. All patients were Turkish children from the southern part of Turkey. In the MCD group, 37 were infrequent relapsers and 10 were frequent relapsers. The control population consisted of 133 living kidney donors. They were unrelated to each other and were healthy Turkish people from the southern part of Turkey.

HLA typing was performed using the standard microlymphocytotoxicity test[3]. Separated lymphocytes were used for HLA -A, -B and -C

typing by the microlymphocytotoxicity technique; some separated lymphocytes were treated with magnetic beads for separation of class II positive lymphocytes. Acridine orange/ethidium bromide staining of B cells was performed for HLA DR typing; fluorescence microscopy was used for this purpose. The significance of association was tested by Fisher's exact test or the chi-square test, as appropriate. All p values were corrected with the Benferroni correction. The relative risk (RR) was calculated by Odd's ratio. Ninety-five percent confidence intervals (95% CI) for relative risk were calculated by ANOVA test.

Results

A significant increase in HLA B13, Cw5, Cw7, DR4, DR7, DRw10, DRw15(2), and DQ2 and a significant decrease in HLA A24(9), Bw4, Bw6, DR2, and DR5 were found in the MCD group when compared with the control healthy group. HLA-B17 was found in 17 percent of the patients in the non-MCD group, but in none of the MCD patients ($p < 0.005$). Seven of the 31 non-MCD patients were positive for HLA DRw12 while none of the MCD patients was positive, but the difference was not statistically significant. In the non-MCD group, A31, B8, B13, B17, Cw2, Cw6, Cw7, Drw10 and DRw12 antigens were found statistically significantly increased and Bw4 Bw6, Cw4, DR5 antigens were found statistically significantly decreased when compared with the healthy group (Table I-IV). MCD patients with frequent relapses had higher frequencies of both Cw6 (40% vs. 5% in infrequent relapsers $p < 0.005$) and DR1 (40% vs. 5% in infrequent relapsers, $p < 0.005$). Cw7 occurred in 38 percent of patients who were infrequent relapsers ($p < 0.05$) (Table V). The other antigens in these group were not different.

Table I. HLA-A in Patient and Control Groups

Antigens	MCD Group (n: 47) %	Non-MCD Group (n: 31) %	Control Group (n: 133) %			
A1	11	13	18			
A2	45	28	48			
A3	28	10	21			
A11	6	3	8			
A23(9)	0	0	1			
A24(9)	2	3	12	*$p < 0.05$	RR:1.31	CI:1.12-1.52
A26(10)	0	0	1			
A28	6	3	7			
A29	2	4	4			
A30	4	13	5			
A31	4	7	0	**$p < 0.05$	RR:5.92	CI:4.20-8.35
A32	6	0	1			
AW33	0	0	2			
Aw34	0	0	1			

HLA : human leukocyte antigen.
MCD: minimal change disease.
RR : relative risk.
CI : confidence interval.

* Demonstrates statistics with MCD patients and control.
** Demonstrates statistics with non-MCD patients and control.

Table II. HLA-B in Patient and Control Groups

Antigens	MCD Group (n:47) %	Non-MCD Group (n:31) %	Control Group (n:133) %			
B5	13	19	17			
B7	4	9	8			
B8	11	19	5	**p < 0.05	RR:3.10	CI:1.48-6.00
B12	9	6	3			
B13	26	24	5	*p < 0.0001	RR:3.08	CI:1.98-4.78
				**p < 0.001	RR:3.64	CI:1.93-6.87
B16	0	0	2			
B17	0	17	4	**p < 0.05	RR:3.16	CI:1.54-6.50
				***p < 0.005	RR:2.95	CI:2.13-4.09
B18	11	4	15			
B21	2	0	4			
B27	6	13	5			
B32	0	0	6			
B35	13	7	21			
B38(16)	0	0	6			
B39(16)	4	0	0			
B40	0	0	5			
B44	19	10	8			
B49(21)	2	3	6			
BW50(21)	2	3	0			
BW53	4	3	0			
BW55	0	3	4			
BW4	23	26	53	*p < 0.001	RR:1.35	CI:1.14-1.61
				**p < 0.05	RR:1.52	CI:1.14-2.03
BW6	34	19	60	*p < 0.05	RR:1.33	CI:1.10-1.60
				**P < 0.0005	RR:2.02	CI:1.52-2.68

HLA: human leukocyte antigen; MCD: minimal change disease; RR: relative risk; CI: confidence interval.

* Demonstrates statistics with MCD patients and control.
** Demonstrates statistics with non-MCD patients and control.
*** Demonstrates statistics with MCD patients and non-MCD patients.

Table III. HLA-C in Patient and Control Groups

Antigens	MCD Group (n:47) %	Non-MCD Group (n:31) %	Control Group (n:133) %			
Cw1	15	9	7			
Cw2	8	14	4	**p < 0.05	RR:2.72	CI:1.20-6.13
Cw3	8	16	8			
Cw4	21	10	33	**p < 0.05	RR:1.20	CI:1.06-1.36
Cw5	12	3	2	*p < 0.05	RR:2.78	CI:1.63-4.74
Cw6	12	19	5	**p < 0.05	RR:2.98	CI:1.48-6.00
Cw7	29	41	10	*p < 0.005	RR:2.40	CI:1.49-3.85
				**p < 0.0001		CI:2.33-7.74
					RR:4.25	

HLA: human leukocyte antigen; MCD: minimal change disease; RR: relative risk; CI: confidence interval.

* Demonstrates statistics with MCD patients and control.
** Demonstrates statistics with non-MCD patients and control.

Table IV. HLA-DR in Patient and Control Groups

Antigens	MCD Group (n:47) %	Non-MCD Group (n:31) %	Controls (n:133) %			
DR1	12	12	12			
DR2	6	9	22	*p < 0.05	RR:1.29	CI:1.11-1.50
DR3	8	12	11			
DR4	21	6	8	*p < 0.05	RR:2.04	CI:1.20-3.47
DR5	2	0	24	*p < 0.005	RR:1.41	CI:1.25-1.60
				**p < 0.005	RR:1.29	CI:1.17-1.41
DRw6	0	0	3			
DR7	34	19	10	*p < 0.0001	RR:3.48	CI:1.81-66.8
DRw8	2	9	3			
DRw9	3	6	6			
DRw10	4	10	1	*p < 0.05	RR:6.87	CI:1.20-39.33
				**p < 0.05	RR:3.62	CI:1.63-8.04
DRw12	0	7	0	**p < 0.05	RR:5.90	CI:4.20-8.35
DRw15(2)	10	6	1	*p < 0.05	RR:14.14	CI:1.69-118.00
DR52	31	31	23			
DR53	10	16	10			
DQ2	24	22	10	*p < 0.05	RR:1.98	CI:1.17-3.34
DQ3	21	25	21			

HLA: human leukocyte antigen; MCD: minimal change disease; RR: relative risk; CI: confidence interval.

* Demonstrates statistics with MCD patients and control.

** Demonstrates statistics with non-MCD patients and control.

Table V. HLA Frequencies in Frequent and Infrequent Relapser Groups

Antigens	Frequent Relapser Group in MCD (n:10) (%)	Infrequent Relapser Group in MCD (n:37) (%)			
Cw6	40	5	p < 0.005	RR:4.55	CI:1.79-11.55
Cw7	0	38	p < 0.05	RR:1.43	CI:1.14-1.79
DR1	40	5	p < 0.005	RR:4.55	CI:1.79-11.5

HLA: human leukocyte antigen; MCD: minimal change disease; RR: relative risk; CI: confidence interval.

Discussion

Non-MCD nephrotic syndrome may be clinically indistinguishable from MCD at onset, and renal biopsy helps in the differential diagnosis. The immunologic basis of these disorders has been the subject of a large number of studies. High prevalence of HLA DR7 has been well documented in MCD of childhood. In Australian, French, Spanish, Chinese and Arab studies with steroid responsive nephrotic syndrome (SRNS), a high prevalence of HLA DR7 was demonstrated when compared with healthy controls[4-8]. In a Turkish study from Central Anatolia, HLA DR7 and DRw53 were found more frequently in the MCD group than in the control group[9]. In our study, HLA B13, Cw5, Cw7, DR4, DR7, Drw10, DRw15(2) and DQ2 were found significantly higher than in the healthy control group. Especially HLA DR7 positivity was more predominant ($p < 0.0001$). Unlike the previous studies, not only HLA DR7, but also the distribution of other HLA groups in our nephrotic patients (MCD and non-MCD) were significantly different from the healthy controls. Although most of the studies from different regions revealed a predominance of HLA DR7 in nephrotic syndrome, varied results were reported by other study groups. In an Arab study, HLA DR2 frequency was found lower in SRNS when compared with the control group, but it was not statistically significant[8]. In our study we also observed significantly lower HLA A24(9), Bw4, Bw6, DR2, and DR5 when compared with the healthy control group.

Early studies of HLAs in nephrotic syndrome reported that HLA Bw44 was found to be

significantly more frequent in Indian nephrotic children[10]. In contrast, African children with membranous nephropathy had a significantly increased frequency of HLA Bw21[10]. Glicklich et al.[11] demonstrated that HLA DR4 was found significantly increased in FSGS patients when compared with the control group. In our study, A31, B8, B13, B17, Cw2, Cw6, Cw7, DRw10 and DRw12 antigens were found statistically significantly increased in the non-MCD dgroup when compared with the control group. HLA-B17 was found in 17 percent of the patients in the non-MCD group, but in none of the MCD patients ($p < 0.005$). Furthermore, HLA DRw12 was found in 23 percent non-MCD patients but in none of the MCD patients. Nevertheless, the difference was not statistically significant.

In a French study, Bouissou et al.[12] found significant associations with HLA DR7 and DQ2 and with the phenotypic combination HLA DR3/DR7 in the SRNS group. Significant negative associations were encountered with HLA DR2, DR6 and DQ1. The associations were stronger in frequent relapser/steroid dependent patients than in infrequent relapsers, and were not significant in non-relapsers in their study. In steroid resistant patients, the only significant association found was with the combined occurrence of HLA DR3/DR7. In our study, we found that Cw6 and DR1 were associated with frequency of relapse; in the infrequent relapsing group, Cw7 was more predominant. In a Chinese study[7], it was found that HLA DR9 was associated with the frequency of relapse and therefore with the severity of the disease. However, Ruder et al.[13] found HLA DR3 and Tümer et al.[9] found DRw53 were associated with the frequency of relapse. As Bakr[14] suggested, these differences may be explained by ethnical variations of HLA groups.

In conclusion, certain HLAs may predict the clinical course in nephrotic syndrome and may be responsible for the frequency of relapses in MCD. Further work on the ethnical variations of these factors will be worthwhile additions to the literature.

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Combined use of chemotherapy and ^{131}I-metaiodobenzylguanidine in the treatment of advanced-stage neuroblastoma

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SUMMARY: Sarı O, Uğur Ö, Emir S, Akyüz C. Combined use of chemotherapy and ^{131}I-metaiodobenzylguanidine in the treatment of advanced-stage neuroblastoma. Turk J Pediatr 2001; 43: 29-33.

Despite intensive chemotherapy, surgery and/or radiation, prognosis continues to be very poor in disseminated neroblastoma. Owing to neuroblastoma sensitivity progress might be achieved with high-dose radiation. Metaiodobenzyl guanidine (MIBG) coupled with ^{131}I provides the opportunity for highly selective radiation treatment of neuroblastoma, which could potentially deliver five to 10 times the dose of conventional external-beam treatment without specific tissue toxicity. To improve the long-term results in advanced-stage neuroblastoma, we integrated this new treatment modality with conventional chemotherapy. Eight neuroblastoma patients refractory to conventional treatment were treated with ^{131}I-MIBG-chemotherapy (vincristine, VP16, iphosphamide, carboplatin, epirubicin, cyclophosphamide) combination. Five of the eight patients responded to ^{131}I-MIBG treatment (2 complete and 3 partial responses). There were also three patients with stable disease. Median survival was 48 months (range 1 to 84 months), and five patients relapsed in their follow-up and died of progressive disease. We concluded that a combined ^{131}I-MIBG and chemotherapy approach is useful in advanced-stage neuroblastoma patients, with considerably less side effects. Although survival is improved when compared to conventional treatment, the overall prognosis is still poor. More lethal radionuclide conjugation to MIBG which will deliver higher tumor and lower critical organ doses may offer the best solution for targeted radionuclide therapy of neuroblastoma.

Key words: ^{131}I-metaiodobenzylguanidine (MIBG), neuroblastoma, radionuclide therapy.

Despite intensive chemotherapy, surgery and/or radiation, prognosis continues to be very poor in disseminated neuroblastoma[1]. Even with myeloablative megatherapy regimens combined with stem-cell transplantation, the five-year survival for children with metastatic neuroblastoma is less than 20 percent[2,3]. Owing to neuroblastoma sensitivity, progress might be achieved with high-dose radiation. However, delivery of high-dose radiation is limited by host tolerance. This has led to a search for new treatment approaches that will not increase toxicity to normal tissues but will allow greater antitumor efficacy[4]. Metaiodobenzylguanidine (MIBG) is a guanethidine derivative with a structure analogous to norepinephrine which permits selective concentration in sympathetic nervous tissue[5]. MIBG coupled with ^{131}I provides the opportunity for highly selective radiation treatment of neuroblastoma[6]. The most important feature of this approach is the ability to specifically target the tumor tissue while limiting or minimizing the radiation dose to most normal organs, which could potentially deliver five to 10 times the dose of conventional external-beam treatment without specific tissue toxicity[7]. Although complete and partial responses have been reported in patients resistant to conventional therapy with ^{131}I-MIBG as a first-line treatment at diagnosis, long-term results are still unsatisfactory[8,9]. Inhibition of repair of potentially lethal radiation damage and a synergistic action are possible with the combined use of chemotherapeutics and ^{131}I-MIBG[10].

To impprove the long-term results in advanced-stage neuroblastoma, we integrated this new treatment modality with conventional chemotherapy.

Material and Methods

Patients

Eight patients (6 girls, 2 boys) with histologically proven neuroblastoma refractory to conventional treatment and whose tumors had concentrated ^{131}I-MIBG on diagnostic imaging were entered into the study between 1995-1999. Ages ranged from four to 12 years, and a life expectancy of at least four weeks as required to enter the study. Patients were staged occording to the Evans staging system[11]. Four were stage IV and four were stage III at the time of diagnosis. Five patients had right adrenal lesion, one had left adrenal lesion, one had presacral and orbital lesion and one had left adrenal, bone and bone marrow involvement.

Treatment with ^{131}I-MIBG

Patients were prepared for the ^{131}I-MIBG with thyroid blocking agent potassium iodide (lugol's solution) starting three days prior to treatment for two weeks to prevent uptake of radioactive iodine by the thyroid gland. Drugs known or expected to reduce MIBG uptake were discontinued one week prior to treatment. ^{131}I-MIBG shipped in dry ice was thawed and diluted in 200 ml 0.9% sodium chloride according to the manufacturer's instructions (Amersham, UK) and administered intravenously via a lead shielded system over two hours. Appropriate radiation safety measures were taken, and patients stayed in hospital isolation until the exposure measure 1 meter from the patient's surface was less then 4 mR/hour. A total of 15 ^{131}I-MIBG therapies were given. The administered activity ranged between 100-200 mCi per treatment, and the radiounclide therapy was repeated at a minimum of four to six week intervals with a maximum cumulative activity of 450 mCi (range: 100-450 mCi).

Chemotherapy Regimens

Two different types of combined chemotherapy regimens were used before ^{131}I-MIBG therapy. Two patients were treated with the classic NBL protocol consisting of vincristine (1.4 mg/m^2), cyclophosphamide (800 ng/m^2), and cisplatin (90 mg/m^2), weekly for three weeks.

Bristol II chemotherapy regimen consisting of vincristine (1.4 mg/m^2), VP-16 (100 mg/m^2 over 3 days), carboplatin (250 mg/m^2), and epirubicin (50 mg/m^2) was administered to three patients at four-week intervals.

Definition of Response Status

Investigations for response evaluations included computed tomography and/or ultrasound, diagnostic MIBG scans, ^{99}mTc-MDP bone scans, bone marrow aspiration and measurement of urinary catecholamine metabolites. International Neuroblastoma Response Criteria were used to describe response[13]. Complete remission corresponds to complete disappearance of all measurable tumor. Partial remission describes a greater than 50 percent disease reduction in primary and metastatic sites. Stable disease and minor response refer to any response of less than 50 percent. Progressive disease indicates progression at any preexisting tumor site or appearance of a new leison.

Results

Patient characteristics and response to treatment are listed in Table I.

Table I. Patient Characteristics and Response to Treatment

Patient no.	Sex/age (years)	Tumor localization at diagnosis	Stage at diagnosis	Chemotherapy protocol	Cumulative MIBG dose and number of treatments	Outcome	Response to treatment	Survival (months)
1. ZY	M/5	Left adrenal	III	Bristol	150 (1)	Exitus	PR	48
2. ANÇ	F/4	Presacral, orbital	IV	Classic NBL	225 (2)	Exitus	CR	18
3. CB	F/2	Right adrenal	III	Classic NBL	275 (2)	Exitus	SD	12
4. FA	F/4	Right adrenal	III	Classic NBL	100 (1)	Exitus	CR	23
5. TG	F/5	Bone, bone marrow, left adrenal	IV	Bristol	200 (1)	N/A	SD	1
6. SÖ	F/10	Right adrenal	III	Bristol	400 (3)	Exitus	PR	84
7. EGD	F/5	Right adrenal	IV	Classic NBL+Bristol	450 (2)	Alive	PR	40
8. AÖ	M/14	Right adrenal	IV	Classic NBL+Bristol	450 (3)	Alive	SD	31

CR: complete; PR: partial remission; SD: stable disase; MIBG: metaiodobenzylguanidine; N/A: not available (lost to follow-up).

Toxicity of the ^{131}I-MIBG Treatment

Most patients reported mild nausea on the first day. Mild to moderate hematopoietic toxicity occurred in three patients, with a decrease in platelet and white blood cell counts. One patient developed hypothyroidism diagnosed by elevated thyroid-stimulating hormone and low thyroxine levels.

Response and Survival

Five of the eight patients responded to ^{131}I-MIBG treatment (2 complete and 3 partial responses). In two patients, response was achieved after one course of treatment, and in three patients response was achieved after more than one course. There were also three patients with stable disease. This disease stabilization occurred in patients with actively progressing disease at the time of treatment.

Survival is shown in Figure 1. The median survival was 48 months with Kaplan-Meier analysis (range 1 to 84 months). Five patients relapsed in their follow-up and died of progressive disease (Fig. 2). One patient's survival was unknown as he did not admit to haspital again. Two patients are still alive, one with progressive disease and one with stable disease; both received more than one course of treatment and a total cumulative dose of 450 mCi (Fig. 3).

Discussion

Outcome of advanced-stage neuroblastoma patients is still poor despite intensified chemotherapy regimens and bone marrow rescue. Stage III and IV neuroblastoma patients have two-year survival rates of only 30 and 10 percent,

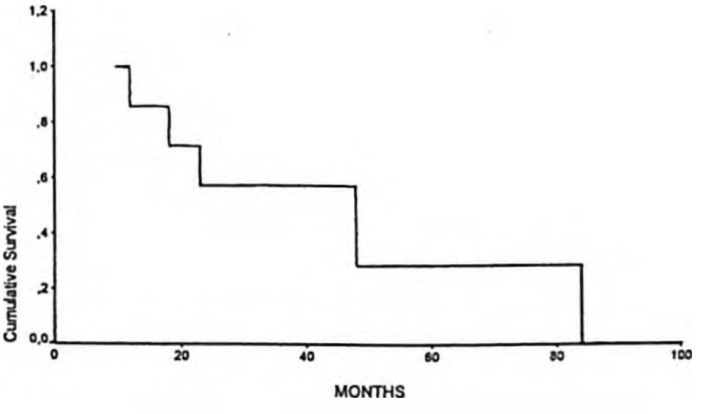

Fig. 1. Survival of patients treated with ^{131}I-MIBG-chemotherapy combination.

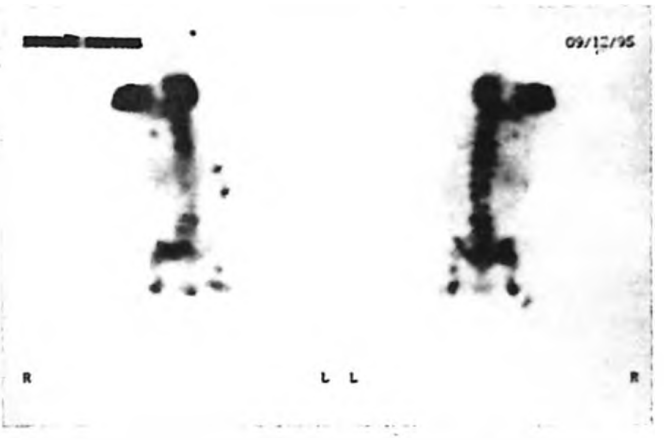

Fig. 2. Post-therapy ^{131}I-MIBG scan of patient (no. 6) treated with a cumulative dose of 400 mCi of ^{131}I-MIBG. Patient had a very good response to initial therapy but died of progresive disease at the end of 84 months.

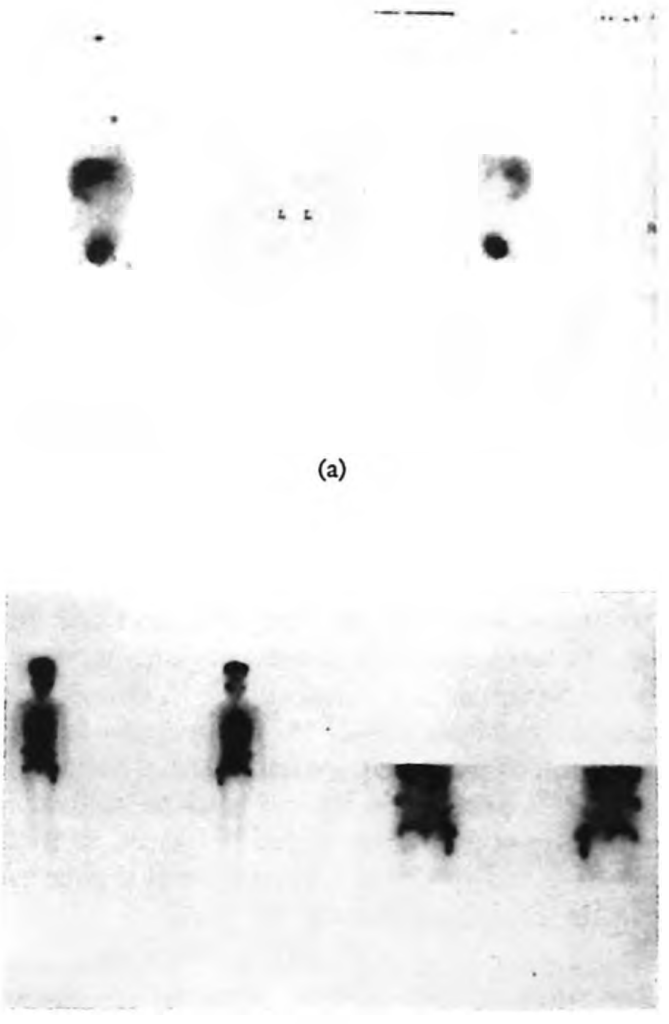

Fig. 3: Whole body scintigraphies of patient no. 7 after 1st (a) and 3rd (b) course of ^{131}I-MIBG treatment. After a good partial remission patient showed a progressive trend and widespread metastasis occurred, including brain metastases.

respectively[12]. The relapse rate is high among these patients and many of them die because of drug resistance of the recurrent tumor.

In this study we treated eight patients using a combination of ^{131}I-MIBG and chemotherapeutics which resulted in a median survival of 48 months at the end of a four-year follow-up. Two children with severe pain due to bone metastases who were unable to walk began walking and their pain medication was decreased. The acute toxicity was mild in comparison to that with intensive chemotherapy. Although the combined treatment approach increased survival and life quality of these patients,, overall prognosis was still poor. Five of our patients died due to recurrent disease and one of them developed progressive disease after a good response to initial ^{131}I-MIBG treatment. However, the patients studied here were heavily pretreated, with highly resistant disease. Moreover, the very extensive prior treatment may have increased the severity of the hematological toxicity. We believe ^{131}I-MIBG combined with chemotherapy should be attempted at an earlier stage of the disease, with the possibility of even better results and less hematological toxicity. De Kraker et al.[9] treated 33 previously untreated advanced-stage neuroblastoma patients with ^{131}I-MIBG and concluded that ^{131}I-MIBG as a first-line therapy is at least equal to chemotherapy, with less side effects. The integration of this new treatment modality with chemotherapy as a first-line therapy may give better results. However, dose schedule studies are required to establish toxicity and efficacy[14].

Preclinical trials in cultured cells and animal tumors have established a synergism between chemotherapeutics and radiation[15,16]. One of the possible mechanisms of this synergism is the inhibition of repair of potentially lethal radiation damage[17]. Better results can also be achieved by the use of no-carrier-added ^{131}I-MIBG so that the predicted tumor absorbed dose is higher by a factor of approximately 2.3[18].

We conclude that a combined ^{131}I-MIBG and chemotherapy approach is useful in advanced-stage neuroblastoma patients with considerably less side effects. Although survival is significanly improved compared to conventional treatment, the overall prognosis is still poor. More lethal radionuclide conjugation to MIBG which will deliver higher tumor and lower critical organ doses may offer the best solution for targeted radionuclide therapy of neuroblastoma[19].

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The role of pulmonary artery anatomy in repair of tetralogy of Fallot

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Pulmonary artery anatomy is the key factor that determines the type of surgical treatment required in tetralogy of Fallot. Despite the fact that routine primary repair is now done on infants, inadequate pulmonary artery size can dictate the need for staged surgical repair in even the oldest age groups. From October 1986 to October 1998, 361 patients at our clinic underwent surgery to correct tetralogy of Fallot. A total of 292 cases were treated with primary repair, 69 surgeries were palliative, and 30 of these 69 underwent corrective surgery. The Nakata index was used as a pulmonary artery index (PAI), and PAI< 200 was the criterion for requirement of two-stage repair.

Of the 30 patients that underwent staged repair, the Blalock-Taussig shunt (BTS) procedure was used in 24; the remaining six patients had right ventricular outflow tract reconstruction (RVOTR). The mean age of all the palliative surgery patients was 3.4 years (range 6 months to 11 years), and of those who received corrective surgery was 5.5 years (range 2-12 years). These patients' PAI values were 181 ± 37.5 mm^2/m^2 and 359 ± 130.7 mm^2/m^2, respectively. The period between the two operations ranged from two months to four years.

Mortality rates were 2.8 percent for palliative surgery as a whole, 4.1 percent for primary repair, and 16.6 percent for staged repair. Our policy with regard to corrective surgery for tetralogy of Fallot is to do primary repair regardless of a patient's age and weight, except in cases where the pulmonary artery anatomy is appropriate for the patient's body size.

Key words: Fallot tetralogy, Blalock-Taussig shunt.

Surgical strategy in cases of tetralogy of Fallot has been discussed since the first repair was done by Lillehei in 1954[1]. A two-stage approach was adopted initially due to the excellent results that were achieved[2,3] but, in the early 1990s, several studies of primary repair revealed comparable results[4-8].

In two-stage repair, the most common palliative procedure is the Blalock-Taussig shunt (BTS), which is then followed by total repair at an older age. In an asymptomatic patient with a hypoplastic pulmonary artery, delay of corrective surgery does not lead to improvement of the pulmonary artery tree with age. Therefore, some researchers have advised right ventricular outflow tract reconstruction (RVOTR) and have disputed the importance of pulmonary artery size. In 1980, Naito et al.[9] developed a list of criteria to indicate the need for RVOTR in corrective repair, and four years later Nakata et al.[10] published a method for calculating a patient's pulmonary artery index (PAI). In this study, we discuss two-stage repair of tetralogy of Fallot with a focus on pulmonary artery anatomy.

Material and Methods

Between October 1986 and October 1998, 361 patients at our clinic underwent surgery for

This study was presented at the 5th National Thoracic and Cardiovascular Meeting, October 20-24, 1998, Antalya, Turkey.

tetralogy of Fallot. Patients with pulmonary atresia or complex congenital cardiac anomalies were excluded from the study. Primary repair was carried out in 292 cases and 30 patients underwent two-stage repair. Palliative procedures alone were done on the remaining 39 patients, all except for two of whom were waiting for corrective surgery.

The BTS technique was used in 24 patients. In 21 cases this technique, the treatment of choice at our clinic in terms of palliative procedures, was done based on low PAI. Three patients with good PAIs had BTS operations under emergency conditions due to intractable cyanotic attacks. Goretex grafts were used in 23 patients, and one underwent a classical BTS procedure (Table I).

Table I. Palliative Procedures Performed

RVOTR	6 cases
BT Shunt	24 cases
Right modified	2
Left modified	21
Right classic	1

RVOTR: Right ventricular outflow tract reconstruction.
BT : Blalock-Taussig.

Right ventricular outflow tract reconstruction (RVOTR) was performed in six cases, the main indication for this approach being asymmetry of the left and right pulmonary arteries. In fact, two patients in this group had good PAIs but their left pulmonary arteries were very narrow, so RVOTR was performed in an attempt to encourage growth of the left pulmonary artery. Autogenous pericardium was used in five of the RVOTR cases, and the width of the pericardial graft was determined according to patient weight and height, as described by Naito[9]. In one patient, the width of the outflow patch was readjusted at the level of the pulmonary annulus after the termination of cardiopulmonary bypass; flow ratios were calculated in the operating room in order to prevent pulmonary overflow. The PAI and age information on the 30 patients prior to their palliative and corrective repair procedures are shown in Table II.

Primary repair was carried out in 292 patients. Ventricular septal defects were closed using dacron patches with interrupted sutures. Most cases had extensive myectomy in the septoparietal and ventriculo-infundibular fold regions, and the outlet septum was almost totally resected, as described by Kurosawa et al.[11]. Autogenous pericardium was used for outflow patches.

Results

The mean PAI of patients that underwent palliative procedures was 181 ± 37.5 mm^2/m^2, and this rose to 359 ± 130.7 mm^2/m^2 prior to corrective surgery. The mean time interval between the two operations was 23 months (range 2 to 48 months).

Of the BTS patients, one underwent postoperative exploration for hemorrhage and two experienced late obstructions. Pulmonary artery distortion was diagnosed at the anastomosis sites in two other cases. In the RVOTR patient group, the growth of the left pulmonary artery was insufficient with regard to the right in one case, but in other instances the growth of both pulmonary arteries was adequate. In the primary repair group, transannular autogenous pericardial patches were used in 259 (88%) cases, with the right ventriculotomy closed primarily in only one patient. In the remaining 32 individuals, closure of the right ventriculotomy was achieved using autogenous pericardium. Of the patients who had undergone previous palliative procedures, a transannular patch was used in 26 (86%). The operative mortality rates were 4.1 percent (12 patients) in the primary repair group and 16.6 percent (5 patients) for the staged repair group. Overall mortality for all the palliative procedures done on tetralogy cases at our clinic was 2.8 percent (two of 69 patients) (Table II).

Discussion

The aim in surgery for tetralogy of Fallot is to close the ventricular septal defect completely and to relieve the right ventricular outflow tract. Any residual pathology can place the patient in

Table II. Patient Age and Pulmonary Artery Index (PAI) in Relation to Procedure and Associated Mortality

	Age	PAI	Mortality Rates (%)
Palliative procedure	3.4 yrs (6 mo-11 yrs)	181(± 37.5)	2.8*
Two-stage repair	5.4 yrs (2-12 yrs)	359 (± 130.7)	16.6
Primary repair	4.6 yrs (8 mo-14 yrs)	363 (± 54.3)	4.1

* overall mortality in 69 patients.

a critical condition, especially during the early postoperative period. To achieve total correction of this anomaly, the patient must either undergo a staged or primary repair strategy. Initially, two-stage repair gained popularity[2,3] based on earlier studies that reported low mortality rates, but today many experts cite the advantages of primary repair at any age[4-8].

The main purpose of staged repair of tetralogy of Fallot is to reduce the risk of mortality in the neonatal period. The palliative portion of this strategy, usually BTS, can be performed at relatively low risk during the neonatal stage. Corrective surgery two to three years after the first operation completes this accepted operative procedure[2]. Despite the excellent results achieved with staged repair, it has been discovered that palliative procedures are also associated with high mortality and morbidity rates. Complications with pulmonary artery distortion and partial or total occlusion after BTS operations are not uncommon. Authors have reported post-BTS pulmonary artery distortion rates of 18 to 36 percent[12-14].

In our series, pulmonary artery distortion was observed in two patients (8.3%), and total occlusion of the ipsilateral pulmonary artery was diagnosed in one individual (4.1%) through angiography. A total of 12.5 percent of the patients in our series had pulmonary artery abnormalities due to previous BTS operations.

In our study, the mortality rate for staged corrections was higher than that of primary repair, but the decision to perform staged repair was not related to patient age and body weight. The only indication for palliation in our series was low PAI. In his original article, Nakata[10] stated that a PAI above 100 indicated corrective surgery, but he still discussed the postoperative heart failure problems of patients whose PAIs were between 100 and 150. It is our experience that a PAI above 200 is safer in terms of the postoperative period. Wu[15] stated that tetralogy of Fallot could be corrected under any circumstances with a detailed evaluation of the patient, but we noted that, in cases with low PAI, underdevelopment of the pulmonary artery was not restricted to major branches. Under such circumstances, graft reconstruction to the level of the hilus does not relieve the pressure gradient between the pulmonary artery and the hilus. This results in elevated right ventricular pressure and high mortality.

Mortality is closely related to residual pulmonary stenosis, which is easily assessed by calculating RV/LV (right ventricular pressure, left ventricular pressure) ratio. An RV/LV greater than 0.8 coupled with a ratio of reconstructed pulmonary artery area to ideal pulmonary artery area for that body surface area of less than 0.7 predict increased risk of mortality[9,16]. These two parameters are directly related to PAI. Unless a patient has adequate pulmonary artery size, surgical procedures done proximal to the hilus do not result in good RV/LV results.

We conclude that the operative mortality in corrective surgery for tetralogy of Fallot depends on several factors. As we presented here, problems with pulmonary artery anatomy, especially distal stenosis, are the most important features to correct. We performed two-stage corrective surgery on 27 patients in order to obtain appropriate pulmonary artery sizes and decrease mortality, though this rate remains high compared to that for primary repair.

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Enuresis: point prevalence and associated factors among Turkish children

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SUMMARY: Öge Ö, Koçak İ, Gemalmaz H. Enuresis: point prevalence and associated factors among Turkish children. Turk J Pediatr 2001; 43: 38-43.

The aim of this study was to establish the prevalence and associated factors of enuresis nocturna and to better understand nocturnal bladder control in Turkish children.

A randomized epidemiological study was performed among primary school children, aged four to 12 years, living in Aydın, Turkey. After data collection via a self-administered questionnaire completed by the parents, data of 2,300 children were accepted for the analysis.

The overall prevalence of reported marked nocturnal enuresis (at least weekly) was 11.6 percent and of day wetting 0.8 percent. Enuresis was more frequent in boys than in girls. Age, family history of enuresis, large family size, urinary tract infections and low parental socioeconomic class were all statistically associated with reported enuresis nocturna. Familial history among the enuretics and non-enuretics was 40.7 percent and 9.5 percent, respectively. Of the enuretics, 11 percent were treated professionally, 65 percent were treated traditionally by the family and 25 percent sought no help to manage the enuresis. A reference age of 2.9 ± 1.6 years was calculated for nocturnal bladder control of the children studied.

These results suggest that prevalence of enuresis nocturna and development of bladder control in Turkish children are not so different from that seen in other European and Middle East countries, and that the most significant factors associated with enuresis are socioeconomic and familial ones. Turkish families do not have a high level of concern about enuresis, even in the older children. This study demonstrated that enuresis is a sizable problem in Turkey and that a great ignorance about enuresis by both parents and physicians exits.

Key words: enuresis, prevalence, children.

Enuresis nocturna (EN) is a common problem among children presenting to clinical settings. Due to its nature as a self-limiting disorder with no major health risks, many parents do not have a high level of concern about EN especially in younger children. Families commonly try to manage this problem with observation or traditional methods. Therefore, EN should be considered a more prevalent problem in the pediatric population than is seen in the clinical setting. The assessment of the epidemiology and natural history of EN by population-based studies will assist with better management of it according to the characteristics of different communities. More importantly, a reference age for nighttime bladder control according to all communities should be determined. Somewhere between two and four years of age, most children gain control of incontinence, and this corresponds to the time of toilet training[1]. The prevalences reported vary depending on the geographical areas involved[2-6]. The lack of epidemiological studies on the prevalence of EN from the Balkans and Middle East in the literature led us to conduct a prevalence study in Turkey, as the data from our country may reflect similar results seen from these areas.

The purpose of the study was to describe and analyze the profile of enuresis in schoolchildren living in Aydın, a western city of Turkey.

Material and Methods

A self-administered questionnaire was completed voluntarily by the parents (to minimize embarrassment to children) of 4,000 children for to 12 years old attending a primary school in Aydın. Figure 1 shows the distribution of the subjects according to age. The study consisted of 10 schools selected randomly.

After a 76 percent response rate, 2,300 completed surveys were accepted valid and evaluated for the study. The study group comprised 1,112 girls and 1,188 boys with a mean age of 8.9 ± 1.8 years. For statistical analysis chi-square and Fisher's exact tests were used and a p-value < 0.05 was considered as statistically significant. The indicated permissions for the study were obtained from appropriate committees.

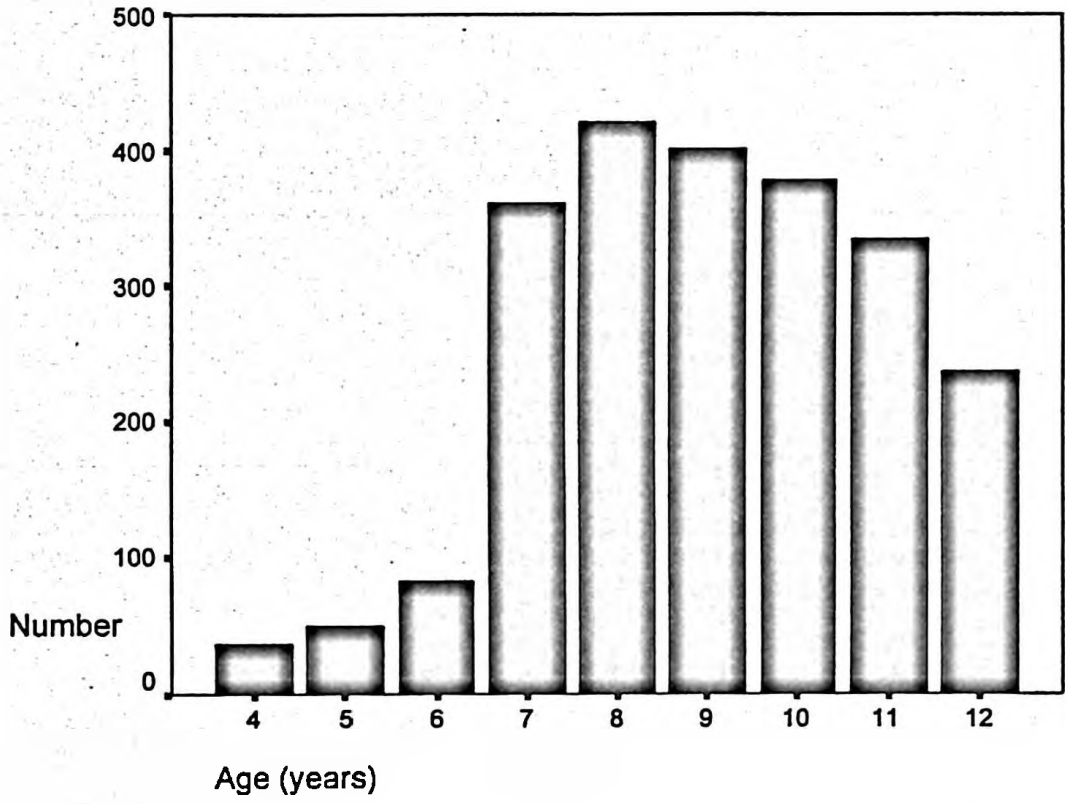

Fig. 1. Distribution of the subjects according to age.

The questionnaire was comprised of three parts. The first part was designed to investigate risk and precipitating factors, and the second part was planned to determine type and prevalence of enuresis. The aim of the third part was to describe treatment modalities for EN among parents and physicians.

Primary EN was defined as bed-wetting at least once a week in a child who had never had nighttime bladder control for a period greater than six months. Secondary enuresis was considered "when the child has been toilet trained for at least six months after the age of bladder control, and bladder control is subsequently lost"[7].

Results

Prevalence of Enuresis

The overall prevalences of enuresis nocturna and diurna was 11.6 (267) and 0.8 percent[19], respectively; none of the subjects had diurnal wetting without night wetting. Overall, EN was more prevalent in boys than in girls ($p < 0.05$). The properties of EN according to gender are shown in Table I.

The highest prevalence overall was observed at eight years of age, with a rate of 15.7 percent. Because of the small number of subjects four and five years of age, no statistical comparison

with the prevalence rate at the age of eight years could be done. The higher prevalence seen at eight years of age than at ages six and seven was statistically significant, but when reevaluated excluding the day-wetters and secondary enuretics, the prevalence between these ages were similar. A more steady decline in prevalence of enuresis by age was present in girls, while a notable increase was observed around the ages of seven to nine years in boys. EN was primary in 87 percent and secondary in 13 percent of cases. The distribution of secondary enuresis among boys and girls was similar (48.5 versus 51.5%), and the onset of secondary enuresis was observed more commonly (69%) around the ages of seven to nine in both genders. Secondary enuresis was more frequent (72%) in children whose parents had low educational and socioeconomic levels. Figure 2 demonstrates the prevalence rates in boys and girls separately according to age. Enuresis prevalence was more dominant in boys at every age, except at the age of six years. At the age of 12, enuresis prevalence among boys and girls was 8.2 and 4.0 percent respectively.

Table I. Properties of Enuresis by Gender

Gender	Number	Enuresis nocturna (%)	Primary Monosymptomatic EN (%)	Secondary Monosymptomatic EN (%)	ED (%)
Boys	163	13.7	11.7	1.3	0.6
Girls	104	9.4	6.8	1.5	1
Total	267	11.6	10	1.5	0.8
p-value		< 0.01	< 0.01	NS	NS

NS: non-significant; ED: enuresis diurna.

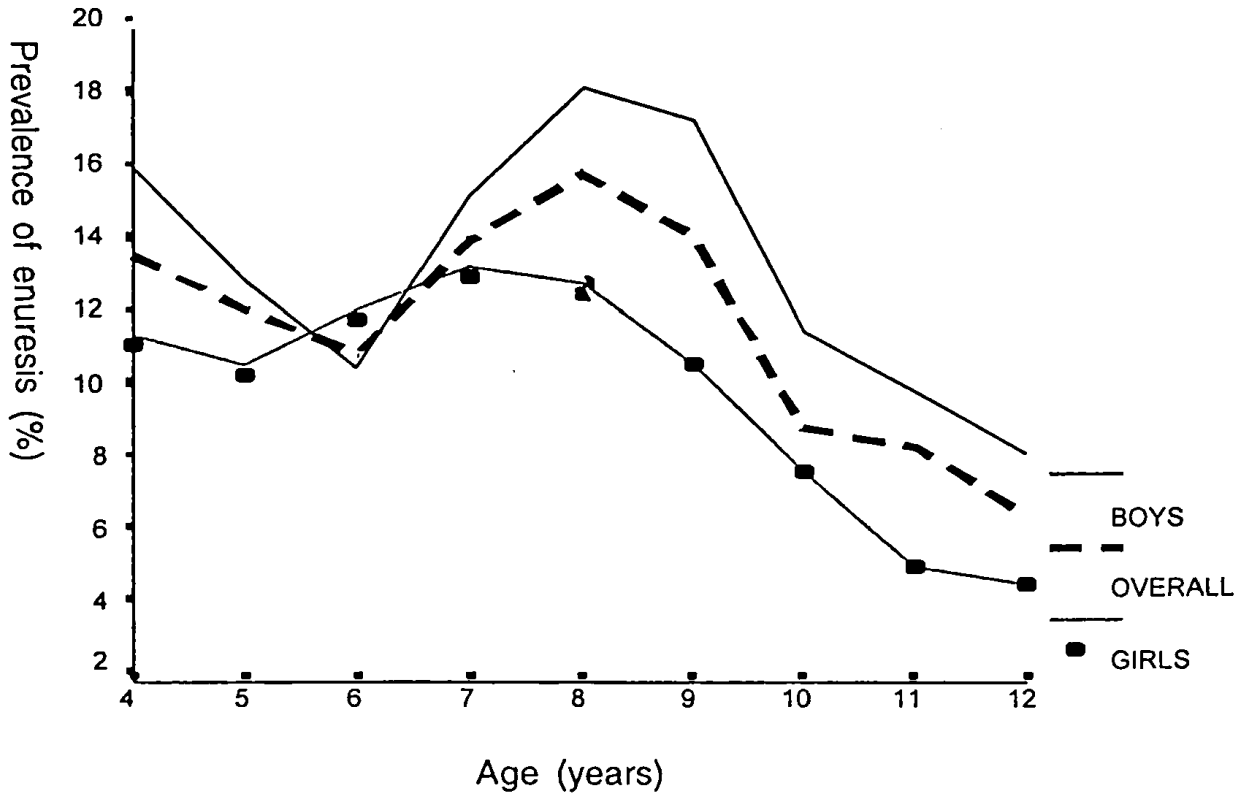

Fig. 2. Prevalence rates in boys and girls according to age.

Of the enuretics, 58 percent reported wetting more than three times per week and 29 percent noted wetting every night. Six percent of girls and 8.5 percent of boys were wetting only once a week. Wetting frequency was similar among boys and girls, with an average of four nights per week in both groups.

Night-time Bladder Control

In light of data noted by the parents, the age of gaining nocturnal bladder control was earlier in girls than in boys ($p < 0.001$). Among the current non-enuretics, 93 percent were toilet trained before the age of five, and this rate reached 97.8 percent at the age of seven. The mean age for nocturnal bladder control was 2.9 ± 1.6 overall, and a t value of 3.62 was calculated according to Student's t test. The mean ages of night-time bladder control in boys and girls were 3.1 ± 1.6 and 2.8 ± 1.5, respectively. The development of bladder control was strongly associated with the level of parental education ($p < 0.001$). In subjects with no family history of enuresis, nocturnal bladder control began earlier in comparison to ones with a history of enuresis among their siblings or parents ($p < 0.05$).

Factors Associated with Enuresis

Positive family history of enuresis was found to be the most significant factor associated with enuresis ($p < 0.001$). The rates of a reported enuresis history among the parents or siblings of enuretics and non-enuretics were 40.5 and 9.5 percent, respectively. No significant difference was obtained when the history of enuresis was reevaluated according to history of parents or siblings separately. The rate of documented urinary tract infections was significantly higher in enuretics (18.5%) compared to the non-enuretic (85%) population ($p < 0.05$). Urinary tract infection was found in 42 percent of day-wetters and of these, 40 percent of cases were recurrent. Low socieconomic status, low parental education and large family size were the other significant enuresis-related factors ($p < 0.05$). There was no factor showing significant difference according to primary or secondary onset of enuresis.

Management of Enuresis

Among the enuretics, only 11 percent were reported to have received medical treatment for enuresis, and of them, 75 percnet had no family history of enuresis, Imipramine and oxybutynin were the drugs most commonly (85%) used by the physicians. Sixty-four percent of families were trying to manage this problem traditionally. Table II shows the methods used in the management of enuresis.

Table II. Treatment Methods

Method	Percent
Awaking to void	52
Diapers	19
Fluid restriction	15
Medication	11
None	25

Discussion

Enuresis nocturna is a common problem in the pediatric population[8-10]. The present study has demonstrated that enuresis is a more crucial problem than seen in the clinical setting. The outcome of this surveillance from Turkey was consistent with the large spectrum of prevalence rates documented in many previous reports from Europe and the Middle East[3,6,8,11-13]. In our study, the prevalence was high, although enuresis was considered as only wetting at least once per week. Our results were similar with the results of a previously reported study which screened children living in a different area of Turkey[8].

Age, as expected, was a significant factor associated with the prevalence of enuresis. However, we did not find a decline in the prevalence by increasing age as rapid as estimated. The highest prevalence was at the age of eight years and, around the ages of seven to nine years, enuresis was generally more prevalenet. The highest prevalence at the age of eight years was due to addition of secondary enuresis which occurred more commonly around this age and to over-representation of day-wetters. The data in the present study is not sufficient to discuss the prevalence among the ages of four and five due to the small number of subjects in this age group. The slightly increasing rates around the ages of eight to 10 found in two reports from Asia supported our result, although the younger group was seven years old in both of those studies[11,14].

Of the enuretics, 40.5 percent had a history of enuresis among their parents or siblings compared with 9.5 percent among non-enuretics. This finding supports the role of heredity as an important factor associated with enuresis[15].

We calculated the reference age of nocturnal bladder control for Turkish children as 2.9 years, and girls were more likely to get toilet trained earlier than boys. As seen in the literature, in our study enuresis was more prevalent among boys than girls. Since it has been suggested that EN is primarily a maturational delay, it could be expected that boys would demonstrate this delay more dominantly than girls[16-18].

As previously reported, we also found that large family size and low socioeconomic status were significant factors related to enuresis[19,20]. As children of well educated parents have a lower prevalence of enuresis in and are also toilet-trained earlier, it is difficult to state with certainty whether stressful life conditions or the parents' low educational status is more responsible for enuresis. On the other hand, the correlation between secondary onset of enuresis and low parental socioeconomic level supports the effect of stress factors on enuresis.

The history of urinary infection was higher in enuretic children than in non-enuretics. This association points to a possibility of abnormalities in the urinary tract or nervous system of the enuretic children.

The present data showed that 65 percent of enuretic children were managed primarily within the family, and Turkish families were more prone to use traditional treatments for enuresis. Remedial methods comprised of restriction of fluid intake, usage of diapers, and waking of the child during sleep to void. As a result, it is clear that EN was not of great concern to Turkish families, even in the older children. Twenty-five percent of enuretic children received no help to manage their enuresis. Some families with high education levels are probably successfully treating enuresis via the traditional methods, as some were being used adjacent to modern treatment modalities. However, in low educational and socioeconomic status families, enuretics have less opportunity for modern treatment. Only anticholinergics or imipramine was used in the professional management of enuresis. Of the parents of medically treated enuretics, 75 percent had no history of enuresis. This data shows that inexperienced parents have more concern about enuresis than the ones who have family history of enuresis.

Enuresis nocturna is not perceived as a serious problem in our country even by physicians. The major reason is that enuresis is assumed harmless and self-limited, and the prejudice is common among families as well as physicians[5,6,21]. According to a recent research, however, this is not true[22]. In children aged seven years, more than five percent report enuresis, and in the adult population one percent[9,10]. Hence, many enuretic children will remain as bedwetters unless treated. Compared with other chronic illnesses, paroxysmal nocturnal enuresis (PNE) has a greater negative effect on the child's mental and social health[22,23]. Parental skepticism may also exist toward the modern therapeutic possibilities; this finding has been reported before[24]. As the child grows older, parents are more likely to seek medical help due to anxiety of an unknown serious disorder and to reduced parental tolerance[25,26]. It must be pointed out that treatment of enuresis is justified as soon as the child suffers a sense of failure and inferiority[27].

In conclusion, the prevalence of EN in Turkish children is not so different from that seen in other European countries, and the most significant factors associated with enuresis are socioeconomic and familial ones. Turkish families do not have a high level of concern about enuresis. There is also no great attention to the disorder given in the professional field, and modern treatment used is limited. Special attention should be given to this community problem, especially by parents and professionals.

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MR imaging of pelvic and thigh muscles in congenital muscular dystrophy

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SUMMARY: Oto A, Aydıngöz Ü, Başgün N, Talim B, Karaağaoğlu E, Topaloğlu H. MR imaging of pelvic and thigh muscles in congenital muscular dystrophy. Turk J Pediatr 2001; 43: 44-51.

To define and compare the magnetic resonance (MR) imaging findings of pelvic and thigh muscles in merosin-deficient and merosin-positive congenital muscular dystrophy, 10 patients with merosin-positive and six patients with merosin-deficient muscular dystrophy were examined in a 0.5 T MR imaging unit. Intensity and atrophy scores were given to individual muscles by two radiologists and were calculated for three muscle groups (pelvic, anterior thigh and posterior thigh muscles). Rectus femoris was affected less than the vastus muscles in 40 percent of cases in merosin-positive patients, whereas there was no selective sparing in merosin-deficient patients. Sartorius and gracilis were relatively spared in both groups. The most consistently affected muscles were gluteus maximus, adductor magnus and brevis in merosin-positive patients. Atrophy was more prominent in the adductor muscles in the merosin-deficient group. Intensity scores of anterior thigh muscles of the merosin-positive group were significantly higher than those of the merosin-deficient group ($U = 8$, $p = 0.016$). When stepwise logistic regression model was applied, intensity score of the anterior thigh muscles was found to be the best differentiating variable. The regression analysis model formed was able to differentiate the two forms with a sensitivity of 80 percent and specificity of 83 percent.

Key words: muscle, muscular dystrophy, magnetic resonance imanging.

Congenital muscular dystrophy (CMD) is a heterogeneous group of diseases characterized by muscle weakness at birth or within the first few months of life, dystrophic changes in muscle, early onset hypotonia, joint contractures, delayed motor milestones and a relatively slow progression[1]. At least three different types can be identified within CMD nosology: Type I (classical form) with a normal intelligence and no apparent central nervous system (CNS) involvement, Type II (Fukuyama CMD) presenting with severe CNS manifestations, and uncommon forms such as muscle-eye-brain disease and Walker-Walburg syndrome[2]. The discovery of merosin deficiency in some CMD patients has led to subclassification of the classical form to the merosin-positive CMD and merosin-deficient CMD forms[3]. Merosin-deficient CMD is a clinically homogeneous disorder caused by mutations of the LAMA 2 gene[4]. Three genes responsible for merosin-positive CMD have been mapped so far: Fukuyama CMD on 9q31, CMD with early rigidity of the spine (CMD-RSS) on 1p35-36, and muscle-eye-brain disease on 1p32-34[5-7]. When compared to the merosin-positive form, merosin-deficient CMD is more uniform in its clinical and pathological features and tends to be more severe, with marked motor disability and associated severe respiratory problems[8]. Merosin-deficient CMD and merosin-positive CMD have been further distinguished by the demonstration of CNS anomalies and white matter changes in magnetic resonance (MR) imaging studies of merosin-deficient CMD patients[9,10]. However, there is no study in the literature comparing the muscle involvement patterns of the two

groups. In this study our purpose was to define and compare the MR imaging findings of pelvic and thigh muscles in merosin-deficient and merosin-positive CMD patients.

Material and Methods

Ten merosin-positive CMD patients (6 males, 4 females, mean age: 7 years) and six merosin-deficient CMD patients (4 males, 2 females, mean age: 3.8 years) were included in our study (Table I). MR imaging was performed in a 0.5 Tesla system (Gyroscan T5, Philips, The Netherlands). T1-weighted (TR = 475, TE = 25), proton density weighted (TR = 2500, TE = 25), and T2-weighted (TR = 2500, TE = 80) axial images were obtained with a surface coil, and additional T1-weighted coronal images were taken using the body coil. Slice thickness was 5 mm with a gap of 2 mm (FOV: 220-280 mm, NSA: 2, matrix: 154 x 256). Ten patients (5 males, 5 females, mean age: 7 years) without any neuromuscular problems or malnutrition were also scanned using the same protocol, forming the control group. Normal and patient volunteers all gave informed consent according to the guidelines and procedures approved by the local human studies committee.

Table I. Diagnosis and Clinical Features of Our Patients

Case	Age (year)	Sex	Diagnosis	Functional status
1	12	M	MP-CMD	sits w/o support
2	4	M	MP-CMD	sits w/o support
3	7	M	MP-CMD	sits w/o support
4	9	F	MP-CMD	sits w/o support
5	10	F	MP-CMD	walks alone
6	5	M	MP-CMD	sits w/o support
7	7	M	MP-cMD	stands w/o support
8	5	F	MP-CMD	walks alone
9	2	M	MP-CMD	sits w support
10	9	F	MP-CMD	sits w/o support
11	1	M	MD-CMD	no head control
12	2	F	MD-CMD	no head control
13	11	M	MD-CMD	sits w support
14	4	M	MD-CMD	sits w/o support
15	4	M	MD-CMD	sits w/o support
16	1	F	MD-CMD	sits w support

M: male; F: female; MN-CMD: merosin-deficient congenital muscular dystrophy; MP-CMD: merosin-positive congenital muscular dystrophy; w: with; w/o: without.

All studies were retrospectively reviewed by two radiologists. Iliopsoas, gluteus maximus, gluteus medius, gluteus minimus, obturator internus, piriformis, and pectineus muscles (in the pelvis); rectus femoris, vastus lateralis, vastus medialis, vastus intermedius, sartorius, and gracilis muscles (in the anterior thigh); and biceps femoris, semimembranosus, semitendinosus, adductor magnus, adductor brevis and adductor longus muscles (in the posterior thigh) were evaluated for atrophy and intensity changes. Atrophy in muscles was evaluated by a four-grade scale by comparing the muscle size with the control group:

0: no atrophy.
1: mild atrophy.
2: moderate atrophy.
3: severe atrophy.

Intensity changes observed in muscles were also graded on a four-level scale[11]:

1: normal muscle signal intensity (homogeneous, hypointense signal contrasting sharply with subcutaneous and intermuscular fat).

2: slightly hyperintense, patchy intermuscular signal changes.

3: markedly hyperintense, patchy but widespread intramuscular signal changes.

4: total, homogeneous hyperintense signal change throughout the entire muscle, egual to the signal intensity of adjacent subcutaneous or paramuscular fat.

Atrophy and intensity scores of pelvic (gluteus muscles, iliopsoas, pectineus, piriformis), anterior thigh (sartorius, gracilis, quadriceps femoris) and posterior thigh (semimembranosus, semitendinosus, biceps femoris, adductor muscles) muscle groups were calculated for each patient. The scores of merosin-deficient and merosin-positive CMD patients for each of these muscle groups were compared by Mann-Whitney U test. Atrophy and intensity scores of merosin-deficient and merosin-positive CMD patients were also investigated by logistic regression analysis and stepwise logistic regression analysis.

Results

Atrophy and intensity scores of patients are summarized in Tables II and III. In merosin-positive CMD patients, intensity changes in the vastus muscles were prominent, and intensity scores were either 3 or 4 in nine cases (n = 9.90%). There was no clear sparing of the rectus femoris muscle within the quadriceps muscle group. However, the intensity score of

Table II. Atrophy Scores of Pelvic and Thigh Muscles

Case	Iliopsoas	Gluteus maximus	Gluteus medius	Gluteus minimus	Obturator internus	Piriformis	Pectineus	Sartorius	Gracilis	Rectus femoris	Vastus medialis	Vastus intermedius	Vastus lateralis	Semimembranosus	Semitendinosus	Biceps femoris	Adductor longus	Adductor magnus	Adductor brevis
1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1
2	3	3	3	3	3	3	1	2	1	3	3	3	3	3	3	3	3	3	3
3	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	0	0
4	1	0	0	0	1	3	2	0	0	0	0	0	0	0	0	0	2	2	2
5	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
6	2	1	1	1	1	0	2	0	0	0	2	2	2	1	1	1	0	2	2
7	3	2	2	2	2	2	2	2	1	3	2	2	2	2	2	2	2	2	2
8	1	2	2	2	0	0	0	0	0	0	1	1	1	0	0	0	1	3	3
9	3	3	3	2	2	2	2	3	3	1	3	3	3	3	2	3	2	1	1
10	3	3	3	2	3	2	2	2	0	2	3	3	3	1	0	2	1	3	3
11	1	1	1	1	1	2	1	1	1	2	2	2	2	1	1	2	3	3	3
12	1	2	1	1	2	1	0	1	1	1	1	1	1	1	1	1	3	3	3
13	1	0	0	0	1	1	1	0	0	1	1	1	1	0	0	0	0	0	0
14	1	3	3	3	2	3	1	1	1	2	2	2	2	2	2	2	2	2	2
15	1	0	0	0	1	1	0	0	0	1	1	1	1	1	1	1	3	3	3
16	0	2	2	2	2	2	0	1	1	2	2	2	2	2	3	3	3	3	3

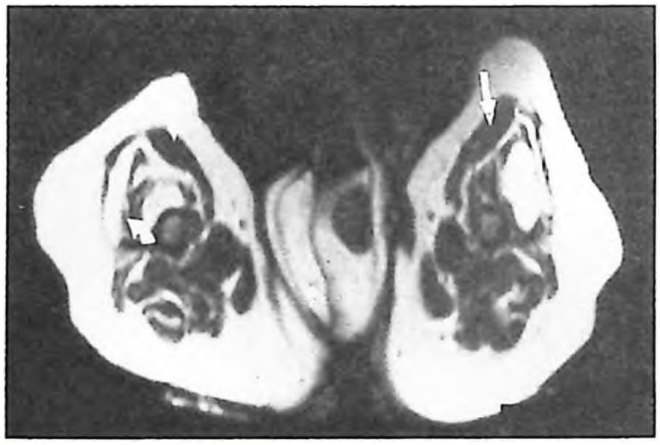
0: no atrophy.
1: mild atrophy.
2: moderate atrophy.
3: severe atrophy.

Table III. Intensity Scores of Pelvic and Thigh Muscles

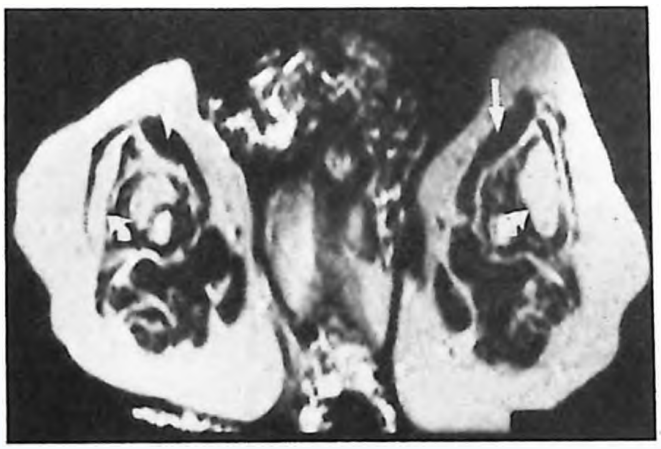
Case	Iliopsoas	Gluteus maximus	Gluteus medius	Gluteus minimus	Obturator internus	Piriformis	Pectineus	Sartorius	Gracilis	Rectus femoris	Vastus medialis	Vastus intermedius	Vastus lateralis	Semimembranosus	Semitendinosus	Biceps femoris	Adductor longus	Adductor magnus	Adductor brevis
1	3	3	3	3	3	2	3	2	1	4	4	4	4	3	3	3	2	3	3
2	1	1	1	1	1	1	1	1	1	1	4	4	4	1	1	1	1	1	1
3	2	4	4	4	2	3	4	2	2	4	4	4	4	4	4	4	2	4	4
4	4	4	4	4	3	3	4	2	2	4	4	4	4	4	4	4	2	4	4
5	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	3	2	3
6	2	4	2	2	1	1	1	2	1	2	4	4	4	3	2	2	1	4	4
7	2	3	2	2	1	1	2	3	2	3	3	3	3	2	2	3	2	2	2
8	2	4	2	2	1	1	2	1	1	2	2	2	2	1	1	1	2	4	4
9	3	4	1	1	2	2	1	4	4	1	4	4	4	1	4	4	1	2	2
10	3	4	2	2	4	2	2	4	1	2	4	4	4	4	1	4	2	4	4
11	1	2	2	3	3	2	1	1	1	3	3	3	3	2	2	3	3	3	3
12	2	3	3	3	2	2	1	1	1	2	2	4	2	1	2	2	4	4	4
13	3	4	4	4	4	4	4	2	2	3	3	3	3	3	3	3	3	3	3
14	1	3	3	3	3	3	2	2	2	2	3	3	3	3	3	3	3	1	3
15	2	4	4	4	1	2	4	1	1	4	3	3	3	1	2	1	1	3	3
16	1	2	2	2	1	2	1	1	1	2	3	3	3	2	2	2	1	3	3

1 : normal muscle signal intensity (homogeneous, hypointense signal contrasting sharply with subcutaneous and intermuscular fat).
2 : slightly hyperintense, patchy intermuscular signal changes.
3 : markedly hyperintense, patchy but widespread intramuscular signal changes.
4 : total, homogeneous hyperintense signal change in whole muscle, equalling the signal intensity of adjacent subcutaneous or paramuscular fat.

the rectus femoris was less than that of the vastus muscles in four cases (40%). Gracilis seemed to be spared with no atrophy in seven cases (70%), and with intensity scores of 1 or 2 in eight patients (80%) (Fig. 1). Although not as prominent as with the gracilis, the sartorius also seemed to be relatively spared compared to other thigh muscles. Its atrophy score was 0 in six cases (60%), 2 in three cases (30%), and 3 in two cases (20%), and its intensity score was 1 or 2 in six cases (60%).



(a)



(b)

Fig. 1. Four-year-old patient with merosin-positive congenital muscular dystrophy (CMD) (Case 2). T1-weighted (a) and T2-weighted (b) axial images of thigh muscles. Intensity score of rectus femoris muscle (arrows) is 1 whereas it is 4 for the vastus muscles (curved arrows). Atrophy scores of these muscles are all 4.

Gluteus maximus was the most consistently affected muscle in merosin-positive CMD patients, with an intensity score of 3 or 4 in nine cases (90%) (Fig. 2). Adductor magnus and brevis also demonstrated significant and consistent intensity changes, with intensity scores of 3 or 4 in eight cases (80%). In contrast, the intensity score of the adductor longus was either 1 or 2 in all 10 cases (100%).

In patients 3, 4 and 5, atrophy score was either 0 or 1, despite high intensity scores in all muscles (Fig. 3). However, although these patients demonstrated a common muscle involvement pattern on MR imaging, their clinical presentation was heterogeneous: patients 3 and 4 could only sit without support and patient 5 could walk alone.

Atrophy scores of the vastus muscles were less than 3 in all patients (100%) with merosin-deficient CMD (Fig. 4). Selective sparing of the

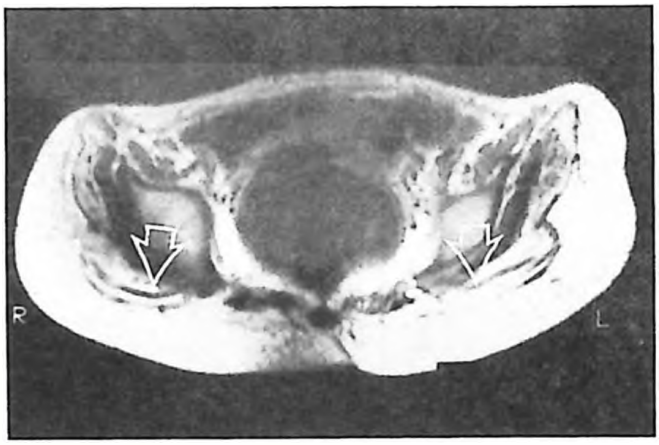


Fig. 2. Nine-year-old patient with merosin-positive congenital muscular dystrophy CMD (Case 10). T1-weighted axial images of pelvic muscles demonstrate severe atrophy and intensity changes in the gluteus maximus muscles (open arrows).

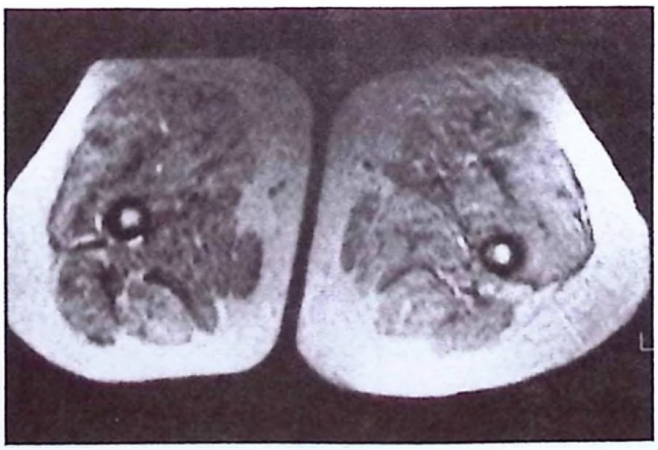


Fig. 3. 10-year-old patient with merosin-positive congenital muscular dystrophy CMD (Case 5). T2-weighted axial images of thigh muscles. Severe intensity changes (intensity score is 4 in semitendinosus, 2 in adductor longus and 3 in other thigh muscles) are noted in the thigh muscles without accompanying atrophy.

rectus femoris muscle was not observed. Intensity scores of the sartorius and gracilis were either 1 or 2, maximum atrophy score was 1 in all six cases (100%). Iliopsoas muscle seemed to be affected less than the other muscles. Atrophy was most prominent in the posterior thigh muscles, especially in the adductors (Fig. 5). Atrophy score of the adductors was either 3 or 4 in five patients (83%). In three patients, atrophy in the adductor muscles was not accompanied by intensity changes (50%).

The only statistically significant difference between the atrophy and intensity scores of merosin-deficient and merosin-positive CMD patients was the intensity score of the anterior thigh muscles. The intensity scores of the anterior thigh muscles of merosin-positive CMD patients were significantly higher than those in the merosin-deficient CMD patients ($U = 8$, $p = 0.016$). The differences between the other corresponding atrophy and intensity scores of merosin-deficient and merosin-positive CMD patients were not significant.

Logistic regression analysis was applied to determine the significance of atrophy and intensity scores in differentiation between the merosin-deficient and merosin-positive CMD patients. The success of the model is summarized in Table IVA and IVB. The model formed using the atrophy scores of pelvic and thigh muscles (IVA) was 100 percent sensitive and 67 percent specific in differentiating merosin-positive from merosin-deficient CMD patients. The model formed using the intensity scores of pelvic and thigh muscles (IVB) was 90 percent sensitive and 67 percent specific in differentiating merosin-positive from merosin

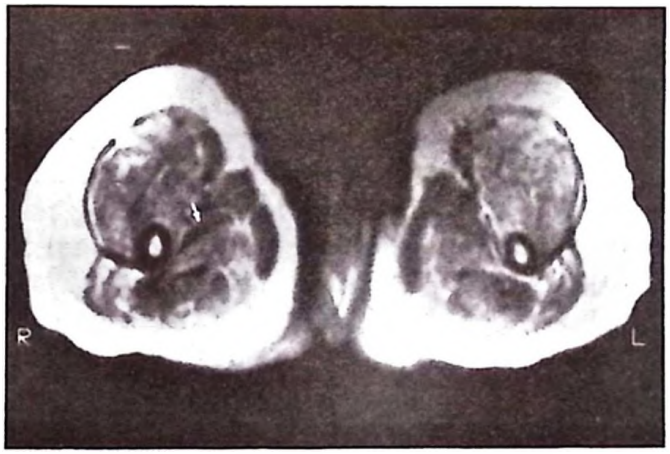


Fig. 4. Four-year-old patient with merosin-deficient congenital muscular dystrophy CMD (Case 15). T2-weighted axial images of thigh muscles show more prominent atrophy in adductor muscles compared to the other thigh muscles (small arrow).

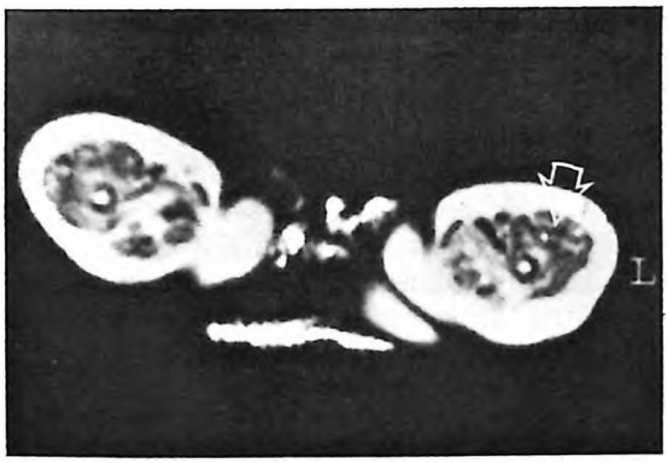


Fig. 5. Two-year-old patient with merosin-deficient congenital muscular dystrophy CMD (Case 12). T2-weighted axial images of thigh muscles. Relative sparing of anterior thigh muscles compared to the posterior high muscles is noted (open arrow).

Table IV-a. Logistic Regression Analysis Table Formed Using the Atrophy Scores of Pelvic Anterior and Posterior Thigh Muscles

		Predicted		
		Mer+CMD	Mer-CMD	Total
Observed	Mer+CMD	12	0	12
	Mer-CMD	2	4	6
	Total	14	4	18

Logistic regression coefficients.
exp (0.1042-0.6527VI+0.4156V2+0.2858V3).
V1: total atrophy scores of pelvic muscles;
V2: total atrophy scores of anterior thigh muscles.
V3: total atrophy scores of posterior thigh muscles.
Mer+CMD: merosin-positive congenital muscular dystrophy.
Mer-CMD: merosin-deficient congenital muscular dystrophy.

Table IV-b. Logistic Regression Analysis Table Formed Using the Insensity Scores of Pelvic Anterior and Posterior Thigh Muscles

		Predicted		
		Mer+CMD	Mer-CMD	Total
Observed	Mer+CMD	11	1	12
	Mer-CMD	2	4	6
	Total	13	5	18

Logistic regression coefficients.
exp (6.932+0.2385V4-0.6831V5-0.0543V6).
V1: total atrophy scores of pelvic muscles;
V2: total atrophy scores of anterior thigh muscles.
V3: total atrophy scores of posterior thigh muscles.
Mer+CMD: merosin-positive congenital muscular dystrophy.
Mer-CMD: merosin-deficient congenital muscular dystrophy.

deficient CMD patients. When stepwise logistic regression analysis was applied, the intensity score of the anterior thigh muscles was found to be the best differentiating variable between merosin-deficient and merosin-positive CMD patients. The success of the model is summarized in Table V. The model formed using the intensity score of anterior thigh muscles was 80 percent sensitive and 83 percent specific in differentiating merosin-positive from merosin-deficient CMD patients.

Table V. Logistic Regression Analysis Table Formed Using the Intensity Scores of Anterior Thigh Muscles

		Predicted		
		Mer+CMD	Mer-CMD	Total
Observed	Mer+CMD	11	1	12
	Mer-CMD	1	5	6
	Total	12	6	18

Logistic regression coefficients.
exp (7.1949-0.478V5).
V5: total intensity score of anterior thigh muscles.
Mer+CMD: merosin-positive congenital muscular dystrophy.
Mer-CMD: merosin-deficient congenital muscular dystrophy.

Discussion

Imaging methods have been utilized more frequently in the evaluation of primary skeletal muscle diseases in recent years. These methods include conventional radiography, scintigraphy, ultrasonography (US), computed tomography (CT) and, more recently, MR imaging[12-16]. MR imaging can display both normal and pathological skeletal muscle[16]. It can characterize the muscle diseases in terms of the involved muscles, distribution of the involved muscles and pattern of fatty replacement. The thin intermuscular fat planes are easily imaged, allowing identification of individual muscles and muscle groups. Increased intramuscular signal intensity observed in most muscular diseases on both T1- and T2-weighted images is thought to represent fatty changes[17]. This increased intensity also facilitates the identification of the diseased muscle. The fatty nature of these intramuscular changes has been confirmed by chemical shift imaging[18]. Increased water content in the dystrophic muscles also adds to the increased signal intensity on T2-weighted images[19].

Different MR sequences have been used in the evaluation of primary muscle diseases. Murphy et al.[16] reported no advantage of IR (inversion recovery) or T2-weighted sequences over T1-weighted sequences. However, T2-weighted images seemed to be helpful in childhood inflammatory myopathies, with the increased contrast of diseased muscle[20]. Again, in inflammatory myopathies, increased signal on T2-weighted images has been reported to be present before any detectable abnormality on T1-weighted images[21,22]. In our study, intensity changes were best demonstrated on T1-weighted images. None of our cases displayed abnormal signal intensity on T2-weighted sequences in the absence of abnormality on T1-weighted sequences. However, T2-weighted sequences were helpful for the accurate grading of the muscles. We used mainly axial images in our evaluation. Coronal images provided additional information about the extent of the disease in a very few cases.

Although MR imaging findings of muscles in Duchenne muscular dystrophy have been well studied, with even an MR imaging grading system with functional correlation having been established, there is, to our knowledge, no report in the literature designed to study the muscle MR imaging findings in congenital muscular dystrophies[19,21,22]. Muscle involvement patterns in merosin-deficient and merosin-positive CMD patients have also not been investigated. Lamminen et al.[11] studied muscle MR imaging findings of muscular dystrophies, including nine patients with muscle-eye-brain disease, and concluded that the gracilis, sartorius and rectus femoris were relatively spared. Apart from this one stduy, all other muscle imaging studies in CMD have been performed with US[24-27]. Topaloğlu et al.[24] reported selective sparing of the rectus femoris muscle in eight out of 26 CMD patients. Heckmatt and Dubowitz[26] also reported one CMD case with selective sparing of the rectus femoris. However, in their series of 14 CMD cases, the same authors did not mention any selective involvement pattern identified by US[15]. Similarly, in another series of eight CMD patients studied with US, selective involvement or sparing of muscles was not reported[27]. In our study, the rectus femoris was affected less than the vastus muscles in 40 percent of cases in merosin-positive CMD patients, whereas there was no selective sparing in merosin-deficient CMD patients. The sartorius and gracilis were the two muscles which seemed to be relatively

spared in both merosin-deficient and merosin-positive CMD patients. We also noted a common involvement pattern in three cases in the merosin-positive group characterized by significant intensity changes in muscles without any atrophy. The most consistently affected muscles in merosin-positive CMD patients were the gluteus maximus, adductor magnus and adductor brevis according to the intensity scores, whereas the adductor longus was relatively spared among the adductors. Another striking feature was the more prominent atrophy of the adductors in the merosin-deficient CMD group. We think that these different patterns may help the clinician identify appropriate muscles for biopsy and plan courses of physical and rehabilitation therapy.

Ours is the first study to use atrophy and intensity scores for a regression analysis model to differentiate two separate muscle diseases. The regression analysis model formed by the intensity scores of the anterior thigh muscles could differentiate the merosin-deficient from merosin-positive CMD patients with a high level of sensitivity and specificity (80% and 82%, respectively). The intensity scores of the anterior thigh muscles in the merosin-positive CMD patients were significantly higher than in merosin-deficient CMD patients. These findings suggest that muscle MR imaging can also be used in the non invasive diagnosis of muscle diseases. However, further studies with larger series of patients are necessary in order to increase the confidence in the diagnosis.

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Diastolic forward blood flow in the pulmonary arteries of normal children: a Doppler echocardiographic study

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SUMMARY: Eroğlu AG, Sarıoğlu A. Diastolic forward blood flow in the pulmonary arteries of normal children: a Doppler echocardiographic study. Turk J Pediatr 2001; 43: 52-54.

Pulmonary arterial flow was examined in 60 normal children with a mean age of 8.5±3.7 years (range 3.3 to 17.9 years) and mean body surface area of 0.95 ± 0.3 m^2 (range 0.6 m^2 to 1.7 m^2) by pulsed Doppler echocardiography. Two distinct antegrade waveforms during diastole were detected. The peak velocities of early diastolic forward flow ranged from 20 to 30 cm/s (mean 26 ± 4) and the late diastolic forward flow ranged from 16 to 29 cm/s (mean 23 ± 3). The integrals of early diastolic forward flow ranged from 2.1 to 4.7 cm (mean 3.1 ± 0.7) and late diastolic forward flow ranged from 1 to 3.6 cm (mean 2.1 ± 0.7). Duration of early diastolic forward flow ranged from 161 to 256 ms (mean 187 ± 29) and late diastolic forward flow ranged from 82 to 188 ms (mean 133 ± 29). Data analysis for age indicated no significant difference in these measurements between children three to nine years old (n = 33) and children 9.1 to 18 years old (n = 27). The effect of respiration was observed in 10 randomly chosen subjects (mean age 8.6±4.1 years). Although early and late diastolic peak forward flow velocities, flow velocity integrals and flow duration during inspiration tended to be larger than during expiration, only late diastolic peak forward flow velocities during inspiration were significantly larger than during expiration (24.2 ± 3.2 versus 18.2 ± 3 cm/s, p = 0.001). This study defines normal Doppler ultrasound pulmonary arterial flow velocities, flow velocity integrals and flow duration during diastole in normal children. These results can be used for comparison with patterns found in disease states.

Key words: echocardiography, pulmonary artery, diastolic function.

Several recent reports have suggested that late diastolic forward flow in the pulmonary artery throughout the respiratory cycle could be of diagnostic value in children with restrictive right ventricular physiology[1-6]. In this study, we examined the normal patterns of pulmonary blood flow and provide quantitative normal values for the major waveforms seen during diastole in normal children.

Material and Methods

This study group consisted of 60 normal children with a mean age of 8.5±3.7 years (range 3.3 to 17.9 years) and mean body surface area of 0.95 ± 0.3 m^2 (range 0.6 m^2 to 1.7 m^2). They had normal physical and echocardiographic examinations. Transthoracic echocardiography was performed with 4 MHz transducer interfaced with an Acuson 128/XP 10 ultrasound system. Measurements were made with simultaneous recording of the electrocardiogram. Spectral recordings were made, with minimal filtering, on paper at a speed of 100 cm/s. After the diagnostic imaging pulsed Doppler recordings were made with the subject in the lateral decubitus position. Pulmonary arterial flow was determined by placing the pulsed Doppler sample at the midpoint between the pulmonary valvar leaflets and the bifurcation of the pulmonary trunk in short axis at the left parasternal edge. Peak velocities, velocity integrals and duration of forward flow in systole, early diastole and late diastole were measured. All time intervals were corrected by the RR intervals on the electrocardiogram as follows: corrected time interval = time interval/$\sqrt{RR}$. Six cardiac cycles

were analyzed, and the results for each index averaged to minimize the effects of respiration. Data are expressed as mean ± SD. Student's t test was used to compare normally distributed variables; otherwise, a Mann-Whitney U test was performed. Statistical significance was inferred at a value of $p < 0.05$.

Results

All 60 subjects had tracing adequate for analysis. The spectral display of pulmonary arterial blood flow obtained by pulsed Doppler echocardiography had three distinct waveforms during each cardiac cycle. The initial waveform was antegrade waveforms during systole. Two distinct antegrade waveform during diastole were detected, the first occurring in early diastole and the second in late diastole. Figure 1 shows the pulsed Doppler recording from the pulmonary artery of a normal child. Table I displays the mean values and the ranges of peak flow velocities, flow velocity integrals and duration of antegrade flow during systole, early diastole and late diastole. In the 60 normal children, the peak velocities of early diastolic forward flow ranged from 20 to 30 cm/s (mean 26 ± 4) and the late diastolic forward flow ranged from 16 to 29 cm/s (mean 23 ± 3). The integrals of early diastolic forward flow ranged from 2.1 to 4.7 cm (mean 3.1 ± 0.7) and late diastolic forward flow ranged from 1 to 3.6 cm (mean 2.1 ± 0.7). Duration of early diastolic forward flow ranged from 161 to 256 ms (mean 187 ± 29) and late diastolic forward flow ranged from 82 to 188 ms (mean 133 ± 29). Two subgroups were defined to assess the effects of age. The 60 children were categorized by age: three to nine years (n = 33) and 9.1 to 18 years (n = 27). Data analysis for age indicated no significant difference in peak forward flow velocities, flow velocity integrals and flow duration during systole, early diastole and late diastole between children three to nine years old and children 9.1 to 18 years old. The effect of respiration was observed in 10 randomly chosen subjects (mean age 8.6 ± 4.1 years). Although early and late diastolic peak forward flow velocities, flow velocity integrals and flow duration during inspiration tended to be larger than during expiration, only late diastolic peak forward flow velocities during inspiration were significantly larger than during expiration (24.2 ± 3.2 versus 18.2 ± 3 cm/s, p=0.001) (Table II).

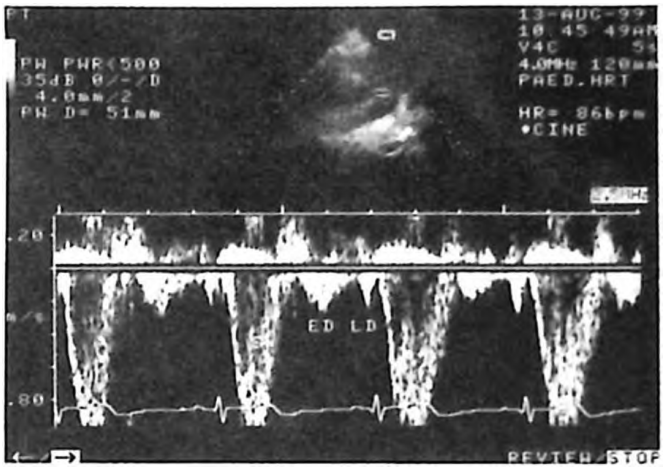

Fig. 1. Pulsed-Doppler recording from the pulmonary artery of a normal child. S = systolic flow; ED: early diastolic flow; LD = late diastolic flow.

Table I. Pulmonary Arterial Forward Flow Velocity, Flow Velocity Integral and Flow Duration During Systole, Early Diastole and Late Diastole in 60 Normal Children

Parameter	Mean±SD	Range
Systolic forward flow velocity, cm/s	104±16	82-128
Systolic forward flow integral, cm	21±3	16-28
Systolic forward flow duration, ms	369±34	307-474
Early diastolic forward flow velocity, cm/s	26±4	20-30
Early diastolic forward flow integral, cm	3.1±0.7	2.1-4.7
Early diastolic forward flow duration, ms	187±29	161-256
Late diastolic forward flow velocity, cm/s	23±3	16-29
Late diastolic forward flow integral, cm	2.1±0.7	1-3.6
Late diastolic forward flow duration, ms	133±29	82-188

Table II. Effect of Respiratory Phase on Diastolic Pulmonary Arterial Forward Flows in 10 Normal Children

Parameter	Inspiration	Expiration	p
Early diastolic forward flow velocity, cm/s	25±3	23±4	0.24
Early diastolic forward flow integral, cm	3.1±1	2.4±0.5	0.12
Early diastolic forward flow duration, ms	191±29	170±22	0.11
Late diastolic forward flow velocity, cm/s	24±3	18±3	0.001*
Late diastolic forward flow integral, cm	2±0.5	1.5±0.5	0.10
Late diastolic forward flow duration, ms	143±26	129±27	0.31

Discussion

Recently, pulmonary arterial forward flow patterns during late diastole have been reported as a sensitive mean of recognizing right heart filling abnormalities noninvasively[1-6]. It has been proposed that increased late diastolic forward flow in the pulmonary artery reflects reduced right ventricular diastolic compliance, suggesting that the right ventricle is unfillable and truly restrictive at end diastole, so acting as a passive conduit between the right atrium and pulmonary artery during atrial systole[1]. Less cardiomegaly and improved exercise performance have been demonstrated in patients with restrictive right ventricular physiology after tetralogy of Fallot repair at long-term follow-up[2]. We have recently demonstrated that increased late diastolic forward flow (> 30 cm/s) in the pulmonary arteries of patients with tetralogy of Fallot at mid-term follow-up, subsequent to repair using a transannular patch, is associated with smaller right ventricular size and less prolongation of QRS complex. The purpose of this study was to establish normal values for pulmonary arterial diastolic forward flow velocities, flow velocity integrals and flow duration in normal children for future comparison with values obtained in cardiac diseases. As previously reported[7], there are two distinct forward flow waveforms in pulmonary arteries of normal subjects during diastole. Gibbs et al.[7] reported pulmonary arterial forward flow velocities during early and late diastole in 50 normal infants and adults aged two months to 42 years (mean 14.3 years), using pulsed wave Doppler recordings, that were smaller than those observed in our normal children. In their study, peak early diastolic forward flow velocities ranged from 15 to 30 cm/s (mean 21) and peak late diastolic forward flow velocities ranged from 20 to 30 cm/s (mean 25). The difference may be due to age difference between the two study subjects. Their study population included normal adults in addition to normal children and their mean age was greater than ours.

The 60 children were divided into a younger and an older group, and no differences were found between these two groups in forward flow velocities, flow velocity integrals or flow duration during early diastole and late diastole. The present study indicates that age has no influence on diastolic forward flow measurements in pulmonary arteries of normal children.

The effect of respiration was examined. Although early and late diastolic peak forward flow velocities, flow velocity integrals and flow duration during inspiration tended to be larger than during expiration, only late diastolic peak forward flow velocities reached statistical significance.

This study defines normal Doppler ultrasound pulmonary arterial flow velocities, flow velocity integrals and flow duration during diastole in normal children. These results can be used for comparison with patterns found in disease states.

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Pediatricians' opinions about the problems between the departments of pediatrics and child psychiatry and possible solutions

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SUMMARY: Çengel SE, Semerci ZB. Pediatricians' opinions about the problems between the departments of pediatrics and child psychiatry and possible solutions. Turk J Pediatr 2001; 43: 55-58.

The necessity of collaboration between the Departments of Pediatrics and Child Psychiatry is an acceptèd idea. However, relevant literature reveals that collaboration between the two departments is not satisfactory. Rearrangement of relations between the two departments in Hacettepe University İhsan Doğramacı Children's Hospital has been designated a goal. An education program will be planned accordingly. A questionnaire was designed to determine 65 pediatricians' knowledge, thoughts, expectations and needs about collaboration between the two departments; all were working in Hacettepe University Children's Hospital, in inpatient services, outpatient clinics or emergency services. An education program for consultation-liaison activities has been constituted to achieve the desired results. Efficacy of the program was discussed considering the features and tendencies of the two departments.

Key words: child psychiatry, pediatrics, collaboration.

Child Psychiatry and Pediatrics are two departments that have to collaborate in many fields. Such collaboration is especially important in evaluating a child with chronic illness at follow-up and emergent problems like suicide, child abuse and neglect. It is also important to understand the problems of the staff in these two departments in determining boundaries of responsibility, i.e. establishing the situations that should be shared with the other department and requesting help from each other in certain cases, such as differentiation of illnesses originating from organic and psychological factors versus organic brain syndrome originating from a primary central nervous system disorder.

These steps are necessary for these two departments to be able to work in an easier and more harmonious way and for the patients to be ensured the help that they need. One of the most important problems has been defined as insufficient training of pediatricians in evaluating the emotional, behavioral and family problems, which are the most probable causes of the symptoms[1]. Education programs on this issue must be handled at three levels: medical students, research assistants, and specialists.

In this paper, we reevaluate current education programs designed to solve the problems encountered by staff of both departments in Hacettepe University Faculty of Medicine in inpatient and outpatient services. We attempted to establish the thoughts, knowledge and expectations of pediatricians regarding child psychiatry, for the purpose of developing an education program to be conducted during medical school, at the level of research assistants.

Material and Methods

The questionnaire, consisting of 47 questions, was given to all research assistants (65) training in İhsan Doğramacı Children's Hospital at Hacettepe University. According to the results of the available 44 questionnaires, the needs of the research assistants were taken into consideration and the content of a proposed program was discussed.

Results

From the 65 questionnaires distributed, 44 (67.7%) were completed and returned by the research assistants. Some demographic features of the participants are shown in Table I. The age of the participants ranged between 24 and 33 years old and the mean age was 27.3 ± 1.7 years. Among the participants, 56.8 percent (n: 25) chose the pediatric specialty program as their first choice in the specialty examination; 75 percent (n: 33) of the pediatric research assistants had graduated from Hacettepe University Faculty of Medicine.

Table I. Some Demographic Characteristics of the Research Assistants

Sex
Female 54.5% (n: 24)
Male 45.5% (n: 20)
Years of Experience as Research Assistants
First year 22.7% (n: 10)
Second year 27.3% (n: 12)
Third year 27.3% (n: 12)
Fourth year and above 22.7% (n: 10)
Child Psychiatry Rotation
Completed 6.8% (n: 3)
Not completed 93.2% 8n: 41)

It was determined that 36.4 percent (n: 16) received training about patient-physician relations in medical school. While all of them received training about adult psychiatry, only 59.0 percent (n: 26) received training in child psychiatry during medical school. Forty-one (93.2%) had no clinical experience in the Child and Adolescent Department as a research assistant. Among participants, 79.4 percent (n: 27) agreed that psychiatric training is important and necessary, while 11.8 percent (n: 4) considered psychiatry an unsuccessful and abstract field. Regarding training in the Child Psychiatry Department, 69.8 percent (n: 30) thought that it should be obligatory, 27.9 percent (n: 12) felt it should be optional, and 2.3 percent (n: 1) preferred it not be included in the education program.

Opinions of the research assistants on special topics such as child abuse and neglect and general attitudes are given in Table II.

Although 73.2 percent (n: 30) of participants mentioned that a psychological examination definitely must be done, 80.5 percent (n: 33) did not practice this and 62.5 percent (n: 25) gave as a reason "lack of time". In the event of an important illness, 25.0 percent (n: 10) mentioned that a psychiatrist must talk with the child and provide information about the illness. Twenty-five (62.5%) thought that pediatricians must talk with the child, whereas 12.5 percent (n: 5) preferred the parents talk with the child. It was found that 68.4 percent (n: 26) gave no information to the child about the illness or its treatment and considered it sufficient to give such information to the parents. Prior to an invasive intervention, 80.5 percent (n: 33) stated that they definitely gave information to the child.

Table II. Opinions of Research Assistants on Special Topics such as Child Abuse and Neglect and General Attitudes

	N	%
Opinions About Psychological Evaluation of Child		
Must definitely be done	30	73.2
Not necessary all the time	11	26.8
Research Assistants...		
Who practice psychological assessment	8	19.5
Who do not	33	80.5
Consultation Due to Family Characteristics		
Research assistants who demand	25	67.6
Research assistants who do not	12	32.4
Opinions on Follow-up When Child Abuse or Neglect is Suspected		
Child psychiatry consultation	9	25.0
Interview with family	20	55.5
Physical examination	2	5.6
No idea	2	5.6
Attitude When Child Abuse or Neglect is Detected		
Judicial case application	28	76.5
No idea	4	11.8

Whereas 40.5 percent (n: 17) of participants suggested that child psychiatry consultation was necessary in one to 10 percent of the inpatients, 33.3 percent (n: 14) considered it to be necessary in 30 percent or more of cases. In contrast, the ratio of observed child psychiatry consultation varied between one and five percent of the inpatients.

The most frequent problems for which pediatricians needed child psychiatry consultation at inpatient services are shown in Table III.

Twenty-seven (67.5%) research assistants considered child psychiatry consultation necessary at the inpatient services.

Twenty-nine (72.5%) considered necessary in-hospital support through provision of services such as school, playroom, and dining room. But it was observed that only 53.7 percent (n: 22) used these systems and occasionally monitored

the patient's use of them. Furthermore 92.9 percent (n: 39) of the participants stated that inpatient services' staff were not sufficiently qualified in child development.

Table III. Most Frequent Problems for Which Pediatricians Needed Child Psychiatry Consultation at Inpatient Services

Problems	N	%
Depression	24	60.0
Refusal of treatment and the illness	17	42.5
Chronic illness	14	35.0
Conversion disorder	10	25.0
Suicide attempt or thoughts	10	25.0
Conduct disorder	9	22.5
Adjustment disorder	8	20.0
Agitation	8	20.0

Whereas 65.5 percent (n: 19) of participants suggested that child psychiatry consultation was necessary in one to 10 percent of the outpatients, 34.2 percent (n: 10) considered it necessary in 11 percent or more of cases. On the other hand, the ratio of observed child psychiatry consultation among outpatients varied between one and five percent.

The most frequent problems for which the pediatricians needed child psychiatry consultation at outpatient services are shown in Table IV.

Table IV. Most Frequent Problems for Which Pediatricians Needed Child Psychiatry Consultation at Outpatient Services

Problems	N	%
Attention deficit and hyperactivity disorder	13	48.1
Enuresis	11	40.7
Depression	10	37.0
Conversion disorder	10	37.0
Failure at school	6	22.2
Conduct disorder	4	14.8

Twenty-four (60%) participants suggested that 40 percent of these consultations were the decision of the physician, not a result of the parents' demand.

The most frequent problems for which the pediatricians needed child psychiatry consultation at emergency services are shown in Table V.

Thirty-nine (95.1%) participants considered the psychiatrist to be helpful in the consultation-liaison relationship. The opinions of research assistants on the consultation-liaison relationship and on the approach of the psychiatrist are shown in Table VI.

Thirty-one (79.5%) found the current consultation-liaison relationship between the two departments insufficient, and 95.2 percent (n: 40) stated that they do not have enough training in consultation-liaison relations. Suggestions of the research assistants for improving the consultation-liaison relationship between the two departments are shown in Table VII.

Table V. Most Frequent Problems for Which Pediatricians Needed Child Psychiatry Consultation at Emergency Services

Problems	N	%
Suicide	18	64.2
Conversion disorder	18	64.2
Child abuse and neglect	4	14.3
Depression	4	14.3
Delirium	3	10.7
Anorexia nervosa	3	10.7
Amputation	3	10.7
Patients already followed up by psychiatry	3	10.7
Conduct disorder	3	10.7
Tic disorders	2	7.1

Table VI. Opinions of Research Assistants About the Consultation-Liaison Relationship and About the Approach of Psychiatrists

	N	%
Opinions on how to request consultation		
It must be written	2	4.9
It must be verbally	5	12.2
It must be done both verbally and in writing	34	82.9
Opinions on how the psychiatrist should share thoughts about the consulted case		
It must be done both verbally and in writing	25	57.0
It must be done with the pediatrician	19	43.2
Opinions about the attitudes of psychiatrist		
Sufficient	20	51.3
Insufficient	19	48.7
Opinions about the role of pediatricians during the consultation		
They always have a role	23	54.8
They never have a role	3	7.1
They occasionally have a role	16	38.1
Opinions about the role of pediatricians		
To help with the organic problem and continued participation in the treatment process	16	50.0
To implement the suggestions of the psychiatrist	12	37.5
To receive education in the process of collaboration with child psychiatry	4	12.5

Table VII. Suggestions of the Research Assistants on How to Improve the Consultation-Liaison Relationship Between the Two Departments

Suggestions	N	%
Common	32	76.2
Bedside visits when necessary	32	76.2
Lectures and seminars for both departments	25	59.5

Discussion

Although 73.2 percent (n: 30) of the research assistants in pediatrics stated that a psychological evaluation should be done in every patient, only 19.5 percent practice this, with 62.5 percent giving as a reason "lack of time". This is unsatisfactory, since the research assistants work in a university hospital where all laboratory evaluations in addition to the long physical examinations are considered to be routine.

Especially in emergency services, child abuse and neglect cases are referred to a pediatrician, which is why their ability to detect and handle these cases is so important. It was found that 11.8 percent of pediatric research assistants did not know how to handle such cases. While 76.5 percent stated they would immediately start the judicial procedure, only 25 percent stated that they would demand child psychiatry consultation.

According to the results of this study, research assistants in pediatrics have insufficient training on the consultation-liaison issue, and difficulties in evaluating the psychological state of families and child. They also had different views about the timing and manner of consultation, about collaboration with the Child Psychiatry Department and about what should be achieved.

Among the participants, 36.4 percent took courses about the patient-physician relationship during their education. Even though all received training in adult psychiatry, only 59.0 percent received training in child psychiatry during medical school. We definitely found that the ones with training in both child and adult psychiatry were more qualified and had a more affirmative attitude[2]. Clinical experience and education in the Child Psychiatry Department has been effective in educating research assistants in pediatrics in psychiatry[3]. Regarding clinical training in the Child Psychiatry Department, 69.8 percent of research assistants stated that it must be obligatory, and 27.9 percent thought that it should be optional in the education program. Developing collaboration between the two disciplines also includes constituting a common terminology and a common model for understanding the psychological aspects of a physical illness. Both disciplines stress their need for further education about the professional perspective of each discipline and about collaboration in the treatment of the physical illness and cure of the child[4]. Research assistants felt that in addition to clinical training, case report meetings (76.2 percent), bedside visits when necessary (76.2 percent), and seminars and lectures (59.5 percent) were other ways to further the efficacy of the work between the two disciplines. In general, research assistants were aware of deficiencies in their training and had realistic suggestions. Moreover, they recognized the importance of the support facilities like the playroom and the necessity to educate staff on child development. However, they were unable to use the support facilities effectively or to contribute to the proper training of the other staff. This is perhaps due to the tendency of the ones who educate them especially as a research assistant.

Suggestions

1. Each step of the education process in pediatrics should emphasize that the psychological and social problems of the child and the family are as serious as physical ones and are important components of physical problems.

2. It will be useful for research assistants to have child and adolescent psychiatric training.

3. Theoretical lessons on the psychological problems that are frequently faced and on the physician-family-child relationship will improve the relationship between the two departments.

4. Organization of meetings between the Pediatrics and Child Psychiatry Departments to decide on common ways of treatment-observation will be helpful for patients as well as efficacious for both the pediatrician and psychiatrist.

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Endovascular stent implantation in congenital heart defects

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We report the immediate and short-term results of endovascular stent implantations from our center. We performed stent implantations in four patients (3, 12, 18 and 20 years old) with different stenoses or obstructions: right ventricular outflow conduit obstruction, left Blalock-Taussig obstruction, post-operative recoarctation and cavopulmonary anastomosis obstruction. Stent were implanted successfully. The mean diameters of stenoses were expanded from 4.5 ± 3.5 (2-7) mm to 9 ± 1. 2 (8-10) mm, and the complaints of patients were improved significantly by stent implantation. There was no complication related to the procedures. All patients are living except one who died from cerebrovascular event unrelated to the stent implantation. The mean follow-up period of three living patients is 6.3 ± 5.5 (1-2) months. As of the last control, all have remained at the caliber achieved at original placement. In light of our limited experience and previous reported studies, we conclude that intravascular stents are safe and can be used effectively in selected patients with congenital heart defects.

Key words: stent implantation, children, congenital heart defects.

Stent implantation was first suggested and performed experimentally by Dotter[1] in the late 1960s. Stent technology and concept were developed in the early 1980s. Balloon-expandable and self-expanding stents have been used with increasing frequency in children with congenital heart defects since the late 1980s[2,3]. Endovascular stents have been successfully performed in selected patients with various obstructive lesions[2,4-9]. Almost all authors conclude that stent implantations are effective and safe in selected patients with congenital heart disease. Although this technique has been performed in many centers all over the world for more than 10 years, it has been used only recently in Turkey. For this reason we report the immediate and short-term results of stent implantations in four cases from our center.

Case Reports

Case 1

A 20-year-old female with isolated dextrocardia with double outlet right ventricle (DORV), atrioventricular discordans, transposition of great arteries, pulmonary stenosis, and single functional ventricle initially presented at age one with cyanosis. She had cardiac catheterization and angiography at age three in 1981. She then uderwent Blalock-Taussig shunt operation in 1982. In her follow-up, progressive cyanosis and hypoxia developed and cardiac catheterization in 1996 revealed partial obstruction and decreased flow in the shunt. Due to the complex cardiac pathology and difficult anatomic nature of her condition, a second right-side Blalock-Taussig (BT) shunt surgery was planned instead of corrective surgery. However, general anesthesia was contraindicated because of severe kyphoscoliosis and decreased lung capacity. For this reason balloon angioplasty and stent implantation were decided in order to maintain flow by widening of the shunt. Left BT shunt was reached retrogradely through the right femoral artery. Aortic injection showed an almost complete obstruction of the shunt that prevented even 0.025 inch guide wire insertion (Fig. 1). The 0.014 inch coronary guide wire was led throught left BT shunt towards right pulmonary artery, and balloon angioplasty was

performed by coronary balloon catheter 2 mm in diameter and 2 cm in length. In a repeat catheterization procedure in 15 days, left BT shunt angioplasty was performed by Thysak balloon catheter 5 mm in diameter and 10 mm in length. Post procedure angiography revealed sufficient flow. Following this procedure, 7F (2.33 mm) Easy Wallstent Nom. 10-20 mm (fully open size) self-expandable stent was placed in left BT shunt. While oxygen saturation and diameter of obstructed region were 53.7 percent and 2 mm, respectively, they improved to 92.7 percent and 8 mm by stent implantation (Fig. 2). Heparine infusion (400 IU/kg/day) was continued for 48 hours following procedure and then acetysalycylic acid was initiated as an antithrombotic agent. No complication related to catheter or stent implantation was noted. After one, six and 12 months, repeat Doppler echocardiographic examinations showed satisfactory shunt flow, and arterial oxygen saturation was 84 percent. During the one-year follow-up period the patient was improved, and we did not see a significant decrease in shunt flow with Doppler echocardiographic study. She also tolerated the Bruce protocol treadmill, testing up to seventh stage without significant reduction in arterial oxygen saturation, in her last control.

Case 2

A 12-year-old male with DORV, malposition of great arteries, ventricular septal defect (VSD), pulmonary stenosis and patent foramen ovale was initially brought to our center at age four with severe cyanosis and hypoxic spells. After echocardiographic study the diagnosis was confirmed by cardiac catheterization and angiographic study. He then underwent left BT shunt operation at age five in 1991 and Rastelli's operation at age nine in 1996. In his follow-up, progressive weariness, palpitation and exercise intolerance developed at age 12, and cardiac catheterization in 1999 demonstrated stenosis of the right ventricular conduit (Fig. 3). There was also 150 mmHg systolic flow gradient between the pulmonary arteries and right ventricle. Double balloon angioplasty with Thysak balloon catheter (12 mm in diameter and 4 cm in length) and Z-Med (B. Braun Medical Inc.) balloon catheter (10 mm in diameter and 4 cm in length) was performed to stenotic conduit. Dilatation of stenosis was possible but the stenosis did not remain expanded. Stent impmlantation was then decided in order to prolong the conduit life and to delay re-operation. The right ventricle was reached through the right femoral vein, and right ventricle injection showed stenosis of the

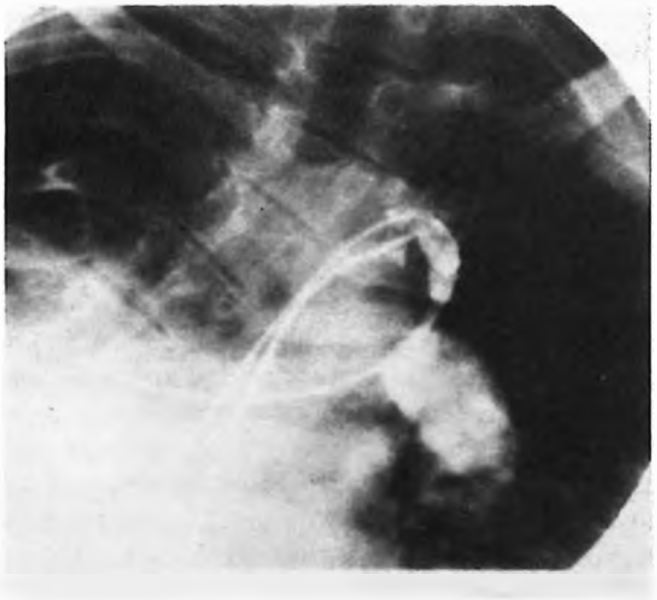

Fig. 1. Left Blalock-Taussig shunt injection showing almost complete obstruction.

Fig. 2. Expanded left Blalock-Taussig shunt after the self-expandable stent implantation.

conduit 2.5 mm in diameter (Fig. 3). An 11F long sheath were advanced over the guide wire into position well across the narrowing. We loaded Palmaz-Schatz 308 balloon-expandable stent (Johnson and Johnson Interventional Systems, Warren NJ) on the balloon angioplasty catheter 10 mm in diameter and 4 cm in length. The balloon and stent were advanced over the wire and into the long sheath. When the stent was in place and centered at the stenosis, the sheath was gradually withdrawn. The balloon was inflated until the narrowing in the balloon disappeared. The stent remained expanded after balloon deflation. After stent implantation, the diameter of the stenosis expanded to 8 mm, and systolic flow gradient through the conduit decreased to 70 mmHg (Fig. 4). There was no complication related to catheterization or stent implantation. His complaints were improved. In his first control one month after procedure, echocardiographic study revealed no significant increase in Doppler gradient across right ventricular outflow tract.

Case 3

A.B. is an 18-year-old young female who presented to our center with fatigue and hypertension at age eight. Physical examination revealed a 2/6 continuous heart murmur, heard best in the posterior left scapular region, weak femoral arterial pulses and phenotype of William syndrome. Echocardiography demonstrated

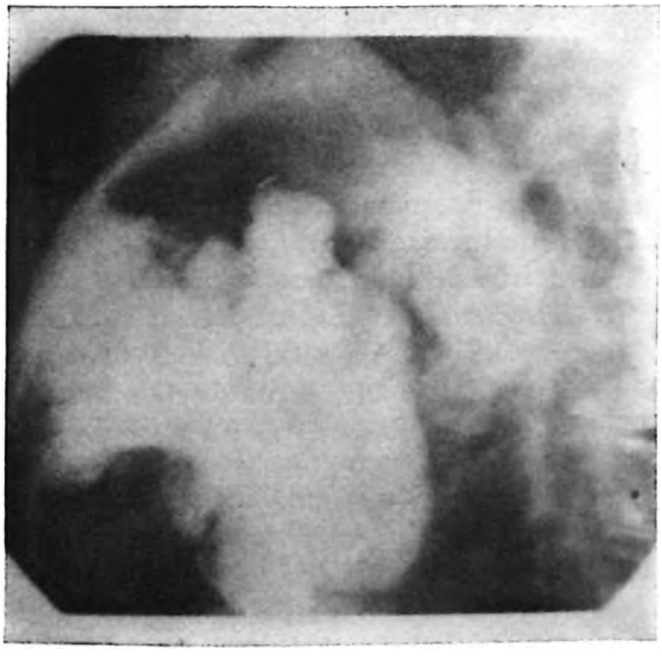

Fig. 3. The stenotic right ventricular conduit.

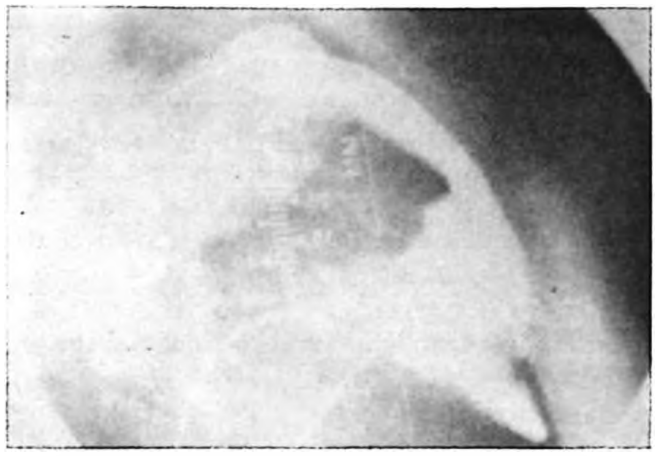

Fig. 4. Expanded right ventricular conduit after the balloon-expandable stent implantation.

coarctation of aorta with an Doppler gradient of 50 mmHg. The diagnosis was comfirmed by cardiac catheterization. Coarctation surgery (resection of coarctation segment and end to end anastomosis) was performed in 1988. During her post-operative follow-up, after 10 years, hypertension was detected. After echocardiography and cardiac catheterization, we found re-coarctation of aorta with a gradient of 40 mmHg through the re-coarctation. The diameter of coarctation was 7 mm and diameter of isthmic aorta was 12 mm. Stent implantation was decided. By using balloon angioplasty catheter (12 mm in diameter and 4 cm in length), Palmaz Schatz P308 (30 mm in length, 3.5 mm in nominal diameter), a balloon-expandable stent (Johnson and Johnson Interventional System, Sommerville, NJ) was placed in post-operative recoarcted segment using the standard method[4]. After the procedure, gradient was reduced to 20 mmHg. Because of residual gradient, repeat balloon dilatation of the stent was performed after two months and the coarcted segment was expanded to maximum of 10 mm and the gradient was reduced to 10 mmHg. There was no complication related to the procedure. Blood pressure was reduced from 160/120 mmHg to 125/85 mmHg. A follow-up period of six months after stent placement demonstrated 24-hour ambulatory blood pressure monitoring in the normal range and a stable Doppler gradient.

Case 4

A three-year-old boy with single ventricle had undergone a pulmonary banding operation at six months of age and a de-Leval operation at

18 months of age. He presented at age three with hypoxia, edema (especially in upper extremities), and bilateral hydrothorax and was immediately hospitalized in the intensive care unit. Cardiac catheterization revealed stenosis in the anastomosis between the vena cava superior and pulmonary artery. Through the anastomosis, mean gradient was 4 mmHg. Because of his severe symptoms and findings, general anesthesia and surgery were thought to be contraindicated for the patient, and stent implantation was decided. Palmaz Schatz P308 balloon-expandable stent was placed into the cavo-pulmonary anastomosis using Z-Med balloon angioplasty catheter (12 mm in diameter and 3 cm in length). The stent implantation procedure was as described previously by O'Laughlin et al.[4]. Stent implantation resulted in an immediate gradient reduction from 4 mmHg to 0 mmHg and the obstructed segment diameter increased from 5.5 mm to 10 mm. There was no complication related to the catheterization and stent implantation. The patient tolerated the procedure. Although there was some decrease in edema, the patient died at the 24th hour after the procedure because of a cerebrovascular event unrelated to the stent implantation. No autopsy was allowed but postmortem study demonstrated the patency of the stent. Therefore, although stent embolization was not present, complications caused by the stent implantation cannot be clearly ruled out in this patient. However, due to placement of the stent in the cavopulmonary anastomosis, any possible embolization would have been pulmonary in nature, so we thus considered that there was no complication related to stent implantation in this patient.

Discussion

Endovascular stent implantation is mostly used in selected patients for the treatment of stenotic branch pulmonary arteries[4], stenotic atriopulmonary and cavopulmonary anastomoses[5], postoperative systemic venous and systemic venous baffle obstructions[6], coarctation of aorta, especially segmentary, tortuous and with isthmic hypoplasia[2,7], obstructed right ventricular conduits[8] and for maintenance of ductal patency in neonates and children[9]. We performed stent implantation in four different stenoses or obstructions: right ventricular outflow conduit obstruction, left Blalock-Taussig shunt obstruction, postoperative recoarctation and cavopulmonary anastomosis obstruction (Table I). Many authors consider stent implantation to right ventricular outflow conduit obstructions, coarctation of aorta, stenotic aortopulmonary collaterals and obstruction of cavopulmonary anastomosis in selected patients a feasible and effective alternative to surgical therapy[2,8,10-12].

Table I. Patient Data 1

Name	Age (years)	W	Diagnosis	Stenosis	Stent type	Stent size
RP	20	50	DORV, VSD PS, L-BT shunt	L-BT shunt	Self exp.	8x27 mm
ET	12	33	DORV, VSD, PS, Rastelli op.	RV conduit	Balloon exp.	P308
SA	3	10	Single V, de-Leval op.	VCS-PA anastomosis	Balloon exp.	P308
AB	18	35	CA, surgery for CA	Post-op. recoarctation	Balloon exp.	P308

W : weight.
DORV : double outlet right ventricle.
PS : pulmonary stenosis.
V : ventricle.
PA : pulmonary artery.
exp : expandable.
L-BT : left Blalock-Taussig.
VSD : ventricular septal defect.
op : operation.
VCS : vena cava superior.
CA : coarctation of aorta.

If we look at the previous studies involved with stent implantation into right ventricular conduits, the mean reduction in the gradient across the conduits varies between 33 and 55 percent[8]. There was no significant mortality and morbidity in the previous studies. Authors are suggesting that the stent implantation into the right ventricular outflow tract can provide significant reduction in gradient, and reduction in the number of open heart procedures and conduit replacements[8]. In our patient with right ventricular outflow conduit obstruction, we demonstrated that the obstructed conduit could be expanded by balloon angioplasty, but it

returned to the predilation size after withdrawal of the balloon catheter; the reduction in gradient across outflow tract by stent implantation was 53 percent. So we thus managed a reduction similar in gradient to that seen in the literature. Although a significant reduction was achieved, the patient still has a gradient of 70 mmHg across the conduit (Table II). For this reason, we plan a second redilatation of the stent and, if necessary, a second stent implantation.

these advantages, arrival at the stenosis in an abnormal area is easier than with balloon expandable stents. After the implantation, arterial oxygen saturation and PO_2 improved significantly from 53 to 92 percent (Table II). Acetylsalycylic acid was started in the patient after the procedure and continued for six months. An effective palliation was provided by stent implantation in this patient. We have followed the patient with better exercise

Table II. Patient Data 2

Name	Gradient (before P)	Gradient (after P)	Diameter (before P)	Diameter (after P)	Follow-up	Result
RP	53%*	92%*	2 mm	8 mm	1 year	Alive
ET	150 mmHg	70 mmHg	2.5 mm	8 mm	1 month	Alive
SA	4 mmHg	0 mmHg	5.5 mm	10 mm	1 day	Died
AB	40 mmHg	10 mmHg	7 mm	10 mm	6 months	Alive

* Systemic arterial oxygen saturation.
P: procedure.

Many authors have shown the availability of self-expanding stent implantation to stenotic aortopulmonary collaterals in progressively hypoxemic patients and stenotic right and left lobe collaterals in a case with complex pulmonary atresia[10,11]. For example, McLeod et al.[11] demonstrated an increase in arterial oxygen saturation from 78 to 85 percent by stenting of stenosed aortapulmonary collaterals. In our patient with left B-T shunt, because of deeper localization, surgical treatment was thought to be difficult. And decreased lung capacity resulting from severe progressive kyphoscoliosis contraindicated general anesthesia. We know that surgical results of patients with cmoplex DORV have not been completely satisfactory. Sometimes patients are not suitable for corrective surgery. In such cases with pulmonary stenosis, in order to improve hypoxemia, an adequate aortopulmonary shunt is necessary. Some patients like ours may require a second surgery because of shunt stenosis. On the other hand, due to previous thoracotomy and increased risk of postoperative bleeding and atelectasis, a second surgery may not be favorable. Balloon angioplasty and stent implantation were thus decided in this patient as an alternative to surgery. We selected a self-expanding stent, because it and its delivery system have an advantage of flexibility compared with balloon-expandable stents. Furthermore, during delivery they do not require a stiff guiding long sheath. Given all capacity and oxygen saturation (stable at 84%) for one year (Table II). There was no significant reduction in oxygen saturation during the follow-up period.

Authors suggest that stenting of aortic coarctation in selected patients is a feasible and effective alternative to surgical or balloon therapy[2,12]. But the indications for stent implantation are not clearly defined. On the basis of limited experience, the indications are hypoplasia of isthmus or of transverse aortic arch and tortuous coarctation with malalignment of the proximal with the distal aortic segment, which are difficult to treat surgically[2]. Recurrent aortic coarctation or small aneurysm after previous surgical or balloon therapy may be another indication for implantation of stents[2]. If we give an example from the previous studies, Bülbül et al.[13] reported stent implantation results of six patients with coarctation of aorta and demonstrated a reduction in the systolic pressure gradient from 36.7 ± 16.9 to 13.3 ± 23.2 mmHg. They also performed a successful further dilatation of a stent in one patient. A balloon angioplasty was first performed in our patient with postoperative re-coarctation, but it was unsuccessful, probably due to natural elastic recoil or resistance or remnant scar tissue due to previous surgery. Because of the surgical risks of reoperation, we chose stent implantation. At the time of stent implantation the systolic gradient decreased

from 40 mmHg to 20 mmHg. Because of this residual gradient, we made a further successful balloon dilation two months later and the gradient decreased to 10 mmHg. As a result of stent implantation and a further balloon dilatation, we achieved a good reduction in the systolic gradient (from 40 to 10 mmHg) similar to reported studies, and we could control the systolic blood pressure (Table II). The last control of the patient was done six months after the procedure, and Doppler echocardiographic study revealed no increase in gradient, and ambulatory blood pressure monitoring showed normal values.

In our patient with the obstruction of cavopulmonary anastomosis, there were symptoms related to the superior vena cava syndrome. Surgical relief of such obstruction generally requires cardiopulmonary bypass and often fails to satisfactorily relieve the obstruction[6]. Balloon dilatation may also provide only transient relief of such obstructions because of the elastic recoil of the obstructing tissue or because of restenosis[6]. In such cases Ward et al.[6] showed a reduction of the systolic gradient from 12 ± 8.4 to 1.3 ± 1.4 mmHg by stent implantation. Given the severe clinical condition of our patient and high risks of reoperation, we decided to implant a stent after which the stenosis and gradient were completely resolved (from 4 to 0 mmHg) (Table II).

We did not see any complications related to the stent implantation during the procedure ar follow-up, nor did we find evidence of stent compression or fracture or changing of stent position. One patient died 24 hours after the procedure but from causes unrelated to the stent implantation.

Based on our limited experience and previous reported studies, we conclude that intravascular stents are safe and can be used effectively in selected patients with congenital heart defects. Especially in patients with lesions that are difficult or impossible to treat surgically and in high risk patients, stent implantation can be an alternative and life-saving therapy, at least providing a significant reduction in the number of open heart surgeries.

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Henna - induced hemolytic anemia and acute renal failure

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SUMMARY: Devecioğlu C, Katar S, Doğru Ö, Taş MA. Henna-induced hemolytic anemia and acute renal failure. Turk J Pediatr 2001; 43: 65-66.

Henna is a traditional cosmotic agent and is used worldwide, especially in the Middle East. Its active agent is lawsone (2-hydroxy-1,4-naphthoquinone). Henna is not only applied to hands or hair as a cosmotic agent in traditional ceremonies, but is also applied to the body on lesions in the treatment of seborrheic dermatitis or fungal infections. However, its application over the body or in newborns is rare. Here we report a 27-day-old boy who developed hemolytic anemia and acute renal failure following topical application of henna to his abdomen, intertriginous region and legs to treat diaper rash.

Key words: henna, G6PD enzyme deficiency, hemolysis, acute renal failure.

The crushed leaves of henna are used worldwide, and especially in the Middle East, as a cosmetic agent. Lawsone (2-hydroxy-1,4-naphthoquinone) is a chemical present in henna, and has been shown to cause severe hemolytic anemia and renal tubular necrosis in animals. Henna may cause hemolysis in G6PD (glucose-6-phosphate dehydrogenase) enzyme deficiency in regions where it is commonly used. Although henna has low allergenic potential, it may also cause contact dermatitis. This case is presented because a thorough review of the literature showed no report of acute hemolysis and acute renal failure after henna application.

Case Report

A 27-day-old boy was admitted to our hospital with a four-day history of dyspnea, paleness, low amount of urine and icterus. The patient had no complaints four days previously, when henna was applied to his abdomen, intertriginous region and legs to treat diaper rash.

Dyspnea and paleness developed after henna application and the amount of urine decreased two days later. Past history revealed the patient was born at term, in hospital, cried immediately after birth, had no cyanosis, was breastfed, and had no vaccination, medication or aspiration. The parents were unrelated; the first child was a two-year old boy, who was alive and healthy. On physical examination length, weight and head circumference were between 25th-50th percentile. Axillary temperature was 37 °C, blood pressure was 102/62 mmHg and heart rate was 184/min. General appearance was poor, with the child hypoactive, very pale and icteric. Skin from the patient's knees to the umbilical level had apparently been dyed a reddish color. When the parents were questioned, we learned that they had applied henna four days previously. The patient was dyspneic and intercostal and subcostal retractions were present. The liver was 4 cm palpable subcostally in the midclavicular line. Reflexes were diminished.

Laboratory examination revealed: Hb 5.6 g/L, Hct 17.6%, WBC 22,300/mm^3, erythrocytes 1,800,000/mm^3, and platelets 291,000/mm^3, On peripheral smear there were 48% PMNL, 44% lymphocytes, 8% bands, and 12% normoblasts; thrombocytes were adequate and clustered. Erythrocyte morphology: anisocytosis and fragmented erythrocytes were present. There was no spherocytosis or elliptocytosis. Sickling test was negative, and reticulocytes were 8%. Osmotic fragility test was negative. G6PD enzyme was found to be qualitatively deficient. Urea was 149 mg/dl, creatinine 4 mg/dl, Na 148 mEq/L, K 5.7 mEq/L, ALT 126 IU/L, AST 106 IU/L, blood glucose 47 mg/dl, total bilirubin 14.6 mg/dl, and direct bilirubin 2 mg/dl. Urine analysis revealed pH 5, density 1010, protein (+), bilirubin (+), and hemoglobin (+), and 1-2 epithelial cells were seen at each field on microscopic examination. Both the patient and

his mother were blood group 0 Rh (+); direct Coombs test was negative. On blood gas analysis pH was 6.8, pCO_2 33 mmHg, pO_2 29 mmHg, HCO_3 5.9 mmol/L, and BE -25 mmol/L. Blood culture was negative. Abdominal ultrasonography performed 40 hours after blood transfusion was normal. Previously determined hepatomegaly was thought to be due to anemia and heart failure, and it disappeared after blood transfusion. After $NaHCO_3$ deficit therapy and blood transfusion, hematocrit increased to 28 and pH was 7.02, Na 129 mEq/L, K 5.2 mEq/L, HCO_3 13.4 mmol/L, BE -14 mmol/L, urea 216 mg/dl, and creatinine 5.6 mg/dl. Oliguria was also present and peritoneal dialysis was planned, but the patient's condition deteriorated, and he died at 56th hour of admission to hospital.

Discussion

Henna is a traditional cosmetic agent and is used worldwide, especially in the Middle East. The active agent in henna is lawsone[2-4]. Although henna low allergenic potential, it has been shown to cause contact dermatitis[2-5]. Henna is not only applied to hands or hair as a cosmetic agent in traditional ceremonies, but is also applied to the body on lesions in the treatment of seborrheic dermatitis or fungal infections. Analgesic, antipyretic and anti-inflammatory effects of henna have been shown in rats[6], which may account for its use as a medication; however, its application over the body or in newborns is rare.

In a study from Sudan, Sir Hashim et al.[8], presented 31 cases who were hospitalized due to henna intoxication. All cases developed severe angioneurotic edema, and emergency tracheostomy was required for 15 cases due to airway obstruction. Acute renal failure occurred in five cases, and all cases recovered after peritoneal dialysis. However, 13 deaths occurred within 24 hours of presentation.

Munday et al.[1], in a study from New Zealand, showed that lawsone, the active agent of henna, may cause hemolysis in a dose-dependent manner, has a nephrotoxic effect, and may cause tubular necrosis and an increase in urea and creatinine levels[1]. It is known that percutaneous henna application may cause hemolysis in G6PD-deficient red blood cells, but few cases have been reported in literature[3-4]. G6PD is an important X-linked enzyme deficiency at the pentose phosphate pathway. Drugs, infections, nutriments or oxidizing agents may cause nonspherocytic hemolytic anemia in G6PD enzyme-deficient patients. In our case, no medication, nutriment or infection that could cause hemolytic anemia in G6PD deficiency was determined, and hemolysis was thought to be due to henna application to a G6PD enzyme-deficient infant. Acute renal failure seemed to be a result of the nephrotoxic effect of the henna. Although anti-inflammatory, antipyretic and analgesic effects of henna have been documented, in most regions, as in our country, henna is widely used as a traditional cosmetic agent. However, it has been shown to be nephrotoxic and cytotoxic, and may cause cantact dermatitis, hemolytic anemia, and hyperbilirubinemia in the newborn, effects which may cause severe problem. Regional health education programs should be planned in common G6PD enzyme-deficient regions in order to prevent henna application and resultant hemolysis in G6PD enzyme-deficient cases.

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Antenatal diagnosis of postductal coarctation of the aorta A Case Report

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SUMMARY: Öztunç F, Eroğlu AG, Aksoy F, Saltık İL, Turan A. Antenatal diagnosis of postductal coarctation of the aorta: a case report. Turk J Pediatr 2001; 43: 67-69.

Fetal echocardiography can be used to detect congenital heart disease prenatally with a high degree of accuracy, and complex heart malformations have also been clearly described in the fetus. However, it is difficult to diagnose correctly or to exclude definitely aortic coarctation by fetal echocardiography. A 23-year-old woman was referred for fetal echocardiographic examination at 21 weeks' gestation after discovery of hydrops fetalis (nonimmune) on an obstetric ultrasound examination. Aortic isthmus appeared hypoplastic with a diameter ≤3rd percentile for gestational age. There was a narrowing within the descending aorta immediately distal to the origin of the ductus arteriosus. Color flow imaging demonstrated acceleration and turbulent flow and the peak pressure gradient was measured 83 mmHg by continuous wave Doppler in the same area. The pregnancy terminated in spontaneous abortion at 22 weeks' gestation. The fetus was stillborn. The autopsy findings confirmed the prenatal diagnosis. We conclude that together with the quantitative estimation of the aortic arch, color Doppler and continuous wave Doppler are helpful in diagnosis and estimation of the pressure gradient.

Key words: echocardiography, fetus, coarctation.

Fetal echocardiography can be used to detect congenital heart disease prenatally with a high degree of accuracy, and complex heart malformations have also been clearly described in the fetus[1]. However, a growing body of evidence has shown that it is difficult to diagnose correctly or to exclude definitely aortic coarctation by fetal echocardiography, even though there might be a high index of suspicion for the diagnosis in the presence of ventricular diameter imbalance or aortic arch hypoplasia [2-5].

We present the in utero echocardiographic features of a patient with severe postductal coarctation of the aorta and nonimmune hydrops.

Case Report

A 23-year-old woman, gravida 4, para 1, was referred for fetal echocardiographic examination at 21 weeks' gestation after discovery of hydrops fetalis (nonimmune) on an obstetric ultrasound examination. The first and second pregnancy had terminated spontaneously and both fetuses had been stillborn. Fetal echocardiography during those pregnancies and postmortem examinations had not been done. The fetal echocardiography in our case was performed with a 3.5 MHz transducer interfaced with an Acuson Sequoia C 256 ultrasound system. The fetus was found to have hydrops with marked ascites and pericardial effusion (Fig. 1). The right ventricle/left ventricle ratio was normal and the pulmonary artery/aorta ratio was above the normal range. The ascending and descending aortae were normal in size but the aortic isthmus appeared hypoplastic with a diameter ≤ 3rd percentile for gestational age (Fig. 2). A contraductal shelf was not visible. There was a narrowing within the descending aorta immediately distal to the origin of the ductus arteriosus. Color-flow imaging demonstrated acceleration and turbulent flow (Fig. 3), and the

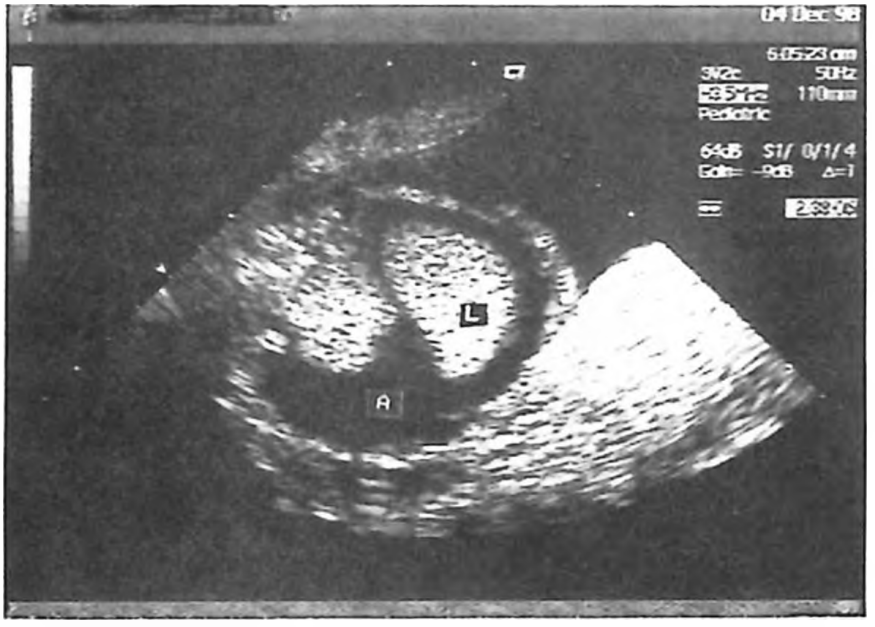

Fig. 1. Horizontal section across the fetal abdomen shows marked ascites. A: ascites; L: liver; S: spleen.

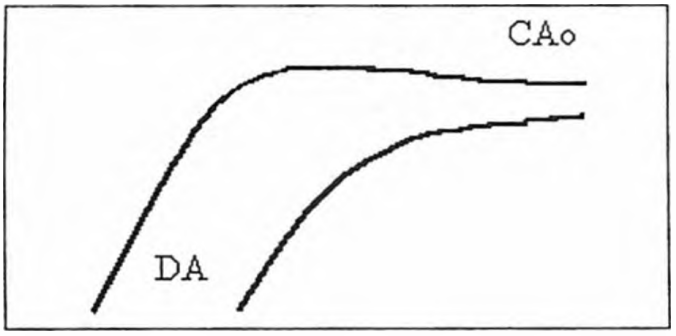

Fig. 2a. Color Doppler flow mapping shows turbulent flow in the coarctation area. CAo: coarctation of the aorta: DA: descending aorta.

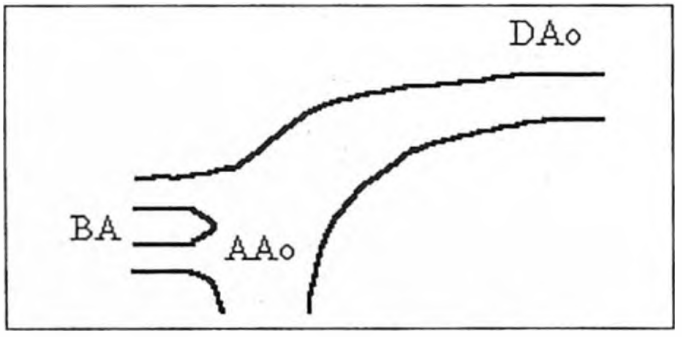

Fig. 2b. Image of dilated brachiocephalic arteries. AAo: ascending aorta: BA: brachiocephalic arteries; DAo: descending aorta.

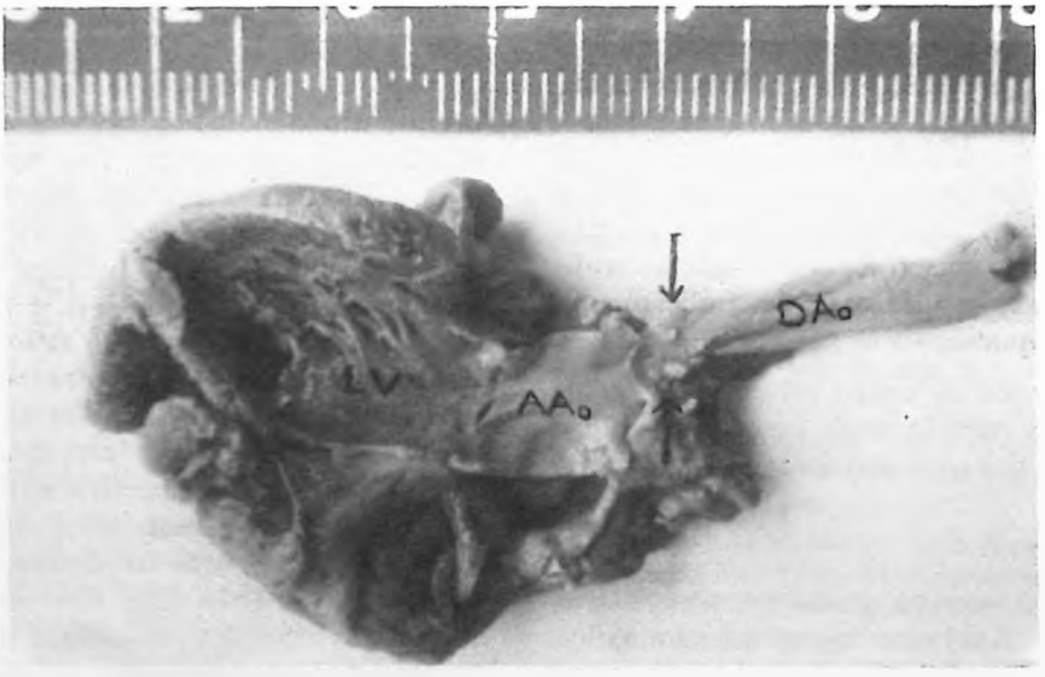

Fig. 3. Necropsy of the fetal heart shows postductal coarctation of the aorta.

peak pressure gradient was measured 83 mmHg by continuous wave Doppler in the same area. Color Doppler study revealed severe tricuspid regurgitation. The pulmonary valve velocity, the aortic valve velocity and the peak systolic flow velocity in the ductus arteriosus were increased. The diastolic velocity in the ductus arteriosus was normal.

The pregnancy terminated in spontaneous abortion at 22 weeks' gestation. The fetus was stillborn. The autopsy findings confirmed the prenatal diagnosis.

Discussion

Initial reports of antenatal detection of coarctation of the aorta consisted of isolated cases within several large series directed toward the in utero diagnosis of congenital heart disease[1]. In these earlier studies, the diagnosis of coarctation was based primarily on the two dimensional echocardiographic appearance of the arch at the site of the contraductal shelf and the accompanying area of the distal aortic arch hypoplasia[1]. Others[2-4] emphasized associated findings that might provide a clue to in utero diagnosis of aortic coarctation. A greater than usual discrepancy in ventricular size favoring the right ventricle and an increase in pulmonary artery size relative to the aorta were suggested by some investigators[2-4]. By spectral Doppler echocardiography, increased tricuspid valve flow velocities and decreased aortic flow were other in utero findings associated with coarctation. However, all of these are indirect observations and are not specific for this condition although they are consistent with present theories of the pathogenesis of aortic coarctation. Recent reports have emphasized quantitative hypoplasia of the isthmus, and transverse arch has been the most consistent observation and, therefore, the most definitive antenatal sign of postnatal coarctation[5].

In our case, there was a narrowing within the descending aorta immediately distal to the origin of the ductus arteriosus. The color-flow imaging demonstrated acceleration and turbulent flow and the peak pressure gradient was markedly increased by continuous wave Doppler in the coarctation area. Hypoplasia of the aortic isthmus and increased pulmonary artery size relative to the aorta were other in utero findings associated with coarctation.

When all the echocardiographic features of coarctation are present in early pregnancy, the diagnosis is highly likely to be correct and the outlook for postnatal survival is poor[4]. The mortality in these series is 64 percent in continuing pregnancies where the diagnosis was made before a gestational age of 24 weeks[4]. The prognosis of nonimmune hydrops in general is poor, with 82 percent mortality, and the atrioventricular valve regurgitation makes the prognosis even poorer[8]. This pregnancy terminated in spontaneous abortion at 22 weeks' gestation, and the fetus was stillborn.

We conclude that together with the quantitative estimation of the aortic arch, color Doppler and continuous wave Doppler are helpful in the diagnosis and estimation of the pressure gradient.

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Pseudohypoparathyroidism type IA and II with severe neuropsychic manifestations

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SUMMARY: Kutílek Š, Kabíček P, Nedvídková J, Bayer M. Pseudohypoparathyroidism type Ia and II with severe neuropsychic manifestations. Turk J Pediatr 2001; 43: 70-75.

Pseudohypoparathyroidism (PHP) is characterized by unresponsiveness of target tissues to the biological actions of the parathyroid hormone (PTH), with resulting hypocalcemia and hyperphosphatemia, despite the elevated serum levels of PTH. PHP is divided into types Ia, b, c and II, depending on the presence of Albright's hereditary osteodystrophy (AHO), defective urinary excretion of phosphate (U-P) and response in urinary excretion of cyclic adenosine monophosphate (U-cAMP) after the administration of exogenous PTH. Patients with PHP might exhibit various manifestations of neuropsychic disturbances. We present two boys, aged 14 and 16 years, both with paresthesia, anxiety and epilepsy; the former patient also suffered from mild mental retardation. In both patients, hypocalcemia and hyperphosphatemia together with increased serum levels of PTH suggested the diagnosis of PHP. After administration of exogenous PTH (Ellsworth-Howard test), there was a drop in U-P in both patients, while U-cAMP was decreased in the first patient and increased in the second one, thus confirming the diagnoses of PHP Ia and II, respectively. Neuropsychic disturbances and epilepsy resolved completely in both patients after treatment with calcium and dihydrotachysterol. Evaluation of calcemia and phosphatemia should be mandatory in all patients with neuropsychic disorders. Ellsworth-Howard test remains a useful tool in the differential diagnosis of PHP.

Key words: hypocalcemia, parathyroid hormone, pseudohypoparathyroidism, epilepsy.

Pseudohypoparathyroidism (PHP) is represented by a heterogeneous group of disorders, whose common feature is resistance to biological actions of the parathyroid hormone (PTH). Most patients with PHP are hypocalcemic and hyperphosphatemic, despite elevated concentrations of PTH in plasma. Clinical features and location of the putative defect causing hormone resistance permit separation of PHP in types I and II, the former divided into subtypes a, b and c[1-3]. PHP types I and II are distinguishable by different responses in urinary cyclic-adenosine monophosphate (U-cAMP) after administration of exogenous PTH (Ellsworth-Howard test)[1-3]. Although it is possible to provide proper treatment without differentiating between the various types of PHP, genetic counseling and full understanding of the rare forms of these syndromes require testing of renal responsiveness to PTH[1,3]. We report two boys with severe neuropsychic disturbances together with hypocalcemia and hyperphosphatemia, where diagnosis of PHP types Ia and II was established. The neuropsychic disorders resolved after correction of calcemia.

Case Reports

Case 1

A 14-year-old boy had been treated unsuccessfully since the age of 11 years for grand mal epilepsy, mild mental retardation (IQ = 67) and manifest tetany. Due to accidentally revealed hypocalcemia (ionized Ca 0.7 mmol/L, ni 1.0-1.15 mmol/L) and hyperphosphatemia (2.83 mmol/L, n: 0.8-1.6 mmol/L), he was referred to our department. The boy had a very round face without any other dysmorphic features or deformities of the

extermities. On admission his height was 174 cm (+0.5 SD) and weight 60 kg (+0.27 SD). The serum concentrations of natrium, potassium and magnesium were within normal reference ranges, as were the serum activities of alkaline phosphatase and aminotransferases. Computed tomography (CT) of the brain revealed calcifications in the basal ganglia (Fig. 1). X-ray of the chest and echocardiography were normal, without any signs of calcification. The X-ray of his hand revealed normal bone age and no signs of brachymetacarpia. Treatment was immediately started with perorally administered calcium citrate (1000 mg Ca/day) and dihydrotachysterol (2 x 0.5 mg/day). The serum levels of ionized calcium reached 1.1 mmol/L within six days upon the initiation of the therapy. No further grand mal seizures occurred. The serum levels of intact parathyroid hormone (S-PTH) were repeatedly measured by radioimmunoassay (RIA) after the initiation of the treatment and always exceeded the upper reference range (14 and 14.7 pmol/L, n: 0.7-5.5), suggesting the diagnosis of PHP. Therefore, a modified Ellsworth-Howard test was performed to distinguish the type of PHP[2]. After the first morning void, the fasting patient ingested 200 ml of water and urine was collected, both one hour prior to the 10 minute infusion of 200 units of synthetic polypeptide hormone consisting of the 1-34 fragment of human PTH (Parathar-Rorer Pharmaceuticals), and at the 0-30 minute and 30-60 minute postinfusion time periods. Blood was collected prior to the Parathar infusion and at 10 and 60 minutes' postinfusion for the evaluation of serum phosphate (5-P) and creatinine. The urinary phosphate (U-P), creatinine (U-Cr) and U-cAMP excretion was measured. The U-cAMP results were corrected for U-Cr. The tubular maxiumm of phosphate/glomerular filtration rate (TmP/GFR) was obtained using a relationship derived by Walton and Bijvoet[4]. There was a decrease in both U-cAMP and U-P levels, with increased TmP/GFR (Table I), therefore the diagnosis of PHP Ia was established. The boy has been followed in our department for four years, receiving daily doses of 1000-1500 mg of calcium and 1 mg of dihydrotachysterol. Currently, he is in a good state of health, both physically, with no more seizures, and mentally (IQ = 84).

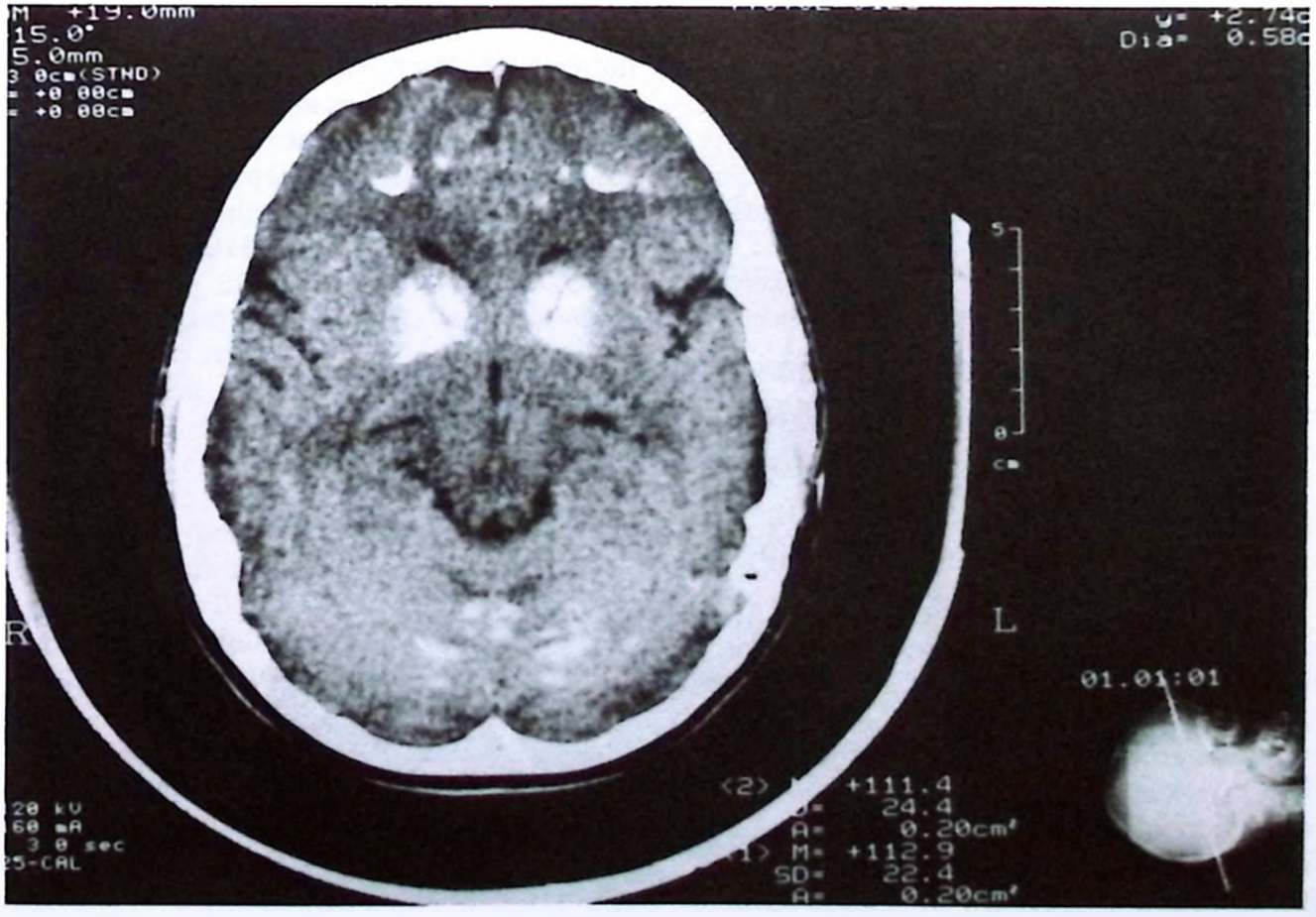

Fig. 1. Calcifications in basal ganglia as revealed by CT.

Table I. Changes in TmP/GFR (mmol/L) and U-cAMP (nmol/mg of creatinine) During the First Hour After Infusion of PTH (1-34)

	Baseline		30 minutes		60 minutes	
Time	TmP/GFR	U-cAMP	Tmp/GFR	U-cAMP	TmP/GFR	U-cAMP
Case 1	2.90	5.90	4.85	0.80	4.45	0.60
Case 2	3.10	4.10	3.50	66.80	3.30	42.20

TmP/GFR : tubular maximum of phosphate/glomerular filtration rate.
U-cAMP : urinary cyclic-adenosine monophosphate.
PTH : parathyroid hormone.

Case 2

A 16-year-old boy with normal physical appearance was admitted with history of recurrent faintings since the age of 11, and an intractable pain of the cervical spine. Those symptoms were erroneously diagnosed as epilepsy and cervicocranial syndrome. Calcemia was never assessed before he reached our department. On admittance, he was pale and exhausted, showed signs of ataxia and manifest tetany, and complained of diplopia, paresthesia, anxiety and severe pain of the neck. Biochemical evaluation revealed severe hypocalcemia (ionized Ca 0.667 mmol/L), hyperphosphatemia (S-P 4.2 mmol/L), hypocalciuria and hypophosphaturia. The serum concentrations of natrium, potassium and magnesium were within normal reference ranges, as were the serum activities of alkaline phosphatase and aminotransferases. Additional abnormal findings included calcification of basal ganglia revealed by computed tomography (Fig. 2) and mild cortical cataract. Abdominal sonogram showed bilateral nephrocalcinosis. There were normal findings on the X-ray of the chest and echocardiography. The boy received immediately intravenous infusion of 10 percent calcium gluconate (1.5 ml/kg/day) and calcitriol (2x0.25 µg/day). Within the first day his state improved dramatically, and all symptoms disappeared within 10 days. The serum concentration of ionized calcium reached the reference level of 1.1 mmol/L on day 8. The intravenous administration of calcium was replaced on the third day by peroral supplementation of calcium citrate (1000 mg Ca/day). S-PTH was measured by RIA before and after the normalization of serum calcium levels and repeatedly exceeded the upper reference range (9 and 10 pmol/L, n: 0.7-5.5). The combination of severe hypocalcemia and elevated S-PTH suggested the diagnosis of PHP. Therefore, the modified Ellsworth-Howard test was performed. There was a decrease in U-P reflected by an increase in TmP/GFR, and a 16-fold increase in U-cAMP after the PTH infusion (Table I). The diagnosis of PHP type II was established in this patient. He has been followed for five years in our department, with an uneventful course, receiving daily doses of calcium (1500-2000 mg) and dihydrotachysterol (2x0.5 mg). No neurologic problems have occurred since the normalization of calcemia.

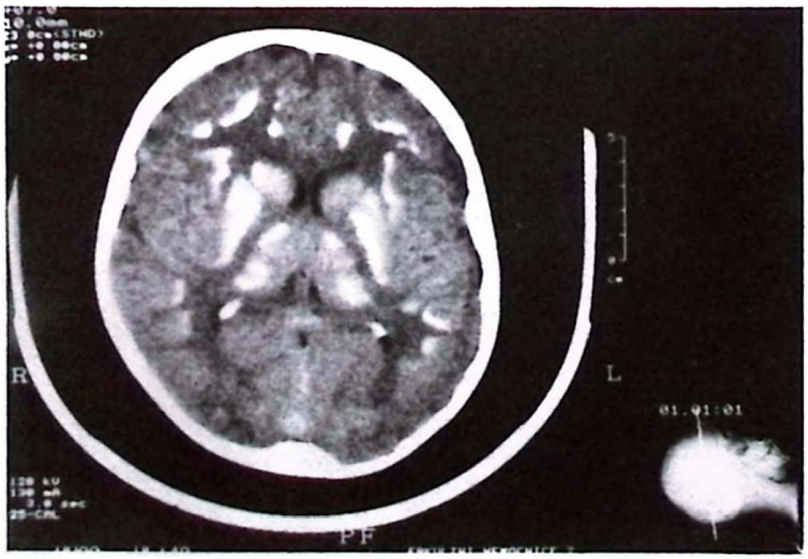

Fig. 2. Calcifications in basal ganglia as revealed by CT.

Parents of both patients had normal physical appearance and normal calcemia and phosphatemia.

Discussion

Parathyroid hormone plays an essential role in the maintenance of calcium and phosphate homeostasis by mobilizing calcium from bone to the extracellular fluid and by increasing urinary phosphate excretion and enhancing renal calcium reabsorption. Furthermore, PTH stimulates conversion of 25-OH-vitamin D to 1,25 $(OH)_2$ vitamin D, thus controlling intestinal calcium absorption[1,3].

Under physiological conditions, the PTH binds to its specific cell-surface receptor. Activated receptor interacts with one or more members of a family of guanine nucleotide binding proteins (G-proteins) to facilitate release of guanosinediphosphate (GDP) and binding of guanosinetriphosphate (GTP). GTP-bound G-proteins in turn interact with specific effectors that catalyze formation of intracellular second messengers, including cAMP, which mediates the phosphaturic and bone resorptive actions of PTH and is the most probable second messenger of PTH action on 1-alfa hydroxylase. The formation of cAMP from ATP and Mg is catalyzed by adenyl cyclase, which is under dual regulation by distinct G proteins, both stimulatory (Gs) and inhibitory (Gi)[1,5].

Defects at different sites in the PTH response pathway result in end-organ resistance to PTH, and are responsible for distinct foms of PHP. Defects proximal to cAMP production result in PHP type I, while defects distal to cAMP generation result in PHP type II. Biochemical abnormalities in all types of PHP include hypocalcemia, hyperphosphatemia and hypophosphaturia with normal renal function. On physical examination, patients exhibit symptoms of neuromuscular irritability secondary to hypocalcemia, such as paresthesia, latent and manifest tetany, and seizures. Mood disorders may be present[6]. Other features include dental defects (enamel hypoplasia), cataracts and calcifications in subcutaneous tissue, in basal ganglia and in the myocardium[1,3,5,7-9]. Hypocalcemia may not be evident immediately in the neonatal period, but usually becomes symptomatic within the first ten years of life, sometimes even later[9,10].

Pseudohypoparathyroidism type I can be further divided in PHP type Ia, Ib and Ic. PHP type Ia is a familial form with Gs protein deficiency which is maped to the distal long arm of chromosome 20. Inheritance is autosomal dominant[1,11]. Clinical features include Albright's hereditary osteodystrophy (AHO) with short stature, obesity, rounded face, short stubby fingers, and shortened metacarpals and metatarsals[1,3,8], all of which may be the result of premature skeletal maturation and closure of epiphyses[12]. Other symptoms include mild mental retardation, headaches, and olfactory and sensorineural hearing dysfunction[1,3], which might be attributed to chronic hypocalcemia. Several other endocrinopathies including growth hormone deficiency and resistance to thyrotropin, gonadotropin and glucagon have been described in patients with PHP Ia[1,3,13] and have been postulated as results of Gs protein deficiency[1,13,14]. Soft tissue calcifications and mental deficiency are typical signs of PHP Ia[5]. However, in some patients with PHP Ia, many of these features may be subtle or absent[14].

Pseudopseudohypoparathyroidism (PPHP) consists of AHO with normal biochemical values, including serum calcium (S-Ca) and S-PTH. Genetic linkage between PHP Ia and PPHP has been proposed. concerning variable expressivity of the Gs protein deficiency[1].

In PHP type Ib, physical appearance is normal and resistance is limited to PTH, with similar biochemical properties and similar neurologic and mental symptoms as in PHP Ia, but with normal Gs protein activity[5]. Round face, soft tissue calcifications, brachymetacarpia and mental deficiency never occur in PHP Ib[5]. PHP Ib may be both familial and sporadic[1,3,5]. Pseudohypoparathyroidism type Ic is represented by AHO, generalized hormone resistance, normal Gs protein activity and hypocalcemia. Inheritance and molecular defect remain unknown[3]. PHP Ia, b, c are all characterized by impaired phosphaturic and U-cAMP response to exogenous PTH.

Pseudohypoparathyroidism type II is characterized by impaired phosphaturic response and normal U-cAMP response after the application of exogenous PTH. The physical appearance is normal in 50 percent of the patients with PHP II. Soft tissue calcifications, small stature,, obesity, mental deficiency and seizures might occur in 50 percent of patients with PHP II, while round face has never been observed[5].

A case of PHP II associated with Bartter's syndrome has been reported[15]. PHP II is considered a rare acquired disease[1,3]. PHP types I and II have been described in different family members[6]. The clinical findings as revealed by a multicenter study of 71 children with PHP[5] are summarized in Table II.

Findings similar to PHP II have been described in some patients with severe vitamin D deficiency, as U-cAMP was normal and U-P defective after PTH infusion[16]. Clinical studies have reported end-organ resistance to PTH action in hypocalcemic patients with magnesium deficiency, with either normal or blunted U-cAMP response to exogenous PTH[17]. The bone remodeling response to PTH is relatively intact in many patients with PHP, however, bone resorption may exceed bone formation, resulting in osteopenia, especially in patients with PHP Ib[14,18,19]. Treatment of all types of PHP is lifelong and rests in the application of calcium and vitamin D, while closely monitoring calcemia and calciuria to avoid under or over-treatment[1].

Table II. Clinical Findings in 71 Children with PHP

Clinical findings	PHP Ia (n = 45)	PHP Ib (n = 8)	PHP Ic (n = 6)	PHP II (n = 2)	PPHP (n = 10)
Seizure %	38	0	66.7	50	0
Subcutaneous calcification %	42.3	0	16.7	50	50
Soft tissue calcification %	41	0	66.7	50	0
Brachymetacarpia %	86.7	0	66.7	0	80
Round face %	82.3	0	66.7	0	90
Height < SD %	38.4	0	0	50	88.9
Weight > SD %	48.5	0	40	0	0
Weight excess %	64	0	40	50	12.5
Mental deficiency %	40	0	40	50	40

Adapted from Marguet et al.[5].
PHP : pseudohypoparathyroidism.
PPHP : pseudopseudohypoparathyroidism.

The differential diagnosis of PHP types I and II rests in the evaluation of U-P and U-cAMP after intravenous application of 200 units of exogenous PTH 1-34. While there is no increase in U-P (therefore no decrease in TmP/GFR) in either PHP I or II, there is at least a six-fold increase in U-cAMP (nmol/mg of creatinine) in PHP type II 30 minutes after the PTH infusion, with no increase of U-cAMP in PHP Ia, or b[2] (Table III).

Table III. Differential Diagnosis of PHP

Diagnosis	AHO	S-Ca	S-P	S-PTH	Gs protein activity	U-P	U-cAMP (after PTH)
PHP Ia	Yes	Low	High	High	Low	Low	Low
PHP Ib	No	Low	High	High	Normal	Low	Low
PHP Ic	Yes	Low	High	High	Normal	Low	Low
PHP II	No	Low	High	High	Normal	Low	High
PPHP	Yes	Normal	Normal	Normal	Low	Normal	High
HP	No	Low	High	Low	Normal	Low	High

OH : Albright's hereditary osteodystrophy.
S-Ca : serum calcium.
S-P : serum phosphate.
S-PTH : serum parathyroid hormone.
Gs : G (stimulatory).
U-P : urinary phosphate.
U-cAMP : urinary cyclic-adenosine monophosphate.
PHP : pseudohypoparathyroidism.
PPHP : pseudopseudohypoparathyroidism.
HP : hypoparathyroidism.

Case 1 had a rounded face, intracerebral calcifications, mental deficiency, seizures, hypocalcemia, hyperphosphatemia, elevated S-PTH and blunted response in U-P and U-cAMP after the PTH infusion, all compatible with the features of PHP Ia[5] (Tables I-III).

In Case 2, normal physical appearance, severe hypocalcemia and hyperphosphatemia, together with neuropsychic symptoms, cataracts and soft tissue calcifications in the basal ganglia and kidneys, high S-PTH and physiological U-cAMP response to infusion of exogenous PTH pointed to the rare diagnosis of PHP II. In both patients, the S-PTH remained elevated even after the correction of calcemia, thus ruling out vitamin D deficiency. Serum magnesium concentrations were normal in both patients. There were no signs of subcutaneous or cardiac calcifications.

In conclusion, we reported two patients with PHP who were originally erroneously diagnosed as epilepsy. This resolved after the normalization of calcemia. Therefore, the evaluation of calcemia should be mandatory in all patients with various neurologic and mental disorders and psychomotor retardation. Elevated S-PTH in the presence of hypocalcemia suggests the diagnosis of PHP. The modified Ellsworth-Howard test remains the most useful tool in arriving at such a diagnosis and helps to differentiate between PHP types I and II.

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Possible asymptomatic carrier of salmonella typhimurium in the preputium: A case report

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Salmonella infections lead to several clinical syndromes such as acute gastroenteritis and bacteremia. Less frequent manifestations are extraintestinal focal infections, including urinary tract infections. A 10-month-old boy was admitted to the hospital with recurrent urinary tract infections treated with antibiotics. Salmonella typhimurium was isolated from the urine samples obtained in urine bags. The organism was also grown from a suprapreputial swab, but was not grown in the suprapubic urine specimen. Renal ultrasonography, intravenous pyelography and voiding cystourethrogram were found normal. The patient was then circumcised, following with no uropathogens were isolated from the urine. It is believed that circumcision not only prevented further urinary tract infection and protected the case from becoming a carrier of Salmonella typhimurium, it also halted a possible spread of Salmonella infection to the general public.

Key words: Salmonella typhimurium, antibiotic resistant, preputium, circumcision.

Salmonella infections develop worldwide[1]. Several distinct clinical syndromes can occur in children depending on host factors and specific serotype involved[1]. Although acute gastroenteritis and bacteremia are the most common presentations[1,2], less frequent manifestations are extraintestinal focal infections, including urinary tract infections[3-5]. Chronic enteric state is more common; however, urinary tract carrier state may also occur, though rarely[3,5]. Chronic urinary carriers may continue to excrete a large number of bacilli in their urine for months or years[5]. Chronic carrier state of the urinary tract is supposed to occur in individuals with structural or functional abnormalities of the urinary tract[4]. In addition, many studies have reported that uncircumcised boys have an increased risk of urinary tract infections[6,7].

Isolation of Salmonella from urine is reported as a rare event, even in areas endemic for this infection[4]. To our knowledge, there is no report about the carrier state of Salmonella in the preputium.

We present an infant who was a possible asymptomatic carrier of Salmonella typhimurium in the preputium.

Case Report

A 10-month-old boy was admitted to the hospital with recurrent urinary tract infections. Three episodes of urinary tract infections with coagulase-negative staphylococci at the age of four, five and six months were treated with antibiotics due to antibiotic susceptibility tests. He also had phimosis and balanitis on these three occasions. Renal sonography, intravenous pyelography and voiding cystourethrogram were found normal. To prevent the recurrences of urinary tract infection, nitrofurantoin (2 mg/kg/day) was given once a day at bedtime for two months. At the age of 10 months, Salmonella typhimurium was isolated from the urine samples obtained in urine bags on three consecutive occasions during a month. The organism was also grown from a subpreputial swab, but was not grown in the suprapubic urine specimen.

It was then learned that the patient and his mother had acute gastroenteritis for two days, when the child was three months old. They had no stool culture and both recovered without any treatment.

Routine urine analysis and serum concentrations of blood urea nitrogen, creatinine and immunoglobulins were normal. Widal's reaction was negative. No pathogenic organism was found in the stool of the patient or from his family members on three consecutive tests.

Urine samples were collected by sterile perineal bags and 10 µl of specimens were inoculated onto blood agar and eosin methylene blue (EMB) agar plates. The specimens were cultured at 35 °C and were interpreted following an incubation period of 18 to 24 hours. Salmonella species were isolated $4x10^4$, $3x10^5$ and $5x10^4$ CFU/ml on blood agar and EMB agar plates on 1st, 3rd, and 8th day of three consecutive urine specimens. This strain was identified by conventional tests and Api 20 E (bioMerieux) and serogrouped polyvalent antisera (Difco Laboratories), primarily. Further identification and serotyping of this strain was performed, and it was serotyped as Salmonella typhimurium 1,4,5,12:i:1,2. Antibiotic susceptibility testing was done by disc diffusion methods on Mueller-Hinton agar with commercial antibiotic discs (Oxoid) according to the recommendation of the National Committee for Clinical Laboratory Standards[8]. These isolates were resistant to ampicillin, ceftriaxone, cefotaxime, cefoperazone and susceptible to trimethoprim-sulfamethoxazole, chloramphenicol, tetracycline, cefoxitin and nitrofurantoin. The extended-spectrum beta-lactamases (ESBL) were performed by double-disc synergy test with discs of cefotaxime/ceftazidime and amoxicillin-clavulanic acid, and were positive.

Cefoxitin (30 mg/kg/day) was administered intramuscularly due to antibiotic susceptibility test. After the antibiotic treatment, Salmonella typhimurium was still isolated from the urine. The patient then underwent circumcision at the age of 14 months at the Department of Pediatric Surgery. Three postoperative urine cultures were normal. During the one-year follow-up after circumcision, no uropathogens were isolated from the urine.

Discussion

Isolation of Salmonella from the urine and urinary tract carrier state occur only rarely[3,5]. We could not find another reference in the literature to the isolation of this organism from the subpreputial area. This patient was noteworthy for localization of Salmonella typhimurium in the preputium. Although it is suggested that the patient was one of solely subpreputial carriage because of negative stool cultures, it is also well known that the excretion of the organism is intermittent and may be missed even on three consecutive stools. The accepted definition of a Salmonella 'chronic carrier' is someone harboring the organism for more than one year[1,2,5]. It is hard to describe the patient as a chronic carrier of Salmonella, because it was isolated from the urine for only a month. It is also difficult to determine the primary source of Salmonella typhimurium in this patient. It may be speculated that the source of the organism was the feces of the infant or his mother, since there is a strong association of periurethral flora with stool flora. Many studies have reported that uncircumcised boys are at an increased risk for urinary tract infection[5,6]. Because our patient was an uncircumcised boy with phimosis, we thought the foreskin was the most important risk factor. Chronic carrier state of the urinary tract is supposed to occur in individuals with structural or functional abnormalities of the urinary tract[4]. This boy had no urogenital abnormalities on renal imaging and no other factors predisposing to Salmonella in the urine, such as renal tuberculosis, Schistosomal infections or immunosuppression. Functional abnormalities and/or antibiotic therapies for recurrent urinary tract infections might play a role in the occurrence of the carrier state. The role of sterile perineal collectors in the diagnosis of urinary tract infections is controversial. Isolation of bacteria in amounts of $4x10^4$, $3x10^5$, $5x10^4$ CFU/ml quantitatively in bag specimens and no growth in suprapubic aspiration suggest that false positive results may be caused by sampling in bag specimens. The microbiological quantitative count does not seem to related to carrier state. However, it may be better for urine collectors to resample the urine by suprapubic aspiration technique in such positive cases[9].

Salmonella typhimurium is the most common Salmonella species isolated in Turkey[2,10]. Unfortunately, an increased multiple antibiotic resistance to S. typhimurium has been reported[10-13]. ESBL test is made to determine the existence of the extended spectrum beta-

lactamase enzyme. Even when the ESBL-positive species are evaluated as in vitro effective, they are accepted as resistant to all large spectrum penicillins, cephalosporins and monobactams, except cefamycine and carbapenems. Furthermore, transfer of this resistance from ESBL-positive species to other bacteria by conjugation may result in an increase of resistant species[14-15]. Vahaboğlu et al.[11] reported that ESBL was found as PER-1 beta-lactamases in S. typhimurium strains in Turkey. S. typhimurium strain isolated from our patient produced ESBL and was susceptible to chloramphenicol, gentamicin, tobramycin, amikacin, and trimethoprim-sulfamethoxazole. It is obvious that Salmonella infection is an important epidemiological problem. Asymptomatic urinary excretion of nontyphoidal Salmonella is significant for its potential transmission of the infection to other individuals[4]. Although patients who excrete nontyphodial Salmonella usually do not need antimicrobial therapy, public health implications stress the need for treatment of the asymptomatic carrier of Salmonella typhi[3]. This child did not respond to appropriate medical therapy alone. Circumcision was successful in eliminating Salmonella typhimurium from the preputium. During the one-year follow-up period after circumcision, no uropathogens were isolated from the urine of the patient.

In conclusion, since circumcision was helpful in our case in preventing urinary tract infection with Salmonella typhimurium, it may represent an adjunctive treatment for infants who are asymptomatic subpreputial carriers.

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The de Barsy syndrome

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SUMMARY: Arazi M, Kapıcıoğlu MİS, Mutlu M. The de Barsy syndrome. Turk J Pediatr 2001; 43: 79-84.

We report a child with de Barsy syndrome, which is a very rare, genetically transmitted clinical entity associated with mental and growth retardation, severe cutis laxa, joint laxity and various ocular and skeletal system findings. The patient was operated to treat her orthopedic disabilities. Typical findings of this case with eight-year follow-up beginning from birth are described and compared with previously reported cases. The main aim of this paper was to describe the diagnostic and therapeutic difficulties of this rarely encountered syndrome.

Key words: de Barsy syndrome, hypermobility, elastin, cutis laxa, children.

The de Barsy syndrome (BS) is rare and one of the progeria syndromes. The first case was reported by de Barsy et al.[1]. Cutis laxa, aged appearance, growth and mental retardation, joint hypermobility, facial grimacing with athetoid movements, severe myopia, cataract, corneal clouding, large helices and various orthopedic manifestations including scoliosis, dislocation of the hip joint, and severe foot and hand deformities are the main striking features[1-5]. Here we report a girl who had the characteristic features of BS.

Case Report

The patient was born in November 1989, as the third child of healthy parents who were first cousins. There were no similar symptoms in the family. The mother had five pregnancies, the second and fourth ending in miscarriages. The patient was born at term and the delivery was normal. Her birth weight was 2400 g (3^{rd}-10^{th} percentile) and length was 47 cm (10^{th} percentile). After the delivery she was admitted to various hospitals because of facial grimacing, eye abnormalities, hypotonia and foot deformities. Congenital dislocation of the right hip was diagnosed and treatment with conservative methods was attempted in another hospital at the age of six months.

She was first admitted to our clinic with unreducible dislocation of the right hip at the age of 18 months. Physical examination revealed wrinkled, thin, translucent skin over all parts of the body; large and low-set helices; sparse and fine hair; and long and narrow face (Fig. 1). Her weight was 9300 g (10^{th} percentile) and length was 75 cm (10^{th} percentile). Her general appearance was aged. She had congenital vertical talus deformity on the right and club foot on the left (Fig. 2). Extreme hyperlaxity of the small joints and bilateral adduction deformity of the thumbs were also observed.

X-ray findings verified dislocation of the right hip joint and vertical talus on the right and club foot on the left. Pulmonary x-ray and abdominal sonography were normal. Ophthalmologic examination revealed bilateral conjunctivitis; the fundus was normal. Neurological examination revealed a moderate muscular hypotonia. The chromosomal analysis and routine blood studies were normal.

For histopathological studies of the skin biopsies, the tissue sample was processed for both T-lymphocyte specific alpha-naphthyl acetate esterase demonstration[6] and elastic fiber staining[7]. Collagen fiber were stained with Crossman's trichrome stain[8]. Plasma cell counts were determined on methyl green-pyronin stained sections using a square ocular micrometer. The elastic fiber of the dermis were observed as extremely reduced in number, shortened, broadened and also frayed in some localized areas (Fig. 3a). Epidermis was rather thin and characterized by hyperkeratosis. Collagen fiber of the dermis were normal (Fig. 3b). There were no histological findings suggesting immunological reactions such as infiltration of T-lymphocytes or increase in plasma cells in the area.

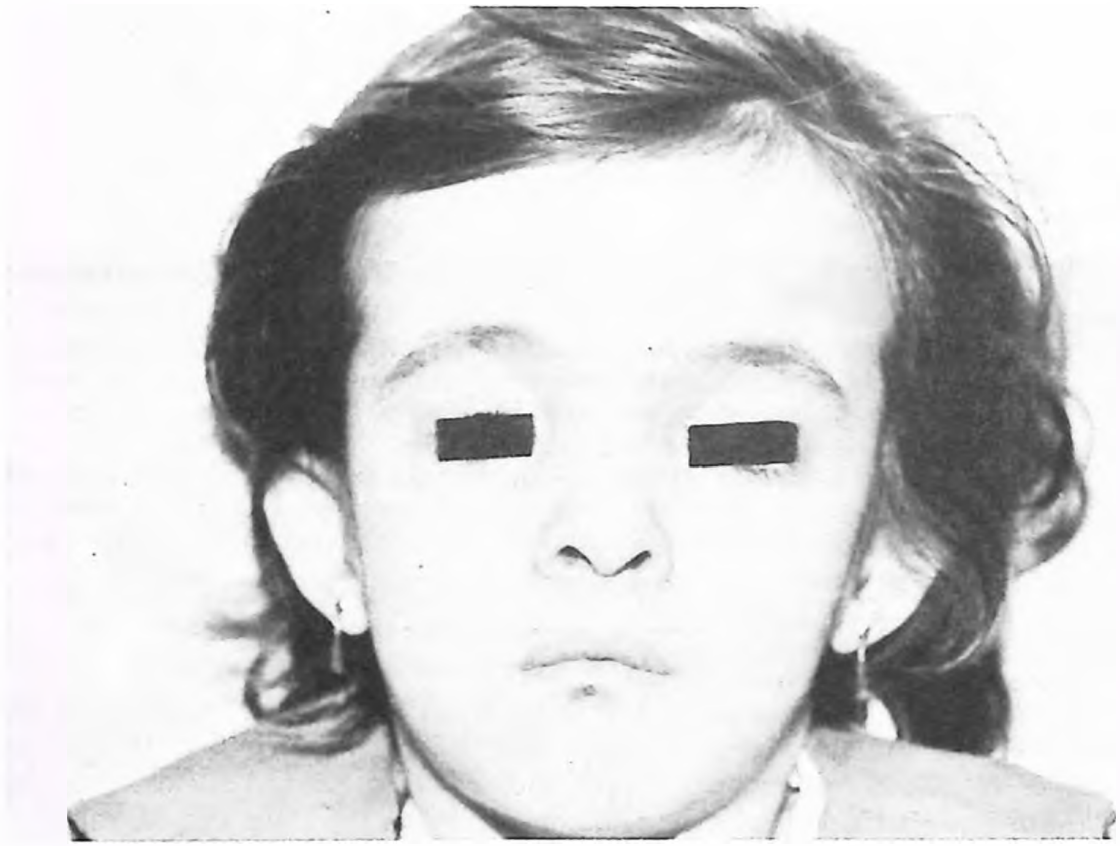


Fig. 1. Typical facial appearance. Note high forehead, large and low-set helices and sparse hair.

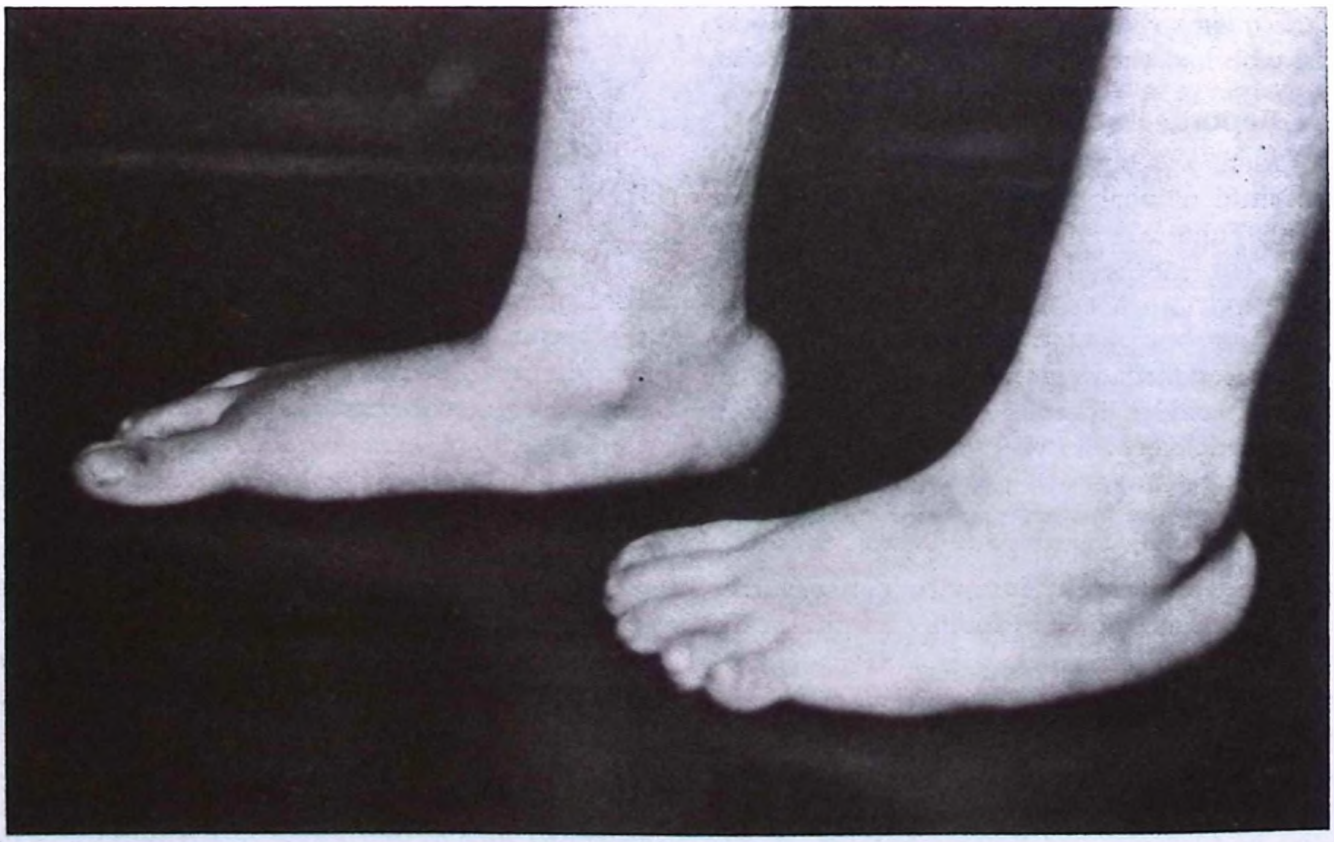
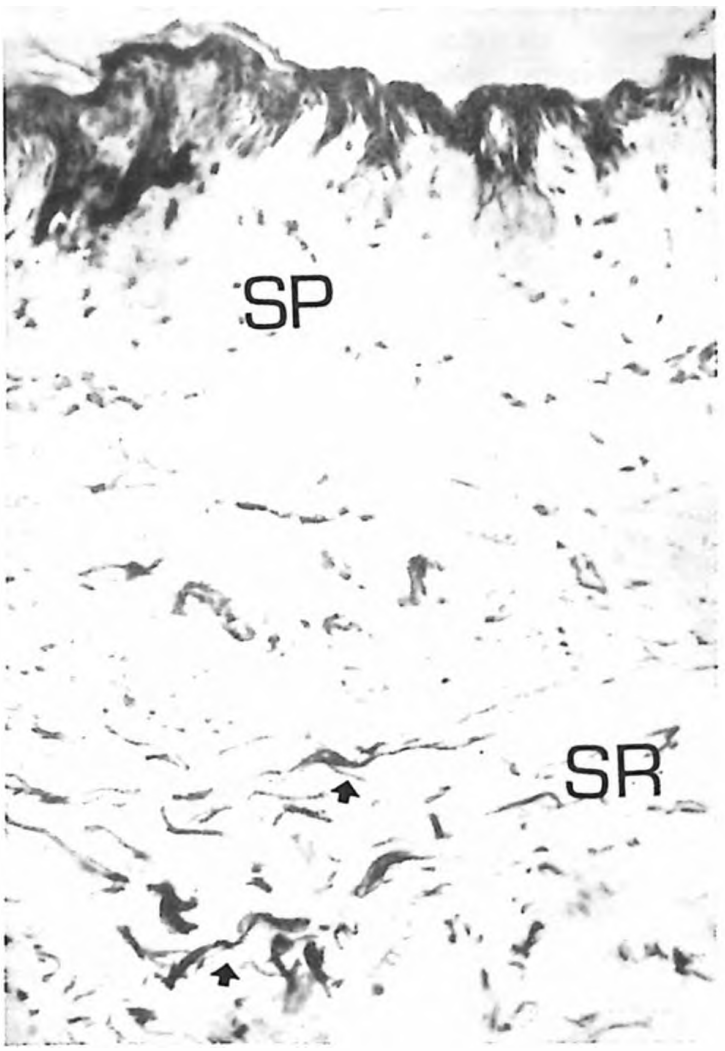


Fig. 2. Convex pes planovalgus deformity of the right foot secondary to vertical talus and club foot of the left can be seen.



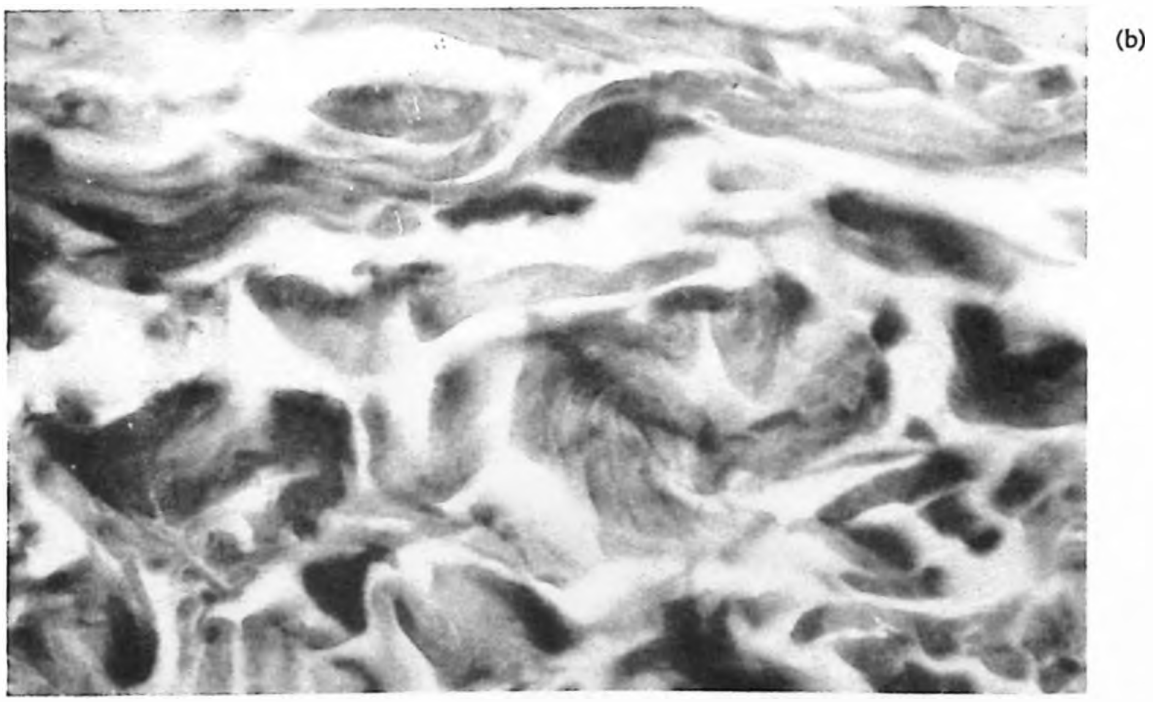
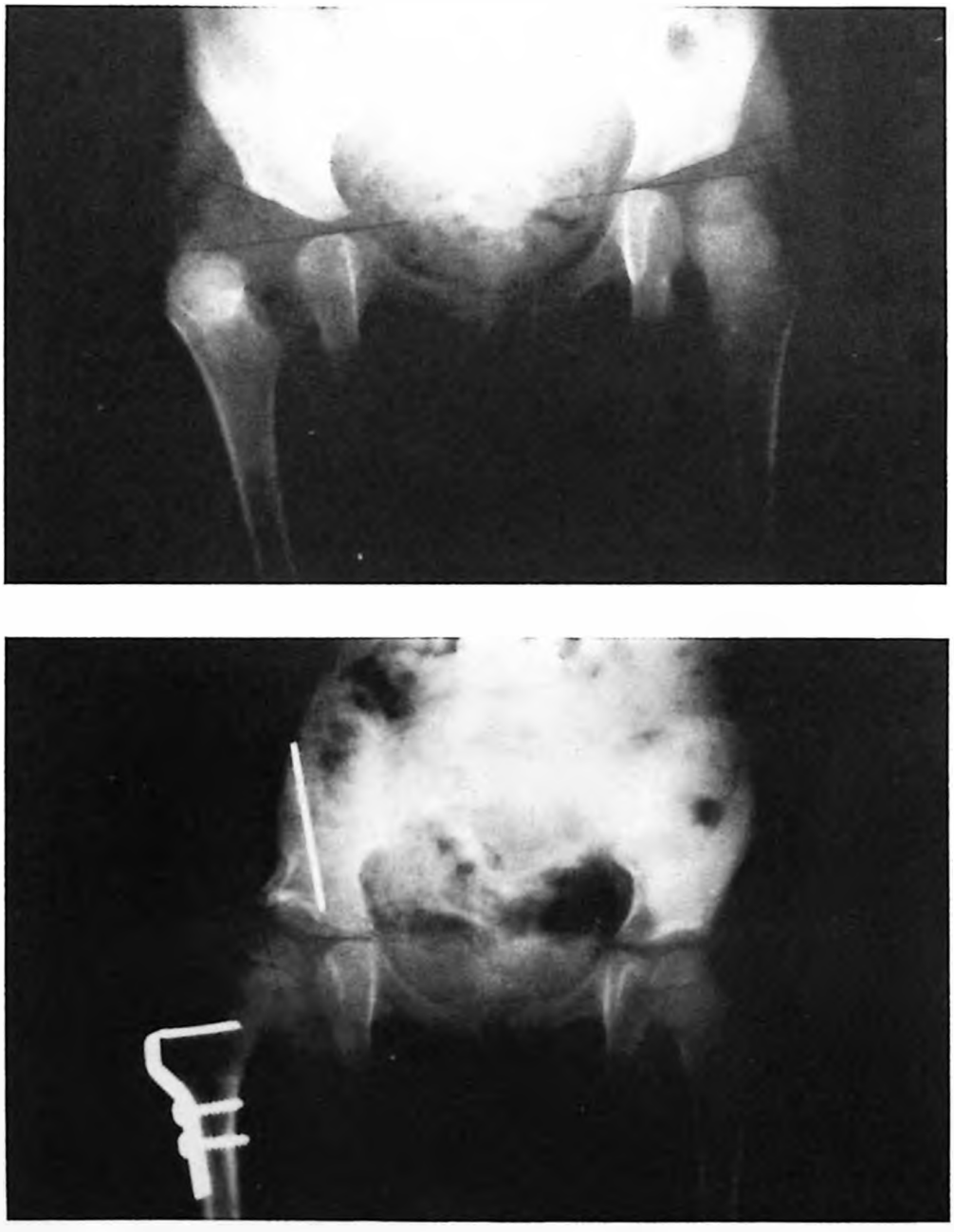


Fig. 3a, b. Histological appearance of the skin demonstrating a marked reduction in the number of shortened and frayed elastic fiber (arrows) in the reticular layer (SR) of the dermis. There were no elastic fiber in either papillary layer (SP) or dermal papillae (Verhoeff's elastic fiber stain, X260), (A); Well-stained thick bundles of Type-I collagen fiber in the reticular layer of dermis (Crossman's trichrome stain, X60) (B).

The patient was treated for her orthopedic disabilities in our clinic. Anterior open reduction and Salter innominate osteotomy were performed at the age of 18 months for redislocation of the previously treated hip. Redislocation was noticed two months later, so we operated the hip again, and re-reduction of the hip with proximal femoral varus-derotation osteotomy was performed. Painless and full range of motion of the hip was observed at 4.5-year follow-up. X-rays showed acceptable reduction (Figs. 4a, 4b). Foot deformities were also treated surgically at the age of three years. Posteromedial soft tissue release was performed for club foot deformity and open reduction of the talonavicular joint with soft tissue release was performed for vertical talus. Since she was too young, a bony procedure such as subtalar arthrodesis was not performed for the vertical talus deformity. At five years of age, moderate residual metatarsus adductus deformity on the left foot was treated with tarsometatarsal and intermetatarsal capsulotomy operation. Mild pes planus on the right foot and minimal forefoot adduction on the left foot were observed, but the feet were painless and functional at the age of six years.



Figs. 4a, b. Initial pelvic radiograph of the patient at the 18th month. Note the unreduced dislocation of the right hip joint (A). Radiographic appearance of the hip joint at the age of six years seen relatively normal after two consecutive operations (B).

At eight years of age, weight was 18 kg (3rd-10th percentile) and height was 117 cm (3rd-10th percentile). Slight residual foot deformities persisted, but she was able to walk without any support. We thus did not plan any further operation for residual foot deformities. Minimal impairment of intellectual status was recorded, and ophthalmologic re-examination at this time revealed severe myopia (right eye: -8.0 dioptri, left eye: -8.0 dioptri) and microcornea in both eyes.

Discussion

To date, 14 cases of BS have been reported in the English literature[1-5,9-11]. It is interesting that five of the previously reported patients with this syndrome were reported from Turkish children. Four cases were from the same Turkish family[9] and the fifth was a six-month-old Turkish boy[11].

The orthopedic manifestations in BS, including dislocation of the hip, vertical talus, scoliosis, hand deformities, and hypermobility of the joints, were described by Stanton et al.[4] in 1994 This was the first detailed study about orthopedic features of the syndrome. Dislocation of the hip was the most commonly reported orthopedic manifestation in previous reports[3,4,11]. Stanton et al.[4] expressed that management of the mentioned deformities are usually complicated. They advised long-term cast application after hip surgery to prevent redislocation of the hip joint because of generalized ligamentous laxity. Our results supported this finding. The presented patient had been unsuccesfully treated for dislocation of the right hip when she was admitted to our institution. Nevertheless, two further operations were required for treatment of the dislocation. She also had a severe club foot deformity and required a second operation for residual deformity.

In previous histopathological studies, elastin structure of the dermis was reported as abnormal in BS[1,3,9,11]. Pontz et al.[11] Reported that the collagen fiber were normal. We had similar findings in our case. The histopathological results confirmed cutis laxa.

Intellectual impairment has been reported in a wide range from severe mental retardation including no speech, athetoid movements, grimacing and generalized hyperreflexia to normal mental status[1-4,5,9,11]. The presented case had slight intellectual impairment; however, she was able to attend primary school at the last examination.

No chromosomal anomaly was reported in all described cases. The presented patient's analysis was also normal. Consanguineous marriages were responsible in some cases and this finding suggested an autosomal reessive inheritance[3-5,9].

Ophthalmologic symptoms are corneal clouding, cataract, esotropia and severe myopia[10,11]. Fundus is usually normal. In our patient, severe myopia, recurrent and persistent conjunctivitis and microcornea were observed. Microcornea has not been reported in previous cases.

The BS should be considered in the differential diagnosis of cutis laxa, in early life. Pediatricians and orthopedic surgeons who have major roles in the management of this syndrome should be alert to this very rare and difficult to treat syndrome.

Acknowledgements

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Sepsis and multiple brain abscesses caused by Salmonella paratyphi B in an infant: Successful treatment with sulbactam-ampicillin and surgical drainage

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SUMMARY: Yıldıran A, Siga E, Baykal S, Ökten A. Sepsis and multiple brain abscesses caused by Salmonella paratyphi B in an infant: successful treatment with sulbactam-ampicillin and surgical drainage. Turk J Pediatr 2001; 43: 85-87.

Abscess formation by Salmonella species is an uncommon but significant manifestation of salmonellosis, because this type of infection has high morbidity and mortality rates and is a potential nosocomial hazard. In infants, history of consumption of contaminated water should be especially quired.

We report a case who had sepsis and multiple brain abscesses due to Salmonella paratyphi B and who responded to sulbactam-ampicillin (SAM) therapy. Sulbactam-ampicillin combination may be preferable due to its immunomodulator effect.

Key words: abscess, Salmonella, sulbactam-ampicillin.

Supurative abscesses due to Salmonella are reported in less than two percent of patients, and Salmonella choleraesuis is responsible for more than 50 percent of these[1]. However, symptomatic Salmonella infections usually manifest as self-limited gastrointestinal distress unless the patient has underlying systemic disease such as sickle cell anemia or immunodeficiency[1-4]. Abscess due to Salmonella has been described in lymph nodes, perineal tissues, testes, renal parenchyma, subphrenic spaces and, rarely, in the brain[1-5].

Case Report

A two-month-old female infant, suffering from dyspnea, abdominal distention and constipation for the previous two days, was admitted to the hospital in September 1998. Although she was a breast/fed infant, she was given contaminated tap-water occasionally. Physical examination on admission showed temperature 36 °C, pulse 164 beat/min, and blood pressure 72/33 mmHg. There was no skin rash, and her abdomen was distended.

Laboratory evaluation showed hemoglobin 7.9 g/dl, leukocyte count $23x10^9$/µl (segmented 60%, band 3% and lymphocytes 37%) and platelets $160x10^9$/µl. Erythrocyte sedimentation rate was 56 mm/h. Serum electrolytes, blood gases, and liver and kidney functions were all normal. Her roentgenogram showed hyperinflation of the lung and intestines (Fig. 1). Cerebrospinal fluid (CSF) analysis at the beginning showed 40 polymorph/µl, glucose 12 mg/dl (normal range 75-115 mg/dl), and protein 300 mg/dl (normal range 15-45 mg/dl). Ceftriaxone and amikacin were given empirically for sepsis suspicion after blood urine and stool cultures were taken; over the metronidazole was added to this therapy for the probability of necrotizing enterocolitis. Over the subsequent five days, her abdominal distention increased and constipation continued. CSF culture on the 10^{th} day yielded Salmonella paratyphi B, but there were no pathogens in any other cultures. Then, according to the antibiogram, sulbactam ampicilline (SAM) was given and the other antibiotics were stopped. The patient had generalized convulsions on the 15^{th} day. Computerized tomography (CT) scan showed multiple brain abscesses (Fig. 2). Surgical drainage was performed and the same pathogen was also isolated from this material. Ventriculo-peritoneal shunt was placed after the CSF was completely clear.

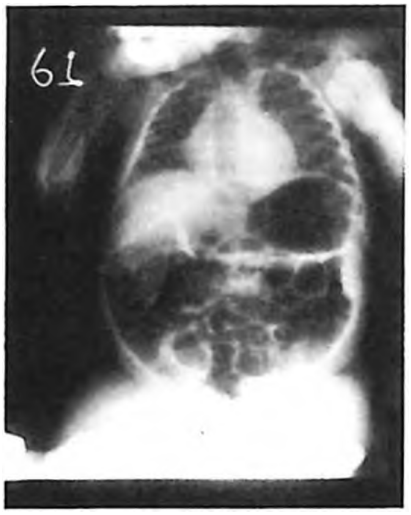

Fig. 1. The roentgenogram showing hyperinflation of the lungs and intestines.

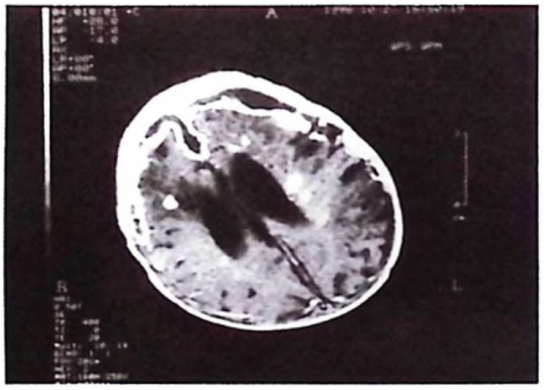

Fig. 2. Computerized tomography (CT) scanshowing multiple brain abscesses.

Discussion

Humans, who are the only hosts of Salmonella species, usually ingest salmonellae from contaminated food, water and milk[6]. The salmonellae produce disease by adhering to and then penetrating intestinal mucosal cells by endocytosis, and bacterial proliferation occurs in the lamina propria and mesenteric nodes. Salmonellae seem to survive in an intracellular location, and are protected from antibodies and antibiotics[3].

This gastrointestinal disease course in humans is usually limited unless the patient has underlying systemic disease such as sickle cell anemia or immunodeficiency[3,4]. In recent years, a major cause of immunocompromisation is human immunodeficiency virus (HIV) infection[3,4]. There was no HIV infection, but cellular and humoral immunity in our case was not completely developed at two months of age, and there was a history of contaminated water consumption. Salmonella infection in the first two years of life exhibits certain differences from the clinical course in adults[3]. Bradycardia and leukopenia are not the rule in this group[3]; our patient had leukocytosis and tachycardia. In most cases, supurative abscesses have been reported due to Salmonella choleraesuis and typhi[1,3]. Salmonella paratyphi B was isolated in our case.

Since Salmonella is seldom suspected as a cause of soft tissue infections, there is usually a dangerous delay in the institution of appropriate antimicrobial therapy and isolation procedures[6]. Abdominal distention, which is a later finding and could lead to intestinal perforation, is well known in adults[3]. Abdominal distention and history of contaminated water consumption in our case alerted us to initiate metronidazole at the beginning of the therapy for the possibility of anerobic infection. Atypically, there was hyperinflation of the lungs in our case. We changed the therapy when the CSF culture was positive for Salmonella.

There were successful treatments with chloramphenicol[3], ciprofloxacin[7] and 3rd generation cephalosporins[8]. But we preferred SAM therapy according to the antibiogram, because there was no sign of improvement with ceftriaxone and amikacin therapy. Sulbactam combination with ampicillin is preferable, because it has an immunomodulator efficacy in inducing the release of TNF, IL-1 alpha, and IL-6 from monocytes, and in releasing IL-4 and IFN-tau from lymphocytes[9,10].

We believe that a history of contaminated water consumption in developing countries and gastorintestinal symptoms, especially abdominal distention, should be evaluated carefully in infants. In such cases, SAM therapy is a good alternative.

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Chronic inflammatory bowel disease in a patient with common variable immunodeficiency

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SUMMARY: Kütükçüler N, Yağcı RV, Aydoğdu S, Aksu G, Genç B. Chronic inflammatory bowel disease in a patient with common variable immunodeficieny. Turk J Pediatr 2001; 43: 88-90.

Common variable immunodeficiency (CVID) is a primary defect of the immune system involving an increased risk of respiratory and digestive tract infections and autoimmune diseases. Recently, it has been reported that chronic inflammatory bowel disease (CIBD) might occur with increased frequency (20%) in patients with CVID. A nine-year-old boy with CVID developed CIBD during follow-up and periodic intravenous immunoglobulin administration. Serum tumor necrosis factor-α concentration, which is suggested to show disease activity in CBD, was very high. The patient's radiological evaluation, both in active and remission periods, had characteristic features of CBD. We herewith present and discuss this case with both diseases, CVID and CIBD.

Key words: common variable immunodeficiency, chronic inflammatory bowel disease.

Common variable immunodeficiency (CVID) is a primary defect of the immune system involving an increased risk of respiratory and digestive tract infections[1]. Recurrent pyogenic infections usually appearing in late childhood, an increased incidence of autoimmune disease and total immunoglobulin levels below 300 mg/dl (with the IgG level below 250 mg/dl and normal B cell numbers) are the major immunological features of CVID[1-5]. Digestive tract infections are important due to frequent modifications of the intestinal bacteria which can give rise to severe malnutrition[6]. Many functional and anatomic irregularities of the gastrointestinal tract have been described during CVID, chiefly due to a defective immune response of the mucosal membranes[6]. Recently, it has been reported that chronic inflammatory bowel disease (CIBD) might occur with increased frequency in patients with CVID[7]. We present here a nine-year-old boy with CVID who developed CIBD during follow-up and periodic intravenous immunoglobulin (IVIG) administration.

Case Report

A nine-year-old boy with CVID has been followed-up for three years in the Pediatric Immunology Unit. On admission, he had mild growth retardation, recurrent upper and lower respiratory infections and mild diarrhea. After laboratory evaluation, he was diagnosed as CVID. Immunological findings were as follows: IgG: 207 mg/dl, IgM 24 mg/dl, IgA 6.6 mg/dl, IgG1 1.8 g/L, G2-G3-G4 undetectable, gamma globulin in protein electrophoresis 0.9%, CD3+ T lymphocytes 58%, CD19+ B cells 16%, CD4+ cells 22%, CD8+ cells 40%, and CD16+56+ cells 16%. Three years previously examinations for malabsorption, such as endoscopy of the gastrointestinal tract, duodenal biopsy, parasitic examinations and carbohydrate, protein and lipid malabsorption tests were all normal. The patient was on monthly administered IVIG treatment (500 mg/kg), and he was extremely well until one year ago.

A year ago, the patient began to admit to the hospital with severe diarrhea, nausea and vomiting which could not be explained with bacteriologic, fungal, viral (rotavirus), or parasitic examinations or malabsorption tests. The diarrhea was not bloody and presented over two months with remissions and exacerbations. Colonoscopy to the middle part of the transverse colon was performed and biopsies were obtained. In colonoscopy, the mucosa was hyperemic, edematous and friable. There was a

loss of vascular (submucosal vessels) pattern. Several acute and chronic ulcerations representing a more severe disease were the other endoscopic findings. Presence of mixed inflammatory cell infiltrates of the lamina propria, increased number of neutrophils in some mucosal glands, and destruction of mucosal surface epithelium were the biopsy features showing an inflammatory disease. An air-contrast barium enema was performed (Fig. 1). The roentgenograms showed involvement of the entire colon. There was a severe loss of haustration and many superficial ulcerations with 2-3 mm diameters. Terminal and distal ileum were normal. Based on these colonoscopic, histologic and X-ray features, the patient was diagnosed as chronic ulcerative colitis. Serum concentration of tumor necrosis factor-α (TNF-α) was measured for this patient by enzyme linked immunosorbent assay (ELISA) and was found to be very high (51.2 pg/ml).

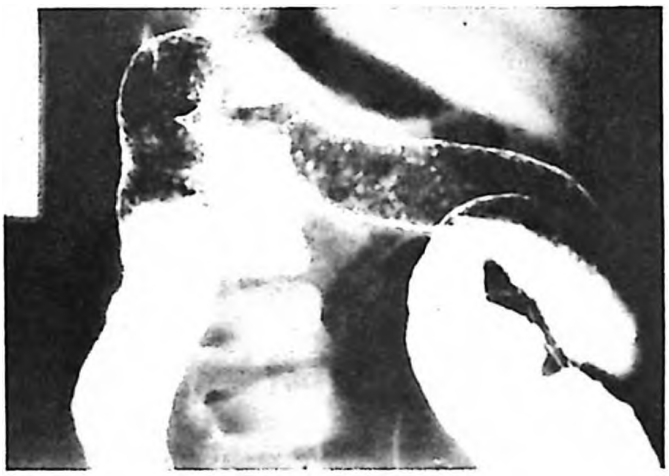

Fig. 1. Superficial ulcerations and severe loss of haustration in air-contrast barium enema.

Besides regular IVIG therapy, 1.5 mg/kg oral prednisolone and 1500 mg/day mesalazin (5-aminosalicylic acid) were given to the patient. In three weeks, all symptoms including diarrhea disappeared and the child had no pathologic symptoms. The dose of prednisolone was tapered gradually to 10 mg/day and then switched to alternate day therapy. Besides prednisolone, mesalasin was also tapered to 750 mg/day. Colonoscopy was performed every four months, and colonoscopic and histologic features resolved gradually. A year after the diagnosis, in the new air-contrast colon roentgenograms, the characteristic features such as complete disappearance of haustral markings, and shortening of the colon and uniform reduction in its caliber (lead pipe colon) were found (Fig. 2). These findings were expected in long-term management. However, the ulcerations observed previously had disappeared, and dilatation of the ileocecal valve and terminal ileum (backwash ileitis) was observed. Serum TNF-α concentration was 29.7 pg/ml in this period.

Fig. 2. After treatment: complete disappearance of haustral markings, shortening of the colon and uniform reduction in its caliber (lead pipe colon); disappearance of the ulcerations observed before; and a dilatation of the ileocecal valve and terminal ileum are seen.

The patient is still in follow-up and has had no complaints related to the gastrointestinal system except for mild abdominal distension.

Discussion

A consensus exists that the mucosal immune system is responsible for tissue damage in CIBD[8]. Two potential mechanisms for the involvement of the gut. associated lymphoid tissue in the pathogenesis of CIBD are postulated[8]. First, disordered immunoregulation leads to immune activation of the T cells, leading to nonspecific tissue injury, enhanced antibody production and chronic inflammation[8]. The activated T cells are postulated to cause tissue injury by the production of lymphokines and cytokines. Second, an autoimmune process

has been postulated by which specific immune response is directed against epithelial cell antigens[8]. On the other hand, it has been reported that patients with CVID were prone to a variety of autoimmune diseases[1,7]. Luzi[9] revealed that inflammation in the bowel, usually affecting the colon and ileum, occurs in at least 20 percent of CVID patients. Our patient also had the characteristic features of both diseases, CVID and CIBD.

Serum concentrations of TNF-α in childhood CIBD have been measured in several studies[10-12]. Serum TNF-α levels were found to be highly elevated in active disease state, and measurement of serum TNF-α levels has been accepted as a simple way of assessing disease activity in patients with CIBD[10,11]. In our patient, serum TNF-α concentrations were measured in the active and remission periods, and were found to be 51.2 pg/ml and 29.7 pg/ml, respectively. In another study, serum TNF-α concentrations were measured in healthy children and the mean ± standard deviation was 3.1 ± 2.2 pg/ml[13]. As seen, our patient's serum TNF-α level was extremely high in the active disease period, and then a decrease was observed after treatment. However, the serum TNF-α level was still high, suggesting the inflammatory process was continuing.

In conclusion, physicians should be aware that CIBD might occur in children with CVID. If a child with this humoral immunodeficiency presents with symptoms of chronic diarrhea, abdominal pain, nausea, vomiting, weight loss and growth retardation, the physician has to suggest and examine CIBD.

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Noninvasive diagnosis and surgical management in total anomalous pulmonary venous return draining into the coronary sinus: Report of 2 cases

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SUMMARY: Tavlı V, Kayhan B, Okur FF, Kırman M, Tekdoğan M. Noninvasive diagnosis and surgical management in total anomalous pulmonary venous return draining into the coronary sinus: report of 2 cases. Turk J Pediatr 2001; 43: 91-93.

Total anomalous pulmonary venous return results from nondevelopment of the common pulmonary vein, with consequent enlargement of embryonic collaterals between the lungs and the systemic veins. In this report, two patients with this anomaly draining into the coronary sinus who presented in infancy are described. One of the patients was referred because of growth and development failure and chronic constipation, while the other had tachypnea as the presenting problem. Both were diagnosed during the echocardiographic examination. Typical echocardiographic findings were a small left atrium, a sausage-shaped dilated coronary sinus receiving the pulmonary veins in the subcostal short axis, and flying seagull configuration in the subcostal long axis views. Both had a large interatrial communication. The patients underwent corrective surgery. The aim of the presentation is to emphasize the role of segmental echocardiography in the differential diagnosis.

Key words: total anomalous pulmonary venous return, echocardiography.

Total anomalous pulmonary venous return (TAPVR) results from nondevelopment of the common pulmonary vein, with consequent enlargement of embryonic collaterals between the lungs and the systemic veins. It comprises approximately one to two percent of all congenital heart diseases[1,2]. An obligatory right to left shunt either through the atrial septal defect or patent foramen ovale is usually present. Presence of an obtructive lesion in the anomalous pulmonary venous channel profoundly influences the hemodynamic state and clinical features in a case of TAPVR. The aim of the presentation was to emphasize the role of segmental echocardiography in the differential diagnosis and management of TAPVR draining into the coronary sinus[3-6].

Case Reports

Case 1

A 15-month-old boy (weight: 8 kg) was referred to our hospital because of growth and development failure and chronic constipation. A grade 3/6 systolic murmur was heard best along the left third intercostal space. The second heart sound was loud and fixed split. He also had coloboma of the iris, right-sided pre-auricular skin tag and frontal bossing. There was cardiomegaly and prominent pulmonary trunk on his chest X-ray. Right ventricular hypertrophy was present on his echocardiography (ECG). On his 2-D echocardiography, the left atrium (LA) and left ventricle (LV) were small. The pulmonary veins were seen to collect in a common chamber (PVC) unrelated to the LA (Fig. 1). There was a 12 mm secundum type atrial septal defect (ASD). Posterior angulation in the interrogation of the four-chamber view revealed a very enlarged coronary sinus (Fig. 2). Subcostal short axis view revealed a sausage-shaped pulmonary venous trunk draining into the right atrium (RA) via the coronary sinus, which should be considered typical for this type of TAPVR (Fig. 3). Hemodynamic assessment revealed mildly elevated pulmonary artery pressure.

This Case Report was Presented at the VI[th] BALKAN Pediatric Cardiology and Cardiovascular Surgery Congress, 4-7 November 1998, Antalya, Turkey.

Pulmonary artery angiogram revealed abnormal pulmonary venous return into the RA through the enlarged coronary sinus. The LV was small. The patient was schleduled urgently for cardiac surgery. Under cardiopulmonary by pass, the repair was done from inside the RA. The coronary sinus was incised into the LA, and the entire area was covered with a pericardial patch. Both pulmonary venous return and coronary sinus blood flow were directed into the LA, creating a small obligatory right to left shunt that was well tolerated. The patient was extubated the next day and remained in the intensive care unit for one day. He was discharged within six days. He has remained well for a follow-up period of two years and markedly gained weight and height. On his latest chest X-ray, the border of the RA was less prominent and the cardiothoracic ratio within normal limits. Post-operative echocardiography revealed a larger LV volume and appropriate drainage of the pulmonary veins into the LA.

Case 2

A two-month-old girl presented with tachypnea. On her examination there was a 2-3/6 grade systolic murmur on the third left intercostal space. Her echocardiography revealed a large ASD, small LA and LV, and an enlarged coronary sinus receiving the pulmonary venous return which resembled a flying seagull (Fig. 4). Selective left and right pulmonary angiograms were performed. Left and right sided pulmonary venous return was to the RA via the coronary sinus. She was operated at another institution and has remained healthy.

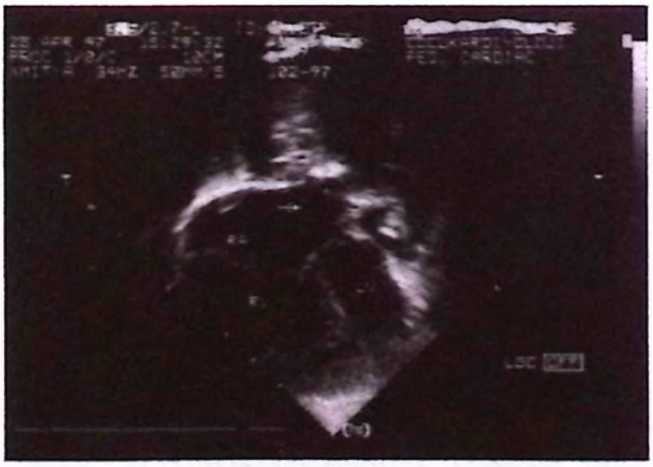

Fig. 1. The pulmonary veins are seen to collect in a pulmonary venous trunk posterior to the small left atrium (LA) in Case 1 (arrows). ra: right atrium; rv: right ventricle; lv: left ventricle.

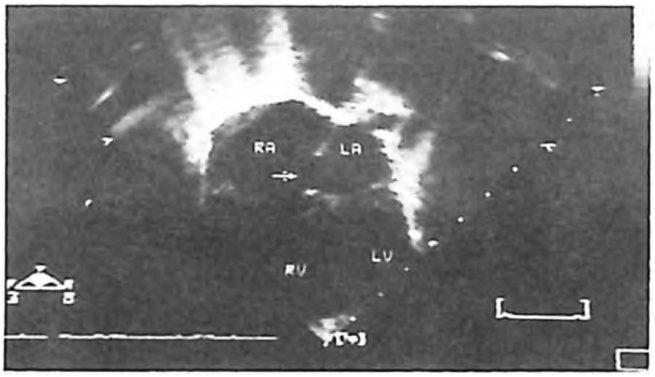

Fig. 2. An enlarged coronary sinus is seen in the posterior angulation of the four-chamber view in Case 1.

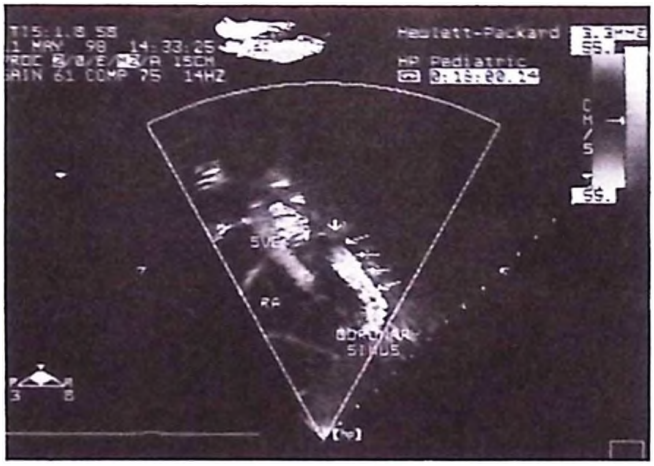

Fig. 3. Subcostal short axis view in Case 1 showing typical sausage-shaped dilated coronary sinus.

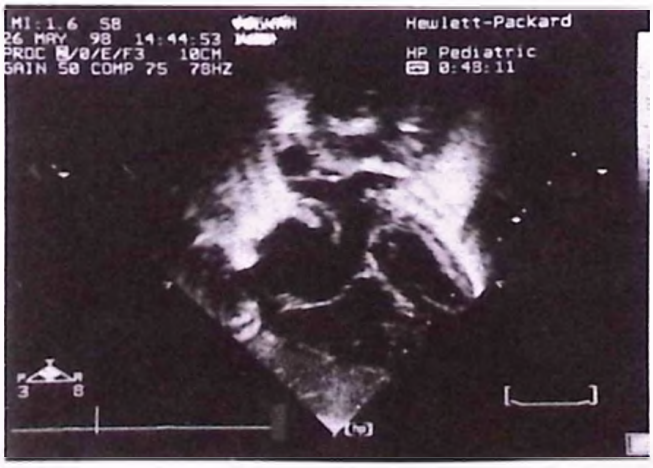

Fig. 4. Subcostal four-chamber view in Case 2. The flying seagull configuration is seen, with the wings being the pulmonary veins and the remainder being the enlarged coronary sinus receiving the pulmonary veins.

Discussion

In the classification by Darling and co-workers[2], TAPVR anomalies are divided into four types: supracardiac (45%), cardiac (25%), infracardiac (25%) and mixed (5%)[3]. The frequency of TAPVR drainage into the coronary sinus was 18 percent. TAPVR can also be classified by the presence or absence of venous obstruction[1-3,7]. Although obstruction is very common in the infracardiac types, it is less likely to be seen in the other types. The treatment of TAPVR is surgical drainage[7,8]. The timing of surgery should be determined by the presence or absence of pulmonary venous obstruction. Because there is no possibility of spontaneous resolution of obstructed TAPVR, the diagnosis alone is an idication for surgery. Early mortality during the first year of life has been 8-11 percent; late mortality was reported as 2-3 percent[7]. Both of the cases were operated once the diagnoses were made with very good early and short-term outcomes.

Segmental echocardiography performed in the subcostal long and short axes, and apical four-chamber and parasternal views with the aid of Doppler echocardiography should allow for the accurate noninvasive diagnosis of the intracardiac form of TAPVR[4-6]. Ostium primum type ASD should be differentiated from an enlarged coronary sinus, which is best interrogated in the posterior angulation of the four-chamber view. A small left atrium with the pulmonary veins draining into the typical sausage-shaped dilated coronary sinus is readily identified, particularly in the subcostal short axis view (Fig. 3). Slightly posterior and oblique angulation of the transducer in the acquisition of the subcostal four-chamber view may reveal a typical flying seagull configuration with the wings being the pulmonary veins and the remainder being the enlarged coronary sinus receiving the pulmonary veins (Fig. 4).

In conclusion, following the course of the pulmonary veins through orthogonal planes and the appearance of a relatively small LA and LV should alert the physician for the definitive noninvasive diagnosis of TAPVR to the coronary sinus.

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Systemic lupus erythematosus presenting with generalized lymphadenopathy A case report

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SUMMARY: Biner B, Acunaş B, Karasalihoğlu S, Vatansever Ü. Systemic lupus erythematosus presenting with generalized lymphadenopathy. A case report. Turk J Pediatr 2001; 43: 94-96.

Systemic lupus erythematosus (SLE) is an immune complex disease with many different clinical presentations. Here we report a 13-year-old female patient presenting with generalized lymphadenopathy, who meanwhile developed butterflly rash and pericarditis. The diagnosis of SLE was based on the clinical features, positive antinuclear antibody, and positive antibodies to dsDNA. The patient had an active disease and developed renal involvement, despite steroid therapy. The patient's clinical presentation, course and response to therapy are detailed, and the literature on lupus lymphadenitis is reviewed.

Key words: lymphadenopathy, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a challenging autoimmune disease of interest to general pediatricians because the wide variety of its manifestations necessitates its inclusion in the differential diagnosis for children and adolescents presenting with many different complaints[1]. SLE is an episodic, multisystem, autoimmune disease characterized by the widespread inflammation of blood vessels and connective tissues and by the presence of antinuclear antibodies (ANAs), especially antibodies to native (double-stranded) deoxyribonucleic acid (nDNA)[2]. Its clinical manifestations are extremely variable, and its natural history is unpredictable. The diagnosis of SLE is a clinical one and is supported by specific laboratory abnormalities[1,2]. No single clinical, laboratory or pathologic finding is sufficient to establish the diagnosis of SLE[3]. It remains a diagnosis of exclusion, requiring a combination of findings from a limited set of possible features. The American College of Rheumatology (ACR) has published 11 criteria for the diagnosis of definite SLE[4]. About half of chíldren with SLE have localized or generalized lymphadenopathy (LAP)[1,2,5,6]. Here we report a case presenting with generalized LAP who was diagnosed as SLE, and we review the relevant literature.

Case Report

A 13-year old girl was admitted with the complaints of cervical, axillary, and inguinal masses, periorbital swelling and erythema. Four months previously, periorbital swelling and erythema were noticed and she was evaluated as an outpatient in our hospital: compelete blood count, urinalysis and biochemistry were normal. Her complaints recurred, and cervical, axilary and inguinal masses appeared 15 days before admission.

There was no history of malignancy or autoimmune disease in the family.

Physical examination revealed mild periorbital edema, and blood pressure of 110/80 mmHg. Occipital, bilateral posterior cervical, bilateral axillary and bilateral inguinal multiple LAP (1.5 x 2 cm) were remarkable. Her liver and spleen were palpable 2 cm and 1 cm, respectively, below the costal margins on the midclavicular line. The remainder of the examination was normal.

Laboratory investigations revealed a Hb value of 11.1 g/dl, leukocyte count of 12,000/mm^3 with 60% neutrophils and 40% lymphocytes, platelet count of 194,000/mm^3 and erythrocyte sedimentation rate of 80 mm/h. Urinalysis, renal

and liver function tests, and coagulation tests were within normal limits. Chest roentgenogram was normal, cervical ultrasonography revealed multiple conglomerates of LAP without necrotic pattern. Abdominal ultrasonography disclosed hepatosplenomegaly. Echocardiography displayed pericardial effusion. Microbiological tests were negative for a pathogen microorganism. Salmonella and Brucella aglutination tests were negative. The serological tests were negative for Epstein-Barr virus, cytomegalovirus and toxoplasma.

The patient was first evaluated for the diffential diagnosis of generalized LAP. Infectious diseases like typhoid fever and brucellosis were eliminated by negative serological tests and culture results.

She developed malar rash on the second day of hospitalization. When she was evaluated for the diagnosis of SLE, ANA was positive, anti-dsDNA was 170 IU/ml (0-7), anti-Sm (+) C3 38.5 mg/dl (50-90), C4 25 mg/dl (10-40), direct Coombs' (-), anti-thrombocyte antibody (-), VDRL (-), and IgG 2920 mg/dl (800-1700). Four of the 11 criteria of ACR were fulfilled (malar rash, pericarditis, ANA positivity, anti-dsDNA antibodies and anti-Sm nuclear antigen antibodies), and the patient was diagnosed as SLE.

During hospitalization she developed purpuric rash and arthralgia. The patient was started on 60 mg prednisone daily, and in a few days pericardial effusion and LAP resolved, complement levels returned to normal and anti-dsDNA antibody titer decreased. At the end of six weeks, the prednisone dose was tapered by 5 mg at two-week intervals to a minimum dose sufficient to maintain clinical and serological remission. Parallel to the tapering of the prednisone dose, C3 and C4 levels decreased again. Although the patient was asymptomatic, complement levels were continuously low. In a short time proteinuria (0.7 g/m^2/d) had amenorrhea developed. Urinalysis showed erythrocyte casts and 2 + proteinuria, and the patient was referred to a center for renal biopsy. Later it was learned that her renal biopsy revealed Grade 3 SLE nephritis, and she was treated with cyclophosphamide pulses.

Discussion

Generalized LAP is defined as LAP involving two or more noncontiguous lymph node regions. Bacterial, viral, and protozoal infections; connective tissue disorders; hypersensitivity states; lymphoproliferative disorders; neoplastic diseases; storage diseases and granulomatous diseases should be taken into consideration in the differential diagnosis of generalized LAP[7]. In the case of a problem in diagnosis, excisional lymph node biopsy is indicated. No infectious etiology could be found in our patient. During her saty in our hospital, she developed butterfuly rash, and the laboratory findings revealed the diagnosis of SLE. It is known that about half of children with SLE have localized or generalized LAP[1,2,5,6]. Occasionally this may be extreme, suggesting a diagnosis of Hodgkin's disease, a malignancy that rarely has been reported in association with childhood SLE[8]. In recent series from the literature, the prevalence of LAP is 12 to 59 percent of patients with SLE[9].

Bhalla et al.[10] reported 14 SLE cases with Hodgkin's disease; mediastinal LAP was found in 58 percent of the cases, and retroperitoneal LAP in 17 percent. They concluded that a feature of LAP due to SLE was their peripheral localization. It is generally accepted that mediastinal and abdominal lymph nodes are always pathologic, if enlarged[7]. Our case also had only peripheral LAP; neither a mediastinal nor abdominal LAP was found. Bhalla et al.[10] also called attention to severe itching that was found in 63 percent of SLE patients with Hodgkin's disease; only 2.8 percent of SLE cases had itching. Eisner et al.[9] described the most commonly involved nodal groups in SLE as cervical (43%), mesenteric (21%), axillary (18%) and inguinal (17%).

The description of the lymph node pathology in SLE is paracortical foci of necrosis and infiltration by histiocytes, lymphocytes, plasma cells and immunoblasts; the hematoxylin body, an amorphic aggregate of basophilic material, is pathognomonic of lupus adenitis[2,9]. The necrotizing lymphadenitis of SLE was found to be similar pathologically to Kikuchi-Fujimoto disease, which is a distinctive, self-limited form of necrotizing lymphadenitis[9,11].

Chandrasekaran et al.[12] analyzed 59 children with SLE whose initial manifestations were fever (67%), arthritis (61%), skin rash (59%) and LAP (27.1%). The cumulative clinical features observed were arthritis (86.6%), fever (79.8%),skin rash (69.4%), LAP (61%) and hepatosplenomegaly (39.9%). On the other

hand, Cassidy et al.[13] evaluated the initial and cumulative manifestations of 58 children with SLE, and LAP were not mentioned.

In a report of 28 SLE patients, anti-Sm antibody was found in 30 percent of cases, particularly in those patients with LAP and fever[14]. Antibodies to Sm are closely linked to SLE, found roughly in two-thirds of patients with active SLE[1]. But in a study of 22 children with SLE, anti-Sm was found to be present in only 14 percent[2]. Antibodies to Sm antigen complex, in the absence of other autoantibody activity, have been related to central nervous system (CNS) disease[16,17]. Our patient had positive anti-Sm antibody but did not have CNS symptoms.

In a previous report by Shapira et al.[18], LAP was present in 26 percent of of 90 patients. Patients with LAP had significantly more constitutional symptoms of fatigue, fever and weight loss, more cutaneous symptoms and signs, a higher rate of hepatomegaly and splenomegaly, increased anti-dsDNA antibodies and decreased complement levels. Although disease activity index was higher among patients with LAP, there was no difference in renal or CNS involvement between patients with LAP and those without LAP. Our case also had a fulminant course with renal involvement.

In conclusion, arthritis and skin lesions are the most frequent and wellknown manifestations of SLE, but SLE should also be considered in patients presenting with generalized LAP.

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