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CONTENTS

Clinical outcomes of consanguineous marriages in Turkey

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SUMMARY: Tunçbilek E. Clinical outcomes of consanguineous marriages in Turkey. Turk J Pediatr 2001; 43: 277-279.

Turkey has a high rate of consanguineous marriages. Different nationwide surveys indicate that today 20-25% of marriages are consanguineous, with the rate having increased over the last 15 years. The results of many studies show that the rate of consanguinity among parents of children with rare recessive diseases is quite above Turkey's average and that the high consanguinity rate is one of the underlying factors of high infant and child mortality and fertility in Turkey.

Key words: autosomal recessive disease, consanquinity, fertility, infant mortality.

Turkey has a high rate of consanguineous marriage, indicating a strong preference for this form of union. Turkey's Demographic and Health Surveys reflect the trend in this respect since 1968[1-5]. In 1968, the rate of consanguinity between couples was around 30%. Fifteen years later (1983) it was 20%, and then the rate began to increase again at that point, reaching 25% 15 years later (Table I).

Table I. Distribution (%) of Consanguineous Marriages in Turkey by Region

Region	1968*	1983*	1988*	1993*	1998*
West	16.6	10.1	12.8	13.7	16.3
South	38.0	29.4	29.6	28.6	29.9
Center	29.1	22.4	20.8	25.6	27.4
North	26.0	21.7	23.3	22.1	24.2
East	37.8	32.9	30.8	34.4	39.2
Turkey	29.2	20.9	21.1	23.0	25.1

* Turkey's Demographic and Health Surveys.

The aim of this paper was to show the relation between consanguinity and infant mortality and the frequency of parental consanguinity in some autosomal recessive diseases in Turkey. Due to the biological effects of human inbreeding, consanguineous marriages, which are widely practiced in Turkey, may be considered as one of the important variables explaining high infant mortality through autosomal recessive diseases.

The impact of consanguineous marriages on mortality and fertility was analyzed from the 1988 Turkish Population and Health Survey[6]. The sample was a nationally representative probability sample of households, and the consanguinity rate was 21.1% in this survey. The pattern observed in consanguineous marriages indicated traditional behavior, mostly practiced among people of low socioeconomic level. However, when two important variables affecting infant mortality, education level and size of settlement place, were controlled in urban areas where living conditions are better than in rural areas, the difference in infant mortality due to first-cousin marriages was clearly observed. In rural areas this differential was not so apparent, possibly due to the concentration of many other adverse factors affecting infant mortality[6].

In the above-mentioned study, total marital fertility rates, mean number of total pregnancies, children even born and living children were found significantly high for women in first-cousin marriages. The study results showed that couples with first-degree consanguinity have high fertility as compared to those in nonconsanguineous unions. Therefore, consanguineous marriages may also be considered as one of the factors underlying the high total fertility in Turkey[6].

The high mortality rates in consanguineous families can be explained by the deleterious effects of recessive genes. In fact, in many autosomal recessive disorders, consanguinity between parents is much higher than seen in the general population.

Patients admitted to the Department of Genetics of Hacettepe University Children's Hospital were analyzed to determine the relationship

between consanguinity and recessive disorders. Among the parents of the patients diagnosed with a recessive disease, consanguinity was 75.5%. For multifactorial disorders this figure was 34.9% and for autosomal dominant, X-linked, chromosomal and sporadic disorders 22.7%.

Various studies in Turkey revealed that parental consanguinity in autosomal recessive disease shows a spectrum from 100 percent to near Turkey's average rate of consanguinity (Table II). The highest figures belong to propionic acidemia (100%) and Friedreich's ataxia (96.4%) and the lowest figure belongs to familial Mediterranean fever (FMF), which is one of the common autosomal recessive diseases in Turkey. The carrier frequency of FMF was calculated as 1:12 and parental consanguinity was determined as 28.7% in a study comprised of 610 patients with FMF[27].

Table II. Parental Consanguinity Rate in Various Diseases in Turkey

Disease	Consanguinity rate (%)	References
Organic aciduria	70.4	15
Propionic acidemia	100.0	7
Methylmalonic acidemia	87.5	7
Maple syrup urine disease	84.0	7
Friedreich's ataxia	96.4	8
Limb-girdle muscular dystrophy	90.0	9
Bloom's syndrome	90.0	10,11
Fanconi's aplastic anemia	78.0	12
Glycogen-storage disease type I	77.8	13
DIDMOAD syndrome	72.7	14
Laron type growth hormone insufficiency	70.0	16
Congenital muscular dystrophy	68.4	17
Congenital adrenal hyperplasia	56.4	18
Thalassemia	65.0	19
Ataxia-telangiectasia	65.0	20
Type 1 hereditary tyrosinemia	63.6	21
Phenylketonuria	59.0	22
Wilson's disease	57.3	23
Spinal muscular atrophy	57.0	24
Urea cycle enzyme defect	53.4	15
Cystic fibrosis	44.2	25
Cystinuria	37.5	26
Familial Mediterranean fever	28.7	27
Cleft lip ± cleft palate	27.0	28
Insulin-dependent diabetes mellitus	23.9	29
Cleft palate	22.0	28
Neural tube defects	20.0	30

The importance of consanguinity in various congenital malformations inherited multifactorially, such as neural tube defects and cleft lip and/or palate (CL ± CP) is relatively small. In a series with 140 patients, the frequency of parental consanguinity was 22% among CP cases and 27% in cases with CL ± CP[28]. Among 93 cases with neural tube defect followed in the Genetic Unit of Hacettepe University Children's Hospital, consanguinity was 22%[30].

Diabetes mellitus is also a multifactorially inherited chronic disease in childhood. Parental consanguinity among the patients with insulin-dependent diabetes mellitus was 23.9% which is near the average rate in Turkey[29].

All the above-mentioned studies show that when a recessive trait has a high frequency in a population, such as FMF in Turkey, the rate of consanguinity is not very high, whereas in diseases in which the carrier frequency is low, the consanguinity rate among parents of children with such diseases, such as some metabolic and neurologic disorders, is high. However, even in the diseases with high carrier frequency such as cystic fibrosis, phenylketonuria and thalassemia, the parental consanguinity rate is quite above Turkey's average. This shows that a high consanguinity rate together with a high gene frequency is responsible for the high incidence of these autosomal recessive diseases in Turkey.

In conclusion, the high consanguinity rate in Turkey causes the high incidence of many autosomal recessive disorders and is one of the underlying factors of high infant and child mortality and fertility.

REFERENCES

1. Timur S. Türkiye'de Aile Yapısı. Doğuş Matbaacılık Ltd. Ankara. Hacettepe Üniversitesi Yay. D-15; 1972.
2. Hacettepe University Institute of Population Studies. 1983 Turkish Population and Health Survey. Ankara, HIPS; 1987.
3. Hacettepe University Institute of Population Studies. 1988 Turkish Population and Health Survey. Ankara, HIPS; 1989.
4. Ministry of Health. Hacettepe University Institute of Population Studies and Macro International Inc. Turkish Demographic and Health Survey 1993. Ankara; 1994.
5. Hacettepe University Institute of Population Studies and Macro International Inc. Demographic and Health Survey 1998. Ankara, HIPS; 1999.
6. Tunçbilek E, Koç I. Consanguineous marriage in Turkey and its impact on fertility and mortality. Ann Hum Genet 1994; 58: 321-329.
7. Tokatlı A, Coşkun T, Özalp I. A retrospective evaluation of 78 cases with organic acidaemia. Doğa Tr J Med Sci 1993; 18: 47-53.
8. Alikaşifoğlu M, Topaloğlu H, Tunçbilek E, et al. Clinical and genetic correlates in childhood onset Friedreich ataxia. Neuropediatrics 1999; 30: 72-76.

9. Dinçer P, Leturc F, Richard I, Piccolo F, Yalnızoğlu D, de Toma C. A biochemical, genetic and clinical survey of autosomal recessive limb girdle muscular dystrophies in Turkey. Ann Neurol 1997; 42: 222-229.
10. Boduroğlu K, Tunçbilek E. Two siblings with Bloom's syndrome exhibit different clinical features: possible effect of sex. Turk J Pediatr 1999; 41: 107-111.
11. Balcı S, Aktaş D. Mucinous carcinoma of the colon in a 16-year-old Turkish boy with Bloom syndrome: cytogenetic, histopathologic, TP53 gene protein expression studies. Cancer Genet Cytogenet 1999; 111: 45-48.
12. Altay C, Alikaşifoğlu M, Kara A, et al. Analysis of 65 Turkish patients with congenital aplastic anemia (Fanconi anemia and non-Fanconi anemia): Hacettepe experience. Clin Genet 1997; 51: 296-302.
13. Saltık IN, Özen H, Ciliv G, et al. Glycogen storage disease type Ia: frequency and clinical course in Turkish children. Indian J Ped 2000; 67: 497-501.
14. Yordam N, Şimşek E, Böke B, et al. Review of Turkish patients with Wolfram (DIDMOAD) syndrome. Horm Res 1997; 48 (Suppl): 159.
15. Tokatlı A, Coşkun T, Özalp I. Fifteen years' experience with 212 hyperammonaemic cases at a metabolic unit. J Inherit Metab Dis 1991; 14: 698-706.
16. Yordam N, Kandemir N, Erkul I, Kurdoğlu S, Hatun Ş. Review of Turkish patients with growth hormone insensitivity (Laron type): Eur J Endocrinol 1995; 133: 539-542.
17. Topaloğlu H, Kale G, Yalnızoğlu D, et al. Analysis of "pure" congenital muscular dystrophies in thirty-eight cases. How different is the classical type 1 from the occidental type cerebromuscular dystrophy? Neuropediatrics 1994; 15: 94-100.
18. Kandemir N, Yordam N. Congenital adrenal hyperplasia in Turkey: a review of 273 patients. Acta Paediatr 1997; 86: 22-25.
19. Altay Ç, Başak N. Molecular basis and prenatal diagnosis of hemoglobinopathies in Turkey. Int J Pediatr Hem Oncol 1995; 2: 283-290.
20. Ersoy F, Berkel I, Sanal Ö, et al. Twenty-year follow-up of 160 patients with ataxia telengiectasia. Turk J Pediatr 1991; 33: 205-215.
21. Coşkun T, Özalp I, Koçak N, et al. Type I hereditary tyrosinaemia: presentation of 11 cases. J Inherit Metab Dis 1991; 14: 765-770.
22. Coşkun T, Özgüç M, Tokatlı A, et al. Phenylketonuria in Turkey: epidemiological, clinical and genetic aspects. Dev Brain Dysfunc 1993; 6: 134-140.
23. Yüce A, Koçak N, Gürakan F, et al. Wilson's disease with hepatic presentation in childhood. Indian Pediatr 2000; 37: 31-36.
24. Erdem H, Pehlivan S, Topaloğlu H, et al. Deletion analysis in Turkish patients with spinal muscular atrophy. Brain Dev 1999; 21: 86-89.
25. Göçmen A, Özçelik U, Kiper N, et al. Kistik fibrozisli 104 hastanın klinik ve laboratuvar özellikleri. Çocuk Sağ ve Hast Derg 1995; 38: 21-31.
26. Gültekin A, Özalp I, Tanzer F, et al. Türk çocuklarında sistinürinin görülme sıklığı. Çocuk Sağ ve Hast Derg 1990; 23: 1-8.
27. Saatçi Ü, Özen S, Özdemir S, et al. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. Eur J Pediatr 1997; 156: 619-623.
28. Tunçbilek G. Dudak-damak yarıklarında kalıtım ve epidemiyoloji. In: Erk Y, Özgür F (eds). Dudak ve Damak Yarıkları. İşkur Matbaacılık Ltd. Şti. Ankara; 1999: 7-16.
29. Kandemir N, Açıkgöz E, Yordam N. The epidemiology of juvenile-onset insulin-dependent diabetes mellitus in Turkish children. A retrospective analysis of 477 cases. Turk J Pediatr 1994; 36: 191-195.
30. Unpublished data.

Fiberoptic phototherapy versus conventional daylight phototherapy for hyperbilirubinemia of term newborns

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SUMMARY: Sarıcı SÜ, Alpay F, Dündaröz MR, Özcan O, Gökçay E. Fiberoptic phototherapy versus conventional daylight phototherapy for hyperbilirubinemia of term newborns. Turk J Pediatr 2001; 43: 280-285.

The efficacy and wavelengths of fiberoptic phototherapy and conventional daylight phototherapy were compared in a relatively larger series of term newborns with nonhemolytic and significant hyperbilirubinemia than reported in previous studies. One hundred and nine term newborns were randomly assigned to receive either fiberoptic phototherapy on a fiberoptic phototherapy pad or overhead conventional phototherapy consisting of five daylight fluorescent lamps. Although the average spectral irradiance measured during the study period was significantly greater in the fiberoptic phototherapy group (9.2 ± 1.2 $\mu W/cm^2/nm$ vs 7.1 ± 1.1 $\mu W/cm^2/mm$, $p < 0.05$), conventional phototherapy was significantly more effective in decreasing bilirubin levels: the duratilon of exposure to phototherapy was significantly shorter (49.4 ± 14.4 hours vs 61 ± 13.1 hours, $p < 0.05$), and overall bilirubin decline rate as mg/dl/h and percent/h was significantly greater in the conventional phototherapy group (0.15 ± 0.06 mg/dl/h vs 0.11 ± 0.05 mg/dl/h, and 0.81 ± 0.34 percent/h vs 0.60 ± 0.28 percent/h, $p < 0.05$). There were four failures of phototherapy in the fiberoptic phototherapy group whereas no phototherapy failure was observed in the conventional phototherapy group ($p < 0.05$). The emission spectrum of the daylight fluorescent lamp revealed a broad emission between the violet and red spectra with tiny narrow peak emission bands in 405 nm, 436 nm, 546 nm and 577 nm, while a broad emission through the blue and green wavelengths (mainly in the green spectrum) without any peak emissions was detected in the tungsten-halogen lamp of the fiberoptic phototherapy system. Conventional phototherapy with daylight fluorescent lamps shoud be preferred to fiberoptic phototherapy administered with fiberoptic phototherapy and in the treatment of term newborns with nonhemolytic hyperbilirubinemia.

Key words: conventional daylight phototherapy, fiberoptic phototherapy, hyperbilirubinemia, newborn.

Although conventional overhead phototherapy is still the treatment of choice for neonatal hyperbilirubinemia, it has several difficulties and disadvantages including respiratory obstruction from eye patches sliding over the newborn's nose, irritation of the eyes, and disturbances of the newborn's circadian rhythm[1,2]. The conventional phototherapy units consisting of special blue lamps can hinder clinical observations by masking skin color changes, such as cyanosis, and can cause nausea, giddiness and headache which discomfort the caregivers in the nursery[2,3].

These difficulties and disadvantages of conventional phototherapy units have prompted clinicians to search and use newer systems which are as efficacious as, but more practical and advantageous than, conventional phototherapy systems. In fiberoptic phototherapy, a recently developed technique of phototherapy, therapeutic light is delivered from a tungsten-halogen lamp through a fiberoptic cable and is emitted from the sides and ends of the fibers inside a plastic pad. Phototherapy is administered to either the newborn's front or back while the newborn lies on the pad. Using eye patches during fiberoptic

phototherapy is considered unnecessary as the newborn is unlikely to be in a position to look directly at the light source.

In two studies carried out with preterm babies, fiberoptic phototherapy was reported as efficacious as conventional phototherapy[4,5]. In two studies comparing the efficacy of fiberoptic phototherapy and conventional phototherapy in term newborns, serum bilirubin levels at the initiation of phototherapy were not high enough for starting phototherapy[6,7]. In another study fiberoptic phototherapy was compared with conventional phototherapy consisting of special blue light, but not daylight[8].

We performed this study to compare both the efficacy and wavelengths of fiberoptic phototherapy and conventional daylight phototherapy in a relatively larger series of term newborns with nonhemolytic and more significant hyperbilirubinemia than reported in previous studies.

Material and Methods

This study was performed at the Department of Pediatrics of Gülhane Military Medical Academy. It was approved by the local ethics committee, and written informed consent was obtained from parents before the randomization procedure. Healthy term newborns with birth weights of ≥ 2500 g and with nonhemolytic indirect hyperbilirubinemia normal hemoglobin, normal reticulocyte count, negative results of a direct antiglobulin test, and no evidence of blood group isoimmunization were enrolled into the study. Patients with direct hyperbilirubinemia, enclosed hemorrhage, infection, or any congenital malformations were excluded from the study. Gestational ages of the newborns were determined according to the maternal history and Ballard's scoring system[9]. Phototherapy was initiated at serum bilirubin levels of ≥ 15 mg/dl.

A total of 109 newborns were randomly assigned to receive either fiberoptic phototherapy or conventional phototherapy. Attending nurses sequentially allocated the newborns to one of the study groups, and they were not informed about the total serum bilirubin levels of the newborns at the study entry.

Newborns in the fiberoptic phototherapy group received fiberoptic phototherapy on a fiberoptic phototherapy pad (Walley II Phototherapy System, Fiberoptic Medical Products Inc, Allentown, PA, USA) which was in direct contact with the skin during phototherapy and provided an illumination area of 7.6 x 35.5 cm. Greatest care was taken to ensure that the active newborns were immediately placed back onto the phototherapy pad if they crawled off and moved out of the illumination area of the phototherapy pad.

Newborns in the conventional phototherapy group received conventional phototherapy below a standard phototherapy unit (Ohio Medical Products, Airco Inc, WIS, USA) consisting of five daylight fluorescent lamps (Sylvania Standard Daylight F 18 W/154, Sylvania Inc., MASS, USA) that was placed 30 cm above the newborns.

Phototherapy was administered to newborns of both groups in the prone position. They were diapered with disposable diapers folded to allow maximum skin exposure to phototherapy. The eyes of the newborns in the conventional phototherapy group were covered with eye patches during phototherapy, but these eye patches were not used in the fiberoptic phototherapy group. Phototherapy was administered continuously except during minor procedures such as feeding, physical examination and diapering. The newborns in both groups were fed with formula milk during phototherapy, and the daily fluid volume was adjusted according to clinical status and body weight loss associated with phototherapy. Newborns were closely monitored for possible side effects of phototherapy including changes in skin color, body temperature and weight, and gastrointestinal system functions.

Criterion for phototherapy failure was defined as continued increase in bilirubin concentration on two successive determinations beyond the pretreatment bilirubin level. The efficacy of phototherapy was compared by the following criteria: the duration of phototherapy (h) and the overall decerase in bilirubin concentration related to the total exposure time and expressed as a proportionate decrease per hour (mg/dl decline/h percent decline/h).

Direct bilirubin measurement, direct antiglobulin test, blood group typing, reticulocyte count, and complete blood count with differential were performed at entry into the study. Total serum bilirubin levels at entry into and during the study were measured in capillary blood samples every six to eight hours by direct spectrophotometry (Bilirubin Analyzer Bil Micro Meter Erma Inc. Kohsoku Denki Co, Ltd, Tokyo, Japan).

Phototherapy was terminated when total serum bilirubin levels had declined to < 12 mg/dl, but newborns were followed for at least 24 hours in case of rebound.

The spectral irradiance of light emitted during fiberoptic phototherapy was measured with Joey Dosimeter JD-101 (Fiberoptic Medical Products, Inc, Allentown, PA, USA) sensitive to wavelengths of 400-500 nm, and that of the conventional phototherapy system was measured with a standard radiometer (Minolta/ Air Shields Vickers Fluoro-Lite Meter 451) sensitive to wavelengths of 400-500 nm. By making serial measurements at the skin surface level of each newborn during the study, the average spectral irradiance was determined for each case. The emission spectra of the two different lamps used in the study groups were determined with monochromator (Garrel-Ash 50 cm, USA) at the Turkish Atomic Energy Authority. The data were statistically compared with the Student's t test.

Results

During the study period five newborns in the fiberoptic phototherapy group and four newborns in the conventional phototherapy group were excluded from the study due to various diagnoses such as hypothyroidism, infection and sepsis.

There were no significant differences between the fiberoptic phototherapy group and conventional phototherapy group with respect to factors that may influence the efficacy of phototherapy such as gestational age, birth weight, postnatal age, and bilirubin and hematocrit values at start of the treatment (Table I).

The posttreatment body weights also did not differ significantly between the fiberoptic phototherapy and conventional phototherapy groups (3420 ± 330 g and 3460 ± 290 g, respectively). During the study one newborn in the fiberoptic phototherapy group and one newborn in the conventional phototherapy group had transient erythema, and three newborns in each group had mild watery stool defecation not leading to dehydration. No other complications were observed during the sutdy.

There were four failures of phototherapy in the fiberoptic phototherapy group whereas no phototherapy failure was observed in the conventional phototherapy group ($p < 0.05$). These cases were transferred to our double phototherapy unit with high irradiance[10].

Phototherapy was effective in decreasing bilirubin levels in both groups, but the response was greater in the conventional phototherapy group; the duration of exposure to phototherapy was significantly shorter ($p < 0.05$), and overall bilirubin decline rate as mg/dl/h and percent/h was significantly greater in that group ($p < 0.05$; Table II).

Table I. Clinical and Laboratory Data of Study Groups

	Fiberoptic Phototherapy (n=50)	Conventional Daylight Phototherapy (n=50)	p
Male to female ratio	26/24	28/22	> 0.05
Gestational age (wk)	38.9 ± 0.7	39.2 ± 0.67	> 0.05
Birth weight (g)	3350 ± 410	3410 ± 300	> 0.05
Age phototherapy initiated (h)	106.0 ± 44.7	104.8 ± 41.3	> 0.05
Bilirubin (mg/dl)	17.8 ± 2.7	18.2 ± 2.8	> 0.05
Hematocrit (%)	54.1 ± 4.5	53.3 ± 4.7	> 0.05

Values are given as mean ± SD.

Table II. Responses of Groups to Phototherapy

	Fiberoptic Phototherapy (n=50)	Conventional Daylight Phototherapy (n=50)	p
Duration of phototherapy (h)	61 ± 13.1	49.4 ± 14.4	< 0.05
Overall bilirubin decline rate (mg/dl/h)	0.1 ± 0.05	0.15 ± 0.06	< 0.05
Overall bilirubin decline rate (percent/h)	0.6 ± 0.3	0.8 ± 0.3	< 0.05
Posttreatment bilirubin (mg/dl)	11.3 ± 0.5	10.9 ± 0.7	> 0.05

Values are given as mean ± SD.

After terminating the phototherapy, two newborns in the fiberoptic phototherapy group and three newborns in the conventional phototherapy group had rebound bilirubin values exceeding the pretreatment values, and these babies needed a second phototherapy exposure. The difference between groups was not statistically significant ($p > 0.05$).

The average spectral irradiance measured during the study period was significantly greater in the fiberoptic phototherapy group (9.2 ± 1.2 mW/cm²/nm vs 7.1 ± 1.1 μW/cm²/nm, $p < 0.05$). The emission spectra of the daylight and tungsten-halogen lamps of the conventional phototherapy unit and fiberoptic phototherapy system, respectively, are shown in Figure 1. In daylight lamps, a broad emission between the violet and red spectra with tiny narrow peak emission bands in 405 nm, 436 nm, 546 nm and 577 nm was detected. In the tungsten-halogen lamp on the other hand, a broad emission through the blue and green wavelengths (mainly in the green spectrum) without any peak emissions was detected (Fig. 1).

Discussion

The minimum average spectral irradiance level required for an effective phototherapy has been recommended to be between 4 to 12 μW/cm²/nm[11,12]. Considering this recommended range, mean spectral irradiances in both of our study groups were high enough to provide an effective phototherapy.

In the first studies comparing the efficacy of fiberoptic phototherapy and conventional phototherapy in term babies, fiberoptic phototherapy was reported as efficacious as conventional phototherapy[13,14]. In two other studies, fiberoptic phototherapy was used as an alternative to conventional home phototherapy, and equal efficacy was reported in the treatment of term newborns at home[15,16]. However, the bilirubin levels at the start of treatment in all these studies were between 11 to 14 mg/dl, and these low pretreatment levels might not accurately reflect the efficacy of phototherapy, and might render it difficult to make of correct comparison between various phototherapy methods[3]. Cases in our study

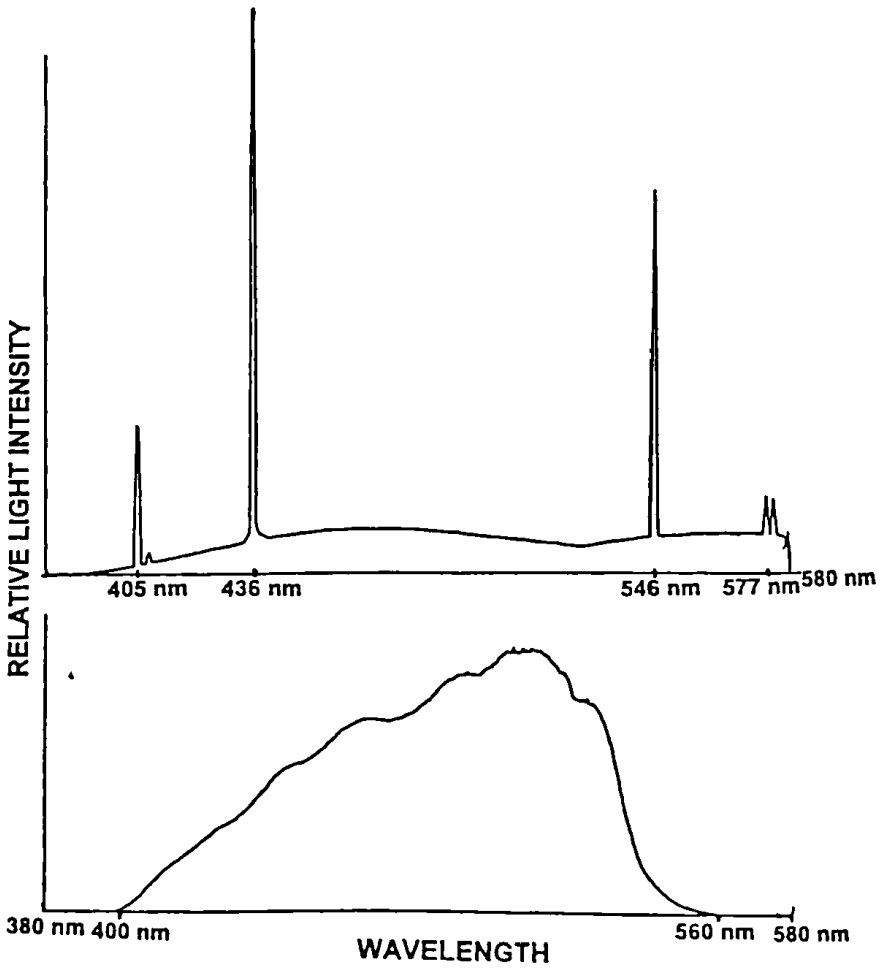

Fig. 1. Emission spectra of a daylight lamp (Sylvania Standard Daylight F 18 W/154) (top) and of a Tungsten-halogen lamp (fiberoptic phototherapy) (bottom).

groups had significant hyperbilirubinemia, and the mean bilirubin values at the initiation of treatment were significantly higher than those in all previous studies performed with fiberoptic phototherapy.

In preterm babies fiberoptic phototherapy was reported as efficacious as conventional phototherapy[4-6]. It was claimed that the efficacy of fiberoptic phototherapy in preterm babies was due to the skin properties of these babies which would permit increased light dosage absorption and better light penetration[6,17].

In two studies comparing the efficacy of in-hospital administration of fiberoptic phototherapy and conventional phototherapy in term babies, conventional phototherapy had significantly more efficacy[6,7]. Holtrop and associates[7] compared fiberoptic phototherapy and conventional phototherapy consisting of daylight and blue lamps, and they reported conventional phototherapy 2.5 times more effective than fiberoptic phototherapy after 18 h of treatment. They claimed that the increased efficacy was due to the significantly higher spectral irradiance of conventional phototherapy. Tan[6] compared fiberoptic phototherapy and conventional daylight phototherapy, and reported a mean decline rate of 0.49 pecent/h in 86.6 h in term babies with fiberoptic phototherapy. He stated that fiberoptic phototherapy in term babies, despite its higher irradiance, was not as efficacious as it was in preterm babies. Although the bilirubin decline with a mean rate of 0.60 percent/h in 61 h in our fiberoptic phototherapy group is seemingly more efficient than that see in Tan's study and in other studies, fiberoptic phototherapy was also less efficacious than conventional phototherapy in our study. The present study is the first study comparing fiberoptic phototherapy and conventional daylight phototherapy in term newborns with such significant hyperbilirubinemia.

Why fiberoptic phototherapy with higher irradiance was less efficacious than conventional phototherapy with less irradiance in our study must have been due to its feature of wavelength. The tungsten-halogen lamp of fiberoptilc phototherapy had an emission spectrum mainly in the green spectrum. The inability of green light to produce more bilirubin photoisomers than daylight, and the resultant decreased clinical efficacy of green light, have been shown previously[18,19]. We previously presented and compared the absorption spectra of fiberoptic phototherapy and conventional special bule light phototherapy in another study[8]. The absorption spectrum of daylight shown in the present study is the same as demonstrated earlier[20,21]. To our knowledge, ours is the first study comparing fiberoptic phototherapy and conventional daylight phototherapy by simultaneously demonstrating of their light sources.

Although fiberoptic phototherapy was less efficacious in this study, it had some practical advantages such as comfort of use, no need for eye patches, and easy accessibility and handling of newborns during phototherapy.

In phototherapy treatment of a relatively larger series of term newborns with more significant hyperbilirubinemia than reported in previous studies, conventional phototherapy with daylight fluorescent lamps demonstrated efficacy superior to fiberoptic phototherapy administered with phototherapy pad. Conventional phototherapy should be preferred to fiberoptic phototherapy in the treatment of term newborns with nonhemolytic hyperbilirubinemia.

REFERENCES

1. Al-Salihi FL, Curran YP. Airway obstruction by displaced eye mask during phototherapy. Am J Dis Child 1975; 129: 1362.
2. Fiberoptic Phototherapy Systems. Health Devices 1995; 24: 134-152.
3. Tan KL. Phototherapy for neonatal jaundice. Clin Perinatol 1991; 18: 423-439.
4. Donzelli GP, Moroni M, Pratesi S, Rapisardi G, Agati G, Fusi F. Fibreoptic phototherapy in the management of jaundice in low birthweight neonates. Acta Pediatr 1996; 85: 366-370.
5. van Kaam AH, van Beek RH, Vergunst van Keulen JG, et al. Fibre optic versus conventional phototherapy for hyperbilirubinaemia in preterm infants. Eur J Pediatr 1998; 157: 132-137.
6. Tan KL. Comparison of the efficacy of fiberoptic and conventional phototherapy for neonatal hyperbilirubinemia. J Pediatr 1994; 125: 607-612.
7. Holtrop PC, Madison K, Maisels MJ. A clinical trial of fiberoptic phototherapy vs conventional phototherapy. Am J Dis Child 1992; 146: 235-237.
8. Sarıcı SÜ, Alpay F, Ünay B, Özcan O, Gökçay E. Comparison of the efficacy of conventional special blue light phototherapy and fiberoptic phototherapy in the management of neonatal hyperbilirubinaemia. Acta Paediatr 1999; 88: 1249-1253.
9. Ballard JL, Novak KK, Driver M. A simplified score for assessment of fetal maturation of newly born infants. J Pediatr 1979; 95: 769-774.

10. Sarıcı SÜ, Alpay F, Ünay B, Özcan O, Gökçay E. Double versus single phototherapy in term newborns with significant hyperbilirubinemia. J Trop Pediatr 2000; 46: 36-39.
11. Maisels MJ. Jaundice. In: Avery GB, Fletcher MA, MacDonalds MG (eds). Neonatology: Pathophysiology and Management of the Newborn. Philadelphia, PA: JB Lippincott Company; 1994: 630-725.
12. Warshaw JB, Gagliardi J, Patel A. A comparison of fluorescent and nonfluorescent light sources for phototherapy. Pediatrics 1980; 65: 795-798.
13. Gale R, Dranitzki Z, Dollberg S, Stevenson DK. A randomized, controlled application of the Wallaby Phototherapy System compared with standard phototherapy. J Perinatol 1990; 10: 239-242.
14. Rosenfeld W, Twist P, Concepcion L. A new device for phototherapy treatment of jaundiced infants J Perinatol 1990; 10: 243-248.
15. Schuman AJ, Karush G. Fiberoptic vs conventional home phototherapy for neonatal hyperbilirubinemia. Clin Pediatr 1992; 31: 345-352.
16. Woodall D, Karas JG. A new light on jaundice. Clin Pediatr 1992; 31: 353-356.
17. Tan KL. Phototherapy for neonatal jaundice. Acta Paediatr 1996; 85: 277-279.
18. Tan KL. Efficacy of fluorescent daylight, blue, and green lamps in the management of nonhemolytic hyperbilirubinemia. J Pediatr 1989; 114: 132-137.
19. Ennever JF, McDonagh AF, Speck WT. Phototherapy for neonatal jaundice: optimal wavelengths of light. J Pediatr 1983; 103: 295-299.
20. Ennever JF, Sobel M, McDonagh AF, Speck WT. Phototherapy for neonatal jaundice: in vitro comparison of light sources. Pediatr Res 1984; 18: 667-670.
21. Agati G, Fusi F, Pratesi R. Configurational photoisomerization of bilirubin in vitro-II. A comparative study of phototherapy fluorescent lamps and lasers. Photochem Photobiol 1985; 41: 381-392.

Prevalence of asthma and other allergic disorders among schoolchildren in Diyarbakır, Turkey

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This study was performed to describe the prevalence rates of allergic diseases among children in southeast Anatolia. A questionnaire survey of children six to 15 years old was conducted using a modified version of the Turkish translated ISAAC protocol, with additional questions concerning sociodemographic and environmental characteristics of children that could be potential risk factors for allergic disorders. Questionnaires were distributed to parents of all children aged below 11 years and to children themselves aged over 11 for completion. A total of 3,040 children returned the questionnaires. The lifetime prevalence rates of asthma, wheezing, allergic rhinitis and atopic dermatitis were 14.1%, 22.4%, 12.9%, and 7.8%, respectively. The prevalence of wheezing, rhinitis and chronic rash in the last 12 months were 14.7%, 39.9%, and 11.8%, respectively. The prevalence rates of symptoms and diagnoses of allergic disorders were similar in boys and girls. Passive smoking, pet ownership, number of household and socioeconomic status were not significant risk factors for allergic diseases. Family history of atopy was the most prominent risk factor for all types of allergic diseases. high prevalence rates of asthma, rhinitis and eczema exist among schoolchildren in southeast Anatolia.

Key words: asthma, atopy, childhood, prevalence, Turkey.

In order to remove the differences regarding methodological issues in asthma prevalence studies, the International Studies of Asthma and Allergic Diseases (ISAAC) constituted a standard questionnaire[1]. Application of ISAAC protocol enabled comparison of the results derived from studies in various parts of the world. Thus, by using the standard ISAAC questionnaire in studies on asthma prevalence, differences regarding prevalence of asthma cannot be explained by differences in methodology.

Asthma prevalence studies in children suggest a high prevalence of asthma in the United Kingdom and Australia, moderate prevalence rates in many of the western countries and low prevalence rates in Eastern Europe and developing countries[2-7]. Moreover, the prevalence of asthma varies between different centers within the same country[6-8]. The reasons for these differences are still contradictory. Genetic, lifestyle and environmental factors may play a role in these variations[9-12]. There are various populations with different sociodemographic characteristics in distinct part of Turkey. These demographic variations and accompanying environmental factors may be responsible for the different results derived from asthma prevalence studies in the north, west and central parts of Turkey[13-18]. To our knowledge no study has been performed to date concerning the prevalence of asthma and other allergic diseases in southeast Anatolia using the ISAAC questionnaire.

In this study, a survey, using the ISAAC questionnaire, was performed to evaluate the prevalence of asthma, allergic rhinitis and eczema, and some relevant potential risk factors including age, gender, passive smoking, pet ownership, family history of atopy and socioeconomic status among children living in southeast Anatolia as their native region.

Material and Methods

A cross-sectional study was conducted between September 1999 and April 2000 using the ISAAC methodology. A Turkish translated modified version of the ISAAC questionnaire, validated by previous studies[15,17], was distributed through schools to the parents of 1,800 children aged 6-10 years. An additional 1,700 questionnaires were given to children aged 11-15 years, for self-completion. Thus, a total of 3,500 questionnaires were given to children from 15 different primary schools in Diyarbakır, a province in the southeast of Turkey. We obtained a list of schools from the Department of National Education in Diyarbakır. Schools participating in survey were selected by stratified randomization method.

Questions concerning sociodemographic characteristics, symptoms and diagnoses of asthma and other allergic disorders and their possible risk factors were included in the questionnaire. Since our study population consisted of children with different sociodemographic characteristics from different parts of the country, a response to the question "what is your homeland?" was requested in order to determine the native characteristics. Since there is no single word to encompass the meaning of wheezing, "wheeze" was translated into Turkish as "whistling sound coming from the chest".

Children whose parents or who themselves reported asthma were classified as "asthma ever" in the text and Tables. In southeast Anatolia, "allergic bronchitis" is commonly used interchangeably with asthma by physicians to preclude parental anxiety. Although we believe that most of the children labeled as "allergic bronchitis" in reality have asthma, we evaluated allergic bronchitis with a different question. Thus, one of our additional questions was "Has your child or you ever had allergic bronchitis?" On a separate page, questions concerning potential risk factors for asthma and other allergic symptoms were added to the ISAAC questionnaire (see Appendix). These questions were concerning the number of siblings and household, mean number of cigarettes smoked at home/day, the presence of dampness and of a pet at home and the type of heating system. In order to evaluate the socioeconomic status of the families, the highest degree of paternal education was also assessed. The family history of allergic diseases was assessed by four different questions enquiring "Have father, mother, siblings, or any other family member ever suffered from asthma, hay fever, or eczema?".

Statistical Analysis: Prevalence rates were calculated, and chi-square test and odds ratios were used to assess the differences between the two groups. A multivariate logistic regression analysis was used to estimate risk factors for asthma and other allergic diseases. Estimates of the odds ratio (OR) and 95% confidence intervals (95% CI) were based on the asymptomatic likelihood theory. A p value less than 0.05 was considered as significant. The SPSS software package version 7.5 was used for all statistical analyses.

Appendix: Additional Questions to Turkish Translated ISAAC Questionnaire

1. What is your homeland?
2. How many siblings does child have?
3. How many persons live in your house?
4. Does anyone smoke in your house?
5. Is father a smoker?
6. Is mother a smoker?
7. What is the mean number of cigarettes smoked daily in your house?
8. Has your house been moldy from dampness?
9. Which heating system is mainly used in your house?
10. Do you have pets in your house and, if yes, which pets are these? (in two questions).
11. What is the highest education degree of father and mother? (in two questions).
12. Have father, mother, siblings or other family members ever suffered from asthma, hay fever, eczema, or allergic rhinitis? (in four questions).

Results

Of the 3,500 questionnaires, 3,085 (88.1%) were returned. Fourty-five questionnaires were excluded from the analysis as they were incomplete. Thus, data from 3,040 children were eligible for final analysis.

Of all children, 72.1% were from urban Diyarbakır, 10.3% from surrounding towns of Diyarbakır, 6.2% from rural areas transported for education from villages and 9.0% from other administrative provinces of southeast Anatolia. Only 73 children (2.4%) were from other regions of Turkey.

The mean (± SD) age of the children was 10.7 ± 2.6 years. The male to female ratio was 1.40. Children were mainly aged 7-9 years and 12-14 years. The age and gender distribution of the study population is shown in Table I.

Table I. Distribution of Study Population According to Age and Gender

Age (years)	Boys n (%)*	Girls n (%)*	Total n (%)*
6	12 (0.4)	25 (0.8)	37 (1.2)
7	238 (7.8)	218 (7.2)	456 (15.0)
8	277 (9.1)	231 (7.6)	508 (16.7)
9	126 (4.2)	89 (2.9)	215 (7.1)
10	40 (1.3)	39 (1.3)	79 (2.6)
11	71 (2.3)	75 (2.5)	146 (4.8)
12	346 (11.4)	299 (9.8)	645 (21.2)
13	373 (12.3)	222 (7.3)	595 (19.6)
14	199 (6.5)	54 (1.8)	253 (8.3)
15	90 (3.0)	16 (0.5)	106 (3.5)
Total	1772 (58.3)	1268 (41.7)	3040 (100.0)

* % of total study population.

The cumulative and current (last 12 months) prevalence of allergic diseases, as well as the prevalence rates of symptoms, diagnoses and treatment related to asthma in boys and girls are given in Tables II-V. In our study population, the lifetime prevalence rates of various symptoms and diagnoses were as follows: wheezing, 22.4%; self-reported asthma, 14.1%; hay fever, 12.9%; eczema, 7.8%; and allergic bronchitis, 5.8%. The current (in the past year) prevalence rates were: wheezing, 14.7%; weezing with exercise 9.8%; rhinitis, 39.9%, associated conjunctivitis, 18.9%; itchy rash, 11.8%; drug usage for asthma and wheezing, 6.9%; and hospital admissions due to wheezing, 2.6%. With acceptance of most of allergic bronchitis cases as asthma, the prevalence of asthma ever would reach 19.9%. Except for male predominance of wheezing in the past year and wheezing with exercise ($p = 0.011$ and $p = 0.033$, respectively), prevalence rates of symptoms related to asthma were similar in boys and girls ($p > 0.05$) (Table II). There was no significant difference between boys and girls in the prevalence rates of symptoms and diagnoses concerning rhinitis and eczema (Table IV). The combination of asthma, eczema and rhinitis was seen in 1.5% of girls, 1.4% of boys and 1.4% of all children; whereas 25.7% of girls, 26.7% of boys and 26.3% of all children had asthma or eczema or rhinitis. Allergic rhinitis (hay fever) was reported by 31.5% of boys and 34.1% of girls with asthma, respectively. Atopic eczema was reported by 17.8% and 26.8% of boys and girls with asthma, respectively. The families of 529 children (17.4%) had pets at home, with birds the most common (228 families, 7.5%), and cat (73 families, 2.4%) the second most common. The parents of 2,003 (65.9%) children were reported to be smoking at home. There was no significant difference between the children reported to have or not have asthma in terms of the number of the household or siblings or the mean number of cigarettes smoked daily at home ($p > 0.05$, data not shown). The type of heating system and parental educational status were different in children with and without asthma ($p < 0.05$). Children with asthma had more frequent exposure to heating with wood or coal stove than that of the children without asthma (56.9% vs. 50.4%, respectively, $p < 0.001$). The frequency of more educated father (high school and over) was found to be higher in the families of children without asthma than those of children with asthma (42.6% vs. 38.6%, respectively, $p < 0.001$). Tables V, VI and VII show the association between various ymptoms and potential risk factors. There was no association between exposure to passive smoking at home and asthma, ever wheezing or wheezing with exercise ($p > 0.05$). Family history of atopic disease was reported for mothers in 654 families (21.5%), for fathers in 401 families (13.2%), and for a family member other tan parents and siblings in 623 families (20.5%). History of atopic heredity was the most outstanding and consistent risk factor for all allergic conditions (Table V-VII).

With logistic regression analysis, family history of atopic disease was found as a significant risk factor for almost all symptoms and diagnoses of allergic diseases in children. In addition to history of atopic heredity, dampness at home was found to be a ristk factor for ever asthma; smoking at home for ever rhinitis; and number of household, dampness and central heating (odds ratio = 0.64, 95% CI = 0.43-0.94, $p = 0.024$) for ever hay fever. The number of household and dampness were also additional risk factors for ever eczema (Table VII).

Table II. Prevalence (%) of Symptoms and Diagnosis of Allergic Respiratory Diseases Among Boys and Girls

Symptoms	Boys* (n=1772)	Girls* (n=1268)	Total (n=3040)	*P value
Ever wheezed	22.4	22.5	22.4	NS
Wheezed in the past year	15.8	13.2	14.7	0.011
Number of episodes				
< 4	8.5	8.2	8.4	
4-12	3.1	2.8	3.0	NS
> 12	3.8	2.0	3.3	
Sleep disturbance	10.6	9.2	10.0	NS
Severe episode	5.2	5.7	5.4	NS
Ever had asthma	14.8	13.2	14.1	NS
Wheezing with exercise in the past year	10.5	8.1	9.8	0.033
Night cough	35.2	35.2	35.2	NS
Allergic bronchitis	6.3	5.0	5.8	NS

NS: Not significant.

Table III. Frequency (%) of Positive Responses Regarding Asthma Treatment in the Past Year in Both Genders (p > 0.05)

Questions regarding asthma treatment	Boys (n=1772)	Girls (n=1268)	Total (n=3040)
Medicine for asthma and wheezing	6.6	7.3	6.9
Medicine for exercise-related wheezing	1.4	1.2	1.3
Written plan for asthma	1.9	2.2	2.0
Peak flow meter usage at home	1.4	2.0	1.6
Visits for wheezing	5.8	5.1	5.5
Visits for asthma check-up	2.3	2.3	2.3
Hospital admissions due to wheezing	2.8	2.4	2.6
Visits to paramedical person	3.0	2.7	2.9
Allergy injection for asthma	3.2	4.1	3.6
School days missed	6.7	7.0	6.8

Table IV. Prevalence (%) Symptoms Related to Rhinitis and Eczema in Boys and Girls (p > 0.05)

Symptoms	Boys (n=1772)	Girls (n=1268)	Total (n=3040)
Rhinitis			
Ever had rhinitis	51.6	49.2	50.6
Rhinitis in the past year	39.8	39.9	39.9
Associated itchy eye in the past year	18.2	19.8	18.9
Season			
Spring	6.6	5.0	5.9
Summer	4.6	4.1	4.4
Autumn	10.3	10.8	10.5
Winter	19.2	18.7	19.0
Interference with daily activity			
Not at all	8.5	9.0	8.7
Little	24.0	22.2	23.3
Moderate	8.2	6.6	7.5
Severe	3.8	4.3	4.0
Ever had hay fever	13.1	12.5	1.29
Eczema			
Chronic itcy rash ever	14.4	14.5	14.4
Chronic rash in the past year	11.6	12.0	11.8
Chronic rash with typical distribution	9.3	10.2	9.7
Healing in the past year	8.3	9.8	8.9
Sleep disturbance due to itch	9.0	8.8	8.9
Ever had eczema	7.1	8.8	7.8

Table V. Prevalence (%) of Potential Risk Factors Related to Ever Asthma Response

Risk factors	Ever Asthma Yes* (n=430) %	Ever Asthma No* (n=2610) %	OR (95% CI)	*P value
Father smoking	60.7	57.6	1.14 (0.79-1.63)	0.53
Mother smoking	22.3	20.3	1.13 (0.74-1.08)	0.58
Smoking at home	69.3	65.3	1.20 (0.83-1.75)	0.35
Daily number of cigarettes smoked at home > 10	18.8	15.7	1.14 (0.72-1.79)	0.55
Dampness in the house	16.1	9.7	1.79 (1.09-2.91)	0.03
Pet ownership	17.0	19.3	0.85 (0.53-1.36)	0.56
Highly educated parents (high school and over)	38.5	42.9	0.83 (0.58-1.19)	0.36
Household > 5	65.1	60.5	1.23 (0.85-1.79)	0.30
Siblings > 2	62.6	59.6	1.12 (0.78-1.59)	0.59
Male gender	61.2	57.9	1.15 (0.93-1.41)	0.22

OR : Odds ratio.
CI : Confidence interval.
* : According to χ^2 test.

Table VI. Effects of Family History of Atopy on Reported Wheezing, Asthma, Ever Rhinitis, Hay Fever, Chronic Itchy Rash and Eczema

	Maternal history of atopy OR (95% CI)	Paternal history of atopy OR (95% CI)	History of atopy other than perants Or (95% CI)
Asthma ever	2.22 (1.52-3.24)	3.55 (2.34-5.37)	1.71 (1.14-2.56)
Wheeze ever	2.15 (1.54-2.99)	2.84 (1.94-4.15)	1.94 (1.37-2.76)
Rhinitis ever	2.20 (1.63-2.98)	2.90 (1.99-4.22)	2.35 (1.71-3.23)
Hay fever	2.96 (2.03-4.31)	3.41 (2.23-5.19)	1.96 (1.32-2.93)
Chronic rash ever	1.69 (1.14-2.50)	2.49 (1.62-3.84)	1.54 (1.02-2.33)
Eczema ever	2.54 (1.56-4.11)	4.12 (2.47-6.88)	2.43 (1.48-4.01)

OR : Odds ratio.
CI : Confidence interval.

Table VII: Significant Risk Factors on Reported Symptoms of Allergic Diseases Using Logistic Regression Analysis [OR (CI)]

Symptoms	Dampress at home	Paternal history of atopy	Maternal history of atopy	Number of household
Ever wheezed		2.81 (1.91-4.16)***	1.99 (1.39-2.87)**	
Ever asthma	1.80 (1.08-3.02)*	3.50 (2.29-5.35)***	2.01 (1.32-3.06)**	
Ever rhinitis		3.14 (2.14-4.61)***	1.94 (1.39-2.70)**	
Ever hay fever	1.73 (1.04-2.89)**	3.13 (2.03-4.81)***	2.66 (1.77-3.99)***	1.08 (1.01-1.16)*
Chronic rash		2.71 (1.74-4.21)***	1.66 (1.08-2.56)*	
Ever eczema	1.66 (1.08-2.56)**	4.40 (2.59-7.47)***	1.88 (1.09-3.22)*	1.12 (1.03-1.22)**

OR : Odds ratio.
CI : Confidence interval.
*** : $p < 0.001$, ** : $p < 0.01$, * : $p < 0.05$.

Discussion

The results of this study demonstrated that the prevalence of asthma and other allergic diseases differs in the southeast of Turkey from that seen in other parts of the country. Asthma and eczema were significantly more common among children in Diyarbakır than in some other parts of Turkey. However, the prevalence of hay fever was similar to the results of studies conducted in Ankara, Samsun and Edirne[13,14,16].

Although the ISAAC questionnaire has been tested and validated[1] and its validity and repeatability have been confirmed in relation to bronchial hyperreactivity[19] and physician-diagnosed asthma[20], some methodological problems may still exist. One problem is about

the questions concerning the lifetime prevalence and doctors' diagnoses of allergic diseases, which are subject to recall bias and may reflect the attitude of the parents toward health issues and the accesibility of the health care system, which may be worse in our region than in western regions of Turkey. Another problem may be related to hay fever. Since the term "hay fever" is not a very commonly used expression in the Turkish language, questions concerning hay fever may have resulted in an over reporting of common cold symptoms rather than symptoms of allergic rhinitis in children. Finally, the term allergic bronchitis is frequently used interchangeably with asthma by most physicians in Turkey. Although an objective of the survey was not to differentiate allergic and viral components of rhinitis, the questionnaire has been validated previously, with the combination of itchy eyes in addition to nasal symptoms being found to be most closely related to allergic sensitization. Of the total study population, 18.9% had associated itchy eye together with rhinitis in the past year. Thus, nearly half of the reported prevalence of 39.9% for rhinitis in the past year may be of viral origin.

Season of response has been shown to bias rhinitis, especially in the spring/early summer, but not eczema or most asthma symptoms. Our study was conducted between November and April, before the start of the pollen season. Thus, seasonal bias might have been eliminated in our study.

There was not any gender difference in respiratory symptoms in our study. Although some studies reported a male predominance of asthma symptoms in 5-7-year-old children, self-completed questionnaires in older children generally showed a female predominance of asthma symptoms[4]. Previous studies have shown a higher incidence of atopy in boys compared with girls at age 12. Anderson et al.[21] suggested that by 16 years, the sex ratio reverses. Equal distribution of symptoms between boys and girls in our study may be explained by the fact that 57.4% of our study population consisted of children aged over 11 years, and among adolescent children, boys might tend to underestimate, and girls overestimate, the severity of disease.

We found a strong association between reported asthma symptoms and symptoms of allergic rhinitis and eczema. Considering the association of allergic rhinitis and eczema with asthma in children, Anderson et al.[21] showed that it was a characteristic feature of atopic trait. We found atopic heredity as the most prominent risk factor for all allergic diseases studied. We did not find parental smoking or smoking at home as risk factors for asthma, wheezing, rhinitis or eczema in our study. Although the percentage of children exposed to parental smoking was higher in children reported to have asthma and wheezing than in others, this difference was not statistically significant (Table VI). This may be the result of widespread parental smoking, since 71.1% of the parents of our study population smoked at home. Comparing our study with other studies performed in other parts of Turkey, our prevalence rates of asthma, rhinitis and eczema were similar to those of the study conducted in Edirne, and were higher than reported rates of studies in Ankara, İstanbul and Samsun[13,17]. In those studies, prevalence of asthma was reported as 6.9-8.1% in Ankara, 10.2% in Samsun, 9.8 in İstanbul, and 16.4% in Edirne. However, when compared with the results of a recent study from England, our prevalence rates were significantly lower, except for ever rhinitis and hay fever. In that study from England, prevalence rate of ever asthma was 22.7%, ever wheeze 29.6%, ever eczema 27.8%, current rhinitis 20.5% and hay fever 10.1%[4].

High socioeconomic status and "western" lifestyle were supposed to be responsible for high prevalence of asthma and oher allergic diseases. The results of our study were contradictory, since the socioeconomic levels of our study population were lower than in other parts of Turkey and our prevalence of asthma was higher than in other regions of the country. In a recent study, no statistically significant association was determined between the prevalence of asthma, rhinitis and atopic dermatitis and socioeconomic status in children 6 to 7 years of age in Spain[22]. Thus, we can suggest that our high prevalence rates may be derived from genetic factors, i.e. atopic heredity. Genetic and environmental factors might account for the difference in the prevalence of asthma and other allergic diseases between different regions of the same country[10].

The results of this study demonstrate a high prevalence of asthma and rhinitis in southeast Anatolia. More than 25% of children were found to have at least one allergic disease and 23% had more than one. This highlights the importance of allergic diseases in children of this region.

In conclusion, our study provides a description of the scale and distribution of asthma, rhinitis and eczema in 6-15 year-old children from the southeast of Turkey. The study would be a suitable baseline source for future trends in the prevalence rates, diagnoses and severity of asthma, rhinitis and eczema among these children.

REFERENCES

1. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995; 8: 483-491.
2. Pearce N, Weiland S, Keil U, et al. Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: an international comparison using the ISAAC protocol. Eur Respir J 1993; 6: 1455-1461.
3. Austin JB, Kaur B, Anderson HR, et al. Hay fever, eczema, and wheeze: a nationwide UK study (ISAAC, International Study of Asthma and Allergies in Childhood). Arch Dis Child 1999; 81: 225-230.
4. Shamssain MH, Shamsian N. Prevalence and severity of asthma, rhinitis, and atopic eczema: the northeast study. Arch Dis Child 1999; 81: 313-317.
5. Björksten B, Dumitrascu D, Foucard T, et al. Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe. Eur Respir J 1998; 12: 432-437.
6. Kabesch M, Schaal W, Nicolai T, von Mutius E. Lower prevalence of asthma and atopy in Turkish children living in Germany. Eur Respir J 1999; 13: 577-582.
7. Weiland SK, von Mutius E, Hirsch T, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification Eur Respir J 1999; 14: 862-870.
8. Pekkanen I, Remes ST, Husman T, et al. Prevalence of asthma symptoms in video and written questionnaires among children in four regions of Finland. Eur Respir J 1997; 10: 1787-1794.
9. Beckett WS, Belanger K, Gent JF, Holford TR, Leaderer BP. Asthma among Puerto Rican Hispanics: a multiethnic comparison study of risk factors. Am J Respir Crit Care Med 1996; 154: 894-899.
10. International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence and symptoms of asthma, allergic rhino conjunctivitis, and atopic eczema: ISAAC: Lancet 1998; 351: 1225-1232.
11. Kalyoncu AF, Stalenheim G. Serum IgE levels and allergic spectra in immigrants to Sweden. Allergy 1992; 47: 277-280.
12. Pararajasingam CD, Sittampalam L, Damani P, Pattemore PK, Holgate ST. Comparison of the prevalence of asthma among Asian and European children in Southampton. Thorax 1992; 47: 529-532.
13. Saraçlar Y, Yiğit Ş, Adalıoğlu G, Tuncer A, Tunçbilek E. Prevalence of allergic diseases and influencing factors in primary-school children in the Ankara region of Turkey. J Asthma 1997; 34: 23-30.
14. Selçuk ZT, Çağlar T, Enünlü T, Topal T. The prevalence of allergic diseases in primary school children in Edirne, Turkey. Clin Exp Allergy 1997; 27: 262-269.
15. Öneş Ü, Sapan N, Somer A, et al. Prevalence of childhood asthma in İstanbul, Turkey. Allergy 1997; 52: 262-269.
16. Küçüködük Ş, Aydın M, Çetinkaya F, Dinç H, Gürses N, Saraçlar Y. The prevalence of asthma and other allergic diseases in a province of Turkey. Turk J Pediatr 1996; 38: 149-153.
17. Saraçlar Y, Şekerel BE, Kalaycı O, et al. Prevalence of asthma symptoms in school children in Ankara, Turkey. Respir Med 1998; 92: 203-207.
18. Karaman Ö, Türkmen M, Uzuner N. Allergic disease prevalence in İzmir. Allergy 1997; 52: 689-690.
19. Shaw R, Woodman K, Ayson M, et al. Measuring the prevalence of bronchial hyperresponsiveness in children. Int J Epidemiol 1995; 24: 597-602.
20. Jenkins MA, Clarke JR, Carlin JB, et al. Validation o questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. Int J Epidemiol 1996; 25: 609-616.
21. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992; 5: 930-935.
22. Suarez-Varela MM, Gonzalez AL, Martinez Selva MI. Socioeconomic risk factors in the prevalence of asthma and other atopic diseases in children 6 to 7 years old in Valencia Spain. Eur J Epidemiol 1999; 15: 35-40.

Atrial septal aneurysm in children

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SUMMARY: Baysal K, Belet N, Kolbakır F, Yalın T. Atrial septal aneurysm in children Turk J Pediatr 2001; 43: 293-297.

Atrial septal aneurysm (ASA) has rarely been described in children. In this study, we evaluated the incidence and natural course of this anomaly in children. ASA was found in 30 patients (1%); 16 patients had type 1R and 14 patients had type 2L ASA. Twenty patients with ASA were followed: in four the ASA disappeared and in three patients with type 2L an atrial septal defect (ASD) developed during follow-up. The most common associated lesion was patent foramen ovale (PFO).

We conclude that ASAs in children are not rare lesions, and that these aneurysms, particularly type 2L aneurysms, should be followed for occurrence of ASD.

Key words: atrial septal aneuryms, echocardiography, children.

An atrial septal aneurysm (ASA) is a localized protrusion of the interatrial septum into the right or left atrium, or both, caused by bulging of the primary component of the septum through the oval fossa[1] Interatrial septal aneurysm has been detected with increasing frequency since the advent of two-dimensional echocardiography. The incidence of interatrial septal aneurysm has been reported to be 1.7% to 4.9% in children and infants[2,3]. Several cardiac defects have been noted to be associated with such aneurysms, including atrial septal defect and prolapse of the leaflets of the mitral and tricuspid valves[1,4,5]. Arrhythmias have also been reported both in postnatal patients and fetuses[1,6,7]. Its pathogenesis is controversial, but it is believed to depend on two predisposing factors: abnormal hemodynamic conditions and inherent structural weaknesses of the neonatal atrial septum[1,2]. The occurrence of an ASA after spontaneous closure of an atrial septal defect has also been reported.

The purpose of the study was to determine the prevalence of ASA and associated cardiac lesions in pediatric patients and the natural course of the defect, and to analyze the motion pattern of ASA.

Material and Methods

Echocardiographic examinations were performed in 3000 consecutive patients suspected of having cardiac abnormalities at the Pediatric Cardiology Unit between January 1993 and October 1998. Patients were included in the study if the interatrial septum could be satisfactorily visualized from both the subcostal and apical four chamber views. Ages of subjects ranged from 2 days to 11 years. Echocardiographic studies were performed by the same pediatric cardiologist using either a TOSHIBA SSA 160A with 2.5, 3.25, and 3 MHz or an ATL-HDL 3000 CW with 3-5 and 4-7 MHz transducers.

Each patient was evaluated for cardiovascular disease clinically and by chest radiography, electrocardiography (ECG), two-dimentional echocardiography (2DE), and color-flow Doppler echocardiography. Two types of atrial septal aneurysms were defined: type 1R if the bulging were in the right atrium only, and type 2L if the bulging were in the left atrium only (Figs 1 and 2)[8]. Each patient with an ASA was evaluated for coexistent atrioventricular valve prolapse. Evaluation of the interatrial shunts and diagnosis of accompanying cardiac anomalies were performed by Doppler echocardiography and contrast echocardiography (with D-galactose 300 mg/ml).

Patients with ASA were reevaluated serially by clinical examination, 2DE, and Doppler echocardiography. At each follow-up visit, the size and motion pattern of the ASA were compared to its appearance at initial diagnosis.

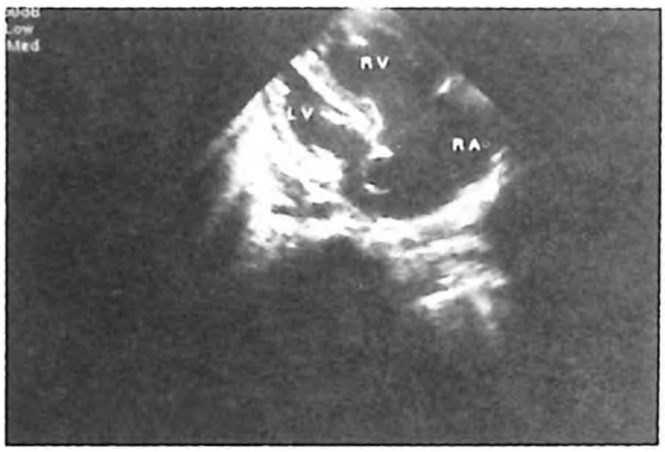

Fig. 1. Case 1. Two-dimensional echocardiogram in apical four-chamber view. Atrial septal aneurysm protruding into left atrium is noted.

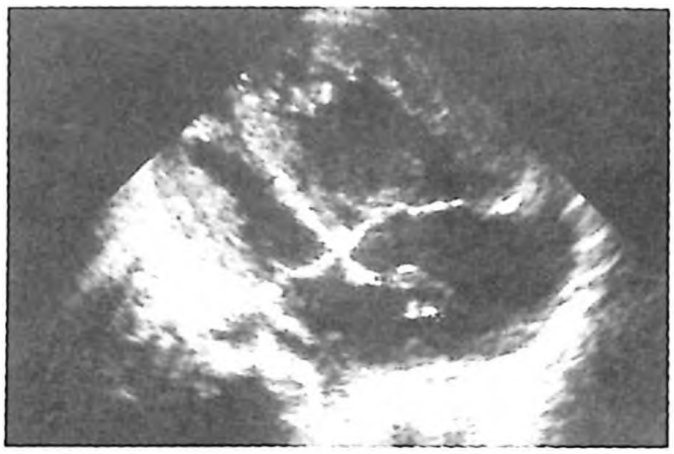

Fig. 2. Case 22. Two-dimensional echocardiogram in apical four-chamber view. Atrial septal aneurysm protruding into the right atrium is noted.

Results

Atrial septal aneurysm was found in 30 of 3000 patients (1%). There were 13 females and 17 males. The age at diagnosis of these ranged from 2 days after birth to 11 years. The follow-up period of these patients ranged from 4 to 31 months. Follow-up echocardiography was performed every four or five months once an aneurysm had been detected.

Sixteen patients had type 1R and 14 patients had type 2L ASA. Initially five patients showed an isolated aneurysm of the atrial septum. Three of these patients with type 2L ASA developed an atrial septal defect (ASD) during the follow-up period, one at the 6th month, one at the first year and one at the 18th month. All three patients were operated, for the defect. When associated with ASD, the direction of the ASA motion and that of the shunt found by Doppler echocardiography were similar. All other patients showed associated cardiac abnormalities (93%). The most common lesions were patent foramen ovale (PFO, 36.6%) and ventricular septal defect (VSD, 23.3%). The clinical and echocardiographic findings of the patients with ASA are summarized in Table I. No patient had associated atrioventricular valve prolapse. In 10 of 30 patients, follow-up tests were not performed. Four of these patients were lost to follow-up, one died due to respiratory failure and five patients were recently diagnosed. Disappearance of ASA was found in four of our patients (13.3%).

Table I. Characteristics of Patients With Atrial Septal Aneurysm

Patient	Age at Dx	Sex	Associated cardiovascular disease	Direction of ASA protrusion	Length of follow-up (mo)	Follow-up		Extracardiac findings
						ASA Dis	ASA Flow	
1[a]	10 mos	M	ASD	LA → RA	11 mos	0	No change	
2	7 mos	M	PFO	LA → RA	9 mos	0	No change	
3	52 days	M	PFO	RA → LA	4 mos	+	Dis	
4	9 mos	F	Cardiomyopathy	LA → RA	4 mos	+	Dis	
5	5 mos	F	PDA	RA → LA	7 mos	0	No change	
6	2 days[d]	M	PDA, VSD	RA → LA	31 mos	+	Dis	
7	7 mos	M	VSD	RA → LA	27 mos	0	No change	
8	3 mos	M	VSD	RA → LA	24 mos	0	No change	
9	9 days	M	PFO, VSD	RA → LA	16 mos	0	No change	OI
10	40 days	M	PDA	RA → LA	NF			MRD
11	16 mos	F	PFO	RA → LA	24 mos	0	No change	
12	4 mos	F	PFO	LA → RA	23 mos	0	No change	
13	3 years	F	PFO	RA → LA	NF			
14	3 mos	M	PFO	LA → RA	12 mos	0	No change	
15	3 mos	M	None	RA → LA	Ex			
16	43 days	M	PFO	LA → RA	6 mos	0	No change	
17	10 days	F	TF	RA → LA	20 mos	0	No change	Down syndrome

Table I. Continued

Patient	Age at Dx	Sex	Associated cardiovascular disease	Direction of ASA protrusion	Length of follow-up (mo)	Follow-up		Extracardiac findings
						ASA Dis	ASA Flow	
18	2 mos	F	VSD	LA → RA	Recently			
19	3 days	F	PFO	RA → LA	14 mos	+	Dis	
20	11 years	F	TF	LA → RA	NF			
21	5 mos	M	VSD	LA → RA	Recently			Down syndrome
22	5 mos	M	PFO	LA → RA	16 mos	0	No change	Down syndrome
23	2 mos	F	TF	LA → RA	Recently			
24	18 days	M	VSD	LA → RA	Recently			
25	9 mos	F	None	LA → RA	NF			
26	6 mos	F	PFO, TF, PS	LA → RA	Recently			
27	18 mos	M	TF	RA → LA	24 mos	0	No change	CAH
28	34 days	F	None	LA → RA	Recently			
29[b]	16 mos	M	ASD	LA → RA	16 mos	0	No change	
30[c]	7 years	M	ASD	LA → RA	3 years	0	No change	

ASA : atrial septal aneurysm.
ASD : atrial septal defect.
Dis : disappearance.
Dx : diagnosis.
LA : left atrium.
NF : no follow-up.
PDA : patent ductus arteriosus.
PS : pulmonary stenosis.
RA : right atrium.
TF : tricuspid failure.
VSD : ventricular septal defect.
PFO : patent foramen ovale.
CAH : congenital adrenal hyperplasia.
OI : osteogenesis imperfecta.
MRD : multiple renal dysplasia.
Ex : Exitus.
a : ASD ocurred at the 6th mo.
b : at the first year.
c : at the 18th month.
d : This patient is term infant.

Associated noncardiac anomalies were found in seven patients: four Down's syndrome, one osteogenesis imperfecta, one multicystic renal dysplasia, and one congenital adrenal hyperplasia (3-β hydroxysteroid dehydrogenase deficiency).

Discussion

Atrial septal aneurysm prevalence might have been underestimated in the past because of absence of symptoms and lack of noninvasive techniques for its diagnosis. 2DE is currently the best method for in vivo diagnosis of ASA[1,6,9,10]. Several studies have described ASA and its incidence in adults and children[1-3,6]. The reported incidence of ASA in the literature varied depending on the age of the study population and on the dignostic method used. Hanley et al.[1] found a higher incidence of ASA in children less than nine years old, very low incidence in adolescents and young adults, and increased incidence in older patients. Wolf et al.[2] identified ASA in 1.7% of infants and children who had undergone an initial diagnostic 2DE evaluation. Shiraishi et al.[3] reported the prevalence as 0.9% in children and 4.9% in infants. Brand et al.[11] showed an ASA incidence of 1% in infants and children. Rice and colleagues[7] found a very high incidence (64%) of ASA in fetal echoes of patients who were referred for the evaluation of fetal arrhythmia, compared to a 26% incidence in the fetuses referred for ruling out congenital heart disease. The prevalence of ASA detected by echocardiographic examination in adults is 0.2-0.5%[1-9]. This discrepancy between infants and adults implies the atrial septum is easily visualized in infants compared to adults, and that some of the aneurysms in infancy may disappear spontaneously with growth. ASA incidence was 1% in our study and similar to the general population is still unknown, since both present and previous studies specifically examined individuals with suspected cardiovascular disease.

Most previously published reports of ASA in children were associated with cardiac anomalies, such as ASD[1,10], tricuspid atresia[13], hypoplastic right heart syndrome[14] and transposition of the great vessels[16]. In adults, the associated cardiac defects were mitral valve prolapse[9], mitral stenosis or regurgitation[1], aortic stenosis and ASD. Rarely ASA occurs as an isolated pathologic finding. Pathologic examinations of ASA suggest a frequent association of this entity with interatrial communication. Mügge et al.[16] found that interatrial shunts, in particular foramen ovale, were the most common

abnormalities associated with ASA in adults. Barbosa et al.[17] in a mixed series of adults and children reported a 50% ratio of ASD among ASA patients. Brand et al.[11] showed in children that the most common associated lesion was atrial septal defect (69%); other associated cardiac lesions were VSD (28.5%), pulmonary stenosis (PS) (14%), patent ductus arteriosus (PDA) (11.5%) and coarctation or interruption of the aorta with subaortic membrane (6%). In our study, 93% of patients with ASA had additional cardiac anomalies; 7% occurred as an isolated lesion. Most frequently these included PFO (36.6%), although more complex defects were also found. Other associated cardiac lesions were VSD (23.3%), PDA (10%), (F) (16.6%), ASD (10%), and cardiomyopathy (3.3%). As noted in preious reports, ASA was often associated with interatrial communication (46.6%, 11 PFO, 3 ASD). In adults, thrombus formation, systemic emboli, atrioventricular and pulmonary vein obstructions, and atrial tachyarrhythmias were described in patients with ASA. No such complications were noted in our patients.

In our study, there were four children with Down's syndrome among ASA patients. Barbosa et al.[17] reported one Down's syndrome in 14 ASA patients. Further investigations are necessary to reveal the true relationship and incidence of ASA in patients with chromosomal abnormalities.

Several studies have suggested that interatrial septal aneurysms may be an initiating mechanism of atrial arrhythmis in adults and children. Miga et al.[18] suggested that ASAs are not a predisposing factor for the development or recurrence of atrial arrhythmias in infants. They appear to be an incidental finding without significant long-term complications. In our study, none of the patients had a history of arrhythmias.

Various mechanisms of the formation of ASAs have been postulated[1,2,10]. Wolf et al.[2] suggested that ASA formation in infants is related to abnormal hemodynamic conditions in the atrium (structural heart disease or arrhythmias) and inherent structural weaknesses of the neonatal septal tissue. The occurrence of an ASA after spontaneous closure of an ASD has also been reported[11]. Moreover, association of ASA with mitral valve prolapse or Marfan's syndrome implies that congenital connective tissue laxity is also responsible for ASA formation[12]. No patient in this study had atrioventricular valve prolapse or evidence of a systemic connective tissue disorder that might account for ASA formation. These findings suggest that such an aneurysm develops from other causes.

The majority of ASAs in infants will involute or completely resolve with age and intracardiac growth once normal atrial hemodynamics have been established. Brand et al.[11] found that the rate of the disappearance of ASAs was 45% in their patient. The aneurysm disappeared in most patients who had spontaneous closure of an associated ASD. Awan et al.[10] also described a case of spontaneous closure of an ASD with disappearance of ASA. In our study, ASA disappeared in four patients (13.3%). We observed that an ASD occurred in three patients during follow-up initially having type 2L ASA. Contrary to the literature, we observed that ASA, particularly type 2L aeurysms, may cause ASD.

In conclusion, ASA is not rare among children and it must be followed since type 2L ASA may cause ASD. In addition, interatrial shunts are frequent in ASA patients, and should be evaluated by Doppler and contrast echocardiography.

REFERENCES

1. Hanley PC, Tajik AJ, Hynes JK, et al. Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: report of 80 consecutive cases. J Am Coll Cardiol 1985; 6: 1370-1382.
2. Wolf WJ, Casta A, Sapire DW. Atrial septal aneurysms in infants and children. Am Heart J 1987; 113: 1149-1153.
3. Shiraishi I, Hamaoka K, Hayashi S, Koh E, Onouchi Z, Sawada T. Atrial septal aneurysm in infancy. Pediatr Cardiol 1990; 11: 82-85.
4. Ilicetos S, Papa A, Sorino M, Rizzon P. Combined atrial septal aneurysm and mitral valve prolapse: detection by two-dimensional echocardiography. Am J Cardiol 1984; 54: 1151-1153.
5. Roberts WC. Aneurysm (redundancy) of the atrial septum (fossa ovale membrane) and prolapse (redundancy) of the mitral valve. Am J Cardiol 1984; 54: 1153-1154.
6. Hauser AM, Timmis GS, Stewart JR, et al. Aneurysm of the atrial septum as diagnosed by echocardiography: analysis of 11 patients. Am J Cardiol 1984; 53: 1401-1402.
7. Rice MJ, McDonald RW, Reller MD. Fetal atrial septal aneurysm: a cause of fetal atrial arrhythmias. J Am Coll Cardiol 1988; 12: 1292-1297.
8. Olivares-Reyes A, Chan S, Lazar EJ, Bandlamudi K, Narla V, Ong K. Atrial septal aneurysm: a new classification in two hundred five adults. J Am Soc Echocardiogr 1997; 10: 644-656.
9. Gallet B, Malergue MC, Adams C, et al. Atrial septal aneurysms-a potential cause of systemic embolism. An echocardiographic study. Br Heart J 1985; 53: 292-297.

10. Awan IH, Rice R, Moodie DS. Spontaneuous closure of atrial septal defect with interatrial aneurysm formation. Documentation by noninvasive studies, including digital subtraction angiography. Pediatr Cardiol 1982; 3: 143-145.
11. Brand AB, Keren A, Branski D, Abrahamov A, Stern S. Natural course of atrial septal aneurysm in children and the potential for spontaneous closure of associated septal defects. Am J Cardiol 1989; 64: 996-1001.
12. Arvan S. Incidental interatrial septal aneurysm associated with mitral valve prolapse. Am Heart J 1986; 111: 603-605.
13. Reder RF, Yeh HC, Steinfed L. Aneurysm of the interatrial septum causing pulmonary venous obstruction in an infant with tricuspid atresia. Am Heart J 1981; 102: 786-789.
14. Sahn DJ, Allen HDN, Anderson R, Goldberg SJ. Echocardiographic diagnosis of atrial septal aneurysm in an infant with hypoplastic right heart syndrome. Chest 1978; 73: 227-230.
15. Gondi B, Nanda NC. Two dimensional echocardiographic features of atrial septal aneurysms. Circulation 1981; 63: 452-457.
16. Mügge A, Daniel WG, Angermann C, et al. Atrial septal aneurysm in adult patients. Circulation 1995; 91: 2785-2792.
17. Barbosa MM, Pena Motta MM, Fortes PR. Aneurysms of the atrial septum diagnosed by echocardiography and their associated cardiac abnormalities. Int J Cardiol 1990; 29: 71-78.
18. Miga DE, Case CL, Gillette PC. Interatrial septal aneurysms and atrial arrhythmias in infants. Am Heart J 1996; 132: 776-778.

A study of the prevalence of having fractures and the affecting factors in young male adults throughout childhood and adolescence

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Injuries due to accidents in children and adolescents, who are more sensitive to different risk factors in their social and physical environments, play an important part in mortality and morbidity. Fractures are the most commonly seen problems among these injuries.

This cross-sectional study was carried out in a two-year vocational military school in Ankara between 1-10 May 2000. All, 2720 students in the school were included and data were collected via a questionnaire distributed to the students.

It was found that 418 (17%) out of 2,461 students we could interview had had a fracture. No statistically meaningful relationship was found between the frequency of having fractures and the educational status of the parents or employment status of the mother. However, it was seen that the frequency of fractures increased as the economical status of the parents increased.

The high frequency of fractures in childhood and adolescence in young males, and the traditional practice of going to unlicensed and medically untrained adults, and "bonesetters" (27% of those surveyed) are two important findings that should be taken into consideration.

Key words: fracture, prevalence, injury prevention.

Injuries due to accidents in children and adolescents, who are more sensitive to different risk factors in their social and physical environments, play an important part in mortality and morbidity. Primary reasons for the increase seen in the frequency of injuries in children and young adults are the increases in traffic and industrial accidents due to adolescents being more involved in working life and sports[2].

Injuries that do not result in death are still an important public health problem. In England 20-30% of children are seen in emergency services because of these injuries every year[3]. According to the U.S. National Health Research Community data, 25% of people between the ages of 0-21 have an injury once a year, and the yearly cost of this is US $347 billion. Seventeen billion dollars of this cost is for medical care, 72 billion is the loss of potential labor in the future, and 257 billion is loss of quality of life. According to a study carried out in 1994 in 22 countries by the WHO on children between the ages of 11-15, the percentage of children who needed medical care in one year due to an injury was reported as 17.4% in Wales, 8.9% in Norway, and 6.8% in Sweden[5]. It was found that sport injuries formed 36% of all injuries and that the injury rate increased as age increased in children and adolescents[2]. Moreover, it was also seen that injuries that do not result in death were observed more in males and were affected by factors like environment, socioeconomic level and climate[1,6].

Fracture is a traumatic injury in which bone structure is completely or partly destroyed, and it constitutes 10-25% of all injuries in childhood[7,8]. In recent years there has been an increase in epidemiological studies, but these are usually carried out among groups of the elderly. On the other hand, there are very few

studies carried out on children and adolescents who are an important group in terms of frequency and cost[9].

Most of the fractures are due to sport or entertainment injuries. Sport injuries constitute 48% of all fractures[2]. Moreover, in some countries an increase has been observed in the rate of fractures and dislocations. A study carried out in Sweden reported that fractures due to sport increased five-fold between 1950 and 1979[10].

The aim of this study was to determine the frequency of fractures in male children and adolescents in Turkey, to evaluate the role of bonesetters in treating fractures (an important problem in our country) in terms of the treatment of fractures and dislocations and to identify the sociodemographic factors related to the prevalence of fractures.

Material and Methods

This cross-sectional study was carried out in a two-year vocational military school in Ankara between 1-10 May 2000. 2,720 male students in the school were included in the study.

Data for the study were obtained through a questionnaire consisting of 20 questions prepared by the researchers in order to collect information about the characteristics of the subjects, to identify whether they had had a fracture and, if yes, to find its localization, and to learn how the fracture occurred. The students were asked the questions during their periodical inspections. The data were analyzed by the researchers using SPSS for Windows 9.0.

Results

The questionnaire was given to 2,461 of 2,720 students. Two hundred fifty-nine students were excluded for reasons such as refusal to take part in the study, not appearing for examinations, or for health problems.

Four hundred and eighteen out of 2,461 students (17%) reported that they had had a fracture once in their life. The mean age of students with a fracture at some time was 21.7 ± 2.23, and of students who never had a fracture was 21.7 ± 4.69. When we look at the distribution of the age of having fractures (Fig. 1), we see that fractures primarily occurred between the ages of 10-15 years.

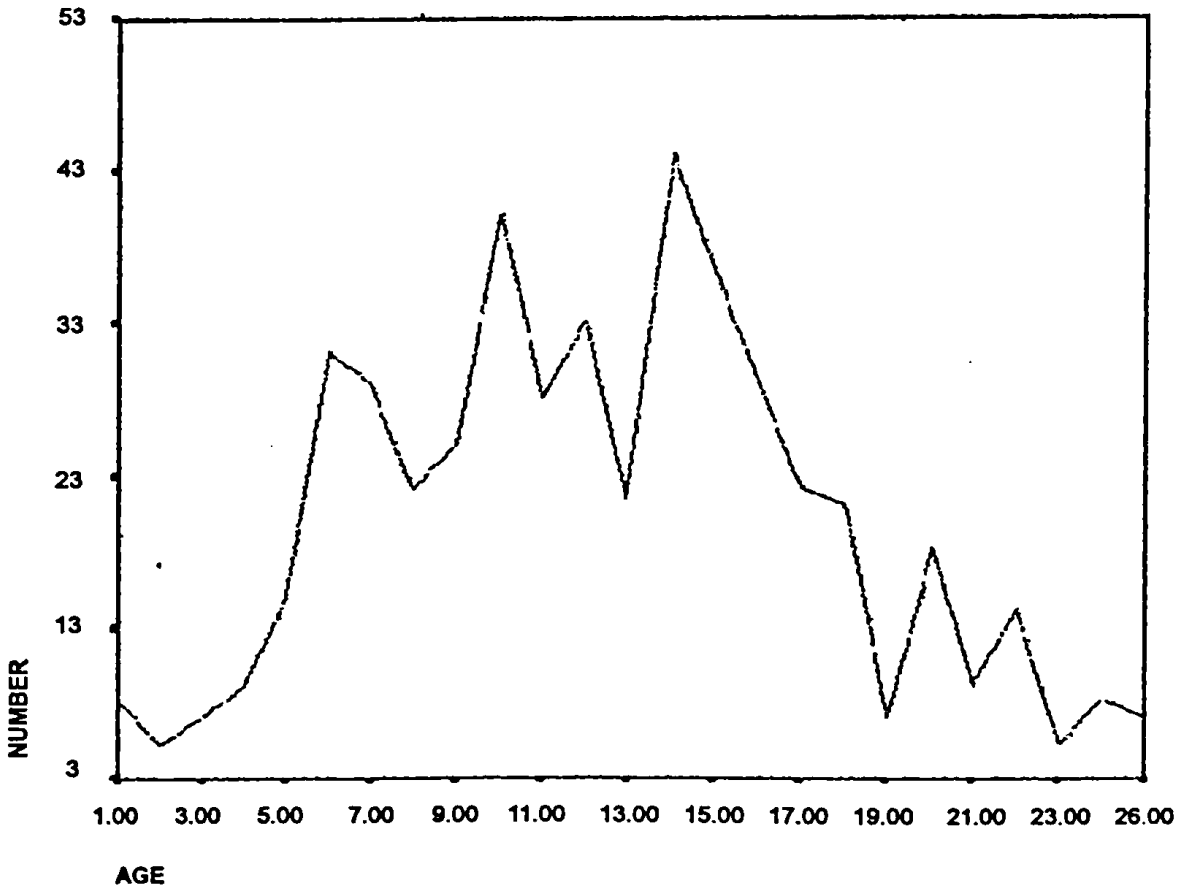

Fig. 1. The distribution of the age of having fractures of the subjects.

Concerning employment of the fathers of the subjects, 34% were civil servants and 24.6% farmers, and 12.9% did not have a job (Table I).

Table I. Distribution of the Paternal Employment

Job	Number	%
Civil servant	142	34.0
Farmer	103	24.6
Worker	72	17.2
Unemployed	54	12.9
Small-scale retailer	34	8.2
Other	13	3.1
Total	418	100.0

When we look at some of the characteristics of the students who had fractures at some time in their lives, we can see that 7.4% had an operation, 53.1% went to an orthopedic surgeon, versus 26.8% who went to a bonesetter, and 5% did not go anywhere. It was found that 73.9% had only one fracture whereas 2.9% had fractures four times in their lives.

Table II. Distribution According to Specific Parameters

	Number (n: 418)	Percentage (%)
Operated	31	7.4
Not operated	387	92.6
Treatment By		
Orthopedic surgeon	222	53.1
Bonesetter	112	26.8
General practitioner	58	13,9
Nobody	21	5.0
Unanswered	5	1.2
Fracture Number		
1	309	73.9
2	79	18.9
3	16	3.8
4	12	2.9
Unanswered	2	0.5

Twelve point one percent of students whose fathers were illiterate and 21.6% of students whose fathers were university graduates had had fractures. Sixteen point three percent of students whose mothers were illiterate and 15.4% of those whose mothers were university graduates had had fractures (Table III). No relation could be identified between the educational status of parents and having a fracture ($p < 0.005$).

Twenty point eight percent of students whose mothers worked and 16.9% of those whose mothers did not work had had fractures. No relation between working mothers and having a fracture could be established ($p > 0.005$).

Fifteen point seven percent of students whose family's monthly income was lower than 150 million TL had had fractures, while in the group of students whose family's monthly income was more than 300 million TL, this rate was 18.8%. A statistically meaningful relationship was found between the income level of the family and having a fracture ($p<0.01$) (Table III).

Table III. Distribution According to Parental Education, and Work and Income Status

	No fracture		Fracture		
	Number	% (*)	Number	% (*)	Statistical results
Father's educational status					
Illiterate	203	87.9	28	12.1	$X^2=7.65$
Primary/secondary school	1506	83.2	304	16.8	P=0.054
High school	265	79.8	67	20.2	
University	69	78.4	19	21.6	
Mother's educational status					
Illiterate	697	83.7	126	16.3	$X^2=2.54$
Primary/secondary school	1277	82.1	278	17.9	p=0.468
High school	58	82.9	12	17.1	
University	11	84.6	2	15.4	
Employed mother	61	79.2	16	20.8	$X^2=0.812$
Unemployed mother	1982	83.1	402	16.9	p=0.368
Income status (monthly)					
< 150 Million TL	1022	84.3	190	15.7	$X^2=12.5$
150-300 Million TL	944	82.7	197	17.3	p=0.002
> 300 Million TL	77	71.2	31	18.8	
Total	2043	83.0	418	17.0	

*: Line percent.

The most common reasons for fractures were falling from a high place (45.7%), sport injuries (41.1%) and traffic accidents (6.5%) (Table IV).

Table IV. Distribution of Fracture Causes

Fracture cause	Number (n)	Percentage (%)
Falling from a high place*	193	46.2
Sport injuries#	172	41.1
Traffic accidents	27	6.5
Others	16	3.8
Gunshot wounds	9	2.2
Unanswered	1	0.2
Total	418	100.0

* rooftops, windows, children's play area, furniture, trees.
# football, basketball, cycling, slipping on ice, ice-skating.

Fractures occurred mostly in the forearm (40.2%), wrist (25.8%) and ankle (17.2%) (Table V). Wrist dislocation was the most common dislocation (41.9%), followed by ankle (27.9%) and elbow (12.2%).

Table V. Distribution of Fracture Localization

Localization	Number	Percentage
Arm	168	40.2
Wrist	108	25.8
Foot	53	12.7
Ankle	29	6.9
Elbow	25	6.0
Head	21	5.0
Other	12	2.8
Unanswered	2	0.5
Shoulder	-	-
Knee	-	-
Total	418	100.0

Discussion

Any problem in public health can be considered a priority problem if it occurs frequently and/or is serious, and if it is amenable to measures for its treatment or, better still, its prevention. Fractures are a frequent problem, although our knowledge of their frequency is poor and biased[11].

The prevalence of having a fracture at some point in the subjects' lives was 17%. In different countries, subjects that would represent the whole country were chosen and the yearly fracture rate in children was found as 36/1,000 in Wales and 16/1,000 in Norway[3]. In a study carried out among a group of children in England who were 12 years old or younger the yearly fracture incidence was identified as 16/1,000[9]. In another study carried out in Sweden among a group of children between 1993-1994, the yearly fracture rate was 235/10,000 in males and 149/10,000 in females[10].

Fifty three point one percent of the subjects who had had fractures said that they went to an orthopedic surgeon, and 26.8% to a bonesetter, and 5% said they did not go anywhere (Table II). As can be seen, a significant percentage of people by tradition go to bonesetters, but they have no education in the treatment of fractures. It is known that fractures can cause damage in the adjacent tissues, neuromuscular structures, skin, muscles, and organs[12,13], thus there is a high risk of defect developing in the area of the fracture as a result of incorrect treatment. It can be understood, therefore, why this is an important public health problem when the social and economical costs of this situation are considered.

It has been reported that most fractures in childhood and adolescence occur between the ages of 10-13 years[14]. In different studies carried out recently, it has been observed that the childhood fracture rate increases with age[1,2,6,9]. In our study, when we looked at the distribution of the age for having fractures, we found that most occurred between 10 and 15 years old. Thus, our results are similar to the literature.

In a study carried out in the U.S. in an age group of 0-21, the highest rate of injury was found in the group whose family's monthly income was lower than $5000[4]. This result is different from ours. In our study, the fracture rate was relatively higher in the group whose family's monthly income was more than 300 million TL than in the group whose family's monthly income was lower than 150 million TL (18.8% and 15.7% respectively) ($p < 0.01$). In our country, it is observed that some health problems, like obesity, increase as an individual's socioeconomic level increases. This situation in Turkey, which is also identified in fracture prevalence, might result from the fact that an increase in income does not necessarily parallel an increase in education level, whereas in developed countries it usually does.

In our study the most common reasons for fractures were falling from a high place (rooftops, windows, children's play area, furniture, trees) (45.7%), sport injuries football, basketball cycling, slipping on ice, ice skating (41.1%), and traffic accidents (6.5%) (Table IV). In a study performed in England it was reported that fractures often occur around houses or as a result of falling from somewhere in the house[9]. In another study carried out in the U.S. with a group between the ages of 5-17, 30% of sport and entertainment injuries were a result of falling down in school[2]. The most common reason for injuries between the ages of 15-24 years was reported to be sport injuries[15]. Our results are similar to the results of these studies (Table IV).

In a study performed in Sweden it was reported that fractures were most commonly seen in the distal of the forearm (26%), phalanges (16%), and clavicle (9%)[6]. Worlock and Stower[9] reported in their study in England that the most common fracture site was the distal of the

forearm (36%)[9]. Our findings were similar to the results of these studies, with fractures most commonly seen in the humerus (40.2%), wrist (25.8%), and foot (12.7%) (Table V). However, we decided to consider the forearm and arm as one fracture area due to the fact that data was collected with a retrospective questionnaire which was dependent on the memory of the subjects. In our study, some of the fractures defined as arm or wrist fractures were evaluated as fractures of the forearm and distal radius (Table V).

Fractures are an important public health problem in our country and are much more expensive than their prevention, even though the cost of prevention is generally greatly underestimated. There is need for some studies in order to determine the magnitude of the problem.

An important percentage of the Turkish population utilize bonesetters (26.8%) who treat fractures in ignorance. In order to prevent possible problems in treatment, necessary precautions should be taken, the first being education. To improve public health, more importance should be given to precautions about accidents, and injuries that might result from them, and to fighting chronic and infectious diseases. In this way, fractures, and the physical disabilities that might result from them, will also be prevented.

Acknowledgements

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REFERENCES

1. Hintor Y, Lincoln A, Crockett MM. Fractures of the femoral shaft in children. J Bone Joint Surg 1999; 81-A: 500-509.
2. Bijur PE, Tramble A, Harel Y, et al. Sports and recreation injuries in US children and adolescents. Arch Pediatr Adolesc Med 1999; 149: 1009-1016.
3. Lyons RA, Sellstrom E, Delahunty AM, Loeb M. Incidence and cause of fractures in European districts. Arch Dis Child 2000; 82: 452-455.
4. Danseco ER, Miller TR, Spicer RS. Incidence and costs of 1987-1994. childhood injuries: demographic breakdowns. Pediatrics 2000; 105e: 27.
5. WHO World Health Statistics Annual 1996. Geneva: World Health Organization,1999.
6. Tiderius CJ, Landin L, Duppe H. Decreasing incidence of fractures in children. Acta Orthop Scand 1999; 70: 622-626.
7. Sibert JR, Maddocks GB, Brown BM. Childhood accidents-an endemic of epidemic proportions. Arch Dis Child 1981; 56: 225-227.
8. Hilt NE, Cogburn SB. Manual of Orthopedics. London: C.V. Mosby Company; 1980: 343-345.
9. Worlock P, Stower M. Fracture patterns in Nottingham children. J Pediatr Orthop 1986; 6: 656-660.
10. Landin LA. Fracture patterns in children. Acta Orthop Scand 1983; 54 (Suppl): 1-95.
11. Romer CJ, Manciaux M. Accidents in chilhoods and adolescence: a priority problem worldwide. In: Romer CJ, Manciaux M (eds). Accidents in childhood and Adolescence: The Role of Research (1st ed.) Geneva: World Health Organization; 1991: 1-6.
12. Ege R. Travma (Yaralanmalar). Ankara: Emel Yayıncılık; 1981: 36-40.
13. Mellick LB, Reesor K, Demers D, Reinker KA. Tibial fractures of young children. Pediatr Emerg Care 1988; 4: 97-101.
14. Cheng JC, Shen WY. Limb fracture pattern in different pediatric age groups. J Orthop Trau 1993; 7: 15-22.
15. Garraway WM, Strauffer RN, Kürtlan LT. Limb fractures in defined population. Mayo Clin Proc 1979; 54: 701-707.

Height prognosis in children with late - diagnosed congenital hypothyroidism

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SUMMARY: Kandemir N,Yordam N. Height prognosis in children with late-diagnosed congenital hypothyroidism. Turk J Pediatr 2001; 43: 303-306.

It is a general belief that early and adequate thyroid hormone replacement achieves normalization of growth as well as disappearance of clinical sings and symptoms of hypothyroidism. Due to the lack of comprehensive growth studies, height prognosis has remained controversial in late-diagnosed hypothyroidic children. The limited number of previous studies have suggested permanent height deficit in these children.

In this study we present longitudinal growth and final height of 20 children (14 females and 6 males) in whom the duration of hypothyroidism before onset of therapy varied from three to 12.6 years. The etiological distribution of cases revealed ectopic thyroid tissue in nine cases, agenesis in seven, and dyshormonogenesis in four cases. At the time of the diagnosis all hypothyroidic children had severe growth retardation (mean height SDS ± SD -3.95 ± 1.07) due to prolonged hypothyroidism. Although the catch-up spurt corrected an important part of the initial height deficit in all patients, only nine patients reached or exceeded their target height, and the final height of five patients remained below 2 SD of mean. Despite treatment, prolonged hypothyroidism may result in compromised adult height in some patients. The contributing factors to this height deficit may include the duration of hypothyroidism, the height deficit at the time of the diagnosis, etiological differences and the diminished potential for catch-up growth in late-diagnosed hypothyroidism.

Key words: congenital hypothyroidism, short stature.

Thyroid hormone action is essential for normal growth and bone maturity. It is established that growth is normal in children with congenital hypothyroidism (CH) detected by screening and treated from the early neonatal period[1-3]. However, due to the lack of comprehensive growth studies, height prognosis has remained controversial in late-diagnosed hypothyroidic children. The limited number of previous studies have suggested permanent height deficit in children with late-diagnosed congenital and acquired hypothyroidism[4-6].

In this study we present longitudinal growth and final height of late-diagnosed children with CH.

Material and Methods

Twenty children (14 females and 6 males) in whom the duration of hypothyroidism before onset of therapy varied from three to 12.6 years were included in the study. Hormonal determination of T_3, T_4 and TSH were made by radioimmunoassay. Etiological diagnosis was based on the results of technetium-99 scan. The etiological distribution of cases revealed ectopic thyroid in nine cases, agenesis in seven and hyperplastic thyroid in four. All patients were given thyroid hormone replacement therapy ($L\text{-}T_4$) at a dose of 100-125 $\mu g/m^2$/day and were followed every 3-6 months during the therapy.

The height and weight were determined and serum thyroid hormone tests performed at each visit, and the dose of $L\text{-}T_4$ was adjusted accordingly. Bone age was determined every six months or yearly using Greulich and Pyle standards[7]. Height SDS was calculated as follows:

$\frac{X-M}{SD}$ with X the height of the patient expressed in centimeters, M the mean height for the patient's chronological age

and SD the standard deviation of the mean height according to Tanner's standard[8]. Target height was calculated using standard equations for boys) [1/2 (maternal + paternal height + 13)] and girls [1/2 (maternal + paternal height-13)].

Statistical analysis was performed using tests Statistical Package for the Social Sciences, update 1996, version 7.5 (SPSS, Chicago). Results were expressed as mean ± SD. Differences between mean values were tested using Mann-Whitney U test for non-paired samples and Wilcoxon test for paired samples. Pearson or Spearman's correlation analysis was used accordingly.

Results

The clinical characteristics of the hypothyroidic children are shown in Table I. The mean pretreatment chronological age was 5.7 ± 3.2 years, the mean bone age was 1.9 ± 1.8 years, and the mean height SDS for chronological age was -3.95 ± 1.1 in all patients. The mean pretreatment T_4 level was 1.8 ± 1.1 µg/dl and TSH level was 102.2 ± 47.6 mIU/L (normal T_4 4.5-12 µg/dl and normal TSH 0.49-4.67 mIU/L). During treatment, serum T_4 levels were in normal range in all patients; however, serum TSH levels remained high in some patients (Figs. 1, 2).

The mean final height in both boys and girls was less than the mean target height, although the difference was not statistically significant ($p > 0.01$). (Table II). Only nine patients reached or exceeded their target height, and the final height of five patients remained below 2 SD of mean (Fig. 3). The final height SDS was correlated with height SDS at diagnosis ($r = 0.453$, $p < 0.05$) but not with age at diagnosis ($r = -0.098$, $p > 0.05$). There were no correlation between the deficit in adult height and chronological age, height age or bone age at diagnosis ($r = 0.253$, $p = 0.282$; $r = 0.025$, $p = 0.920$; $r = 0.240$, $p = 0.322$, respectively).

Table I. Clinical Characteristics of 20 Children With Congenital Hypothyroidism at the Time of Diagnosis

	Agenesis n=7	Ectopic thyroid n=9	Hyperplasia n=4
Age*	6.4 ± 3.8	5.7 ± 3.0	4.6 ± 2.9
Height SDS*	-4.6 ± 1.3	-3.8 ± 0.8	-3.3 ± 0.9
Bone age*	2.6 ± 2.6	1.8 ± 1.5	1,3 ± 0.9
T_4*(µg/dl)	1.2 ± 0.8	2.3 ± 1.3	1.8 ± 0.7
TSH* (mIU/L)	117.7 ± 51.6	94.1 ± 42.4	93.2 ± 58.1

* mean ± SD, year.

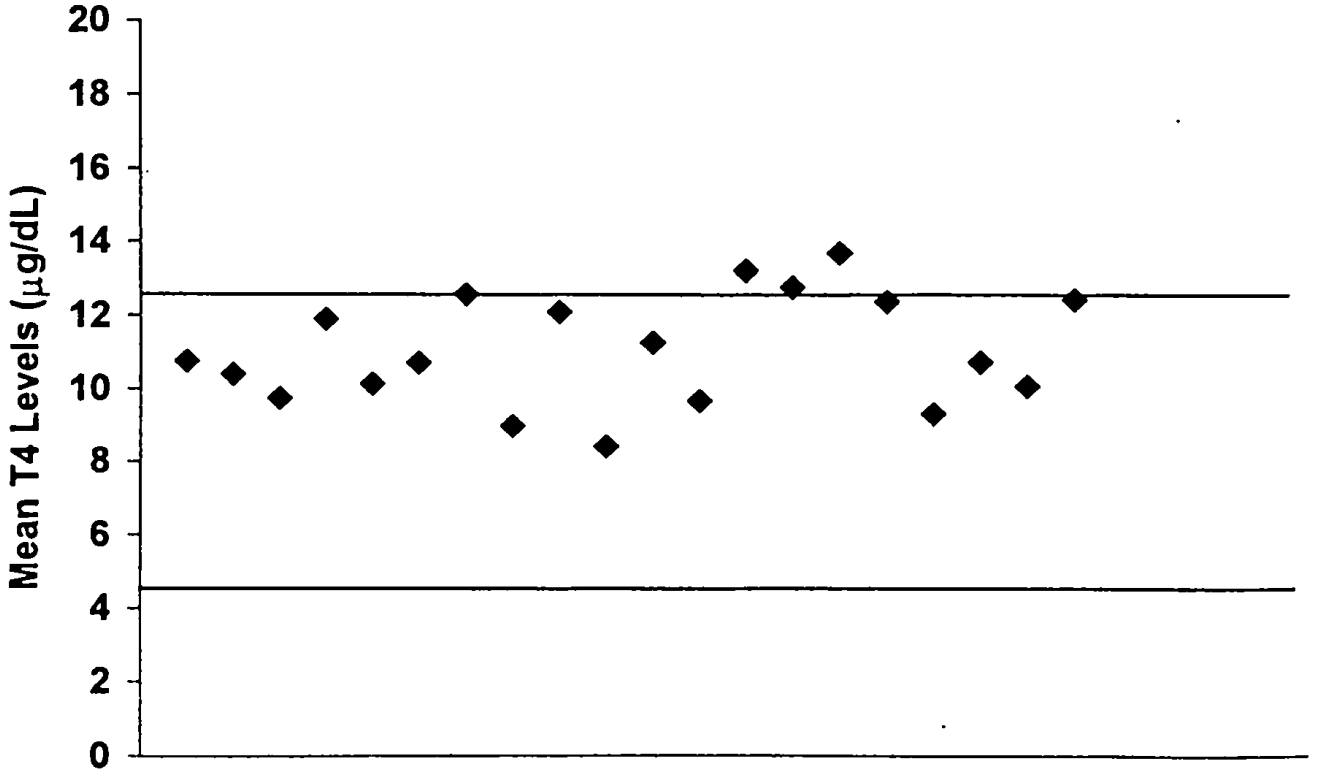

Fig. 1. The mean serum T_4 levels of 20 patients with congenital hypothyroidism during L-T_4 replacement therapy.

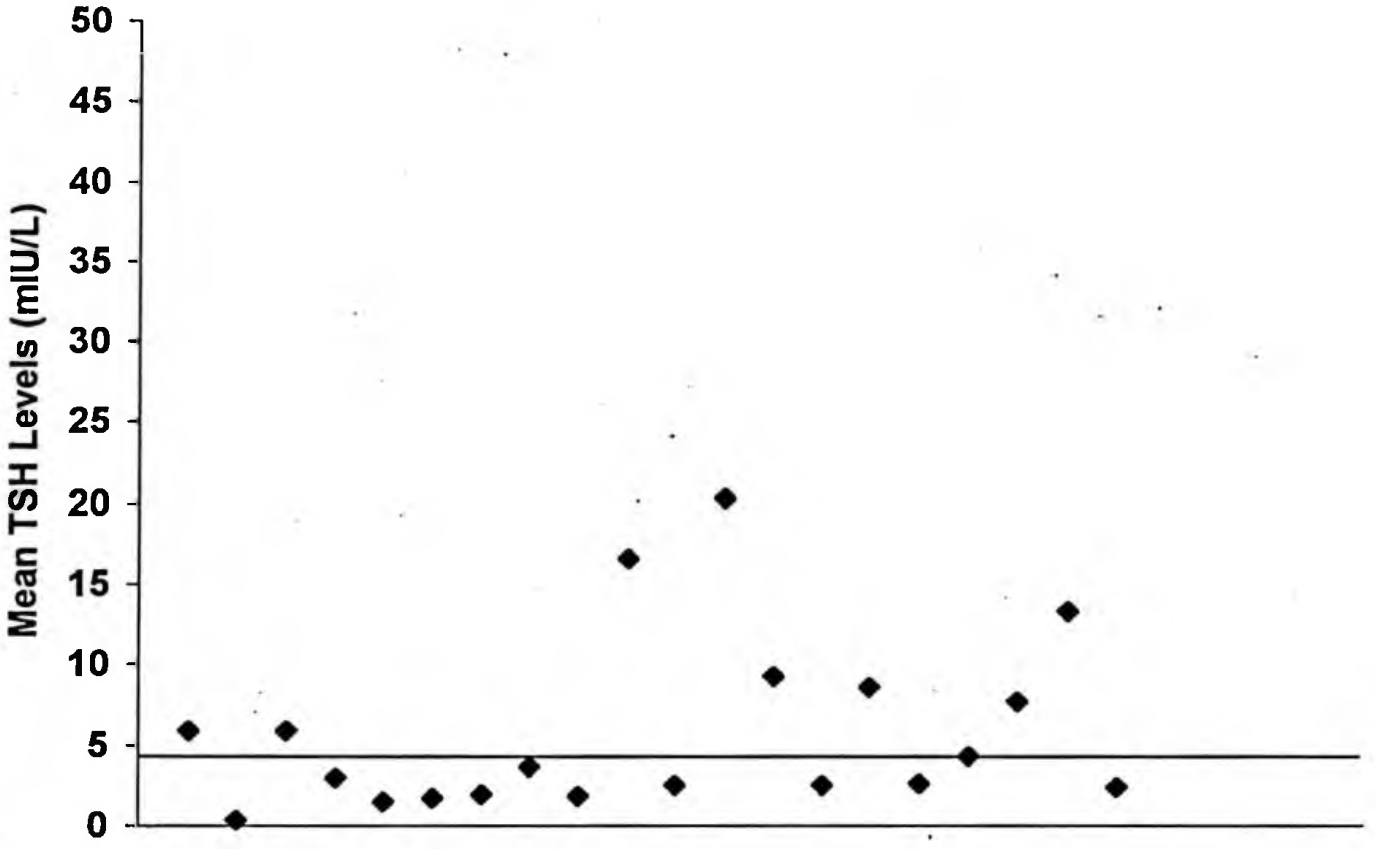

Fig. 2. The mean serum TSH levels of 20 patients with congenital hypothyroidism during L-T_4 replacement therapy.

Table II. Height Prognosis of the Patients With Congenital Hypothyroidism

	Girls (n=14) (mean ± SD)	Boys (n=6) (mean ± SD)
Target height (cm)	155 ± 4.7	168.3 ± 3.2
Final height (cm)	152.7 ± 4.3	166.3 ± 4.97
Target height SDS	-1.2 ± 0.8	-0.9 ± 0.5
Final height SDS	-1.6 ± 0.7	-1.2 ± 0.8
Final height vs target height	$p > 0.01$	$p > 0.01$

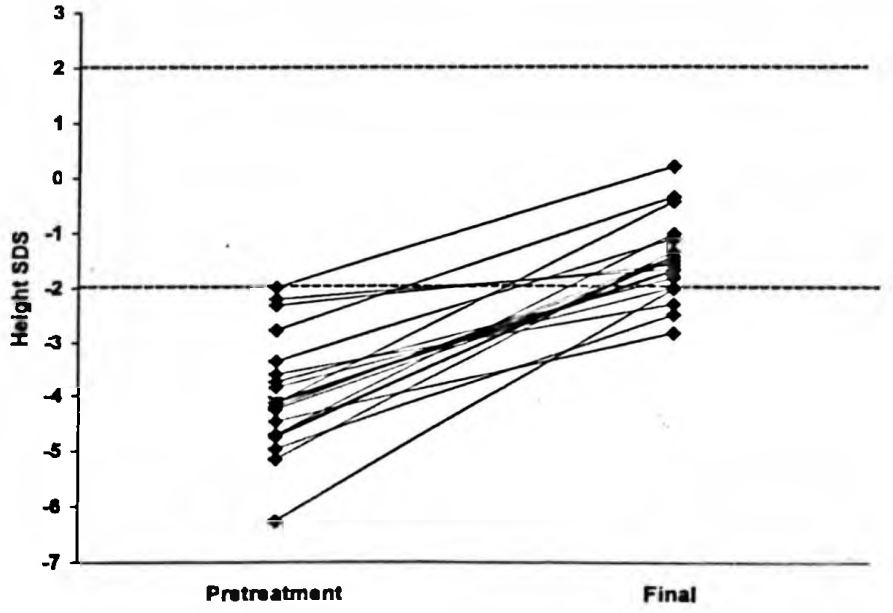

Fig. 3. The pretreatment and final height SDS of children with congenital hypothyroidism.

The final height SDS was -1.42 ± 0.34 (min -2.0, max. -1.0) in children with thyroid agenesis, -1.7 ± 0.8 (min -2.8, max -0.4) in the ectopic thyroid group and -1.15 ± 0.96 (min -2.0, max -0.2) in patients with hyperplastic thyroid tissue. Final height SDS did not show significant difference according to the etiology of hypothyroidism ($r = -0.104$, $p = 0.662$). The deficit in adult height also did not correlate with the etiology of hypothyroidism ($r = -0.102$, $p = 0.668$).

Discussion

The introduction of a neonatal screening program for CH during the past two decades has enabled early diagnosis and prompt initiation of L-T_4 treatment in infants with CH. It is well known that early diagnosis and appropriate daily doses of L-T_4 result in normal growth, normal puberty and achievement of normal adult height[1-3]. Unfortunately, a nationwide neonatal screening program for CH has still not been implemented in many countries, including Turkey, where screening is performed only in certain local centers[9]. Therefore, severe growth retardation (together with mental and motor retardation) is still a problem in these late-diagnosed patients.

Due to the lack of comprehensive growth studies, height prognosis has remained controversial in late-diagnosed hypothyroid children. The limited number of previous studies have suggested permanent height deficit in children with late-diagnosed CH or juvenile acquired hypothyroidism[4-6]. Although the catch-up spurt corrected an important part of the initial height deficit, prolonged hypothyroidism resulted in compromised final height. Bucher et al.[4] reported normal growth only when therapy was begun before the first year of life. Pantsiotou et al.[10] and Rivkees et al.[6] reported that despite treatment, prolonged juvenile acquired hypothyroidism results in a permanent height deficit related to the duration of thyroxine deficiency before treatment. Although the precise mechanism by which adult stature is compromised was not identified in these studies, several explanations were suggested: Firstly, hypothyroidism may directly diminish the potential for catch-up growth; Rivkess et al.[6] reported that permanent height deficit is related to the duration of thyroxine deficiency before treatment. Secondly, overtreatment with L-T_4 may stimulate skeletal maturation too much in the study of Casado de Frias et al.[11] progressive acceleration of bone age limited final height in some children. Administration of replacement therapy too soon before or during puberty may also limit catch-up growth and loss of normal harmony between growth and sexual maturation.

In this study, the correlation between the final height SDS and height SDS at the time of diagnosis suggested that the initial height deficit is an important factor for the deficit in final height. Due to the limited number of patients in each etiological group, the role of etiological differences could not be examined in this sudy.

We conclude that adequate replacement treatment with thyroxine does not lead necessarily to the normalization of growth. Early diagnosis improves normal growth and final height in children with congenital hypothyroidism.

REFERENCES

1. Aronson R, Ehrlich RM, Bailey JD, Rovet JF. Growth in children with congenital hypothyroidism detected by neonatal sreening. J Pediatr 1990; 116: 33-37.
2. Grant DB. Growth in early treated congenital hypothyroidism. Arch Dis Child 1994; 70: 464-468.
3. Dickerman Z, De Vries L. Prepubertal and pubertal growth, timing and duration of puberty and attained adult height in patients with congenital hypothyroidism (CH) detected by neonatal screening programme for CH a longitudinal study. Clin Endocrinol 1997; 47: 649-654.
4. Bucher H, Prader A, Illig R. Head circumference, height bone age and weight in 103 children with congenital hypothyroidism before and during thyroid hormone replacement. Helv Paediatr Acta 1985; 40: 305-316.
5. Boersma B, Otten BJ, Stoelinga GB, Wit JM. Catch-up growth after prolonged hypothyroidism. Abstracts; International Symposium; Developmental Issues in Pediatric Endocrinology 1995: 4.
6. Rivkess SA, Bode HH, Crawford JD. Long term growth in juvenile acquired hypothyroidism. N Engl J Med 1988; 318: 599-602.
7. Greulich W, Pyle SJ. Radiographic Atlas of Skeletal Development of the Hand and Wrist (2nd ed) Stanford, California: Stanford University Press; 1959; 1-276.
8. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity of British children. Arch Dis Child 1965; 41 (Part I): 457-471; (Part II): 613-635.
9. Yordam N, Çalikoğlu AS, Hatun Ş, et al. Screening for congenital hypothyroidism in Turkey. Eur J Pediatr 1995; 154: 614-616.
10. Pantsiotou S, Stanhope R, Uruena M, Preece MA, Grant DB. Growth prognosis and growth after menarche in primary hypothyroidism. Arch Dis Child 1991; 66: 838-840.
11. Casado deFrias E, Ruibal JL, Reverte F, Bueno G. Evaluation of height and bone age in primary congenital hypothyroidism. Clin Pediatr 1993; 32: 426-432.

Low plasma apolipoprotein A-I level: new prognostic criterion in childhood cirrhosis?

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SUMMARY: Selimoğlu MA, Aydoğdu S, Yağcı RV. Low plasma apolipoprotein A-I level: new prognostic criterion in childhood cirrhosis? Turk J Pediatr 2001; 43: 307-311.

Apolipoprotein A-I (apo A-I) has been found to be decreased in adults with cirrhosis, but it has not been routinely used for prognostic purposes thus far. This study was performed to determine apo A-I levels in childhood cirrhosis and to establish some prognostic cut-off values. Apo A-I levels of 78 children with chronic liver disease, 38 of whom had cirrhosis as well, were studied. Mean values of cirrhotic, non-cirrhotic and healthy children were not different ($p > .05$). However, in cirrhotic children, the highest value was detected in the Child-Pugh A group, and it was different from those of the B and C groups ($p < .05$ and $p < .001$, respectively). Apo A-I was the lowest in the moderate risk group of Malatack's model, and was significantly different from the low risk group ($p < .05$). Apo A-I was inversely correlated with Malatack score, Child-Pugh score, total bilirubin, conjugated bilirubin, and prothrombin time ($p < .01$, $p < .01$, $p < .01$, $p < .01$, $p < .05$, respectively). In cirrhotic children with cholestasis, apo A-I was lower than in non-cholestatic children ($p < .05$). Apo A-I value < 80 mg/dl had 84% specificity and 84% negative predictive value for the high risk group of Malatack's model. Similarly, Apo A-I value < 83 mg/dl had 95% specificity and 87% negative predictive value for the Child-Pugh C group.

We concluded that Apo A-I is a sensitive and specific parameter of poor prognosis in childhood cirrhosis.

Key words: apolipoprotein A-I, cirrhosis, prognosis, children.

Apolipoprotein A-I (apo A-I) is the major protein of high-density lipoprotein cholesterol (HDL) and is primarily synthesized in the liver and small intestine. It is secreted as pro apo A-I, and by pro apo A-I converting enzyme, it becomes mature[1]. Plasma apo A-I level is a routine test evaluating lipid profile in diseases affecting lipid metabolism. It has been found that serum pro apo A-I converting enzyme activity is decreased in patients with acute liver disease and cirrhosis, diseases in which alterations of lipid metabolism is observed[1-5]. However, to the best of our knowledge, clinicians have not used this parameter as a prognostic criterion in childhood cirrhosis thus far. In this study, we investigated plasma apo A-I levels in respect to the other well known prognostic criteria in children with cirrhosis.

Material and Methods

Thirty-eight children with cirrhosis and 40 children with chronic liver disease without cirrhosis, followed by Ege University Pediatric Gastroenterology and Nutrition Department, and 20 healthy children were included in this study. Mean age of the patients was 10.0 ± 4.9 years (3 months-20 years) and of the healthy children was 8.8 ± 5.8 years. Diagnosis of cirrhosis and chronic liver disease as based on physical examination, laboratory investigations, and liver biopsies. Of cirrhotic patients, 11 had Wilson's cirrhosis, seven had autoimmune hepatitis, four had biliary atresia, four had paucity of intrahepatic bile ducts and 12 had cryptogenic cirrhosis. Of patients with chronic liver disease, 36 had chronic hepatitis B infection and four had metabolic disease (not lipid metabolism

disorder). For the determination of the prognosis, Child-Pugh and Malatack's classifications were used[6,7]. With Child-Pugh clasisfication, of cirrhotic patients, 23 (60.5%) were in group A, six (15.8%) were in group B and nine (23.7%) were in group C. In respect to the Malatack scoring model, 28 (73.7%) were in low risk, four (10.5%) were in moderate risk and six (15.8%) were in high risk groups. After 12-hour fasting, plasma apo A-I, serum cholesterol, total and conjugated bilirubin, albumin and prothrombin time were studied.

For statistical study mean ± standard deviation, Student's t test, Pearson's and Spearman's correlation tests and regression analysis were used.

Results

Mean apo A-I values of cirrhotic, non-cirrhotic and healthy children were 101.0 ± 7.2 mg/dl, 113.0 ± 14.4 mg/dl and 115.1 ± 17.7 mg/dl, respectively. No statistical difference was detected between them ($p > .05$). Cirrhotic children classified according to Child-Pugh and Malatack's classifications were re-evaluated. Results of these two evaluations are shown in Table I.

prothrombin time ($p < .01$, $p < .01$, $p < .01$, $p < .01$, $p < .05$, respectively), but no correlation was found between apo A-I and cholesterol or albumin ($p > .05$ and $p > .05$).

Figures 1 and 2 show the linear regression analysis of apo A-I and Malatack score and of apo A-I and Child-Pugh score.

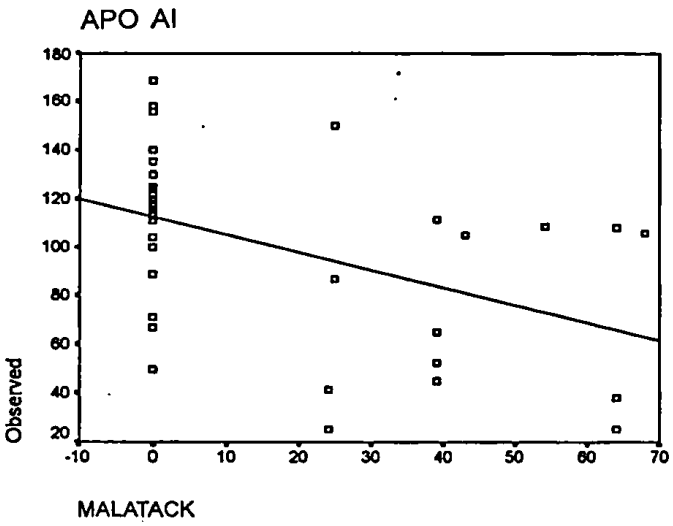

Fig. 1. Regression analysis of apo A-I and Malatack scores.

Table I. Mean Apo A-I Levels and Child-Pugh and Malatack Classifications

	Child-Pugh A	Child-Pugh B	Child-Pugh C
Apo A-I (mg/dl)	n=23	n=6	n=9
	117.4 ± 26.4	80.5 ± 46.1	72.7 ± 34.3
	Low risk	Moderate risk	High risk
Apo A-I (mg/dl)	n=28	n=4	n=6
	109.5 ± 36.6	68.8 ± 20.0	81.8 ± 39.2

Mean apo A-I value was the highest in Child-Pugh A group and was statistically different from Cihld-Pugh B and C groups ($p < .05$ and $p < .001$). The mean apo A-I level was the lowest in the moderate risk group of Malatack's model, and was significantly different from the low risk group ($p < .05$). The mean apo A-I value of six patients who died while awaiting transplantation was 65.2 ± 34.8 mg/dl.

When cirrhotic children were re-evaluated in respect to the presence of cholestasis, mean apo A-I values were 89.0 ± 41.0 mg/dl in the cholestatic group and 117.6 ± 23.2 mg/dl in the non-cholestatis group ($p < .05$).

A negative correlationwas found between apo A-I level and Malatack score, Child-Pugh score, total bilirubin, conjugated bilirubin, and

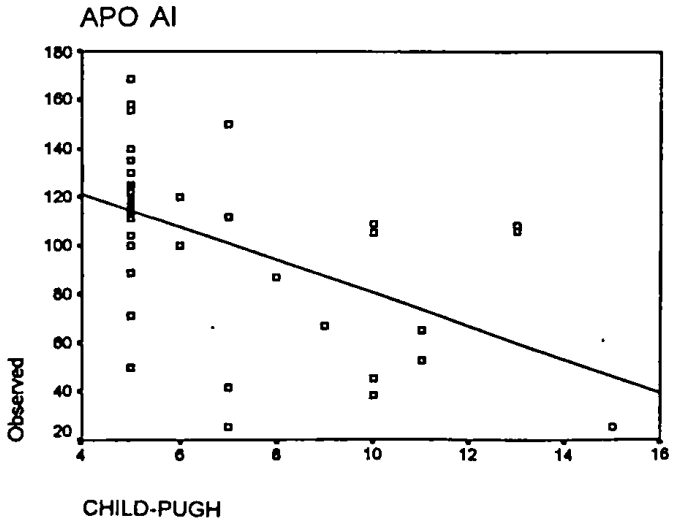

Fig. 2. Regression analysis of apo A-I and Child-Pugh scores.

Regression analysis, showed the following equations.

Apo A-I: 148.5 – (6.8 x Child-Pugh score).

Apo A-I: 112.7 – (0.734 x Malatack score).

With these equations, apo A-I values pairing with cut-off values of Child-Pugh and Malatack stage scores were found. Table II shows the pairing values.

Sensitivity, specificity, and positive predictive and negative predictive values of these cut-off values are shown in Tables III and IV.

Malatack et al.[6] established a prognostic criteria model to predict survival in children with cirrhosis. The four variables with high proportional risk, which included serum cholesterol level, indirect bilirubin level, PTT over 20 seconds, and a positive history of ascites, were placed in a multiplicative exponential model, and this model was used to develop survival curves predictable of survival over a given time[5].

Another widely used prognostic classification for the cirrhotic child is Child-Turcotte, modified by Pugh et al. This model also involves

Table II. Apo A-I Values Pairing With Cut-off Values of Child-Pugh and Malatack Staging Scores

	Child-Pugh A	Child-Pugh B	Child-Pugh C
Apo A-I value (mg/dl)	> 101	80-101	< 80
	Low risk	Moderate risk	High risk
Apo A-I value (mg/dl)	> 92	83-92	< 83

Table III. Sensitivity, Specificity, and Positive and Negative Predictive Values of Cut-off Apo A-I Levels for Child-Pugh Classification

Apo A-I	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative pedictive value (%)
> 101 mg/dl for Child-Pugh A	80	57	72	66.6
80-101 mg/dl for Child-Pugh B	20	93	33.3	87.5
< 80 mg/dl for Childh-Pugh C	55.5	84	55.5	84

Table IV. Sensitivity, Specificity, and Positive and Negative Predictive Values of Cut-off Apo lA-I Levels for Malatack Model

Apo A-I	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative pedictive value (%)
> 92 mg/dl for LRG[1]	72	44.4	78.2	36.4
83-92 mg/dl for MRG[2]	30	93.3	0	87.5
< 83 mg/dl for HRG[3]	25	95.4	50	87

[1] Low group.
[2] Moderate risk group.
[3] High risk group.

Discussion

An accurate and informative test of liver function should indicate early in the patient's course when irreversible and potentially fatal changes have occurred. In addition, it should pose no risk to the patient. The standard measurements of hepatic function involve a number of tests, few of which actually measure liver function. Most available tests have poor predictive value until almost complete liver failure has occurred, and none is specific for patients with cirrhoiss[5].

bilirubin, albumin, prothrombin time, and additionally the presence of ascites and encephalopathy[7].

Apo A-I, synthesized in hepatocytes, was measured in serums of cirrhotic adult patients and found to be lower than normal[4,8-11]. Both apo A-I and pro apo A-I converting enzyme activity were found to be lower in adult patients with acute hepatitis and liver cirrhosis than in healthy ones[1,12,13].

Apo A-I has been evaluated according to the prognosis of cirrhosis in only a few studies[2]. Ciccarese et al.[2] studied this parameter in 84

cirrhotic patients and reported a gradual decrease from Child-Pugh A to Child-Pugh B group.

We studied apo A-I in 38 cirrhotic children, and evaluated the results in respect to the routinely used prognostic criteria. Although apo A-I values tended to gradually decrease in the cirrhotic group, we found no statistically significant difference between mean apo A-I values in cirrhotic, non-cirrhotic and healthy children. However, in the cirrhotic group, according to Child-Pugh classification, this decline was more prominent and statistically significant ($p < .05$ and $p < .001$). The non-significant difference between cirrhotic and healthy children was due to the porportionally high case number participating in the Child-Pugh A group, where the mean apo A-I value was non-significantly higher than that of controls (117.4 ± 26.4 and 115.1 ± 17.7, respectively).

When this parameter was evaluated in respect to the scoring model that Malatack et al.[6] established, the mean value was lower in the moderate risk group than in the low risk group ($p < .05$). For a healthy evaluation, this parameter was tested to determine whether it was correlated with widely accepted prognostic criteria such as cholesterol, total and direct bilirubin, prothrombin time, and albumin. By using these correlation tests, we found an inverse correlation between apo A-I and both total and direct bilirubin, and prothrombin time ($p < .01$, $p < .01$, and $p < .05$, respectively). These results were confirmed by non-parametric correlation tests between apo A-I and both Child-Pugh and Malatack scoring models ($p < .01$ and $p < .01$, respectively).

Cholestasis caused low levels of apo A-I; this is consistent with the inverse correlation between bilirubin and apo A-I ($p < .01$). Floren et al.[3] also observed low levels and an inverse correlation with bilirubin levels in cholestatic cirrhotic adult patients. This result may be attributed to the fact that the majority of cholestatic patients were in the Child-Pugh B or C groups. In addition, it is known that apolipoproteins are decreased or absent in very low density lipoprotein (VLDL) particles in cholestasis[14]. This result suggests that a low apo A-I level is also a good indicator of cholestasis.

There is no functional difference between pro and mature apo A-I in respect to LCAT (lecithin-cholesterol acyltransferase) enzyme activation, high density lipoprotein (HDL), and chylomicron interaction[1]. For that reason, it is not clear what kind of lipid metabolism abnormality is caused by that impaired enzyme activity in liver disease. Since some studies revealed that apo A-I catabolism increases two- to four-times normal level, especially in alcoholic hepatitis, it was speculated that low levels found in liver diseases were due to an increase in catabolism rather than to a synthetic disorder[14] In this study, we detected no correlation between apo A-I level and albumin, an indicator of the liver's synthetic capacity. In some studies this correlation has been reported in adults[2,10]. Our finding reveals two speculations: whether apo A-I is a more sensitive indicator of impaired synthesis than albumin, and whether cirrhosis really causes increased catabolism of apo A-I. Apo A-I and A-II, in the plasma of patients with liver disease, often show complete dissociation and lose their binding capacity. It is possible that this dissociation is a major reason for their accelerated catabolism, and this may well result from a disturbed generation of mature HDL from nascent HDL[14]. In liver diseases, HDL fraction not only shows decreased concentrations of apo A-I and A-II, but also a marked increase in apo e; the same picture is defined for familial LCAT deficiency[14].

To date, no study has established a cut-off value for apo A-I predicting poor prognosis. We tried to establish this value using routinely accepted scoring models, Malatack's and Child-Pugh classifications. With the equations we found by regression analysis, we detected the paired values with cut-off scores of these two parameters. In addition, we calculated the positive and negative predictive values, specificity, and sensitivity. We observed that the specificity and negative predictive values we found were becoming higher in worse prognoses. This means that a low apo A-I level is more specific to end-stage liver disease and less specific to liver injury scored as Child-Pugh A or low risk. This result can be confirmed by the non-significant difference between all cirrhotic patients, consisting mainly of Child-Pugh A patients, and healthy children. Consequently, a low apo A-I level is not a laboratory marker of cirrhosis, but an indicator of poor prognosis in cirrhotic patients.

To the best of our knowledge, apo A-I has not been used routinely in gastroenterology clinics for prognostic purposes in cirrhotic patients, especially in pediatric age groups. This study is

a first-step investigation for determining the cut-off values of apo A-I predicting poor prognosis. This routinely used parameter may be employed in prognostic staging models. We believe that with long-term studies, these cut-off values can be confirmed or modified.

REFERENCES

1. Oseb H, Sakai H, Satoh M, Sakamoto S, Koga S, Nawata H. Decreased proapolipoprotein A-I converison. Clin Chim Acta 1990; 189: 303-312.
2. Ciccarese M, Tonolo G, Brizzi P, et al. Serum apolipoprotein (a) concentrations and Apo (a) phenotypes in patients with liver cirhosis. Am J Gastroenterol 1998; 93: 1505-1509.
3. Floren CH, Gustafson A. Apolipoprotein A-I, A-II and E in cholestatic liver disease. Scand J Clin Lab Invest 1995; 45: 103-108.
4. Vergani C, Trovato G, Pietrogrande M,m Crocchiolo P, Dioguardi N. Behaviour of total lipids, cholesterol, lipoproteins and apolipoprotein A in the blood of subjects with acute hepatitis and chronic hepatopathy. Minerva Med 1978; 69: 2081-2094.
5. Hardy SC, Kleinman RE. Cirrhosis and chronic liver failure. In: Suchy FJ (ed.) Liver Disease in Children. St. Louis: Mosby; 1994: 214-248.
6. Malatack JJ, Schaid DJ, Urbach AH, et al. Choosing a paediatric recipient for orthotopic liver transplantation. J Pediatr 1987; 111: 479-489.
7. van Dam GM, Gips CH, Reisman Y, et al. MAjor clinical events, signs and severity assessment scores related to actual survival in patients who died from primary biliary cirrhosis. A long-term historical cohort study. Hepatogastroenterology 1999; 46: 108-115.
8. Suehiro T, Yamamoto M,m Yoshida K, Ohno F. Increase of plasma pro apolipoprotein A-I in patients with liver cirrhosis and its relationship to circulating high-density lipoproteins 2 and 3. Clin Chem 1993; 39: 60-65.
9. Jorge AD, Ponce G, Milutin C, et al. Importance of apolipoproteins A-I and B in acute viral hepatitis and hepatic cirrhosis. Acta Gastorenterol Latinoam 1986; 16: 39-46.
10. Nayak SS, Ramani A, Kamath SS, Kundaje GN, Aroor AR. Serum apoproteins A and B and the lecithin: cholesterol acyl transferase activities in liver cirrhosis and hepatic coma patients. Biochem Med Metab Biol 1988; 40: 299-304.
11. Matsuura T, Koga S, Ibayashi H. Increased proportion of pro apolipoprotein A-I in HDL from patients with liver cirrhosis and hepatitis. Gastroenterol Jpn 1988; 23: 394-400.
12. Malmendier CL, Mailier EL, Amerijckx JP, Fischer ML. Plasma levels of apolipoproteins A-I, A-II and B in alcoholism. Relation to the degree of histological liver damage, and to liver function tests. Hepatogastroenterology 1983; 30: 236-239.
13. Paynard T, Abella A, Pignon JP, Naveau S, Leluc R, Chaput JC. Apolipoprotein A-I and alcoholic liver disease. Hepatology 1986; 6: 1391-1395.
14. Siedel D. Lipoproteins in liver disease. J Clin Chim Biochem 1987; 25: 541-551.

The role of heterotopic gastric mucosa with or without colonization of Helicobacter pylori upon the diverse symptomatology of Meckel's diverticulum in children

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SUMMARY: Oğuzkurt P, Talim B, Tanyel FC, Çağlar M, Şenocak ME, Büyükpamukçu N. The role of heterotopic gastric mucosa with or without colonization of Helicobacter pylori upon the diverse symptomatology of Meckel's diverticulum in children. Turk J Pediatr 2001; 43: 312-316.

The roles of heterotopic gastric mucosa either with or without colonization of Helicobacter pylori (HP) upon the diverse symptomatology of Meckel's diverticulum (MD) in children have been evaluated retrospectively. The medical records of 92 patients who underwent MD excision either incidentally or symptomatically between 1976 and 1997 were reviewed retrospectively. Age at admission and symptoms were recorded. The slides were stained with hematoxylin eosin and Giemsa to identify the presence of heterotopic tissue, ulceration, hemorrhage, inflammation and HP. Bleeding, obstruction and inflammatory groups were statistically compared with chi-square test. The age of the patients ranged between 1 day and 14 years with a mean of 3.5 ± 3.8 years. The male: female ratio was 3.6:1. Among 92 MD, 18 (19.5%) were removed incidentally, one of which had heterotopic gastric mucosa. The indications for surgical removal of MD were intestinal obstruction, diverticulitis and bleeding in 45 (48.9%), 11 (11.9%) and 18 (19.5%) patients, respectively. Heterotopic gastric mucosa was detected in 28 (30.4%) patients, of whom 8, 3, and 16 presented with intestinal obstruction, diverticulitis and bleeding, respectively.

Helicobacter pylori was not detected in one patient with incidental removal of MD; with heterotopic gastric mucosa however, three patients with obstruction, one patient with diverticulitis and one patient with bleeding had HP in the heterotopic gastric mucosa located in MD. MD may become symptomatic due to a complicated course such as rectal bleeding, intestinal obstruction or diverticulitis. The presence of heterotopic gastric mucosa in MD seems to mainly associate with rectal bleeding. The presence of HP colonization in heterotopic gastric mucosa does not increase the incidence of rectal bleeding. The other complications of MD, including intestinal obstruction and diverticulitis, are not directly related to the presence of heterotopic gastric mucosa in the MD. However, colonization of heterotopic gastric mucosa by HP seems to increase the incidence of these complications.

Key words: Meckel's diverticulum heterotopic gastric mucosa Helicobacter pylori.

Meckel's diverticulum (MD) is the most common congenital anomaly of the gastrointestinal tract. It represents the failure of regression of the vitelline duct, a process that normally occurs between the 5th and 7th week of fetal life[1,2]. The incidence of MD is reported to vary between 0.3 and 3.0% of the population[3].

While the majority of MD cases are asymptomatic and are detected incidentally during laparotomy in adult series[2], MD is usually symptomatic in childhood. The clinical presentations are usually associated with complications. The most common clinical presentations of MD are lower gastrointestinal

bleeding, intestinal obstruction due to intussusception, volvulus or band, and inflammatory complications[1]. Complications are often reported to be associated with the presence of heterotopic mucosa within the diverticulum, with gastric heterotopia being the most common type[2,3].

Helicobacter pylori (HP) is a microorganism which locates in the gastric mucosa. It may also locate in gastric mucosa at heterotopic locations. HP located in heterotopic gastric mucosa has been suggested to associate with a complicated course. Hemorrhagic cystitis following bladder augmentation with the use of stomach and rectal bleeding due to heterotopic gastric mucosa have been implicated to be associated with the presence of HP[4,5].

Since the MD frequently contains heterotopic gastric mucosa, a retrospective study was planned to define the role of heterotopic gastric mucosa either with or without superimposed HP colonization on the complicated course of MD in children.

Material and Methods

During a 21-year period from 1976-1997 inclusive, a total of 92 surgically removed MD cases were evaluated retrospectively. The medical records of the patients were reviewed and age at admission and symptoms were recorded. In addition to initial slides, 10 additional slides were prepared from the paraffin blocks for each of the specimens. The slides were stained by hematoxylin-eosin and Giemsa, and were evaluated for the presence of heterotopic tissue, ulceration, hemorrhage, inflammation and HP. While the presence of lymphocytes and plasma cells was accepted as chronic inflammation, additional presence of neutrophils was regarded as active chronic inflammation. Identification of characteristic curved wavy to spiral bacilli in hematoxylin-eosin and Giemsa stained sections indicated the presence of HP. All of the samples were evaluated by two pathologists of the study group.

The patients were classified according to the clinical picture that necessitated the removal, and included incidental, obstructive, inflammatory and bleeding groups.

Removal of MD during laparotomies for other reasons such as intestinal atresia, gastroschisis, omphalocele, malrotation, appendicitis and during splenectomies for hematologic diseases constituted the incidental diverticulectomies.

Patients with obstructions were further divided into subgroups according to the mechanism of obstruction. If the MD was the leading point in intussusception, those patients were regarded as having invaginating MD. If the obstruction was associated with a persisting omphalomesenteric band from the tip to the umbilical region, patients were included into the omphalomesenteric band MD group. If the obstruction developed due to the adherence of MD to neighborhood structures resulting in volvulus due to kinking, twisting or internal herniation in the absence of an omphalomesenteric band, the obstruction was regarded as adhesive MD obstruction.

Patients with inflammation or perforation due to diverticulitis were accepted as diverticulitis associated MD.

If the reason for removal was rectal bleeding, these patients were classified as bleeding MD.

Incidences of presence of gastric mucosa and of HP in the heterotopic gastric mucosa were determined. The mean ages of the patients among the groups were compared with Student's t-test, and the incidence of heterotopic gastric mucosa and HP among the groups was compared using chi-square test. P values less than 0.05 were considered significant.

Results

Ninety-two patients (72 males, 20 females; male to female ratio 3.6: 1) were included in the study. The ages of the patients ranged between newborn to 14 years with a mean age of 3.5 ± 3.8 years.

Among 92 diverticulectomies, 18 (19.5%) were performed incidentally. The reasons for surgical intervention were intestinal obstruction, diverticulitis and bleeding in 45 (48.9%), 11 (11.9%) and 18 (19.5%) patients, respectively. Statistical analysis of mean ages of the patients between groups revealed no difference ($p > 0.05$). Adhesion of the MD to surrounding structures including mesentery and adjacent intestinal loops was the most common mechanism of obstruction, encountered in 31 patients (68.8%). Obstruction resulted from invaginating MD in 12 patients (26.6%) and from omphalomesenteric band MD in two patients (4.4%).

Evaluations revealed the presence of heterotopic gastric mucosa in 28 patients (30.4%). Heterotopic gastric mucosa was present more frequently among the symptomatic children

($p < 0.0001$). Heterotopic gastric mucosa was determined in one patient (1.08%) who underwent incidental removal of MD, and in eight (8.7%), three (3.2%) and 16 (17.3%) patients who presented with intestinal obstruction, diverticulitis and bleeding, respectively (Table I). Gastric mucosa had significantly higher incidence ($p < 0.05$) in the bleeding MD group when compared to the obstructive MD and diverticulitis associated MD groups.

Among the 45 patients with obstruction, the presence of gastric mucosa varied according to the mechanism of obstruction. Six among 31 patients with adhesive MD and one patient from each of the groups of invaginating MD and omphalomesenteric band MD had heterotopic gastric mucosa (Table II). No significant difference was found in the presence of heterotopic gastric mucosa between the groups with various obstructive mechanisms ($p > 0.05$).

All three patients with HP colonization in the obstruction group had adhesive MD obstruction (Table I). Comparison of bleeding and other complications of MD, including the obstruction and diverticulitis groups, revealed that the presence of HP in the heterotopic gastric mucosa increased the incidence of complications other than bleeding significantly ($p < 0.05$).

Among 23 patients with heterotopic gastric mucosa but without HP colonization, seven patients (30.4%) had no additional histopathologic findings. Superficial submucosal and serosal hemorrhage were detected in three specimen. Hemorrhage with active chronic inflammation or chronic inflammation was detected in two and one patients, respectively. While ulceration with active chronic inflammation was detected in five specimens, chronic inflammation was associated with ulceration in one specimen. Hemorrhage, ulceration and active chronic inflammation were detected in another specimen.

Table I. Clinical Data of Patients Who Underwent Meckel's Diverticulum Removal Either Incidentally or Symptomatically

Reason	Mean age of the patients	No. of patients	Patients with gastric mucosa n (%)	Patients with HP n (% in total), (% in gastric mucosa)
Incidental	4.1 ± 4.5	18	1 (1.08)	–
Obstruction	2.9 ± 3.5	45	8 (8.70)	3 (3.20) (10.7)
Bleeding	2.5 ± 2.6	18	16 (17.3)*	1 (1.08) (3.50)
Diverticulitis	6.2 ± 5.0	11	3 (3.20)	1 (1.08) (3.50)
Total	3.5 ± 3.8	92	28 (30.4)	5 (5.40) (17.8)

HP: Helicobacter pylori.
* Significanly different from other groups within the column ($p < 0.05$).

Table II. Clinical Data of Patients in Obstructive Meckel's Diverticulum Group According to the Mechanism of Obstruction

Mechanism of obstruction	Mean age of the patients	No. of patients	Patients with gastric mucosa	Patients with HP
Intussusception	2.8 ± 3.5	12	1	0
Omphalomesenteric band	7.4 ± 9.3	2	1	0
Adhesive	3.2 ± 3.3	31	6	3
Total	2.9 ± 3.5	45	8	3

HP: Helicobacter pylori.

Helicobacter pylori was not detected in the paitent with incidental MD removal who had heterotopic gastric mucosa. On the other hand, HP was found in the heterotopic gastric mucosa of three, one and one patients who presented with intestinal obstruction, diverticulitis and bleeding, respectively.

Among the five patients with HP colonization, two had hemorrhage accompanied by a mild active chronic inflammation, one had hemorrhage, ulceration and active chronic inflammation, one had hemorrhagic necrosis and active chronic inflammation, and one had only active chronic inflammation.

Discussion

The incidence of heterotopic gastric mucosa in MD is reported to range between 10 to 25% in adult series. According to the reported two series in the literature evaluating pediatric patients, 179 patients were asymptomatic and 202 were symptomatic[7,8]. Five percent of the asymptomatic and 56% of the symptomatic patients had heterotopic gastric mucosa[7,8]. Among symptomatic patients, heterotopic gastric mucosa was detected in 80% of patients who presented with rectal bleeding[7,8]. Although the exact rate of heterotopic gastric mucosa incidence has not been reported in children, 54% of the symptomatic patients were reported to have heterotopic mucosa in the diverticulum, most of which was gastric mucosa[1]. Among our patient population, 28 paitents (30.4%) out of 92 with MD had heterotopic gastric mucosa. All but one of the patients with heterotopic gastric mucosa presented with signs directly related to MD or to the complications of the MD. If incidental diverticulectomies were excluded and only symptomatic patients considered, the incidence of heterotopic gastric mucosa reached 36.5%. The only patient who was incidentally found to have MD with gastric mucosa had been operated for duodenal web and malrotation.

Helicobacter pylori is a small, spiral Gram-negative bacillus that can colonize only in human gastric mucosa[9,10]. Colonization of the gastric mucosa with HP is a very common finding in duodenal ulcers and active chronic gastritis[10]. Outside the stomach, HP has always been associated with gastric type mucosa, such as gastric heterotopia in the duodenum and in Barrett's esophagus[9]. It has been reported that HP could also colonize the heterotopic gastric epithelium in the rectum and in the stomach which has been used for bladder augmentation, and the heterotopic gastric mucosa of MD, though these are rarely encountered[4,5,11]. In the English language literature there are adult series reviewing the presence of HP in heterotopic gastric mucosa located in MD. DeCothi et al.[12] reported that eight of 13 patients with heterotopic gastric mucosa had evidence of histologic gastritis, but only four patients had HP-like organisms. On the other hand, Morris et al.[11] reviewed 228 diverticula, of which 65 contained gastric mucosa. Of the four cases with inflammation restricted to gastric mucosa, HP-like organisms were detected in one. In the series of Fich[9], no evidence of HP was detected in the gastric epithelium of MD. Bemelman et al.[6] reported that of the 18 patients with gastric mucosa in MD, 16 were with inflammation. HP-like organisms were identified in one of the patients who underwent an incidental diverticulectomy.

When bleeding is the presenting manifestation of MD, gastric mucosa is almost always present[1]. Heterotopic gastric mucosa was detected in 98% of the patients presenting with rectal bleeding[7,8]. In the present series, of 28 patients with heterotopic gastric mucosa, 16 (57.1%) were admitted with rectal bleeding. Among 18 patients who presented with rectal bleeding, 16 (89%) had heterotopic gastric mucosa. Among those patients, HP was detected in only one patient. In 11 patients presenting with other complications of MD such as diverticulitis and obstruction, which are not directly related to the presence of heterotopic gastric mucosa, HP was detected in four of the resected specimens. In all patients with HP colonization, active chronic inflammation accompanied by submucosal and serosal hemorrhages, ulcerations or hemorrhagic necrosis was detected.

The presence of heterotopic mucosa in MD, of which 65-90% has been reported to be gastric mucosa, has been implicated as causing the symptoms and complications in more than 50% of the symptomatic cases[2,3]. However, gastric mucosa was detected in 36.5% of the symptomatic patients in our series. The rate of heterotopic gastric mucosa incidence was 89% in the patients who presented with rectal bleeding. The association of the presence of heterotopic gastric mucosa and bleeding is significant. This result is compatible with the other large series in the literature[7,8]. Therefore, bleeding MD seems to be mainly related to the presence of heterotopic gastric mucosa.

Among the reported 114 symptomatic patients with heterotopic gastric mucosa in MD, 23 (20%) presented with intestinal obstruction or inflammation[7,8]. Therefore, the presence of heterotopic gastric mucosa in MD has not been accepted as a contributory factor to complications such as obstruction and diverticulitis. In the present series, among 27 symptomatic patients with heterotopic gastric mucosa, three and eight patients, respectively, had diverticulitis and

obstruction. On the other hand, among 47 symptomatic patients without gastric mucosa, 37 presented with obstruction and eight presented with diverticulitis. Therefore, our series also confirmed that the presence of heterotopic gastric mucosa does not contribute to complications other than bleeding. Furthermore, the presence of gastric mucosa does not seem to mandate histopathological findings even in symptomatic patients. The histologic examination of six paitents (27%) without HP colonization revealed normal histology in our series.

Helicobacter pylori colonization in the heterotopic gastric mucosa did not increase the risk of bleeding. On the other hand, incidence of other complications, including obstruction and diverticulitis, seemed to be increased with the colonization of HP.

Meckel's diverticulum may present with diverse symptomatology such as rectal bleeding, intestinal obstruction or acute abdomen due to inflammatory complications. The presence of heterotopic gastric mucosa does not always cause histopathological findings even in symptomatic patients. Heterotopic gastric mucosa does not seem to contribute to the symptomatology of MD other than bleeding. On the other hand, colonization of HP causes an active chronic inflammation in the heterotopic gastric mucosa, and it seems to increase the risk of diverticulitis and intestinal obtruction.

REFERENCES

1. Amoury RA, Synder CL. Meckel's diverticulum. In: O'Neill JA, Rowe MI, Grosfeld IL, Fronkalsrud EW, Coran AG (eds). Pediatric Surgery (4th ed) Vol II. St Louis: Year Book Med Pub; 1998: 1173-1184.
2. Arnold JF, Pellicane JV. Meckel's diverticulum: a ten-year experience. Am Surg 1997; 63: 354-355.
3. Cserni G. Gastric pathology in Meckel's diverticulum. Am J Clin Pathol 1996; 106: 782-785.
4. Kestemberg A, Marino G, de Lima E, Garcia FT, Carrascal E, Arredondo JL. Gastric heterotopic mucosa in the rectum with Helicobacter-pylori like organisms: a rare cause of rectal bleeding. Int J Colorect Dis 1993; 8: 9-12.
5. Cleyair S, Göksel S, Ünal T, Büyükünal SN. Helicobacter pylori infection in a child with gastric augmentation. J Pediatr Surg 1997; 32: 1757-1758.
6. Bemelman WA, Bosma A, Wiersma PH, Rauws EA, Brummelkamp WH. Role of Helicobacter pylori in the pathogenesis of complications of Meckel's diverticula. Eur J Surg 1993; 159: 171-175.
7. St-Vil D, Brandt ML, Panic S, Bensoussan AL, Blanchard H. Meckel's diverticulum in children. J Pediatr Surg 1991; 26: 1289-1292.
8. Vane DW, West KW. Grosfeld JL. Vitelline duct anomalies. Experience with 217 childhood cases. Arch Surg 1987; 122: 542-547.
9. Fich A, Talley NJ, Shorter RG, Phillips SF. Does Helicobacter pylori colonize the gastric mucosa of Meckel's diverticulum? Mayo Clin Proc 1990; 65: 187-191.
10. Hui PK, Chan WY, Cheung PS, Chan JK, Ng CS. Pathologic changes of gastric mucosa colonized by Helicobacter pylori. Human Pathol 1992; 23: 548-556.
11. Morris A, Nicholson G, Zwi J, Vanderwee M. Campylobacter pylori infection in Meckel's diverticulum containing gastric mucosa. Gut 1989; 30: 1233-1235.
12. De Cothi GA, Newbold KM, O'Connor HJ. Campylobacter pylori like organisms and heterotopic gastric mucosa in Meckel's diverticula. J Clin Pathol 1989; 42: 132-134.

Estimation of pulmonary artery pressure by contrast-enhanced Doppler signals and comparison with catheter-measured pressures

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SUMMARY: Akalın N, Tunaoğlu FS, Olguntürk R, Kula S. Estimation of pulmonary artery pressure by contrast-enhanced Doppler signals and comparison with catheter-measured pressures. Turk J Pediatr 2001; 43: 317-322.

Determination of pulmonary artery systolic pressure (PASP) is essential for the diagnosis, and the timing and type of management of patients with congenital heart disease (CHD). Usually cardiac catheterization, an expensive and invasive technique, is required for accurate measurement. A number of noninvasive methods for the assessment of PASP have been developed, one of which is estimation of PASP using contrast-enhanced tricuspid regurgitation Doppler signals (TRDS).

In this study, right ventricular systolic pressures (RVSP) and PASP of 36 patients (19 girls, 17 boys; aged 5 months to 15 years) with CHD were estimated by TRDS before and after galactose solution (GS) and were compared with catheterization measurements. Significant TRDS (> 1 m sec.) were obtained in nine of 36 (25%), patients before GS and in 23 of 36 patients (64%) after GS. TRDS were increased significantly by contrast agent. Estimated RVSP and PASP were significantly different from the measured pressures before and after GS. There were significant correlations between the estimated RVSP and PASP and measured RVSP after GS. Estimated pressures were underestimated.

We conclude that it is better to use the estimated PASP on patients with significant TRDS for the classification of PASP.

Key words: contrast enhancement, tricuspid regurgitation, pulmonary artery systolic pressure.

Determination of pulmonary artery systolic pressure (PASP) is essential for the diagnosis, and the timing and type of management of patients with congenital heart disease (CHD)[1]. Usually cardiac catheterization is required for accurate measurement; however, during follow-up, it cannot be used routinely because it is an expensive and invasive technique. A number of noninvasive methods for the assessment of PASP have been developed[2-8]. Estimation of the right ventricular systolic pressure (RVSP) and PASP using the tricuspid regurgitation, peak systolic velocity with the Bernoulli equation is widely accepted[4,5]. However, PASP estimation is not possible if the tricuspid regurgitation Doppler Signals (TRDS) are weak, as this situation causes recording problems. Intravenous contrast medium has been used in recent years to enhance TRDS and to obtain a significant velocity envelope used for the estimation of PASP[9-10].

The purpose of this study was to estimate PASP by the contrast-enhanced tricuspid regurgitation in children with CHD, and to determine its correlation with the catheter-measured PASP.

Material and Methods

The study papulation consisted of 36 patients (19 girls and 17 boys; aged 5 months to 15 years, mean 5.2 ± 3.9 years) who were admitted for cardiac catheterization. Cardiac diagnoses of patients were as follows: VSD in 20 patients, VSD + ASD in 2 patients, VSD + PDA in 1 patient, and AVSD in 1 patient. Body weights of patients ranged between 3.5 and 43.0 kg (mean: 17.2 ± 3.9 kg). Written informed consent was obtained from the parents.

Echocardiographic studies were performed by same echocardiographer using the System VS-Vingmed Sound IA 09423 D equipment with

3.5 and 5 MHz transducers. The Doppler flow velocity pattern and simultaneous lead II electrocardiogram were displayed on a monitor and recorded on videotapes and on a strip-chart recorder at a paper speed of 50-100 mm/sec.

Mean and maximum velocities and velocity time integrals (VTI) of tricuspid regurgitant jet and pulmonary artery (PA) systolic flows were obtained using 2D, color-guided continuous wave Doppler echocardiography. The three consecutive best developed spectral displays swere measured, and average values were used in the calculations. TR jet was recorded by placing the transducer at the cardiac apex and obtaining a four-chamber view. The color-guided ultrasound beam was directed through the tricuspid valve and aligned parallel to the high velocity jet between the right ventricle. Pulmonary artery systolic flow Doppler signals were obtained at the parasternal short axis view.

Galactose solution (GS) (13.5 cc solution and 3 g galactose granules, Ekovist-Schering™) was used as a contrast-enhanced medium. Hand agitation was performed for 10 seconds. Milky white solutions were injected rapidly fom the right brachial or the cubital vein via 22 gauge intravenous catheter. Echocardiographic measurements were redone just after the injection. No complication was observed due to the echo-contrast agent.

Cardiac catheterization was performed within one to three days of echocardiographic study. Pulmonary artery blood flow volume was calculated using the Fick method. Pressures were measured by a fluid-filled end-hole 5-7F NIH catheter connected to the pressure transducer (Siemens Record M: 6030253, E 287 E) which was pulled back from the PA to the right atrium.

Calculations

The systolic pressure of the right ventricle and PASP were estimated using the following formulas:

RVSP = 4V2 (peak tricuspid regurgitant jet velocity) + 10 mm Hg (as a constant right atrial mean pressure).

PASP = RVSP-peak pressure gradient across the pulmonary valve[11].

All patients were clinically stable, and none showed overt signs of congestive heart failure dring the study. The use of contrast medium did not cause any complications during the study.

Statistical Analysis

All data is expressed as a mean value ± SD (minimum-maximum) in the text and the Tables. A two-tailed unpaired t-test was used for statistical comparison by SPSS (The Statistical Package for the Social Science Program) and $p < 0.05$ indicated a significant difference between groups.

Results

Tricuspid regurgitant Doppler signals were recorded in 21 of 36 patients (58%) with CHD. However, TRDS were trivial in 12 of 21 patients (33% of 36). Nine of 21 patients (25% of 36) had significant TRDS (> 1 m/sec). TRDS were not detected in 15 of 36 patients (42%). After galactose solution infection, TRDS were detected in 27 of 36 patients (75%). In 23 of 27 patients (64% of 36), contrast-enhanced TRDS (> 1 m/sec) were sufficient to estimate the PASP (Fig. 1).

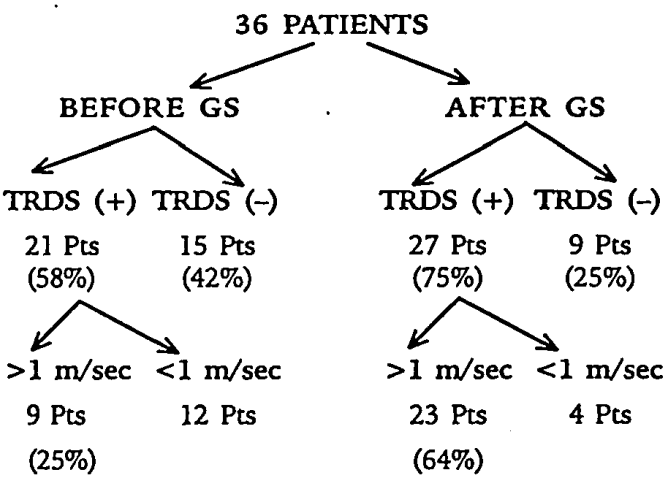

Fig. 1. TRDS positivity before and after galactose solution. TRDS: tricuspid regurgitant Doppler signals; GS: galactose solution.

Tricuspid regurgitant Doppler signals (TRDS) and VTI of TR were enhanced significantly by the GS (Table I). Estimated RVSP and PASP were also significantly increased by the GS (Table I).

Catheter-measured RVSP and PASP of 36 patients are shown in Table II. There were significant differences in the estimated and measured RVSP and PASP before and after GS. There were no significant correlations between the estimated and the measured RVSP and PASP.

After GS, Estimated RVSP and PASP did show significant correlations with the catheter-measured RVSP (r values 0.448 and 0.453,

respectively). Velocities and VTI values of TRDS did show significant positive correlation with the catheter-measured RVSP, before and after GS.

shown in Table III, and all of them increased significantly after GS. After GS, estimated PASP and the RVSP did show significant correlations

Table I. Echocardiographic Measurements of Patients (n = 36)

	Before GS*	After GS*	p
Velocity of TRDS	06525 ± 0.80 (0.00-3.19)	1.9361 ± 1.52 (0.00-131.20)	0.002
VTI of TRDS (cm)	14.36 ± 20.07 (0.00-79.60)	41.82 ± 38.93 (0.00-131.20)	0.006
RVSP (mmHg)	14.19 ± 8.35 (10.00-50.70)	34.02 (10.00-102.16)	0.03
PASP (mmHg)	14.19 ± 8.35 (10.00-50.70)	26.11 ± 19.91 (8.00-84.00)	0.039

*: mean ± SD (min-max).
GS : galactose solution.
TRDS: tricuspid regurgitant Doppler signals.
RVSP : right ventricular systolic pressure.
PASP : pulmonary artery systolic pressure.
VTI : velocity time integrals.

Table II. PA and RV Systolic Pressures of Patients (n=36)

Measurements	Estimated by ECHO*		Catheter*	p
RVSP (mmHg)	Before GS	16.33 ± 9.87 (10.00-50.70)	59.64 ± 27.21 (25.00-119.00)	< 0.0001
	After GS	47.12 ± 24.64 (14.75-102.16)		< 0.0001
PASP (mmHg)	Before GS	16.33 ± 9.87 (10.00-50.70)	46.65 ± 2.82 (19.00-101.00)	< 0.037
	After GS	34.91 ± 20.14 (8.00-84.00)		< 0.038

*: mean ± SD (min-max).
PA : pulmonary artery.
RVSP : right ventricular systolic pressure.
PASP : pulmonary artery systolic pressure.
GS : galactose solution.

The pressure gradient between the right ventricle and pulmonary artery systolic pressure estimated by ECHO and measured by catheterization were as mean ± SD (min-max) 10.90 ± 5.06 mmHg (1.00-19.00 mmHg) and 10.90 ± 7.68 mmHg (0.00-35.00 mmHg). Estimated and measured pressure gardients did not show a significant difference.

Twenty-three patients did show significant increases (0.5 m/sec) in the velocity of TRDS after the GS, and all of them had sufficient velocities of TRDS (> 1 m/sec) for the estimation of RVSP and PASP. Their echocardiographic measurements are

with the catheter-measured RVSP (r values 0.448 and 0.046). There were significant differences in the estimated and measured RVSP and PASP before GS ($p < 0.0001$) (Table IV). Although estimated RVSP and PASP increased significantly after GS, there were significant differences in the estimated and measured RVSP and PASP ($p < 0.038$). There were no significant correlations between the estimated and measured RVSP and PASP before GS the RVSP and PASP estimation by the contrast-enhanced Doppler signals using GS showed significant correlations with the RVSP measurement by cardiac catheterization (r values 0.510 and 0.476, respectively).

Table III. Echocardiographic Measurements of Patients (n = 23)

	Before GS*	After GS*	p
Velocity of TRDS (m/sn)	0.91 ± 0.80 (0.00-3.19)	2.86 ± 1.06 (1.09-4.80)	< 0.0001
VTI of TRDS (cm)	20.01 ± 22.94 (0.00-79.60)	63.09 ± 32.71 (13.68-131.20)	< 0.0001
RVSP (mmHg)	16.33 ± 9.87 (10.00-50.70)	47.12 ± 24.64 (14.75-102.16)	< 0.0001
PASP (mmHg)	16.33 ± 9.87 (10.00-50.70)	34.91 ± 20.14 (8.00-84.00)	< 0.0001

*: mean ± SD (min-max).
GS : galactose solution.
TRDS: tricuspid regurgitant Doppler signals.
RVSP : right ventricular systolic pressure.
PASP : pulmonary artery systolic pressure.
VTI : velocity time integrals.

Table IV. RVSP and PASP of Patients (n=23)

Measurements	Estimated by ECHO*		Catheter*	p
RVSP (mmHg)	Before GS	14.19 ± 8.35 (10.00-50.70)	55.75 ± 24.66 (25.00-119.00)	< 0.0001
	After GS	34.02 ± 26.35 (10.00-102.16)		< 0.0001
PASP (mmHg)	Before GS	14.19 ± 8.35 (10.00-50.70)	45.88 ± 21.04 (19.00-101.00)	< 0.0001
	After GS	26.11 ± 19.91 (8.00-84.00)		< 0.0001

*: mean ± SD (min-max).
RVSP : right ventricular systolic pressure.
PASP : pulmonary artery systolic pressure.
GS : galactose solution.

In general, PASP and RVSP estimated by the contrast-enhanced Doppler signals were underestimated when compared with cardiac catheterization data. The repeatability of the estimated and measured RVSP and PASP were 0.4269 (43%) and 0.4094 (41%), respectively.

Discussion

Contrast echocardiography is used for the detection of valve insufficiencies, intracardiac shunts and flow dynamics[9,10,12,13]. Using the contrast medium, trivial valve regurgitations can be enhanced to obtain the optimum levels for the calculations[14]. Contrast agents are used usually in adults for visulization of the myocardium of the left ventricle[15]. There are several reports about contrast echocardiography in children[16].

In this study, galactose solution was used as a contrast agent in children with CHD. TR in 21 of 36 patients with CHD was detected. However, 12 o 21 patients had trivial TR, and only nine of 36 patients had TR higher than 1 m/sec. With the GS injection, sufficient TR for the estimation of RVSP and PASP could be obtained in 23 of the 36 patients. The GS injection enhanced the TRDS significantly.

It is well known that regurgitant jet Doppler signals are detected in healthy children[17,19]. There are some criteria, such as the time, the duration and the velocity of regurgitation for the definition. Therefore, VTI along with the peak velocity of TR were used for the comparison. Although a correlation of VTI of TR and estimated PASP was found, there was no correlation with the measured PASP.

Sufficient TRDS for the estimation of RVSP and PASP were obtained in 23 of 36 patients with the GS injection. Their estimated values were increased and close to the measured values, but were still significantly different.

The result of the studies about estimation of PASP and RVSP using contrast-enhanced Doppler echocardiography in children and adults showed significant correlations between the estimated and measured pressures. Differences in the results of this study with these other studies may be due to the contrast agent we used[19-20]. Tokushima et al.[20] and Ishii et al.[16] concluded that sonicated albumin was superior to hand-agitated 5% glucose as an enhancer of Doppler signals from the view of a fine, clear demonstration of the velocity envelope of tricuspid regurgitation[16,20]. Galactose solution microbubles were larger than the albumin, so we could not obtain a fine spectral display.

Another important point of argument is right atrial pressure. Multiple approaches for estimating the right atrial pressure have been proposed. They include a clinical evaluation of the jugular venous pulse[12], inferior vena collapsibility index[20], or a constant[21]. We added 10 mmHg to all patients' values as the right atrial pressure. In general, catheter-measured right atrial pressures were under this value in our study. Also, right atrial pressure will increase in the presence of right ventricular dysfunction or dilated right or left heart. The other limitation is detecting the accurate TRDs because of individual sensitivity problems due to the patient and imaging device. These factors could affect the relation between the estimated and measured pressures. In this study, significant enhancement of Doppler imaging by contrast medium, leading to increased sensitivity for flow detection and therefore increased areas of Doppler flow display, were obtained. However, we could not show correlation between the estimated and measured PASP. Our estimated pressures were underestimated as in other studies[20-21]. These results emphasize a basic relation between TRDS and RVSP and PASP, but sohuld not be accepted as a reliable method in the decision making process for heart surgery without cardiac catheterization. It is better to use the estimated PASP by contrast-enhanced agent in patients with significant TRDS for the classification of PASP.

REFERENCES

1. Kinsella JP, Neish SR, Abman S, Wolfe RR. Therapy for pulmonary hypertension. In: Garson A, Bricker JT, Fisher DJ, Neish SR (eds). The Science and Practice of Pediatric Cardiology (2nd ed). Baltimore: William and Wilkins; 1998: 2345-2366.
2. Yener A, Günaydın S, Olguntürk R, Tunaoğlu S, Özdoğan ME. Technetium-99m hexamethyl propyleneamine oxime lung clearance in the estimation of pulmonary hypertension in congenital heart disease: a preliminary comparative study with cardiac catheterization and pathology. Pediatr Cardiol 1999; 20: 270-277.
3. Duran RM, Larman M, Trugede A, Prada JV, Ruano J. Comparison of Doppler-determined elevated pulmonary artery pressure with pressure measured at cardiac catheterization. Am J Cardiol 1986; 57: 859-863.
4. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J Am Coll Cardiol 1985; 6: 359-361.
5. Feigenbaum H. Echocardiography (5th ed). Philadelphia, London: Lea and Febier; 1994: 203-205.
6. Anconina J, Danchin N, Selton-Suty C, Isaaz K, Juliere Y. Noninvasive estimation of right ventricular dP/dt in patients with tricuspid valve regurgitation. Am J Cardiol 1993; 71: 1495-1497.
7. Skinner JR, Stuart AG, O'Sullivan J, Heads A, Boys R. Right heart pressure determination by Doppler in infants with tricuspid regurgitation. Arch Dis Child 1993; 69: 216-220.
8. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with trecuspid regurgitation. Circulation 1984; 70: 657-662.
9. Suzuki Y, Kambara H, Kadota K, et al. Detection and evaluation of tricuspid regurgitation using a real-time, two-dimensional, color-coded, Doppler flow imaging system: comparison with contrast two-dimensional echocardiography and right ventriculography. Am J Cardiol 1986; 57: 811-815.
10. Wagganer AD, Barzilai B, Perez JE. Saline contrast enhancement of tricuspid regurgitant jet detected by Doppler color flow imaging. Am J Cardiol 1990; 65: 1368-1371.
11. Snider RA, Serwer GA, Ritter SB. Echocardiography in Pediatric Heart Disease (2nd ed). St. Louis: Mosby; 1997: 164-168.
12. Hatle L, Angelsen BA, Tromsal A. Non-invasive estimation of pulmonary artery systolic pressure with Doppler ultrasound. Br Heart J 1981; 45: 157-165.
13. von Bibra H, Becker H, Firschke C, Schlief R, Emslander HP, Schöming A. Enhancement of mitral regurgitation and normal left atrial color Doppler flow signals with peripheral venous injection of a saccharide-based contrast agent. J Am Coll Cardiol 1993; 22: 521-528.
14. Schwarz KQ, Bezante GP, Chen X, Philips D, Schlief R. Hemodynamic effects of microbubble echo contrast. J Am Soc Echocardiogr 1996; 9: 795-804.

15. Berwing K, Schlepper M. Echocardiographic imaging of the left ventricle by peripheral intravenous injection of echo-contrast agent. Am Heart J 1988; 115: 399-407.

16. Ishii M, Kato H, Inoue O, Takagi T, Akagi T, Miyake T. Noninvasive evaluation of systolic pressure of pulmonary artery and right ventricle using contrast-enhanced Doppler echocardiography: comparative study using sonicated albumin or glucose solution. Pediatr Cardiol 1996; 17: 175-180.

17. Shan D, Maciel BC. Physiological valvular regurgitation. Dopler echocardiography and the potential for iatrogenic heart disease. Circulation 1988; 78: 1075-1076.

18. Van Dijk AP, Van Oort AM, Daniels O. Right-sided valvular regurgitation in normal children determined by combined colour-coded and continuous-wave Doppler echocardiography. Acta Paediatr 1994; 83: 200-203.

19. Brand A, Dollberg S, Keren A. The prevalence of valvular regurgitation in children with structurally normal hearts: a color Doppler echocardiographic study. Am Heart J 1992; 123: 177-180.

20. Tokushima T, Utsunomiya T, Yoshida K, et al. Estimation of the systolic pulmonary arterial pressure using contrast-enhanced continuous-wave Doppler in patients with trivial tricuspid regurgitation. Jpn Heart J 1999; 40: 311-320.

21. Lavine SJ. Noninvasive estimation of right-sided pressures from spectral Doppler recordings of tricuspid and pulmonic regurgitant velocities. Chest 1999; 116: 1-3.

An open trial and discontinuation study of fluoxetine in children and adolescents with obsessive-compulsive disorder

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SUMMARY: Semerci ZB, Unal F. An open trial and discontinuation study of fluoxetine in children and adolescents with obsessive-compulsive disorder. Turk J Pediatr 43: 323-328.

The purpose of this study was to examine the efficacy and safety of fluoxetine for short-term and long-term treatment in children and adolescents with obsessive-compulsive disorder (OCD). Twenty-three children and adolescents (mean age 12.0, SD = 2.3) treated with fluoxetine for OCD with or without Gilles de la Tourette's syndrome were the subjects of this study. The design was an open-label trial for 20 weeks of fixed-dose fluoxetine (20 mg/day). OCD symptom severity was measured with the Maudsley OCD scale and with Clinical Global Impression Scale (CGI). All of the patients were followed-up after discontinuation of the drug for 24 months. Patients with OCD showed a significant decrease in the severity of their OCD symptoms according to Maudsley OCD scores ($p < 0.001$) and CGI scores ($p < 0.001$). Fluoxetine was generally well tolerated, and side effects were relatively mild. Ten patients (43.5%) with OCD who responded to fluoxetine relapsed in the follow-up period, but responded well to fluoxetine. These results indicate that fluoxetine is effective and safe for short-term and long-term treatment of OCD in children and adolescents.

Key words: obsessive-compulsive disorder, children, adolescents, follow-up, fluoxetine.

Recent epidemiological data shows that obsessive-compulsive disorder (OCD) occurs in children and adolescents as in adults. The point and life-time prevalence of OCD in children and adolescents are 1% and 1.9% respectively[1]. Approximately 80% of adults with OCD reported an onset of symptoms before 18 years[2]. OCD appears to be similar in children, adolescents and adults in terms of clinical features and treatment[3,4]. The etiology of OCD has been explained by genetic, biological, behavioral and psychodynamic theories[5]. Tic disorder is the most common comorbid disorder in children with OCD. Assessment of the other disorders, particularly tics, is important and may help in determining treatment[6].

Several studies have established the safety and efficacy of the serotonergic tricyclic antidepressant clomipramine in children and adolescents with OCD[1,3]. Common side effects are generally related to the anticholinergic and alpha-adrenergic effects[5]. In recent years, there has been increasing interest in the use of specific serotonin reuptake inhibitors (SSRI's) in the treatment of OCD. Some studies have demonstrated that fluoxetine, a SSRI, is effective in reducing OCD symptoms in children and adolescents as well as in adults, but there is no follow-up study that evaluates the discontinuation period. The purpose of this study was to examine the efficacy and safety of fluoxetine in short-term and long-term treatment of OCD in children and adolescents.

Material and Methods

Twenty-three children and adolescents representing a consecutive series treated with fluoxetine for OCD with or without Gilles de la Tourette's syndrome (GTS) at the Child and Adolescents Psychiatry Department of the University of Hacettepe were the subjects of this study. The study design included an open-label trial for 20 weeks and an open discontinued follow-up period of 24 months. The study was approved by the institutional ethics committee and signed consent were obtained from parents.

All subjects were evaluated independently by two child and adolescent psychiatrists and all met the DSM-IV diagnostic criteria for OCD[7].

Ten of the subjects received an additional diagnosis of GTS according to the DSM-IV. No other comorbid diagnosis was made according to the DSM-IV criteria. The exclusion criteria were life-time and current mental retardation, psychotic disorders, major depressive disorder, organic or neurological problems and laboratory abnormalities.

The symptom severity of OCD was measured with the Maudsley OCD Scale[8] translated and standardized for Turkish population[9] and with the Clinical Global Impression Scale (CGI) at the beginning and end of the study. Severity ratings on the CGI scale was as follows: 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = marked, 6 = severe, 7 = extreme. The agreement between the interviewers was high (Kappa: 0.803).

At the first examination, medical assessments including physical and neurological examination weight and blood pressure measurement; and clinical laboratory studies including electrocardiogram (ECG), and routine clinical chemistry, blood count, and urinalysis were done. These variables were reassessed monthly in the treatment phase.

After these assessments, fluoxetine was administered at a fixed dose (20 mg/day) every morning. No other treatment was given (family therapy, individual psychotherapy, behavioral-cognitive therapy), except pimozide for GTS. Pimozide dose was stable for each patient with GTS (mean dose: 2 mg/day).

During the 20-week study period, patients were, evaluated by the clinicians every fourth week and the symptom severity was rated on the CGI scale. The safety of the treatment was also assessed monthly by monitoring vital signs, laboratory tests and ECG. Furthermore, a semi-structured interview according to a body-system classification was developed and applied every fourth week to record systematically all adverse events.

At the end of 20 weeks, fluoxetine administration was discontinued. Twenty-three patients were longitudinally followed-up for a total period of 24 months. They were evaluated every two months for the first 12 months and every six months for the last 12 months. OCD symptom severity was measured with the CGI. The Maudsley OCD scale was used to screen obsessive-compulsive symptoms at the end of the 12-month and 24-month period. Fluoxetine (20 mg/day) was the choice of drug in case of recurrences. The dosage of the drug was increased up to 60 mg/day for patients who did not respond to 20 mg/day, and side effects were assessed for all relapsing patients.

Statistical analysis was performed with a computer package program (Statistical Package for Social Sciences, For Windows Release 5.0.1, SPSS Inc., 1992). Chi-square test, Wilcoxon test, Kruskal Wallis test and Mann Whitney U test were used with non-parametric data and t-test with parametric data. Fisher's exact test was applied when necessary and all tests were two-tailed.

Results

The age range of the sample was from 8 to 16 years; the mean age was 12.0 years (SD=2.3). There were 13 females (56.5%) and 10 males (43.5%).

None of the subjects had prior history of treatment with psychotropic medication before receiving fluoxetine. As a concurrent medication, pimozide was used in 10 subjects (43.5%), for the treatment of comorbid GTS (Table I).

Table I. Clinical Characteristics of the Subjects

		n	%
Age			
Mean Age	12.0 ± 2.3 years	23	100
Range	8-16 years		
Sex			
Male		10	43.5
Female		13	56.5
Comorbid Disorders			
GTS		10	43.5
None		13	56.5
Concurrent medication			
Pimozide (only for children with comorbid GTS)		10	43.5
None		13	56.5

GTS: Gilles de la Tourette's syndrome.

The age of onset for the OCD symptoms ranged from 7 to 15 years, mean 10.7 years (SD = 2.2). The interval between the onset of the symptoms and the diagnosis ranged from 3 to 48 months, mean 16.1 months (SD = 12.1). GTS symptoms started before OCD symptoms in ten patients with GTS.

Most of the patients (n: 11, 47.8%) were mild cases according to CGI scores and only one patient (4.3%) was rated as 'severe' by both clinicians. The severity of the OCD symptoms according to the Maudsley OCD scores showed a significant decrease in the treatment phase,

and did not change significantly at the end of the follow-up period. The symptomatic improvement during fluoxetine treatment was observed generally in the first month on the CGI scores. All patients' CGI scores continued to decrease monthly in the treatment phase. This decrease was statistically significant for every four-week interval except for the last month of the treatment phase. At the end of the treatment phase, 21 patients (91.3%) responded well to fluoxetine treatment according to CGI scores (patients who received 1 in CGI).

As 10 patients (43.5%) relapsed after the discontinuation of fluoxetine in the first 8-16 weeks (mean = 13.0, SD = 4.1 weeks), a statistically significant increase in the CGI scores in the second month of the follow-up period was observed. The CGI scores decreased in the eight month of the follow-up period with the recovery of these patients (Fig. 1 and Table II).

Fluoxetine (20 mg/day) was applied for all relapsed patients, but three of them needed an increase to 40 or 60 mg/day. All but one patient recovered completely in 16 to 40 weeks. This 13-year-old girl's subclinical symptoms remained. A 10-year-old boy showed an additional relapse eight months after recovery from his first relapse (Table III).

The associations between age, gender and other demographic variables, and clinical and therapeutic features such as comorbid diagnosis, concurrent medication, and onset of the illness were examined. Relapsing and non-relapsing patients did not differ in terms of age, sex, comorbidity of GTS or severity of OCD, therefore, no risk factors could be determined for relapses.

The relapsed patients required a significantly shorter time to achieve a '1' in the CGI scale during the treatment phase (mean: 3.4 months

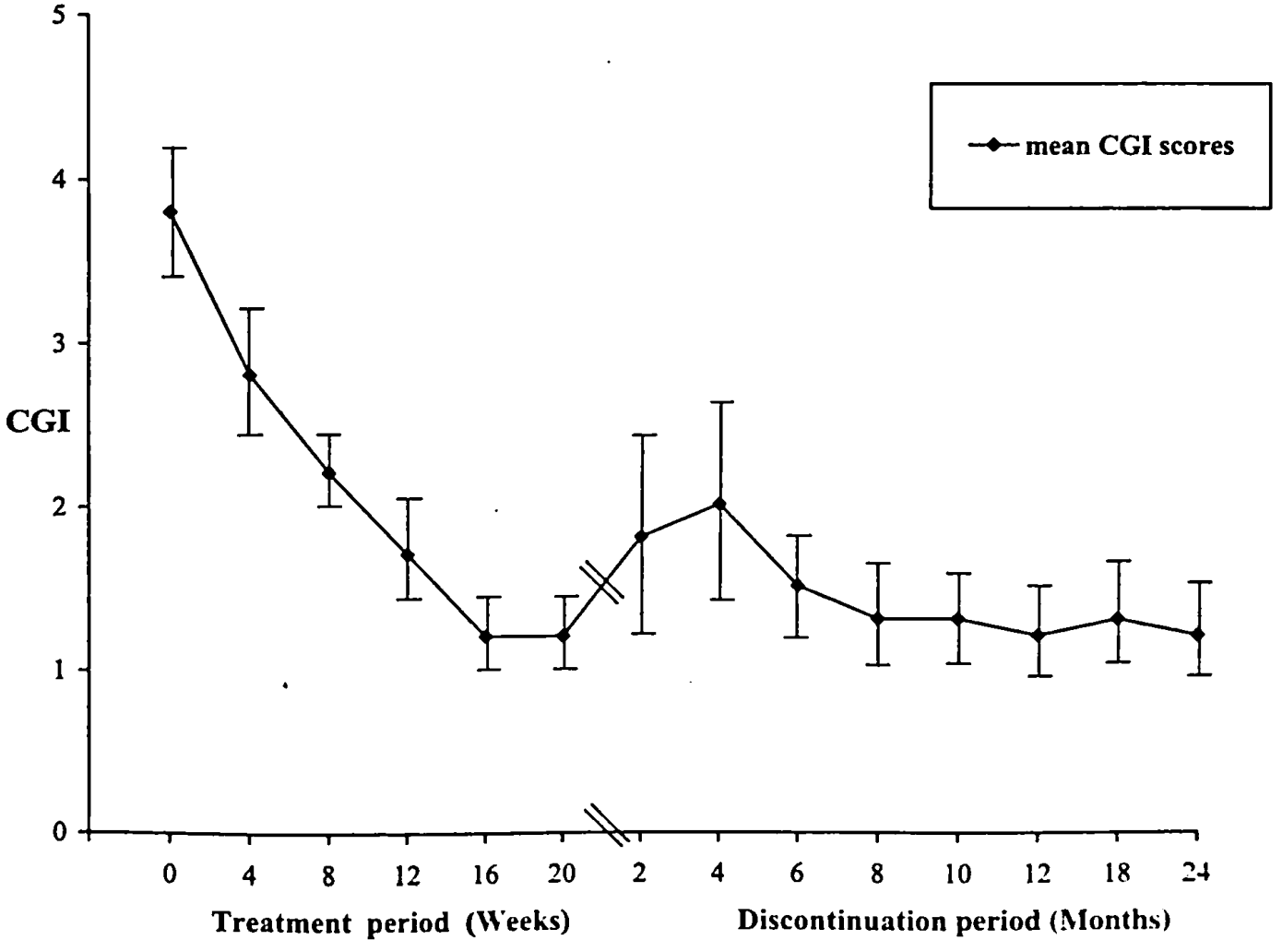

Fig. 1. Mean CGI Scores during the Treatment and Discontinuation Periods.

SD = 0.7) than in the follow-up phase (mean: 5.5 months SD = 2.1) (z: 2.37 p: 0.018). However, the recovery time in the treatment phase of these patients (n: 10, mean: 3.4 months SD = 0.7) and of the patients who did not relapse (mean: 3.5 months SD = 0.5) was similar (z: 0.42, p: 0.68).

Fluoxetine was generally well tolerated. Side effects reported in our sample included dyspepsia and nausea in three patients (13.0%) and skin rash in one patient (4.3%). Those side effects were relatively mild and not severe enough to discontinue the drug. They appeared during the first few days of treatment and disappeared in almost one week. No side effects were noticed during the use of fluoxetine in recurrences, even with high dosages. There were no significant ECG changes, laboratory abnormalities, or blood pressure or weight changes during the study.

Table II. Symptom Severity During the Treatment and Discontinuation Periods

	CGI scale[a]	t	df	Maudsley OCD scale[a]	t	df
Baseline	3.8 ± 0.9			21.6 ± 4.4		
4th Week	2.8 ± 0.9[b]	9.18	22			
8th Week	2.2 ± 0.4[b]	4.60	22			
12th Week	1.7 ± 0.7[b]	4.49	22			
16th Week	1.2 ± 0.4[b]	4.90	22			
20th Week	1.1 ± 0.3[NS]			9.3 ± 4.2[b]	16.56	22
2th Month	1.8 ± 1.2[b]	3.01	22			
4th Month	2.0 ± 1.1[NS]					
6th Month	1.5 ± 0.7[b]	3.87	22			
8th Month	1.3 ± 0.6[c]	2.47	22			
10th Month	1.3 ± 0.5[NS]					
12th Month	1.2 ± 0.5[NS]			8.9 ± 4.2[NS]		
18th Month	1.3 ± 0.6[NS]					
24th Month	1.2 ± 0.5[NS]			8.8 ± 3.8[NS]		

[a] : All statistical comparisons were made with the former measurement.
[b] : $p < 0.001$.
[c] : < 0.05.
[NS]: not significant.
CGI: Clinical Global Impression, OCD: Obsessive-compulsive disorder.

Table III. Clinical Characteristics of the Relapsed Patients

	Age	Sex	GTS	Relapsed (CGI=3) at week	Recovered (CGI=1) at week
Case 1	12	female	–	8	32[b]
Case 2	10	female	–	8	32[b]
Case 3	9	male	–	16	- [c, m]
Case 4	13	female	–	8	- [c, s]
Case 5	10	male	–	8	32[a, r]
Case 6	8	male	+	8	24[a]
Case 7	13	male	+	16	32[a]
Case 8	13	male	+	8	48[c]
Case 9	9	male	+	16	32[a]
Case 10	14	female	+	8	24[a]

Recovered with: [a] 20 mg/day, [b] 40 mg/day, [c] 60 mg/day fluoxetine.
[m]: recovered partially and remained with mild symptoms (CGI = 3).
[s]: recovered partially and remained with subclinical symptoms (CGI = 2).
[r]: relapsed again at week 72 but responded well to 20 mg fluoxetine.
GTS: Gilles de la Tourette's syndrome, CGI: Clinical Global Impression.

Discussion

The results of this open-label clinical study suggest that fluoxetine is an effective treatment in children and adolescents with OCD. A decrease in the severity of OCD symptoms was reflected in the Maudsley OCD scores and CGI scores. These results were similar to those of previously reported studies[10-15]. The symptomatic improvement during fluoxetine treatment was generally observed in the first month, both clinically and on the CGI scores. A plateau in

improvement was noticeable in the last month. Riddle et al.[14] reported that OCD symptom severity decreased about 30 to 45% after eight weeks. This result suggests that fluoxetine is effective for short-term treatment of OCD.

Several controlled studies established the efficacy of clomipramine in the short-term treatment of children and adolescents with OCD[3,16]. Leonard et al.[17] also showed the efficacy of clomipramine in the long-term treatment of children and adolescents with OCD. However, clomipramine was associated with anticholinergic adverse effects, intolerable for some patients. Fluoxetine treatment was generally well tolerated. A significant number of subjects (83%) did not report any side effects. Dyspepsia and nausea were also the most common side effects in previous studies, and were generally transient[10,14], as in our sample. Also, a study in children and adolescents with another SSRI (citalopram) suggested that side effects were minor and transient[18]. The absence of side effects during the use of fluoxetine in recurrences supports the safety of this drug for long-term use in children and adolescents.

There were no significant ECG changes, laboratory abnormalities, or blood pressure or weight changes during the study, as expected from previous reports[10,13-14]. However, there is no data on long-term effects of fluoxetine on these variables. This report supports that fluoxetine may be safe alternative treatment for children and adolescents with OCD, both in the short-and long-term.

Ten recurrences were observed during the follow-up period. Relapsing and non-relapsing patients did not differ in terms of age, sex, comorbidity of GTS or severity of OCD; therefore, no risk factors could be determined for relapses.

The same dose (20 mg/day) was readministered to patients who relapsed. However, the need for doses as high as 40-60 mg/day in three patients elongated the recovery time compared to the first treatment period, suggesting a development of tolerance to the medicine.

Although there are no objective data, the clinical observations of the clinicians following-up these cases suggested that families of relapsing patients were less supportive and less involved with their child compared to those of other patients. Family attitudes as a factor influencing the prognosis of OCD have been reported in some studies[19].

The duration of medical treatment in OCD is controversial. Some clinicians advise at least six months' treatment in order to improve subclinical findings and prevent relapses[20]. The occurrence of relapses after 8-16 weeks of the discontinuation of fluoxetine suggests that 20 weeks' treatment may be too short, and that the treatment should be extended even in the absence of symptoms to prevent relapses.

Despite its two major limitations, its open-label design and fixed dosage, this study is one on the largest series of children and adolescents treated with fluoxetine. However, the most important aspect of this study is that a follow-up, evaluating long-term effects and side effects in fluoxetine treatment, could be conducted so that the rate of recurrences could be established. The findings indicate that fluoxetine is effective and safe in short-term and long-term treatment of OCD in children and adolescents. Future studies should determine the effective blood levels of fluoxetine and the minimum duration of treatment in children and adolescents.

REFERENCES

1. Flament MF, Rapoport JL, Berg CJ. Clomipramine treatment of childhood obsessive compulsive disorder: a double-blind controlled study. Arch Gen Psychiatry 1985; 42: 977-983.
2. Pauls DL, Alsobrook JP 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. Am J Psychiatry 1995; 152: 76-84.
3. Leonard HL, Swedo SE, Rapoport JL, et al. Treatment of obsessive-compulsive disorder with clomipramine and imipramine in children and adolescents. Arch Gen Psychiatry 1989; 46: 1088-1092.
4. Rapoport JL, Swedo SE, Leonard HL. Childhood obsessive compulsive disorder. J Clin Psychiatry 1992; 53: 11-16.
5. Riddle MA. Obsessive-compulsive disorder in children and adolescents. Br J Psychiatry 1998; 173 (Suppl): 91-96.
6. Swedo SE, Rapoport JL, Choslow DL, et al. High prevalence of obsessive-compulsive symptom in patients with Sydenham's chorea. Am J Psychiatry 1989; 146: 246-249.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association; 1994.
8. Hodson RJ, Rachman S. Obsessional-compulsive complaints. Behav Res Ther 1977; 15: 389-395.
9. Erol N, Savaşır I. [The translation and standardization of the Maudsley OCD scale in Turkish]. Free Communication in the 24th National Psychiatry Congress, Ankara, Turkey; 1988.

10. Como PG, Kurlan R. An open-label trial of fluoxetine for obsessive-compulsive disorder in Gilles de la Tourette's syndrome. Neurology 1991; 41: 872-874.

11. Geller DA, Biederman J, Reed E, Spencer T, Wilens TE. Similarities in response to fluoxetine in treatment of children and adolescents with obsessive compulsive disorder. J Am Acad Child Adolesc Psychiatry 1995; 34: 36-44.

12. Kurlan R, Como PG, Deeley C, McDermott M, McDermott MP. A pilot controlled study of fluoxetine for obsessive-compulsive symptoms in children with Tourette's syndrome. Clin Neuropharmacol 1993; 16: 167-172.

13. Riddle MA, Hardin MT, King R, Scahill L, Woolston JL. Fluoxetine treatment of children and adolescents with Tourette's and obsessive compulsive disorders: preliminary clinical experience. J Am Acad Child Adolesc Psychiatry 1990; 29: 45-48.

14. Riddle MA, Scahill L, King R, et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive compulsive disorder. J Am Acad Child Adolesc Psychiatry 1992; 31: 1062-1069.

15. Emslie GJ, Walkup JT, Pliszka SR, Ernst M. Nontricyclic antidepressants: current trends in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999; 38: 517-528.

16. DeVeaugh-Geiss J, Moroz G, Biederman J, et al. Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder: a multicenter trial. J Am Acad Child Adolesc Psychiatry 1992; 31: 45-49.

17. Leonard HL, Swedo SE, Lenane MC, et al. A 2 to 7-year follow-up study of 54 obsessive-compulsive children and adolescents. Arch Gen Psychiatry 1993; 50: 429-439.

18. Thomsen PH. Child and adolescent obsessive-compulsive disorder treated with citalopram: findings from an open trial of 23 cases. J Child Adolesc Psychopharmacol 1997; 7: 157-166.

19. Riddle MA, Scahill L, King R, et al. Obsessive compulsive disorder in children and adolescents: phenomenology and family history. J Am Acad Child Adolesc Psychiatry 1990; 29: 766-772.

20. March JS, Leonard HL. Obsessive compulsive disorder in children and adolescents: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1996; 34: 1265-1273.

Severe hemolytic anemia after repair of primum septal defect and cleft mitral valve

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SUMMARY: Alehan D, Doğan R, Özkutlu S, Elshershari H, Gümrük F. Severe hemolytic anemia after repair of primum septal defect and cleft mitral valve. Turk J Pediatr 2001; 43: 329-331.

Two cases are described in which severe mechanical hemolytic anemia developed after surgical repair of primum atrial septal defect (ASD) and cleft mitral valve. In both cases there was residual mitral regurgitation after repair. Moderate mitral regurgitation and collision of the regurgitant jet with the teflon patch used for repair of the primum ASD were detected by color-Doppler echocardiography imaging. Laboratory tests showed normochromic normocytic anemia, increased indirect serum bilirubin, decreased plasma haptoglobin and hemoglobinuria. The peripheral blood smear contained numerous fragmented red cells. Following another surgical correction of the mitral valve (repair or mitral valve replacement), there was no more hemolysis. The two presented cases show that foreign materials in association with localized intracardiac turbulence may cause severe hemolysis.

Key words: hemolytic anemia, primum ASD, cleft mitral valve, mitral regurgitation.

Hemolytic anemia is an infrequent but well documented complication following the insertion of intracardiac or intravascular prosthetic materials. It was first reported by Sayed et al.[1] in a patient who had closure of an ostium primum atrial septal defect with a teflon patch. Hemolytic anemia has also been reported after mitral valve repair[2-9]. With the improvement of surgical materials and techniques, this complication has recently become exceptionally rare. We describe two children who developed severe hemolysis after repair of primum atrial septal defect (ASD) and cleft mitral valve in association with mitral insufficiency. The anemia was corrected by mitral valve replacement or repair.

Case Report

Case 1

An eight-year-old girl diagnosed with a primum ASD and cleft mitral valve underwent an intracardiac repair through median sternotomy using a teflon patch closure of the primum ASD and stitch closure of the cleft in the anterior leaflet of the mitral valve according to Rowlatt formula[10]. Postoperative transthoracic echocardiography revealed good biventricular function and moderate mitral valve regurgitation, but no evidence of residual ASD.

The patient was well until four months postoperatively when she was admitted to our hospital with history of fatigue, lethargy and loss of appetite. Evaluation revealed jaundice without fever or lymphadenopathy. She had an enlarged liver palpable 4 cm below the right costal margin at the midclavicular line. On cardiac examination a regular rhythm, tachycardia and pansystolic murmur over the mitral area were detected.

Laboratory studies revealed a hemoglobin level of 5.0 g/dl. The leukocyte count was 9600/mm^3 with a normal differential count, the platelet count was 242,000/mm^3, red cells were 1.9 x 10^{12}/L, reticulocyte count was 4.4%, and haptoglobin level was low. The peripheral blood smear showed a number of red cell fragments, spherocytes, normoblasts and marked polychromasia. The patient's serum total and direct bilirubin were 6.24 and 0.63 mg/dl, respectively, and lactic dehydrogenase was 5045 IU/L. The urine contained increased amounts of urobilinogen and urobilin. Coombs' test was negative. Transthoracic

color-Doppler echocardiography showed a moderate mitral regurgitation with a central regurgitant jet directly striking the teflon patch. The diagnosis of mechanical severe hemolytic anemia due to mitral regurgitation was suspected. Despite a trial of medical treatment and blood transfusions, the anemia persisted and it was decided to reoperate. The mitral valve was found to be severly deformed; therefore, valve replacement was carried out. The postoperative course was unremarkable. The patient had an uneventful recovery with no further blood transfusion, and hemolytic anemia was cured. The hemoglobin level was 13.8 g/dl and all other tests for hemolysis reverted to normal.

Case 2

A three-year-old girl developed severe hemolytic anemia following surgical correction of a partial atrioventricular canal and closure of a mitral cleft. The patient underwent closure of the ASD with a teflon patch and the mitral cleft was repaired with four sutures.

Two months postoperatively, the patient was admitted to the hospital with severe hemolytic anemia (hemoglobin 6.0 g/dl). All laboratory investigations performed revealed evidence of hemolytic anemia. Transthoracic echocardiography showed good shape and satisfactory function of the reconstructed mitral valve. However, color-Doppler echocardiography revealed a small eccentric high-velocity jet of mitral regurgitation originating from the anterior leaflet of the valve and striking the teflon patch. Reoperation was required for control of the uncompensated hemolysis.

Intraoperative exploration of the mitral valve showed leaking through the stitches of the anterior leaflet. In this case, clinically manifest hemolysis ceased after the mitral valve repair.

Discussion

Hemolytic anemia in association with congenital heart disease is rare and clinically significant. Hemolysis following cardiac surgery is uncommon. Sayed and colleagues[1] described a patient who developed severe intravascular hemolysis after teflon patch closure of a partial atrioventricular canal. At reoperation, a regurgitant jet of blood through a mitral valve cleft was directed against a bare patch of teflon. Covering the teflon with endocardium eliminated the hemolysis. Similar patients were described by Verdon[11] and Sigler et al.[12]. It was concluded that the hemolysis was due to excessive local blood velocity with altered intracardiac morphology resulting in critical turbulence and red cell damage.

Moisey et al.[5] reported a case of severe hemolytic anemia in association with hemodynamically moderate mitral regurgitation. In this case, valve replacement eliminated the hemolysis. Stoschitzky and colleagues[7] reported a patient with hemolytic anemia after mitral valve repair who eventually required valve replacement. The patient had a high velocity jet of mitral regurgitation that struck at a right angle the opposite wall of the left atrium, although the amount of regurgitation was assumed to be hemodynamically insignificant.

A recent report by Yeo et al.[13] suggested that hemolysis after mitral valve repair is due to the high shear stress produced by the regurgitant jet, independent of the severity of mitral regurgitation, and that the most commonly observed mechanism of hemolysis involved direct collision of the regurgitant jet with a prosthetic surface. In vitro studies have domonstrated that shear forces > 3000 dynes/cm^2 are associated with significant red cell destruction[14].

In the present two cases, the most likely source of the hemolysis was the residual mitral regurgitant jet which probably erodes the endothelium, thereby exposing a portion of the teflon surface and hence introducing the risk of hemolysis occurring at that site. This report demonstrates that severe hemolysis may also be caused by mitral regurgitation without hemodynamically significant dysfunction. We suggest that mitral valve repair and mitral regurgitation should be considered in the differential diagnosis of hemolytic anemia even without significant hemodynamic effects. In conclusion, the present two cases confirmed other reports that in the presence of severe hemolytic anemia, a mechanical cause should be investigated. The peresence of cardiac surgery and of intracardiac foreign material makes this diagnosis more likely, and the definitive treatment is surgical repair of the anatomic defect.

REFERENCES

1. Sayed HM, Decie JV, Handley DA, Lewis SM, Cleland WP. Haemolytic anemia of mechanical origin after open heart surgery. Thorax 1961; 16: 335-360.
2. Dilip KA, Vachaspathy P, Clarke B, et al. Hemolysis following mitral valve repair. J Cardiovasc Surg 1992; 33: 568-569.

3. Gupta SC, Suryaprasad AG. Mechanical hemolytic anemia after repair of ruptured chordae tendineae of mitral valve-apparatus. Angiogology 1979; 30: 776-779.
4. Mestres CA, Soo CS, Sim EK, et al. Intravascular hemolysis after mitral valve repair: a word of caution. Eur J Cardiothorac Surg 1992; 6: 103-105.
5. Moisey CU, Manohitharajah SM, Tovey LA, Deverall PB. Hemolytic anemia in a child in association with congenital mitral valve disease. J Thorac Cardiovasc Surg 1972; 63: 765-768.
6. Mok P, Lieberman EH, Lilly LS, et al. Severe hemolytic anemia following mitral valve repair. Am Heart J 1989; 117: 1171-1173.
7. Stoschitzky K, Starz I, Anelli-Monti M, et al. Transfusion-requiring hemolytic anemia after mitral valve repair. Lancet 1996; 347: 765.
8. Warnes C, Honey M, Brooks N, et al. Mechanical hemolytic anemia after valve repair operations for nonrheumatic mitral regurgitation. Br Heart J 1980; 44: 381-385.
9. Wilson JH, Rath R, Glaser R, Panke T. Severe hemolysis after incomplete mitral valve repair. Ann Thorac Surg 1990; 50: 136-137.
10. Rowlatt UF, Rimoldi HJ, Lev M. The quantitative anatomy of the normal child's heart. Pediatr Clin North Am 1963; 10: 499.
11. Verdon TA, Forrester RH, Crosby WH. Hemolytic anemia after open-heart repair of ostium primum defects. N Engl J Med 1963; 65: 342.
12. Sigler AT, Forman EN, Zinkham WH, Neill C. Severe intravascular hemolysis following surgical repair of endocardial cushion defects. Am J Med 1963; 35: 467.
13. Yeo TC, Freeman WK, Schaff HV, Orszulak TA. Mechanisms of hemolysis after mitral valve repair: assessment by serial echocardiography. J Am Coll Cardiol 1998; 32: 717-723.
14. Nevaril CG, Lynch EC, Alfrey CP, Hellums JD. Erythrocyte damage and destruction induced by shearing stress. 1968; 74: 784-790.

Pulmonary arteriovenous fistula in the newborn
A case report of Rendu-Osler-Weber syndrome and a review of the literature

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SUMMARY: Olguntürk R, Oğuz D, Tunaoğlu S, İkizler C, Sezgin A, Kula S. Pulmonary arteriovenous fistula in the newborn: a case report of Rendu-Osler-Weber syndrome and a review of the literature. Turk J Pediatr 2001; 43: 332-337.

In most instances, congenital arteriovenous fistula is only one manifestation of a more widespread abnormality; 60% of patients also have hereditary hemorrhagic telengiectasis (Rendu-Osler-Weber syndrome). Among those with congenital pulmonary arteriovenous fistula, the diagnosis is made during infancy in only 15% of patients.

We present a case of pulmonary arteriovenous fistula in a newborn and review the literature. This rare condition of newborns can be treated with different surgical procedures. Only 17 cases of newborn pulmonary arteriovenous fistula/ have been reported, and only two of those had associated Rendu-Osler-Weber syndrome. The results of surgical procedures were good in most of these cases. We treated our case with lobectomy successfully.

Key words: arteriovenous fistula, Rendu-Osler-Weber syndrome.

Pulmonary arteriovenous fistula (PAVF) is one of the rare causes of persistent cyanosis in the newborn. Only 17 cases in the newborn period have been reported to date[1-17]. PAVF is usually associated with Rendu-Osler-Weber (ROW) syndrome in adults and children. However, in newborns only two cases among the 17 were reported to have this syndrome. Most PAVF cases are diagnosed at older ages because it is infrequently considered in the differential diagnosis of neonatal cyanosis and respiratory distress syndrome. The results of surgical repair are usually good even during the neonatal period. We present this rare case with a review of the literature in order to emphasize its diagnostic, clinical and therapeutic features.

Case Report

A 3250 g female baby of 36 weeks' gestation was delivered by cesarean section. Generalized cyanosis was noticed within the first hours, but there were no signs of respiratory distress. The focal dense area at the right upper hemithorax suggested pulmonary arteriovenous malformation, and computerized tomography supported the diagnosis. However, the parents refused further evaluation of the cyanosis, and baby was discharged.

Seven months later, on her second admission, the baby was still deeply cyanotic and without any respiratory problem. Her motor and mental development were normal. The family history was significant with telangiectases in her father, paternal grandfather, and paternal aunt and uncle. Her paternal grandfather had an accessory kidney in the pelvic region. Pedigree of the case is shown in Figure 1. On physical examination: weight was 9500 g, length 75 cm, heart rate 114 beats/min, blood pressure 90/60 mmHg and respiratory rate 62/min. She had generalized cyanosis with minimal clubbing. Pulse oximetry showed O_2 saturation as 65%. There was a 2 x 2 mm telangiectasia on the forehead and 2 x 2 cm hemangioma on the interscapular region. A low-grade continuous murmur was heard at the back on the right side. The liver was palpated 1 cm below the right costal margin. The rest of the physical examination was within normal limits.

Laboratory findings: hemoglobin level was 15.9 g/dl, hematocrit was 47.4%, and methemoglobin level was 1.4% (N: < 15%).

The electrocardiogram and the echocardiogram were in normal limits. Chest X-ray revealed a dense region at the upper and middle lobe of the

right hemithorax. Pulmonary arteriovenous malformation was suspected (Fig. 2), and was supported by thoracal computerized tomography.

The venous and arterial O_2 saturations at the cardiac catheterization were 40% and 59%, respectively. The right heart pressures were within normal limits. A pulmonary arteriovenous fistula involving the upper and middle segments of the right pulmonary artery was seen on the selective posteroanterior cineangiocardiograms (Fig. 3). Nephrogram showed two collecting systems on the right side which abdominal ultrasonography later confirmed to be an extra kidney on the right.

The baby was operated for right upper and middle lobectomy. Postoperative course was uneventful, with no cyanosis or respiratory problems.

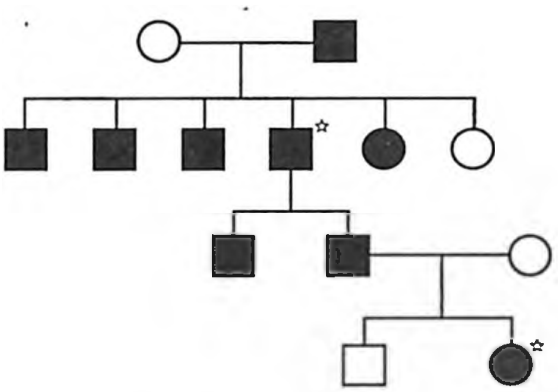

Fig. 1. Pedigree of the case. ☆: Hereditary hemorrhagic telangiectasia (HHT) + kidney anomaly.

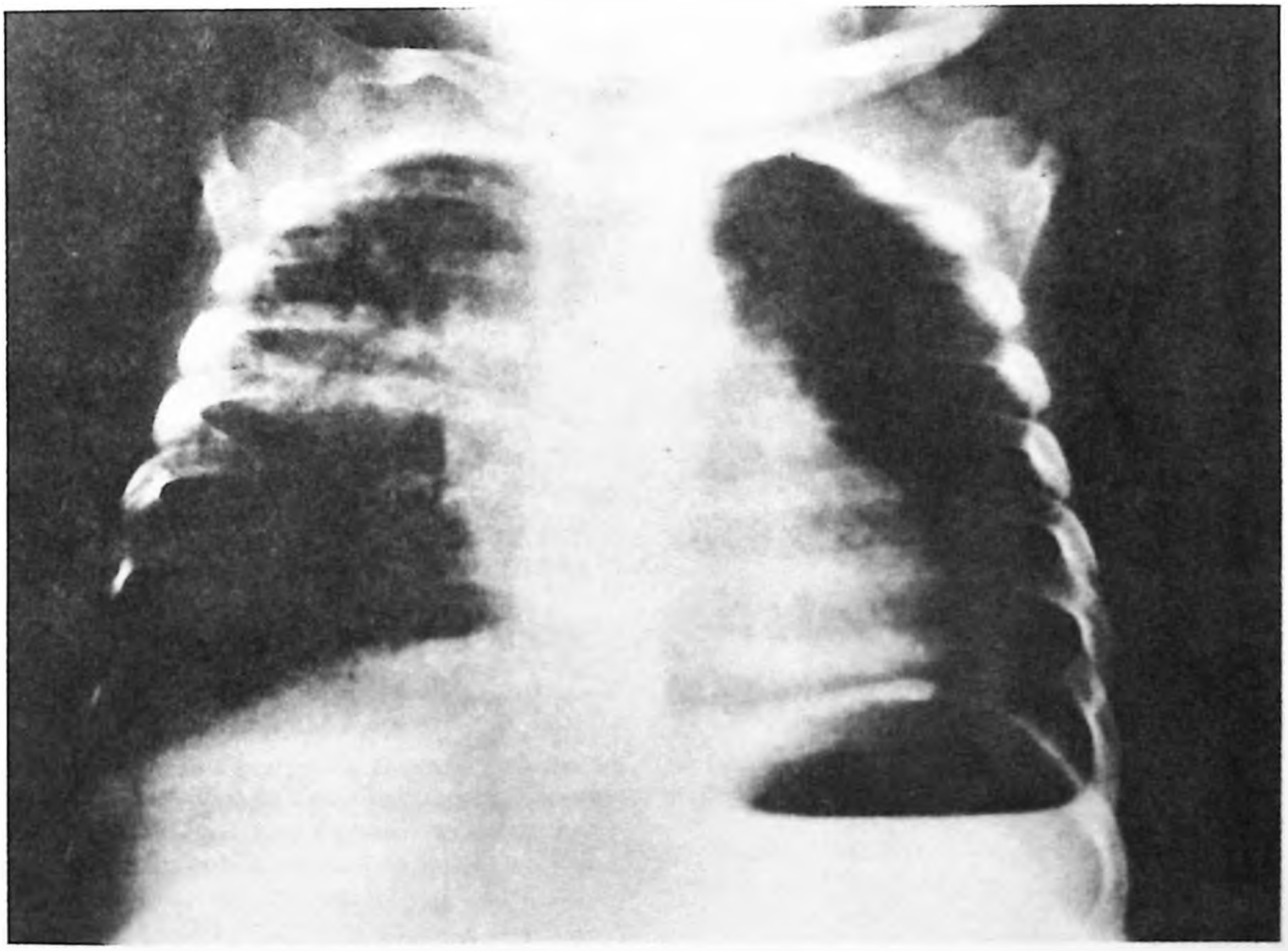

Fig. 2. Chest X-ray.

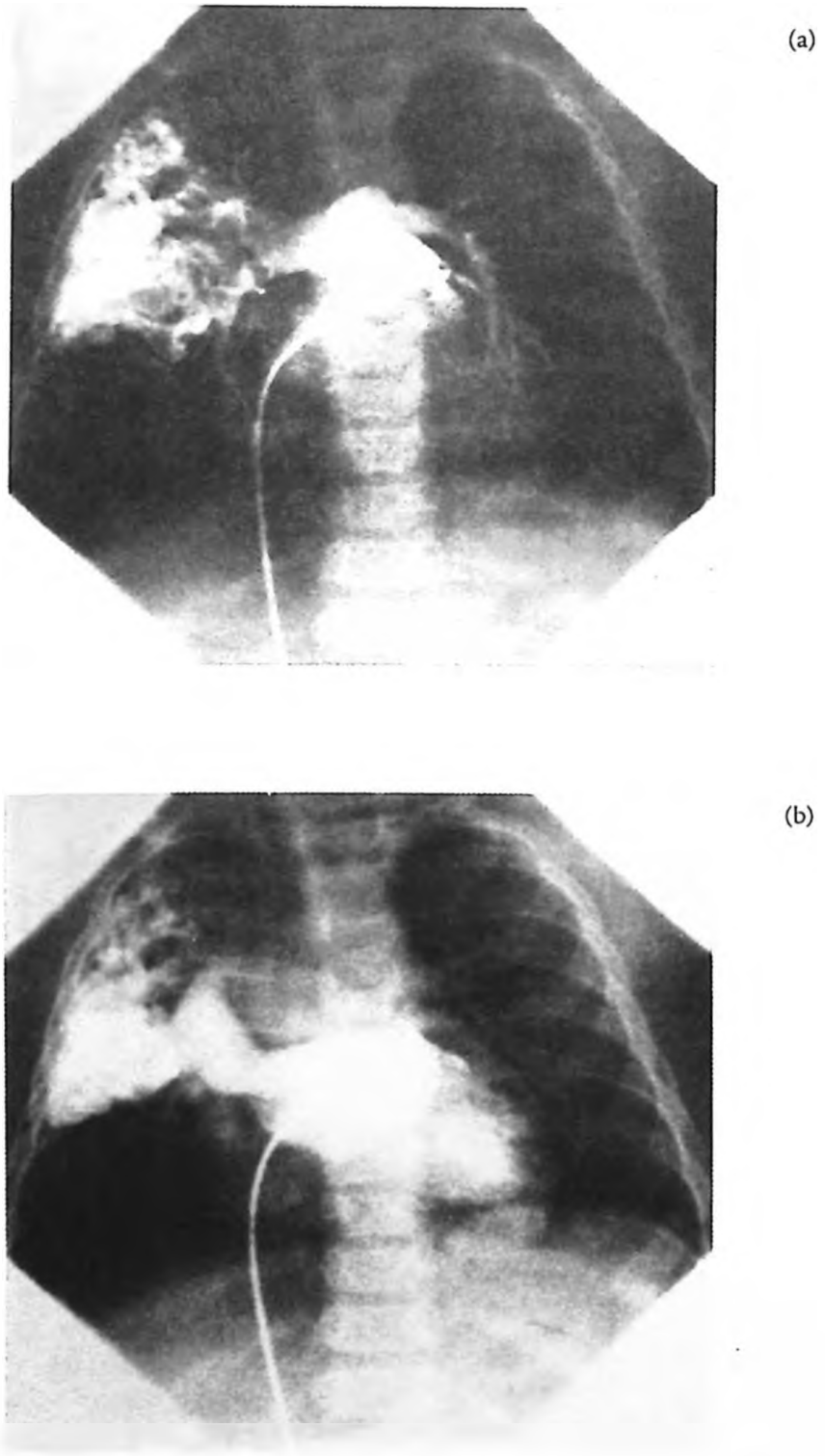

Fig. 3. Pulmonary arteriogram: a) pulmonary arteriogram capillary phase. b) pulmonary arteriogram venous phase.

Discussion

Pulmonary arteriovenous fistula is a congenital malformation of the pulmonary vasculature in which there is persistence of one or more sizable communications that bypass the pulmonary capillary bed, thus diverting unoxygenated pulmonary arterial blood directly into the pulmonary venous system. Familial cases are usually associated with Rendu-Osler-Weber syndrome or hereditary hemorrhagic telangiectasia (HHT), which is an autosomal dominant disorder characterized by multiple mucous membranes and cutoneous telangiectasia, and PAVF's. Previous reports of PAVF have noted the occurrence of HHT in as many as 35-50% of adult cases (Table I)[4-6].

Table I. Summary of the Reported Case of PAVF Presenting in the Newborn

Author Year	Age at diagnosis sex	Cyanosis arterial O_2 % Saturation	Murmur	CHF	Respiratory distress	Diagnosis				Treatment and age	Outcome	+ Anomaly or syndrome
						Chest X-ray	Angiography	CT MRI	Echo USG			
Sweet (17) 1947	1 day Male	Yes	No	No	No	RML	+			Lobectomy 2 years	Good	–
Kafka (1) 1961	2 days Male	Yes	No	No	No	RML	+			Lobectomy 2 years	Good	
Hall (8) 1965	3 days Male	Yes	Yes CM	Yes	No	LLL	+			Resection 6 days	Good	
Crosby (9) 1975	1 day Male	Yes	Yes CM	No	No	LLL	+			Resection 36 hours	Good	PA
Batisse (10) 1977	1 day Male	No	No	Yes	Yes	RML	+			Lobectomy 20 months	Good	–
Batisse (10) 1977	1 day Male	Yes	Yes CM	No	No	LUL	+			Lobectomy 2 months	Good	–
Clarke (11) 1976	1 day Male	Yes	Yes	Yes	Yes	RML	+			Resection	Died	–
Clarke (11) 1976	3 days Male	Yes	Yes	Yes	No	LLL	+			Resection	Good	–
Gula (12) 1981	4 days Male	Yes	Yes	Yes	No	RUL	+			Resection	Good	–
Fried (13) 1982	1 day Female	Yes 27	Yes CM	Yes	Yes	RML+RLL	+	–	+	Death at catheterization	Died	–
Taylor (6) 1983	1 day Male	Yes 30	Yes SM	Yes	Yes	LUL	+	–	+	Death at Surgery	Died	–
Gonzalez (3) 1985	Newborn Female	?	?	No	?	RLL			+	Resection 5 months	Good	ROW?
Vincent (14) 1986	1 day Male	Yes	No	Yes	No	RLL	+			Lobectomy	Good	–
Milovic (15) 1989	2 weeks Female	Yes	No	No	No	LUL	+			Resection	Good	Hemothorax
Allen (4) 1993	1 day Male	Yes 70-80	Yes CM	Yes	No	RLL	+		+	Lobectomy 4 days	Good	ROW
Mitchell (16) 1993	2 weeks Female	Yes 88	Yes SM	No	No	RML	+	–	–	Lobectomy 35 months	Good	
Amaral (2) 1996	6 Days ?	Yes	No	Yes	Yes	LUL			+	Death	Died	?
Olguntürk 1998 (Present Case)	1 day Female	Yes 50	Yes CM	No	No	RUL+RML	+	+	+	Lobectomy 12 months	Good	ROW Accesory kidney

LLL: left lower lobe; RML: right middle lobe; RUL: right upper lobe; RLL: right lower lobe; LUL: left upper lobe; ROW: Rendu-Osler-Weber; PAVF: pulmonary arteriovenous fistula; CHF: congestive heart failure.

Pulmonary arteriovenous fistulas, although recognized as a congenital abnormality, are not often diagnosed until adulthood. Though there are numerous cases of PAVF reported in adults and children, only 17 have been reported in the newborn period (Table I). This is mostly due to the absence of cyanosis in 73% of the newborns affected. Other presenting singns for the newborn are congestive heart failure, dyspnea, bleeding, heart murmur and abnormal chest x-ray. The size of the malformation and the amount of right-to-left flow in these infants determine the symptoms and the time of presentation. Chest X-ray abnormalities occur in 100% of cases. Computerized tomography (CT) and magnetic resonance imaging (MRI) usually confirm the diagnosis[5]. Our case is the only case of a PAVF detected by computerized tomography. A prominent main pulmonary artery, marked pulmonary oligemia and a focal pulmonary density are typical radiological findings[6]. Although noninvasive techniques should be preferred for making the diagnosis, pulmonary artery angiography is still the method of choice. The size and the number of the lesions and the amount of the right-to-left shunt can be determined by cardiac catheterization and angiography. Contrast echocardiography was found successful in determining the diagnosis in one neonate among reported cases[4]. Other echocardiographic clues can be a dilated pulmonary artery, and enlarged left atrium and left ventricle.

Review of te literature as well as our case showed a striking male dominance (12 of 18 cases), in contrast to that seen in older children and adults. Cyanosis was present in almost all cases; murmur and congestive heart failure were the other important symptoms appearing, in 11 and 10 cases, respectively. Respiratory distress was reported in five cases, and four of them died. Respiratory distress as a presenting symptom seems to be a bad prognostic criteria. The location of the lesion, the size of the fistula, and the nature of the rest of the pulmonary arterial bed are the other determinants of survival and of the outcome of surgical correction.

Accessory kidney in our case was probably coincidental. Family history or HHT was mentioned in two previous reports.

Resection of the lesion was performed in all cases and the outcome was satisfactory in 15 cases. Classical treatment in these patients is resection of the lesion or lobe or, infrequently, pneumectomy. Good results have been reported lately with coil embolization, selective miniballoon occlusion and Nd-YAG laser, but these methods are not generally available yet[7]. The risk of systemic embolization also sometimes precludes their use in neonates. The association of Rendu-Osler-Weber syndrome increases the incidence of multiple fistulas. It is important to inform the patient and family of the gastrointestinal, neurologic and genetic aspects of the disease so that appropriate counseling and care may be provided.

REFERENCES

1. Kafka V, Pakorcova H, Kabelka M, Klient Z. A congenital arteriovenous pulmonary aneurysm in a two-and-one-half-year-old boy (case report and review of the literature). J Cardiovasc Surg 1961; 2: 396-399.
2. Amaral FV, Felix PR, Granzotti JA, Rugolo LM, Bernardes TA, Nunes MA. Massive pulmonary arteriovenous fistula. A rare, potentially curable cause of hypoxia in the newborn. Arq Bras Cardiol 1996; 66: 353-355.
3. Gonzalez R, Pieper WM, Hofmann-V Kapoherr S. Pulmonary arteriovenous fistula in childhood. Z Kinderchir 1985; 40: 101-103.
4. Allen SW, Whitfield JM, Clarke DR, Sujansky E, Wiggins JW. Pulmonary arteriovenous malformation in the newborn: a familial case. Pediatr Cardiol 1993; 14: 58-61.
5. Berthezene Y, Howarth NR, Revel D. Pulmonary arteriovenous fistula, detection with magnetic resonance angiography. Eur Radiol 1998; 8: 1403-1404.
6. Taylor GA. Pulmonary arteriovenous malformation: an uncommon cause for cyanosis in the newborn. Pediatr Radiol 1983; 13: 339-341.
7. Jackson JE, Whyte MK, Allison DJ, Hughes JM. Coil embolization of pulmonary arteriovenous malformations. Cor Vasa 1990; 32: 191-196.
8. Hall RJ, Nelson WP, Blake HA, Geiger JP. Massive pulmonary arteriovenous fistula in the newborn. A correctable from of cyanotic heart disease. An additional cause of cyanosis with left axial deviation. Circulation 1965; 31: 762-765.
9. Crosby IK, Tombkins DG, Carpenter MA. Pulmonary arteriovenous fistula in the newborn infant. J Pediatr 1975; 86: 986-987.
10. Batisse A, Kachaner J, Thibert M, Lemoine G. [2 cases of solitary pulmonary arteriovenous fistula presenting in the neonatal period.] Arch Franc Ped 1977; 34: 439-448.
11. Clarke C, Goh T, Blackwood A, Venables A. Massive pulmonary arteriovenous fistula in the newborn. Br Heart J 1976; 38: 1092-1095.
12. Gula G, Nakvi A, Radley-Smith R. The spectrum of pulmonary arteriovenous fistulae. Clinicopathologic correlations. Thorac Cardiovasc Surg 1981; 29: 51-54.

13. Fried R, Amberson JB. Congenital pulmonary arteriovenous fistula producing pulmonary artery steal syndrome. Ped Cardiol 1982; 2: 313-318.

14. Vincent RN, Casiro OG, Pelech AN, Collins GF. Evaluation of pulmonary vascular resistance in the presence of a large pulmonary arteriovenous malformation. J Am Coll Cardiol 1986; 7: 1104-1106.

15. Milovic I, Oluic D. Congenital pulmonary arteriovenous fistula with haemothorax in a neonate. Z Kinderchir 1989; 44: 109-110.

16. Mitchell RO, Austin EH. Pulmonary arteriovenous malformation in the neonate. J Pediatr Surg 1993; 28: 1536-1538.

17. Sweet RH. Case records of the Massachussets General Hospital. N Engl J Med 1947; 230: 951-953.

Giant cell pneumonia in a leukemic child in remission
A Case Report

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SUMMARY: Kanra G, Çetin İ, Akçören Z, Çağlar M, Cengiz AB, Baykan A, Kara A. Giant cell pneumonia in a leukemic child in remission: a case report. Turk J Pediatr 2001; 43: 338-341.

Giant cell pneumonia is a rare and uncommon type of lung infection developing as a complication of measles, especially in immunocompromised patients, whether their immune systems are affected primarily or whether they have acquired immune defects. As well as being uncommon, it is also atypical because of absence of the characteristic rash and of absent or low antibody titers against measles in most of the cases. It is known that cellular immunity is more important than humoral immunity in the host response to measles, so hypogammaglobulinemic patients with normal cellular immunity usually recover uneventfully from measles and also have the characteristic rash. We report a case with giant cell pneumonia that was confirmed by postmortem histopathological examination. We especially want to point out that even in the absence of rash, with the clinical and radiological features of pneumonia, measles should be considered in a patient, whether in remission or not, receiving immunosuppressive treatment.

Key words: measles, pneumonia, leukemia, giant cell pneumonia, childhood.

Giant cell pneumonia is a rare and uncommon type of lung infection developing as a complication of measles, especially in immunocompromised patients, whether their immune systems are affected primarily or whether they have acquired immune defects[1-5]. As well as being uncommon, it is also atypical because of the absence of the characteristic rash and of absent or low antibody titers against measles in most of the cases[2,3,6]. It is known that cellular immunity is more important than humoral immunity in the host response to measles, so hypogammaglobulinemic patients with normal cellular immunity usually recover uneventfully from measles and also have the characteristic rash[2,3]. As a consequence of the increasing number of cellular immune deficiencies resulting from an increase in the number of children with malignancy that use chemotherapeutic drugs which prolong survival of the primary and secondary immunodeficiencies, giant cell pneumonia may become more frequent.

Here we report a case with giant cell pneumonia that was confirmed by postmortem histopathological examination. We especially want to point out that even in the absence of rash, with the clinical and radiological features of pneumonia, measles should be considered in a patient, whether in remission or not, receiving immunosuppressive treatment[4-9].

Case Report

A 10-year-old girl diagnosed as having acute lymphoblastic leukemia was in remission four years later following steroid, vincristine, daunomycin, asparaginase, etoposide, and cytarabine. Remission was maintained with methotrexate and 6-mercaptopurine together with steroid, vincristine, asparaginase and cytarabine. At the 95th week of the maintenance therapy she was seen in our infectious disease outpatient clinic with the complaints of fever, cough, malaise and dyspnea persisting for almost a week. As well as these complaints there was also an erythematous maculopapular rash, especially at the proximal parts of the arms and legs, together with a slight conjunctival hyperemia, and the body temperature was subfebrile. There was no Koplik spot, and immunization history for measles was uncertain. The mother stated that her daughter had not experienced a similar exanthematous disease

before. There was also partial alopecia, facial desquamation, postnasal and right external auditory purulent drainage, bilateral multiple micro-lymphadenopathies at cervical chain and widespread rales together with rare ronchi at both lungs, especially at basal areas. Other physical findings were unremarkable. Patient was hospitalized for parenteral therapy because of pneumonia and also because of suspected measles infection.

Laboratory studies revealed hemoglobin 11.3 g/dl, white blood cell count 12,800/mm^3 with 2% lymphocytes and 40% toxic granulation, thrombocyte count 188,000/mm^3, and erythrocyte sedimentation rate 120 mm/hr with normal renal and liver functions. Blood gas measurement included pCO_2 as 25.7 mmHg. At chest roentgenogram there was bilateral paracardiac infiltrates together with bilateral minimal pleural effusion (Fig. 1). Cultures were negative for any microbial agent.

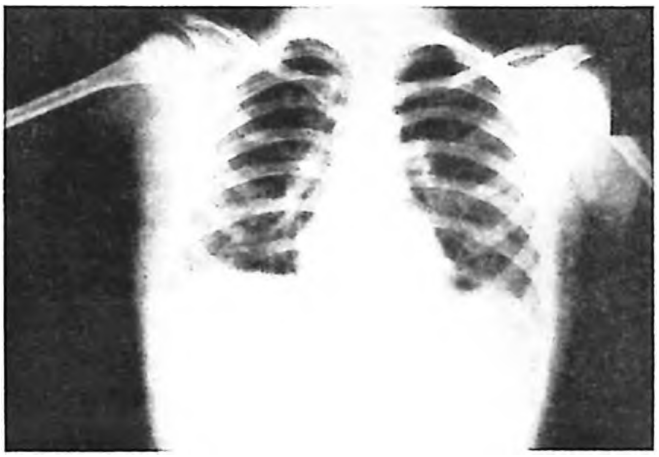

Fig. 1. Chest roentgenogram showing bilateral paracardiac infiltrates together with bilateral minimal pleural effusion on the first hospital day.

Despite initiation of therapy with sulbactam-ampicillin, because of tachypnea and low oxygen saturation at arterial blood gas studies together with enlargement of infiltrated areas at repeated chest roentgenograms taken the day following admission, therapy was changed to ciprofloxacin, vancomycin and amikacin. At the same time, despite negative fungal cultures, due to sudden worsening of patient's condition, amphotericin B was added to the therapy together with TMP-SMX against P. carinii pneumonia. A single high-dose vitamin A was given orally because of rash mostly resembling that seen in measles. On 3rd day of hospitalization her condition worsened further and she developed respiratory distress together with hypotension and tachycardia. It was learned that the antibodies against measles were negative. At chest X-ray there were fine but diffuse micronodular densities (Fig. 2). Arterial blood gas studies showed deep hypercarbia. Patient was intubated and mechanical ventilation was instituted. Intravenous fluids were then given according to central venous pressure measurements with positive inotropic agents. A high-dose steroid was also given because of the possibility of methotrexate pneumonia and also because of the possibility of infiltration by primary malignancy. But progressive worsening of respiratory insufficiency resulted in bradycardia and cardiac arrest and the patient died on the 4th day of hospitalization despite excessive effort. An autopsy was performed.

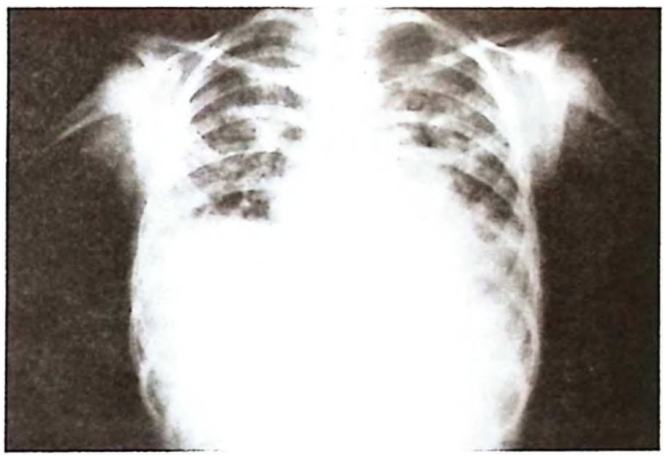

Fig. 2. Chest roentgenogram showing fine but diffuse micronodular densities on the third hospital day.

Postmortem Findigs: Postmortem studies were limited to the lungs, heart, thymus and incision materials of liver and kidney. Macroscopically, lungs were heavily consolidated and showed patchy hemorrhagic areas. Microscopic examination revealed a diffuse interstitial pneumonitis with giant cells and some areas of intraalveolar hemorrhage (Fig. 3). Numerous multinucleated giant cells were present and most of these giant cells demonstrated eosinophilic intranuclear and cytoplasmic inclusions typical of classic measles pneumonia. Bronchial and bronchiolar epithelial proliferation and squamous metaplasia were also seen. Hyaline membranes and alveolar hemorrhage were prominant in some areas. Thymus and lymph nodes showed lymphocyte depletion and atrophy. Congestion and fatty degeneration were noted in the liver. Microscopy of kidney revealed small areas of

glomerular and interstitial fibrosis, probably due to a previous pyelonephritis. No evidence of leukemic infiltration was present in any of the examined organs.

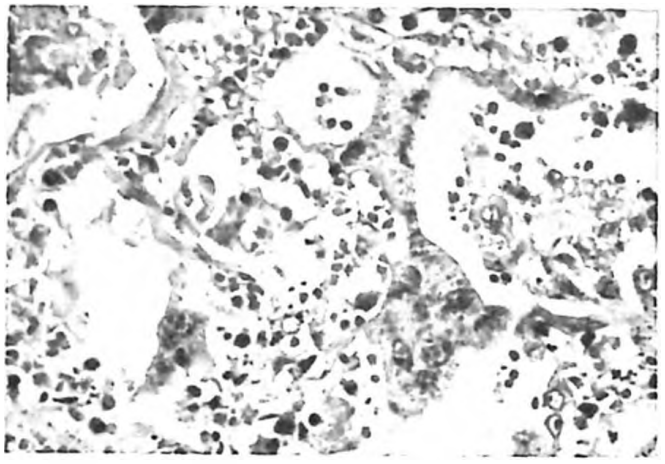

Fig. 3. Diffuse interstitial pneumonitis with giant cells (H & E X 132).

Discussion

As mentioned previously, immunosuppressed patients cannot generate specific antibodies against measles and they are at high risk of developing measles giant cell pneumonia as a result of uncontrolled multiplication of measles virus in the respiratory tract[1,9]. This is one of the characteristic properties of giant cell pneumonia. The others are the persistence of virus without rash, no rise in antibody titer, having a hematologic malignancy (especially leukemia) and interstitial pneumonia with giant cells[9,10]. All these properties thus describe an unusual infection in a compromised host, and in some report an association is made between giant cell pneumonia and leukemia[5,9]. If the rash is regarded as a good predictor of cellular immunity, absence or short duration of the rash may be interpreted as a sign of immunosuppression[4]. Patient's primary disease and the chemotherapeutic treatment are two main factors for the immunocompromised state in leukemia. In children whose immune systems are working well, the measles infection has a time-limited course, but in immunocompromised patients, especially those with cellular immune defects, because of the long-standing viremia, secondary infections of measles could frequently be seen. Due to our patient's being in remission at the time of giant cell pneumonia, the chemotherapeutic treatment most likely had a major role in its development[4,6].

It was proposed that giant cell pneumonia is a reinfection of primary measles after an asymptomatic period, but the variability of that period between measles infection and giant cell pneumonia is still a question, together with the factors affecting this period[4,5,8]. In patients with short time periods, it may be a continuing primary infection of measles. Here the immune systems of patients gain importance because of their effect on the viremia period of measles; that is if a patient is more compromised, the time period becomes shorter[8,9]. In immunocompromised patients presenting with respiratory insufficiency and unresponsive to nonspecific therapy, measles should always be considered as a causative agent, even without a history of contact with measles, and without characteristic rash and specific antibody rise against measles. The diagnostic gold standard in these paients is "open lung biopsy"[3]. Rapid results could also be obtained by direct immunofluorescent studies of bronchoalveolar lavage specimens or nasopharyngeal secretion[7]. Otherwise, giant cell pneumonia is still going to be a postmortem diagnosis in future in spite of excessive effort to eradicate this infection.

Similar multinucleated giant cells in the lungs could be seen in some other diseases, especially with viral infections, but measles is the only virus producing multinucleated giant cells with both eosinophilic intranuclear and cytoplasmic inclusions[3,10]. Inclusion bodies seen with Respiratory syncytial virus, cytomegalovirus, herpesvirus and some parainfluenza strains are not eosinophilic and giant cells are also usually smaller with a different pattern[3]. Some granulomatous diseases may show multinucleated giant cells but these cells always lack inclusions[10]. The other important disease is methotrexate pneumonia, which should always be included in the differential diagnosis, especially in patients given methotrexate for any reason. It is also characterized by fever, cough, dyspnea and cyanosis together with fine scattered opacities on direct chest x-rays. The most important tool for making the differential diagnosis is a good response to steroids in the case of methotrexate pneumonia[7]. P. carinii pneumonia also presents itself with cough, malaise, slightly increased body temperature, and respiratory distress, the most frequently seen features of giant cell pneumonia, and it should also be included in the differential diagnosis[1,9].

Therapeutic measures for measles infection in compromised patients are still limited. Most often used today is the high-dose intravenous pooled immunoglobulin which, if given in early days of exposure (postexposure prophylaxis), may protect or modify measles infection. Ribavirin and also vitamin A supplementation have been considered to be beneficial in these patients in recent studies[3,4,7]. However, gammaglobulin, which can prevent or modify measles in normal hosts, is not protective in compromised patients[8]. However, there are some reports underlying the beneficial effects of high-dose gammaglobulin, especially for inhibiting viremia and thus inhibiting dissemination of virus[4,5,7].

In summary, one of the most important points to emphasize is that because of the possibility of severe measles infection in immunocompromised patients, it is important to complete the immunization chart of the patient before beginning chemotherapy in newly diagnosed patients. Also, if there is lung infection in such a child, possibilities of giant cell pneumonia should be considered even in a child with a complete immunization chart.

REFERENCES

1. Hervas JA, Henales V, Serra JE, Mas JM. Measles giant cell pneumonia. Pediatr Infect Dis J 1990; 9: 529.
2. Joliat G, Abetel G, Schindler AM, Kapancı Y. Measles giant cell pneumonia without rash in a case of lymphocytic lymphosarcoma. Virchows Arch Abt A Path Anat 1973; 358: 215-224.
3. Nadel S, McGann K, Hodinka RL, Rutstein R, Chatten J. Measles giant cell pneumonia in a child with human immunodeficiency virus infection. Pediatr Infect Dis J 1991; 10: 542-544.
4. Tınaztepe K, Örmeci AR, Tınaztepe B. Giant cell pneumonia associated with Hodgkin's disease. Turk J Pediatr 1987; 29: 61-65.
5. Tınaztepe K, Örmeci AR, Tınaztepe B, Göçmen A, Buyan N, Dereli O. Giant cell pneumonia in childhood: report of seven cases emphasizing histopathological findings and associated conditions. Turk J Pediatr 1983; 25: 211-226.
6. Pullan CR, Noble TC, Scott DJ, Wisniewski K, Gardner PS. Atypical measles infections in leukaemic children on immunosuppressive treatment. Br Med J 1976; 1: 1562-1565.
7. Lewis MJ, Cameron AH, Shah KJ, Purdham DR, Mann JR. Giant cell pneumonia caused by measles and methotrexate in childhood leukaemia in remission. Br Med J 1978; 1: 330-331.
8. Siegel MM, Walter TK, Ablin AR. Measles pneumonia in childhood leukemia. Pediatrics 1977; 60: 38-40.
9. Young LW, Ross DW. Radiological case of the month. Am J Dis Child 1980; 134: 511-512.
10. Harboldt SL, Dugan JM, Tronic BS. Cytologic diagnosis of measles pneumonia in a bronchoalveolar lavage specimen: a case report. Acta Cytol 1994; 38: 403-406.

Intraperitoneal involvement in rhabdomyosarcoma CT findings in a child

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SUMMARY: Oto A, Başgün N, Kutluk T, Eryılmaz M, Oran M, Besim A. Intraperitoneal involvement in rhabdomyosarcoma: CT findings in a child. Turk J Pediatr 2001; 43: 342-344.

Intraperitoneal neoplastic involvement in rhabdomyosarcoma is rare and its incidence and imaging characteristics need to be further described. We present the computerized tomography (CT) findings of a case with pelvic rhabdomyosarcoma and intraperitoneal neoplastic involvement. Enhanced peritoneal and retroperitoneal masses were seen around the liver, spleen, in the paracolic gutters, and in the lesser sac without evidence of ascites, mesenteric nodules or omental caking. Our case also showed that absence of ascites does not preclude the presence of peritoneal involvement. Progression in the peritoneal disease was also well demonstrated by CT.

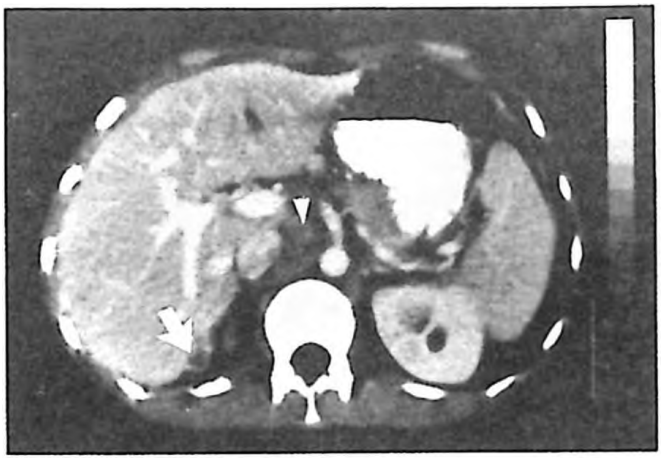
Key words: computerized tomography, rhabdomyosarcoma, peritoneum.

Rhabdomyosarcoma accounts for 5% to 8% of childhood cancer and presents in a wide variety of histologic types and of spread patterns of the tumor. The tumor infiltrates locally, invades lymphatics and blood vessels, and frequently presents with distant hematogenous metastases to lung, bone marrow and bone. Intraperitoneal rhabdomyosarcoma has been previously reported in adults; however, it presence in children was only recently described[1,2]. Chun et al.[2] reported an incidence of 11% for peritoneal involvement in rhabdomyosarcoma over the course of the disease and of 7% at the time of initial diagnosis. Despite this relatively high incidence, only six cases with radiological findings of rhabdomyosarcoma with peritoneal involvement have been described so far. Thus, imaging characteristics of intraperitoneal neoplastic involvement of rhabdomyosarcoma and its true incidence need to be further described. We present the computerized tomography (CT) findings of a child with pelvic rhabdomyosarcoma and peritoneal neoplastic involvement.

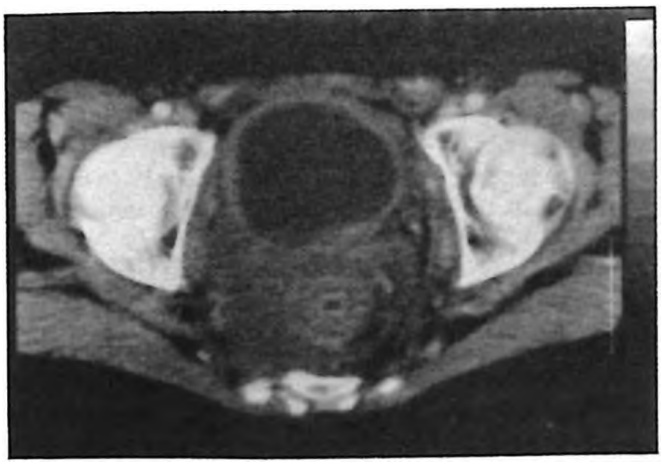
Case Report

A 16-year-old male with a 10 x 9 cm pelvic mass was dignosed as rhabdomyosarcoma by biopsy. In the initial postoperative CT, a small peritoneal nodule posterior to the right lobe of the liver and paraceliac adenopathy were seen (Fig. 1a). There was also a soft tissue mass encircling the rectum (Fig. 1b). This residual mass could not be separately identified from prostate, posterior wall of the bladder or other pelvic structures. There were no other peritoneal, mesenteric, omental or retroperitoneal masses or nodules. No ascites was noted. Histopathological subtype could not be identified. The tumor was accepted as stage III according to the IRS staging system (Intergroup Rhabdomyosarcoma Study Group)[3]. A chemotherapy regimen including vincristine, epirebicine, and cyclophoshamide plus radiotherapy was given. Since there was no response at the end of two months, chemotherapy regimen was changed to ifosphamide, cisplatin and vincristine. Six months after diagnosis a debulking surgery was performed. Nine months after diagnosis, a follow-up CT was performed, on which the previously observed perihepatic nodule and paraceliac adenopathy were increased in size. There were new perihepatic peritoneal masses with scalloped borders similar in appearance to pseudomyxoma peritonei (Fig. 2a). New peritoneal masses were also identified near the spleen, in the lesser sac, in both paracolic gutters, anterior to the transverse colon and in the falciform ligament (Fig. 2b). No omental

caking, mesenteric nodules or ascites was observed. All of the peritoneal masses were enhanced with central hypodense areas most likely consistent with necrosis. Peritoneal and retroperitoneal masses tended to displace the adjacent anatomic organs rather than invade them. Calcification was not observed in either the peritoneal or retroperitoneal masses. Recurrent pelvic mass was stable in size and appearance on the follow-up CT. He died with progressive disease at 22 months from diagnosis.

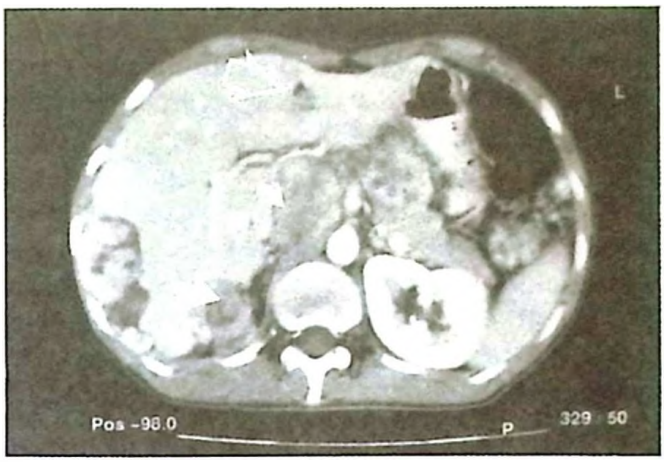


(a)

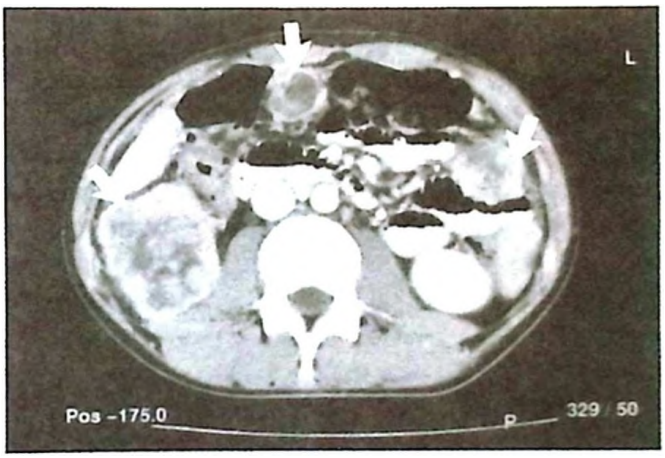


(b)

Fig. 1. Post-operative axial contrast-enhanced CT images of a 16-year-old boy with the dignosis of prostatic rhabdomyosarcoma. CT scan at the level of liver (A) shows small perihepatic peritoneal nodule (arrow) and paraceliac adenopathy (arrowhead). In pelvis (B) note the infiltrative soft tissue mass surrounding the rectum, prostate and posterior wall of the bladder.



(a)



(b)

Fig. 2. Follow-up (9 months later) axial constrast-enhanced CT scans of the same patient. CT scan at the level of liver (A) demonstrates increase in the size of the previously noted perihepatic nodule (arrow) and paraceliac adenopathy (curved arrow). Additional new peritoneal masses around liver, spleen, in the falciform ligament (open arrow), and in the lesser sac are also seen. Lower image through the abdomen (B) demonstrates preitoneal masses in the paracolic gutters and anterior to the transverse colon (arrows). Note the absence of ascites.

Discussion

Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood, representing about 5-15% of all solid malignancies in children[4]. It is thought to arise from primitive mesenchymal cells, and it may arise from almost any organ in the body. Histologically there are two major subtypes (embryonal and alveolar) that have different

propensities for primary site and metastatic potential[5]. Embryonal rhabdomyosarcoma is most common in the head and neck, genitourinary tract and extremities. It has a more favorable outcome than the alveolar subtype. Alveolar rhabdomyosarcoma is more aggressive, often presenting with metastatic disease, and is more commonly located in the extremities, trunk and perineum. Head and neck (40%) and the genitourinary tract (20%) account for most primary rhabdomyosarcomas[4].

Intraperitoneal neoplastic involvement in children is less common, and limited information is available about its incidence and imaging features. There is only one series in the literature about malignant intraperitoneal neoplasms of childhood[6]. Most of the data are from case reports. Lymphoma, mesothelioma, desmoplastic small round cell tumor, malignant fibrous histiocytoma, immature teratoma, germ cell tumors, Wilm's tumor, neuroblastoma and intracranial tumors via ventriculoperitoneal shunts have been previously described to have either primary or metastatic neoplastic peritoneal involvement[7-15]. Another distinct entity causing multiple discrete tumor nodules in the peritoneum, mesentery and omentum is peritoneal leiomyosarcomatosis[16]. Recently rhabdomyosarcomas have also been reported to have intraperitoneal neoplastic involvement[2]. Detection of the peritoneal involvement is clinically very important since its presence alters the management. In their series of 55 children with rhabdomyosarcoma, Chung et al.[2] reported three cases with primary peritoneal rhabdomyosarcoma, two cases with pelvic rhabdomyosarcoma (paratesticular and prostate) and one case of extremity rhabdomyosarcoma with metastatic peritoneal involvement. Ascites, which was present in all cases with peritoneal involvement in Chung's series, was not noted either CT scan of our patient, despite the presence of extensive peritoneal metastases. Our case showed that absence of ascites does not preclude the possibility of intraperitoneal spread in rhabdomyosarcoma. Mesenteric nodules described in three of the six patients in Chung's series were not seen in our case. We did not see any omental caking, similar to the three patients in Chung's series with primary extraperitoneal rhabdomyosarcoma. All of the peritoneal masses in our case were enhanced, despite some of the reported non-enhanced peritoneal masses described by Chung et al.[2]. The presence of peritoneal involvement in children with rhabdomyosarcoma requires the use of more intensive treatment regimens. Computerized tomography could successfully monitor the peritoneal disease and demonstrate its progression.

REFERENCES

1. Stout AP, Hendry J, Purdie FJ. Primary solid tumors of the great omentum. Cancer 1963; 16: 231-243.
2. Chung CJ, Fordham L, Little S, et al. Intraperitoneal rhabdomyosarcoma in children: incidence and imaging characteristics on CT. AJR 1998; 170: 1385-1387.
3. Pizza PA, Poplack DG. Principles and Practice of Pediatric Oncology (3rd ed). Philadelphia: Lippincott-Raven Publishers; 1997: 799-829.
4. Cohen MD. Imaging of Children with Cancer (1st ed). St. Louis: Mosby Year Book; 1992: 308-337.
5. Coffin CM, Dehner LP. The soft tissues. In: Stocker JT, Dehner LP (eds). Pediatric Pathology. Philadelphia: JB Lippincott; 1992: 1102-1107.
6. Chung CJ, Bui V, Fordham LA, Hill J, Bulas D. Malignant intraperitoneal neoplasms of childhood. Pediatr Radiol 1998; 28: 317-321.
7. Fraire AE, Cooper S, Greenberg SD, Buffler P, Langston C. Mesothelioma of childhood. Cancer 1988; 62: 838-847.
8. Frappaz D, Bouffet E, Dolbeau D, et al. Desmoplastic small round cell tumors of the abdomen. Cancer 1994; 73: 1753-1756.
9. Kim OH, Lee KY. Malignant fibrous histiocytoma of primary omental origin in an infant. Pediatr Radiol 1994; 24: 285-287.
10. Spurney RF, McCormack KM. Immature omental teratoma. Arch Pathol Lab Med 1987; 111: 762-764.
11. Lev BH, Blickman JG. Extragonadal yolk sac tumor: sonographic and CT findings. AJR 1993; 160: 370-371.
12. Jacobs JE, Salhany KE, Fox KR, Birnbaum BA. Omental caking in Hodgkin's disease: computed tomography findings. Clin Imaging 1996; 20: 253-255.
13. Fernbach SK. Ascites produced by peritoneal seeding of neuroblastoma. Pediatr Radiol 1993; 23: 569.
14. Slasky BS, Bar-Ziv J, Freeman AL, Peylan-Ramu N. CT appearances of involvement of the peritoneum, mesentery and omentum in Wilm's tumor. Pediatr Radiol 1997; 27: 14-17.
15. Newton HB, Rosenblum MK, Walker RW. Extraneural metastases of infratentorial glioblastoma multiforme to the peritoneal cavity. Cancer 1992; 69: 2149-2153.
16. Choi BI, Lee WJ, Chi JG, Han JK. CT manifestations of peritoneal leiomyosarcomatosis. Am J Roentgenol 1990; 155: 799-801.

Prenatal echocardiographic diagnosis of situs inversus totalis and transposition of the great arteries
A case report

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SUMMARY: Öztunç F, Beşikçi R, Türkoğlu H, Saltık İL. Prenatal echocardiographic diagnosis of situs inversus totalis and transposition of the great arteries: a case report. Turk J Pediatr 2001; 43: 345-347.

A case of situs inversus totalis and transposition of the great arteries (TGA) was diagnosed prenatally at 25 weeks' gestation. Postnatal echocardiographic examination confirmed the antenatal findings. This case underscores the importance of recognizing situs abnormalities during obstetric and fetal echocardiographic examination, as they are often associated with cardiac anomalies. Accurate prenatal diagnosis of structural heart defects is extremely important in family counselling and in planning obstetric and postnatal treatment.

Key words: transposition of great arteries, prenatal, fetal echocardiography, situs inversus.

The use of echocardiography in the human fetus has paralleled the development of echocardiographic technology and has permitted prenatal diagnosis of structural and functional abnormalities of fetal circulation. Thus the most complex cardiac defects can be investigated noninvasively, allowing appropriate prenatal counselling and postnatal treatment, if appropriate.

We report a case of prenatal diagnosis of situs inversus totalis and transposition of the great arteries (TGA) and stress the importance of accurate sequential diagnosis.

Case Report

A 24-year-old female was referred to our center for specialized fetal echocardiography because of gestational diabetes mellitus. She was not insulin dependent. Previous obstetric ultrasound examination revealed a normal four-chamber view of the heart and no extracardiac abnormalities. The echocardiographic examination at 25 weeks of gestation showed the heart on the right side of the thorax with a rikght-sided apex (Fig. 1). In the abdomen, the arrangement of the viscerae and abdominal vessels was mirror-image of normal, with the stomach to the right and liver to the left side of the fetus. There was no abnormality on the four-chamber view. The atrioventricular connectilon was concordant. The foramen ovale was seen in the atrial septum, with the flap valve within the left atrium. Imaging of the arterial trunks showed the great arteries in parallel fashion rather than in a spiral relationship (Fig. 2). The aorta originated from the right ventricle, and the pulmonary artery originated from the left ventricle and was typically bifurcated (Fig. 3). Mitral-pulmonary continuity was present. Pulsed and continuous wave Doppler examinations were normal. The echocardiographic findings were compatible with situs inversus totalis and TGA.

Based on the above diagnosis, the family was counselled and the obstetrician informed. The family decided to continue with the pregnancy. Subsequent follow-up was carried out jointly by the pediatric cardiologist and the obstetrician. A term baby was delivered vaginally, uneventfully. Birth weight was 4.5 kg, length 51 cm and Apgar score 9 at 5 minutes. Mild-to-moderate cyanosis was present at birth. Cardiovascular examination revealed a short systolic murmur at the upper left sternal border. Second heart sound was single. Pulses were equal in both upper and lower extremities. Postnatal echocardiographic examination was performed during the first hours of life and confirmed the intrauterine

diagnosis. The ductus arteriosus was open and the atrial septal defect was of adequate size. At two hours of age the baby was referred to a cardiac surgical center and operated in optimal conditions on day seven.

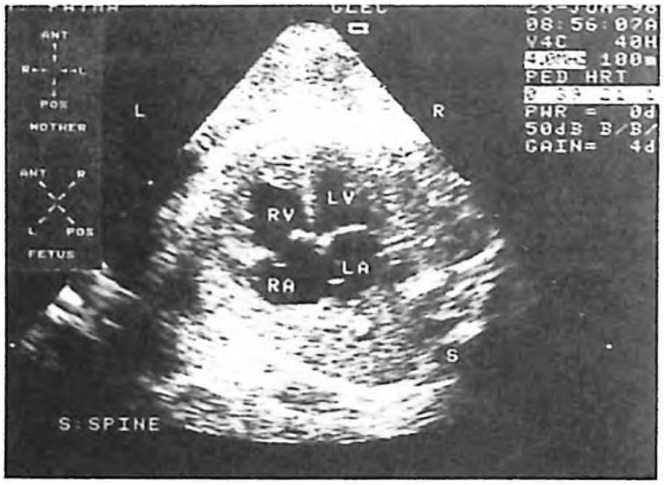

Fig. 1. Transverse section-through the fetal chest. Four-chamber view of the fetal heart; spine is on the left side of the mother. Note the fetal heart and apex on thi right side (fetal head is inferiorly located). S: spine, R: right side of the fetus; L: left side of the fetus; RA: rikght atrium; LA: left atrium; RV: right ventricle; LV: left ventricle.

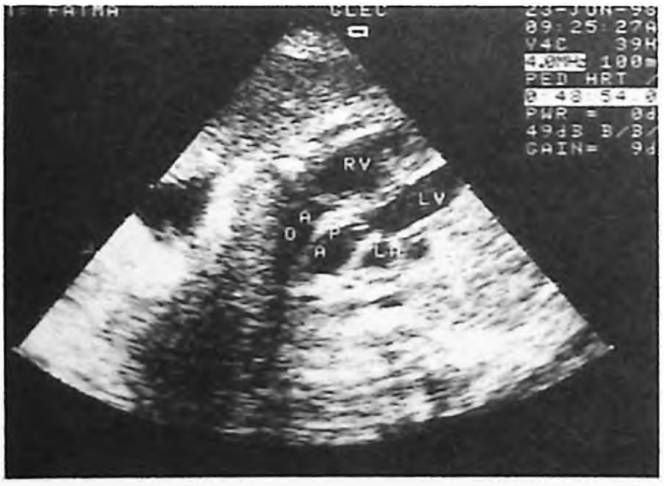

Fig. 2. View of the outflow tracts, color-Doppler flow. Note the parallel orientation of the aorta (Ao) and pulmonary artery (PA). S: stomach.

Discussion

Since the early 1980s, fetal echocardiography has proved to be a reliable tool for prenatal diagnosis of congenital heart diseases with a high degree of accuracy[1-4]. Over this time, complex heart malformations have been clearly described in the fetus. The prenatal diagnosis of TGA is possible and has been reported[1-4].

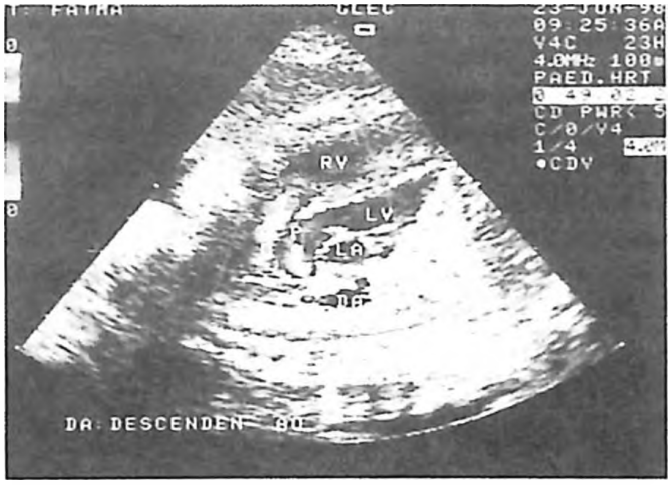

Fig. 3. Long axis view of the ventricular outflow tracts. The pulmonary artery (PA) arising from the left ventricle (LV) and the aorta (AO) arising from the right ventricle (RV). LA: left atrium.

This case, as far as we know, is the first case in Turkey that has been intrauterine diagnosed as situs inversus totalis and TGA.

In order to make the diagnosis, the transducer must be angled superiorly (towards the baby's head) to allow visualization of the ventricular outflow tracts[3], and thus determine the ventriculo-arterial connection. However, fetuses with simple transposition are frequently not referred for specialized fetal echocardiography, as most obstetric ultrasound screening programs rely on visualization of the four-chamber view alone and this view shows no obvious abnormalities. The diagnosis is therefore often missed in routine obstetric screenings. Furthermore, as the condition is well tolerated in the fetus, there is no evidence of heart failure or hemodynamic compromise that might lead to prenatal cardiac referral. During detailed examination of the heart, it is important to determine visceral and atrial situs as part of the sequential chamber localization[5]. Determination of fetal laterality and position of the viscerae during obstetric ultrasound examination, however, is not performed routinely[6]. This is exemplified in our cases where previous obstetric ultrasound had failed to show the abnormal position of the viscerae. Overall frequency of situs inversus is estimated at 1/10,000 births and is often associated with congenital heart defects[5-7]. In utero diagnosis of situs anomalies during obstetric ultrasound examination should be an indication to explore cardiac anomalies. In our patient the heart was located on the same side as the stomach. This can frequently be mistaken as the left side

if fetal laterality is not considered. When the right and left sides of the fetus were determined according to fetal orientation within the uterus, we noticed the mirror-image arrangement of all viscerae.

Accurate prenatal diagnosis of structural heart defects is extremely important for planning obstetric and postnatal treatment.

This case emphasizes the importance of fetal echocardiographic examination in complex cardiac pathologies where early surgical intervention is required.

Acknowledgement

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REFERENCES

1. Allan LD, Sharland GK, Milburn A, et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol 1994; 23: 1452-1458.
2. Smythe JF, Copel JA, Kleinman CS. Outcome of prenatally detected cardiac malformations. Am J Cardiol 1992; 69: 1471-1474.
3. Kirklin JW, Colvin EV, McConnell ME, Bargeron LM. Complete transposition of the great arteries: treatment in the current era. Pediat Clin North Am 1990; 37: 171-177.
4. Benacerraf BR, Pober BR, Sanders SP. Accuracy of fetal echocardiography. Radiology 1987; 165: 847-849.
5. Carvalho JS, Kyle PM. Situs inversus with complete transposition in the fetus. Diagnostic antenatal sequential segmental analysis. Circulation 1997; 96: 4432-4433.
6. Carvalho JS, Doya EH, Freeman L, Clough A. Identification of fetal laterality and visceral situs should be part of all routine obstetric anomaly scans. The Second World Congress of Pediatric and Cardiac Surgery, Hawaii, 1997: 23.
7. Abossolo T, Alessandri JL, Saltet A, Dancoisne P, Pilorget H, Sommer JC. In utero diagnosis of situs abnormalities. A case of prenatal diagnosis of visceral situs inversus with corrected transposition of great vessels. J Gynecol Obstet Biol Reprod Paris 1996; 25: 267-273.

A case of Sandifer's syndrome with hand tremor

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SUMMARY: Demir E, Saka E, Aysun S. A case of Sandifer's syndrome with hand tremor. Turk J Pediatr 2001; 43: 348-350.

A 1.5-month-old boy with Sandifer's syndrome is described. After an uneventful delivery, he presented torticollis, seizure-like dystonic neck movements usually associated with feeding, episodic vomiting, inspiratory stridor and hand tremor in the first month of life. Barium esophagogram demonstrated gastroesophageal reflux, for which medical therapy was started. Children with torticollis and dystonic movements should be evaluated for Sandifer's syndrome. Early diagnosis and treatment of gastroesophageal reflux may prevent complications.

Key words: Sandifer's syndrome, hand tremor, dystonic movement.

Sandifer's syndrome, first described by Kinsbourne[1] in 1964, is a rare clinical entity which is characterized by dystonic body movements, paroxysmal torticollis and gastroesophageal reflux (GER) with or without hiatal hernia[2-4]. The mechanism of dystonic movements in Sandifer's syndrome has not been clearly understood. Treatment of GER improves symptom complex completely[5]. Identification of this syndrome is very important in order to avoid unnecessary investigations and achieve good therapeutic results. Here, we present a 1.5-month-old boy with Sandifer's syndrome who displayed recurrent vomiting, torticollis, paroxysmal dystonic movements and hand tremor.

Case Report

A 1.5-month-old boy, the first child of first-degree consanguineous parents, was referred for evaluation of torticollis. His birth weight was 3,500 g. He had history of mild hypoxia during delivery after an uneventful pregnancy. He had suffered for one month from recurrent vomiting and associated intermittent movements like bending backward, tilting the head to lateral and back side and shaking in his hands. Parents reported these movements occurring immediately after feeding. He was conscious during attacks. On physical examination, his length and weight were 58 cm (50p) and 4 kg (3p), respectively. His head circumference was 38 cm (50p). Inspiratory stridor was prominent. Dystonic movements, characterized by backward curving of trunk in opustotonus position, tilt of head and coarse tremor in hands, were observed during examination, lasting 30 seconds. They were recorded by video (Fig. 1). Cervical X-rays were normal. Direct laryngoscopy revealed normal anatomical structure of larynx, consistent with laryngomalacia. Electroencephalography record during an attack of dystonic movement was interpreted as normal. Cranial computerized

Fig. 1. (a)

Fig. 1 (a-d). Sequential images of a dystonic movement.

Fig. 1. (b)

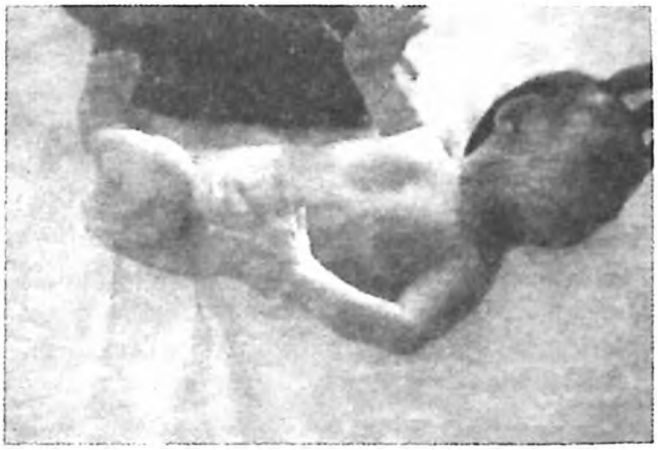

Fig. 1. (c)

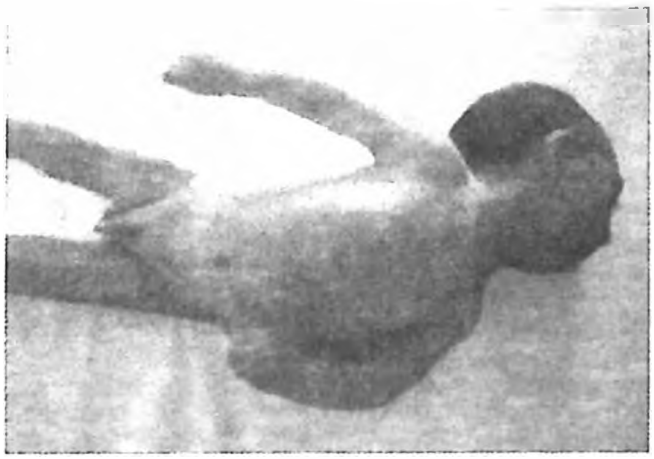

Fig. 1. (d)

tomography (CT) was normal. Biochemical investigation, including glucose, calcium and magnesium, was normal. Plasma and urinary amino acids were normal. Thyroid hormones were normal. Barium esophagogram showed significant GER (Fig. 2). We started at first with cisapride, but had no opportunity to follow-up. We later learned that he had died as a result of an aspiration episode.

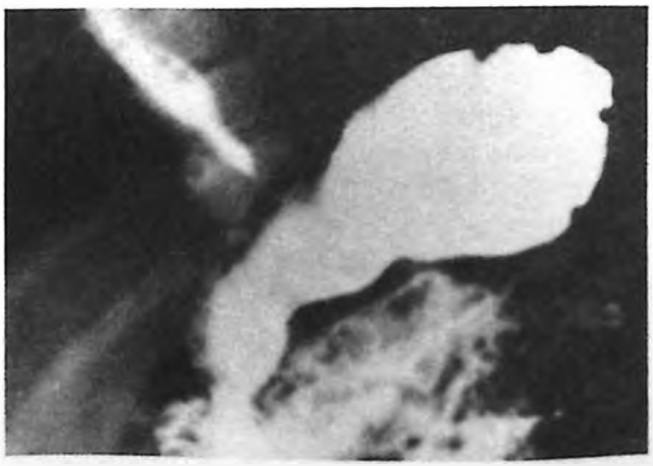

Fig. 2. Barium esophagogram revealing gastroesophageal reflux.

Discussion

Sandifer's syndrome is more common than generally recognized[4]. It is difficult to estimate the real frequency of the syndrome, as misdiagnosis may occur due to variable clinical presentation and features overlapping with other diseases[4,6]. Both normal and mentally retarded infants manifest Sandifer's syndrome. Neurological manifestations of Sandifer's syndrome in children with brain damage or metabolic disease may be falsely attributed to their basic disorder.

Gastroesophageal reflux could play a role in the pathogenesis of Sandifer's syndrome. However, most children with GER do not develop abnormal posture, and the connection between reflux and dystonia has been a matter for speculation[7,8]. Some authors postulated that children with this syndrome have an increased esophageal sensitivity to refluxed gastric contents so that even minimal exposure to acid may initiate the symptom complex[4]. It has been suggested that the movements in some way

bring about symptomatic relief[1,5]. Manometric study of a patient with Sandifer's syndrome showed low amplitude and slow propagation of esophageal peristalsis. And, dystonic posturing was shown to produce an increase in the velocity and amplitude of the peristaltic waves in the esophagus, relieving the symptoms by promoting the clearance of acid from the lower esophagus[7]. Subsequently, esophageal dysmotility was again found as the most frequent alteration in manometric studies of eight children with Sandifer's syndrome[9]. Furthermore, delayed gastric emptying was shown in a patient with Sandifer's syndrome by ultrasonography[10]. These evidence imply motility defect which may be primary or secondary to esophagitis.

Sometimes, unexplained irritability and paroxysmal movements like jerks and shaking may accompany this symptom complex[4]. Our patient also had coarse tremors in his hands. We could find no underlying cause for the tremors. It may have been an early manifestation of this association.

Medical therapy of GER generally relieves symptoms[3]. If medical therapy fails, then surgery should be performed[11,12].

We conclude that children with torticollis, dystonic body movements, unexplained jerks and hand tremor should be evaluated for Sandifer's syndrome.

REFERENCES

1. Kinsbourne M, Oxon DM. Hiatus hernia with contortions of the neck. Lancet 1964; 1: 1058-1061.
2. Gellis SS, Feingold M. Syndrome of hiatus hernia with torsion spasms and abnormal posturing. Am J Dis Child 1971; 121: 43-54.
3. Murphy WJ, Gellis SS. Torticollis with hiatus hernia in infancy: Sandifer syndrome. Am J Dis Child 1977; 131: 564-565.
4. Werlin SL, D'Souza B, Dodds WJ, Arndorfer RC. Sandifer syndrome: an unappreciated clinical entity. Dev Med Child Neurol 1980; 22: 374-377.
5. Bray PF, Herbst JJ, Johnson DG, Book LS, Ziter PA, Condon VR. Childhood gastroesophageal reflux. JAMA 1977; 237: 1342-1345.
6. Mandel H, Tirosh H, Berant M. Sandifer syndrome reconsidered. Acta Paediatr Scand 1989; 78: 797-799.
7. Puntis JW, Smith HL, Booth IW. Effect of dystonic movements on oesophageal peristalsis in Sandifer's syndrome. Arch Dis Child 1989; 64: 1311-1313.
8. Stucliffe J. Torsion spasms and abnormal postures in children with hiatus hernia Sandifer's syndrome: In: Kaufman HJ (ed). Progress in Pediatric Radiology Vol. 2. Chicago: Karger; 1969: 190-197.
9. Gorrotxategi P, Reguilon MJ, Arana J, et al. Gastroesophageal reflux in association with the Sandifer syndrome. Eur J Pediatr Surg 1995; 5: 203-205.
10. Cardi E, Corrado G, Cavaliere M, et al. Delayed gastric empying in an infant with Sandifer syndrome. Ital J Gastroenterol 1996; 28: 518-519.
11. Şenocak ME, Arda IS, Büyükpamukçu N. Torticollis with hiatus hernia in children. Sandifer syndrome. Turk J Pediatr 1993; 35: 209-213.
12. Leape LL, Ramenofsky ML. Surgical treatment of gastroesophageal reflux in children. Results of Nissen's fundoplication in 100 children. Am J Dis Child 1980; 134: 935-938.

Two male patients with nevoid basal cell carcinoma syndrome from Turkey

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SUMMARY: Tümer C, Er N, Balcı S, Ataç A. Two male patients with nevoid basal cell carcinoma syndrome from Turkey. Turk J Pediatr 2001; 43: 351-355.

Nevoid basal cell carcinoma syndrome, also known as Gorlin's syndrome, is a familial autosomal dominant syndrome characterized by multiple basal cell carcinomas, multiple odontogenic keratocyts of the jaws, and skeletal anomalies. Both tumors and malformations of the central nervous system occur with nevoid basal cell carcinoma. Medulloblastoma is the primary brain tumor most frequently associated with this syndrome. The authors report in this article two male patients with nevoid basal cell carcinoma syndrome: a 22-year-old male patient with multiple odontogenic keratocyts, who had medulloblastoma at two years and multiple basal cell carcinoma at 10 years of age, and a 15-year-old male patient with skeletal abnormalities and multiple odontogenic keratocyts in the jaws.

Key words: nevoid basal cell carcinoma syndrome, odontogenic keratocyst, basal cell carcinoma, medulloblastoma.

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin's syndrome, was first reported in 1894 by Jarisch and White, but was not delineated until 1960 by Gorlin and Goltz[1,2]. Gorlin and Goltz in 1960 suggested a well defined symptom complex consisting of multiple basal cell carcinomas, jaw cysts and skeletal anomalies[1]. The basal cell carcinomas occur on nonexposed as well as sun-exposed areas of the skin on any part of the body, but are mostly seen on the face. Other manifestations include multiple odontogenic keratocysts in the maxilla and mandible, bifid ribs, kyphoscoliosis or other vertebral anomalies, pectus excavatum or carinatum, Sprengel's deformity of the scapula, marfanoid build, mild hypertelorism, palmar and plantar pits, calcified falx cerebri, childhood medulloblastoma, craniopharyngioma and neurofibroma[3-5]. NBCCS is a rare entity, with only around 500 cases having been reported as far as we know[2,6]. In this article, we report two male patients with NBCCS.

Case Report

Case 1

A 22-year-old male patient with a history of medulloblastoma in the posterior fossa operated at two years of age and basal cell carcinoma diagnosed at 10 years of age was referred to Hacettepe University Faculty of Dentistry, Department of Oral Surgery with a complaint of swelling on his mandibular region. On clinical examination, the patient showed typical facial and physical appearance characterized by severe growth retardation (height 1.47 cm and weight 35 kg at 22 years, both below the 3rd percentile), basal cell carcinomas on the scalp and the anterior trunk (Figs. 1, 2), and palmar and plantar pits (Fig. 3). Panoramic radiograph revealed multiple odontogenic cysts in the mandible and maxilla (Fig. 4). Skeletal radiographic survey showed basal and falx cerebral calcifications, bifid ribs and fusion of the cervical vertebrae.

The jaw cysts were excised under general anesthesia. Microscopic examination of the mandibular and maxillar cysts revealed odontogenic keratocysts with hyperchromatic basal cell layer and parakeratinized surface (Fig. 5).

Based on the above, the patient was accepted as NBCCS. Family history was negative for NBCCS. The patient's family was examined and was found to have no jaw cysts. The patient had a normal 20-year-old sister and a 18-year-old brother who was mentally normal but had glaucoma. Chromosome analysis from peripheral blood was normal (46 XY) and sister chromatid exchange (SCE) was found within normal limits (4.4).

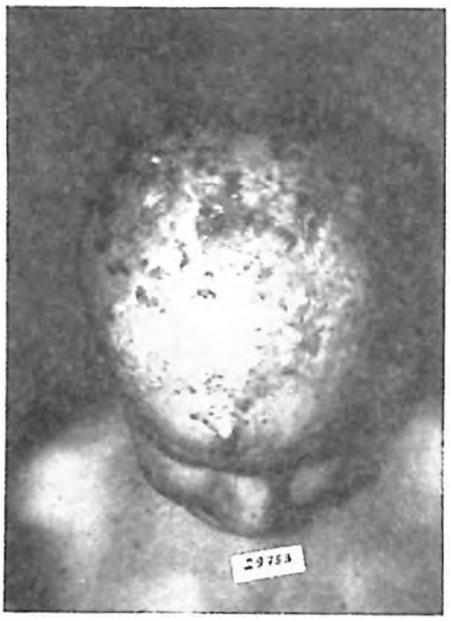

Fig. 1. General appearance of the scalp with multiple erythematous plaques and nodules.

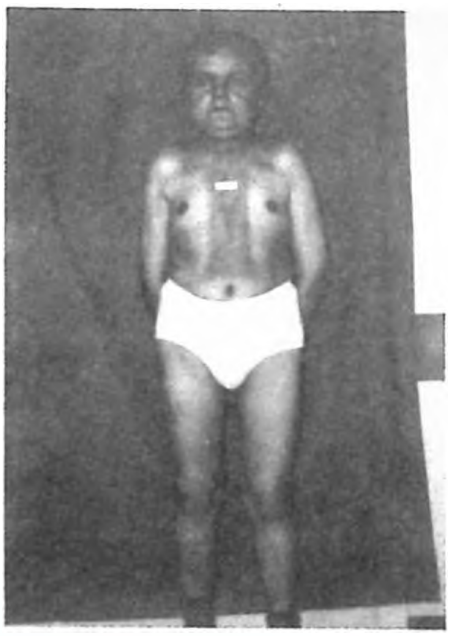

Fig. 2. Multiple erythematous plaques located on the anterior aspect of the trunk, clustered around the midline.

Case 2

15-year-old male patient who suffered from swelling on the right side of his face for two years was referred to the Department of Oral Surgery. Intraoral examination showed a fluctuating expansive mass at the right posterior mandibular alveolar ridge and another fluctuating mass between the teeth in the right anterior maxilla. On his clinical examination, the patient had characteristic facial appearance with enlarged occipitofrontal circumference (head circumference

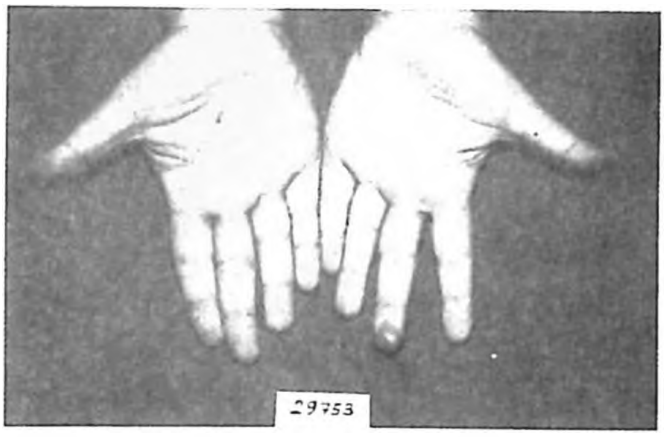

Fig. 3. Palmar and plantar pits of the first patient.

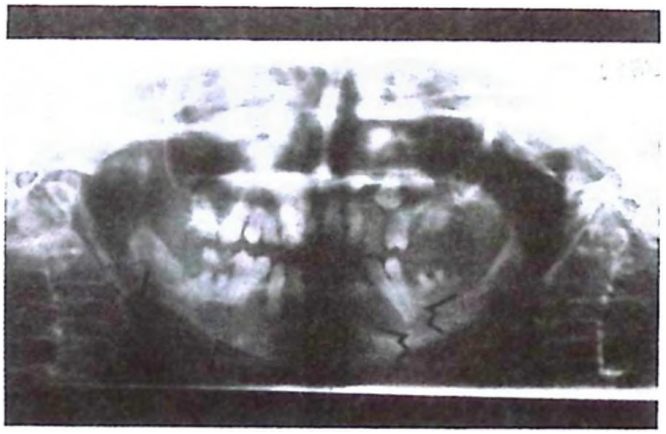

Fig. 4. Panoramic radiograph of the first patient revealing multiple odontogenic jaw cysts.

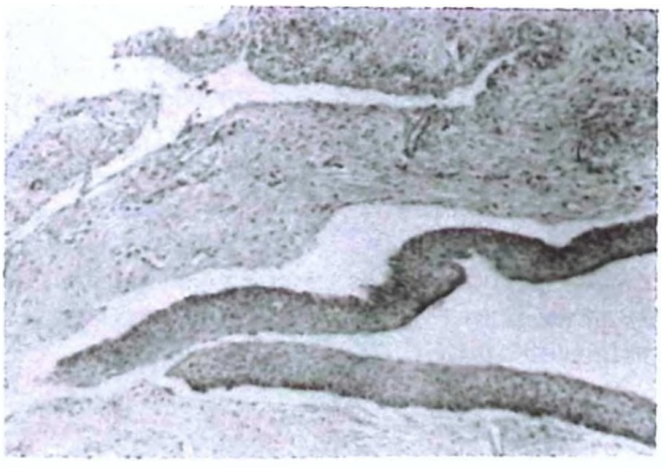

Fig. 5. Odontogenic keratocyst. Cyst epithelium with hyperchromatic basal cell layer and parakeratinized surface. Detachment of the epithelium from the capsule is obvious (HE X 200).

was 56 cm, chest circumference was 66 cm). frontal bossing, and mild hypertelorism (Fig. 6), and he had marfanoid build (height was 170 cm, weight was 43 kg), kyphoscoliosis and Sprengel's deformity of his scapulae (Figs. 7, 8). There was a surgical scar on his chest for pectus excavatum. Panoramic radiograph revealed multiple odontogenic cysts in the mandible and the maxilla (Fig. 9). Chest radiograph demonstrated bifid, fused and missing ribs, hemivertebra and scoliosis (Fig. 10). Computed tomography scans of the brain did not reveal any intracranial mass. Multiple odontogenic cysts of the jaws were excised under general anesthesia. Histopathologic examination revealed odontogenic keratocysts with daughter cysts in the fibrous wall of the cyst (Figs. 11, 12). Family history of this patient revealed that he was the second child. The patient's father, mother and the other two brothers were normal. Chromosome analysis of our patient was normal (46, XY). Based on his clinical, radiological and histopathologic findings, the patient was accepted as NBCCS, in

Fig. 6. General facial appearance of the second patient.

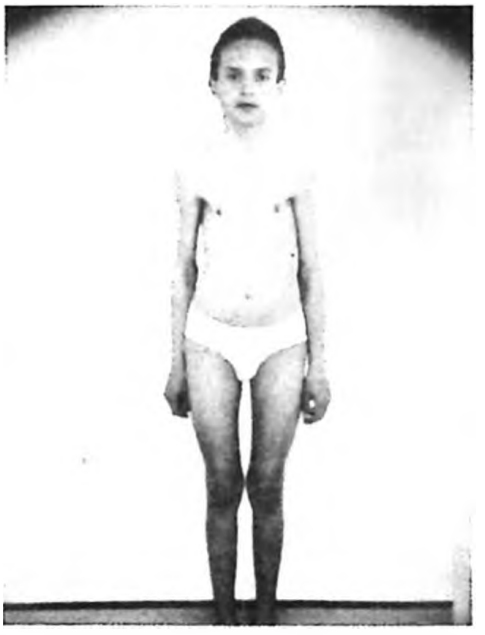

Fig. 7. Skeletal abnormalities and marfanoid appearance of the second patient.

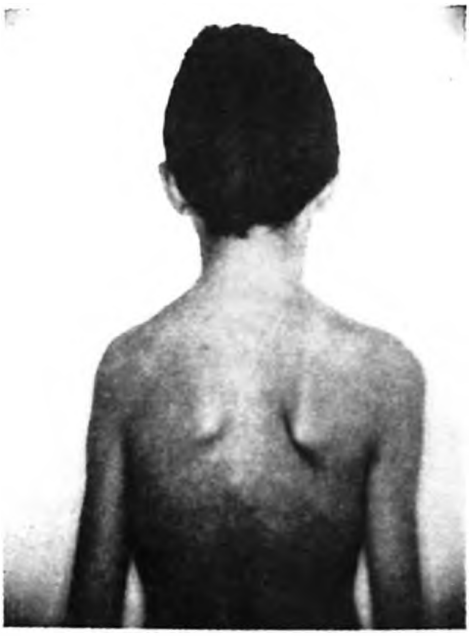

Fig. 8. Kyphoscoliosis and Sprengel's deformity of the second patient.

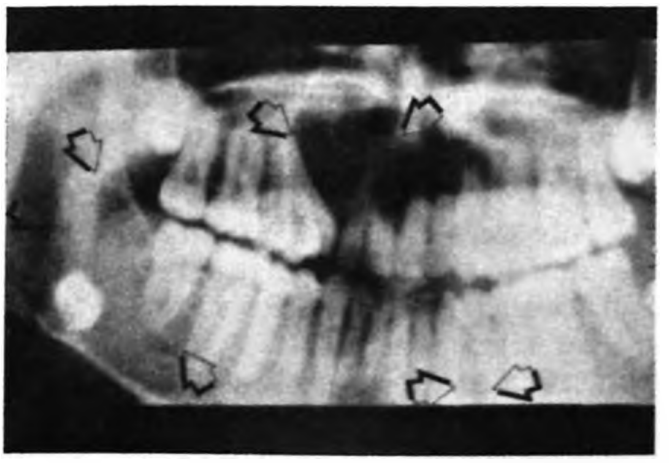

Fig. 9. Panoramic radiograph of the second patient revealing multiple odontogenic jaw cysts.

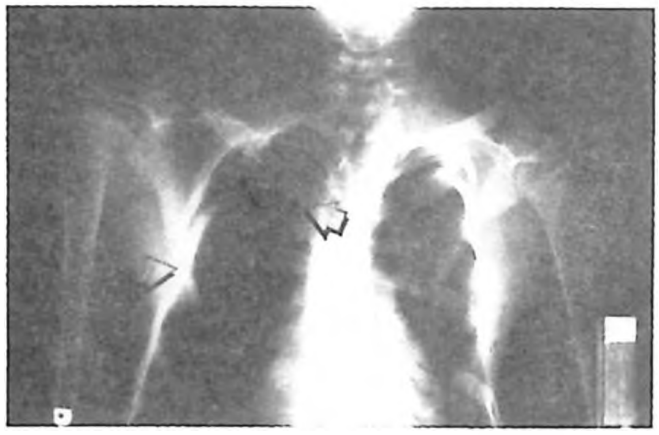

Fig. 10. Chest radiograph demonstrating rib anomalies, hemivertebra and scoliosis.

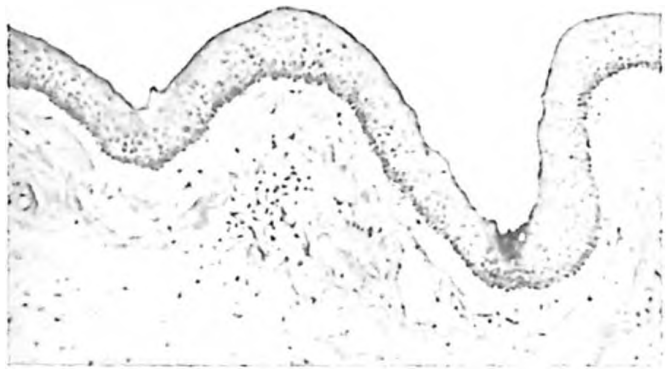

Fig. 11. Odontogenic keratocyst. Cyst epithelium shows hyperchromatic basal cell layer and parakeratinized surface (HE X 400).

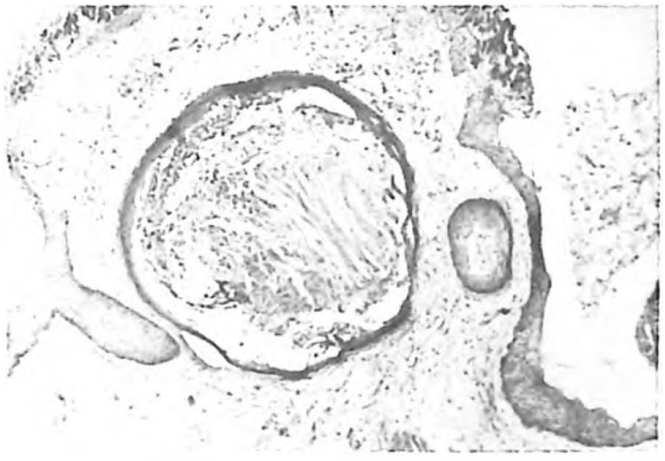

Fig. 12. Odontogenic keratocyst. Daughter cysts are seen in the fibrous wall of the cyst (HE X 100).

spite of absence of brain tumors and skin carcinomas at this age. The patient is being followed for future development of skin, intracranial or other malignancies.

Discussion

The mode of inheritance in Gorlin's syndrome is autosomal dominant[2]. The gene has been mapped to chromome 9q22-3-q31 and most likely functions as a tumor suppressor gene[6]. Recently, Cohen[8] showed that the cause of this syndrome was a single point mutation in one patched allele. This may be responsible for the malformations found in NBCCS. Inactivation of both patched alleles results in formation of tumors and cysts[8]. Older paternal age is a factor in fresh mutations. In our patients, the paternal age was 32 years in the first case and 30 years for the second case.

Evans et al.[3] reported two cases (1-2%) of NBCCS among 173 consecutive cases of medulloblastoma. This figure is lower than previous estimates. Medulloblastoma in NBCCS occurs at an average age of about two years, whereas sporadic cases of medulloblastoma occur at an average age of about six years[2,3,7]. Evans et al.[9] in his 173 consecutive cases of medulloblastoma suggested that patients with NBCCS-associated medulloblastoma tend to survive longer than patients with sporadic medulloblastoma. Ten patients with NBCCS had survived more than 10 years after removal of a medulloblastoma[3,7]. The 20-year survival of our patient after medulloblastoma resection is therefore not unusual for a patient with NBCCS.

Skin lesions are common in patients with NBCCS. Basal cell carcinomas usually appear largely between puberty and 35 years of age,

although they can be seen as early as the second year of life[2]. Approximately 2% of patients under 45 years of age with basal cell carcinomas have NBCCS. These tumors usually grow slowly, but some become invasive and if untreated cause tissue damage[10].

Odontogenic keratocysts account for 3% to 10.5% of all jaw cysts. Most odontogenic keratocysts are often asymptomatic and are discovered on routine radiological examinations[11]. The average age for diagnosis of NBCCS is 13 years, but keratocysts have been reported in patients as young as eight years. The development of odontogenic keratocysts peak[5] during the second or third decade[2,11]. This is approximately a decade earlier than the isolated odontogenic keratocysts not associated with the syndrome[2]. The most common locations, in order of decreasing frequency, are the mandibular third molar region, maxillary third molar region, and mandibular first and second molar region[11]. As these cysts have a tendency to recur, they must be treated aggressively. Enucleation of the cysts and irrigation of the cavity with Carnoy solution helps in preventing recurrence[12]. The odontogenic keratocysts in our two cases were typical for localization and time of appearance. As these cysts are usually asymptomatic, routine panoramic radiographic controls are essential in patients with NBCCS. Earlier diagnosis and treatment of these lesions will prevent the development of large jaw defects, make surgery easier and prevent tooth loss.

In this article, we report two new patients with NBCCS. It is important that these cases are all followed up by pediatricians, while the diagnosis of NBCCS is established by oral surgeons. Furthermore, in medulloblastoma and skin carcinoma cases of childhood, further evaluation for jaw cysts is necessary for the accurate diagnosis of NBCCS.

For the first time, we studied SCE in a case with NBCCS who demonstrated all of the findings of this syndrome at 22 years of age. However, the second case showed only skeletal malformations and jaw cysts. We are therefore closely following this case for the possible development of brain tumors and skin carcinomas.

REFERENCES

1. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid ribs. A syndrome. N Engl J Med 1960; 262: 908-912.
2. Gorlin RJ, Cohen MM, Levin LS. Syndromes of the Head and Neck (3rd ed). New York: Oxford University Press; 1990: 372-380.
3. Evans DG, Birch JM, Orton CI. Brain tumours and the occurrence of severe invasive basal cell carcinoma in first degree relatives with Gorlin syndrome. Br J Neurosurg 1991; 5: 643-646.
4. Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA. Complication of the nevoid basal cell carcinoma syndrome: results of a population based study. J Med Genet 1993; 30: 460-464.
5. Gorlin JR. Nevoid basal cell carcinoma syndrome. Medicine 1987; 66: 98-113.
6. Jones KL. Smith's Recognizable Patterns of Human Malformation (5th ed), Philadelphia: WB Saunders Co; 1997: 528-529.
7. Albrrecht S, Goodman JC, Rajagopolan SR, Levy M, Cech DA, Cooley LD. Malignant meningioma in Gorlin's syndrome: cytogenetic and p53 gene analysis. J Neurosurg 1994; 81: 466-471.
8. Cohen MM. Nevoid basal cell carcinoma syndrome: molecular biology and new hypotheses. Int J Oral Maxillofac Surg 1999; 28: 2126-223.
9. Evans DG, Farndon PA, Burnell LD, et al. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer 1991; 64: 959-961.
10. Springate JE. The nevoid basal cell carcinoma syndrome. J Pediatr Surg 1986; 21: 908-910.
11. Hall J, Johnston K, McPhillips JP, Barnes SD, Elston D. The nevoid basal cell carcinoma syndrome in a black child. J Am Acad Dermatol 1998; 38: 363-365.
12. Voorsmith RA, Stoelinga PJ, Van Haelst J. The management of keratocysts. J Oral Maxillofac Surg 1981; 9: 228-236.

Familial arthropathy with camptodactyly: reports of two families

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SUMMARY: Soylu A, Türkmen M, Kavukçu S, Özer E, Canda T. Familial arthropathy with camptodactyly: reports of two families. Turk J Pediatr 2001; 43: 356-361.

Familial association of congenital camptodactyly and arthropathy without evidence of concurrent inflammation has an autosomal recessive pattern of inheritance. We describe four children born to consanguineous parents in two families with congenital camptodactyly and polyarthropathy which were misdiagnosed and treated as juvenile rheumatoid arthritis (JRA) for some time. The siblings in the second family also had fibrosing pleuritis. Histopathological examination of the synovial tissues of the children in the first family revealed synovial hypertrophy and presence of multinucleated giant cells with minimal inflammation and vasculitis. On the other hand, prominent fibrosis with no inflammation was present in the synovial tissue of the elder boy in the second family. Thus, while the children in the first family had the phenotypic characteristics of congenital familial hypertrophic synovitis, the latter siblings probably represent a form of the familial fibrosing serositis.

Key words: camptodactyly, childhood, familial arthropathy, familial fibrosing serositis, juvenile rheumatoid arthritis.

Camptodactyly is used to describe nontraumatic flexion deformity of the proximal interphalangeal joints[1]. After the first description of familial association of congenital camptodactyly and arthropathy in 1965, additional cases of camptodactyly associated with noninflammatory arthropathy have been reported[2]. Characteristic features of the syndrome are its familial nature, congenital or early-onset camptodactyly and polyarthropathy associated with synovial hyperplasia but without evidence of concurrent inflammation[2,3]. An autosomal recessive pattern of inheritance has been proposed for this condition[4]. Presence of additional features has led to various acronyms for the syndrome as CAP (camptodactyly-arthropathy-pericarditis) or CAC (camptodactyly-arthropathy-coxa vara). However, genetic evaluation of the families with different manifestations has led to the localization of the gene to chromosome 1, thus the combined term CACP (camptodactyly-arthropathy-coxa vara-pericarditis) was suggested for this entity[2]. In addition, progressive fibrosing pleuritis has recently been described as a component manifestation of this familial syndrome, and the term familial fibrosing serositis was proposed for this distinct condition[3].

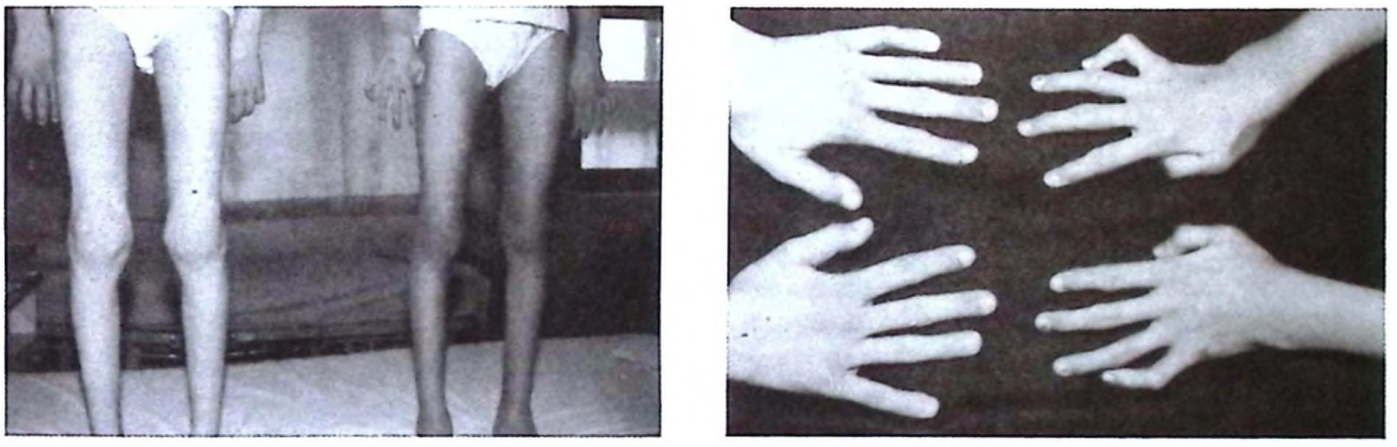
We describe four children in two families with congenital camptodactyly and polyarthropathy which were misdiagnosed and treated as juvenile rheumatoid arthritis (JRA) for some time. The siblings in the second family also had pleuritis as a component of the syndrome.

Case Reports

Family 1
Case 1

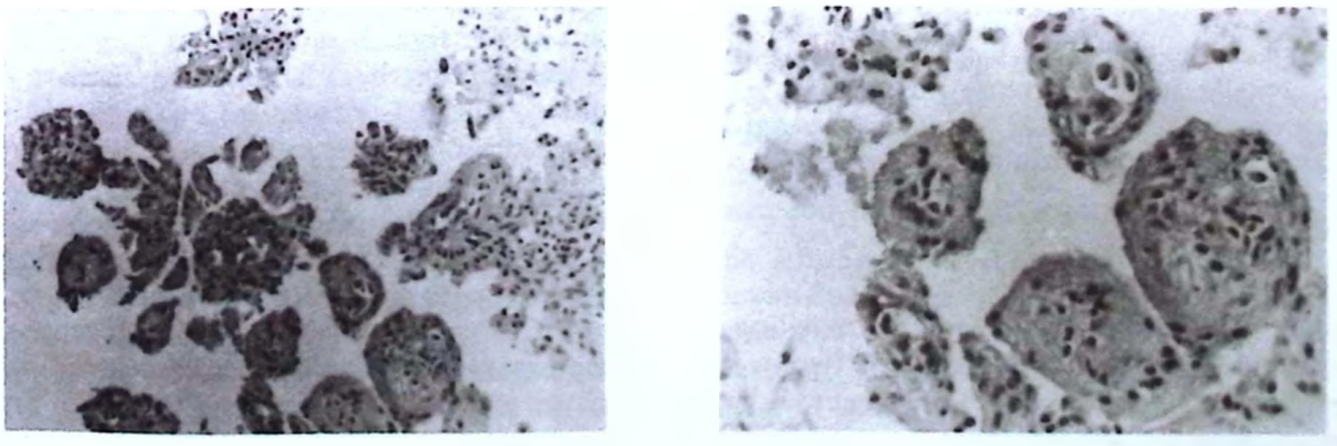
A six-year-old girl presented with the complaints of swelling in both knees for two years. Her past history was marked by congenital flexion contractures in both thumbs, difficulty for two years in squatting and an operation performed due to a bent thumb. Her parents were first-degree relatives; however, there was no history of a similarly affected relative other than her brother. Physical examination revealed bilateral swelling in her wrists, knees, ankles, and proximal and distal interphalangeal joints (PIP and DIP), bilateral hallux valgus deformity, and bilateral flexion contractures in her fingers, most prominent in the first and fifth fingers. No erythema, tendemess or warmth was present over the involved joints. Ophthalmologic examination was normal.

Laboratory analyses were characterized by normal complete blood count and erythrocyte sedimentation rate (ESR) and negative C-reactive protein (CRP), antinuclear antibody (ANA) and rheumatoid factor (RF) tests. Joint X-rays demonstrated only soft tissue swelling. She was treated with indomethacin as polyarticular JRA at that point. However, this therapy was stopped after six months by the parents due to its ineffectiveness. When she presented the second time approximately three years later, in addition to her previous complaints, growth failure and swelling and flexion contractures in both elbows and knees were determined (Fig. 1a). Laboratory analyses were normal again. At that time, she was treated with deflazacort (0.5 mg/kg/day) and methotrexate (10 mg/m^2/week) for one year with no benefit. After that, she was followed by another physician team and congenital familial hypertrophic synovitis (FHS) was suspected on the basis of history and clinical examination. Thus, a biopsy was undertaken to obtain synovial tissue and synovial fluid from her right knee. Synovial fluid analysis revealed reactive synovial cells and multinucleated giant cells with no inflammatory cells. In histopathological examination, synovial tissue was fragmented and there were papillary buds of synovial cells over fibrocollagenous stroma (Figs. 2a and 2b). These findings were compatible with congenital FHS variant of familial arthropathies[3]. The medications were stopped, and physiotherapy was instituted.



(a) (b)

Fig. 1a. Swelling in both knees. b) swelling and flexion contractures in the fingers of both siblings (female on the right).



(a) (b)

Fig. 2a. Hyperplastic synovial cells with papillary appearance (H and E x 40), and b) synovial cells, minimal mononuclear infiltrate and lack of vascular proliferation (H & E x 100) in the synovial biopsy specimen of Case 1.

Case 2

An eight-year-old male sibling of the previous case presented with the complaint of swelling in both knees and wrists with no pain, erythema or warmth. Past history was marked by an operation involving both knees performed due to swelling. On physical examination, swelling in his shoulders, elbows, wrists and knees and limitation in the range of motion of his elbows were determined. In addition, there was mild flexion contractures of PIP joints in his fifth fingers bilaterally. There was no tenderness, erythema or warmth over his joints. Laboratory analyses demonstrated normal complete blood count and ESR and negative CRP, ANA and RF tests. Joint X-rays were normal other than soft tissue swelling. He was also diagnosed as polyarticular JRA and given indomethacin like with his sister. This treatment was continued for six months with no benefit. Three years later, he presented with growth failure, bilateral flexion contractures in his knees and elbows, and swelling and limitation in the range of motion in his ankles, in addition to the previous findings (Fig. 1b). Laboratory analyses were normal again. At that point, he was treated with deflazacort and methotrexate for one year, again like his sister. After that, he was followed by another physician team and the diagnosis of congenital FHS was made on the basis of history and clinical examination. Synovial biopsy from his right knee was performed which revealed papillary buds of synovial cells and areas of hyalinization with minimal inflammatory cell infiltration and vascular proliferation (Fig. 3). Synovial fluid analysis revealed only reactive synovial cells and multinuclear giant cells. His medications were stopped, and physiotherapy was instituted as with his sister.

Cross-examination of the biopsy materials of the siblings obtained in another hospital six years ago revealed similar histopathological characteristics with minimal inflammation.

Family 2

Case 3

A four-year-old boy presented with swelling of both knees and wrists for the last two years. He had been given salicylate treatment with no benefit. The parents were second-degree cousins. On examination, his height and weight were in 25th and 75th percentiles, respectively. Examination of joints revealed swelling and

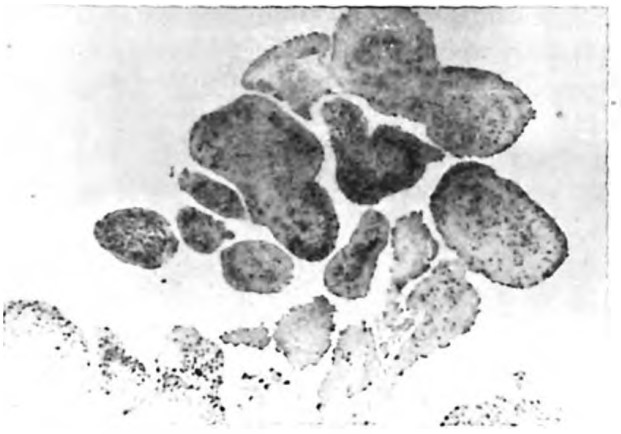
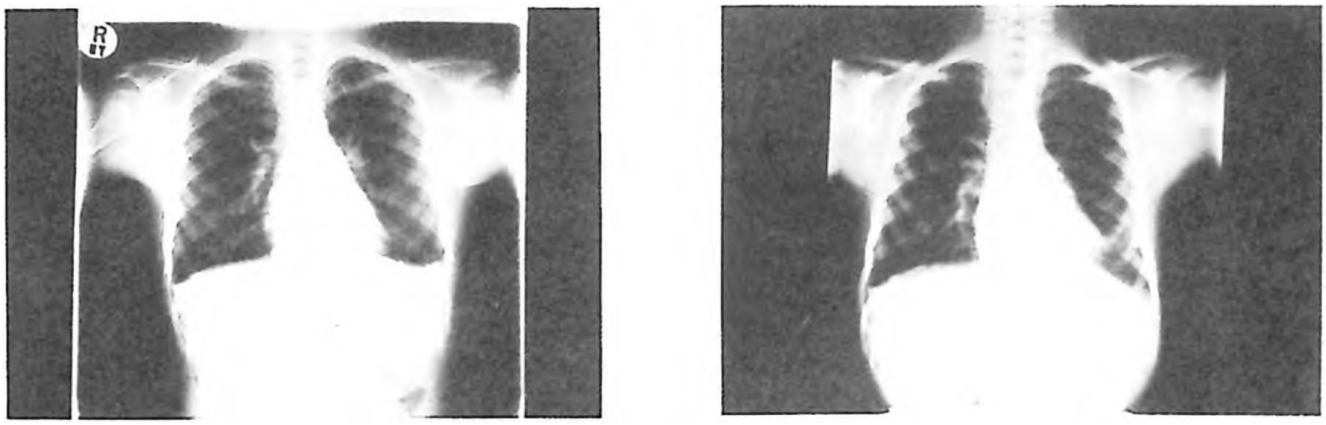


Fig. 3. Papillary buds of synovial tissue in the synovial biopsy specimen of Case 2 (H and E x 40).

limitation of motion in both knees with fluctuation on the left. PIP joints had fusiform swelling and contractures. He also had flexion contractures at elbows, synovial cysts at wrists and ankles, and bilateral hallux valgus deformity. The rest of the physical examination including ophthalmologic examination was normal. Complete blood count and ESR were normal, and CRP, ANA and RF were negative. Joint X-rays revealed widened joint spaces, osteoporosis and soft tissue swelling. Magnetic resonance (MR) evaluation of the cervical vertebrae and ophthalmologic examination were normal. He was diagnosed as JRA and given naproxen with no improvement in his complaints. Methotrexate was instituted at fourth year of follow-up due to worsening of complaints and physical signs. However, no improvement in the clinical course was noted. MR evaluation of the knees demonstrated intraarticular collection of viscous fluid and diffuse synovial proliferation with normal menisci. Vertebral X-ray revealed osteopenia, and fissuritis of the left lung was noticed in addition. Chest X-ray showed blunting of the costophrenic sinuses bilaterally (Fig. 4a). Ultrasound examination revealed only pleural thickening without effusion. White blood cell count and ESR were normal. PPD caused an induration with a diameter of 10 mm (he had two BCG scars). He had no respiratory symptom, but was given a macrolide antibiotic for two weeks. Repeat chest x-ray after one month was similar to the previous one. Echocardiography was normal. Synovial biopsy showed profuse fibroadipose tissue without inflammatory cell infiltration (Fig. 5)



(a) (b)

Figs. 4a and b. Chest x-rays of the siblings in the second family demonstrating pleuritis manifested by blunted costophrenic sinuses bilaterally.

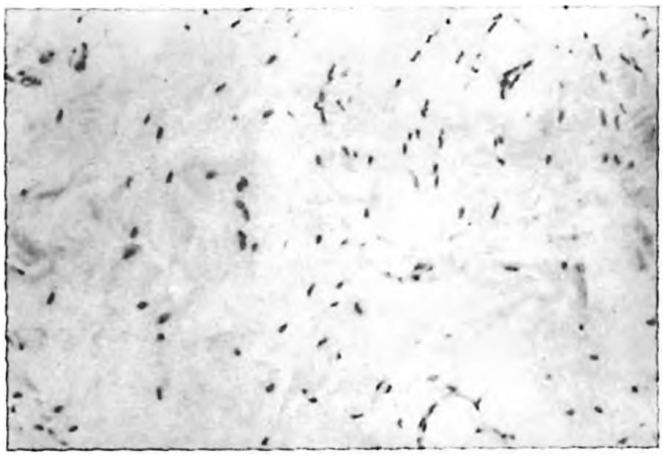


Fig. 5. Prominent fibrous tissue in the synovial biopsy specimen of Case 3 (H&E x 100).

Case 4

The younger brother of the propositus was three years old at presentation. He had had swelling without any other complaint in both knees for one year. Physical examination was characterized by normal anthropometric features (height and weight at 50th percentiles), swelling and palpable effusion in both knee joints, and swelling and contractures in PIP joints. Ophthalmologic examination was normal. Laboratory analyses including complete blood count, differential white blood cell count, ESR, CRP, ANA and RF were normal or negative. X-rays of the knees revealed minimal joint effusion along with normal bony structures. He was diagnosed as JRA, and given nonsteroidal antiinflammatory drugs with no improvement in his complaints. MRI of the knees performed one year later demonstrated increased joint fluid and synovial proliferation. Chest X-ray, obtained after demonstration of pleuritis in his brother, revealed that his costophrenic sinuses were also blunted (Fig. 4b). Ultrasound examination showed pleural thickening and no fluid. Echocardiography was normal. PPD was negative, and ESR was within normal ranges.

Discussion

The major differential diagnosis of arthritis in childhood includes JRA and its clinical subgroups. Although our patients met some of the criteria of the American College of Rheumatology necessary for the diagnosis of JRA[5], none of them had tenderness, pain on motion or increased heat on the involved joints. In addition, none of them had any sign of systemic inflammation. Furthermore, MR evaluation of the knee joints of the siblings in the second family did not show the features described in patients with JRA other than increased joint fluid[6]. Finally, none of the cases showed any improvement of disease symptoms and signs despite long-term treatment with adequate doses of various drugs used in the treatment of JRA.

The siblings in the second family also had serositis with polyarthritis which are also seen in familial Mediterranean fever (FMF) and systemic lupus erythematosus (SLE)[7,8]. However, absence of recurrent febrile episodes and signs of serosal inflammation, presence of many joint deformities starting from early infancy, and persistence of pleural reaction for the last six months in our cases excluded FMF

as a possible diagnosis. Absence of systemic inflammatory signs and ANA, presence of joint deformities, and familial nature of the disease also ruled out SLE in these cases.

The first case in the second family had a PPD reaction of 10 mm in addition to chest X-ray findings. However, the size of this reaction was within the normal limits described in children with two BCG scars[9]. In addition, absence of systemic inflammatory findings and familial nature of the disease were not compatible with tuberculosis in this patient.

The main features of our patients were camptodactyly associated with polyarthropathy presenting at young age, absence of local and systemic signs of inflammation, and the familial nature of these complaints (Table I). Thus, our patients fulfilled the criteria to be categorized as "familial arthropathy and camptodactyly" that has four subgroups: 1) Congenital FHS which is characterized by nonimflammatory arthropathy, congenital flexion contractures of the fingers, and synovial hyperplasia with a large number of multinucleated giant cells. 2) Familial arthritis and camptodactyly: Here the patients have inflammatory changes in the synovial biopsy specimens, later onset of camptodactyly, iridocyclitis, elevated ESR, and erosive changes. 3) Blau syndrome which is a familial granulomatous arthritis, uveitis, rash and camptodactyly. 4) CAP syndrome in which the patients have additional findings of constrictive pericarditis with effusion and prominent fibrosis with mild inflammatory cell infiltration of the synovium and the pericardium[3].

The first two cases described here had the clinical and histopathological features of the first subgroup, and they were categorized as congenital FHS. On the other hand, the siblings in the second family had additional findings of bilateral pleural thickening and, for Case 3, prominent fibrosis in the synovial biopsy specimen. Although pericarditis has been described relatively frequently and accepted as a phenotypic variant of this syndrome[2,3,10,11], pleuritis was reported first in 1995[3]. However, the patients described in the latter paper also had pericardial effusion, and prominent fibrosis with minimal inflammation was reported to be present in the synovium/pericardium/pleura. The authors proposed the term "familial fibrosing serositis" for this entity. Echocardiography of our patients were normal. In addition, we did not perform pleural biopsy. However,

Table I. Clinical and Laboratory Features of the Cases

	Family 1		Family 2	
Characteristics	Case 1	Case 2	Case 3	Case 4
Camptodactyly	+	+	+	+
Arthropathy-large joints[1]	+	+	+	+
Coxa vara	–	–	–	
Sex	F	M	M	M
Age at onset of camptodactyly (year)	Birth	Birth	Birth	Birth
Age at evaluation (year)	6	8	4	3
Response to therapy[2]	–	–	–	–
Signs of systemic inflammation[3]	–	–	–	–
Signs of local inflammation[4]	–	–	–	–
Uveitis	–	–	–	–
Synovial biopsy	Synovial hyperplasia with giant cells	Synovial hyperplasia with giant cells	Prominent fibrosis	Not performed
Pericarditis	–	–	–	–
Pleuritis	–	–	+	+

[1] Bilateral wrists, elbows, ankles and knees.
[2] Salicylates, nonsteroidal antiinflammatory drugs, steroids and methotrexate.
[3] Fever, rash, malaise, increased erythrocyte sedimentation rate.
[4] Heat, tenderness or pain on motion.

presence of prominent fibrosis in the absence of inflammation in the synovium along with pleural reaction not responding to antibiotic and nonsteroidal antiinflammatory therapy and the familial nature of the disorder suggest that these two siblings are more like the patients described by Verma et al[3].

Camptodactyly with arthropathy has been proposed to result from a regulatory dysfunction in the proliferation of synovial and serosal cells[2]. Autosomal recessive inheritance was suggested on the basis of parental consanguinity in many affected families[4], and the genetic locus has been localized to chromosome 1q25-31[2]. Our patients were also products of consanguineous parents, and no other affected family member was reported.

In summary, the two families described in this report represent two different phenotypic variants of congenital camptodactyly associated with arthropathy. While the siblings in the first family could easily be subclassified as congenital FHS, those in the second family probably represent a variant of familial fibrosing serositis. Furthermore, the siblings in the second family are the first cases, to our knowledge, to have pleural involvement without pericarditis. Whatever the subtype, these cases demonstrate that familial arthropathies should be included in the differential diagnosis of childhood arthritides, especially if more than one family member is affected. Otherwise, these children might be unnecessarily treated with drugs having many side effects for long periods.

REFERENCES

1. Athreya BH, Schumacher HR. Pathologic features of a familial arthropathy associated with congenital flexion contractures of fingers. Arthritis Rheum 1978; 21: 429-437.
2. Bahabri SA, Suwairi WA, Laxer RM, Polinkovsky A, Dalaan AA, Warman ML. The camptodactyly - arthropathy - coxa vara - pericarditis syndrome. Arthritis Rheum 1998; 4: 730-735.
3. Verma UN, Misra R, Radhakrisnan S, Maitra SC, Agarwal SS, Singh RR. A syndrome of fibrosing pleuritis, pericarditis, and synovitis with infantile contractures of fingers and toes in two sisters: familial fibrosing serositis. J Rheumatol 1995; 22: 2349-2355.
4. Martinez-Lavin M, Buendia A, Delgado E, et al. A familial syndrome of pericarditis, arthritis, and camptodactyly. N Engl J Med 1983; 309: 224-225.
5. Cassidy JT, Petty RE. Juvenile rheumatoid arthritis. In: Cassidy JT, Petty RE (eds). Textbook of Pediatric Rheumatology (3rd ed). Philadelphia: WB Saunders Company; 1995: 133-223.
6. Herve-Somma CM, Sebag GH, Prieur A, Bonnerot V, Lallemand DP. Juvenile rheumatoid arthritis of the knee: MR evaluation with Gd-DOTA. Radiology 1992; 182: 93-98.
7. Saatçi Ü, Özen S, Özdemir S, et al. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. Eur J Pediatr 1997; 156: 619-623.
8. Warren RW, Perez MD, Wilking AP, Myones BL. Pediatric rheumatic diseases. Pediatr Clin North Am 1994; 41: 783-818.
9. Ildırım I, Hacımustafaoğlu M, Ediz B. Correlation of tuberculin induration with the number of Bacillus Calmette-Guerin vaccines. Pediatr Infect Dis J 1995; 14: 1060-1063.
10. Bulutlar G, Yazıcı H, Özdoğan H, Schreuder I. A familial syndrome of pericarditis, arthritis, camptodactyly, and coxa vara. Arthritis Rheum 1986; 29: 436-438.
11. Laxer RM, Cameron BJ, Chaisson D, Smith CR, Stein LD. The camptodactyly-arthropathy-pericarditis syndrome: case report and literature review. Arthritis Rheum 1986; 29: 439-444.

Familial microtia in four generations with variable expressivity and incomplete penetrance in association with type I syndactyly

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SUMMARY: Balcı S, Boduroğlu K, Kaya S. Familial microtia in four generations with variable expressivity and incomplete penetrance in association with type I syndactyly. Turk J Pediatr 2001; 43: 362-365.

Familial microtia with external ear canal atresia and conductive deafness is rarely reported. Autosomal dominant and recessive inheritance have been suggested depending on various family reports. Cases with other malformations in addition to microtia have been described, although the microtia generally is an isolated finding. Here we report a family with microtia, external auditory canal atresia and conductive deafness in four generations. The mode of inheritance of the disease was autosomal dominant within this family. Also, variable expressivity, incomplete penetrance and generation skipping are evident in the pedigree. Association of microtia with type I syndactyly, which has never been reported previously, was present in the index case.

Key words: familial microtia, auditory canal atresia, conductive deafness, autosomal dominant inheritance, type I syndactyly.

Hereditary malformations of the external ear, such as microtia and atretic auditory canal, without other congenital defects, are rarely reported[1]. Although microtia with meatal atresia might be a finding of some syndrome such as Goldenhar's or Treacher Collins', it is usually an isolated malformation[2]. Only a few familial cases have been described. Both autosomal recessive and dominant inheritance have been suggested[3,4]. The first familial case from Turkey was reported by Balcı[5] in a father and son with unilateral microtia and meatal atresia.

Here we report a family in which microtia and meatal atresia were observed in four generations. The proband, his father, his paternal grandmother and her grandmother were affected with microtia, suggesting autosomal dominant inheritance. An interesting finding was that the child also had syndactyly between the 3rd and 4th fingers on the left hand. As far as we know this is the first familial microtia case in association with type I syndactyly.

Case Report

A five-year old boy (Case V-1), admitted to our hospital because of bilateral microtia and atresia of the external auditory canal was the first child of consanguineous parents. The mother was 22 and the father was 27. The second child was a two-year-old healthy boy. There was no history of exposure to radiation, infection or drug ingestion during the pregnancy. The delivery was uneventful and the birth weight was 3600 g.

On physical examination his weight was 18 kg (50th percentile), height 106 cm (25th percentile) and head circumference 52 cm. He had microtia and external meatal atresia on both sides (Figs. 1a and 1b). There was partial cutaneous syndactyly between the 3rd and 4th fingers on the left hand, and the first toes were larger than normal on both feet (Fig. 2). Although intelligence was normal, speech delay was evident. Audiogram revealed conductive hearing loss on both sides. Cranial tomography and abdominal ultrasonography were both normal. Peripheral blood chromosome analysis revealed 46,XY karyotype.

Patient was operated under general anesthesia to create an external ear canal. Three months after this successful operation, a 35 dB gain in hearing levels was achieved.

Family history revealed that some other members of the family were affected (Fig. 3).

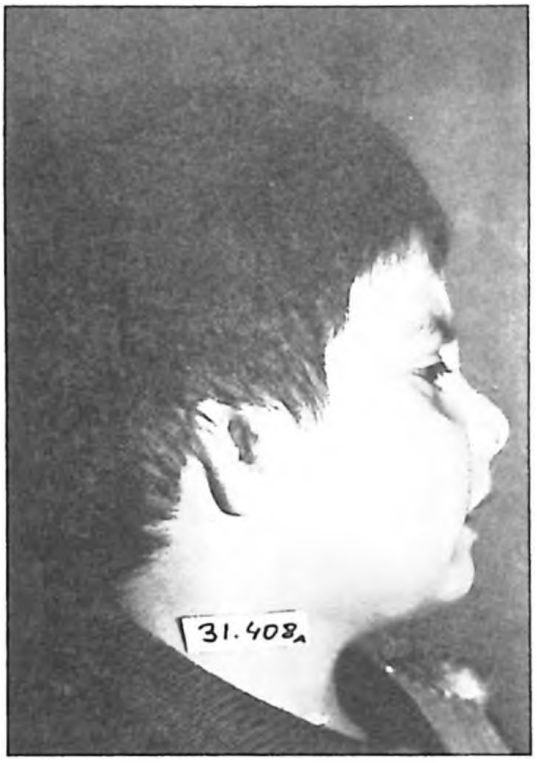

Fig. 1a. Lateral view of the index case (V-1), showing microtia on the right side after the operation.

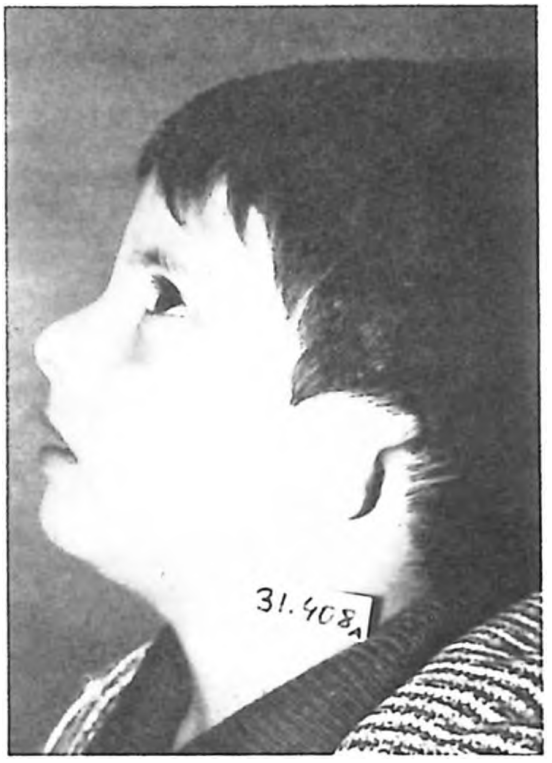

Fig. 1b. Lateral view of the index case (V-1), showing microtia on the left side.

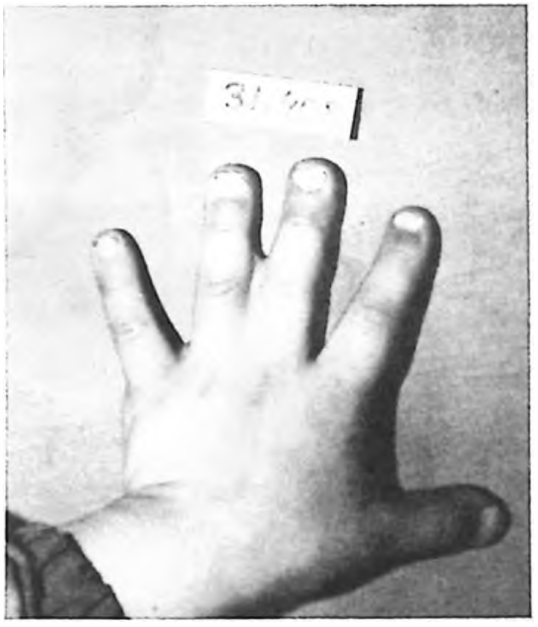

Fig. 2. The left hand of the proband showing cutaneous syndactyly between the third and fourth fingers.

The right ear of the father (Case IV-3) was cup-shaped and the ear lobe was absent. The auditory canal was not atretic (Fig. 4). The paternal grandmother (Case III-3) had findings quite similar with the child on the right ear. There was microtia with atresia of the external meatus and conductive hearing loss (Fig. 5). Abdominal ultrasonographies of both the father and the grandmother were normal. The maternal grandmother of the grandmother (Case I-1) was also reported to have right-sided microtia and external meatal atresia, but her medical reports were not available and a photograph of her could not be obtained. Fingers and toes of Cases IV-3, III-3 and I-1 were normal.

Discussion

Microtia and meatal atresia with or without middle ear involvement can be observed sporadically, associated with some syndromes, or as a multifactorial or a hereditary trait (autosomal recessive or dominant)[2-4,6]. A male preponderance and right-sided involvement are evident in familial cases. Among familial cases transmission is almost always from father to child[6].

In their epidemiological study, Mastroiacovo et al.[1] identified 172 cases with microtia-anotia among 1,173,794 births, of which 66.2% were isolated cases. The occurrence of familial microtia with meatal atresia and conductive deafness in more than one sibling was reported by Ellwood et al.[7], Dar et al.[8], and Schmid et al.[9] but Balcı[5] first reported familial microtia in two generations.

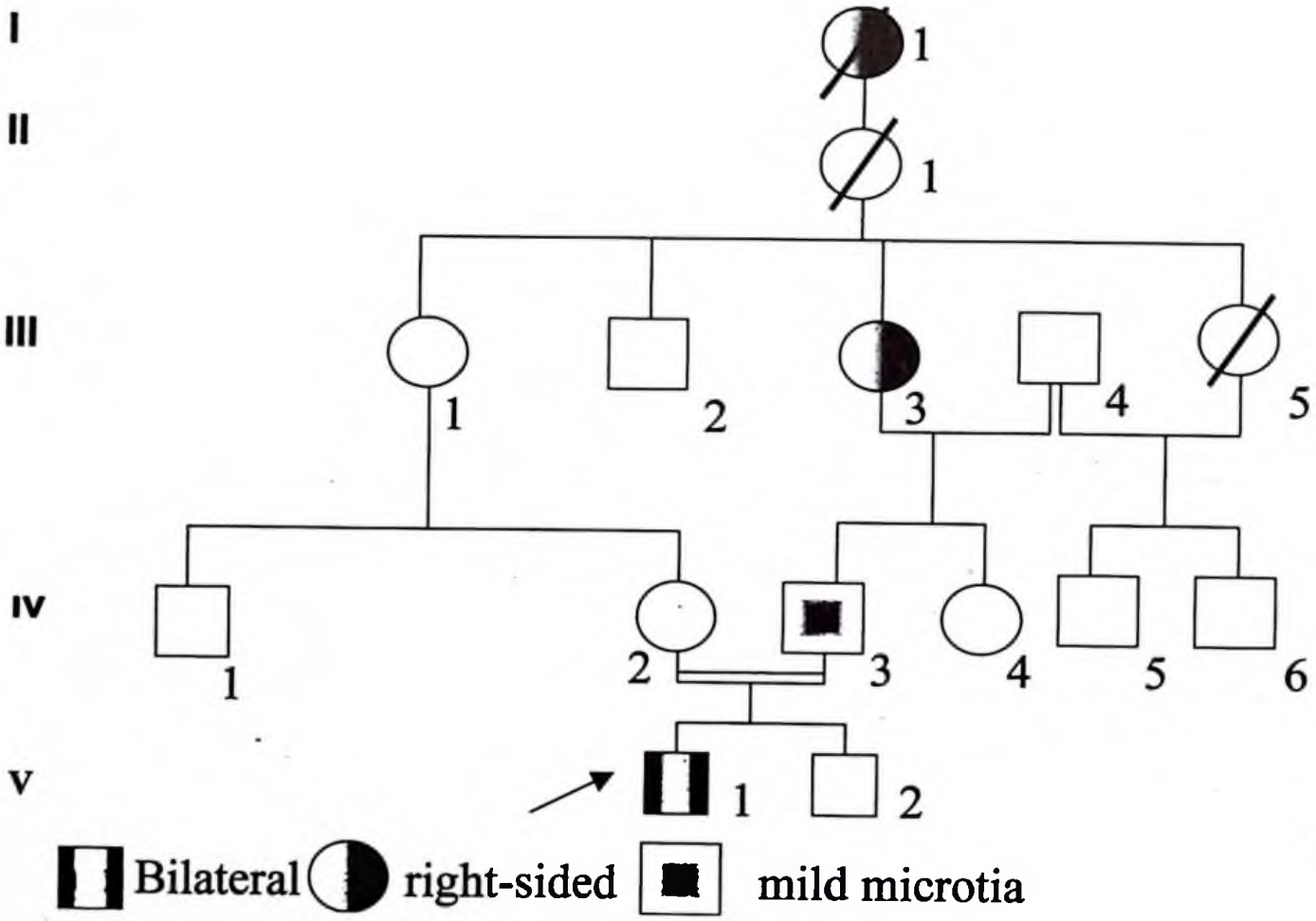

Fig. 3. Pedigree of the family.

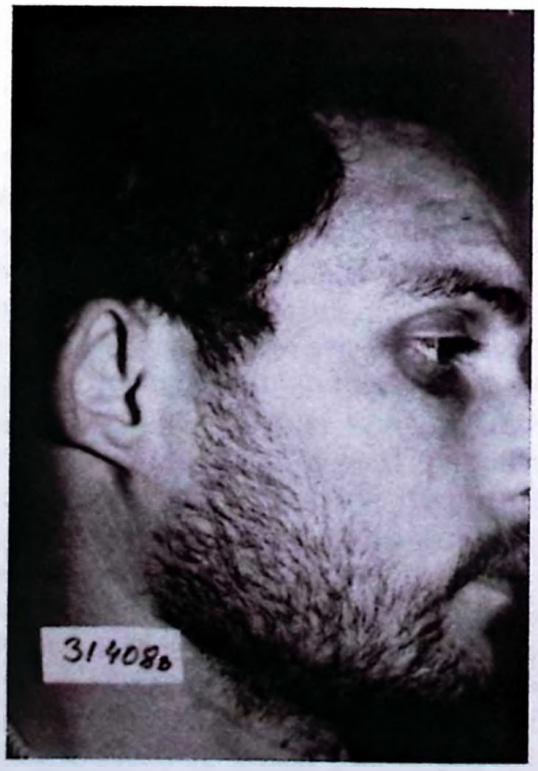

Fig. 4. Rudimentary right auricle of the father (Case IV-3).

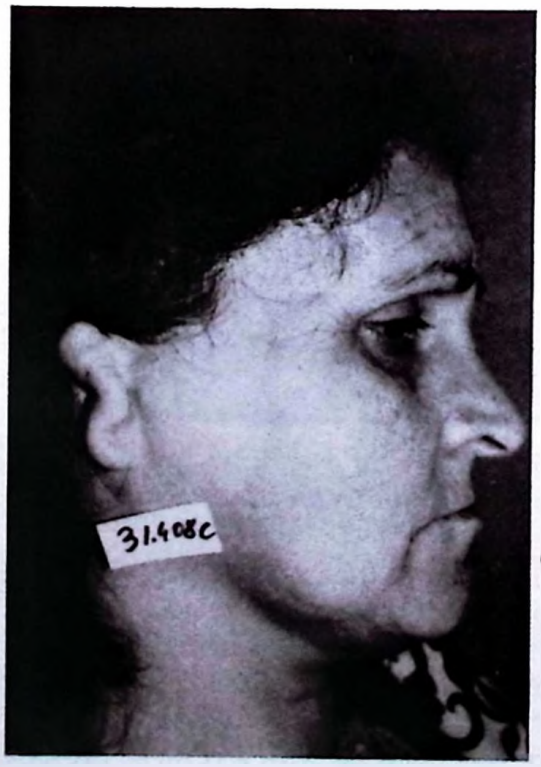

Fig. 5. The right-sided microtia of the paternal grandmother (Case III-3).

Orstavik et al.[3] reported right-sided microtia and conductive hearing loss with variable expressivity in three generations, and they suggested autosomal dominant inheritance as in our family. In our family the father had a slightly malformed ear cup, but his mother had unilateral right-sided microtia and meatal atresia and his son had bilateral microtia and meatal atresia. All three cases were affected in varying severity, confirming the autosomal dominant mode of inheritance with variable expression. At the same time, examples of transmission from mother to son, from father to son and from mother to daughter can all be seen within the same family, and this has not been reported before.

The fourth case in this family was the maternal grandmother of Case III-3. We could not obtain any photograph of her but she was said to have right-sided microtia and meatal atresia, as her granddaughter. However, her daughter was not affected and she had normal ears. Thus, the ear malformation in this family shows incomplete penetrance as well as variable expression. Generation skipping is another property of autosomal dominant diseases.

In a collaborative study, Castilla et al.[10] reported an incidence of syndactyly in 174 of 599,109 consecutive newborn infants (3 per 10,000). In 133, syndactyly was the only diagnosed anomaly. The most common type was isolated syndactyly of toes 2 and 3, the second most frequent form was isolated syndactyly of fingers 3 and 4, and the third was isolated syndactyly of toes 4 and 5[10]. All three fall into the category of type I syndactyly. However, association of type I syndactyly with microtia has never been reported previously.

Consequently, this is an interesting family with regard to the mode of inheritance of microtia and its association with type I syndactyly. In every case of microtia a detailed family history should be taken to determine other members of the family who might have milder or different forms of malformation. While doing so, one must keep in mind that generation skipping and variable expressivity are frequently seen in inheritance of familial microtia and external canal atresia. Awareness of this is also crucial for genetic counselling of these families.

REFERENCES

1. Mastroiacovo P, Corchia C, Botto LD, Lanni R, Zampino G, Fusco D. Epidemiology and genetics of microtia-anotia: a registry based study on over one million births. J Med Genet 1995; 32: 453-457.
2. Jones KL. Smith's Recognizable Patterns of Human Malformations (5th ed). Philadelphia: W.B. Saunder's Company; 1997: 804-805.
3. Orstavik KH, Medbo S, Mair IW. Right-sided microtia and conductive hearing loss with variable expressivity in three generations. Clin Genet 1990; 38: 117-120.
4. Strisciuglio P, Ballabio A, Parenti G. Microtia with meatal atresia and conductive deafness: mild and severe manifestations within the same sibship. J Med Genet 1986; 23: 459-460.
5. Balcı S. Familial microtia with meatal atresia in father and son. Turk J Pediatr 1974; 16: 140-143.
6. Okajima H, Takeichi Y, Umeda K, Baba S. Clinical analysis of 592 patients with microtia. Acta Otolaryngol Suppl (Stockh) 1996; 525: 18-24.
7. Ellwood LC, Winter ST, Dar H. Familial microtia with meatal atresia in two sibships. J Med Genet 1968; 5: 289-291.
8. Dar H, Winter ST. Familial microtia and meatal atresia. J Med Genet 1973; 10: 305-306.
9. Schmid M, Schroder M, Langenbeck U. Familial microtia, meatal atresia, and conductive deafness in three siblings. Am J Med Genet 1985; 22: 327-332.
10. Castilla EE, Paz JE, Orioli-Parreiras IM. Syndactyly: frequency of specific types. Am J Med Genet 1980; 5: 357-364.

A new case of Balcı's syndrome (corneal opacity, microphthalmia, microcephaly, mental retardation, and generalized muscular spasticity associated with congenital heart disease)

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SUMMARY: Balcı S, Demirçeken FG, Öcal B, Zorlu P, Teziç T. A new case of Balcı's syndrome (corneal opacity, microphthalmia, microcephaly, mental retardation and generalized muscular spasticity associated with congenital heart disease). Turk J Pediatr 2001; 43: 366-368.

The association of corneal opacity, microphthalmia, microcephaly, mental retardation, and generalized muscular spasticity with hyperglycinemia was presented for the first time by Balcı and colleagues in 1974. After this report, some similar cases in the literature were referred to as Balcı's syndrome. In this paper we describe a new case of Balcı's syndrome, a 2.5-month-old female patient with corneal opacity, microphthalmia, microcephaly, mental retardation, and generalized muscular spacticity. All of these findings are acceptable as Balcı's syndrome, and in addition she had congenital heart disease (ventricular septal defect) and renal anomalies. In this paper other syndromes associated with corneal opacity and mental retardation are discussed.

Key words: Balcı's syndrome, congenital heart disease, corneal opacity, mental retardation, microcephaly, microphthalmia.

Balcı et al.[1] first described a new autosomal recessive syndrome characterized by corneal opacity, microphthalmia, microcephaly, mental retardation and generalized muscular spasticity associated with hyperglycinemia in 1974. Similarly, an oculocerebral syndrome involving corneal opacity, microphthalmia, mental retardation and spastic cerebral palsy without any metabolic disorders was reported by Pinsky et al.[2] in 1965. After Balcı's report, similar cases were reported by Young et al.[3] in 1982, Siber[4] in 1984, Kaloustian et al.[5] in 1985, and Chenevix-Trench et al.[6] in 1986. We herein present a new case of Balcı's syndrome with additional findings of congenital heart disease.

Case Report

A 2.5-month-old female patient suffering from ocular abnormalities, cyanosis, mental and motor retardation and mild spasticity was admitted to our clinic. The patient was the sixth child of nonconsanguineous parents. The mother and the father were 40 and 38 years old, respectively. The family history revealed that the second male child died at seven days without any specific diagnosis, but he had problems of umbilical bleeding, generalized spasticity, and jaundice. The fifth male child died at seven years old with spasticity, and mental and motor retardation.

On admission the patient's weight was 3600 g (<5th percentile) and her length was 55 cm (10-25th percentile). The had circumference was 35 cm (<3rd percentile). The patient had an unusual and dysmorphic facial appearance. Cloudy corneas, and microphthalmia, and short philtrum, low-set ears and short neck were observed. She usually kept her eyes closed (Fig. 1). There was a III/VI° pansystolic murmur on the third left side intercostal space. She had Simian line bilaterally. There were coarse rales on the lung auscultation indicating an acute respiratory infection disease. All extremities showed mild stiffness.

On laboratory studies serum biochemical values and complete urine analysis were normal. Complete blood count revealed decreased

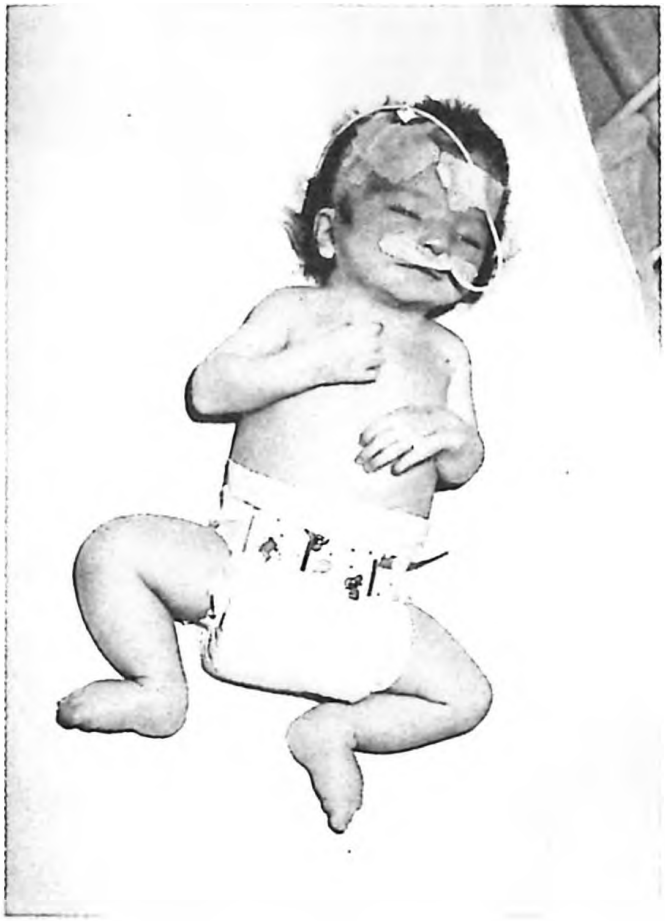

Fig. 1. Facial appearance of the patient showing bilateral diffuse corneal opacity, microphthalmia and generalized spasticity.

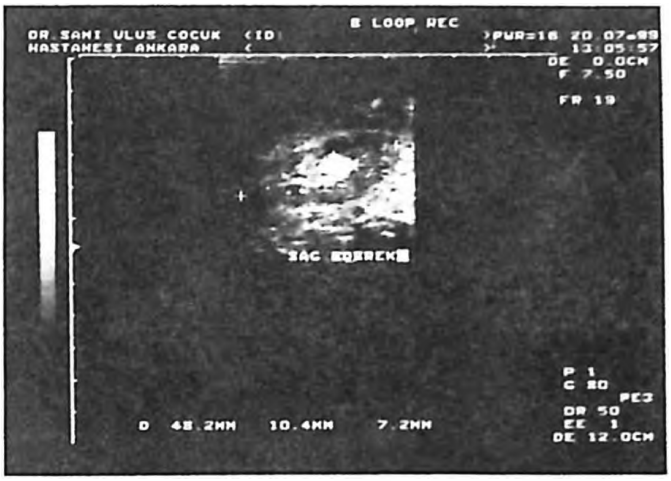

Fig. 2. Renal ultrasonography showing increased echogenicity on the right kidney.

hemoglobin concentration. Peripheral blood chromosome analysis was normal (46 XX pattern). Urine and blood amino acid chromatographic studies were normal at each analysis (three times). TORCH examination was negative. The chest X-ray showed lobar pneumonia on the right side and enlargement of the heart. Renal ultrasonography showed increased echogenicity fetal lobulation, and mild rotational anomalies in the pelvis of the right kidney (Fig. 2). Echocardiogram revealed ventricular septal defect pulmonary hypertension.

The patient died at three and a half months with pulmonary infection and heart failure.

Discussion

Balcı et al.[1] described a new autosomal recessive syndrome characterized by corneal opacity, microphthalmia, microcephaly, mental retardation, and generalized muscular spasticity associated with hyperglycinemia. Later, other entities with corneal opacities, microphthalmia, microcephaly, spastic quadriplegia, hypospadias, and cryptorchidism were reported in three males in two generations by Siber et al.[4], possibly suggesting X-linked recessive inheritance.

Table I shows that corneal opacities or cloudy corneas are associated with many congenital anomalies and syndromes. Diagnosis of this new syndrome is very important for genetic counseling for further pregnancies. Generally, cloudy corneas or corneal opacities occur together with central nervous system (CNS) abnormalities such as microcephaly, spastic quadriplegia, or spastic cerebral palsy, because the CNS and eye come from the same ectodermal origin. Corneal opacity is a very rare congenital eye malformation which can be included in many syndromes such as an oculocerebral syndrome (X-linked recessive) and spastic paresis, glaucoma, and mental retardation – a probable autosomal recessive syndrome (Table I). The chromosome analysis and urine-blood amino acids of our patient were normal, and intrauterine infections were ruled out. Unfortunately, the patient died and the family refused a postmortem examination. For the mother of our patient, there was a 25% risk of recurrence, and microcephaly could be detected in future by early and careful sonography. Our patient did not have any glycinuria or other aminoacidopathy, but she had the additional VSD and renal anomalies compared to previously reported Balcı's syndrome. The importance of this case was the

Table I. Summary of the Syndromes Associated with Corneal Opacity, Mental Retardation and Other Findings

Syndromes	Other findings	Mode of inheritance	References
Microphthalmia, corneal clouding, mental retardation and spasticity	Ventricular septal defect glycinuria	Autosomal recessive	Balcı et al.[1]
Microphthalmia, corneal opacity, mental retardation and spastic cerebral palsy-an oculocerebral syndrome	Mother had microphthalmia and three female offspring had corneal opacity	X-linked recessive	Pinsky et al.[2]
Keratoconus posticus circumscriptus, cleft lip and palate, genitourinary abnormalities, short statuse and mental retardation in sibs	Corneal opacities, retinal coloboma, ptosis, short stature, vertebral anomalies	Autosomal recessive	Young et al[3].
Microencephaly, microphthalmia with corneal opacities, spastic quadriplegia, hypospadias and cryptorchidism	Corneal opacities	X-linked recessive	Siber[4]
Familial spinocerebellar degeneration with corneal dystrophy	—	—	Kaloustian et al.[5]
Spastic paresis, glaucoma and mental retardation - a probable autosomal-recessive syndrome	Secondary cataracts, glaucoma	Autosomal recessive	Chenevix-Trench et al.[6]
Corneal opacity, microphthalmia, microcephaly, mental retardation, and generalized muscular spasticity - a new case of Balcı's syndrome	Ventricular septal defect, renal anomalies	Autosomal recessive	Balcı et al. (present case)

association with cloudy cornea, microphthalmia, microcephaly, spasticity, and VSD, all of which were compatible with Balcı's syndrome (corneal opacities, microphthalmia, microcephaly, and spasticity)[1]. Although there was no consanguinity between the parents, there were two sibling deaths in infancy. There were no known etiological factors in these siblings; however, they may have had the same entity. Furthermore, the presented patient was female, but non-living siblings were male. These points also suggested autosomal-recessive inheritance in spite of absence of consanguinity between the parents. Further studies of similar cases are needed to shed light on the problem. Determination of the mutant gene of this syndrome may be possible through molecular studies.

REFERENCES

1. Balcı S, Say B, Fırat T. Corneal opacity, microphthalmia, mental retardation, microcephaly and generalized muscular spasticity associated with hyperglycinemia. Clin Genet 1974; 5: 36-39.
2. Pinsky L, Digeorge AM, Harley RD, Baird HW. Microphthalmos, corneal opacity, mental retardation and spastic cerebral palsy. An oculocerebral syndrome. J Pediatr 1965; 67: 387-398.
3. Young ID, Macrae WG, Hughes HE, Crawford JS. Keratoconus posticus circumscriptus, cleft lip and palate, genitourinary abnormalities, short stature, and mental retardation in sibs. J Med Genet 1982; 19: 332-336.
4. Siber M. X-Linked recessive microencephaly, microphthalmia with corneal opacities, spastic quadriplegia, hypospadias and cryptorchidism. Clin Genet 1984; 26: 453-456.
5. Kaloustian VM, Jarudi NI, Mikati MA, et al. Familial spinocerebellar degeneration with corneal dystrophy. Am J Med Genet 1985; 20: 325-339.
6. Chenevix-Trench G, Leshner R, Mamunes P. Spastic paresis, glaucoma and mental retardation a probable autosomal recessive syndrome? Clin Genet 1986; 30: 416-421.

ERRATUM

Rapidly progressive bronchiectasis complicating ulcerative colitis in a child

İpek Türktaş, İlknur Bostancı, Buket Altuntaş

Turk J Pediatr 2001, 43: 369

On page 152 of the above-mentioned article, Figures 1 and 2 were duplicates. The following should replace Figure 1 published in that article. The Figure legend should remain as printed.

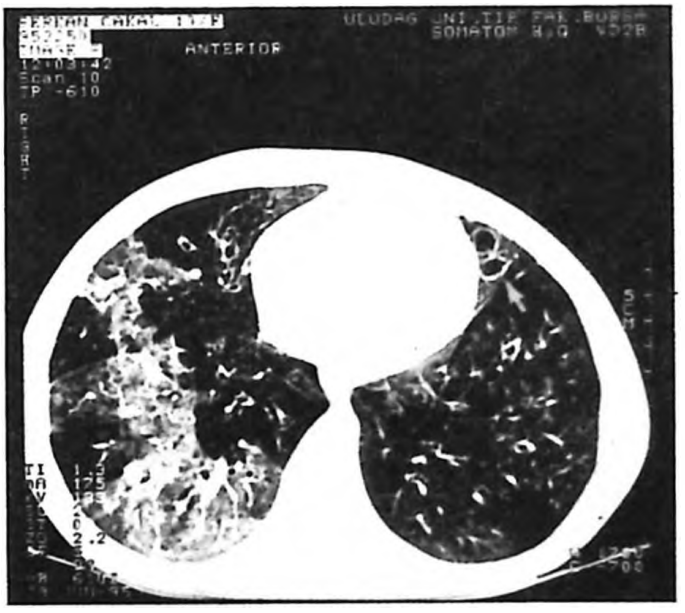

Fig. 1.

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