THE TURKISH JOURNAL OF PEDIATRICS

PUBLISHED BY
Turkish National Pediatric Society,
Hacettepe University
Institute of Child Health and
The Turkish and International
Children's Center

PRINTED IN
Meteksan Anonim Şirketi, Ankara

ISSN 0010-0161

This publication is included in the abstracting and indexing coverage of BIOSIS Previews, CAB Abstracts (Abstracts on Hygiene and Communicable Diseases, Public Health Bulletin, Tropical Diseases Bulletin), EMBASE/Excerpta Medica, IBIDS (International Bibliographic Information on Dietary Supplements), MEDLINE/ Index Medicus, MICROMEDEX for Health Care Series, Research Alert Direct (ISI), Science Citation Index Expanded (ISI), SERLINE and Turkish Medical Index.

EDITORIAL OFFICE
Prof. Dr. Turgay Coşkun
Editor
The Turkish Journal of Pediatrics
P.K. 66, Samanpazarı 06240 Ankara, Turkey
Fax: 90 (312) 324 32 84

SUBSCRIPTION ADDRESS
Prof. Dr. A. Murat Tuncer
Hacettepe University
İhsan Doğramacı Children's Hospital
06100 Ankara, Turkey
Fax: 90 (312) 324 32 84

THE TURKISH JOURNAL OF PEDIATRICS

VOLUME: 42 NUMBER: 2 APRIL - JUNE 2000

CONTENTS

ORIGINAL ARTICLES

CASE REPORTS

The frequency and etiology of anemia among children 6-16 years of age in the southeast region of Turkey

Ahmet Koç[1], Mustafa Kösecik[1], Hüseyin Vural[2], Özcan Erel[2], Ali Ataş[1], M. Mansur Tatlı[2]

[1]Department of Pediatrics, and [2]Department of Biochemistry, Harran University Faculty of Medicine, Şanlıurfa, Turkey

SUMMARY: Koç A, Kösecik M, Vural H, Erel Ö, Ataş A, Tatlı MM. The frequency and etiology of anemia among children 6-16 years of age in the southeast region of Turkey. Turk J Pediatr 2000; 42: 91-95.

The frequency and etiology of anemia were investigated in 2,913 children between six and 16 years of age in Şanlıurfa, in the southeast region of Turkey. Anemia was found in 142 (7.8%) children in the 6-11 years of age group, and in 16 (1.5%) in the 12-16 years of age group; in total, in 158 (5.4%) children. Causes were iron deficiency in 93 (58.9%) children, β-thalassemia heterozygosity in 10 (6.3%) children, chronic disease that causes anemia of inflammation in 30 (19.0%) children, and intestinal parasitic infections in 17 (10.8%) children. In eight (5.1%) children, the cause of anemia could not be determined. The study's results showed that iron deficiency anemia and chronic and parasitic disease are important problems in schoolchildren of Şanlıurfa, while β-thalassemia and hemoglobinopathies have less importance.

Key words: anemia, iron deficiency, inflammation, β-thalassemia trait, parasitic disease.

Anemia is a common problem in the world, and iron deficiency (ID) is the most common cause of childhood anemia in both developing and developed countries[1-5]. Recent studies have indicated a decline in the prevalence of childhood anemia in developed countries, probably due to improvements in iron nutrition during infancy and childhood[6,7]. But there has been little change in the worldwide prevalence[5,8,9]. Although iron deficiency anemia (IDA) is most frequenctly seen in infancy, it also been detected in school-age children and in adolescence and correlated with socioeconomic conditions[8,10,11]. Anemia of inflammation has also been shown frequently in childhood[7,12-14].

In this study, we investigated the prevalence and causes of anemia among 6-16 year-old children living in the province of Şanlıurfa, in the southeast region of Turkey.

Material and Methods

A cross-sectional study was performed in April and May of 1996, in Şanlıurfa. Subjects were selected using group sampling method from seven primary and six secondary schools in six different regions of the city. Two pediatricians first examined the students. Children with any acute illness were excluded because these diseases can affect the hematological status of children[7,12-14]. Capillary blood samples were taken from fingers and hematocrit (Hct) values were determined using the standard centrifugation technique. The following age specific values for Hct were used to define anemia: Hct < 35% for childtren six to 11 years of age; Hct < 36% for girls 12 to 16 years of age; and Hct < 37% for boys 12 to 16 years of age[15].

In the second step, children with anemia were investigated for its etiology. Complete blood counts were performed with automatic analyzer. Serum iron and iron binding capacity measurements were made with a commercial kit (Teca) with colorimetric methods, and transferrin saturation was calculated. Iron deficiency anemia was diagnosed if mean corpuscular volume (MCV) was lower than two standard deviations for ages (MCV < 77 fl for children 6-11 years of age, and MCV < 78 fl for children 12-16 years of age) and transferrin saturation was lower than 16 percent[15]. The remaining children were accepted as non-IDA (NIDA). Hemoglobin electrophoresis was done

with cellulose acetate electrophoresis method if MCV was lower than two standard deviations for ages[15]. Urine analyses and urine cultures for infection and renal diseases, stool examinations for ova and cysts of intestinal parasites, and benzidine tests for occult bleeding were done. Radiological, ultrasonographic and microbiologic investigations for determination of chronic infections were performed if needed. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured to determine undetectable infection or inflammation.

In the non-IDA group, children who had an infectious or inflammatory disease without other causes of anemia were diagnosed anemia of inflammation. If CRP and ESR were high even without any detectable infectious or inflammatory disease, these cases were also accepted as anemia of inflammation.

Statistical analyses were performed using the SPSS computer programs. Mean Hct values of different groups were compared using t test for unpaired samples; anemia rates were compared with chi-square test.

Results

A total of 2,913 children were investigated. The distribution of children and mean Hct values according to age and sex are presented in Table I. Anemia was present in 142 (7.8%) children in the 6-11 years of age group, and in 16 (1.5%) in the 12-16 years of age group; in total, in 158 (5.4%) children. While there were no important differences in mean Hct values and anemia frequency between girls and boys ($p > 0.05$ and $p > 0.05$), the differences between the two age groups were statistically important ($p < 0.001$ and $p < 0.001$).

Anemia was microcytic in 108 (68.4%), and normocytic in 50 (31.7%) children. IDA was the most common cause of anemia (58.9% of anemia cases). Heterozygous β-thalassemia was found in 10 (6.3%) anemic children. This rate constituted 0.4% of all children. Other hemoglobinopathies such as Hb S were not found (Table II).

Tablo II. Definable Causes of Anemia in Children

Disorders	Number of cases	Percentage (%)
Iron deficiency anemia	93	58.86
B-thalassemia trait	10	6.33
Chronic diseases	30	18.99
UTI	11	6.96
URI	8	5.06
LRI	1	0.63
Bronchial asthma	2	1.27
Cutaneous leishmaniasis	4	2.53
Unknown cause (ESR and CRP high)	4	2.53
Intestinal parasitic infections (without IDA)	17	10.76
Unknown origin	8	5.06
Total number	158	100

UTI: Urinary tract infection. URI: Upper respiratory tract infection. LRI: Lower respiratory tract infection. ESR: Erythrocyte sedimentation rate. CRP: C reactive protein. IDA: Iron deficiency anemia.

Occult blood was positive in the stool of 12 (7.6%) children with anemia (9 were IDA). Intestinal parasites were found in the stool examination of 34 (36.6%) children with IDA, and in 17 (26.2%) non-IDA children (Table III). Recurrent or chronic urinary tract infection (UTI) in 11 (7%) (8 girls, 3 boys) and chronic upper respiratory tract infection (URI) in 8 (5.1%) children were defined. Two children had asthma bronchiole and four children had cutaneous leishmaniasis (Table II).

Table I. Mean Hematocrit (Hct) Values of Children According to Age and Sex

Age	Total number	Mean Hct of girls (n)	Mean Hct of boys (n)	p value
6-11 years	1809	37.99±2.56 %(701)	38.0.2±2.35 %(1108)	p>0.05
12-16 years	1104	40.12±2.75 %(178)	40.54±3.05 %(926)	p>0.05
	2913	p<0.001	p>0.001	P value

Table III. Intestinal Parasites in Children with Anemia

Parasites	Parasite numbers in anemia groups IDA*	NIDA	Total	Percentage (%)
Ascaris lumbricoides	14	6	20	37.04
Trichuris trichiura	10	2	12	22.22
Hymenolepis nana	4	0	4	6.90
Entamoeba histolytica	5	7	12	22.22
Giardia intestinalis	4	2	6	11.11
Total	37 (68.52%)	17 (31.48%)	54	100

* Parasite number higher than number of children with parasitic diseases because of polyparasitism.

IDA : Iron deficiency anemia.
NIDA: Non iron deficiency anemia.

Discussion

Although the prevalence of iron deficiency anemia in childhood is lower in developed countries[6,7], it continues to be an important problem in other regions of the world[2,4,5,9,16]. Iron deficiency, with or without anemia, is the most common specific nutritional deficiency in infancy and childhood, even in some developed countries[3,4,17-19]. The results from many studies from Turkey also showed iron deficiency as the most important cause of anemia among preschool and schoolchildren in geographically and economically different regions[20-24]. Iron deficiency with or without anemia may cause impairment in growth, in mental and motor development and in cognitive function in infants and preschoolers, and can affect the attention span, learning and educational performance of schoolchildren[25-30]. It may also cause a deficit in work performance in adolescents and adults[2,31]. These alterations can be reversed with iron treatment[25,27,28].

Inadequate intake of iron is the most important causative factor, particularly when the body is in need of more iron than usual (e.g. during infancy, early childhood, adolescence)[8,17,24,29,32]. High fiber in diets may increase the incidence of iron deficiency anemia because its content of phytate and other inositol phosphates decreases the absorption of iron[29,33,34]. Hallberg et al.[35,36] reported that a high calcium content in meals inhibits the absorption of iron by interfering with the transport of iron through the mucosal cell.

Although IDA is most frequently seen in infancy, our results showed that it is also an important problem for the 6-11 years of age group. We think it is particularly associated with an inadequate intake of iron-rich food, and also with the high consumption rate of high fiber foods, such as eggplant, in this region. It is reported that the inhibitory effect of the phytate in food was overcome by adding different amounts of an ascorbic acid-rich vegetable to the meals[37]. So, this method, together with an increased consumption of iron rich or iron-fortified foods, can be used to prevent iron deficiency[38].

Numerous disease states such as acute and chronic infections, collagen vascular diseases, and traumatic and neoplastic illness can produce the anemia of inflammation[7,13,14,39]. Nineteen percent of children in this study had anemia of inflammation. The most frequent diseases were UTI, URI, and cutaneous leishmaniasis. Possible causes of the anemia of inflammation include decreased red cell life span, impaired reutilization of hemoglobin iron, relative erythropoietin deficiency or impaired responsiveness of bone marrow to erythropoietin, and ineffective erythropoiesis[13,39].

We found intestinal parasitic infection in 51 (32.3%) children with anemia (36.6% in IDA group, and 26.2% in NIDA group). Trichuris trichiura and Hymenolepis nana were especially more frequent in the IDA group than in the NIDA group (Table II). Many studies have shown that intestinal parasitic infections can affect the absorption of trace elements and can be causes of anemia[8,16,40,41]. The study results showed that parasitic infestations are important problems in the region.

The prevalence of β-thalassemia and hemoglobin S (Hb S) is high in the southern region of Turkey[5,42]. Although Şanlıurfa is geographically close to this region, Hb S was not detected, and the rate of β-thalassemia was lower, in only 6.33 percent of anemia cases. Alperin et al.[43] reported that Hb A_2 levels may be decreased in patients with thalassemia trait and IDA, in the case of severe IDA, but they also reported that the mean Hb A_2 levels of these patients were significantly greater than the mean percentage of Hb A_2 for normal subjects. Therefore, the probability of the rate of β-thalassemia trait having been altered by IDA in this study is small. Kılınc et al.[44] found that heterozygous β-thalassemia incidence was 0.6 percent in Şanlıurfa. Thus, the previous and present studies' results have shown that the Şanlıurfa region resembles East Anatolian cities

such as Erzurum[45] and Elazığ[46], rather than South Anatolian cities, for β-thalassemia heterozygosity and hemoglobinopathies.

Şanlıurfa has a low socio-economic condition, but the city is at the center of the Southeast Anatolia Project, Turkey's biggest agriculture and energy project. It is thus expected that important socioeconomic development will occur in the next ten years.

In conclusion, iron deficiency anemia and chronic and parasitic diseases are important problems in schoolchildren in the Southeast region of Turkey, but β-thalassemia and hemoglobinopathies have not been shown as significant problems.

Acknowledgement

The authors thank the manager of national education in Şanlıurfa for help with the study.

REFERENCES

1. Preziosi P, Hercberg S, Galan P, Devanlay M, Cherouvrier F, Dupin H. Iron status of a healthy French population: factors determining biochemical markers. Ann Nutr Metab 1994; 38: 192-202.
2. Cook JD, Skikne BS, Baynes RD. Iron deficiency: the global perspective. Adv Exp Med Biol 1994; 356: 219-228.
3. Taylor PG, Martinez-Torres C, Méndez-Castellano H, et al. The relationship between iron deficiency and anemia in Venezuelan children. Am J Clin Nutr 1993; 58: 215-218.
4. Agha F, Sadaruddin A, Khan RA, Ghafoor A. Iron deficiency in adolescents. JPMA J Pak Med Assoc 1992; 42: 3-5.
5. Kocak R, Alparslan ZNH, Ağrıdağ G, Başlamışlı F, Aksungur PD, Koltaş S. The frequency of anaemia, iron deficiency, hemoglobin S and beta thalassemia in the south of Turkey. Eur J Epidemiol 1995; 11: 181-184.
6. Yip R, Walsh KM, Goldfarb MG, Binkin NJ. Declining prevalence of anemia in childhood in a middle-class setting: a pediatric succes story? Pediatrics 1987; 80: 330-334.
7. Dallman PR, Yip R. Changing characteristics of childhood anemia. J Pediatr 1989; 144: 161-164.
8. Tatala S, Svanberg U, Mduma B. Low dietary iron availability is a major cause of anemia: a nutrition survey in the Lindi District of Tanzania. Am J Clin Nutr 1998; 68: 171-178.
9. Giebel HN, Suleymanova D, Evans GW. Anemia in young children of the Muynak District of Karakalpakistan, Uzbekistan: prevalence, type, and correlates. Am J Public Health 1998; 88: 805-807.
10. Irigoyen M, Davidson LL, Carriero D, Seaman C. Randomized, placebo-controlled trial of iron supplementation in infants with low hemoglobin levels fed iron-furtified formula. Pediatrics 1991; 88: 320-326.
11. Lanzkowsky P. Manual of Pediatric Hematology and Oncology (2nd ed). New York: Churchill Livingstone; 1995: 35-50.
12. Abshire TC, Reeves JD. Anemia of acute inflammation in children. J Pediatr 1983; 103: 868-871.
13. Abshire TC. The anemia of inflammation. A common cause of childhood anemia. Pediatr Clin North Am 1996; 43: 623-637.
14. Cemeroğlu AP, Özsoylu S. Haematologic consequences of viral infections including serum iron status. Eur J Pediatr 1994; 153: 171-173.
15. Lubin BH. Reference values in infancy and childhood. In: Nathan DG, Oski FA (eds). Hematology of Infancy and Childhood (4th ed). Philadelphia: W.B. Saunders Co; 1993: Appendix iii, vi.
16. Ramdath DD, Simeon DT, Wong MS, Grantham-McGregor SM. Iron status of schoolchildren with varying intensities of Trichuris trichiura infection. Parasitology 1995; 110: 347-351.
17. Atalah E. Analysis of the nutritional status of the population from Santiago. Rev Med Chile 1993; 121: 819-826.
18. Hallberg L, Hultén L, Lindstedt G, et al. Prevalence of iron deficiency in Swedish adeloscents. Pediatr Res 1993; 34: 680-687.
19. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. JAMA 1997; 277: 973-976.
20. Patıroğlu T, Özdemir MA, Hasanoğlu E. İlkokul çocuklarında anemi taraması. Çocuk Sağlığı ve Hastalıkları Dergisi 1987; 30: 315-319.
21. Teziç T, Gedik Y,Kumandaş S, Erduran E, Değer O. Trabzon merkez ve köylerindeki 12-17 yaş grubu demir eksikliği prevalansı. Çocuk Sağlığı ve Hastalıkları Dergisi 1990; 33: 209-218.
22. Yıldız S, Kocabay K, Özgür A, Güvenç H, Bektaş S. Elazığ Bölgesi ilkokullarında anemi-bağırsak paraziti sıklığı ve büyüme. Doğa Turk J Med Sci 1991; 15: 263-269.
23. Eroğlu Y, Hiçsönmez G. Hacettepe Üniversitesi Çocuk Hastanesi'nde anemi görülme sıklığı ve nedenleri. çocuk Sağlığı ve Hastalıkları Dergisi 1994; 37: 267-271.
24. Evliyaoğlu N, Kılınç Y, Serbest M, Atıcı A, Karabay A, Çetiner S. Çocukluk çağında demir eksikliği anemisi. MN Klinik Bilimler 1995; 1: 174-176.
25. Latham MC, Stephenson LS, Kinoti SN, Zaman MS, Kurz KM. Improvements in growth following iron supplementation in young Kenyan school children. Nutrition 1990; 6: 159-165.
26. Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. Am J Clin Nutr 1998; 68: 683-690.
27. Soewondo S. The effect of iron deficiency and mental stimulation on Indonesian children's cognitive performance and development. Kobe J Med Sci 1995; 41: 1-17.
28. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deeficient anaemic infants treated with iron. Lancet 1993; 341: 1-4.

29. Bushnell FK. A guide to primary care of iron-deficiency anemia. Nurse Pract 1992; 17: 68, 71-74.

30. Pollite E. Iron deficiency and educational deficiency. Nutr Rev 1997; 55: 133-141.

31. Small E, Bar-Or O. The young athlete with chronic disease. Clin Sports Med 1995; 14: 709-726.

32. Çetin M, Gönül A, Kara A, Kara SP, Yetgin S. Profile of bone marrow iron stores in childhood iron deficiency. Turk J Pediatr 1999; 41: 329-334.

33. Brune M, Rossander-Hultén L, Hallberg L, Gleerup A, Sandberg AS. Iron absorption from bread in humans: inhibiting effects of cereal fiber, phytate and inositol phosphates with different numbers of phosphate groups. J Nutr 1992; 122: 442-449.

34. Rossander-Hultén L, Gleerup A, Hallberg L. Inhibitory effect of oat products on nonhaem iron absorption in man. Eur J Clin Nutr 1990; 44: 783-791.

35. Hallberg L, Rossander-Hultén L, Brune M, Gleerup A. Inhibition of haem-iron absorption in man by calcium. Br J Nutr 1993; 69: 553-540.

36. Hallberg L, Rossander-Hultén L, Brune M, Gleerup A. Bioavailability in man of iron in human milk and cow's milk in relation to their calcium contents. Pediatr Res 1992; 31: 524-527.

37. Tuntawiroon M, Sritongkul N, Rossander-Hultén L, et al. Rice and iron absorption in man. Eur J Clin Nutr 1990; 44: 489-497.

38. Hurrell RF. Preventing iron deficiency through food fortification. Nutr Rev 1997; 55: 210-222.

39. Means RT Jr, Krantz SB. Progress in understanding the pathogenesis of the anemia of chronic disease. Blood 1992; 80: 1639-1647.

40. Sawaya AL, Amigo H, Sigulem D. The risk approach in preschool children suffering malnutrition and intestinal parasitic infection in the city of Sao Paulo, Brazil. J Trop Pediatr 1990; 36: 184-188.

41. Tanyüksel M, Sayal A, Aydın A. Paraziter hastalıklarda eser elementlerin düzeyleri. Türk Parazitoloji Dergisi 1995; 19: 315-321.

42. Yüreğir G, Aksungur P, Burgut R, Solakoğlu A, Atalay Ö, Aksoy M. A survey of high A_2 beta thalassemia, hemoglobin variants, G6PD deficiency and iron deficiency anemia in Karataş, Çukurova, Southern Turkey. Doğa Turk J Med Sci 1989; 13: 203-210.

43. Alperin JB, Dow PA, Pettawy MB. Hemoglobin A_2 levels in health and various hematologic disorders. Am J Clin Pathol 1977; 67: 219-226.

44. Kılınç Y, Tanyeli A, Serbest M, et al. Hemoglobin disorders in southern part of Turkey. XIIIth Meeting of the International Society of Haematology, 3-8 September 1995, İstanbul, Türkiye. Abstract Book: 760.

45. Kürkçüoğlu M, Dağcı A, Gençelli Y, Arcasoy A, Ağbaş A. Doğu Anadolu bölgesi'nde beta-thalassemia ve anormal hemoglobin taraması. Doğa TU Tıp ve Eczacılık Dergisi 1986; 10: 318-325.

46. Koç A, Kocabay K, Öncü T, Güvenç H, Aygün D, Bektaş S. Elazığ yöresinde beta talasemi taşıyıcılığı ve anormal hemoglobin taraması. T Klin Pediatri Derg 1993; 2: 70-71.

Alternative diagnostic method for streptococcal pharyngitis: Breese scoring system

Betül Ulukol[1], Ayla Günlemez[1], Derya Aysev[2], Şükrü Cin[1]

[1]Department of Pediatrics, and [2]Department of Microbiology, Ankara University Faculty of Medicine, Ankara, Turkey

SUMMARY: Ulukol B, Günlemez A, Aysev D, Cin Ş. Alternative diagnostic method for streptococcal pharyngitis: Breese scoring system. Turk J Pediatr 2000; 42: 96-100.

This study was performed to determine the effectiveness of the Breese scoring system for the diagnosis of streptococcal pharyngitis with respect to different age groups. Two hundred and two children aged three years and younger (Group 1), and 514 children over three years old (Group 2) with complaints of acute pharyngitis were evaluated by Breese scoring and throat-swab cultures. In Group 1, no significant difference was detected in Breese scoring between subjects who had positive and negative culture for group A β-hemolytic streptococci (GABHS). However, in Group 2 the mean value of the Breese scores was found to be higher in subjects who had positive GABHS. The diagnostic value of Breese scoring was examined for each group. Its sensitivity, and positive and negative predictive values were higher in Group 2 than in Group 1. In conclusion, Breese scoring was determined to be helpful in the diagnosis of streptococcal pharyngitis in children over three years of age.

Key words: Breese scoring, diagnosis, streptococcal pharyngitis.

Group A beta-hemolytic streptococci (GABHS) are considered the most likely bacterial pathogens in children with symptomatic pharyngitis. Nevertheless, there are still many diagnostic and therapeutic problems concerning streptococcal pharyngitis. The principal importance of this medical condition is related to its suppurative complications such as parapharyngeal or retropharyngeal abscess, bronchopneumonia, and meningitis, and nonsuppurative complications such as rheumatic fever and glomerulonephritis. Accurate diagnosis of GABHS infection requires the taking of a throat-swab culture[1-3]. In cases where a throat-swab culture is unavailable due to technical insufficiency for throat culture or results of a culture cannot be awaited for 18 to 24 hours, differential diagnosis of GABHS is achieved through rapid antigen tests and the observation of clinical signs and symptoms[3-5].

The prevalence of GABHS varies considerably, but has been found to range from 15-20 percent in healthy school children. The observed prevalence depends on the season, sampling method, age group, and socioeconomic and other environmental factors[6]. In Turkey, Aysev[7] found that beta-hemolytic streptococci colonization was 14.0-17.6 percent in different age groups of asymptomatic children. In other studies, Özsan et al.[8] and Gülmezoğlu[9] found that beta-hemolytic streptococci colonization was 8.2-16.7 percent in throat cultures of healthy Turkish children. Microbiological evaluation of all patients with signs and symptoms of upper respiratory infections with throat-swab culture or rapid antigen test may frequently be impossible due to technical insufficiency and high cost. Therefore, clinical diagnosis of streptococcal pharyngitis is more important.

In 1977, Breese[4] developed the nine-factor scoring system which includes complaints, and clinical and laboratory data for tentative diagnosis of GABHS pharyngitis. Because clinical signs and symptoms of streptococcal pharyngitis are different in early childhood[5,10,11], it is difficult to achieve a reliable clinical diagnosis in different age groups using the Breese scoring system.

This study was carried out to determine the significance of the Breese scoring system in diagnosing streptococcal pharyngitis and to evaluate its effectiveness in different age groups.

Material and Methods

Seven hundred and sixteen children with signs and symptoms of upper respiratory infections such as fever, sore throat, cough, pharyngeal abnormality or rhinorrhea who admitted to Ankara University Hospital Out-patient Department of Pediatrics were enrolled in the study. All the patients were clinically diagnosed as having tonsillopharyngitis. Children with acute otitis media and sinusitis were excluded from the study group. The research population was divided into two age groups. Group 1 consisted of children aged three and below. Group 2 comprised children over three years of age. They were then assessed using both the Breese scoring system and throat-swab cultures. The two groups were compared using the Breese scores and GABHS-positivity in throat cultures.

The nine factors utilized in the Breese scoring system are as follows:

1. month of presentation, 2. age, 3. white blood cell (WBC) count, 4. degree of fever, 5. sore throat, 6. cough, 7. headache, 8. abnormal pharynx, and 9. abnormal cervical glands. The patients' signs and symptoms were scored as present (yes), absent (no), unknown or certain levels of these nine factors by the physicians as shown in Table I. The total of all items was accepted as the Breese score of the patient. A few simple rules for the scoring system have been established. For a symptom or sign to be listed as "yes", it should have developed concurrently with the onset of the present illness. The presence of moderate or intense redness or swelling, exudate, petechial bleeding, or ulceration of the throat should always be counted as symptomatic of an abnormal pharynx. The "abnormal cervical glands" are the submandibular or anterior cervical lymph nodes that drain the tonsillar area. They are considered abnormal if they are swollen (larger than 2x2 cm) without being tender or if they are palpable and tender. The presence of rhinorrhea and abdominal pain was also investigated, but these items were not included as factors in the scoring system. The study group was divided into two age groups because clinical manifestations and expressions of complaints are different in early childhood.

The thorat-swabs were smeared on sheep's blood agar plate for the identification of GABHS on throat. The bacitracin and trimethoprim sulfamethoxazole sensitivity tests were used for diferentiating group A beta-hemolytic-strains from non-group A strains.

Table I. Breese Scoring System* for Diagnosis of Pharyngitis due to Group A Beta-Hemolytic Streptococci

	Scores		Scores
1. Season of Year		5. Cough	
February, March, April	4	Yes	2
December, January, May	3	No or unknown	4
June, October, November	2		
July, August, September	1	6. Headache	
		Yes	4
2. Age (Years)		No or unknown	2
5-10	4		
4, 11-14	3	7. Sore Throat	
3, ≥ 15	2	Yes	4
2 ≤	1	No or unknown	2
3. WBC/mm^3		8. Abnormal Pharynx	
≤ 8,400	1	Yes	4
8,500-10,400	2	No	1
10,500-13,400	3	Unknown	3
13,500-20,400	5		
≥ 20,500	6	9. Abnormal Cervical Glands	
Not done	3	Yes	4
		No	2
4. Fever ≥ 38 °C		Unknown	3
Yes	4		
No or unknown	2		

* Breese BB, American Journal of Disease in Childhood, 1977; 131: 514-517.

In both groups, the diagnostic value of the Breese scoring system was determined by comparison with the results of the throat-swab cultures, which were accepted as the reference tests. Breese found that more than 50 percent of the population with positive cultures had a minimum score of 30 and suggested that a minimum of 30 points was enough for the diagnosis of streptococcal pharyngitis[4]. In this study the minimum score for more than 50 percent of the children with streptococcal pharyngitis was 31, but the mean of the Breese scores of all children with positive cultures was 30 points. Therefore, the lowest definitive score for positive diagnosis of streptococcal pharyngitis was accepted to be 30 points as suggested by Breese.

The statistical evaluation of the data was performed using chi-square and student's t tests.

Results

Two hundred and two of the 716 children with tonsillopharyngitis were from Group 1 and 514 were from Group 2. Group 1 consisted of 91 girls

and 111 boys. Group 2 comprised 231 girls and 283 boys. The mean age of the children in Group 1 was 1.9 ± 0.1 years (range: 6 months-3 years) and in Group 2 was 7.4 ± 1.7 years (range: 4-17 years).

The percentage of children diagnosed GABHS-positive as a result of throat-swab cultures was 17.8 percent in Group 1 and 31.3 percent in Group 2. The difference between the two groups in terms of GABHS-positivity was statistically significant ($p < 0.001$).

The Breese scores were between 18 and 33 in Group 1, and 20 and 37 in Group 2. The mean scores of the GABHS-positive children were 25.6 ± 0.6 in Group 1 and 30.7 ± 0.5 in Group 2. This difference between the two groups was statistically significant ($p < 0.0001$).

In Group 1, there was no difference between the mean Breese scores of GABHS-positive and negative children. In Group 2, the mean Breese scores were higher in GABHS-positive than in GABHS-negative children (Table II). The relationship between the Breese scores and GABHS-positivity was determined in both age groups (Table III).

The diagnostic value of the Breese scoring system in Group 1 was: sensitivity, 25.0 percent; specificity, 90.9 percent; positive predictive value, 37.5 percent; and negative predictive value 84.8 percent; and in Group 2: sensitivitiy, 76 percent; specificity, 66.9 percent; positive predictive value, 51.3 percent; and negative predictive value, 86.1 percent.

All the factors included in this study were evaluated in terms of their ability to indicate GABHS as a factor in pharyngtis (Table IV). In Group 1, coughing is the only factor that was observed more frequently than the others. This difference was statistically significant. In Group 2, fever, sore throat, hedache, abdominal pain, and enlarged (abnormal) cervical glands were frequently observed in GABHS-positive children, while coughing and rhinorrhea were frequently observed in GABHS-negative children. There was no difference in the mean of the WBC counts of the two age groups, but in the GABHS-positive children aged three years and above, the mean of the WBC count was higher. A high frequency of GABHS-positive cases was found in September, October, November, December, February, and March of the year of this study.

Table II. Comparison of Mean Breese Scores According to Results of Throat-Swab Culture

	GABHS-positive		GABHS-negative		
Groups	Patients (%)	Breese Score X ± SE	Patients (%)	Breese Score X ± SE	Total n-%
Group 1 ≤ 3 years	17.8	25.6 ± 0.6[a]	82.2	24.5 ± 0.2[a]	202-100.0
Group 2 > 3 years	31.3	30.7 ± 0.5[b]	68.7	27.9 ± 0.1[b]	514-100.0
Total	27.5	29.6 ± 0.3[c]	72.5	26.3 ± 0.2[c]	716-100.0

a: $p > 0.05$; b: $p < 0.0001$; c: $p < 0.0001$.

Table III. Relation of Scores to Assigned Streptococcal Diagnosis and Accuracy of Such Diagnosis in Both Age Groups

	Group 1		Group 2	
Breese score	No. of patients (n)	GABHS-positive patients (n-%)	No. of patients (n)	GABHS-positive patients (n-%)
15-19	3	0-0.0	0	0-0.0
20-24	102	14-13.7	49	5-10.2
25-29	73	13-17.8	225	33-14.7
Total 15-29	178	27-15.2	274	38-13.9
30-34	24	9-37.5	230	114-49.6
35-39	0	0-0.0	10	9-90.0
Total 30-39	24	9-37.5	240	123-51.3

Table IV. Results of Throat-Swab Cultures and Frequency of Signs and Symptoms in Both Age Group

	Group 1			Group 2		
	GABHS			GABHS		
Symptoms	Positive %	Negative %	P	Positive %	Negative %	P
Fever	69	53	NS	78	46	< 0.0001
Sore throat	22	28	NS	78	63	< 0.001
Headache	8	21	NS	65	46	< 0.001
Abdominal pain	6	8	NS	24	13	< 0.01
Cough	50	74	< 0.05	38	67	< 0.0001
Rhinorrhea	47	50	NS	17	39	< 0.0001
Hoarseness	8	8	NS	7	14	< 0.05
Abnormal cervical glands	19	30	NS	70	49	< 0.0001
WBC (/mm^3) (Mean)	10,409	9,768	NS	13,830	9,583	< 0.0001

NS: Not significant.

Discussion

A throat-swab culture is necessary for accurate diagnosis of streptococcal pharyngitis. Recently, a number of rapid diagnostic techniques have become available, allowing a diagnosis of infection due to GABHS within minutes. If the rapid antigen test is positive, treatment is initiated, but negative test results should be confirmed with a throat-swab culture[3,10-12].

Clinical diagnosis is a guide in deciding whether to perform a throat-swab culture or rapid antigen test[3-5]. In 1977, after evaluating 20,000 cases of acute respiratory illness in children, Breese described a scoring system for diagnosis of streptococcal pharyngitis. It was found that in 57.9 percent of the population with scores of 30 or above, the mean percentage of positive cultures was 77.6 percent. It was suggested that antibiotherapy should be given to children with a score above 30 points[4,5].

Streptococcal pharyngitis is rare in children younger than two years of age[6,11], and the symptoms of streptococcal pharyngitis may be different in early childhood[5,6,10]. Of note is that in young children one to three years of age with GABHS, upper respiratory infection may sometimes present with fever and serous rhinitis[10]. Moreover, younger children are often not able to specify their complaints such as dysphagia, headache and abdominal pain. Although age is one of the factors in the scoring system, this study reevaluated the Breese scoring system with two different age groups. In children aged three years and under (Group 1) with scores of 30 or more, the percentage of positive cultures, i.e., the positive predictive value and sensitivity of the scoring system, was very low. These results suggest that the Breese scoring system is not useful with younger children with upper respiratory infections. In Group 2 with scores of 30 or above, the positive predictive value was 51.3 percent and sensitivity was 76.4 percent. The negative predictive value of the scoring system was above 80 percent in both groups. Similarly, Funamura and Berkowitz[13] found the system to be most useful in predicting culture-negative patients (80% accurate) in a study of 892 patients at a teaching hospital.

When the relationship between the culture results and clinical findings was evaluated for each parameter (Table IV), only coughing implied that infection was not bacterial in the children three years of age and younger. However, in the older children, fever, abnormal lymph nodes, headache, sore throat, and abdominal pain implied streptococcal pharyngitis, while rhinorrhea and hoarseness indicated a non-bacterial etiology. These findings show that signs and symptoms of respiratory illness may be helpful for diagnosis of streptococcal pharyngitis in older children.

In conclusion, the Breese scoring system did not seem to be effective in the diagnosis of streptococcal pharyngitis in early childhood. However, in children over three years of age, this scoring system is useful for streptococcal pharyngitis, especially in deciding whether or not to take o throat-swab culture and in cases where there is no opportunity to take a culture and an immediate decision to start antibiotherapy should be made.

REFERENCES

1. Bell SM, Smith DD. Quantitative throat-swab culture in the diagnosis of streptococcal pharyngitis in children. Lancet 1976; 10: 61-63.
2. Klein JO. Diagnosis of streptococcal pharyngitis: an introduction. Pediatr Infect Dis J 1989; 8: 813-815.
3. Pichichero ME: Culture and antigen detection tests for streptococcal tonsillopharyngitis. Am Fam Physician 1992; 45: 199-205.
4. Breese BB. A simple scorecard for the tentative diagnosis of streptococcal pharyngitis. Am J Dis Child 1977; 131: 514-517.
5. Shulman ST. Streptococcal pharyngitis: clinical and epidemiologic factors. Pediatr Infect Dis J 1989; 8: 816-819.
6. Todd J. Streptococcal infections. In: Behrman RE, Kliegman RM, Arvin AM (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: WB Saunders Co; 1996: 750-760.
7. Aysev D. Okul çağı çocuklarında beta hemolitik streptokok görülme sıklığı. İlaç ve Tedavi Dergisi 1994; 7: 163-168.
8. Özsan K, İmamoğlu A, Bilgin Y, et al. Türkiye'de okul çocuklarında streptokok infeksiyonlarının kontrolü. Doğa Tıp ve Ecz Der 1987; 11: 282-
9. Gülmezoğlu E. Çocuk yaşlarda beta hemolitik streptokok infeksiyonları. Çocuk Sağlığı ve Hast Dergisi 1966; 9: 7-11.
10. McCarty JM. Streptococcal pharyngitis. In: Rakel RE (ed). Conn's Current Therapy. Philadelphia: WB Saunders Co; 1996: 224-226.
11. Arnold JE. Infections of the upper respiratory tract. In: Behrman RE, Kliegman RM, Arvin AM (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: WB Saunders Co; 1996: 1185-1198.
12. Bisno AL. Group A streptococcal infections and acute rheumatic fever. N Engl J Med 1991; 325: 783-788.
13. Funamura JL, Berkowitz CD. Applicability of a scoring system in the diagnosis of streptococcal pharyngitis. Clin Pediatr 1983; 22: 622-626.

Poststreptococcal reactive arthritis: clinical course and outcome in 15 patients

Gülendam Koçak, Ayten İmamoğlu, Hasan Ercan Tutar, Semra Atalay, Sadi Türkay

Division of Cardiology, Department of Pediatrics, Ankara university Faculty of Medicine, Ankara, Turkey

SUMMARY: Koçak G, İmamoğlu A, Tutar HE, Atalay S, Türkay S. Poststreptococcal reactive arthritis: clinical course and outcome in 15 patients. Turk J Pediatr 2000; 42: 101-104.

Patients with Group A beta-hemolytic streptococcal infection and articular disease, who do not fulfill the modified Jones criteria for diagnosis of acute rheumatic fever (ARF), have been classified as having poststreptococcal reactive arthritis (PSRA). We reviewed the clinical characteristics, laboratory findings and outcome of 15 patients with PSRA. None of these patients had clinical evidence of carditis. The pattern of joint involvement was variable and included arthritis in five patients and arthralgia in the remaining ten patients. Nine patients were treated with salicylates for one to 16 weeks; the others recovered spontaneously. Usually, the patients with arthralgia responded promptly to salicylates, while the response was poor in patients with arthritis. One patient with monoarthritis developed carditis nine months after his first arthritis attack. Another patient presenting with monoarthritis later had two additional episodes of poststreptococcal reactive arthralgia.

It seems there is a wide spectrum of poststreptococcal rheumatic diseases, and patients with PSRA are also at risk for cardiac disease; therefore, prophylatic antibiotic therapy should be considered in these patients.

Key words: poststreptococcal reactive arthritis/arthralgia, childhood.

Patients developing articular disease following group A beta-hemolytic streptococcal (GABHS) infection who do not meet the modified Jones criteria for diagnosis of acute rheumatic fever (ARF) are defined as poststreptococcal reactive arthritis (PSRA). PSRA is not a well-defined clinical entity as yet. Like ARF, patients with PSRA also have the risk of developing carditis. The objective of this study was to analyze the clinical course and laboratory features as well as the outcome of patients who had articular manifestations (arthritis or arthralgia) and evidence of streptococcal infection. It was also our aim to review the literature and to determine the risk for subsequent development of rheumatic heart disease.

Material and Methods

This is a retrospective study of 15 patients with a diagnosis of poststreptococcal reactive arthritis/arthralgia seen at the Children's Hospital of Ankara University. Between January 1995 and July 1998, 18 children were seen with a diagnosis of PSRA, but only 15 were available for follow-up; the others were excluded from the study. Eight of the patients were female; mean age was 8.8 years (range, 4 to 12 years). All had rheumatologic symptoms following a proven GABHS infection, but none of them fulfilled the modified Jones criteria for a diagnosis of ARF. None of them had a prior history of ARF or arthritis/arthralgia. Laboratory investigations were done for all patients, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antistreptolysin O titer (ASO), throat culture, and white blood cell count, and to some patients complements (C3, C4), antinuclear antibody, and rheumatoid factor. Chest roentgenogram and 12 lead electrocardiogram were performed in 11 patients and echocardiogram in four patients. Fourteen of 15 patients were outpatients; only one of them was hospitalized. Mean follow-up duration was 17 months (range 4 to 35 months).

Results

Demographic characteristics and clinical and laboratory findings of 15 patients are summarized in Table I. Throat culture and/or ASO titration (at the beginning of arthritis and 2 to 3 weeks after) revealed streptococcal infection in all patients; however, only ten of them had a previous history of sore throat. Among the ten patients with antecedent pharyngitis (one patient had scarlet fever), only three patients had received antibiotic therapy. None of these patients had clinical evidence of carditis, chorea, erythema marginatum or subcutaneous nodules. Duration between pharyngitis and joint symptoms varied from four days to 14 days (mean 8.8 days). The pattern of joint involvement was variable and included arthritis in five patients (4 monoarthritis, 1 polyarthritis) and arthralgia in the remaining 10 patients. Polyarthritis and polyarthralgia were migratory or additive in nature. Large joints, primarily the knees, were affected; ankle, wrist, and hip were the other major joints involved. Small joints of hands and only one had arthritis of the metacarpophalangeal joints. Septic arthritis was excluded by joint aspiration in one patient with monoarthritis (Case 9). Chest roentgenograms and electrocardiograms were normal in 11 children tested. Cardiac evaluation with echocardiogram was performed in four patients and found normal.

Throat culture was positive for GABHS in four of 12 children tested. Serial ASO titer was elevated in all patients (800 to 3200 Todd Unit). ESR was elevated in all patients (mean 66.5 mm/hr; range 40 to 120) and RP was positive in all children. Twelve of 15 patients had elevated white blood cell counts with relative neutrophilia. Complements (C3, C4) were in normal limits in four, and rheumatoid factor and antinuclear antibody were negative in 11 children tested. HLA B27 was negative in one child tested (Case 9).

Four patients who had positive throat culture were treated with penicillin. Nine patients were treated with salicylates for one to 16 weeks (mean 3.2 weeks); the others recovered spontaneously. Seven of the nine patients (most of them had arthralgia). recovered rapidly in a few days; however, two patients with arthritis responded slowly to aspirin, hence therapy was prolonged in these patients. The ESR remained elevated for a mean of 15.2 days, range six to 37 days. Six of 15 patients were put on penicillin prophylaxis.

One patient (Case 9) with monoarthritis developed carditis nine months after his arthritis attack. This 11-year-old boy initially presented with pain in his right hip without fever. He had pharyngitis and fever one week before arthritis, but did not receive antibiotic

Table I. Demographic, Clinical and Laboratory Findings of 15 Patients with PSRA

Patient	Sex	Age (years)	Articular involvement	Fever	Antecedent pharyngitis	Positive throat culture	ASO (TU)	ESR (mm/hr)	Theray (Aspirin)	Duration of recovery	Prophylaxis	Outcome
1	F	9	Arthralgia	–	+	+	1200	120	+	in a few days	+	–
2	F	9	Monoarthritis	+	+(Ab)	–	800	45	–	in a few days	+	–
3	M	4	Arthralgia	–	+	–	800	65	+	in a few days	–	arthralgia
4	F	7	Monoarthritis	+	–	+	800	40	+	4 weeks	–	–
5	F	6	Arthralgia	+	–	–	1600	87	–	in a few days	+	–
6	M	11	Arthralgia	–	–	ND	800	70	–	in a few days	–	–
7	F	7	Arthralgia	–	Scarlet fever	–	800	110	–	in a few days	–	–
8	M	12	Polyarthritis	–	+	–	800	46	+	5 weeks	+	–
9	M	11	Monoarthritis	–	+	–	800	110	+	in a few days	–	carditis
10	M	8	Arthralgia	–	+(Ab)	–	3200	45	+	in a few days	–	–
11	M	8	Arthralgia	–	–	+	800	58	+	in a few days	+	–
12	F	10	Arthralgia	–	–	ND	800	44	–	in a few days	–	–
13	F	10	Arthralgia	–	+(Ab)	+	800	50	+	in a few days	+	–
14	M	10	Arthralgia	–	+	ND	800	53	+	in a few days	–	–
15	F	11	Monoarthritis	–	+	–	800	55	–	in a few days	–	–

PSRA : poststreptococcal reactive arthritis.
F : female.
M : male.
(–) : absence.
(+) : presence.
Ab : received antibiotic therapy.
ND : not done.
ASO : antistreptolysin O titer.
ESR : erythrocyte sedimentation rate.

therapy. The throat culture revealed no pathogenic microorganism but ASO titer elevated in the course of time, suggesting antecedent GABHS infection. His cardiac evaluation was normal. He was initially considered as juvenile rheumatoid arthritis or PSRA and was started on therapy with aspirin (80 mg/kg/day). Arthralgia resolved rapidly but ESR remained high until the 28th day of therapy. Nine months after discharge he presented with fever and dyspnea. ASO titer was 1600 TU, ESR was 85 mm/hr, and CRP was 3 (+). Echocardiogram revealed carditis with mitral and aortic insufficiency. He was treated with prednisone and is now on penicillin prophylaxis. One year later, control echocardiogram was found normal. Another patient (Case 3) presenting with monoarthritis later had two additional episodes of poststreptococcal arthralgia. These two patients had not received prophylactic antibiotic therapy after their first attcks. The remaining 13 children had no further complications during the follow-up duration. Case 2, who also presented with monoarthritis, was the sister of Case 9, who developed carditis.

Discussion

In 1945, Rantz et al.[1] wrote that "... rheumatic fever is a part of the whole complex involved in the poststreptococcal state." Since then a lot of reports have revealed the broad spectrum of poststreptococcal rheumatic manifestations extending from ARF with or without carditis to poststreptococcal rheumatic syndrome with either arthriis or arthralgia and systemic symptoms[2-7]. It is known that poststreptococcal rheumatic symptos also include extraarticular clinical manifestations, such as vasculitis and polymyalgia[8,9].

In 1959, Crea and Mortimer[10] reported 18 cases who developed arthritis within The first 10 days after the onset of scarlet fever[10]. In the long term follow-up, a clinical presentation suggesting ARF developed in 10 of these patients. None of them had received penicilin prophylaxis. The authors concluded that "scarlatinal arthritis" is a part of the spectrum of ARF.

The term PSRA was first put forth by Goldsmith and Long[11] in a presentation to the American Rheumatism Association in 1982. They described 12 children with prolonged rheumatologic symptoms following a streptococcal infection. They reported that arthritis in their series persisted for 10 to 28 days (mean 20 days) and that most of the chidren had significant arthralgias for 25 to 150 days (mean 75 days). None of them had carditis. All patients were given aspirin but responded slowly; however, all eventually recovered completely. The authors separated this clinical entity form ARF because of unusually prolonged joint manifestations and poor response to aspirin. They suggested that this clinical progress resembled the reactive arthritis following certain enteric infections.

De Cunto[12] et al. Reviewed 12 chidren with PSRA/ arthralgia in 1988. As with the others, none of them had carditis, and none were gven prophylactic penicillin. One of these patients developed classic ARF (with mitral and aortic insufficiency) 18 months after the first arthritis attack. In addition, four of 12 children had recurrent attacks of arthritis/arthralgia. The authors pointed out the short duration between respiratory infection and joint symptoms (7-10 days) but, on the contrary, response to aspirin was good in their series. Fink[13] explained the role of the streptococcus in PSRA and said that it is a form of ARF, but differs by the early development of arthritis after pharyngitis, by the more prolonged arthritis or arthralgia and by a less dramatic response to aspirin.

We presented 15 patients with PSRA who had various clinical and laboratory findings. The period between pharyngitis and joint symptoms was shorter than that of ARF, which is compatible with the previous reports. Most had arthralgia and elevated acute phase reactants. Only one patient had migratory polyarthritis but had no other criteria for ARF. Four patients had monoarthritis which is not compatible with ARF. Fever was present in only three patients. ESR was high and ASO titers were also elevated in all the patients. Most of the patients with arthralgia responded promptly to salicylates. Only two of 15 patients in our series had a less dramatic response to aspirin, which is one of the important properties of PSRA reported previously.

There are may causes of acute arthritis in children, such as acute septic arthritis, viral arthritis, other reactive arthritis, acute onset rheumatic diseases such as juvenile chromic arthritis, and the other seronegative spondyloarthropathies. PSRA should be borne in mind in any patient presenting with acute onset

arthralgia or arthritis whether including one or more joint. Throat culture and serial serologic testing for GABHS should be performed immediately. The importance of accurate diagnosis is to provide long-term antibiotic prophylaxis to prevent recurrent attacks in RAF. Whether or not all patients with articular symptoms related to a GABHS infection should be started on penicillin prophylaxis remains an unanswered problem. Herold et al.[14] suggested that it is premature to advocate long term prophylaxis for all patients presenting with arthritis/arthralgia in association with a GABHS infection, and recommended individualized management for patients. On the other hand, previous reports have shown the risk for developing carditis in these patients in the follow-up period[12]. We also presented one patient who developed carditis nine months after his previous arthritis attack. The rate of recurrence in PSRA reported as 25-41 percent in the literature[7,12]. Only two of our nine patients who were not on penicillin prophylaxis presented with a recurrence of either arthralgia or carditis (22%). Thus, carditis developed in one (11%), whereas this was reported as eight percent in De Cunto' s series[12]. Hicks and Yim[15] reported the incidence of carditis in PSRA as 40 percent at the 1990 meeting of the American College of Rheumatology. Similarly, Kurahara[16] reported a rate of 35 percent for developing carditis in children with PSRA. In our opinion, this data justifies the use of prophylaxis.

Both ARF and PSRA occur after GABHS infection, but the precise relationship between them remains unclear. The pathogenesis of PSRA and related carditis is not well identified at present; perhaps it is an autoimmune disease such as ARF. It is also known that there is a genetic predisposition for development of ARF[17,18], and recent researches demonstrated genetic similarities in these two entities. Further research would possibly clarify the relationship between bacteria and host properties in disease expression, and the risk factors for developing carditis. Until these factors are determined, prophylactic antibiotic therapy will continue to be discussed in PSRA.

REFERENCES

1. Rantz LA, Boisvert PJ, Spink WW. Etiology and pathogenesis of rheumatic fever. Arch Intern med 1945; 76. 131-138.
2. Arnold MH, Tyndall A. Poststreptococcal reactive arthritis. Ann Rheum Dis 1989; 48: 686-688.
3. Powell RJ, Jenkins S. Poststreptococcal reactive arthritis. Ann Rheum Dis 1989; 49: 270-271.
4. Deighton C. Beta haemolytic streptococci and reactive arthritis in adults. Ann Rheum Dis 1993; 52: 475-482.
5. Schaffer FM, Agarwal R, Helm J, Gingell RL, Roland JM, O'Neil KM. Poststreptococcal reactive arthritis and silent carditis. A case report and review of the literature. Pediatrics 1994; 93: 837-839.
6. Moon RY, Greene MG,Rehe GT, Katona IM. Poststreptococcal reactive arthritis in children: a potential predecessor of rheumatic heart disease. J Rheumatol 1995; 22: 529-532.
7. Birdi N, Allen U, D'Astous J. Poststreptococcal reactive arthritis mimicking acute septic arthritis. A hospital-based study. J Pediatr Orthop 1995; 15: 661-665.
8. Utierrez-Urena S, Molina J, Molina JF, Garcia CO, Cuellar ML, Espinoza LR. Poststreptococcal reactive arthritis, clinical course, and outcome in 6 adult patients. J Rheumatol 1995; 22: 1710-1713.
9. Harats N, Gur H, Rubinow A. Acute poststreptococcal polymyalgia. Ann Rheum Dis 1986; 45: 47-49.
10. Crea M, Mortimer E. The nature of scarlatinal arthritis. Pediatrics 1959; 23: 879-884.
11. Goldsmith DP, Long SS. Poststreptococcal disease of children, a changing syndrome (abstract). Arthritis Rheum 1982; 25 (Suppl): 18.
12. De Cunto CL, Giannini EH, Fink CW, Brewe EJ, Person DA. Prognosis of children with poststreptococcal reactive arthritis. Pediatr Infect Dis J 1988; 7: 683-686.
13. Fink CW. The role of the streptococcus in poststreptococcal reactive arthritis and childhood polyarteritis nodosa. J Rheumatol 1991; 18 (Suppl): 14-20.
14. Herold BC, Shulman ST. Poststreptococcal arthritis. Pediatr Infect Dis J 1988; 7: 681-682.
15. Hicks R, Yim G. Poststreptococcal reactive arthritis (PSRA)-a manifestation of acute rheumatic fever (ARF) (abstract). Arthritis Rheum 1990; 33 (Suppl): 145.
16. Kurahara DK, Hicks R, Tanabe B, et al. Poststreptococcal reactive arthritis in Hawaii, and the presence of myosin antibodies. The Second World Congress of Pediatric Cardiology and Cardiac Surgery, Hawaii 1997; May 11-15: 162.
17. Zabriskie JB, Lavenchy D, Williams RC, et al. Rheumatic fever associated B cell alloantigens as defined by monoclonal antibodies. Arthritis Rheum 1985; 28: 1047-1051.
18. Ayoub EM, Barrett DJ, Maclaren NK, Krischer JP. Association of class II human histocompatibility leukocyte antigens with rheumatic fever. J Clin Invest 1986; 77: 2019-2026.

Clinical trial to evaluate immunogenicity and safety of inactivated hepatitis A vaccination starting at 2-month-old children

Güler Kanra[1], S. Songül Yalçın[2], Mehmet Ceyhan[1], Kadriye Yurdakök[2]

[1]Infectious Diseases Unit, Department of Pediatrics Faculty of Medicine, and [2]Department of Social Pediatrics, Institute of Child Health, Hacettepe University, Ankara, Turkey

SUMMARY: Kanra G, Yalçın SS, Ceyhan M, Yurdakök K. Clinical trial to evaluate immunogenicity and safety of inactivated hepatitis A vaccination starting at 2-month-old children. Turk J Pediatr 2000; 42: 105-108.

Active immunization with hepatitis A vaccine has been shown to provide long-term protection against hepatitis A virus (HAV) infection. However, few data are available regarding use of the hepatitis A vaccine in children under two years of age. The present study was conducted to test the safety and immunogenicity of inactivated hepatitis A vaccine administered to infants, and to evaluate the correlation between mother and infant anti-HAV antibodies. A total of sixty healthy children, two months of age, were enrolled in this study and immunized with 360 EU of inactivated hepatitis A vaccine (Havrix) according to the two, four and six months of age schedule. Blood sampling was performed prior to the first vaccination and one month after the third vaccination at seven months. Venipuncture was also done on mother on admission. The reactogenicity was expressed as the percentage of reported local and systemic reactions. The most common side effects were erythema on the injection site and fever. Infants with passively transferred maternal anti-HAV antibodies had a reduced anti-HAV GMT after vaccination. On admission, only one infant and his mother were seronegative and seroconversion was only detected in this infant. One month after the third dose seven infants (12.3%) were found to be seronegative. The infant without passively acquired maternal anti-HAV had the protective levels with a GMT of 3176 mIU/ml one month following the third dose. There was a significant positive correlation between the titers of mother and infant anti-HAV antibodies ($n = 0.96$, $p < 0.001$) on admission. Hepatitis A vaccine showed no immunogenicity in infants with presence of maternal antibodies. Hepatitis A vaccine is safe but it should be used after the disappearance of maternal antibodies.

Key words: hepatitis A, vaccine, immunogenicity, side effects, infant.

Until recently hygienic measures and passive immunization with immune globulin were used for preventing hepatitis A. However, these methods provide short-term protection, and infection was delayed to a period when morbidity and mortality of the disease are high. Active immunization with hepatitis A vaccine was shown to provide long-term protection against hepatitis A virus (HAV) infection[1]. The similarities between the epidemiology of hepatitis A and poliomyelitis suggest that widespread vaccination of an appropriate susceptible population can substantially lower disease incidence, eliminate virus transmission, and ultimately, eradicate infection. However, few data are available regarding the use of hepatitis A vaccine in children under two yers of age[2-4]. The present study was conducted to test the safety and immunogenicity of inactivated hepatitis A vaccine administered to infants in the second month of age, and to evaluate the correlation between mother and infant anti-HAV antibodies.

Material and Methods

The participants were recruited from infants seen at Hacettepe University İhsan Doğramacı Children's Hospital Well Baby Clinic from December 1996 to July 1997. Children between eight and 10 weeks of age, born after > 37 weeks of pregnancy with a birth weight greater than

2500 g and afebrile on the day of vaccination were included in the study. Infants with an acute or chronic illness or congenital abnormalities were excluded from the study. Informed written consent was obtained from the parents.

A total of sixty healthy children, two months of age (63 ± 5 days, 59-80 days) were enrolled in this study and immunized with 360 ELISA units (EU) of vaccine (Havrix, SmithKline Beecham Biologicals, Rixensart, Belgium, Lot: VHA185A2) according to a two, four and six months of age schedule. All vaccines were administered intramuscularly into the left deltoid muscle. In associated injections, DPT vaccine was injected on the right-hand side.

Vaccinees were monitored for immediate, early and late side effects. For the first 30 minutes after vaccination every child was observed for signs of anaphylaxis, wheezing and urticaria. For early side effects any local reaction (pain, redness and induration at the injection site), the rectal temperature, and any systemic reaction (drowsiness, loss of appetite, vomiting, diarrhea, and any other adverse events) were recorded by the parents on a diary card for seven days following each injection. Additionally, they were asked to record any adverse events and intercurrent illness requiring medical contact occurring between vaccination days. The reactogenicity was expressed as the percentage of reported local and systemic reactions. One infant did not receive the second injection and the mothers of two infants did not allow drawing of second blood samples. Pre- and post-vaccination blood samples were available for 57 infants.

Two blood samples were taken from the infant and one form the mother. Blood sampling was performed prior to the first vaccination and one month after the third vaccination at seven months of age. All samples were screened for anti-HAV antibodies using Enzymun-Test® Anti-HAV (Boehringer Mannheim Immunodiagnostics, Cat no: 354639). An antibody concentration of > 33 mIU/ml was considered protective. Statistical analysis was done using SPSS.

Results

On admission 58 mothers (98.3%) were found to be seropositive and one infant and his mother were seronegative. The infant without passively acquired maternal anti-HAV had the protective levels with a GMT of 3176 mIU/ml one month following the third dose. Seroconversion was detected only in this infant. Other infants with passively transferred maternal anti-HAV had a reduced anti-HAV GMT after vaccination (Table I). One month after the third dose seven infants (12.3%) were found to be seronegative.

Tablo I. Immunogenicity of 3-dose Inactivated Hepatitis A Vaccine in Infants

	No. of subjects	GMT, (range)*	No. of subjects with anti-HAV positive
Mother	59**	8649 (< 33-114,608)	58 (98.3)
Infants			
Prevaccination	60	2110 (< 33-25,543)	59 (98.3)
One month after the third vaccine	57	263 (50-3,176)	50 (87.7)

* mIU/ml.
** Since two infants were twins, there were 59 mothers for 60 infants.

There was a significant positive correlation between the titers of mother and infant anti-HAV antibodies ($r = 0.96$, $p < 0.001$) on admission. The regression line between HAV antibodies of mothers and two-month-old infants is given in Fig 1.

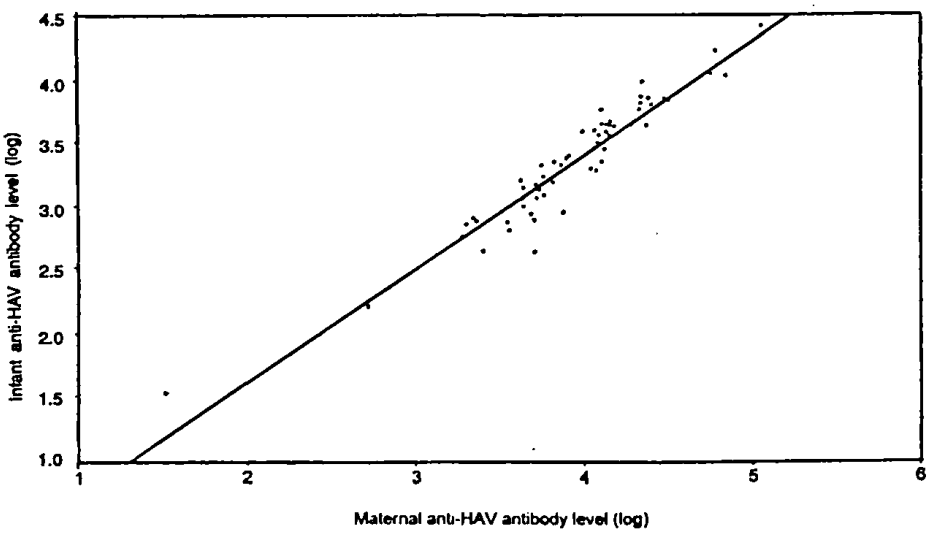


Fig. 1. The regression line between prevaccination levels of anti-HAV GMT levels in infants and anti-HAV GMT levels in their mothers (logarithmic scale) (r2 = 0.91, regression equation: y = 0.89x-0.17).

The most common side effects were erythema on the injection site (up to 6.7%) and fever (Table II). No serious adverse event was seen.

Table II. Number (%) of Infants with Local and General Side Effects within Seven Days After Vaccination

	Vaccination dose no		
	1	2	3
No of subjects	60	59	59
Local side effects			
Pain	–	2 (3.4)	1 (1.7)
Induration	–	3 (5.1)	1 (1.7)
Erythema	4 (6.7)	2 (3.4)	1 (1.7)
General side effects			
Fever ≥ 38.3 °C	2 (3.3)	2 (3.4)	2 (3.4)
Anorexia	–	–	2 (3.4)
Gastrointestinal symptoms (diarrhea, vomiting)	–	–	2 (3.4)
Subjects without side effects	55 (91.7)	54 (91.5)	56 (94.9)

Discussion

Changes in the epidemiology of HAV are evidenced by an increasing age of infection[5-6]. This shift in age of infection to older groups will increase the proportion of cases that cause clinical disease and may increase the case-fatality rate[1,6]. The case fatality rate among persons of all ages is approximately 0.3 percent. However, the case fatality rate is minimal in children aged 5-14 years (0.04%) and considerably higher in adults > 49 years old (2.7%)[1,7]. Although children are less likely than adults to be symptomatic with HAV infection, many children with unrecognized, asymptomatic infection can be a source of infection for others[1,8]. This makes it difficult or impossible to use active or passive immunoprophylaxis on a selective basis[1]. In addition, the availability of hepatitis A vaccine provides an opportunity to substantially lower disease incidence and eradicate infection because humans are the only natural reservoir of the virus[9-11]. As the severity of illness rises with age it is important to administer the vaccine to children and confer durable protection in order to avoid creating a pool of susceptible older subjects[1,5-7].

Few data are available regarding the use of hepatitis A vaccine in children under two years of age[2-4]. Piazza et al.[2] showed that infants vaccinated at five and 11 months of age (720 EU/dose) had 100 percent seroconversion rate. Results from another study indicated that among infants without passively acquired maternal anti-HAV who had been administered hepatitis A vaccine (360 EU/dose) at two, four and six months of age, 100 percent had protective antibody levels with GMT of 794 mIU/mL one month following the third dose[3]. They also reported reduced anti-HAV GMT in infants who had passively acquired antibody because of prior maternal HAV infection[3]. Similarly, in our study infants who were administered Havrix (360 EU/dose) at two, four and six months of age and whose mothers were anti-HAV positive had no response to the vaccination. So optimum immunization age should be determined for each country. Linder et al.[12] reported that protective HAV antibodies were present at birth in 48.3 percent of infants and that by the age of seven months only 13 percent of full-term infants still had protective titers. In our study 98.3 percent of infants by the age of two months had protective titers because of the high rate of maternal HAV seropositivity (98.3%).

In the present study hepatitis A vaccine showed no immunogenicity in infants because of the presence of maternal antibodies at the time of immunization. No severe or persistent side effect was seen among vaccinated children. Hepatitis A vaccine was safe, but it should be used after the disappearance of maternal antibodies. These patients should be followed up to a stage where passive immunity has been eliminated. At this point, a booster vaccination and the child's response to it will help us to evaluate the requirement of the number of vaccinations. This will pose a new model of mass immunization.

REFERENCES

1. Centers for Disease Control and Prevention. Prevention of hepatitis A through active and passive immunization: recommendation of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996; 45 (NO. RR-15).
2. Piazza M, Safary A, Vegnente A, et al. Safety and immunogenicity of hepatitis A vaccine in infants: a candidate for inclusion in the childhood vaccination programme. Vaccine 1999; 17: 585-588.
3. Shapiro CN, Letson GW, Kuehn D, et al. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants [Abstract H61]. In: 1995 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). American Society for Microbiology, 1995: 190.
4. Troisi CL, Hollinger FB, Krause DS, Pickering LK. Immunization of seronegative infants with hepatitis A vaccine (HAVRIX; SKB): a comparative study of two dosing schedules. Vaccine 1997; 15: 1613-1617.

5. Hadler S. Hepatitis A-changing epidemiology and the need for a vaccine. Virus and Life 1992; 2: 14-16.
6. Kane MA. Perspective on the control of hepatitis A by vaccination. Vaccine 1992; 10: S93-S96.
7. Papaevangelou G. Epidemiology of hepatitis A in Mediterranean countries. Vaccine 1992; 10: S63-66.
8. Smith PF, Grabau JC, Werzberger A, et al. The role of young children in a community-wide outbreak of hepatitis A. Epidemiol Infect 1997; 118: 243-252.
9. Horng Y, Chang M, Lee C, Safary A, Andre FE, Chen D. Safety and immunogenicity of hepatitis A vaccine in healthy children. Pediatr Infect Dis J 1993; 12: 359-362.
10. Innis BL, Snitbhan R, Kunasol P, et al. Protection against hepatitis A by an inactivated vaccine. JAMA 1994; 271: 1328-1334.
11. McMahon B, Beller M, Williams J, Schloss M, Tanttila H, Bulkow L. A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis A vaccine. Arch Pediatr Adolesc Med 1996; 150: 733-739.
12. Linder N, Karetnyi Y, Gidony Y, et al. Decline of hepatitis A antibodies during the first 7 months of life in full-term and pre-term infants. Infection 1999; 27: 128-131.

Hodgkin's disease and renal paraneoplastic syndromes in childhood

Münevver Büyükpamukçu[1], Volkan Hazar[2], Keriman Tınaztepe[1], Ayşın Bakkaloğlu[1], Canan Akyüz[1], Tezer Kutluk[1]

[1]Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, and [2]Department of Pediatrics, Akdeniz University Faculty of Medicine, Antalya, Turkey

SUMMARY: Büyükpamukçu M, Hazar V, Tınaztepe K, Bakkaloğlu A, Akyüz C, Kutluk T. Hodgkin's disease and renal paraneoplastic syndromes in childhood. Turk J Pediatr 2000; 42: 109-114.

The purpose of this study was to investigate children followed as having both Hodgkin's disease (HD) and nephropathy and discuss the factors which might play roles in the pathogenesis of this association by reviewing the pertinent literature. Our experience among 661 children with HD revealed ten cases (1.5%) with nephropathy; eight of these were biopsy proven. Tissue diagnoses were amyloidosis (AA type) in four cases, and membranoproliferative glomerulonephritis and minimal change glomerulopathy in two cases each. Sex distribution was equal. There was a predominance of the mixed cellular (MC) histologic type in our patients with HD. Nephropathy was shown to antedate the diagnosis of HD in two cases and to herald a relapse in one. In brief, the development of a nephropathy in a patient with HD can be considered as a paraneoplastic phenomenon. Renal amyloidosis may already be present at the time of diagnosis of HD and must be kept in mind as a cause of proteinuria due to preexisting nephropathy. Developing renal paraneoplastic syndrome, even in early-staged HD, in children, may be a poor prognostic factor.

Key words: nephropathy, paraneoplastic phenomenon, childhood, Hodgkin's disease.

A relation between cancer and nephropathy manifested primarily by the nephrotic syndrome (NS) was first described by Galloway[1]. The incidence of Hodgkin's disease (HD) associated nephropathy is very low[2,3]. Minimal change nephropathy (lipoid nephrosis) is the most common (80%) renal lesion in patients with HD, while membranous glomerulopathy, membranoproliferative glomerulonephritis (MPGN), and focal sclerosis have also been reported in the literature[4-9]. Amyloidosis, also a rare cause of NS occurs in one to four percent of HD[6,9,10].

The purpose of this study was to investigate children followed as HD and nephropathy in Department of Pediatric Oncology of Hacettepe University Hospital and to discuss the factors which might play roles in its pathogenesis.

Material and Methods

Between October 1970 and January 1995, we recorded 661 biopsy-proven and subtyped patients with HD according to Rye modification of Lukes-Butler classification[11]; most were treated with combined chemotherapy (COPP-cyclophosphamide, vincristine, procarbazine, prednisolone; ABVD-adriamycin, bleomycin, vinblastine, dacarbazine) and radiotherapy (low-dose involved-field, 20-25 Gy) in the Department of Pediatric Oncology of Hacettepe University Hospital. Among these patients, there were only 10 patients with HD and nephropathy. Complete blood count, routine urine analysis, blood urea nitrogen (BUN), creatinine, uric acid, serum total protein, albumin, lipid, cholesterol, and qualitative and/or quantitative urine protein loss were investigated. Brief information about patients with nephropathy associated with HD is provided hereunder.

Cases 1 and 2

A 10-year-old boy and his seven-year-old sister were referred to our center in 1973 with twenty-four-and thirty-month histories of hematuria,

edema, decrease in urine output and multiple lymphadenopathy. They were diagnosed as HD, unclassified and lymphocyte depletion subtypes, respectively. Membranoproliferative glomerulonephritis accompanied HD was shown in their renal biopsies taken during staging laparotomy for HD. At that time there was no proteinuria andrenal function tests were in normal limits. Although MOPP (nitrogen mustard, vincristine, procarbazine and prednisolone) chemotherapy regimens were diministered, they died due to progressive HD at the 60th and 72nd months of HD diagnosis, respectively.

Case 3

A 12-year-old girl was referred to our center in 1978 with a seven-year history of HD (MC subtype diagnosis) and treatment with cyclophosphamide, procarbazine and prednisolone. She was treated with radiotherapy and several MOPP chemotherapy regimens for sternum involvement, and axillary and inguinal relapses. In the 10th year of HD diagnosis, she complained of a decrease in urine output and edema. Her biochemical results were BUN 10 mg/dl, creatinine 0.5 mg/dl, Na 133 mEq/L, K 3.5 mEq/L, total protein 5.1 g/dl, albumin 2.8 g/dl, cholesterol 210 mg/dl (N: 110-190 mg/dl), and qualitative and quantitative protein loss in urine 2+ and 46 mg/h/m^2, respectively. Amyloidosis was revealed in the needle biopsy from kidney. She died in a short time after biopsy due to renal insufficiency.

Case 4

A 15-year-old-boy was hospitalized for bilateral enlarged cervical lymph nodes and pretibial edema in 1983. He was diagnosed as HD, lymphocyte predominance subtype, from cervical biopsy. After clinical staging he was stage II. His biochemical data were as follows: BUN 14 mg/dl, creatinine 0.5 mg/dl, Na 132 mEq/L, K 4.2 mEq/L, total protein 4.7 g/dl, albumin 1.8 g/dl, total lipid 1840 mg/dl (N: 400-900 mg/dl), cholesterol 380 mg/dl, and protein loss in urine qualitatively 3+ and quantitatively 41.6 mg/h/m^2. He was treated with cyclophosphamide, vincristine, procarbazine and prednisolone (COPP) and low-dose involved-field radiotherapy. He succumbed from varicella infection thirteen months after diagnosis of HD and NS while neither was in remission.

Case 5

A seven-year-old boy presented with bilateral cervical bulky mass and generalized edema in 1984. He had undergone biopsy from cervical mass at another health center and was reported as HD (MC subtype) one year before admission to our hospital. After histopathological confirmation and clinical staging investigations he was found to have stage II_B disease. The results of the biochemical analyses were as follows: BUN 10 mg/dl, creatinine 0.5 mg/dl, Na 131 mEq/L, K 3.2 mEq/L, total protein 4.6 g/dl, albumin 2.8 g/dl, total lipid 940 mg/dl, cholesterol 210 mg/dl, and quantitative protein loss in urine 4+. He was treated with COPP and low-dose involved-field radiotherapy. He was lost to follow-up eight months after HD diagnosis while both HD and NS were in remission.

Case 6

A 16-year-old boy was referred to our hospital in 1985 with the complaints of weight loss, fever, night sweating, diarrhea and abdominal pain. He had been given COPP chemotherapy regimen for HD, MC subtype, stage IV_B at another health center for two years, after which ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) regimen was started because of relapse. He was treated with ABVD and some other chemotherapy regimens including cisplatin, VP16, CCNU, prednisolone and mantle and inverted Y rediotherapy because of intractable systemic disease. At the 60th month of diagnosis, massive proteinuria (58.0 mg/h/m^2), hypoalbuminemia (2.6 g/dl), and edema developed. At that time, HD was localized on spleen only by radioimaging techniques. Amyloidosis accompanied with HD was shown in the specimens which were taken during splenectomy of abdominal lymph nodes, spleen, liver, and kidney. He died due to systemic disease 79 months after the diagnosis of HD.

Case 7

A six-year-old boy was admitted to our hospital in 1987 with loss of appetite, abdominal distension, and dyspnea. On his chest x-rays there was a mediastinal mass. He was diagnosed as HD (MC subtype) by thoracotomy. After clinical staging procedures, he was accepted as stage IV_A. At the time of diagnosis, his renal function tests were in normal limits. After COPP and low-dose involved-field radiotherapy he was in remission

but relapsed one year later. He was then given ABVD regimen. Proteinuria (qualitatively 4+, guantitatively 43.2 mg/h/m^2), hypoalbuminemia (2.0 g/dl), hypercholesterolemia (590 mg/dl) and edema developed 72 months after HD diagnosis as HD was in remission. Needle biopsy showed minimal change nephropathy. NS was successfully treated with short-term corticosteroid, but systemic relapse was later determined. High-dose chemotherapy with peripheral stem cell rescue was performed. He is alive without disease ten years from the time of HD diagnosis.

Case 8

A seven-year-old girl with a one-year history of cervical lymphadenopathy was admitted to hospital because of generalized edema in 1989. On her physical examination, a right cervical 3x2 cm lymph node and 2+ pretibal edema were determined. Excisional biopsy from cervical lymph node was reported as HD. MC subtype, including amyloid deposition. After clinical staging she was accepted as stage II_A. Her biochemical results were as follows: BUN 10 mg/dl, creatinine 0.5 mg/dl, Na 120 mEq/L, K 2.7 mEq/L, total protein 4.1 g/dl, albumin 1.0 g/dl, cholesterol 206 mg/dl, and protein loss in urine qualitatively 4+ and quantitatively 42.1 mg/h/m^2. She died within one month because of adrenal insufficiency. Amyloidosis was shown in necropsy materials from adrenal glands and kidneys.

Case 9

A seven-year-old girl was admitted to the hospital in 1989 with the complaints of fever, weight loss, a mass localized on the left paravertebral region and edema. On her examination there were bilateral multiple microlymphadenopathies, hepatosplenomegaly, left paravertebral mass (6x7 cm) and pretibial edema. Biochemistry analyses were BUN 10 mg/dl, creatinine 0.4 mg/dl, Na 129 mEq/L, K 2.8 mEq/L, total protein 6.0 g/dl, albumin 1.1 g/dl, cholesterol 314 mg/dl, and protein loss in urine qualitatively 3+, and quantitatively 35.8 mg/h/m^2. Renal needle biopsy demonstrated the presence of amyloidosis at the time of diagnosis. After biopsy from the mass she was treated with ABVD for the diagnosis of HD, nodular sclerosing subtype, stage IV_B. She was lost to follow-up 14 months after diagnosis while HD was in remission and NS in the active phase.

Case 10

A 15-year-old girl presented in 1989 with a history of fever, weight loss, dyspnea, cough and pretibial edema. Supraclavicular lymph node biopsy was reported as HD, MC subtype. Bilateral renomegaly was determined on abdominal ultrasonography. The results of the biochemistry were BUN 12 mg/dl, creatinine 0.7 mg/dl, Na 135 mEq/L, K 4.0 mEq/L, total protein 5.9 g/dl, albumin 1.8 g/dl, and spot urine protein/creatinine 4. Renal needle biopsy was performed and minimal change nephropathy was reported. After clinical staging she was stage IV_B and started on COPP regimen. She died due to neutropenic sepsis one month after diagnosis.

Results

Of 661 patients with HD, 10 patients with a median age of seven were determined to have associated renal pathology consisting of four amyloidosis, two minimal change nephropathy, and two MPGN. Two patients had nephrotic syndrome clinically but no renal biopsy was performed (Cases 4 and 5). The sex distribution was equal. While four patients were early-staged (stages I-II) HD, the others were advanced-staged (stages III-IV). Of 10 patients, only four had systemic symptoms for HD. While Cases 4, 9 and 10 had NS at the time of diagnosis. NS developed after diagnosis of HD in Cases 3, 5, 6, 7 and 8 (range 12-120 months). NS heralded the relapse in Case 7 who was previously in full remission; in Cases 1 and 2 NS had never been observed. All patients in the group in which nephropathy developed after the diagnosis of HD, except Case 7, had active HD at the beginning of nephropathy. Clinical and pathological features of the patients are shown in Table I.

Discussion

Tumors can produce signs and symptoms independent from tumor mass or metastases. These are collectively referred to as "paraneoplastic syndromes". Although association between HD and nephropathies is well-known, it is relatively rare. In a collection of more than 1,700 patients with HD in the literature only nine (0.5%) had nephropathy[12,13]. In our patients with HD, renal paraneoplastic syndromes were found in 1.5 percent. Although the most frequently seen renal pathology in patients with HD is reported as minimal change nephropathy (MCN) in the

Table I. Clinical and Pathologic Features of Hodgkin's Patients with Nephropathy

Case No.	Age (Years)-Sex (Onset of HD)	Type of HD	Stage	Onset of nephropathy* (months)	Type of renal pathology	Diagnostic approach	Follow up and end results (months)
1	10 M	UC	IV_A	-30	MPGN	Incisional biopsy	Exitus in 60 mo.
2	7 F	LD	IV_A	-24	MPGN	Incisional biopsy	Exitus in 72 mo.
3	5 F	MC	II_A	120	Amyloidosis	Needle biopsy	Exitus in 156 mo.
4	15 M	LP	II_A	0	NS	Clinical and Lab.	Exitus in 13 mo.
5	6 M	MC	II_B	12	NS	Clinical and Lab.	Lost to follop-up in 18 mo.
6	14 M	MC	IV_B	60	Amyloidosis	Incisional biopsy	Exitus in 79 mo.
7	6 M	MC	IV_A	72	MCN	Needle biopsy	Alive in 120 mo.
8	7 F	MC	II_A	12	Amyloidosis	Necropsy	Exitus in 1 mo.
9	7 F	NS	IV_B	0	Amyloidosis	Needle biopsy	Lost to follow-up in 14 mo.
10	15 F	MC	IV_B	0	MCN	Needle biopsy	Exitus in 1 mo.

LP : Lymphocyte predominance.
MC : Mixed cellularity.
UC : Unclassified.
MPGN: Membranoproliferative glomerulonephritis.
NS : Nodular sclerosing.
LD : Lymphocyte depletion.
MCN: Minimal change nephropathy.
NS : Nephrotic syndrome.
* Onset of nephropathy vs. onset of HD.

literature, in which the study population had both adult and pediatric patients, only two of eight biopsy-diagnosed cases in the presented pediatric series were observed as MCN[4,5,7]. It was thought that the defect in T lymphocyte function, known to be present in patients with HD, with the elaboration of proteases or lymphokines that alter the selectivity characteristics of the glomerular basement membrane, may play a role in the etiopathogenesis of MCN, although a scientific basis for such a scenario has not emerged[14,15]. It has also been postulated that loss of immunoregulatory functions of arachidonic acid metabolities contributes to the increased glomerular permeability[16]. Unfortunately, we did not study T lymphoycte functions or cytokines in our patients.

Independent of tumor mass or metastases, most patients with a variety of neoplastic diseases are exposed to continuous antigenemia such as tumor-associated antigens, reexpressed fetal antigens, viral antigens and so on[3,14]. These antigens stimulate antibody production and form circulating immune complexes and antiideotypic cryoimmunoglobulins. In many instances these immune reactants are deposited or formed in situ in the glomerular mesangium and capillary walls[8]. Thus glomerulopathies due to immune complexes occur. But NS may not always occur in renal paraneoplastic syndrome due to immune complexes in HD. We did not observe NS in our patients with MPGN. Electronmicroscopic studies were not done in our cases (Cases 1 and 2). Immunopathologic data of renal paraneoplastic cases were reported in detail by Tınaztepe et al[17-19].

Although there is no concensus that age, sex and stage of HD have a bearing on the appearance of renal paraneoplastic syndrome, some authors believe that prevalence of glomerulopathies during the course of HD is greater in males[7,20]. We found that neither age (range: 5-15), sex (5 male, 5 female) nor stage (from IA to IVB) had any predominancy in our patients. But as it is reported being more prone to develop in histologic type of mixed cellularity (MC), half of our patients whose type of HD was specified had MC subtype.

Nephropathy has been shown to antedate the diagnosis of HD or to herald a relapse as seen in our Cases 7, 8 and 9[20-22]. Though Egan and Lewis[3] mentioned that NS in association with HD was rather resistant to the usual modes of treatment of MCN. Case 7, in whom NS heralded a relapse, was treated using prednisolone with a good response. The other case of MCN was remitted by chemotherapy and radiotherapy.

Although amyloidosis is usually seen in nonmalignant diseases, it may accompany HD in childhood[6]. Amyloidosis shown in HD is secondary amyloidosis due to AA protein deposits[6,23]. Amyloid deposits seen in HD can occur in various organs and tissues throughout

the body as in renal cell carcinoma[24]. So one possible mechanism for amyloid production in HD may be one of those seen in renal cell carcinoma: the tumor cells either secrete an amyloidogenic substance or modify by partial proteolysis a serum precursor protein, serum amyloid A protein (SAA), into an amyloidogenic fragment[24]. A second and more likely mechanism involves a stimulus by the tumor to produce SAA protein by monocyte-phagocyte system. SAA is one of the most dramatic forms of acute phase reactants. The production of this protein is altered tremendously (increased greater than 1,000 fold) in response to some cytokines causing inflammation and necrosis[25,26]. Cytokines and acute phase proteins produced by Hodgkin's cells are well-known[27]. Consequently, it may be thought that many cytokines, playing a role in both production of acute phase proteins and inflammatory response, are stimulated to release by Hodgkin's cells. All of them may cause a stimulus to production of SAA protein. Although some authors believe Hodgkin's disease-associated amyloidosis is the consequence of a long-standing insufficiently treated disease, two of our patients were shown to have amyloidosis at the time of diagnosis of HD[9]. It may be that there is a correlation between the power of antigenic stimulation and formation of amyloidosis or that there is a factor contributing to the development of both amyloidosis and HD and appearing before the detection of HD.

Overall survial rates in our institution were 94.7 and 74.6 percent at 10 years for patients with HD without renal paraneoplastic syndrome in stages I-II and stages III-IV, respectively[28]. But seven of the patients with renal paraneoplastic syndrome secondary to HD, three of whom had early-staged HD, died. Therefore, renal paraneoplastic syndrome, even in an early stage, may be a poor prognostic factor.

In conclusion, the development of a nephropathy in a patient with HD can be considered as a paraneoplastic phenomenon. Its incidence is actually very low. Amyloidosis must be kept in mind as a cause of NS associated with HD. Although it is thought that Hodgkin's disease-associated amyloidosis is a consequence of long-standing HD, it may be seen at the time of diagnosis of HD, as in two of our patients. Developing renal paraneoplastic syndrome, even in early-staged HD, in children, may be a poor prognostic factor.

REFERENCES

1. Galloway J. Remarks of Hodgkin's disease. Br Med J 1922; 2: 1202-1205.
2. Ghosh L, Muehrcke RC. The nephrotic syndrome: a prodrome to lymphoma. Ann Intern Med 1970;72: 379-382.
3. Egan JW, Lewis EJ. Glomerulopathies of nekoplasia. Kidney Int 1977; 11: 297-306.
4. Lokich JJ, Garvanel EG, Moloney WC. Nephrosis of Hodgkin's disease. Arch Intern Med 1973; 132: 597-600.
5. Dabbs DJ, Striker LM, Mignon F, Striker G. Glomerular lesions in lymphomas and leukemias. Am J Med 1986; 80: 63-70.
6. Tınaztepe K. Renal amyloidosis in childhood. An overview of the topic with 25 years experience. Turk J Pediatr 1995; 37: 357-373.
7. Alpers CE, Cotran RS. Neoplasia and glomerular injury. Kidney Int 1986; 30: 465-473.
8. Norris SH. Paraneoplastic glomerulopathies. Semin Nephrol 1993; 13: 258-272.
9. Keur I, Krediet RT, Arisz L. Glomerulopathy as a paraneoplastic phenomenon. Neth J Med 1989; 34: 270-284.
10. Bunn PA Jr. Ridgeway EC. Paraneoplastic syndromes. In: Devita VT, Hellman S, Rosenberg SA (eds). Principles and Practice of Oncology. Philadelphia: JB Lippincott Co; 1993: 2026-2071.
11. Lukes RJ, Butler JJ, Hicks ED. Natural history of Hodgkin's disease as related to its pathologic picture. Cancer 1966; 19: 317-344.
12. Plager J, Stutzman L. Acute nephrotic syndrome as a manifestation of active Hodgkin's disease. Am J Med 1971; 50: 56-66.
13. Kramer P, Szoo W, Twiss EE. Nephrotic syndrome in Hodgkin's disease. Neth J Med 1981; 24: 114-119.
14. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T cell function. Lancet 1974; 2: 556-559.
15. Lagrue G. Xheneumo S, Branella A, Weil B. Lymphokines and nephrotic syndrome. Lancet 1975; 1: 271-272.
16. Clive DM, Stoff JS. Renal syndromes associated with non-steroidal anti-inflamatory drugs. N Engl J Med 1984; 310: 563-572.
17. Tınaztepe K, Doğruel N, Tınaztepe B. Nephritis associated with malignant lymphomas of children (abstract). XV[th] International Congress of Pediatrics. Current Topics in Pediatrics. Abstracts and Papers. New Delhi: 1977; 202.
18. Tınaztepe K, Doğruel N, Tınaztepe B. Çocukluk çağı malign lenfomalarına eşlik eden glomerülopati. Patoloji Bülteni 1976; 3: 216-226.
19. Say B, Çıtıpıtıoğlu B,Baykara E, Tınaztepe B. Renal amyloidosis and Hodgkin's disease in a child. Am J Dis Child 1968; 115: 607-610.
20. Shapiro CM, Vancer Laan BF, Jao W, Sloan DE. Nephrotic syndromes in two patients with cured Hodgkin's disease. Cancer 1985; 55: 1799-1804.

21. Korzets Z, Golan E, Manor Y, Schneider M, Bernheim J. Spontaneously remitting minimal change nephropathy preceding a relapse of Hodgkin's disease by 19 months. Clin Nephrol 1992; 38: 125-127.

22. Huisman RM, de Jong PE, de Zeeuw D. Nephrotic syndrome preceding Hodgkin's disease by 42 months. Clin Nephrol 1986; 26: 311-313.

23. Cohen AS, Conners LH. The pathogenesis and biochemistry of amyloidosis. J Pathol 1987; 151: 1-10.

24. Vannata PR, Silva FG, Taylor WE, Costa JC. Renal cell carcinoma and systemic amyloidosis. Hum Pathol 1983; 14: 195-201.

25. Rosenthal CJ, Franklin EC. Variation with age and disease of an amyloid A protein-related serum component. J Clin Invest 1975; 55: 746-753.

26. Benson MD, Scheinberg MA, Shirahama T, Cathcart ES, Skinner M. Kinetics of serum amyloid protein A in casein-induced murine amyloidosis. J Clin Invest 1977; 59: 412-417.

27. Diehl V, von Kelle C, Fonatsch C, Tesch H, Joecker M, Schaadt M. The cell of origin in Hodgkin's disease. Semin Oncol 1990; 17: 660-672.

28. Büyükpamukçu M, Atahan L, Çağlar M, Kutluk T, Akyüz C, Hazar V. Hodgkin's disease in Turkish children: clinical characteristics and treatment results of 210 children, Pediatr Hematol Oncol 1990; 16: 119-129.

Arylsulfatase A pseudodeficiency incidence in Turkey

Serap Emre[1], Meral Topçu[2], Mügen Terzioğlu[1], Yavuz Renda[2]

[1]Department of Medical Biology, and [2]Neurology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Emre S, Topçu M, Terzioğlu M, Renda Y. Arylsulfatase A pseudodeficiency incidence in Turkey. Turk J Pediatr 2000; 42: 115-117.

Pseudodeficiency (Pd) in arylsulfatase A (ASA) is a relatively frequent condition in healthy individuals. It produces a reduction in enzyme activity similar to that found in metachromatic leukodystrophy (MLD). A variable incidence of the Pd allele was found in different populations; it was 10-20 times higher than that of metachromatic leukodystrophy. Twelve of the 52 unrelated, healthy individuals were found to be heterozygous for the ASA Pd allele. In Turkey we estimated the incidence of the Pd allele as 11.5 percent. Out of 18 cases with MLD, one patient was found homozygous for the Pd allele and the other patient was found heterozygous. Turk J Pediatr 2000; 42: 115-116.

Key words: metachromatic leukodystrophy, arylsulfatase A, pseudodeficiency.

Metachromatic leukodystrophy (MLD, McKusick 250100) is a severe lysosomal storage disorder caused by deficiency of the lysosomal enzyme commonly known as arylsulfatase A (ASA) (E.C.3.1.6.1)[8]. Occasionally, low levels of urinary and/or leukocyte ASA activity, similar to those described for MLD, are found in apparently healthy individuals[5,10]. This condition is known as arylsulfatase A pseudodeficiency (ASA Pd). In most Pd cases, two A → G transitions, of which only the one destroying the polyadenylation signal is the cause of the lowered enzyme activity, are the common mutations[7]. Discrimination of MLD and pseudodeficiency based on ASA activity is diffucult and unreliable. This is a serious problem in carrier detection and prenatal diagnosis in MLD families who also carry a Pd allele. Detection of the Pd mutation by polymerase chain reaction (PCR) and Mae III cleavage is very rapid and reliable method[16].

The Pd allele is relatively frequent, with a variable incidence in different populations ranging from 6 to 23%, 6% in Denmark[16], 10% in Australia[13], and Israel[18], 12% in France[3], Spain[2], 13% in the United Kingdom[1], 10.1% in Italy[15], and 23% among the Jewish population from Yemen[18] and 6% in Poland[4].

The aim of the present study was to estimate the prevalence of the Pd allele in a sample of the normal Turkish population. A group of 18 patients are further examined for one mutation previously reported in exon 2[6,14].

Material and Methods

Detection of the Pd-allele: Fifty-two unrelated, healthy volunteers were used as DNA donors. DNA was isolated from peripheral leukocytes by the ammonium acetate salting out procedure[12].

Polymerase chain reaction was carried out using a modification of Salamon's procedure in which one set of primers is used alternatively to amplify the 301 bp fragment of the ASA gene[16]. PCR product was cleaved by IU Mae III in three hours at 55 °C. The bands were separated on a three percent agarose.

Exon 2 of the ASA was amplified by PCR with exon specific primers. The amplified fragment of 350 bp was digested with Mval according to the manufacturer's recommendations, and the products were analysed on a two percent agarose gel[6,14].

ASA activity measurements: ASA was assayed with q-nitrocatechol sulphate in sonicated leukocyte pellets as described by Lee-Vaupel and Conzelmann[9]. Protein was determined by the method of Lowry et al[11].

Results

Because measurement of ASA activity is one of the most frequently performed lysosomal

enzyme tests, the presence of pseudodeficiency mutations in a significant proportion of the population is important in the diagnosis of MLD.

There was a large variation in frequencies of the ASA pseudodeficiency alleles between the populations. The polyadenylation signal site mutation was found only among the Caucasian groups. Interestingly, this allele was found at a very low frequency in the Finnish population as compared to Noth American Caucasians and other European, Middle Eastern, and Australian populations.

In this study, the presence of the ASA Pd allele was analyzed in 52 unrelated healthy individuals. The polyadenylation site mutation was found in 12 out of 104 chromosomes (Table I).

Table I. Frequencies of the ASA Pseudodeficiency Genotypes and Alleles

Genotypes			
no/no	no/pd	pd/pd	Total
40 (76.9%)	12 (23.1%)	–	52
Alleles			
	no	pd	Total
	92 (88.5%)	12 (11.5%)	104

ASA: arylsulfatase A. no: normal allele. pd: pseudodeficiency allele.

Twelve of the 52 unrelated, healthy individuals were found to be heterozygous for the ASA Pd allele. We found the Pd allele with a frequency of 11.5 percent among healthy, unrelated individuals. We asked the donors about their ethnic background, all of them Turkish citizens. Among MLD diagnosed patients (in total 18 patients), Pd allele frequency was 8.3 percent (Table II). Our data suggest that the frequency of the Pd allele is in agreement with previously published results from Australia and western Europe.

Table II. Frequencies of the ASA Pseudodeficiency Genotypes and Alleles

Genotypes			
no/no	no/pd	pd/pd	Total
16 (88.9%)	1 (5.5%)	1 (5.5%)	18
Alleles			
	no	pd	Total
	33 (91.7%)	12 (8.3%)	45

ASA: arylsulfatase A. MLD: metachromatic leukodystrophy. no: normal allele. pd: pseudodeficiency allele.

Discussion

MLD occurs in forms ranging from late-infantile to adult-onset, with age of onset largely determined by the amount of residual ASA enzymatic activity. While reduced levels of ASA enzymic activity in pseudodeficiency do not cause disease, ASA activity in persons with adult-onset metachromatic leukodystrophy and persons homozygous for the pseudodeficiency mutations can be very similar. Identification of patients and carriers of MLD becomes critical when values of ASA activity are below 15% of normal. In such situations, the correct diagnosis can easily be achieved by a PCR test that detects the ASA Pd allele. The technique described here amplifies DNA of the ASA genomic region from a single pair of primers and does not require a specific set for each genetic variant. In addition to DNA analyses, the metabolism of radioactively-labeled sulfatide in cultured fibroblast cells from ASA pseudodeficiency. This is important because the presence of pseudodeficiency mutations does not negate the possibility of an MLD mutation on the same ASA gene[18].

Out of the 18 cases with MLD examined of so far, one patient was found homozygous for the Pd allele and had undetectable enzyme activity. The other patient was found heterozygous for the Pd allele and had undetectable enzyme activity. The remainder of the patients with low ASA activity did not have the Pd mutation. Low ASA activity may be due to other mutations.

The exon 2 donor splice site mutation has been reported to be the most common mutation causing MLD. We did not identify a mutation in exon 2 of the ASA gene in Turkish patients with MLD. Further studies will concentrate on finding population specific mutations for the ASA gene.

REFERENCES

1. Barth ML, Ward C, Harris A, Saad A, Fenson A. Frequency of arylsulfatase A pseudodeficiency associated in a healthy population. J Med Genet 1994; 31: 667-671.
2. Chabas A, Castellvi S, Bayes M, Balcells S, Grinberg D, Vilageliu L. Frequency of the arylsulphatase A pseudodeficiency allele in the Spanish population. Clin Genet 1993; 44: 320-323.
3. Chevalier F, Maire I, Vanier MT, Gieslmann V. Gene frequency of arylsulfatase A pseudodeficiency in the French population. Implication for heterozygote and prenatal detection and diagnosis of leukodystrophy (abstracts). 8th ESGLD Workshop, Annecy 1991, p14.
4. Czartoryska B, Zimowski JG, Bisko M, Gorska D. Arylsulfatase A pseudodeficiency incidence in Poland. Eur J Hum Genet 1996; 4: 301-303.

5. Dubois G, Turpin JC, Baumann N. Absence of ASA activity in healthy father of a patient with metachromatic leukodystrophy. N Engl J Med 1975; 293: 302.
6. Gieselmann V, Fuharty AL, Tonnesen T, von Figura K. Mutations in the arylsulfatase A pseudodeficiency allele causing metachromatic leukodystrophy. Am J Hum Genet 1991; 49: 407-413.
7. Gieselmann V, Polten A, Kreysing J, von Figura K. Arylsulfatase A pseudodeficiency: loss of a polyadenylation signal and N-glycosylation site. Proc Natl Acad Sci USA; 1989; 86: 9436-9440.
8. Kolodny EH, Fluharty AL. Metachromatic leukodystrophy and multiple sulfatase deficiency: sulfatide lipidosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, (eds). The Metabolic and Molecular Bases of Inherited Disease (7th ed). New York: McGraw-Hill; 1994: 2693-2739.
9. Lee-Vaupel M, Conzelmann E. A simple chromogenic assay for arylsulphatase A. Clin Chim Acta 1987; 164; 171-180.
10. Lott IT, Dulaney JT, Milunsky A, Hoefnagel D, Moser HW. Apparent biochemical homozygosity in two obligatory heterozygotes for metachromatic leukodystrophy. J Pediatr 1976; 89: 438-440.
11. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the folin phenol reagent. J Biol Chem 1951; 193: 265-275.
12. Miller SA. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988; 16: 1215.
13. Nelson PV, Carey WF, Morris CP. Population frequency of arylsulfatase A pseudo-deficiency allele. Hum Genet 1991; 87: 87-88.
14. Polten A, Fluharty AL, Fluhart CB, Kappler J, von Figura K, Gieselmann V. Molecular basis of different forms of metachromatic leukodystrophy. N Engl J Med 1991; 324: 18-22.
15. Regis S, Filocamo M, Stroppiano M, Corsolini F, Gatti R. Molecular analysis of the arylsulphatase A gene in late infantile metachromatic leukodystrophy patients and healthy subjects from Italy. J Med Genet 1996; 33: 251-252.
16. Salamon MB, Christensen E, Schwartz M. Searching for mutations in the arylsulphatase A gene. J Inherit Metab Dis 1994; 17: 311-314.
17. Wenger DA, Louie E. Psedodeficiencies of arylsulfatase A and galactocerebrosidase activites. Dev Neurosci 1991; 13: 216-221.
18. Zlotogora J, Furman-Shaharabani Y, Goldfum S, Winchester B, von Figura K, Gieselmann V. Arylsulphatase A pseudodeficiency: a common polymorphism which is associated with unique haplotype. Am J Med Gen 1994; 15: 146-150.

Alimentary tract duplications in children: report of 26 years' experience

İbrahim Karnak[1], Turgay Öcal[2], Mehmet Emin Şenocak[1], F. Cahit Tanyel[1], Nebil Büyükpamukçu[1]

[1]Department of Pediatric Surgery, and [2]Department of Anesthesiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Karnak İ, Öcal T, Şenocak ME, Tanyel FC, Büyükpamukçu N. Alimentary tract duplications in children: report of 26 years' experience. Turk J Pediatr 2000; 42: 118-125.

Duplications of the alimentary tract are one of the rare anomalies of the gastrointestinal system. Because of the wide spectrum of the signs and symptoms, preoperative diagnosis frequently cannot be made. A close familiarity with clinical and surgical characteristics provides appropriate management and treatment of duplications. A retrospective clinical study was conducted to evaluate clinical and surgical characteristics and the treatment of duplications of the alimentary tract.

During a 26-year period between 1971 and 1997, 38 patients with duplications of alimentary tract underwent operation at the Hacettepe University Department of Pediatric Surgery. Forty-two duplications in 38 patients (20 male, 53%; 18 female, 47%) were encountered. Sixty-nine percent of the patients were symptomatic under the age of one year, with 24 percent presenting with symptoms in the neonatal period. There were one sublingual, nine intrathoracic (including 2 thoracoabdominal) and 32 intraabdominal duplications. Abdominal mass, abdominal distention, constipation, vomiting and respiratory distress were the most frequently encountered signs and symptoms. Plain thoracic and abdominal X-rays, ultrasonography, and computed tomography of the chest and abdomen were the most commonly used diagnostic radiological methods. Thirty-three duplications (79%) were spherical and nine (21%) were tubular. Multiple duplications were encountered in two patients (5.3%). Fourteen duplications (33%) contained heterotopic mucosa, mostly gastric type. More than one type of heterotopic mucosa in the same duplication was encountered in four duplications (10%). Additional malformations were encountered in 26 percent of patients. Six patients (15.8%) died from unrelated causes.

The signs and symptoms vary among duplications. Signs and symptoms leading to diagnosis and surgery varied according to the age of patient, location of the duplication, type of mucosal lining, duration of disease anad presence of complication. The ideal surgical treatment of duplication is complete excision. However, the other treatment options should be well known.

Key words: alimentary tract, cyst, duplication, gastrointestinal, tubular.

Alimentary tract duplications (ATD) are rare abnormalities in pediatric surgical practice. They are encountered in two or three cases per year, mostly in large pediatric surgical centers. However, this topic interests most pediatric surgeons, and many papers have appeared on this subject in the English language literature. Since they may occur at any location from the mouth to the anus, the spectrum of signs and symptoms is wide.

The management and treatment of ATD require familiarity with their clinical characteristics and anatomy. Therefore, we reviewed our experience on this subject and undertook a retrospective analysis of 38 cases with 42 ATD, treated at our center over a 26 year period from 1971 to 1997.

Material and Methods

During the 26-year period from 1971 to 1997, we encountered 42 ATD in 38 patients. Hospital

records, radiographs, operative reports and the surgical pathology of 38 patients were evaluated retrospectively. In the early years of this study period, ultrasonography (USG) and computed tomography (CT) were not available in our institute.

Results

There were 20 boys and 18 girls with a male to female ratio of 1.1. Nine patients (24%) were admitted to the hospital in the neonatal period. Seventeen patients (45%) were one to 12 months of age and 12 patients (31%) were older than one years. Thus, 69 percent of the patients were symptomatic under the age of one year. The signs and symptoms leading to diagnosis and the locations of duplications are given in Tables I and II.

Table I. Signs and Symptoms Leading to Diagnosis and Surgery

Signs and Symptoms	Number of patients
Feeding difficulty	1
Sublingual mass	1
Respiratory distress	7
Cough	1
Recurrent respiratory tract infections	1
Abdominal pain	5
Abdominal distention	6
Vomiting	10
Constipation	11
Massive rectal bleeding	1
Abdominal mass	10
Failure to thrive, loss of weight	2
Peritonitis	2
Bladder neck obstruction	1

Note: One patient with gastric duplication cyst and one patient with thoracoabdominal duplication were asymptomatic at the time of surgery.

Table II. Locations of Duplications

	Number of patients	%
Intraoral	1	2.6
Sublingual	1	
Intrathoracic	9	2.37
Esophageal	1	
Enteric	6	
Thoracoabdominal	2	
Intraabdominal	28	73.7
Gastric	1	
Duodenal	3	
Jejunal	2	
Jejunoileal	2	
Ileal	10	
Cecal	6	
Colonic*	2	
Rectal	2	

* One patient also had appendiceal duplication.
Note: One of jejunoileal and one of ileal duplication patients had multiple duplications.

Associated malformations were found in 10 patients (26%) (Table III). Six (15.8%) of the 38 patients died. All these deaths were before 1982 when broad spectrum antibiotics, intensive care facilities and new surgical techniques were not available. Four patients died of sepsis and one patient was complicated by midgut volvulus. One patient with multiple urological abnormalities died of chronic end stage renal failure.

Table III. Congenital Anomalies Associated with Alimentary Tract Duplications

	Number of patients
Encephalocele	1
Meningocele	1
Hemivertebra	1
Inguinal hernia	1
Malrotation*	4
Meckel's diverticulum	2
Ileal atresia	1
Bifid ureters	1
Complex urological abnormalities	1

* Two cases presented with midgut volvulus.

Discussion

Alimentary tract duplications can occur anywhere from the tongue to the anus, and have some basic characteristics. They are attached to at least one point of the alimentary tract, they have a well developed coat of smooth muscle and the epithelial lining of the duplication always resembles some part of the alimentary tract[1]. As one exception, intrathoracic duplications may lie adjacent to or distant from the esophagus without sharing a common muscular wall[2]. ATD may be asymptomatic for years or may present with life-threatening complications such as airway obstruction, pneumothorax, intestinal obstruction and perforation, and massive bleeding[3,4].

Numerous theories have been proposed to explain the occurrence of ATD, including the persistent vacuolization theory by Bremer, the presence of mucosal diverticula by Lewis and Thyng, incomplete coalescence of the lacunae that form between the epithelial cells of the solid core of the elongating gut, and faulty separation of the endoderm and notochord early in development proposed by McLetchie et al. and others[1,3]. Each can explain a particular abnormality, but the split notochord theory is an attractive explanation when the duplication is extensive and when vertebral anomalies are present.

Intraoral Duplications

Enteric duplication cysts of the tongue are unusual lesions (only 0.3 percent of the reported ATD) and are not usually associated with extraoral abnormality. During the formation of the lingual enteric cysts, trapping of epithelium by fusing primordia has been proposed[5]. Additionally, the close relation between the primitive stomach and anlage of the tongue in the midneck region at the same stage of development has been proposed for explanation of heterotopic gastric epithelium which is found in the lingual enteric cysts (enterocystoma)[6]. These lesions present with lingual mass that causes symptoms related to feeding difficulties, infection or bleeding. Lingual enteric cysts must be distinguished from dermoid cysts, hemangiomas, teratomas, hamartomas, thyroid remnants, ranulas and cystic hygromas.

We experienced only one case (2.6%) with a lingual enteric cyst at a sublingual location. This case presented with intraoral mass and feeding difficulty, and was cured by total excision without difficulty.

Intrathoracic Duplications

Intrathoracic ATD can be divided into three headings due to the anatomic location of the duplication: esophageal duplications (ED), enteric duplication cysts and thoracoabdominal duplications.

Esophageal duplications occur mostly in the distal third of the esophagus and locate in the posterior mediastinum, frequently in the right side. They have been reported to be the second most frequent location of ATD (20%) and most of the ED are spherical. Tubular ED may communicate with the stomach or proximal part of the small intestine via an esophageal or aortic hiatus[7-9]. Large cysts usually present with respiratory distress. Small ones may be found as asymptomatic masses on chest roentgenograms. Peptic complications such as hematemesis, hemoptysis, pneumothorax or empyema can occur, and rarely during intrauterine life[7] if they contain gastric mucosa.

Although chest X-ray, barium esophagogram and computed tomography of the thorax (Fig. 1) give sufficient information, endoultrasonographic diagnosis of ED has also been reported in adults[10].

At operation, the muscular coat of the duplication should be dissected without disturbing the esophageal muscosa[11]. We encountered only one ED (2.6%) of a spherical type. This case was an example for difficult surgery due to the closely attached spherical cyst. Perforation of the esophagus complicated our case. The patient required gastrostomy drainage for prolonged esophageal leakage and for feeding. The patient tolerated oral feeding after three weeks.

The second form of intrathoracic duplication is enteric duplication cysts which are not closely attached to the esophagus or intraabdominal part of the alimentary tract[2]. They are large masses and frequently present with airway obstruction and respiratory tract infection (Fig. 2).

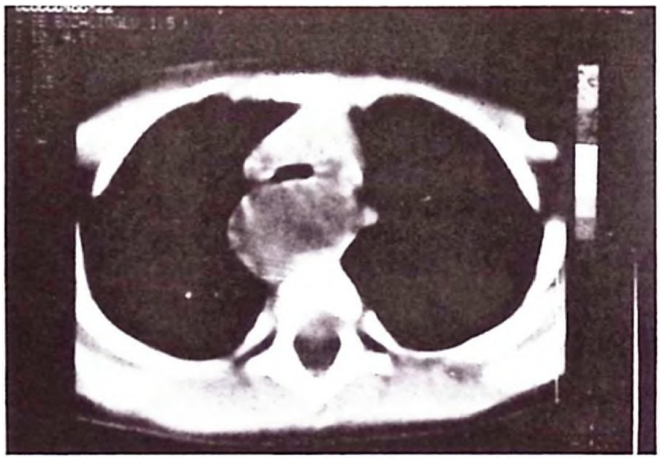


Fig. 1. Chest tomography showing duplication of the esophagus.

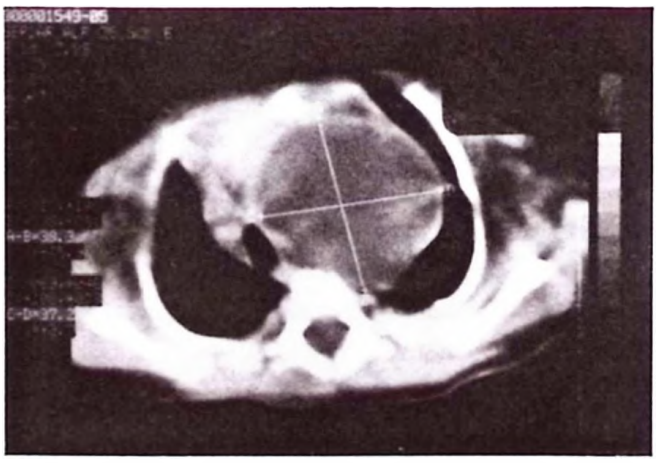


Fig. 2. Huge intrathoracic enteric duplication cyst causing severe mediastinal shift.

We encountered six patients (15.8%) with intrathoracic enteric duplication cysts, all treated by total excision. However, left subclavian artery and left phrenic nerve injury occurred in one patient. Postoperative diaphragmatic eventration was treated by plication one month later.

Thoracoabdominal duplications (TAD) of the alimentary tract are intrathoracic extensions of duplications that originate from the stomach or intestine. They are most likely tubular and are distinct from the esophagus, but may densely attached to the vertebrae and may extend into the neck[1,11]. The symptoms may be related to the thoracic or abdominal part of the duplication. It may be necessary to first excise the symptom-causing part. If there is no acute abdominal picture, the thoracic portion is dealt with first[1]. Any communication with vertebral body must be freed and sutured to prevent postoperative meningitis. If the abdominal procedure was required first, the thoracic procedure should not be delayed.

In our first TAD case, we used a transabdominal approach at first because of prediagnosis of a right-sided diaphragmatic hernia. The intrathoracic portion was excised later. The second case with TAD had undergone excision of a retroperitoneal tubular structure in another hospital. However, the intrathoracic extension of the TAD had been overlooked during the first operation. The patient had gone about nine years, interestingly without having symptoms.

Intrabdominal Duplications

Stomach

Gastric duplications (GD) comprise about 3.8 to 9 percent of all ATD. A third present in the neonatal period and most present within the first two years of life with abdominal mass, vomiting, weight loss and abdominal pain. A third of them have been detected in patients more than 12 years of age. Gastrointestinal bleeding was found in older infants and rarely in neonates[8-10,12-18].

Prenatal diagnosis is also possible in GD and the postnatal course may be asymptomatic[12]. According to the location of the GD, it may not be distinguished from choledochal cyst, duodenal atresia, neuroblastoma, congenital diaphragmatic hernia, mesenteric and surrenal cysts and genitourinary anomalies during USG examination[9,12].

The majority of GD are spherical, located along the greater curvature or posterior wall of the antrum and very rarely do they communicate with gastric lumen. Most of them contain gastric mucosa and sometimes pancreatic tissue[8]. Unusual presentations such as hemoptysis, recurring pancreatitis, and rare association with esophageal, duodenal, and jejunoileal duplications have been reported[8,9,14,16,17]. Adenocarcinoma and carcinoid arising from mucosa of GD have also been reported[18].

Ideally GD are treated by total excision. However, in some cases, due to their location or extensive size, subtotal excision with removal of mucosa or cystogastrostomy has been performed[18].

We encountered only one case of GD (2.6%) in whom prenatal diagnosis was made.

Duodenum

Duodenal duplications (DD) account for four to 12 percent of all ATD and occur with a frequency of 1 in 100,000 births[19-24]. In a large series of congenital duodenal obstruction, DD constituted only one percent of the cases[21]. These cysts most frequently develop in neonates or young children, are most often located in the first or second part of the duodenum and fail to comunicate with the lumen. Because of the close relation of these cysts to important structures, the spectrum of symptoms varies from one to another. The most common picture is duodenal obstruction in infancy; occasional patients later on. Unusual symptoms include relapsing pancreatitis and severe ascites, perforation, bleeding resulting from peptic ulceration or segmental portal hypertension, biliary tract obstruction, and hepatic or mediastinal mass[20,23-28]. Upper gastrointestinal series, USG, CT scan and endoscopic retrograde cholangiogpanceratography can be used to determine the location, size and communication to the pancreatic and biliary tract[23,24].

Surgical options in dealing with DD have varied depending on the location of the lesion and its proximity to, and involvement of , the ampulla of Vater, and the pancreatic ducts and biliary system. Such options have included cystectomy with or without duodenostomy or duodenojejunostomy; partial cystectomy and marsupialization to adjacent stomach, duodenum or jejunum, sometimes with removal of the mucosal lining; and pancreaticoduodenectomy (Whipple's procedure) in cases of cysts within the head of the pancreas[26]. Endoscopic removal of duodenal wall cyst and endoscopic drainage have been reported[24,25,29]. However, the exact diagnosis of DD cannot be made during endoscopic drainage procedures. Additionally,

the presence of heterotopic gastric tissue or malignant transformation of the cyst epithelium cannot be excluded.

We encountered three DD cases (7.9%). They presented with abdominal pain or abdominal mass. Total excision was possible in one patient and two were treated by mucosal stripping and cystoduodenostomy. All survived without later problems.

Small Intestine

About half of the ATD are located in the small intestine (SI). Pooled data from five large series of ATD revealed an ileal site in 41 percent and a jejunal site in 8 percent[30]. Most of the SI duplications are spherical with a diameter less than 10 cm. Tubular duplications represent five to 10 percent of SI duplications; they are rarely longer than 20 cm.

Intestinal duplications may present with vomiting, constipation, intestinal obstruction or as an abdominal mass. Additional presenting symptoms are chronic anemia, growth retardation, massive bleeding, pain and peritonitis. Combined distal ileal and total colonic tubular duplication associated with transmesenteric hernia, retrograde jejunoduodenal intussusception and melanosis peritonei are the rare presentations of SI duplications[31-33].

Heterotopic gastric tissue and communication with the normal bowel are frequently found. Heterotopic tissue other than gastric, such as squamous, transitional or ciliated mucosa, and pancreatic tissue can be found in SI duplications[34]. Congenital anomalies associated with SI duplications are omphalocele, intestinal atresia or stenosis and malrotation. In our series the most frequently asociated anomaly with SI dupliction was malrotation and Meckel's diverticulum. Malignancies have been reported occasionally in adults with SI duplication[35].

Ultrasonography and CT scan can be used for the diagnosis of spherical SI duplications (Fig. 3). Recently many long tubular duplications containing gastric epithelium have been diagnosed using 99mTc-pertechnetate scintigraphy[36-39]. We also diagnosed such a duplication by scintigraphy in a child presenting with massive rectal bleeding (Fig. 4).

Although intraabdominal tubular SI duplications longer than 50 cm have been reported very rarely[40], we encountered long tubular duplications of 80 cm and 100 cm in two cases.

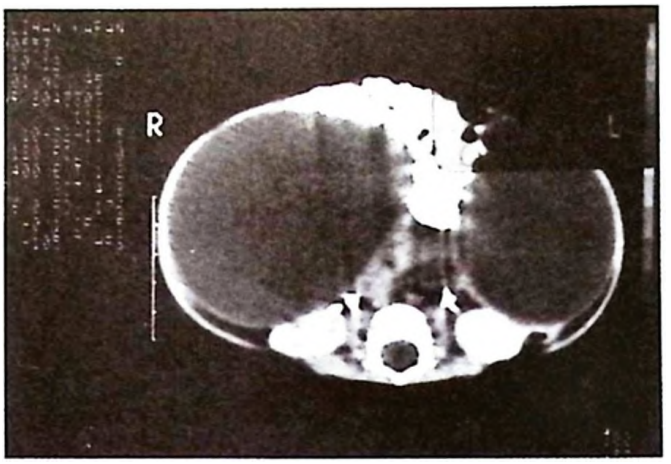


Fig. 3. Duplication cyst of the small intestine presenting with a large intraabdominal mass.

Fig. 4. Scintigraphic visualization of bleeding long tubular duplication.

When tubular duplications are very long, resection may lead to short-gut syndrome. Different surgical techniques have been used to avoid massive intestinal resection: partial resection and marsupialization of the remnant into the alimentary tract, anastomosis of the gastric-linked duplication into the stomach, selective devascularization of the duplication, surgical diversion to the normal bowel for drainage if there is no gastric mucosa, and anastomosis with mucosal stripping if a gastric lining is found, and two-step surgical resection[40]. Tubular duplication may pass in front or behind the mesenteric vessels and may sometimes be adherent to these structures. Very close and gentle dissection of the duplication spares vascular supply to the normal bowel. We were able to dissect long tubular duplications (80 cm and 100 cm) between mesenteric layer

in two cases. The distal 30 and 40 cm of these duplications shared a common wall with a normal bowel. In these cases we tried to dissect the duplicated segment by sacrificing terminal branches of intestinal vessels in only one side of the mesentery. If the duplicated segment cannot be dissected after a point, mucosal stripping should be tried. We did not attempt stripping in these cases but instead resected the terminal 10 and 20 cm of the duplications with the normal bowel and performed end to end anastomosis.

Approximately 20 percent of ATD are multiple[41]. We encountered multiple duplications in two cases (5.3%), one with double and the other with quadruplicate duplications. Therefore, intraabdominal cavity, root of the mesentery and bursa omentalis should be carefully checked for additional duplications.

Retroperitoneal duplications are very unusual. In a series of 78 cases of ATD only two were located in the retroperitoneum[42]. We did not encounter pure retroperitoneal duplication. However, the abdominal part of the duplication in our second TAD case was retroperitoneal.

Colon

Hindgut duplications constitute about 18 percent of all ATD. Twenty-five percent of reported colonic duplications were tubular and three quarters had a proximal, distal, or proximal and distal communication with the adjacent intestine. Those with distal communication tended to drain freely and therefore were associated with fewer symptoms[43,44].

Appendiceal duplication (AD) is a rare abnormality. However, with AD detected in childhood, the patient may have serious associated intestinal or genitourinary malformations[45,46].

Rectal duplications comprise only 2.5 to 3 percent of ATD[42]. Spherical duplications of the distal colon most commnly apear adherent to the posterior rectal wall. Patients may present with transanal prolapse or symptoms secondary to compression.

Duplications that affect the large intestine are commonly associated with genitourinary and anorectal malformations[47-49]. Genitourinary anomalies occur more frequently with tubular duplication of the entire colon. Bladder exstrophy is found 10 to 14 percent, genitourinary duplications are present in 21 to 43 percent, and spina bifida and other vertebral anomalies are seen in 15 percent of these patients[44].

We interestingly encountered cecal duplications (15.8%) as the most frequent location of colonic duplications. All these cecal duplications were spherical and embedded in the wall of the cecum and were very close to the ileocecal valve; dissection was impossible. Therefore, all these cases were treated by ileocecal resection and anastomosis. In one case, the patient presented with palpable mass and with no signs of intestinal obstruction. CT appearance suggested intussusception, and ileocecal intussusception due to cecal duplication was determined at operation (Fig. 5).

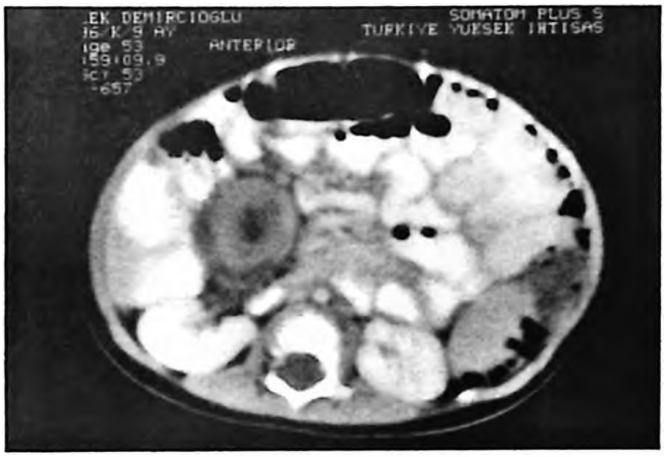


Fig. 5. Ileocecal intussusception due to cecal intramural duplication cyst.

The only case of tubular colonic duplication also had appendiceal duplication and multiple associated abnormalities leading to chronic renal failure. This child was managed by sigmoid colostomy but died of sepsis with end stage renal failure.

The most frequent location of ATD in our series (26.2%) was an ileal site. Intrathoracic enteric duplication cysts (15.8%) and intraabdominal cecal duplications (15.8%) were the second most frequent duplications. ATD present a wide spectrum of signs and symptoms. Although they are rare, one may encounter this abnormality in an unexpected case. Therefore, close familiarity with the anatomy of duplications and adequate knowledge of treatment options, which have to be chosen at operation, are required. Mortalities were encountered in the early years of this series and were closely related to associated abnormalities and sepsis, not to operations.

REFERENCES

1. Lister J. Duplications of the alimentary tract. In: Lister J, Irving IM (eds). Neonatal Surgery (3rd ed). London: Butterwoths; 1990: 474-484.
2. Holcomb GW, Gheissar A, O'Neill JA, Jr et al. Surgical management of alimentary tract duplications. Ann Surg 1989; 209: 167-170.
3. Ravitch MM. Duplications of gastrointestinal tract. In: Welch KJ, Randolp JG, Ravitch MM, O'Neill Ja, Jr Rowe MI (eds). Pediatric Surgery (4th ed) Vol 2. Chicago: Year Book; 1986; 911-919.
4. Pinter AB, Schubert W, Szemlédy F, Göbel F, Schafer J, Kustos G. Alimentary tract duplications in infants and children. Eur J Pediatr Surg 1992; 2: 8-12.
5. Lipsett J, Sparnon AL, Byard RW. Embryogenesis of enterocystomas-enteric duplication cysts of the tongue. Oral Surg Oral Med Oral Pathol 1993; 75: 626-630.
6. La Bagnara J, Zauk A, Rankin L, Valda V. Enteric duplications of the mouth. Otolaryngol-Head Neck Surg 1993; 108: 187-189.
7. Peiper M, Lambrecht W, Kluth D, Hüneke B. Bleeding esophageal duplication detected in utero. Ann Thorac Surg 1995; 60: 1790-1791.
8. Mazziotti MV, Temberg JL. Continuous communicationg esophageal and gastric duplication. J Pediatr Surg 1997; 32: 775-778.
9. Fenton LZ, Williams JL. Bronchopulmonary foregut malformation mimicking neuroblastoma. Pediatr Radiol 1996; 26: 729-730.
10. Geller A, Wang KK, Dimagno EP. Diagnosis of foregut duplication cysts by endoscopic ultrasonography. Gastroentorology 1995; 109: 838-842.
11. Raffensperger JG. Duplication of the alimentary tract. In: Raffensperger JG (ed). Swenson's Pediatric Surgery (5th ed). New York: Appleton and Lange; 1990: 579-585.
12. Özmen MN, Önderoğlu L, Çiftçi AO, Akhan O, Tanyel FC. Prenatal diagnosis of gastric duplication cyst. J Ultrasound Med 1997; 16: 219-222.
13. Fletcher JD, Covell L, Shortsleeve MJ. Calcified gastric duplication. Am J Roentgenol 1994; 163: 994-995.
14. Faerberr EN, Balsara R, Vinocur CD, Chadarevian JP. Gastric duplication with hemoptysis: CT findings. Am J Roentgenol 1993; 161: 1245-1246.
15. Alberti-Flor JJ. Endoscopic appearance of adult gastric duplication cyst. Am J Gastroenterol 1994; 89: 1919-1920.
16. Olsen I, Annerén G, Henze A, Lundkvist K, Lönnerholm T. Multiple intestinal duplications in a child with thoracic myelomeningocele and hydrocephalus. Eur J Pediatr Surg 1992; 2: 45-48.
17. Stannard MW, Currarino G, Splawski JB. Congenital double pylorus with accessory pyloric channel communicating with an intraluminal duplication cyst of the duodenum. Pediatr Radiol 1993; 23: 48-50.
18. Murty TV, Bhargava RK, Rakas FS. Gastroduodenal duplication. J Pediatr Surg 1992; 27: 515-517.
19. Archer D, Somers S. Duodenal duplication cysts: case report and review of the current literature. Can Assoc Radiol J 1992; 43: 49-51.
20. Dimitrewski J, Jurewicz WA. Doudenal duplication cyst causing segmental portal hypertension and massive intestinal haemorrhage. Br J Surg 1993; 80: 1031.
21. Bailey PV, Tracy TF, Connors RH Jr, Mooney DP, Lewis JE, Weber TR. Congenital duodenal obstruction: a 32-year review. J Pediatr Surg 1993; 28: 92-95.
22. Bergman KS, Jacir NN. Cystic duodenal duplication: staged management in a premature infant. J Pediatr Surg 1993; 28: 1584-1585.
23. Okuyama H, Matsuo Y, Fukui Y, Imura K, Kamata S, Okada A. Intrapancreatic duodenal duplication associated with pancreatic pseudocyts. J Pediatr Surg 1992; 27: 1573-1574.
24. Lang T, Berquist W, Rich E, et al. Treatment of recurrent pancreatitis by endoscopic drainage of a duodenal duplication. J Pediatr Gastroenterol Nutr 1994; 18: 494-496.
25. All Traif I, Khan MH. Endoscopic drainage of a duodenal duplication cyst. Gastrointestinal Endoscopy 1992; 38: 64-65.
26. Ng KY, Desmond PV, Collier N. Relapsing pancreatitis due to juxta-pancreatic duodenal duplication cyst with pancreatic ductal communication. Aust NZ J Surg 1993; 63: 224-229.
27. İmamoğlu CH, Walt AJ. Duplication of the duodenum extending into the liver. Am J Surg 1977; 133: 628-632.
28. Sonoda N, Takaya J, Okamoto K. Transdiaphragmatic duodenal duplication in a premature infant. J Pediatr Surg 1987; 22: 372-373.
29. Johanson JF, Geenen JE, Hogan WJ, Heubregtse K. Endoscopic therapy of a duodenal duplication cyst. Gastrointestinal Endoscopy 1992; 38: 60-61.
30. Bissler JJ, Klein RL. Alimentary tract duplications in children: case and literature review. Clin Pediatr 1988; 27: 152-157.
31. Keramidas DC, Demetriades DM. Total tubular duplication of the colon and distal ileum combined with transmesenteric hernia: surgical management and long-term results. Eur J Pediatr Surg 1996; 6: 243-244.
32. Norton KI, Luhmann KC, Dolgin SE. Retrograde jejunal-duodenal intussusception associated with a jejunal duplication cyst in a newborn. Pediatr Radiol 1993; 23: 360-361.
33. Jung YC, Chen CJ, Tzeng CC. Melanosis peritonei associated with enteric duplication cyst. Am J Surg Pathol 1996; 20: 181-186.
34. Sato T, Oyamada M, Chiba H, et al. Ileal duplication cyst associated with heterotopic pancreas: report of a case and literature review. Acta Pathol Jan 1993; 43: 597-602.
35. Orr MM, Edwards AJ. Neoplastic change in duplications of the alimentary tract. Br J Surg 1975; 62: 269-274.
36. Praturi R, Nance RW, Stevens JS. Jr. Technetium pertechnetate scintigraphy in an ileal duplication of the stomach and duodenum. J Nucl Med 1993; 34: 294-296.
37. Kong MS, Huang SC, Tzen KY, Lin JN. Repeated technetium-99m pertechnetate scanning for children with obscure gastrointestinal bleeding. J Pediatr Gastroenterol Nutr 1994; 18: 284-287.

38. Demirkol O, Adalet I, BonevalC, Cantez S. Visualization of a perforated small bowel duplication during Meckel's scintigraphy. Clin Nucl Med 1995; 20: 111-113.

39. Lecouffe P, Spyckerelle C, Venel H, Meuriot S, Marchandise X. Use of pertechnetate 99mTc for abdominal scanning in localising an ileal duplication cyst: case report and review of the literature. Eur J Nucl Med 1992; 19: 65-67.

40. Balén EM, Lizoain JL, Pardo F, Longo JM, Cienfuegos JA, Alzina V. Giant jejunoileal duplication: prenatal diagnosis and complete excision without intestinal resection. J Pediatr Surg 1993; 28: 1586-1588.

41. Duncan BW, Adzick NS, Eraklis A. Retroperitoneal alimentary tract duplications detected in utero. J Pediatr Surg 1992; 27: 1231-1233.

42. Bower RJ, Sieber WK, Kieswetter WB. Alimentary tract duplications in children. Ann Surg 1978; 188: 669-674.

43. McNeill SA, Rance CH, Stewart RJ. Fecolith impaction in a duplex vermiform appendix: an unusual presentation of colonic duplication. J Pediatr Surg 1996; 31: 1435-1437.

44. Criado E, Mesrobian HG, Bethea MC, Azizkhan RG. Heterotopic hindgut duplication: a cloacal remnant associated with exstrophy of the bladder. J Pediatr Surg 1992; 27: 1605-1607.

45. Rızalar R, Saraç A, Görk AS, Somuncu S, Bernay F, Gürses N. Duplication of appendix with segmental dilatation of the colon, myelochisis and anal atresia. Eur J Pediatr Surg 1996; 6: 112-113.

46. Arda IS, Şenocak ME, Hiçsönmez A. Duplication of vermiform appendix: case report and review of the literature. Pediatr Surg Int 1992; 7: 221-222.

47. Dominguez R, Rott J, Castillo M, Pittaluga RR, Corrieer JN. Caudal duplication syndrome. Am J Dis Child 1993; 147: 1048-1052.

48. OkurH, Keskin E, Zorludemir Ü, Olcay I. Tubular duplication of the hindgut with genitourinary anomalies. J Pediatr Surg 1992; 27: 1239-1240.

49. Choo KL, Frank MJ. Urodynamic evaluation of an infant with complete bladder and colonic duplication, sacral dysgenesis, and an imperforate anus. Br J Urol 1996; 77: 749-750.

Intermediate-term follow-up results of pulmonary balloon valvuloplasty in children

Gayaz Akçurin[1], Öz Kahramanyol[2], Canan Atakan[2]

[1]Department of Pediatrics, Akdeniz University Faculty of Medcine, Antalya, and [2]Social Security Children's Hospital, Ankara, Turkey

SUMMARY: Akçurin G, Kahramanyol Ö, Atakan C. Intermediate-term follow-up results of pulmonary balloon valvuloplasty in children. Turk J Pediatr 2000; 42: 126-131.

Twenty-two patients (10 boys, 12 girls) with pulmonary valve stenosis whose mean age was 6.7 ± 4.1 years (range 1 to 14 years) at time of the procedure underwent balloon dilatation angioplasty. All patients had isolated pulmonary valve stenosis with no associated cardiac anomalies, and their pulmonary valvular gradients were greater than 50 mmHg. Diagnostic catheterization and balloon valvuloplasty were performed during the same procedure. The mean peak systolic pressure gradient before balloon dilation of 95.8 ± 29.5 mmHg (54-163 mmHg) was reduced to 30.2 ± 15.8 mmHg (7-64 mmHg) after balloon dilation ($p < 0.001$). A linear relation was found between the predilation pressure gradient and the pressure gradient drop ($r = 0,86$; SE: 28.94) ($y = 0.89x-12.11$). Following a successful valvuloplasty, the mean peak systolic pressure in the right ventricle decreased from 119.0 ± 30.4 mmHg (71-184 mmHg) to 55.2 ± 16.9 mmHg (29-97 mmHg) ($p < 0.001$). Continuous wave Doppler was used for follow-up. Pressure gradients were estimated in 14 patients between one and 29 months after the dilation 120 ± 7.1 months). The mean follow-up gradient was 19.0 ± 6.0 mmHg (11-32 mmHg). No important complication was noted in the immediate course or throughout the follow-up period, but four patients (28.6%) had minimal pulmonary insufficiency. In conclusion, these data confirm that balloon dilation in valvular pulmonary stenosis is safe and effective, and suggest that stenosis does not recur.

Key words: congenital heart disease (CHD), pulmonary valvular stenosis, balloon angioplasty.

Isolated pulmonary valve stenosis is a cardiovascular malformation accounting for seven to 15 percent of patients with congenital heart disease[1]. Pulmonary balloon valvuloplasty (PBV) as an alternative to surgical valvulotomy for treatment of isolated valvular pulmonary stenosis usually results in adequate reduction of the transvalvular gradient. This procedure has been performed several times since 1982 without a reported death or significant morbidity[2-5].

The present report describes the efficacy of this procedure and follow-up in our institution.

Material and Methods

Between June 1993 and March 1995, 22 consecutive patients (10 boys, 12 girls) with pulmonary valve stenosis underwent balloon dilatation angioplasty. Diagnosis was made by physical examination, chest-X-ray, electrocardiogram, and complete two-dimensional and Doppler echocardiographic examination.

All patients had isolated pulmonary valve stenosis with no associated cardiac abnormalities, and their pulmonary valvular gradients were greater than 50 mmHg. Before cardiac catheterization, balloon valvuloplasty was described to the patients and their families as an alternative to the surgical approach, and informed consent was obtained.

All patients underwent diagnostic catheterization and balloon valvuloplasty during the same procedure. Right heart hemodynamic data was obtained before and after (10 minutes or longer) valvuloplasty. The recorded data included right ventricular and main pulmonary artery pressures. Systolic blood pressure was determined with sphygmomanometer in the left upper arm in all

patients every five minutes. Right ventricular or right ventricular outflow tract angiocardiograms were performed using a angiocardiographic catheter, with posteroanterior and cranially angulated views. Accurate measurements of the valve annulus diameter were obtained from the fixed image on the video playback unit. The magnification factor of the cineangiogram was determined by comparing the angiographically determined diameter of the catheter to its actual diameter[2,4].

A balloon with an inflated diameter 30-40 percent greater than the dimension of the valve annulus was selected. Pulmonary balloon valvuloplasty was performed by the trefoil balloon technique using a 3 cm. Mansfield balloon (Boston Scientific Corp., Mansfield Division, Mansfield, MA). Total balloon size was calculated using a previously described formula[5,6].

Pulmonary balloon valvuloplasty has been described in detail in many publications[2-5,7,8-12] (Fig. 1).

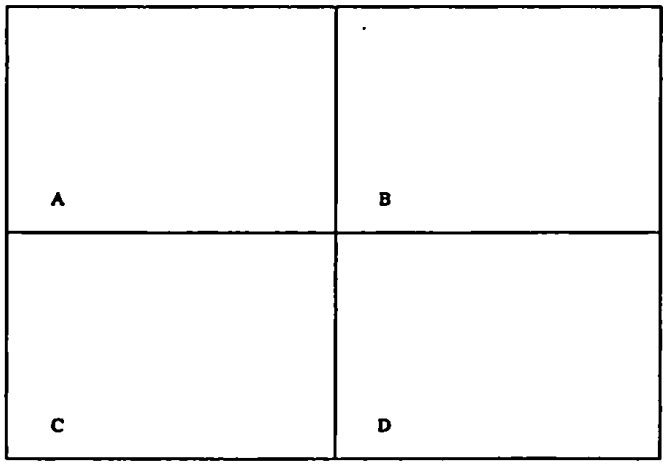


Fig. 1. Right ventricular angiograms of patient 17. A) Right anterior oblique position before PBV. B) "waist" effect with stenotic pulmonary valve. C) Maximum inflation of the balloon without any stenosis. D) Right anterior oblique position after PBV.

Once the operators were satisfied that maximum valve dilation had been achieved, the balloons were withdrawn over the wire and replaced with appropriately sized sheath/dilator sets. Postdilation hemodynamics and angiocardiograms were carried out using these sheaths. Beta blocking drugs were given to all patients (2 mg/kg/day propranolol) routinely. Since there were no complications, all patients were discharged home within 24 to 48 hours following the procedure.

Noninvasive modalities (auscultation, electrocardiogram, chest X-ray and two-dimensional and Doppler examination) were used for follow-up evaluation. Echocardiographic study was performed with Toshiba 160-A. Pulmonary valvar gradient was calculated using modified Bernoulli equation on Doppler echocardiography[13,14].

For statistical analysis, pressure data are presented as mean ± standard deviation. Student's t-test was used to compare paired data. The level of statistical significance was set at $p < 0.05$.

Results

The mean age of patients was 6.7 ± 4.1 years (range 1 to 14 years) at time of the procedure. The ages, pressure data of the patients and balloon sizes are shown in chronological order (according to timing of the procedure) in Table I. There were no complications in performing valvuloplasty in any of these patients.

The mean peak systolic pressure gradient before balloon dilation of 95.8 ± 29.5 mmHg (range 54-163 mmHg) was reduced to 30.2 ± 15.8 mmHg (range 7-64 mmHg) after balloon dilation. Significant reduction of transvalvular gradient occurred in every patient ($p < 0.001$) (Fig. 2).

A linear relation was found between the predilation pressure gradient and the pressure gradient drop ($r = 0.86$; SE: 28.94) ($y = 0.89x-12.11$) (Fig. 3).

Following a successful valvuloplasty, the mean peak systolic pressure in the right ventricle decreased from 119.9 ± 30.4 mmHg (71-184 mmHg) to 55.2 ± 16.9 mmHg (29.97 mmHg) ($p < 0.001$). The mean peak systolic pressures in the pulmonary artery were 23.4 ± 4.5 and 25.2 ± 4.2 mmHg before and after valvuloplasty, respectively, and the difference was not significant ($p > 0.05$) (Fig. 4).

Continuous wave Doppler was used for follow-up. Pressure gradients were estimated in 14 patients between one and 29 months after the dilation (mean 12 ± 7.1 months). In each patient the gradient at follow-up was lower when compared with the immediate post-valvuloplasty gradient. The mean follow-up gradient was 19 ± 6 mmHg (range 11-32 mmHg). No important complication was noted in the immediate course or throughout the follow-up period, but four patients (28.6%) had minimal pulmonary insufficiency (Fig. 5).

Table I. Ages and Pressure Data of the Patients and Balloon Properties

			Before Valvuloplasty							After Valvuloplasty							
			Mean PA			Right Ventricle				Mean PA			Right Ventricle				
No.	Age (year)	Sex	S	D	M	S	D	ED	PGI	S	D	M	S	D	ED	PG2	Bal.
1	5	F	25	15	19	98	0	9	73	22	12	17	29	0	6	7	3x10
2	11	M	19	7	12	84	0	8	65	21	12	17	43	0	8	22	3x15
3*	7	M	28	12	19	160	0	16	132	26	5	11	61	0	6	35	3x12
4	12	F	15	8	11	107	0	3	92	24	11	14	83	0	7	59	3x15
5	9	M	17	7	10	71	0	6	54	21	8	13	45	0	5	24	3x15
6*	9	F	20	9	15	161	0	9	141	25	11	17	60	0	13	35	3x12
7*	13	M	26	8	17	81	0	7	63	25	8	16	59	0	9	34	3x16
8*	4	F	21	8	13	75	0	3	54	25	6	16	46	0	7	21	3x9
9	4	F	27	13	18	129	0	8	102	30	15	21	55	0	18	25	3x10
10*	1	F	22	13	18	100	0	12	78	28	15	20	75	0	4	47	3x8
11*	12	M	24	9	16	122	0	8	98	26	9	14	65	0	5	38	3x15
12	4	M	32	19	24	111	0	18	79	23	17	18	61	0	11	38	3x12
13	3.5	M	20	12	16	150	0	20	130	25	15	20	60	0	10	35	3x12
14	6	F	29	18	21	114	0	11	85	31	13	20	47	0	7	16	3x8
15*	2	F	31	16	19	141	0	5	110	33	21	24	97	0	4	64	3x10
16	3	F	24	8	17	103	0	11	79	25	9	13	43	0	7	18	3x8
17	4	M	27	14	20	116	0	16	89	21	11	13	29	0	3	8	3x12
18	2	F	22	11	17	96	0	10	74	20	5	11	32	0	3	12	3x12
19*	2	F	17	14	11	130	0	9	113	36	11	13	33	0	5	3	3x10
20	12	F	25	18	21	166	0	19	141	26	14	19	65	0	8	39	3x15
21	14	M	26	10	18	118	0	9	92	24	11	16	62	0	9	38	3x16
22	5	M	21	9	13	184	0	12	163	18	7	12	64	0	6	46	3x10
Mean	6.7	10 M	23.5	11.7	16.6	119.0	0	10.4	95.8	25.2	11.2	16.1	55.2	0	7.3	30.2	
SD	4.1	11 F	4.5	3.7	3.6	30.4	0	4.7	29.5	4.2	3.9	3.5	16.9	0	3.4	15.8	

PA: Pulmonary artery, S: Systolic (mmHg), D: Diastolic (mmHg), M: Mean (mmHg), ED: End diastolic (mmHg), PGI: Pressure gradient before valvuloplasty, PG2: Pressure gradient after valvuloplasty, Bal: properties of balloons, *: Follow-up data not available.

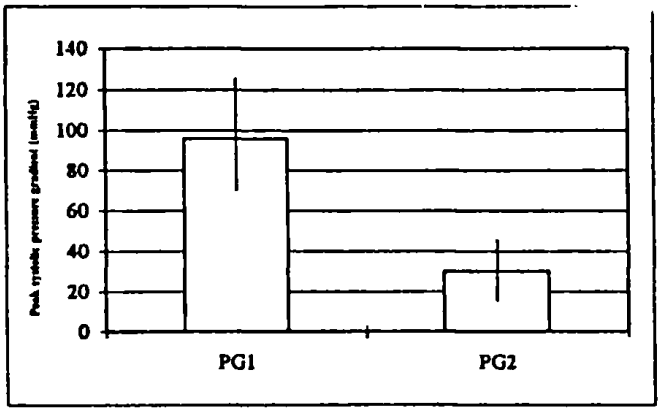


Fig. 2. The mean peak systolic pressure gradient before and after valvuloplasty.

PG1 : The mean peak systolic pressure gradient before valvuloplasty;

PG2 : The mean peak systolic pressure gradient after valvuloplasty (n = 22; p < 0.001).

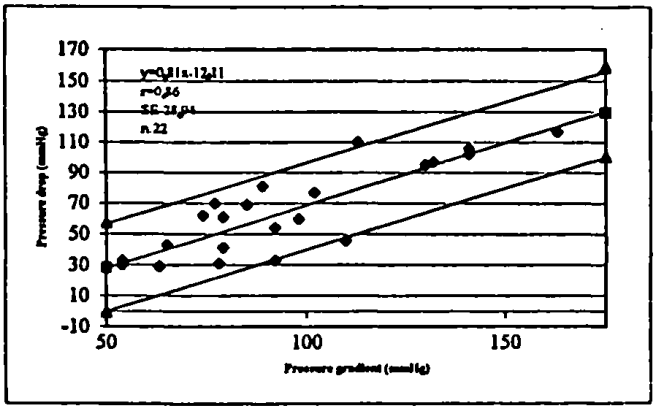


Fig. 3. A linear relation between the predilation pressure gradient and the pressure gradient drop.

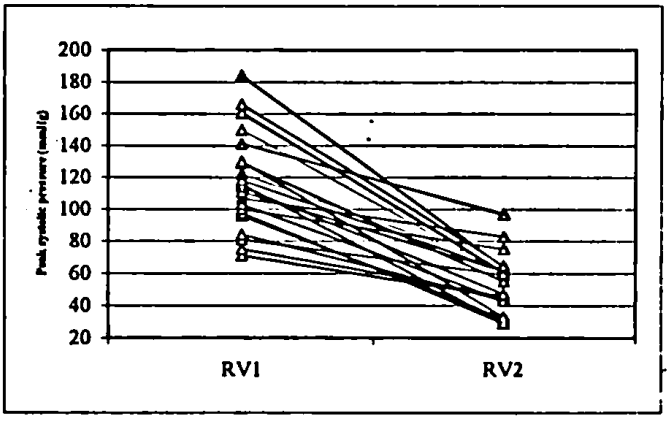


Fig. 4. The right ventricular peak systolic pressure drop after valvuloplasty.

RV1 : The right ventricular peak systolic pressure before valvuloplasty;

RV2 : The right ventricular peak systolic pressure after valvuloplasty.

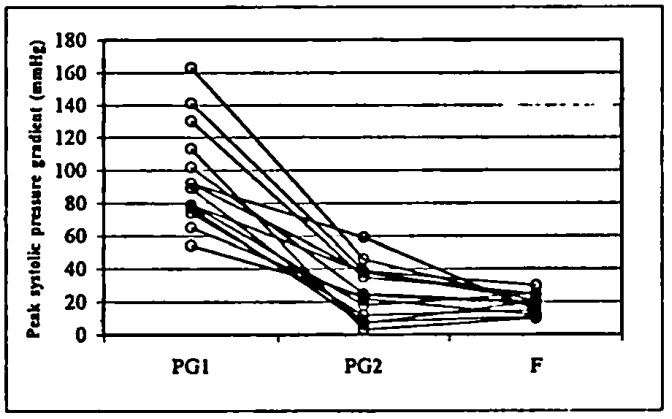


Fig. 5. Pressure gradient data of 14 patients. before, immediately after valvuloplasty, and during follow-up.

PG1 : Before valvuloplasty pressure gradient data;

PG2 : Immediately after valvuloplasty pressure gradient data;

F : Echocardiographic follow-up pressure gradient data.

Discussion

Pulmonary valve stenosis is one of the most common congenital heart disases. Diagnosis is usually established during childhood and treated when the pressure gradient at rest exceeds 50 mmHg. In recent years surgical valvuloplasty has been largely replaced by PBV[2-5].

Although the balloon valvuloplasty is used most frequently in children, it has also been used successfully in neonates[14-18] and in adults[19-24].

Rao et al.[25] recommended that the indications for balloon valvuloplasty be the same as those used for surgical valvuloplasty, and that balloon dilatation should not be performed in patients with peak pulmonary valvular gradients less than 50 mmHg. Wang et al.[26] concluded that asymptomatic patients with a gradient above 50 mmHg should be considered for balloon valvuloplasty, which could provide improvement both in transvalvular gradient and in right ventricular pressure, and that symptomatic patients should also be considered for valvuloplasty, regardless of gradient. Asymptomatic patients with a gradient between 40 to 50 mmHg could also be considered for valvuloplasty, but regular clinical and echocardiographic follow-up is another option. The mean peak systolic valvular gradient of our patients was greater than 50 mmHg.

Our method of pulmonary angioplasty is similar to that described by Kan[12] and others[2-5,9-11]. We used trefoil balloon in all patients and the balloon diameter was 30-40 percent greater than the pulmonary valve annulus. It is generally agreed that a balloon/annulus ratio of greater than 1.0 is associated with better results than a balloon/annulus ratio of less than 1.0, and there is some evidence that a balloon/annulus ratio greater than 1.5 is associated with higher risk of complications[27]. Rao et al.[5,6,25], Melgares et al.[8], and Narang et al.[27] showed that balloon-annulus ratios between 1.2 and 1.5 were more appropriate for pulmonary valvuloplasty for relief of isolated valvar pulmonic stenosis.

Rao and coworkers[25] concluded that when immediate post-valvuloplasty pulmonary valvular gradient is > 30 mmHg, the chance of recurrence of stenosis is high and, therefore, it may be advisable to use larger balloons and reduce the valve gradient to < 30 mmHg. There were 12 patients whose peak systolic pressure gradients were greater than 30 mmHg (4 of these were > 40 mmHg) immediately after valvuloplasty. No follow-up data were available in six of these 12 patients. Because transvalvular gradient on Doppler follow-up was < 30 mmHg in the remaining six patients, secondary pulmonary balloon valvuloplasty procedure was not done.

A linear correlation between the pressure gradient drop and the predilation valvular gradient was found ($r = 0.86$; SE: 28.94) ($y = 0.89x-12.11$) (Fig. 3). This equation may be useful for the cardiologist in predicting the pressure drop after the procedure[4].

The mean peak systolic pressure in the right ventricle decreased from 119.0 ± 30.4 mmHg (71-184 mmHg) to 55.2 ± 16.9 mmHg (29.97 mmHg) after valvuloplasty ($p < 0.001$).

Although some reports showed that the mean peak systolic pressure in the pulmonary artery significantly increased immediately after the valvuloplasty. the mean peak systolic presures in the pulmonary artery in our series were 23.5 ± 4.5 and 25.2 ± 4.2 mmHg before and after valvuloplasty, respectively, and the difference was not significant ($p > 0.05$)[5,7].

Complete right bundle-branch block, transient or permanent complete heart block, cerebrovascular accident, loss of conciousness, cardiac arrest, convulsions, balloon rupture at high inflation pressures, tricuspid valve papillary muscle rupture, and severe infundibular obstruction requiring propranolol administration and/or surgical intervention have been reported. Complications have been remarkably minimal during and immediately after balloon pulmonary valvuloplasty. Transient bradycardia, premature beats, and a fall in systemic pressure during balloon inflation have been noted by all authors as seen in our patients. Although blood loss requiring transfusion has been reported in many studies, our patients did not need any transfusion[5,7,27,29].

Echo-Doppler follow-up studies were possible in 14 children for 12 ± 7.1 months (range 1 to 29 months) following valvuloplasty. The mean peak systolic pressure gradient decreased from 96 ± 31 mmHg (range 54-163 mmHg) to 27 ± 16 mmHg (range 30-117 mmHg) immediately following balloon dilation ($p < 0.001$), which on Doppler follow-up was 19 ± 6.2 mmHg ($p > 0.05$) in these patients. Our follow-up results showed that the mean pressure gradient one year after valvuloplasty was lower than that observed immediately after valvuloplasty.

In conclusion, these data confirm that balloon dilation in valvular pulmonary stenosis is safe and effective, and suggest that stenosis does not recur. We believe that the balloon dilation procedure will decrease the morbidity of pulmonary valve stenosis relief compared to the surgical approach. Two-dimensional and Doppler echocardiographic examination are preferred for noninvasive follow-up and can accurately access the severity of residual pulmonary stenosis.

REFERENCES

1. Cheathan JP. Pulmonary stenosis. In: Garson A Jr, Bricker JT, Fisher DJ, Neish SR (eds). The Science and Practice of Pediatric Cardiology. Baltimore; Williams and Wilkins; 1998: 1207-1256.
2. Kan JS, White RI Jr, Mitchell SE, et al. Percutaneous trasluminal balloon valvuloplasty for pulmonary valve stenosis. Circulation 1984; 69: 554-560.
3. Klein AA, Levin AR. Percutaneous balloon valvuloplasty for the treatment of valvular pulmonic stenosis. Pediatr Ann 1987; 16: 629-631, 633-634.
4. Mullins CE, Ludomirsky A, O'Laughlin MMP, et al. Balloon valvuloplasty for pulmonic valve stenosis-two-year follow-up: hemodynamic and Doppler evaluation. Cathet Cardiovasc Diagn 1988; 14: 76-81.
5. Rao PS. Balloon pulmonary valvuloplasty: a review. Clin Cardiol 1989; 12: 55-74.
6. Rao PS. How big a balloon and how many balloons for pulmonary valvuloplasty? Am Heart J 1988; 116: 577-580.
7. Thapar MK, Rao PS. Significance of infundibular obstruction following balloon valvuloplasty for valvar pulmonic stenosis. Amm Heart J 1989; 118: 99-103.
8. Melgares R, Prieto JA, Azpitarte J. Success determining factors in percutaneous transluminal balloon valvuloplasty of pulmonary valve stenosis. Eur Heart J 1991; 12: 15-23.
9. Witsenburg M, Talsma M, Rohmer J, Hess J. Balloon valvuloplasty for valvular pulmonary stenosis in children over 6 months of age: initial results and long-term follow-up. Eur Heart J 1993; 14: 1657-1660.
10. Özme S, Çeliker A, Özkutlu S, et al. Percutaneous transluminal balloon pulmonary valvuloplasty: immediate and medium-term results. Turk J Pediatr 1990; 32: 25-31.
11. Özyürek R, Narin N, Bakiler AR, et al. Çocuklarda balonla pulmoner kapak dilatasyonu. MN Pediatri 1994; 1: 68-71.
12. Kan JS, White RI Jr, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenitaml pulmonary valve stenoiss. N Engl J Med 1982; 307: 540-542.
13. Goldberg SJ. Doppler. echocardiography. In: Moss AJ, Adams FH (eds). Heart Disease in Infants, Children, and Adolescents. Baltimore; Williams and Wilkins; 1968: 81-93.
14. Khan MA, Al-Yousef S, Huhta JC, et al. Critical pulmonary valve stenosis in patients less than 1 years of age: treatment with percutaneous gradational balloon pulmonary valvuloplasty. Am Heart J 1989; 117: 1008-1014.
15. Weber HS, Cyran SE, Gleason MM, et al. Critical pulmonary valve stenosis in the neonate: a technique to facilitate balloon dilation. Am J Cardiol 1994; 73: 310-312.
16. Kirby WC, Laird Jr, Lovett EJ Jr, Farrell Pe Jr. Fixed-wire balloon dilation of criticalpulmonary stenosis. Am Heart J 1993; 126: 1766-1767.
17. Talsma M, Witsenburg M, Rohmer J, Hess J. Determinants for outcome of balloon valvuloplasty for severe pulmonary stenosis in neonates and infants up to six months of age. Am J Cardiol 1993; 71: 1246-1248.
18. Gildein HP, Kleinert S, Goh TH, et al. Treatment of critical pulmonary valve stenosis by balloon dilatation in the neonate. Am Heart J 1996; 131: 1007-1010.
19. Sievert H, Kober G, Bussman WD, et al. Long-term results of percutaneous pulmonary valvuloplasty in adults. Eur Heart J 1989; 10: 712-717.

20. Fawzy ME, Galal O, Dunn B, et al. Regression of infundibular pulmonary stenosis after successful balloon pulmonary valvuloplasty in adults. Cathet Cardiovasc Diagn 1990; 21: 77-81.
21. Coberly LA, Harrison JK, Bashore TM. Percutaneous balloon pulmonic valvuloplasty following treated endocarditis in a patient with congenital pulmonary valve stenosis. Cathet Cardiovasc Diagn 1990; 21: 245-247.
22. Kaul UA, Singh B, Tyagi S, et al. Long-term results after balloon pulmonary valvuloplasty in adults. Am Heart J 1993; 126: 1152-1155.
23. Chen CR, Cheng TO, Huang T, et al. Percutaneous balloon valvuloplasty for pulmonic stenosis in adolescents and adults. Ne Engl J Med 1996; 335: 21-25.
24. Teupe CH, Burger W, Schrader R, et al. Late (five to nine years) follow-up after balloon dilation of valvular pulmonary stenosis in adults. Am J Cardiol 1997; 80: 240-242.
25. Rao PS, Wis M. Indication for balloon pulmonary valvuloplasty. Am Heart J 1988; 117: 1661-1662.
26. Wang JK, Leu HC, Young ML. Efficacy of balloon valvuloplasty in treating mild pulmonary stenosis. Acta Cardiologica 1992; 4: 349-355.
27. Narang R, Das G, Dev V, et al. Effect of the balloon-annulus ratio on the intermediate and follow-up results of pulmonary balloon valvuloplasty. Cardiology 1997; 88: 271-276.
28. Rao PS, Thapar MK, Kutayli F. Causes of restenosis after balloon valvuloplasty for valvular pulmonary stenosis. Am J Cardiol 1988; 62: 979-982.
29. Bhagwat AR, Loya YS. Sharama S. Transient pulmonary hypertension following pulmonary balloon valvuloplasty. Am Heart J 1992; 123: 1397-1398.

Conversion disorder in children and adolescents: clinical features and comorbidity with depressive and anxiety disorders

Berna Pehlivantürk, Fatih Ünal

Department of Child and Adolescent Psychiatry, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Pehlivantürk B, Ünal F. Conversion disorder in children and adolescents: clinical features and comorbidity with depressive and anxiety disorders. Turk J Pediatr 2000; 42: 132-137.

The aim of this study was to determine some of the demographical and clinical characteristics of conversion disorder in children and adolescents and to ascertain comorbidity with depressive and anxiety disorders. For this purpose 51 children and adolescents (mean age: 13.2 ± 1.9, range: 9-16 years) who met DSM-IV criteria for conversion disorder were compared with a control group. The subjects of this study were mostly postpubertal girls, and pseudoseizure was the most frequent presentation. Misdiagnoses were frequent among these patients. Eight (15.7%) patients received a comorbid diagnosis of major depression and 19 (37.2%) patients had comorbid anxiety disorders according to DSM-IV diagnostic criteria. Significant differences between the two groups on depression and anxiety scales supported the clinical findings. It was concluded that clinicians should screen every patient with conversion disorder for major depression and anxiety disorders for a better outcome.

Key words: conversion disorder, children, adolescents, depression, anxiety.

Medically unexplained physical symptoms have long been recognized as common and problematic in pediatric clinics[1]. Children have immature cognitive and verbal skills and their capacity for emotional expression is limited. Considering the communicative role of somatic symptoms, it is not surprising that somatic complaints are frequent in children[2].

DSM-IV defines conversion disorder as a disorder characterized by the presence of one or more neurological symptoms that cannot be explained by a known neurological or medical disorder. In addition, the diagnosis requires psychological factors to be associated with the initiation or exacerbation of the symptoms[3].

Literature from western countries appears to indicate that a diagnosis of conversion disorder is relatively rare in children and adolescents. In contrast to western samples, the epidemiological or clinical studies from India have found conversion disorder in children and adolescents to be the most common psychiatric disorder[4,5]. The clinical studies from Turkey also showed that conversion disorder is a prevalent psychiatric problem for children and adolescents in this country[6,7].

Although it causes major clinical, social and economic problems[8], the studies on conversion disorder are rare. Studies that compared patients with somatic complaints to healthy controls demonstrated a frequent association between somatic symptoms and psychiatric disorders, particularly depression and anxiety disorders[9-11]. However, psychiatric comorbidity in children and adolescents with conversion disorder is poorly studied[12].

In this study, it was planned to determine some of the demographic and clinical characteristics of conversion disorder in children and adolescents, to ascertain comorbidity with depressive and anxiety disorders and to compare with a control group.

Material and Methods

Sample

Children and adolescents with somatic complaints attending the pediatric and adolescent outpatient clinics of a university hospital were evaluated. After a medical investigation to rule out organic disorders, 98 patients aged 9-16 years were referred to the Department of Child Psychiatry.

From 98 initial inquiries, 27 subjects were excluded because they were better accounted for by other somatoform disorders according to DSM-IV diagnostic criteria. In this group undifferentiated somatoform disorders (n = 13), pain disorders (n = 8), somatoform disorders not otherwise specified (n = 4) and somatization disorders (n = 2) were determined. A further 16 subjects were excluded since their somatic symptoms were better accounted for by anxiety disorders. These patients were diagnosed as panic disorders (n = 7), separation anxiety disorders (n = 5), generalized anxiety disorder (n = 1) and anxiety disorders not otherwise specified (n = 3). Other exclusion reasons included psychotic disorders and mental retardation (n = 4). The remaining 51 children and adolescents with conversion disorder according to DSM-IV diagnostic criteria constituted the conversion disorder group.

Fifty-one patients who were brought to the pediatric and adolescent outpatient clinics and matched to the conversion disorder group for age and gender formed the control group. They were matched to the conversion disorder group for age and gender by the following procedure: when a child was accepted to the conversion disorder group, the first patient with the same gender and age on the pediatric or adolescent outpatient list was included in the control group. Exclusion criteria from the control group were the presence of psychiatric symptoms, clinically determined psychotic disorders or mental retardation and parent's refusal to take part in the study.

Measures

Interview form : The researchers developed an interview form consisting of three parts. The first part was designed to record the demographic data. In the second part, the clinical data including the actual complaints of the patient and the family, duration of the symptoms, precipitating medical and psychosocial factors, complications, previous medical problems, and family history of medical and psychiatric disorders were recorded. Medical history details were confirmed with hospital records. The third part of the form included the DSM-IV diagnostic criteria of somatoform disorders, anxiety disorders and affective disorders.

Children's Depression Inventory (CDI) : The CDI is a downward extension of the Beck Depression Inventory for adults[13]. This is a child self-report measurement for depression, suitable for children aged 6-17 years. Evidence supporting the instrument's reliability and validity for the Turkish population is provided by Öy[14] and its cut-off point for depression is determined as 19 points.

State-Trait Anxiety Inventory (STAI) : This is a self-report instrument developed by Spielberger et al.[5] to measure the subjective level of anxiety both in special situations and in general. STAI state scale measures how the subject feels at a particular moment in time and STAI trait scale assesses the general level of anxiety. The mean values in the normative study of STAI range from 36 to 41 points for children 14 years or older. Higher scores indicate higher levels of anxiety. It was standardized for the Turkish population by Öner and LeCompte[16].

State-Trait Anxiety Inventory for Children (STAIC) : STAIC is a self-report instrument that measures the level of anxiety in children[17]. It is a downward extension of STAI and is widely used for children aged 9-14 years. Data supporting the instrument's reliability and validity for the Turkish population is provided by Özusta[18].

Procedure

Children and adolescents with somatic complaints were assessed initially in the pediatric and adolescent outpatient clinics to rule out organic disorders. This assessment consisted of physical and neurological examinations, appropriate laboratory tests and consultations with a pediatric cardiologist or neurologist when necessary. Children without positive medical findings were referred to the department of Child Psychiatry. Two experienced child and adolescent psychiatrists independently evaluated all of the subjects according to DSM-IV diagnostic criteria. The interrater reliability was high (Kapp = 0.877).

Children's Depression Inventory (CDI) was applied to all subjects. However, division of the conversion disorder group due to the age range in the validity and reliability studies of anxiety scales was unavoidable. Thus, children younger than 14 years filled out the STAIC and adolescents older than 14 years filled out the STAI.

Statistical analysis was performed with a computer package program (SPSS 8.0). Chi-square tests 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

Demographic Characteristics

There were 37 female (72.5%) and 14 males (27.5%) in the conversion disorder group. The age range of this sample was from 9 to 16 years and the mean age was 13.2 ± 1.9 years. Thirty-three patients (64.7%) were adolescents (aged 12 to 16 years) and 18 patients (35.3%) were children (aged 9 to 12 years). The female/male ratio was uniform in these age groups ($x^2 = 0.01$, $p = 0.969$). Mean educational level was 7.0 ± 4.0 years and ranged from 4 to 11 years. The control group consisted of 51 patients who were matched to the conversion disorder group for age and gender. Most of the patients in the conversion disorder group came from middle class nuclear families (68.6%, n = 35), with the mother frequently being a housewife (84.3%, n = 43) and the father an employee of the state (68.6%, n = 35). Mean educational level was 7.0 ± 4.0 years for mothers and 10.0 ± 3.8 years for fathers. There were no statistically significant differences between the conversion disorder group and the control group in the demographical parameters, including family type and size, age, educational level and the professions of the parents, and socioeconomic class.

Clinical Parameters

Pseudosezures were the most frequent (76.5%, n =.39) symptoms in the conversion disorder group. Motor symptoms or deficits in three patients (5.9%) and mixed presentation ('involuntary' movements and sensory deficits) in one patient (2.0%).

The age of onset for the conversion disorder symptoms ranged from 8 to 15 years (mean 12.2 ± 2.0 years), and the interval between the onset of the symptoms and the time of the diagnosis ranged from 1 to 60 months (mean 11.8 ± 13.5 months).

A specific event or condition associated with the onset of somatic smyptoms was reported in 47 patients (92.2%). These were relationship problems in most children and adolescents (52.9%, n = 27). In others (25.5%, n = 13), the initiating factor was a medical illness in the family or close environment. Academic problems were also reported to be associated with the beginning of somatic symptoms (13.7%, n = 7). It was found that absence from school was common (66.7%, n = 32) among the conversion disorders group, and two children left school because of their symptoms.

It was noticed that 37.3 percent of the patients (n = 19) were misdiagnosed as organic disorders (mostly epilepsy, n = 14) and 31.4 percent (n = 16) took medications according to these diagnoses. Organic misdiagnoses were more frequent in children younger than 12 years ($x^2 = 3.98$, $p = 0.045$).

Chronic medical illness in the family and close environment was reported in 24 patients (47.1%) in the conversion disorder group and in 15 patients (29.4%) in the control group. This difference tended to be statistically significant ($x^2 = 3.36$, $p = 0.06$). The corresponding rates for the psychiatric disorders were significantly ($x^2 = 17.26$, $p = 0.00003$) higher in the conversion disorder group (33.3%, n = 17) than in the control group (2.0%, n = 1). The psychiatric disorders in the families of the conversion disorder group were conversion disorder (17.6%, n = 9), affective disorders (5.9%, n = 3), substance abuse (3.9%, n = 2), psychotic (3.9%, n = 2), and obsessive compulsive disorder (2.0%, n = 1).

Comorbid Disorders

Eight (15.7%) patients in the conversion disorder group received a comorbid diagnosis of major depression and 19 (37.2%) patients a comorbid diagnosis of anxiety disorders according to DSM-IV diagnostic criteria. Two of the patients who were diagnosed as anxiety disorders also fulfilled the diagnostic criteria for major depression. Although the association between age and comorbid anxiety disorders was statistically insignificant, this was not the case in patients with comorbid major depression. It was found that all

of these patients were adolescent (12-15 years). The comorbid anxiety disorders were generalized anxiety disorders (9.8%, n = 5), separation anxiety disorders (5.9%, n = 3), social phobia (2.0%, n = 1), specific phobia (3.9%, n = 2), panic disorders (2.0%, n = 1), and anxiety disorders not otherwise specified (13.7%, n = 7).

Scales

The CDI scores in the conversion disorder group were significantly higher than in the control group (Table I). Eight (15.7%) patients in the conversion disorder group scored over the pathological cut-off point of 19, and seven of those were diagnosed as major depression in the interviews. Two patients (3.9%) in the control group scored above this point and this difference was found statistically significant ($x^2 = 3.99$, $p = 0.0457$). The CDI scores in adolescents (12-16 years) with conversion disorder (15.0 ± 9.2) were significantly ($t = 3.65$, $p = 0.001$) higher than those of the control group (8.5 ± 4.7). However, the CDI scores in children (9-12 years) did not differ significantly between the two groups.

Table I. Comparison of the CDI, STAI and STAIC Scores Between the Groups

	Conversion disorder group		Control group			
	$\bar{x}$	sd	$\bar{x}$	sd	t	p
CDI	13.4	8.0	8.3	5.2	3.79	0.0001
STAIC						
State	35.4	7.7	32.8	5.5	1.58	0.12
Trait	39.7	6.4	34.0	5.9	3.77	0.0001
STAI						
State	40.8	10.6	39.1	8.9	0.51	0.61
Trait	48.5	10.1	41.2	8.3	2.34	0.025

CDI: Children's Depression Inventory; STAI: State-Trait Anxiety Inventory; STAIC: State-Trait Anxiety Invertory for Children.

The differences between the two groups on the STAI and STAIC state scores were found statistically insignificant. On the contrary, STAI and STAIC trait scores in the conversion disorder group were significantly higher than those of the control groups (Table I).

Discussion

Conversion disorder is three times more common in girls than in boys, is unusual in children less than nine years old and shows an increasing prevalence with age through adolescence[19-24]. In accordance with these reports, the subjects of this study were mostly postpubertal girls. Pseudoseizure was the most frequent presentation followed by motor symptoms like gait disturbances, which was also consistent with the findings of earlier studies[4,19-21,25-27].

In our clinical survery, the interval between the onset of the symptoms and time of the diagnosis was approximately one year. The late admission to the Child Psychiatry Department and the high rate of misdiagnoses are probably because of the diagnostic difficulties in conversion disorder. The repeated and often extensive medical evaluations may have prolonged this period. Increased health care utilization[28,29] and unnecessary laboratory examinations or medical treatment were also documented in the earlier studies[23,30,31]. In this study, the frequency of te organic misdiagnoses was higher in children younger than 12 years. This may imply the difficulties of evaluating psychological factors in children.

Conversion disorder or somatic complaints might cause evident disability in academic and social function, and school absences might influence the academic success. In this study, it was found that school absences were common among the conversion disorder group, and two children left school because of their symptoms. In several other studes, it was also shown that children with somatic symptoms were more likely to have academic difficulties[9,20,32-34].

The diagnosis of conversion disorder requires psychological factors to be associated with the initiation or exacerbation of the symptoms[3]. It is interesting that most of the parents could recognize the associations between the psychological factors and somatic symptoms. Although this parameter was not comparable with the control group, it is thought that these psychological associations could still contribute to other investigations.

It is known that psychiatric disorders in families of children and adolescents with conversion disorder are prevalent[19,22,35]. Considering that similar results were found in this study, it is suggested that the whole family should be evaluated in conversion disorder. An assessment of the etiological role of medical and psychiatric disorders in the family and close environment could also be helpful.

The majority of the psychiatric comorbidity studies in children and adolescents with somatic symptoms deal with recurrent abdominal

pain[9,10,32,36-38], headache[39-41] or chest pain[11,34,42]. Most of these studies demonstrate a frequent association between somatic symptoms and psychiatric disorders, particularly anxiety and depression.

The present study reports a high frequency of anxiety disorders (37.2%, n = 19) and depression (15.7%, n = 8) among children and adolescents with conversion disorder. These rates are higher than the community prevalence data (1.9% for children and 4.7 to 8% for adolescents)[43-46], but are similar to psychiatric population rates in children (16%) for major depression[47]. In a recent study, higher rates for mood disorders (32%) and separation anxiety (24%) were found in a sample of children and adolescents with pseudoseizures[48].

While the association between age and comorbid anxiety disorders was statistically insignificant, it was found that all of the patients with comorbid major depressive disorder were adolescents. Thus, it may be claimed that anxiety disorders are more characteristic for children and major depression for adolescents with conversion disorder.

High scores in the depression and anxiety scales and differences between the two groups on the CDI, STAI and STAIC trait scores supported the clinical findins. High scores in the control group on the STAI and STAIC state scales, which assess the anxiety in a specific setting, were interpreted as a result of being in a hospital or waiting for an examination. Therefore, it is possible to speculate that the general level of anxiety, which was measured by STAI and STAIC trait scales, could play an important role in various clinical aspects of conversion disorder.

In contrast to western samples, conversion disorder may be among the most common of psychiatric difficulties seen in developing countries, where a medical illness may be more acceptable than a mental illness in terms of seeking help[4]. An emotionally distressed patient is more likely to consult a physician with physical symptoms than to complain directly about psychological or social problems.

Comorbid depressive or anxiety disorders in conversion disorder may remain undetected since these patients often ignore or deny their feelings. The indifference to their disabilities, their immature behaviors and easily recognizable secondary gains may also hinder the empathetic understanding of the patient's problem. Moreover, similar psychodynamic factors between conversion disorder and depression, as pointed out in an early study from Turkey[49], may facilitate the comorbidity of these clinical conditions. Therefore, clinicians should screen every patient with conversion disorder for major depression and anxiety disorders for a better outcome. There is also a need for well-controlled, prospective treatment studies in this population.

Acknowledgement

The authors are grateful for the contributions of Birsen Sonuvar, MD and Ferhunde Öktem, PhD to this study.

REFERENCES

1. Campo JV, Fritsch SL. Somatization in children and adolescents. J Am Acad Child Adolesc Psychiatry 1994; 33: 1223-1235.
2. Garralda ME. A selective review of child psychiatric syndromes with a somatic presentation. Br J Psychiatry 1992; 161: 759-773.
3. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (4th ed). Washington DC: American Psychiatric Association; 1994.
4. Srinath S, Bharat S, Girimaji S, Seshadri S. Characteristics of a child impatient population with hysteria in India. J Am Acad Child Adolesc Psychiatry 1993; 32: 822-825.
5. Chandra R, Sikrinivasan S, Chandrasekaran R, Mahadevan S. The prevalence of mental disorders in school age children attending a general paediatric department in southern India. Acta Psychiatr Scand 1993; 87: 192-196.
6. Turgay A. Conversion reactions in children. Psychiatr J Univ Ott 1980; 5: 287-294.
7. Baysal ZB, Öktem F, Ünal F, Pehlivantürk B. The change in the adolescent psychiatric population in ten years. Athens: ISAP 4th International Congress; 1995.
8. Lipowski ZJ. Somatization: the concept and its clinical application. Am J Psychiatry 1988; 145: 1358-1368.
9. Garber J, Zeman J, Walker LS. Recurrent abdominal pain in children: psychiatric diagnosis and parental psychopathology. J Am Acad Child Adoles Psychiatry 1990; 29: 648-656.
10. Hodges K, Kline JJ, Barbero G, Woodruff C. Anxiety in children with recurrent abdominal pain and their parents. Psychosomatics 1985; 26: 859-866.
11. Kashani JH, Lababidi Z, Jones RS. Depression in children and adolescent with cardiovascular symptomatology: the significance of chest pain. J Am Acad Child Adolesc Psychiatry 1982; 21: 187-189.
12. Fritz GK, Fritsch S, Hagino O. Somatoform disorders in children and adolescent: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1997; 36: 1329-1338.

13. Kovacs M. Rating scales to assess depression in school aged children. Acta Paedopsychiat 1981; 46: 305-315.

14. Öy B. Çocuklar için depresyon ölçeği: geçerlik ve güvenirlik çalışması. Türk Psikiyatri Dergisi (Turkish Journal of Psychiatry) 1991; 2: 132-136.

15. Spielberger CD, Gorsuch RL, Lushene RE. Manual for state-trait anxiety inventory. California: Consulting Psychologists Press; 1970.

16. Öner N, LeCompte A. Durumluluk-Sürekli Kaygı Envanteri El Kitabı. İstanbul: Boğaziçi Üniversitesi Yayınları; 1983.

17. Spielberger CD. Manual for state-trait anxiety invertory for children. Palo Alto: Consulting Psychologists Press; 1973.

18. Özusta Ş. Çocuklar için Durumluluk-Sürekli Kaygı Envanteri Uyarlama, Geçerlik ve Güvenirlik Çalışması. Türk Psikoloji Dergisi (Turkish Journal of Psychology) 1995; 10: 32-44.

19. Goodyer IM. Hysterical conversion reactions in childhood. J Child Psychol Psychiatry 1981; 22: 179-188.

20. Volkmar FR, Poll J, Lewis M. Conversion reactions in childhood and adolescents. J Am Acad Child Adolesc Psychiatry 1984; 23: 424-430.

21. Grattan-Smith P, Fairley M, Procopis AP. Clinical features of conversion disorder. Arch Dis Child 1988; 63: 408-414.

22. Steinhausen HC, Aster M, Pfeiffer E, Göbel D. Comparative studies of conversion disorders in childhood and adolescence. J Child Psychol Psychiatry 1989; 30: 615-621.

23. Goodyer IM, Mitchell C. Somatic emotional disorders in childhood and adolescence. J Psychosom Res 1989; 33: 681-688.

24. Woodbury M, Demaso DR, Goldman SJ. An integrated medical and psychiatric approach to conversion symptoms in a 4 year old. J Am Acad Child Adolesc Psychiatry 1992; 31: 1095-1097.

25. Turgay A. Treatment outcome for children and adolescents with conversion disorder. Can J Psychiatry 1990; 35: 585-588.

26. Kerimoğlu E, Yalın A. Obsessive-compulsive disorder and hysteria (conversion reaction) in children. Journal of Ankara Medical School 1992; 14: 11-18.

27. Avcı A, Aslan H. Çocuklarda obsesif kompulsif bozukluk ve konversiyon bozukluğu: Karşılaştırmalı bir klinik çalışma. Türk Psikiyatri Dergisi (Turkish Journal of Psychiatry) 1995; 6: 49-53.

28. Ford CV. The somatizing disorders. Psychosomatics 1986; 25: 327-337.

29. Smith GR, Rost K, Kashner TM. A trial of the effect of a standardized psychiatric consultation on health outcomes and costs in somatizing patients. Arch General Psychiatry 1995; 52: 238-243.

30. Kim WJ. Psychiatric aspects of epileptic children and adolescents. J Am Acad Child Adolesc Psychiatry 1991; 30: 874-886.

31. Goodyer IM. Epileptic and pseudoepileptic seizures in childhood and adolescence. J Am Acad Child Adolesc Psychiatry 1985; 24: 3-9.

32. Wasserman A, Whitington PF, Rivara FP. Psychogenic basis for abdominal pain in children and adolescents. J Am Acad Child Adolesc Psychiatry 1988; 27: 179-184.

33. Robinson JO, Alvarez JH, Dodge JA. Life events and family history in children with recurrent abdominal pain. J Psychosom Res 1990; 34: 171-181.

34. Pantell RE, Goodman BW. Adolescent chest pain: a prospective study. Pediatrics 1983; 71: 881-887.

35. Ercan ES, Varan A, Veznedaroğlu B, Akdeniz F, Aydın C. Ergenlerde konversiyon bozukluğuna ilişkin özelliklerin araştırılması. Türk Psikiyatri Dergisi (Turkish Journal of Psychiatry) 1998; 9: 165-172.

36. Hodges K, Kline JJ, Barbero G, Flanery R. Depressive symptoms in children with recurrent abdominal pain and in their families. J Pediatr 1985; 107: 622-626.

37. McGrath PJ, Goodman JT, Firestone P, Shipman R, Peters S. Recurrent abdominal pain: a psychogenic disorder? Arch Dis Child 1983; 58: 888-890.

38. Walker LS, Garber J, Greene JW. Somatization symptoms in pediatric abdominal pain patients: relation to chronicity of abdominal pain and parent somatization. J Abnormal Child Psychol 1991; 19: 379-394.

39. Cunnigham SJ, McGarth PJ, Ferguson HB. Personality and behavioral characteristics in pediatric migraine. Headache 1988; 27: 16-20.

40. Kowal A, Pritchard D. Psychological characteristics of children who suffer from headache: a research note. J Child Psychol Psychiatry 1990; 31: 637-649.

41. Larsson B. Somatic complaints and their relationship to depressive symptoms in Swedish adolescents. J Child Psychol Psychiatry 1991; 32: 821-832.

42. Tunaoğlu FS, Olguntürk R, Akçabay S, Oğuz D, Gücüyener K, Demirsoy S. Chest pain in children referred to a cardiology clinic. Pediatr Cardiol 1995; 16: 69-72.

43. Weller E, Weller R. Depressive disorders. In: Lewis M (ed). Child and Adolescent Psychiatry. Baltimore: Williams and Wilkins; 1991: 652-664.

44. Lewinsohn PM, Clarke GN, Seeley JR, et al. Major depression in community adolescents: age at onset, episode duration and time to recurrence. J Am Acad Child Adolesc Psychiatry 1994; 33: 809-818.

45. Flemming JE, Offord D. Epidemiology of childhood depressive disorders: a critical review. J Am Acad Child Adolesc Psychiatry 1990; 29: 571-580.

46. Kashani JH, Beck NC, Hoeper EW. Depression, depressive symptoms and depressive mood among a community sample of adolescents. Am J Psychiatry 1987; 144: 931-934.

47. Alessi NE, Magen J. Comorbidity of other psychiatric disturbances in depressed, psychiatrically hospitalized children. Am J Psychiatry 1988; 145: 1582-1584.

48. Wyllie E, Glazer JP, Benbadis S, Kotagal P, Wolgamuth B. Psychiatric features of children and adolescents with pseudoseizures. Arch Pediatr Adolesc Med 1999; 153: 244-248.

49. Gökler B. A study on the diagnostic validity of childhood depression. Journal of Ankara Medical School 1988; 10: 33-44.

Are the stool characteristics of preterm infants affected by infant formulas?

Nuray Duman, Selvinaz Utkutan, Hasan Özkan, Şebnem Özdoğan

Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

SUMMARY: Duman N, Utkutan S, Özkan H, Özdoğan Ş. Are the stool characteristics of preterm infants affected by infant formulas? Turk J Pediatr 2000; 42: 138-144.

The aim of this study was to investigate the relationship between the type of formula consumed and the stool characteristics and gastrointestinal symptoms of preterm infants prospectively. Seventy-five preterm infants weighing < 2000 g in our neonatal intensive care unit (NICU) were investigated. Four groups of 15 each were fed one of four commercial formula preparations (Prematil, Nenatal, Humana-0 and S-26) and the fifth group was breast-fed in a prospective, randomized, double-blind study. The stool characteristics and gastrointestinal problems were recorded daily from the first day till the time they were discharged by the nurses of NICU. No significant differences of daily weight gain was observed between the groups. No significant difference was observed in daily frequency of stool, distention, vomiting and gas passage between the groups during the enteral+parenteral and full-enteral nutrition periods. The infants fed by Prematil during the enteral+parenteral nutrition period had a higher percentage of hard stool occurrence than infants receiving Humana-0 and breast milk. In the full-enteral nutrition period, infants receiving Prematil had a higher percentage of hard stool occurrence than all the other groups, whereas breast-fed infants had a lower percentage of hard stool than all the other groups. While the group fed with Humana-0 had a higher percentage of green stool occurrence in the enteral+parenteral nutrition period, no significant difference was observed in the full-enteral nutrition period. In the enteral+parenteral nutrition period no additional therapy affected stool characteristics or the gastrointestinal system except in the case of the infant receiving phototherapy for whom the daily number of detections was significantly high. In this study, it was shown that the color and consistency of stool in preterm infant differs according to the preterm infant formulas, but no differences were observed in the frequency of defecation or in gastrointestinal system problems. When the infant formulas were compared with breast milk, it was shown that they cause a higher percentage of hard stool occurrence. An increased number of formula feedings are necessary to obtain a similar daily weight gain, but the color and the frequency of the stool and the gastrointestinal system problems were similar for breast-fed and formula-fed infants.

Key words: breast feeding, infant formulas, stool characteristics.

While the effects of breast-feeding on stool characteristics are well known, few studies have been published about the effects of different formulas[1-3]. Preterm infants, although in need of more, have a lower ratio of breast-feeding due to their prematurity and maternal health problems. However, knowledge about the effects of premature formulas on the stool characteristics in insufficient. What we know is mostly about the effects of enteral nourishment on the first stool passage[4-10]. Many premature infants are switched between multiple formula preparations either in the neonatal intensive care unit (NICU) or after discharge from the hospital because of perceived abnormalities in the stooling pattern as well as gastrointestinal symptoms.

This stuy has been designed prospectively to reveal the effects of breast-milk and four different formulas on stool characteristics and gastrointestinal symptoms of premature infants.

Material and Methods

Infants born in Dokuz Eylül University Hospital or transferred from another hospital on their first day to the NICU between January 1996 and November 1997 with a birth weight less than 2000 g were enrolled in the study. The infants were fed with breast milk or one of four different formulas (Prematil, Nenatal, Humana 0, and S-26) prepared for low birth weight infants in a randomized, double-blind prospective study. Composition of the study formulas is shown in Table I. The formulas were used only in the absence of breast milk. Infants with feeding alterations were excluded from the study (e.g. Infants fed by formulas at the beginning but changed to breast-milk in the following days or those first fed by breast-milk but needing additional nutrients).

Table I. Composition of Study Milk

	Breast	Prematil	Nenatal	Humana 0	S-26
Carbohydrate g/100 ml	6.8 (lactose)	7.7 (lactose, maltodextrine)	8 (lactose, corn syrup solids)	8.2 (lactose, maltodextrine)	8.4 (lactose, maltodextrine)
Protein g/100 ml	0.9 40% casein 60% whey	2 40% casein 60% whey	2.2 40% casein 60% whey	2 50% casein 50% whey	1.6 40% casein 60% whey
Fat g/100 ml	3.8	3.5 (milk, vegetable and animal fats)	4.4 (vegetable and milk fats)	3.8 (vegetable fat)	4.3 (vegetable and animal fats)
Iron mg/100 ml	0.3	0.07	0.9	1.1	0.38
Energy kcal/100 ml	71	70	80	75	79

Infants with anatomic, metabolic or neurological pathologies which could effect gastrointestinal system function were also excluded from the study.

The nurses of the NICU recorded the following daily: the time of passage of first stool and beginning of enteral and full-enteral feeding; the volumes of enteral feeding; changes in body weight; treatments which may affect the stool characteristics (antibiotics, aminophylline, calcium, indomethacin, furosemide, steroid, iron, phototherapy); stool frequency, color and consistency; and gastrointestinal problems (gas, vomiting, distention). The nurses referred to a special card[11] to evaluate the consistency and color of the stool objectively. A scoring system was used for evaluating gas and vomiting characteristics. According to this system no gas was defined as absent or minimal gas (0 point), "mild" connoted gas passed several times during the day (1 point), and "severe" referred to very frequent gas passage (2 points). Vomiting was described as none (0 point), "few" if it occurred no more than twice daily and involved only a mouthful of milk (1 point), and "many" if there were three or more episodes of effortless emesis or forceful vomiting (2 points). All the parameters were evaluated in two different categories, the parenteral+enteral feeding period and the full-enteral feeding period.

Statistical Analysis: Information form the daily logs of stool characteristics was summarized as follows. Totals for the parenteral+enteral and full-enteral feeding periods were obtained by adding daily totals for number of stools, and the number each of yellow, brown, or green stools, and of hard, firm, or watery stools. An average daily stool number was calculated. Stool color and consistency totals were expressed as the percentage of all stools for each feeding period.

The scores of gas and vomiting characteristics and distention occurrence were calculated for each day and expressed as the percentage of the total day per each period. The average of these values for each infant were calculated. Group means for each feeding type were calculated for all these values per each period. Group means for each feeding type were also calculated for the following: birth weight, gestational age, body weight at the time of discharge, time of passage of first stool, time birth weight was

regained and the time enteral and full-enteral feeding were begun. Group means of the daily weight gain and volume of milk ingested were calculated only during the full-enteral feeding period for each feeding type. If the group mean differences were statistically significant with Kruskal-Wallis one-way analysis of variance test ($p < 0.05$), Mann-Whitney U test was used for multiple group comparisons. The effects of additional therapies on stool frequency, color, consistency and gas, distention, and vomiting characteristics during the parenteral+enteral feeding period were evaluated. An error of < 5% was accepted as evidence of statistical significance.

Results

A total of 75 infants, 15 infants from each group, completed the study. Eighteen infants with a deviation from feeding protocol and two infants who were operated because of perforated necrotizing enterocolitis during the parenteral+enteral feeding period (in Humana 0 group) were excluded from the study. No infant was dropped from the study because of milk related problems. The results of the study were derived from the observation of 4,835 stools passed by 75 preterm infants during 2,097 infants days.

The characteristics of the study infants are shown in Table II. Sex, the time of passage of first stool, beginning of enteral feeding, regaining of the birth weight and body weight at the time of discharge were not statistically different for all feeding groups.

However, breast-fed infants had a lower birth weight ($p = 0.485$, $p = 0.0061$, $p = 0.0368$, respectively) and gestational age ($p = 0.0171$, $p = 0.0044$, $p = 0.0172$, respectively) than infants fed by Prematil, Humana 0 or S-26. Full-enteral feeding was started earlier in the Humana 0 group tahn in the breast-fed or Nenatal groups ($p = 0.0021$, $p = 0.0053$, respectively). In the full-enteral feeding period, the volume of milk ingested was less in breast-fed infants than in infants fed Prematil, Nenatal or Humana 0, whereas no significant difference in daily weight gain ($p = 0.0009$, $p = 0.0179$, $p = 0.0051$, respectively) was observed during the same period. But breast-fed infants with a lower birth weight were discharged from the hospital with a lower body weight than infants in the Prematil, Nenatal, and Humana 0 groups ($p = 0.0066$, $p = 0.0249$, $p = 0.0084$, respectiely).

Stool Frequency: The relationship of milk type to stooling frequency is shown in Tables III and IV. No significant difference was observed in the full-enteral feeding period ($p = 0.1224$). Stool numbers were similar in all feeding groups in the same period ($p = 0.1173$). Only stooling frequency was compared in the parenteral+enteral feeding period because it differs from infant to infant, but no significant difference was observed ($p = 0.2569$). Although not statistically significant, stooling frequency was observed to be higher in those infants receiving breast milk compared with the other four formulas in both periods.

Table II. Characteristics of the Study Groups

	Breast	Prematil	Nenatal	Humana 0	S-26
Number completing study	15	15	15	15	15
Birth weight (g)	1340 ± 363* (750-2000)	1642 ± 350 (1030-2000)	1577 ± 288 (995-2000)	1751 ± 283 (1185-2000)	1676 ± 308 (1000-2000)
Gestational age (wk)	29.7 ± 2.4*	31.7 ± 1.8 (28-34)	31.3 ± 2.3 (28-35)	32.3 ± 1.9 (27-35)	32.1 ± 1.9 (28.34)
Male-Female (no)	8/7	7/8	9/6	6/9	5/10
First stool passage time (d)	2 ± 0.9 (1-3)	1.4 ± 0.5 (1.-2)	1.5 ± 0.7 (1-3)	1.6 ± 0.7 (1-3)	1.7 ± 0.9 (1-3)
Length of hospital stay (d)	46.2 ± 30.4 (13-111)	25.2 ± 14.7 (11-64)	29.7 ± 15.7 (13-58)	20.7 ± 11.2 (9-48)	28.6 ± 22.0 (10-59)
Beginning of enteral feeding (d)	4.3 ± 2.6 (2-10)	5.1 ± 4.6 (2-15)	5.0 ± 4.0 (1-16)	3.7 ± 1.8 (2-7)	5.0 ± 6.3 (1-20)
Switch to full-enteral feeding (d)	22.9 ± 14.1 (7-55)	13.5 ± 8.1 (4-30)	19.7 ± 12.8 (7.49)	9.7 ± 4.6* (3.21)	18.4 ± 20.1 (3-53)
Volume of milk ingested in full-enteral feeding (ml)	34 ± 3* (30-41)	36 ± 2 (32-39)	36 ± 2 (34-39)	36 ± 2 (34-38)	35 ± 3 (30-39)
Daily weight gain in full-enteral feeding period (g)	28 ± 8 (10-41)	25 ± 11 (9-46)	28 ± 10 (8-51)	25 ± 10 (9-41)	23 ± 9 (10-37)
Body weight at the time of discharge (g)	1800 ± 154* (1550-2000)	1919 ± 102 (1690-2105)	1909 ± 107 (1745-2055)	1929 ± 101 (1790-2065)	1864 ± 134 (1670-2150)

Data expressed as mean ± standard deviation (min-max) *$p < 0.05$.

Table III. Stooling Frequency in the Full-enteral Feeding Period

Milk type	Total stools/7 days* Mean ± SEM (min-max)	Daily stools* Mean ± SEM (min-max)
Breast	25.07 ± 3.32 (7-41)	3.58 ± 0.47 (1-5.86)
Prematil	18.34 ± 2.4 (7-34)	2.62 ± 0.31 (1-4.86)
Nenatal	17.7 ± 2.1 (8-35)	2.52 ± 0.30 (1.14-5.0)
Humana 0	18.1 ± 1.4 (11-26)	2.63 ± 0.20 (1.57-3.71)
S-26	13.1 ± 2.7 (4-26)	1.87 ± 0.38 (0.57-3.71)

* $p > 0.05$, SEM: Standard error of mean.

Table IV. Stooling Frequency in the Parenteral+Enteral Feeding Period

Milk type	Daily stools* Mean ± SEM (min-max)
Breast	2.79 ± 0.38 (1.24-7.16)
Prematil	2.29 ± 0.23 (1-4)
Nenatal	1.89 ± 0.30 (0.5-4.5)
Humana 0	2.03 ± 0.20 (1.2-4)
S-26	1.98 ± 0.35 (0.67-3.75)

* $p > 0.05$, SEM: Standard error of mean.

Stool color: The relationship of stool color to type of infant feeding is shown in Figs. 1 and 2. In the parenteral+enteral feeding period no significant difference was observed in brown stool where as green stool was more common in the infants fed Humana 0 than in the other groups. However, no significant difference was observed between the groups in stool color during the full-enteral feeding period.

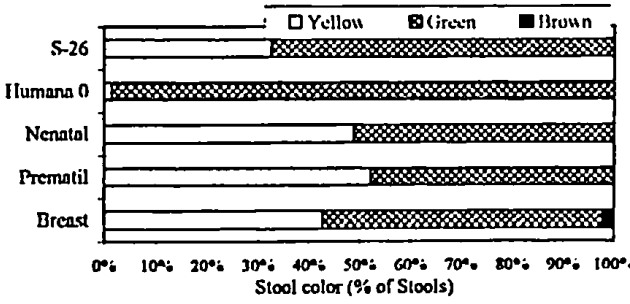


Fig. 1. Relationship of infant formula to stool color in the parenteral+enteral feeding period.

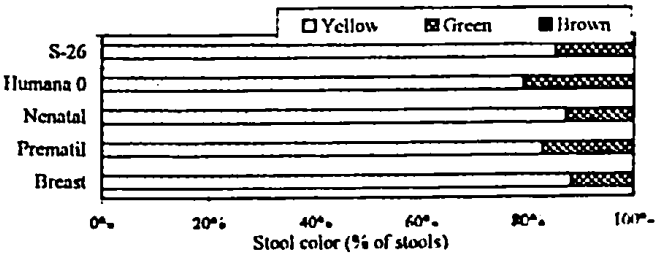


Fig. 2. Relationship of infant formula to stool color in the full-enteral feeding period.

Stool Consistency: In the parenteral+enteral feeding period, hard stools were significantly more frequent in those infants fed Prematil than in the breast-milk or Humana 0 groups ($p = 0.0228$, $p = 0.0033$, respectively) and similarly in infants fed Nenatal than in the Humana 0 group ($p = 0.0352$). No significant difference was observed between the groups in terms of watery stool (Fig. 3). In the full-enteral feeding period, hard stools were significantly more frequent in the Prematil group compared with all the others. In the same period no significant difference was observed in terms of watery stool. However, firm stool was more common in those infants fed Nenatal, Humana 0, S-26 or breast-milk than in the infants fed Prematil ($p = 0.0080$, $p = 0.0036$, $p = 0.0249$, $p = 0.0104$, respectively) (Fig. 4).

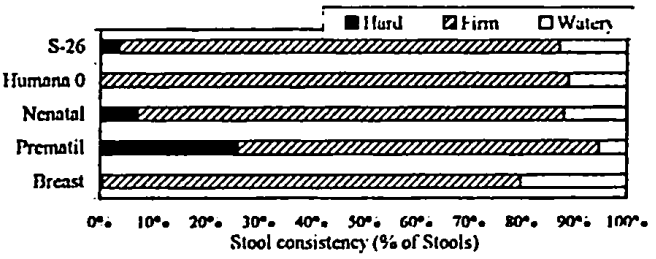


Fig. 3. Relationship of infant formula to stool consistency in the parenteral+enteral feeding period.

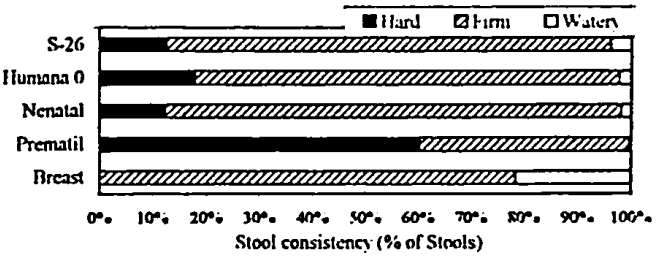


Fig. 4. Relationship of infant formula to stool consistency in the full-enteral feeding period.

Distention, Vomiting and Gas: The relationship of type of milk ingested to gas, distention and vomiting is shown in Figs. 5, 6, 7, 8, 9 and 10, for both feeding periods. No significant difference was observed between the groups.

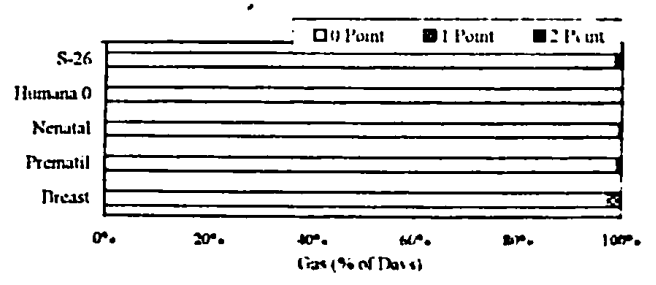


Fig. 5. Relationship of infant formula to gas in the parenteral+enteral feeding period.

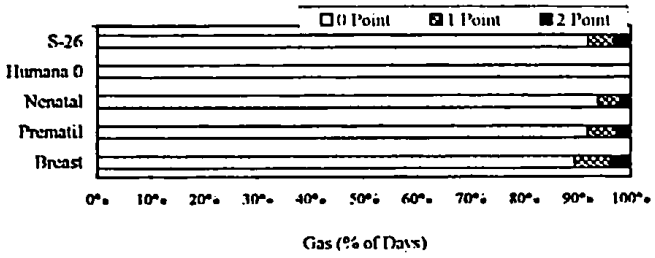


Fig. 6. Relationship of infant formula to gas in the full-enteral feeding period.

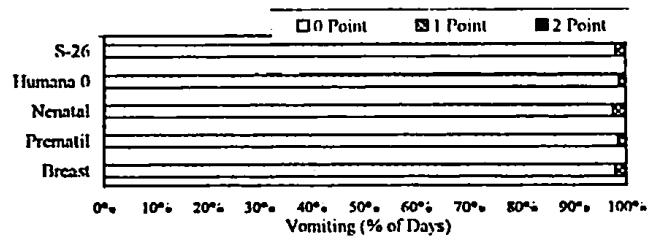


Fig. 7. Relationship of infant formula to vomiting in the parenteral+enteral feeding period.

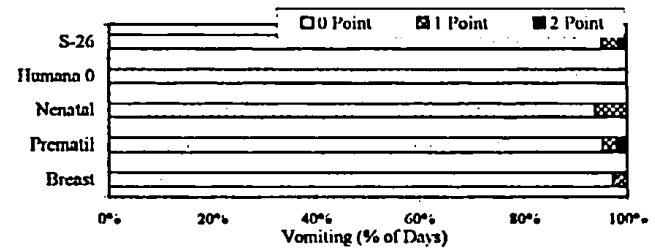


Fig. 8. Relationship of infant formula to vomiting in the full-enteral feeding period.

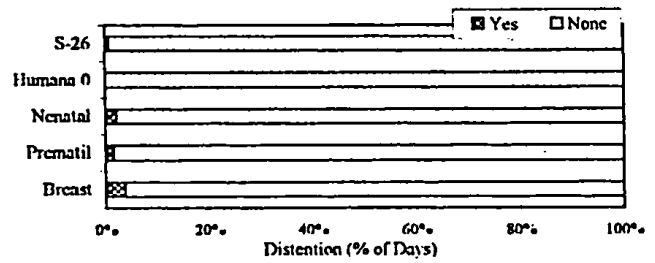


Fig. 9. Relationship of infant formula to distention in the parenteral+enteral feeding period.

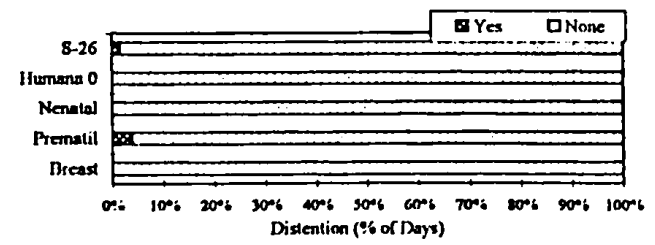


Fig. 10. Relationship of infant formula to distention in the full-enteral feeding period.

Effects of Additional Therapies: In the parenteral+enteral feeding period, additional therapies (antibiotics, aminophylline, calcium, indomethacin, furosemide, corticosteroid, iron) with the exception of phototherapy, had no effect on stool characteristics or gastrointestinal system problems. However, stool frequency of the infants receiving phototherapy was significantly high ($p = 0.0273$).

Discussion

In this prospective study, we investigated the stool characteristics and gastrointestinal system problems of infants with a birth weight less than 2000 g fed by a variety of commercial infant formulas as well as breast-milk in two periods, the parenteral+enteral feeding period and the full-enteral feeding period. Our data show that feeding with breast-milk or the other commercial infant formulas has no effect on the time of passage of the first stool. The inverse relation between gestational age and the time of the passage of first stool has been shown in previous studies. It has been well documented in earlier studies that over 95 percent of healthy full term infants pass their first stool within 24 hours of birth[12]. It has also been recognized that neonates of low birth weight (LBW) may have a delayed passage of meconium; only 80 percent of 500 infants of less than 2500 g passed meconium by 24 hours after birth[4-6]. Delayed passage (more than 48 hours) was also noted in 20.4 percent of 171 very LBW infants[7]. In a recent study including 611 infants with a birth weight less than 1850 g, 57 percent of infants born before 29 weeks' gestation, 66% of infants of 29-32 weeks, and 80 percent of preterm infants of greater than 32 weeks' gestation passed their first stool by the end of the second calendar day[8]. Our data confirm these findings. Delayed passage in infants small for gestational age can be explained by the physiological immaturity of the motor mechanisms of the gut and by the lack of triggering effect of enteral feeds on the gut hormones[9]. Another study, confirming our data, demonstrated that the type of feeding had no effect on the timing of the first stool in very LBW infants who were fed breast-milk or infant formula or on total parenteral nutrition during the first 14 days of life[10].

Stooling frequency, independent from gestational age, was found to be related with the volume of milk ingested. This relation was

found highly significant during the first week, and until the sixth week[8]. In the same study infants with a birth weight less than 1850 g passed one more stool each day for each 50 ml/kg increase in volume of milk ingested during the second to fourth weeks of life. Those infants who received human milk had a greater defecation rate than those receiving cows' milk formula throughout the first eight weeks after birth. The last finding was also shown in term infants[1-3]. We did not observe a direct relation between the volume of milk ingested and the number of stools passed each day in either study period. Although not statistically significant, stooling frequency was observed to be higher in the breast-fed group during the parenteral+enteral and full-enteral feeding periods.

Another effective factor on stooling frequency was phototherapy. In the parenteral+enteral feeding period, infants receiving phototherapy had an increase in stooling frequency, similar to previous studies[13,14], in all feeding groups.

In a study comparing two different fat containing commercial formulas, mean stool frequency was observed to be higher in the infants fed the formulas containing a higher fat ratio, but the mean weight gain was not significantly different[15]. Although all formulas in our study had a similar composition, mean weight gain was also not different between all groups during the full-enteral feeding period. However, it was significant that the mean weight gain of the infants fed by breast-milk was similar with the infants fed by formulas, although the volume of milk ingested is less because of the lower birth weight.

Previous studies demonstrated that green stool was more common with formulas containing more iron and yellow stool was more common with formulas containing less iron[16-18]. In a study designed to compare breast-milk and four different commercial formulas, one month old, healthy, term infants were fed two different iron-containing formulas for one week. Green stools predominated in infants fed by formulas containing more iron[1]. In the same study, it was also demonstrated that formulas containing 60 percent whey, 40 percent casein protein content, soy protein isolate or casein hydrolysate preparation were associated with primarily green stools. In our study no difference in stool color was observed in all groups during the full-enteral feeding period. While we did not observe any brown stool, the percentage of yellow stool was high in all groups. Although the amonut and bioavailability of the iron contents of the formulas were different, similarity to breast-milk explains the higher percentage rate of yellow stool. Stool color was not affected by the formulas containing different amounts of protein. Rates of yellow and green stools were similar during the parenteral+enteral feeding periods in all groups except for infants fed Humana 0. The higher rate of green stool in the full-enteral feeding period could be explained by the occurrence of green stooling after the meconium passage in this period. Also, the high percentage (98.6%) of green stool observed in infants fed Humana 0 could be explained by an earlier onset of the full-enteral feeding period. Because of this, more stool was passed in this period after the meconium passage. Brown stools were observed only in the breast-fed infants, in an insignificant ratio, during the parenteral+enteral feeding period. In a study in which term infants fed either breast-milk or formulas between 2-20 weeks were enrolled, stool color was observed uniformly yellow until the introduction of weaning feeds, when it changed to brown[3].

It was determined that infants fed breast-milk had more firm stool consistency than infants fed by commercial formulas in both term[1-3] and preterm[8] infants. Formulas containing soy protein isolate make the stool consistency firmer because of fiber they contain[1,19]. In a study designed to compare breast-milk and four different commercial formulas in term infants, it was determined that iron amount in formulas did not increase the stool consistency. Additionally, in infants fed breast-milk and lower fat and higher carbohydrate-containing formulas, watery stool was more common because of fast stool passage and looser stool structure[1]. In our study group, infants fed breast-milk had a significantly low percentage of hard stool compared to other groups in the full-enteral feeding period. But we could not explain the higher percentage of hard stool observed in infants fed Prematil than in infants fed other similar formulas in both feeding periods.

In our study group, similar to previous studies[1], no difference was found in the relationship between the feeding type and gas, distention and vomiting in both feeding periods. For this reason, the tendency to switch between multiple

formula preparations because of perceived abnormalities in the stooling pattern and gastrointestinal symptoms, without defined therapeutic goals, should be avoided. Also, additional treatments with the exception of phototherapy had no significant effect on stool characteristics and gastrointestinal system functions.

In this prospective study, the effects of different commercial formulas and breast-milk on stool characteristics were investigated by experienced NICU nurses rather than by parents in a wide perspective and for a long time. When the results were compared with the "gold standard" breast-milk, premature infant formulas caused more frequent hard stools, but in terms of stool color, frequency and gastrointestinal problems, they were similar with breast-milk. Further studies are needed to evaluate the effects of different commercial formulas on preterm infants' feeding. However, it must always be kept in mind that the best nutrient for all infants, especially for premature infants, is breast-milk.

REFERENCES

1. Hyams JS, Treem WR, Etienne N, et al. Effect of infant formula on stool characteristics of young infants. Pediatrics 1995; 95: 50-54.
2. Weaver LT. Bowel habit from birth to old age. J Pediatr Gastroenterol Nutr 1988; 7: 637-640.
3. Weawer LT, Ewing G, Taylor LC. The bowel habit of milk-fed infants. J Pediatr Gastroenterol Nutr 1988; 7: 568-571.
4. Kramer I, Sherry SN. The time of passage of the first stool and urine by the premature infant. J Pediatr 1957; 47: 373-376.
5. Clark DA. Time of first void and first stool in 500 newborns. Pediatrics 1977; 60: 457-459.
6. Mangurten HH, Clade CI, Reidl CJ. First stool in the preterm, low-birth-weight infant. J Pediatr 1973; 82: 1033-1036.
7. Jhaveri MK, Kumar SP. Passage of the first stool in very low birth weight infants. Pediatrics 1987; 76: 1005-1007.
8. Weaver LT, Lucas A. Development of bowel habit in preterm infants. Arch Dis Child 1993; 68: 317-320.
9. Wang PA, Huang FY. Time of the first defaecation and urination in very low birth weight infants. Eur J Pediatr 1994; 153: 279-283.
10. Meetze WH, Palazzolo VL, Bowling D, Behnkke M, Burchfield DJ, Neu J. Meconium passage in very-low-birth-weight infants. JPEN 1993; 17: 537-540.
11. Motonobu F. A Chart of Infant and Children's Stools. Tokyo: Sanposha; 1983.
12. Sherry SN, Kramer I. The time of passage of first stool and first urine by the newborn infant. J Pediatr 1955; 46: 158-159.
13. Wu PY, Moosa A. Effect of phototherapy on nitrogen and electrolyte levels and water balance in jaundiced preterm infants. Pediatrcs 1978; 61: 193-198.
14. Berant M, Diamond E, Brik R, Yurman S. Phototherapy-associated diarrhea. The role of bile salts. Acta Paediatr Scand 1983; 72: 853-855.
15. Spencer SA, McKenna S, Stammer J, Hull D. Two different low birth weight formulae compared. Early Hum Dev 1992; 30: 21-31.
16. Oski FA. Iron-fortified formulas and gastrointestinal symptoms in infants: a controlled study. Pediatrics 1980; 66: 168-170.
17. Malacaman EE, Abbousy FK, Crooke D, Nauyok G. Jr. Effect of protein source and iron content of infant formula on stool characteristics. J Pediatr Gastroenterol Nutr 1985; 4: 771-773.
18. Bradley CK, Hillman L, Sherman AR, Leedy D, Cordano A. Evaluation of two iron-fortified, milk based formulas during infancy. Pediatrics 1993; 91: 908-914.
19. Treem WR, Hyams JS, Blankschen E, Etienne N, Paule CL, Borschel MW. Evaluation of the effect of a fiber-enriched formula on infant colic. J Pediatr 1991; 119: 695-701.

Drug-resistant tuberculosis in Turkish children

Embiya Dilber, Ayhan Göçmen, Nural Kiper, Uğur Özçelik

Chest Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Dilber E, Göçmen A, Kiper N, Özçelik U. Durg-resistant tuberculosis in Turkish children. Turk J Pediatr 2000; 42: 145-147.

The purpose of this study was to determine the prevalence of anti-tuberculosis drug resistance in children followed at Hacettepe University İhsan Doğramacı Children's Hospital. Sixty cases with tuberculosis for whom susceptibility testing was available were searched retrospectively. Teh overall drug resistance was 26.7 percent. Resistance to streptomycin (sm) was the most frequent (18.3%), followed by isoniazid (6.7%), rifampicin (6.5%), and ethambutol (4.2%). Strain resistant to more than one drug was present in two cases (3.3%).

In summary, excluding SM, both single and multidrug resistance were relatively low in our pediatric patients.

Key words: children, tuberculosis, durg resistance.

Since isolation of tubercle bacilli and susceptibility testing take a long time, test results frequently are not available when the patient needs to start on therapy. Also, a subtantial portion of cases of tuberculosis in children are not confirmed by culture, making susceptibility testing impossible[1,2]. Empiric therapy is often necessary. In order to choose an empiric regimen likely to be effective, local patterns of drug resistance must be known. This is especially important in early childhood because the morbidity and mortality of tuberculosis is at its highest during this period[1,2]. Most studies about drug-resistant tuberculosis have been reported in adult patients. Few extensive data are available in children, a problem not only in Turkey, but also in other countries[2,3]. We thus conducted a retrospective study of M. tuberculosis resistance in children followed in our division with culture-positive tuberculosis.

Material and Methods

We included in this study all patients with culture-positive tuberculosis who were followed at Hacettepe University Children's Hospital between 1975 and 1995 and for whom susceptibility testing was performed in Hıfzısıhha Institute, which is a reference laboratory for tuberculosis (TB) studies in Turkey. According to the localization of the disease, most of the specimens investigated were sputum, followed by tissue specimens, cerebrospinal fluid, and peritoneal fluid, respectively.

Both culture and susceptibility testing was performed on Löwenstein-Jensen solid media. Standard proportion method was used for the susceptibility testing. The drug concentrations used were: isoniazid (INH), 0.2 µg/ml; rifampicin (RIF), 40 µg/ml; streptomycin (SM), 4 µg/ml; and ethambutol (EMB), 2 µg/ml. Drug resistance was defined as the presence of at least one percent growth on the drug plate for INH and RIF and 10 percent for SM and EMB when compared with that on the control plate.

Single drug resistance was defined as the presence of resistance to a single drug tested and multidrug resistance as presence of resistance to at least two drugs tested. Drug resistance detected in patients without a history of previous treatment was defined as primary resistance. Resistance in a patient with a history of previous drug treatment was defined as secondary resistance.

Other clinical and demographic information about the patients were obtained from the hospital files. Student's t and chi-square tests were used in the statistical analysis.

Results

Between 1975 and 1995, among the culture-positive patients, 60 cases for whom susceptibility testing was performed in Hıfzısıhha Institute were reported. All isolated strains were M. tuberculosis hominis. Patients were from different regions of the country. Their ages ranged from two months to 15 years (mean 5.2 ± 4.5 years, median 4.0 years). Human immunodeficiency virus serology was not investigated but within the three to 15 year follow-up period (mean 6.05 ± 0.44 years), no patients were diagnosed as acquired immunodeficiency syndrome. Forty-one patients were diagnosed as pulmonary disease and 19 as extrapulmonary tuberculosis. Eight patients with extrapulmonary tuberculosis also had pulmonary involvement. Lymph nodes were the most common extrapulmonary sites (13.3%), followed by tuberculous meningitis (10%), osseous tuberculosis (6.7%), and abdominal tuberculosis (1.8%), respectively.

Overall resistance to at least one antituberculous drug was present in 16 (26.7%) patients (Table I). Strains of M. tuberculosis resistant to a single drug were found in 14 (23.3%) patients. Nine of the single drug-resistant strains were found to be SM-resistant. Multidrug resistance was present in only two (3.3%) cases: one against two drugs and one against three drugs. Strain resistant to more than three drugs was not isolated. The most common drug resistance was found to be SM (18.3%), followed by INH and RIF. No strain was resistant to INH and RIF simultaneously, but resistance to one or the other was present in seven patients. Since there was no history of previous treatment, all resistance was defined as primary resistance.

Table I. Incidence of Anti-Tuberculosis Drug Resistance

	Strains tested	Strains resistant	
Drug	(n)	(n)	(%)
INH	60	4	6.7
RIF	46	3	6.5
SM	60	11	18.3
EMB	44	1	2.3
INH only	60	3	5
RIF only	46	2	4.3
SM only	60	9	15
EMB only	44	–	–
RIF+SM	46	1	22
INH+SM+EMB	44	1	2.3
Overall resistance	60	16	26.7

INH : isoniazid.
RIF : rifampicin.
SM : streptomycin;
EMB : ethambutol.

The number of cases with SM-resistant strains increased from 3/26 (11.5%) to 8/34 (23.5%) (Table II). All four strains resistant to INH were observed in the last ten years (between 1986 and 1995). Neither increase was significantly different (p = 0.23, p = 0.07 respectively). Overall resistance in pulmonary tuberculosis was 21.9 percent, and for extrapulmonary tuberculosis it was 36.8 percent (p = 0.23).

Discussion

The most significant finding in the present study was the high rate of SM resistance, as has been seen in many other reports, including another study from Turkey[3-5]. This is attributed to its being the longest and most frequently used both in TB and other non-TB infections. We excluded SM from intermittent anti-TB therapy in our division after discovering this high resistance rate[6,7]. Indeed, considering our

Table II. Drug Resistance of M. tuberculosis from 1975 to 1995

	Isoniazid			Rifampicin			Streptomycin			Ethambutol		
		Resistant strains			Resistant strains			Resistant strains			Resistant strains	
	Strains Tested	(n)	(5)	Strains Tested	(n)	(%)	Strains Tested	(n)	(%)	Strains Tested	(n)	(%)
1975-1985	26	–	–	14	1	7.1	26	3	11.5	10	–	–
1986-1995	34	4	11.8	32	2	6.3	34	8	23.5	34	1	2.9
Total	60	4	6.6	46	3	6.5	60	11	18.3	44	1	2.3

results, this was an appropriate decision. INH and RIF were the other two drugs with a high resistance rate. On the other hand, resistance to EMB, which is usually employed when the organism is resistant to the more commonly used agents or when there are severe side effects, was low. In this report, EMB had been used in only two cases because of the presence of liver disease.

Two strains showed resistance to more than one drug, but no strain was defined as resistant to both INH and RIF. It is especially important, because these two drugs are the choice in two-drug intermittent regimens in our department. Patients were successfully treated with these regimens and within the three to 15 year follow-up period no relapses were reported.

Resistance rate was unexpectedly higher in patients with extrapulmonary disease (36.8% vs 21.9%). The other report with a similar high drug resistance in extrapulmonary tuberculosis was from Ben-Dov et al.[8]; however, most of their patients had secondary resistance. In our study there was no previous treatment, so all our cases had primary resistance. Because of its high mortality and morbidity when compared to pulmonary disease, we believe that any resistance in extrapulmonary sites is clinically more important.

We observed an insignificant increase in the resistance against SM and INH over the last ten years. Since INH was the drug of choice in the prophylaxis of tuberculosis in our division for many years, more attention should be given to this increase. Rifampicin resistance was not altered during this period.

Few data are currently available about drug-resistant TB in Turkey. In 1992, a study in adult patients revealed that overall drug resistance was 35.5 percent[5]. In the same study, primary and secondary drug resistance were 26.6 and 53.4 percent, respectively. Streptomycin was the drug to which resistance was encountered most frequently, as in our study. Also, in two other studies reported from Turkey, overall and multiple drug resistance were higher[9,10]. The higher drug resistance as compared to our results may be partially due to the high rate of secondary resistance, since there was no secondary drug resistance in our study.

Identification of adult source cases and information about their drug susceptibilities are helpful in the selection of early empirical treatment. In many reports, an excellent correlation of the patient and the adult source was shown[4]. No information about the source case susceptibility pattern was available in our patient files. This is especially important since resistance in our cases, which appeared to be primary, might actually be due to transmission of resistant strains from adult source cases. In sumary, excluding SM, both single and multidrug resistance were relatively low in our pediatric patients. Much attention should be given to adult source case isolation and drug susceptibility pattern. The pattern reported here is important not only for Turkey but also for other developed countries in the selection of empirical regimens for foreign-born patients.

REFERENCES

1. American Thoracic Society and the Center for Disease Control and Prevention. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994; 149: 1359-1374.
2. Ussery XT, Valway SE, Mckenna M, Cauthen GM, Mccray E, Onorato IM. Epidemiology of tuberculosis among children in the United States: 1985 to 1994. Pediatr Infect Dis J 1996; 15: 697-704.
3. Steiner M, Rao M, Mitchell M, Steiner M. Primary drug-resistant tuberculosis in children. Emergence of primary drug-resistant strains of M. tuberculosis to rifampin. Am Rev Respir Dis 1986; 134: 446-448.
4. Steiner P, Rao M, Mitchell M, Steiner M. Primary drug-resistant tuberculosis in children. Correlation of drug-susceptibility pattern matched patient and source case strains of Mycobacterium tuberculosis. Am J Dis Child 1985; 139: 780-782.
5. Tahaoğlu K, Kizkin O, Karagöz T, Tor M, Portal M, Sadoğlu T. High initial and acquired drug resistance in pulmonary tuberculosis in Turkey. Tuber Lung Dis 1994; 75: 324-328.
6. Göçmen A, Özçelik U, Kiper N, et al. Short course intermittent chemotherapy in childhood tuberculosis. Infection 1993; 21: 324-327.
7. Kiper N, Göçmen A, Dilber E, Özçelik U. Effectiveness of short course intermittent chemotherapy for tuberculosis in infants aged less than six months. Clin Pediatr 1998; 37: 433-436.
8. Ben-dov I, Mason GR, Drug resistant tuberculosis in a southern California hospital. Trends from 1969 to 1984. Am Rev Respir Dis 1987; 135: 1307-1310.
9. Tümer F, Osmanlıoğlu G. Memleketimizde 1987-1991 yıllarında tüberküloz ilaçlarına direnç durumu. Tüberküloz ve Toraks 1994; 42: 117-121.
10. Gülmez İ, Sehnem E, Demir R, Özesmi M. Son beş yılda hastanemizde yatarak tedavi edilen tuberküloz olgularının rezistans durumları. Tüberküloz ve Toraks 1994; 42: 176-179.

Pulmonary hemosiderosis with juvenile rheumatoid arthritis: a case report

Rezan Topaloğlu[1], Nural Kiper[1], Ayhan Göçmen[1], Birgül Varan[2], Ümit Saatçi[2]

[1]Department of Pediatrics, Hacettepe University Faculty of Medicine, and [2]Department of Pediatrics, Başkent University Faculty of Medicine, Ankara, Turkey

SUMMARY: Topaloğlu R, Kiper N, Göçmen A, Varan B, Saatçi Ü. Pulmonary hemosiderosis associated with juvenile rheumatoid arthritis: a case report. Turk J Pediatr 2000; 42: 148-150.

Pulmonary hemosiderosis may rarely be associated with juvenile rheumatoid arthritis or can develop during the course of the disease.

We present a three-year-old boy with severe iron deficiency anemia (without any pulmonary symptoms) and arthralgia at the time of diagnosis. Two years after the initial diagnosis he developed pulmonary hemosiderosis and pauciarticular type of juvenile rheumatoid arthritis which progressed to seronegative polyarticular juvenile rheumatoid arthritis. He responded very well to prednisolone and was maintained well on low-dose alternate-day prednisolone and naproxen sodium treatment. This is the only case of association of these two diseases in our experience in both the Pediatric Rheumatology and Pediatric Respiratory Diseases Departments.

Key words: pulmonary hemosiderosis, juvenile rheumatoid arthritis, associate disease.

Pulmonary hemosiderosis is characterized by an abnormal accumulation of hemosiderin following diffuse alveolar hemorrhage. It may occur either as a primary disease of the lungs, idiopathic pulmonary hemosiderosis (IPH) or as secondary to cardiac, hemorrhagic and collagen diseases[1].

Juvenile rheumatoid arthritis (JRA) is the most frequent pediatric collagen disease. Extra-articular manifestations of JRA include uveitis, pericarditis, myocarditis, central nervous system disease, renal glomerulitis, pleuropulmonary disease and pulmonary hemosiderosis[2-7]. We report a patient with pulmonary hemosiderosis associated with pauciarticular JRA and progressed to polyarticular JRA.

Case Report

A three-year-old male patient presented with fatigue, tachycardia with a heart rate of 125/minute, and tachypnea with a respiratory rate of 38/minute. He had a low-grade systolic murmur; the remainder of the physical examination was unremarkable. The laboratory investigations revealed a hemoglobin (Hb) of 2.3 g/dl, hematocrit of 12%, white cell count of 18,000/mm^3, reticulocyte count of 3.85% and hypochromic microcytosis on peripheral smear. The serum iron level and iron binding capacity were 13 mg/dl (normal 60-80) and 404 mg/dl (normal 200-400), respectively, with a transferrin saturation of 3%. The serum ferritin level was 32.1 ng/ml (normal 17-230). The direct and indirect Coombs' tests were negative and the hemoglobin electrophoresis and osmotic fragility tests were normal. The chest X-ray was normal. He was diagnosed as having iron deficiency anemia of unknown cause. The patient responded to iron replacement therapy. Seven months later the patient presented with anorexia and cough. His hemoglobin level and hematocrit were normal (14.2 g/dl and 42%, respectively). Two years later the patient was found to have arthritis and arthralgia of this right knee. He had minimal clubbing and both the liver and spleen were palpable 2 cm below the costal margin. His Hb was 8.6 g/dl, white blood count 12,300/mm^3, erythrocyte sedimentation rate (ESR) 56 mm/hour and C-reactive protein (CRP) (+). Antinuclear antibody test and rheumatoid factor were

negative. Serum complement 3 and 4 were normal. Within a month he developed arthritis of right elbow and ankle along with right knee. His ESR and CRP levels remained elevated. He was put on non-steroidal anti-inflammatory treatment with a diagnosis of JRA. Two months later the patient was admitted to hospital with chest pain and cough. His physical examination revealed tachycardia, tachypnea, clubbing, suprasternal and intercostal retractions and hepatosplenomegaly. Chest X-ray revealed bilateral diffuse reticulo-nodular infiltrates (Fig. 1) with a hemoglobin level of 6 g/dl. His family did not give permission for a lung biopsy but hemosiderin-laden macrophages were found in the gastric washing. Further laboratory examinations revealed serum anti-glomerular basement membrane antibody (anti-GBM) and anti-nuclear cytoplasmic antibody (ANCA) as negative. The pulmonary function test by spirometry (Mirato AS-600 Autospiro) revealed a mild obstructive and moderately restrictive pattern. He was put on 2 mg/kg/day prednisolone with a diagnosis of pulmonary hemosiderosis and JRA. He responded to prednisolone showing a normal chest X-ray (Fig. 2) and pulmonary function test, and the hemoglobin level increased to 12.7 g/dl. The patient continued to have joint symptoms and progressed to polyarticular JRA and was put on naproxen sodium 10 mg/kg/day with alternate-day 5 mg prednisolone. On long term follow-up of five years there was no recurrence of either arthritis or pulmonary hemosiderosis.

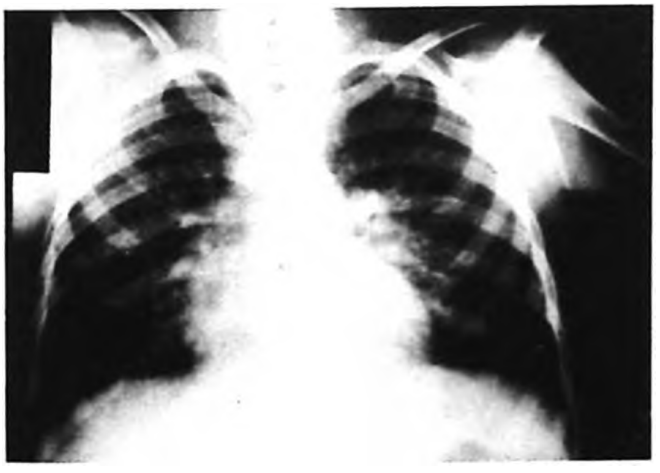


Fig. 1. Chest X-ray showing bilateral fine reticulonodular infiltrates in mid and lower zones.

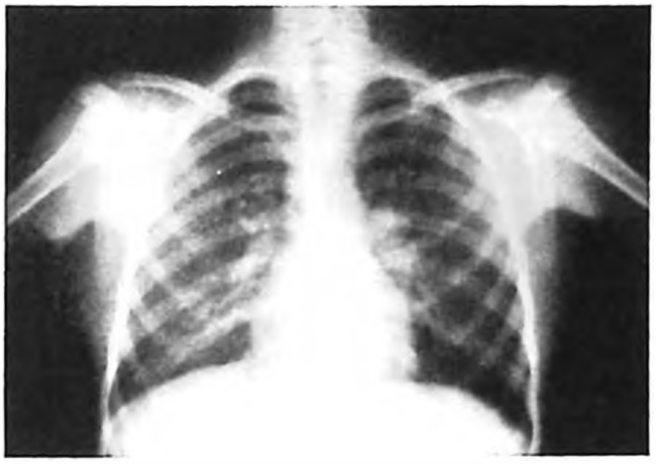


Fig. 2. Note the desappearance of diffuse reticulonodular infiltrates after prednisolone treatment.

Discussion

Manifestations of the pleuropulmonary disease in JRA include transient pneumonitis, interstitial reticular and nodular infiltrates, pleural effusion and patchy pleural infiltrates and, very rarely, hemosiderosis[2,6,8]. Most RA patients with signs of pleuropulmonary disease have other clinical evidence of RA, but in some instances the lung disorder may precede the usual clinical manifestations of RA. In such circumstances, the diagnosis is suggested by serologic tests or may not be suspected until the other obvious manifestations of RA have become evident.

Idiopathic pulmonary hemosiderosis (IPH) is a disease of unknown etiology, usually occurring in children and young adults. Even though the favorable results of immunosuppressive therapy in this disease support the presumed association of the disease with an autoimmune disturbance, this does not necessarily indicate that idiopathic pulmonary hemosiderosis itself is due to an immune disturbance[3]. Damage to pulmonary alveolar tissue by a variety of agents might initiate in some individuals an autoimmune process, or patients with IPH may have a type III immune response with irregular deposition of immune complex material along the basement membrane. In these cases there is no specific antigen-antibody reaction to basement membranes as seen in Goodpasture's syndrome, but instead the basement membranes appear to act as a site for deposition of toxic complexes resulting in tissue damage[3]. On the other hand, whether or not immune deposits in the lung are necessary for pulmonary hemorrhage is controversial. Pulmonary hemorrhage can develop with no detectable immune complex deposits in lung[9].

The association of IPH and RA was first noted by Karlish[4]. Lemley and Katz[3] claimed in their report that as in three other previously reported cases, pulmonary hemosiderosis was not idiopathic but rather a presenting manifestation of rheumatoid arthritis. JRA also may rarely present with pulmonary hemorrhage in children[2,8]. Furthermore, Cunnigham et al.[10] reported a five-year-old female with JRA who developed pumonary hemosiderosis and hematuria two years later and died in respiratory failure. Our patient first presented with iron deficiency anemia with no accompanying pulmonary findings until about seven months later when he had only a cough. Two years later he had developed pauciarticular JRA that progressed to polyarticular JRA. The full-blown picture of alveolar hemorrhage was seen two months after the joint manifestations. He is the only patient to present with JRA and pulmonary hemosiderosis in our experience at the Pediatric Nephrology and Rheumatology Department in the last 20 years. He is also the only patient to have the association out of 23 patients with idiopathic pulmonary hemosiderosis treated between 1980-1998 at the Pediatric Respiratory Diseases Department[11].

Although the significance of the association remains to be elucidated, this case, as do the others previously published, shows the possibility of the association of pulmonary hemosiderosis and rheumatoid arthritis. Associated diseases should be borne in mind in severe iron deficiency anemia of uncertain etiology as well as in IPH.

REFERENCES

1. Soergel KH, Sommers SC. Idiopathic pulmonary hemosiderosis and related syndromes. Am J Med 1962; 32: 499-511.
2. Cassidy JT, Petty RE. Juvenile chronic arthritis. In: Textbook of Pediatric Rheumatology. New York, Edinburgh, London, Melbourne: Churchill Livingstone; 1990: 113-219.
3. Lemley DE, Katz P. Rheumatoid-like arthritis presenting as idiopathic pulmonary hemosiderosis. J Rheumatol 1986; 13: 954-957.
4. Karlish AJ. Idiopathic pulmonary hemosiderosis with unusual features. Proc R Soc Med 1962; 55: 223-225.
5. Ognibene MA, Dito MW. Chronic disease with unusual pulmonary manifestations. Arch Intern Med 1965; 116: 567-572.
6. Smith BS. Idiopathic pulmonary hemosiderosis and chronic arthritis. B Med J 1966; 1: 1403-1404.
7. Dhuillier JP, Desrues B, Chales G, et al. Hemosiderose pulmonaire idiopathique et polyarterite rhumatoide. Rev Pneumol Clin 1988; 44: 136-139.
8. Athreya BH, Doughty RA, Bookspan M, Schumacher HR, Sewel EM, Chatten J. Pulmonary manifestations of juvenile chronic arthritis: a report of eight cases and review. Clin Chest Med 1980; 1: 361-374.
9. Louie S, Russell LA, Richeson RB, Cross CE. Circulating immune complexes with pulmonary hemorrhage during pregnancy in idiopathic pulmonary hemosiderosis. Chest 1993; 104: 1907-1909.
10. Cunnigham R, Hammond D. Pulmonary hemosiderosis associated with a collagen vascular syndrome. Am J Dis Child 1961; 102: 643.
11. Kiper N, Göçmen A, Özçelik U, Dilber E. Idiopathic pulmonary hemosiderosis in Turkish children. Second International Congress on Pediatric Pulmonology 2-6 June 1996 Nice, France.

Salmonella septic arthritis in a patient with acute idiopathic thrombocytopenic purpura treated with steroid

Güler Kanra, Gülten Seçmeer, Müge Toyran, A. Bülent Cengiz
Yasemin Değertekin, Ateş Kara

Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Kanra G, Seçmeer G, Toyran M, Cengiz AB, Değertekin Y, Kara A. Salmonella septic arthritis in a patient with acute idiopathic thrombocytopenic purpura treated with steroid. Turk J Pediatr 2000; 42: 151-154.

Salmonella has three clinical presentations: self-limiting gastroenteritis, a systemic syndrome (enteric or typhoid fever), and bacteremia with focal infection. Hematogenous infections can cause focal lesions, but unusual manifestations occur more often when predisposing factors such as T cell defect, hemolytic disorders (sickle cell disease, malaria) or trauma are present. Salmonella tend to invade bones and joints. There is no mention of acute idiopathic (immune) thrombocytopenic purpura as a predisposing factor for salmonella septic arthritis; however there are reports about the importance of platelets for the immune response. Here we present a case of Salmonella enteritidis septic arthritis following acute idiopathic (immune) thrombocytopenic purpura in a 15-year-old female patient who has been on steroid therapy for the last two weeks.

Key words: idiopathic thrombocytopenic purpura, septic arthritis, Salmonella enteritidis, steroid therapy.

Salmonellosis has three clinical presentations: self-limiting gastroenteritis, a systemic syndrome (enteric or typhoid fever), and bacteremia with focal infection. Asymptomatic intestinal and biliary existence of the microorganism (carrier state) is another clinical form. Focal lesion can involve unusual sites, presenting as meningitis; pleuropulmonary infection; endocarditis; pericarditis; arteritis; osteomyelitis; arthritis; splenic, hepatic, soft tissue and intra-abdominal abscess and urogenital disorders[1]. Hematogenous infections can cause focal lesions in eight percent of patients, but unusual manifestations more often occur when predisposing factors such as T cell defect, hemolytic disorders (sickle cell disease, malaria) or trauma are present[2]. Salmonella tends to invade bones and joints. Salmonella osteomyelitis and, more rarely, septic arthritis are seen, especially in patients with sickle cell anemia[3]. However, salmonella septic arthritis without any predisposing factor is also reported[4,5].

Here we present a case of Salmonella enteritidis septic arthritis following acute idiopathic (immune) thrombocytopenic purpura (ITP). To the best fo our knowledge this is the first salmonella septic arthritis case presented after ITP.

Case Report

A 15-year-old girl followed up by the Pediatric Hematology Department as acute ITP for the previous two weeks presented with right hip pain that limited her walking. Two weeks previously she had complained of sudden bruising and petechia but was in excellent health with an otherwise normal physical examination. Bone marrow aspiration revealed an increased number of megakaryocytes without leukemic cells. She had been treated with high-dose methylprednisolone (3 days 30 mg/kg, 3 days 20 mg/kg, and 4 days 10 mg/kg) as with our other ITP patient[6], but was accepted unresponsive. On the tenth day of therapy she was admitted to the emergency care unit with fever, right hip pain and scattered petechia.

Physical examination revealed tenderness, hyperemia, increased temperature and limited range of motion in the right hip joint, petechia predominantly on her legs and oral mucosa. There were no other remarkable

physical findings. Laboratory findings are given in Table I. Microscopic examination of stained blood film showed thrombocytopenia with leukocytosis, 68% being polymorphonuclear leukocytes with 100% toxic granulation and an erythrocyte sedimentation rate of 60 mm/hour. Emergency ultrasonography was reported as 12 mm effusion in the right hip joint. Hemarthrosis or septic arthritis was suspected; however, her thrombocytopenia prevented us from performing joint fluid aspiration to make differential diagnosis.

Table I. Laboratory Findings

Hemoglobin	: 12.9 g/dl (12-18)
Hematocrit	: 39%
WBC count	: 16,000/mm^3 (4,000-10,000/mm^3)
Platelet count	: 20,000/mm^3 (150,000-400,000/mm^3)
ESR	: 60 mm/h
Blood smear	: 68% PML, 10% lymphocyte, 20% monocyte, 2% eosinophil, toxic granulation 100%, rare and single platelet.
IgA	: 102 mg/dl (100-430 mg/dl)
IgM	: 110 mg/dl (80-400 mg/dl)
IgG	: 1160 mg/dl (800-1700 mg/dl)
C_3	: 123 mg/dl (90-180 mg/dl)
C_4	: 24 mg/dl (10-40 mg/dl)
Anti DNA	: Negative
ANA	: Negative
Anticardiolipin	IgM: Negative
	IgG: Negative
Anti CMV	IgM: Negative
	IgG: 250 IU/ml
Anti EBV	IgM: Negative
	IgG: Pozitive
Anti toxoplasma	IgM: Negative
	IgG: Pozitive
Anti HSV 1	IgM: Negative
	IgG: 1.281 IU/ml
Anti HSV 2	IgM: Negative
	IgG: 1.161 IU/ml
HB_sAg	: Negative
Anti-HB_s	: Negative
Anti-HB_C Total	: Negative
Anti HCV	: Negative
Stool culture	: Negative
Stool cultures (family)	: Negative
Salmonella agglutination	: O Ag group B: negative
	group D: 1/80
	H Ag group B: negative
	group D: negative
Salmonella agglutination (family)	: negative

WBC: white blood cell; ESR: erythrocyte sedimentation rate; PML: polymorphonuclear leukocytes; CMV: cytomegalovirus; EBV: Epstein-Barr virus.

The patient was hospitalized and cephalothin (100 mg/kg/day) and amikacin (15 mg/kg/day) were begun, assuming the patient was a septic arthritis case. Intravenous immunoglobulin (IVIG) treatment (400 mg/kg/day) was given for her thrombocytopenia. On the fifth day of this treatment, her platelet count reached 114,000/mm^3, and joint fulid aspiration was finally performed. Joint fluid was purulent; microscopic examination of Gram and Wright stained joint fluid revealed no microorganism but many polymorphonuclear leukocytes. Emergency exploration and debridement was performed. Purulent fluid in surgery and persistent fever led us to change her antibiotics to vancomycin (40 mg/kg) and amikacin (15 mg/kg). This combination was continued until Salmonella enteritidis was isolated from both blood and joint aspiration fluid culture bacterial susceptibility is given in Table II. In light of the antibiogram ciprofloxacin was started instead. Unfortunately her fever and pain did not subside, so to rule out endovascular complication of salmonella infection and echocardiographic examination was performed which showed normal echocardiographic findings. Sultamicilin was added to her treatment, and MRI of the hip joint revealed joint effusion and intramedullary edema in the femoral head, suggesting osteomyelitis. The joint was explored and the infected bone was debrided in a second operation.

Her clinical condition and laboratory parameters started to improve after the first and third week, respectively, and were normal within four weeks. She is now being followed after four weeks of antimicrobial therapy with a good clinical outcome.

Table II. Antibiotic Susceptibility
Salmonella Enteritidis

	Blood Culture	Joint Aspiration Fluid
Ciprofloxacin	Susceptible	Susceptible
Chloramphenicol	Resistant	Resistant
TMP/SMX*	Resistant	Resistant
Ampicillin	Resistant	Resistant
Amoxicillin/Clavulanic acid	Resistant	Resistant
Cefotaxime	Resistant	Resistant
Ceftriaxone	Resistant	Resistant

* Trimethoprim-sulfamethoxazole.

Discussion

Salmonella septic arthritis is a rare disease occurring in less than 0.3 percent of patients with nontyphoidal salmonellosis[7]. Sickle cell disease one of the well known presenting disorders in salmonella septic arthritis. Prior joint disease (rheumatoid arthritis, osteoarthritis, gout), previous trauma, connective tissue disease, lymphoma, hemolytic diseases and immunosuppressive treatment are

other common predisposing factors. Malnutrition is also accused in populations where salmonella is endemic[8]. Salmonella infection can cause two types of arthritis: monoarticular infectious arthritis and polyarticular subacute reactive arthritis[9]. The presence of bacterial lipopolysaccharides in the joint is a common and pathogenically important feature of reactive arthritis[10]. Circulating immune complexes activating both classical and alternative pathways are also effective in the pathogenesis of reactive arthritis[11].

Salmonella serotypes most commonly causing focal infections are S. hirschfeldii, S. cholerasuis and S. typhimurium. S. virchow has recently been reported as a cause of focal infection[12,13]. In our patient group D salmonella (S. typhi, S. enteritidis, S. gallinarum, S. ontario, S. II zuerich), Salmonella enteritidis (by serotyping study) was isolated from blood and joint aspiration fluid. Serotyping of salmonella species was performed by O somatic antigen, first phase H antigen and second phase antigen. In S. enteritidis, O somatic antigen was 9-12, first phase H antigen was Gm and second phase antigen was absent. In this way it was differentiated from other Group D salmonella. Similar to our case, S. enteritidis was reported in the literature to cause septic arthritis involving both knee joints in a 29-year-old man with Hodgkin's lymphoma[14].

There is no report of ITP as a predisposing factor for salmonella septic arthritis. In spite of this, there are reports about the importance of platelets for the immune response[15,16]. Platelets are known to 1. rapidly respond to sites of endovascular trauma and chemotactic stimuli associated with microbial colonization, and to be the earliest and predominant cells at sites of microbial colonization of vascular endothelium 2. possess surface receptors and cytoplasmic granules comparable in structure and function to neutrophils, monocytes and macrophages 3. adhere directly to and possibly internalize microbial pathogens, enhancing the clearance of these pathogens from the blood stream and limiting their potential for hematogenous dissemination 4. kill or damage bacterial, fungal, and protozoal pathogens in vitro 5. initiate or amplify complement fixation in the presence of microorganisms 6. release microbicidal proteins when stimulated in vitro with microorganisms or platelet agonists associated with infection 7. generate oxygen metabolites and 8. interact synergistically with leukocytes to exert enhanced antimicrobial functions in vitro[16]. Thus, thrombocytopenia increases the susceptibility to and severity of certain infections. Salmonella are in the group of microorganisms which are demonstrated to interact and aggregate with and be inhibited or killed by activated platelets in vitro[17-19]. Some reports implicate that salmonella resistant to platelet-derived microbicidal proteins in vivo may have increased virulence[20,21].

It is known that in systemic lupus erythematosus and hemolytic diseases impaired opsonization is relevant to the predisposition of salmonella septic arthritis[22]. Immune complexes are another common aspect of salmonella arthritis and ITP. ITP is an autoimmune disease in which immune complex formation may take place, and salmonella septic arthritis is associated with immune complexes. This leads one to think that although ITP and salmonella have complex outcomes they interacted some way in our patient.

Steroid therapy as immunosuppressive treatment is also known as a risk factor. The occurrence of salmonellosis may be related to the carrier state of the patient or to exposure to salmonella species. Sytemic lupus erythematosus (SLE) patients who are salmonella carriers are reported to develop septic arthritis when combined cyclophosphamide and prednisolone treatment is given[22]. Salmonella are microorganisms that live intracellularly; therefore, cellular immunity is the main host defense against salmonellosis. It is well known that impaired cellular immunity is a predisposing factor for salmonella septic arthritis. Corticosteroids cause alterations in leukocyte count (neutrophils increase, lymphocytes decrease), redistribution, suppression of migration to sites of inflammation, decreased response to mitogens, and decreased cytotoxicity[1]. Although complaints of our patient started early in steroid therapy, high-dose steroid may also have been a predisposing factor for infections in this patient.

It is concluded that in patients with ITP presented with septic arthritis, Salmonella should be suspected as an etiologic agent; both the disease itself and/or its treatment may predispose to the infections.

REFERENCES

1. Aschkenazi S, Cleary TG. Salmonella infections. In: Nelson WE, Behrman RE, Arvin AM (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: Saunders Company; 1996; 784-787.
2. Saphra I, Winter JW. Clinical manifestation salmonellosis in man: an evaluation of 7779 human infections identified at New York Salmonella Center. N Engl J Med 1957; 256: 1128-1134.
3. Anand AS, Glatt EA. Salmonella osteomyelitis and arthritis in sickle cell disease. Semin Arth Rheum 1994; 24: 211-221.
4. Morgan MG, Forbes KJ, Gİllespie SG. Salmonella septic arthritis: a case report and review. J Infect 1990; 21: 195-203.
5. Govender S, Chotai PR. Salmonella osteomyelitis and septic arthritis. J Bone Joint Surg 1990; 72: 504-506.
6. Özsoylu Ş, Irken G, Karabent A. High dose intravenous methylprednisolone for acute childhood idiopathic thrombocytopenic purpura. Eur J Haematol 1989; 42: 431-435.
7. Cohen JI, Bartlett JA, Corey GR. Extraintestinal manifestations of salmonella infections. Medicine 1987; 66: 349-388.
8. Lavy CB, Lavy VR, Anderson I. Salmonella septic arthritis in Zambian Children. Trop Doct 1995; 25: 163-166.
9. Sweak AJ, Van Soesberger RM, Van der Korst JK. Arthritis associated with salmonella infection. Clin Rheumatol 1982; 1: 275-279.
10. Granfors K, Jalkanen S, Lindberg AA, et al. Salmonella lipopolysaccharide in synovial cells from patients with reactive arthritis. Lancet 1990; 335: 685-688.
11. Manicourt DH, Orloff S. Immune complexes in polyarthritis after salmonella gastroenteritis. J Rheumatol 1981; 8: 613-620.
12. Lalitha MK, John R. Unusual manifestations of salmonellosis-a surgical problem. Q J Med 1994; 87: 301-309.
13. Nathwani D, Morris AJ, Laing RB, Smith CC, Reid TM. Salmonella virchow: abscess former amongst the contemporary invasive Salmonellae? Scand J Infect Dis 1991; 23: 467-471.
14. John R, Mathai D, Daniel AJ, Lalitha MK. Bilateral septic arthritis due to Salmonella enteritidis. Diagn Microbiol Infect Dis 1993; 17: 167-169.
15. Cohen P, Gardner FH. Thrombocytopenia as a laboratory sign and complication of gram-negative bacteremic infection. Arch Intern Med 1966; 117: 113-124.
16. Yeaman MR. The role of platelets in antimicrobial host defense. Clin Infect Dis 1997; 25: 951-968.
17. Miragliotta G, Lafata M, Jirillo E. Anti-bacterial activity mediated by human platelets. Agents Actions 1988; 25: 401-406.
18. Timmons S, Huzoor A, Grabarek J, Kloczewiak M, Hawiger J. Mechanism of human platelet activation by endotoxic glycolipid-bearing mutant Re595 of Salmonella minnesota. Blood 1986; 68: 1015-1023.
19. Mandell GL, Hook EW. The interaction of platelets, Salmonella, and mouse peritoneal macrophages. Proc Soc Exp Biol Med 1969; 132: 757-759.
20. GroismanEa, Parra Lopez C, Salcedo M, Lipps CJ, Heffron F. Resistance to host antimicrobial peptides is necessary for Salmonella virulence. Proc Natl Acad Sci USA 1992; 89: 11939-11943.
21. Field PI, Groisman EA, Heffron FA. Salmonella locus that controls resistance to microbicidal proteins from phagocytic cells. Science 1989; 243: 1059-1062.
22. Van de Laar MA, Meenhorst PL, Van Soesbergen RM, Olsthoorn PG, Van der Korst JK. Polyarticular Salmonella bacterial arthritis in a patient with systemic lupus erythematosus. J Rheumatol 1989; 16: 231-234.

Asplenia in a patient with Fanconi's anemia-like congenital aplastic anemia

Erol Erduran, Ayşenur Ökten, Gülay Kaya, Alişan Yıldıran

Department of Pediatrics, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey

SUMMARY: Erduran E, Ökten A, Kaya G, Yıldıran A. Asplenia in a patient with Fonconi's anemia-like congenital aplastic anemia. Turk J Pediatr 2000; 42: 155-157.

Fanconi's anemia (FA) is an autosomal recessive disease manifested by pancytopenia resulting from bone marrow failure, variable physical anomalies and cancer susceptibility. A seven-year-old girl with Fanconi's anemia-like congenital aplastic anemia and concurrent asplenia without the congenital heart defects or the abdominal heterotaxia is reported. Asplenia was indicated using denatured red cells labelled with^{51} Cr, abdominal ultrasonography and computerized tomography. Immunological studies showed immunoglobulins (IgG, IgA, IgM), C_3 and C_4 levels within normal limits and the percentage of CD_3, and C_4 cells and the CD_4/CD_8 ratio decreased. The patient had not been exposed to recurrent pneumococcal infections. We think that isolated asplenia may occur in patients with Fanconi's anemia-like congenital aplastic anemia without the congenital heart diseases or abdominal heterotaxia.

Key words: asplenia, Fanconi's anemia-like congenital aplastic anemia.

Fanconi's anemia (FA) is an autosomal recessive disease that presents with pancytopenia, bone marrow failure, growth retardation, microcephaly, microphthalmia, hypogonadism, renal anomalies, café-au-lait spots and various skeletal anomalies[1].

Congenital absence of the spleen is rare. Congenital asplenia is usually associated with a characteristic group of anomalies of the cardiovascular and the gastrointestinal systems (asplenia syndrome)[2]. Deficiency or absence of splenic activity in congenital asplenia encompasses complex immunological defects, which in turn result in an increased susceptibility to severe bacteremia[3].

Here we report a Fanconi's anemia-like congenital aplastic anemia patient with asplenia without congenital heart diseases or abdominal heterotaxia; to our knowledge this has not been previously reported.

Case Report

A seven-year-old girl was admitted to our clinic with complaints of paleness and weakness for the previous two years. On physical examination, growth retardation (less than 3rd percentile for weight and height), microcephaly, microphthalmia, café-au-lait spots, and clinodactyly were noted. She had not been exposed to recurrent life-threatening infections related to pneumococci in the past. Her parents had first-degree consanguinity. Laboratory examination revealed hemoglobin 4.6 g/dl, leukocytes $4.1x10^9$/L, platelets $14x10^9$/L, mean corpuscular volume (MCV) 107 fl and reticulopenia (< 1%). Peripheral smear showed relative lymphocytosis, hypochromic-macrocytic erythrocyte morphology and Howell-Jolly body (Fig. 1). Fetal hemoglobin was 14 percent. Bone marrow aspiration showed hypocellularity in all trilineage series. Immunological analyses showed IgG as 980 mg/dl, IgA 84 mg/dl, IgM 155 mg/dl, C_3 45 mg/dl, C_4 110 mg/dl, CD_3 45%, CD4 38%, and the CD_4/CD_8 ratio 0.9 Abdominal computerized tomography (CT scan) didnot show the spleen. Functional spleen tissue was not determined using the denaturated red cells labelled with ^{51}Cr (Fig. 2). Telecardiography, electrocardiography and echocardiography were normal.

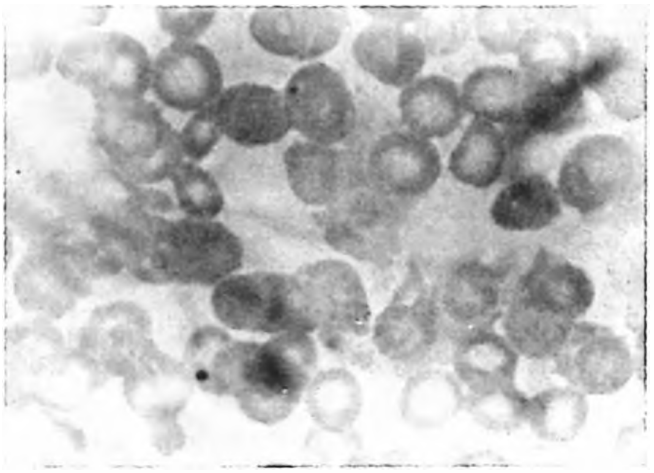


Fig. 1. Peripheral blood smear showing hypochromic-macrocytic erythrocytes and Howell-Jolly bodies (Wright's stain X 100).

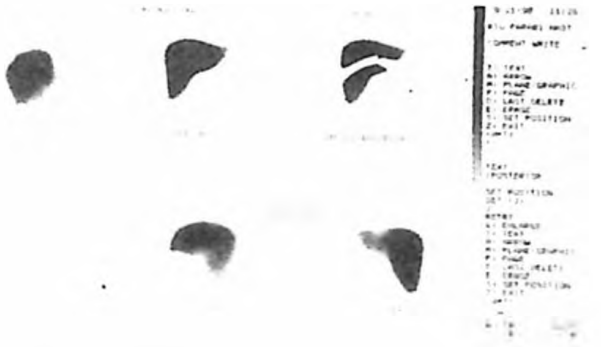


Fig. 2. Functional spleen tissue could not be shown by spleen scintigraphy.

Discussion

Fanconi's anemia is a heterogenous disorder, and the usual age of onset is five to 10 years[4]. It is a rare, autosomal recessive disease characterized by multiple congenital abnormalities, bone marrow failure, and cancer susceptibility[5]. Eight complementation groups of FA (FA-A through FA-H) have been described so far[6]. Complementation groups in FA are likely to represent distinct disease genes, three of which have been cloned (FACA on chromosome 16q24.3, FACC on chromosome 9q22.3 and FACD on chromosome 3p)[7-9]. Some evidence exists that a step in DNA repair is defective[10].

Asplenia syndrome is characterized by complex congenital heart defects and abdominal heterotaxia[2]. The most common congenital heart defects are atrial septal defect, common atrioventricular canal and conotruncal anomalies. With use of current information on timing of normal development, it was hypothesized that most defects originate at Streeter Horizon XIII; patients averaged 3.2 Horizon XIII defects, more than at any other stage. Extracardiac anomalies also exhibited a developmental spectrum. Because the normal spleen develops by Horizon XIII, asplenia originated then or earlier. Abnormal pulmonary lobation has occurred in 80 percent of cases; pulmonary branching asymmetry also originated at or before Horizon XIII. Abdominal heterotaxia has occurred in 72 percent of cases, but the timing of origin is unclear. Anomalies of genitourinary, musculoskeletal, endocrine, and nervous systems develop later (typically XV to XXIII)[11]. Two father-son pairs with isolated nonsyndromal asplenia were also reported. It was suggested that this may represent autosomal dominant inheritance of a mutation in a gene involved with spleen development and that screening for asplenia in first-degree relatives of individuals with asplenia should be considered[12].

The spleen was not determined by spleen scintigraphy, abdominal USG or CT scan in our patient. Therefore atrophy of the spleen, which is common in FA, was excluded. We think that asplenia originated after Horizon XIII in this patient because she had no pulmonary branching asymmetry, which originates at or before Horizon XIII. It is not clear to us why the congenital heart defects and abdominal heterotaxia were not seen in our patient.

It is suggested that IgG, IgA, IgM and C_3 and C_4 values are within normal limits and that the percentages of CD_3 and CD_4 cell and the CD_4/CD_8 ratio are decreased; in FA; therefore, profoundly decreased T cell function might account for the life-threatening infections frequently seen in patients with congenital asplenia[13]. Immunoglobulins, C_3 and C_4 were normal for age and the percentages of CD_4 and CD_8 cells and the CD_4/CD_8 ratio were lower than normal in our patient. It is interesting that the history of recurrent pneumococcal infections did not exist in our patient. Our case shows that isolated asplenia may occur in patients with Fanconi's anemia-like congenital aplastic anemia without the congenital heart defects or the abdominal heterotaxia.

REFERENCES

1. Alter BP, Young NS. Bone marrow failure syndromes. In: Nathan DG, Oski FA (eds). Hematology of Infancy and Childhood (4th ed). Philadelphia: WB Saunders Company; 1993: 216-316.

2. Tu ST, Wu JM, Yeh BH, Ke WL, Lin JH, Tzeng CC. Intestinal obtruction in asplenia syndrome: report of three cases. Acta Paediatr Sin 1994; 35: 70-77.

3. Strasser-Vogel B, Belohradsky BH. Asplenism and hyposplenism as an immune deficiency syndrome. Monatsschr Kinderheilkd 1988; 136: 795-807.
4. Williams DM. Pancytopenia, aplastic anemia, and pure red aplasia. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds). Wintrobe's Clinical Hematology (9th ed). Philadelphia: Lea and Febriger; 1993: 911-943.
5. Kupfer GM, Naf D, D'Andrea AD. Molecular biology of Fanconi anemia. Hematol Oncol Clin North Am 1997; 11: 1045-1060.
6. Joenje H, Oostra AB, Wijker M, et al. Evidence for at least eight Fanconi anemia genes. Am J Hum Genet 1997; 61: 940-944.
7. Pronk J, Gibson RA, Savoia A, et al. Localisation of the Fanconi anemia complementation group A gene to chromosome 16q24.3. Nat Genet 1995; 11: 338-340.
8. Strathdee CA, Duncan AM, Buchwald M. Evidence for at least four Fanconi anaemia genes including FACC on chromosome 9. Nat Genet 1992; 1: 196-198.
9. Whitney M, Thrayer M, Reifsteck C, et al. Microcell mediated chromosome transfer maps the Fanconi anaemia group D gene to chromosome 3p. Nat Genet 1995; 11: 341-343.
10. Auerbach AD, Wolman SR. Susceptibility of Fanconi's anemia fibroblasts to chromosome damage by carcinogens. Nature 1976; 261: 494-501.
11. Phoon CK, Neill CA. Asplenia syndrome: insight into embryology through an analysis of cardiac and extracardiac anomalies. Am J Cardiol 1994; 73: 581-587.
12. Lindor NM, Smithson WA, Ahumada CA, Michels VV, Opitz JM. Asplenia in two father-son pairs. Am J Med Genet 1995; 56: 10-11.
13. Wang JK, Hsieh KH. Immunologic study of the asplenia syndrome. Pediatr Infect Dis J 1992; 10: 819-822.

Prune-belly syndrome associated with extra-abdominal abnormalities in a 7-year-old boy

Nimet Kabakuş[1], Selami Serhatlıoğlu[2], Murat Akfırat[2], Ahmet Kazez[3], Hakan Aydınoğlu[1] İbrahim Özercan[4], A. Denizmen Aygün[1]

Departments of [1]Pediatrics, [2]Radiology, [3]Pediatric Surgery, and [4]Pathology, Fırat University Faculty of Medicine, Elazığ, Turkey

SUMMARY: Kabakuş N, Serhatlıoğlu S, Akfırat M, Kazez A, Aydınoğlu H, Özercan İ, Aygün AD. Prune-belly syndrome associatedwith extra-abdominal abnormalities in a 7-year-old boy. Turk J Pediatr 2000; 42: 158-161.

Prune-belly syndrome (PBS) is an association of abdominal wall deficiency, genitourinary anomalies, and in males, cryptorchidism. Other congenital anomalies are associated with PBS, particularly musculoskeletal deformities and gastrointestinal tract anomalies. In this report, a seven-year-old boy with PBS had mega cisterna magna variant, microcornea, aortic stenosis with bicuspid aortic valves, cholelithiasis, and Hirschsprung's disease. Coexistence of these abnormalities with PBS supports the concept of PBS being caused by an early disturbance of not only mesodermal development but also of the other germ layers. There was maternal ingestion of drugs in the 1st month of gestation. All cases with PBS should be evaluated throughly for extra-abdominal abnormalities resulting from disturbances of ectodermal and endodermal development. Even though disturbances related to ectodermal and endodermal development may be asymptomatic, early diagnosis of the disturbances may help in preventing possible future problems.

***Key words:** prune-belly syndrome, microcornea, aortic valve stenosis, bicuspid aortic valve, cholelithiasis, Hirschsprung's disease, mega cisterna magna variant.*

Prune-belly syndrome (PBS), also called abdominal muscle deficiency or Eagle-Barett syndrome, occurs in approximately 1/30,000-1/50,000 births[1,2]. PBS is defined as the association of abdominal muscle deficiency, genitourinary abnormalities, and in males, cryptorchidism. Other congenital abnormalities are also associated with PBS, including musculoskeletal deformities, and gastrointestinal tract and cardiac abnormalities. In both sexes, expression of the disease is often variable and prognosis depends upon the specific abnormalities present[1-5].

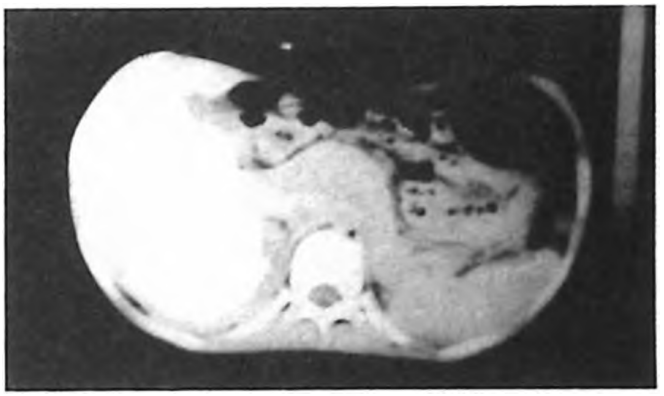
Our patient had underdeveloped muscles in bilateral anterior abdominal wall associated with cerebral, ophthalmic, cardiac, gastrointestinal and genitourinary abnormalities that ranged from mild to severe. This case with PBS was unusual, consisting of several abnormalities, such as mega cisterna magna variant and microcornea, that result from disturbance of ectodermal development. There was maternal exposure to teratogens during the first month of pregnancy that might have contributed to early disturbances of ectodermal and mesodermal development[4,5].

Case Report

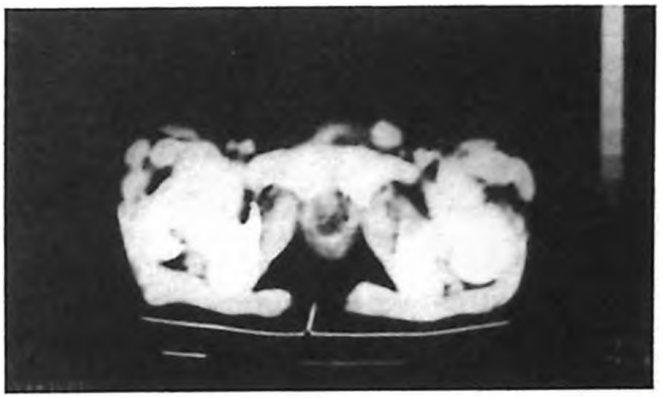
A seven-year-old boy, who previously had gastrointestinal and urinary system complaints (abdominal pain, fever, pain during micturition, chronic constipation) for five months, developed anuria and abdominal distension. His mother had used oral contraceptives and salicylic acid in early pregnancy to induce an abortion. His weight and height were at the third to tenth percentile. Body temperature was 39 °C. The patient was in great pain with right upper quadrant tenderness and a 'potbelly'. He had deficient tone of abdominal muscles and globe vesicale. He had left microcornea (8 mm) and left cryptochidism. There was a grade II/VI systolic ejection murmur at the right upper

sternal border radiating to the neck, and a systolic ejection click at the apex. His mental status was slightly retarded. Other physical findings including neurological examination were normal.

Laboratory tests: hemoglobin 10.7 g/dl, hematocrit 32%, white blood cell count 13,200/mm^3 with 62% neutrophils, platelet count 304,000/mm^3, and erythrocyte sedimentation rate 50 mm/hour. C-reactive protein was strongly positive. Urine specific gravity was 1015. The sediment contained leukocyte casts. Urine culture yielded E. coli, sensitive to ceftazidime. Biochemical tests: blood urea nitrogen 62 mg/dl, creatinine 2.1 mg/dl, uric acid 9 mg/dl, phosphorus 6.3 mg/dl. Glomerular filtration rate (GFR) was 40 ml/min. Chromosomal studies were normal. Abdominal ultrasonography showed bilateral megaureter, bilateral grade III hydronephrosis, bilateral grade V vesicoureteral reflux, anteriolateral displacement of the right ureteral orifice, left cryptorchidism and cholelithiasis (Fig. 1). These ultrasonographic findings were confirmed by voiding cystourethrogram (VCUG) and intravenous pyelography. Absence of an obstructing lesion of the urethra was revealed by VCUG. Computed tomography (CT) revealed underdeveloped anterior abdominal muscles and rotational abnormality of the left kidney (Fig. 2). The axial CT and magnetic resonance imaging (MRI) showed mega cisterna magna variant (Fig. 3). Valvar aortic stenosis and bicuspid aortic valves were demonstrated by echocardiography. Twenty-four-hour delayed X-ray films with barium enema increased suspicion of Hirschsprung's disease (Fig. 4), and rectal suction biopsy demonstrated the absence of ganglion cells in the bowel wall. Initial treatment included temporary drainage procedure (by urinary



(a)



(b)

Fig. 2a. Computed tomography showing hypoplastic anterior abdominal wall muscles associated with right hydronephrosis, and Fig. 2b. showing left cryptorchidism.

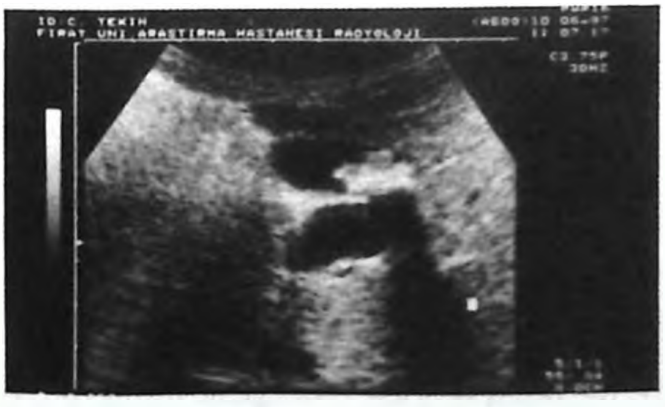
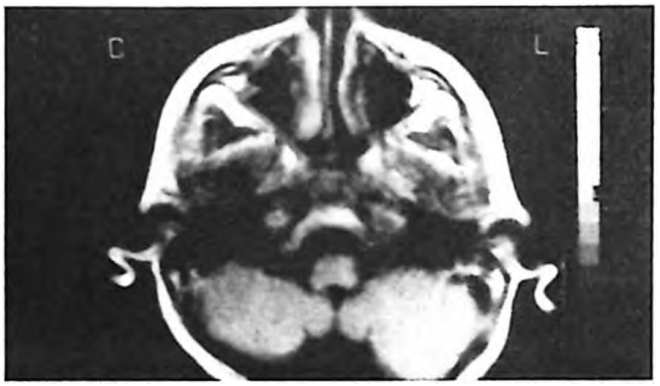
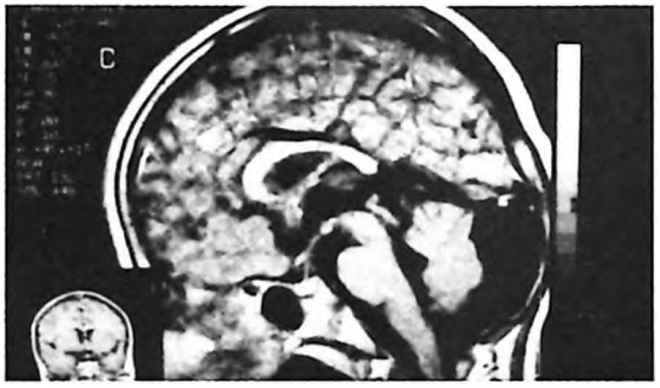


Fig. 1. Ultrasonographic image showing multiple stones within gallbladder.

Fig. 3. Twenty-four-hour delayed X-ray films with barium enema showing dilated colon and delayed evacuation.



(a)



(b)

Fig. 4. MRI showing mega cisterna magna variant. 4a. Axial plane after gadolinium administration and 4b. sagittal plane.

catheter), cholecystectomy (by laparoscopy) and intravenous antibiotherapy (with ceftazidime). On day 10, the patient's renal function and clinical course improved; blood urea nitrogen, creatinine and GFR were 50 mg/dl, 1 mg/dl, 55 ml/min, respectively. The patient was discharged in a stable condition with the urinary catheter. He was well with no severe symptoms over the following six months.

Discussion

Prune-belly syndrome comprises a variable constellation of abnormalities, although the causes remain unproven and controversial[7]. Several theories have been proposed to explain the embryogenesis of PBS. The more tenable theory is that the muscular deficiencies of both the abdominal wall and urinary tract result from an early disturbance of embryogenesis. The postulated teratogenic insult could be a disturbance of mesodermal development in the third week of gestation, which would account for all parts of the triad[1,8,9]. There is no definite genetic influence, although PBS cases in twins and PBS cases associated with trisomy of the long arm of chromosome 1 have been reported[10,11].

There appear to be subgroups of PBS. The first group has an obtructing lesion of the urethra, while the more common second group has functional abnormality of bladder emptying, but no obstruction. In the first group, most infants die shortly after birth, while patients in the second group survive the neonatal period and have chronic urinary tract problems later. In the first group, the problem usually is urethral atresia, and associated abnormalities include malrotation of the intestine, intestinal atresia, imperforate anus, skeletal abnormalities, specific congenital heart disease, Hirschsprung's disease, and congenital cystic adenomatoid malformation. In the second group, associated congenital abnormalities do not occur. It has been suggested that there may be a deficiency in the autonomic innervation of the urinary tract[1,8].

Our patient had features of both subgroups with involvement of extra-abdominal organs including aorta (valvar aortic stenosis and bicuspid aortic valves), cornea (microcornea), brain (mega cisterna magna variant), and autonomic innervation (Hirschsprung's disease). In addition to PBS, urinary tract infection (UTI), renal failure secondary to urinary tract obstruction and findings of cholelithiasis were the dominant clinical features.

To our knowledge, only a few cases with PBS including brain and eye abnormalities have been reported[1]. Our patient's mother had used some medications including oral contraceptives and salicylic acid during the first month of pregnancy. This history might explain development of PBS, because in a trilaminar embryo such remedies may have teratogenic effects[13].

Interlobular bile ducts with PBS have been reported[11], but there is no information about cholelithiasis. In our patient, biochemical tests for cholelithiasis were normal. In our view this condition may be explained by coexistence of the other gastrointestinal abnormalities, such as Hirschsprung's disease, in which the enterohepatic circulation rate is increased.

In conclusion, these observations indicate that: 1. PBS and other coexistent abnormalities could be the result of some teratogenic insult to the embryo or fetus. 2. Abnormalities associated with PBS may originate from disturbance of

ectodermal as well as mesodermal development. 3. All cases with PBS should be examined thoroughly for extra-abdominal abnormalities including disturbances of the other germ layers, even though these may be asymptomatic. 4. History of prenatal exposure to teratogens during the first trimester should be sought. This approach may help to detect and treat future possible problems like mega cisterna magna variant manifesting with a mass effect or seizures[3,4]. It will contribute to the understanding of the pathogenesis of PBS.

REFERENCES

1. Wheatley JM, Stephens FD, Hutson JM. Prune-belly syndrome: ongoing controversies regarding pathogenesis and management. Semin Pediatr Surg 1996; 5: 95-106.
2. Gonzales R. Urologic disorders in infants and children. In: Behrman RE, Kligman RM, Arvin AM, et al. (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: WB Saunders Co; 1996; 1539-1540.
3. Donelly LF, Johnson JF. Unilateral abdominal wall hypoplasia: radiographic findings in two infant girls. Pediatr Radiol 1995; 25: 278-281.
4. Sugama S, Atsukava K, Kusano K, et al. Epilepsy in patient with structural autosomal abnormality. No To Hattatsu 1994; 26: 486-492.
5. Kollias SS, Ball WS Jr, Prenger EC. Cystic malformations of the posterior fossa: differential diagnosis clarified through embryologic analysis. Radiographics 1993; 13: 1211-1231.
6. Urtila R, Popa I, Berinde L, et al. A case of the prune belly syndrome. Pediatrie 1992; 41: 61-65.
7. Sutherland RS, Mevorach RA, Kogan BA. The prune-belly syndrome: current insights. Pediatr Nephrol 1995; 9: 770-778.
8. Haden CK, Swischuk LE. Pediatric Ultrasonography. Baltimore: William and Wilkins; 1987: 344-345.
9. Güvenç M, Güvenç H, Aygün AD, et al. Prune-belly syndrome associated with omphalocele in a female newborn. J Pediatr Surg 1995; 30: 896-897.
10. van Buggenhout G, Cooreman G, Thienpoint L, et al. Early urethal obstruction sequence and trisomy of the long arm of chromosome 1. Ann Genet 1995; 38: 106-107.
11. Monfort G, Simenoni J. The prune-belly syndrome. Pediatric Cerrahi Dergisi 1995; 9: 217-222.
12. Aanpreung P, Beckwith B, Galansky SH, et al. Association of paucity of interlobular bile ducts with PBS. J Pediatr Gastroenterol Nutr 1993; 16: 81-86.
13. Jacop LS. Pharmacology (4th ed). Philadelphia: Williams and Wilkins; 1996: 225.

Juvenile rheumatoid arthritis presented with thrombocytopenia

Ahmet Koç, Mustafa Kösecik, M. Mansur Tatlı, Ali Ataş, H. Haldun Emiroğlu

Department of Pediatrics, Harran University Faculty of Medicine, Şanlıurfa, Turkey

SUMMARY: Koç A, Kösecik M, Tatlı MM, Ataş A. Emiroğlu HH. Juvenile rheumatoid arthritis presented with thrombocytopenia. Turk J Pediatr 2000; 42: 162-164.

Leukopenia and thrombocytopenia are rare findings in systemic onset juvenile rheumatoid arthritis (S-JRA), and if present, bone marrow (BM) examination is necessary to exclude malignant diseases. We report here a 13.5-year-old boy with S-JRA who had severe thrombocytopenia and mild leukopenia, without arthritis, at the onset of the disease. BM was hypercellular with increased numbers of myeloid precursors and megakaryocytes. After treatment with acetylsalicylic acid, leukocyte and platelet counts returned to normal levels, and after two months chronic arthritis developed.

Key words: systemic onset juvenile rheumatoid arthritis, thrombocytopenia, fever.

Anemia, leukocytosis and thrombocytosis are frequently seen hematological disorders in systemic onset juvenile rheumatoid arthritis (S-JRA)[1,2]. It has been known that leukocyte and platelet counts are increased, especially in the active stage of disease[2,3]. Leukopenia and thrombocytopenia are very rare in S-JRA, and if present, bone marrow (BM) examination is necessary to exclude malignant diseases such as leukemia[1,4,5].

We report here a child with S-JRA who had thrombocytopenia at the onset of the disease.

Case Report

A 13.5-year-old boy was admitted to the hospital with a one-month history of fever and headache. He had no history of other complaints. He had been treated with ampicillin-sulbactam and paracetamol with a diagnosis of sinusitis for two weeks, without any improvement.

Physical examination revealed a body temperature of 37 °C, weight at the 10th percentile and height at the 25th percentile for age. The liver was palpable 1.5 cm and the spleen 2.5 cm below the respective costal margins. The other systems were normal. Laboratory investigations showed hemoglobin (Hb) 11.6 g/dl, white blood cell (WBC) count 4400/mm^3 (60% neutrophils, 34% lymphocytes, 2% monocytes and 2% eosinophils), platelet count 130,000/mm^3, anti-streptolysin O (-), c-reactive protein (CRP) (++), rheumatoid factor (-), erythrocyte sedimentation rate 36 mm/h, serum albumin 3.7 g/dl, globulin 3.9 g/dl. Chest radiograph was normal and serological tests for brucella and salmonella were negative. Throat, urine, stool and blood cultures showed no pathogen bacteria.

In the follow-up, daily spikes of fever with rapid returns to normal levels were shown. On the 7th day, complete blood count revealed Hb 10.2 g/dl, WBC 3600/mm^3 (55% neutrophils, 42% lymphocytes, 3% monocytes), and platelet counts 39,000/mm^3. In peripheral blood (PB) smear, there were only a few platelets with normal erythrocyte and leukocyte morphology. Prothrombin and activated partial thromboplastin times, and hepatic function tests were in normal limits. Urine analysis was also normal. On 8th day, no platelet was shown in PB smear, so bone marrow (BM) aspiration was performed to explain thrombocytopenia and exclude a malignant disorder. BM was hypercellular with an increased number of both myeloid precursors and megakaryocytes as seen in immune thrombocytopenias (ITP), and so malignancy was excluded.

The diagnosis of S-JRA was made on the 10th day in view of daily spikes of fever, transient erythematous rash on the trunk and arms, and

the absence of other diseases, although no arthritis had been documented. Therefore, acetylsalicylic acid (100 mg/kg/day) was given both for the diagnosis and treatment. After acetyl-salicylic acid was started, the fever disappeared and after 10 days, platelet and WBC counts returned to normal levels[6]. About two months later, arthritis developed at the right knee and right wrist. The chronic progress of the arthritis confirmed the diagnosis of S-JRA. The patient was treated with naproxen with clinical benefit. During the past 2.5 year follow-up, he has had only intermittent arthritis at knees, wrists and ankles which could be controlled with naproxen therapy, without joint deformity.

Discussion

We report a patient with S-JRA associated with severe thrombocytopenia and mild leukopenia. Acute ITP is the major cause of thrombocytopenia in childhood and is frequently associated with viral illness or immunization one to three weeks prior to presentation[7]. The PB and BM findings of this patient resembled ITP, but the fever could not been explained by ITP alone.

Disseminated intravascular coagulation (DIC) and hemolytic uremic syndrome (HUS) may be the causes of thrombocytopenia in a patient with high fever[7], but these disorders were excluded by normal PB smear findings (except thrombocytopenia), normal urine analysis and normal coagulation tests. Thrombocytopenia may be seen in bacterial and viral infections[3,7], but the physical examination and laboratory investigations did not reveal any infectious disease, and there were no medications known to be the cause of thrombocytopenia[7], at least during the 15 days prior to thrombocytopenia being found. Thrombocytopenia with increased numbers of BM megakaryocytes may be seen in systemic lupus erythematosus (SLE), but the absence of other characteristic manifestations of SLE at the beginning of the disease and in the 2.5 years of follow-up excluded this probability[8]. Inflammatory conditions such as JRA may cause anemia by a different mechanism[9]. Inflammation was considered as the possible cause of mild anemia in this patient. There are a few reports of thrombocytopenia in S-JRA. Sherry et al.[10] reported three patients with S-JRA; they had transient thrombocytopenia seven, four and two years after diagnosis, in follow-up. Ewer et al.[3] reported a patient with S-JRA who developed pancytopenia due to bone marrow hypoplasia 21 days after her illness began. They suggested that autoimmunity might be a possible cause of pancytopenia, but also that acute hepatic dysfunction and side effects of medications (aspirin, co-trimaxazole) might be responsible. Thrombocytopenia has also been reported secondary to DIC in patients with S-JRA[11,12]. Scopelitis et al.[5] reported two cases of leukopenia in S-JRA, one had mild and the other had moderate thrombocytopenia. In the second patient, WBC and platelet counts increased promptly after the splenectomy. Our patient had thrombocytopenia at the onset of disease, and the had no other findings to support a diagnosis of DIC. He was also different from Ewer et al's. patients[3] because of the BM hypercellularity and no associations with medications. He was similar to Scopelitis et al's. cases[5], he also had mild leukopenia, lathough absolute neutrophil and lymphocyte counts were in normal limits[6].

Arthritis may be absent at presentation of S-JRA, and may not develop for months or even years, causing difficulty in diagnosis[1,13]. The diagnosis of S-JRA was delayed in this case because of the absence of arthritis at the onset of disease. But in the follow-up, S-JRA was suspected because of daily spikes of fever, transient erythematous rash, positive CRP, inversion of serum albumin/globulin ratio, and the absence of other disease[1,2,13]. Disappearance of fever with aspirin, and chronic arthritis, which began two months later, confirmed the diagnosis. Increased megakaryocytes in BM with peripheral thrombocytopenia indicate peripheral platelet destruction, like ITP. This condition suggests that autoantibodies might also be present against platelets in S-JRA, which is an autoimmune disease itself. The presented case has demonstrated that S-JRA should also be suspected in unexplained febrile situations associated with thrombocytopenia, although it is an unusual finding.

REFERENCES

1. Martin K, Davies EG, Axford JS. Fever of unknown origin in childhood: difficulties in diagnosis. Ann Rheum Dis 1990; 53: 429-433.
2. Schaller JG. Juvenile rheumatoid arthritis. In: Behrman RE, Kliegman RM, Arvin AM (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: WB Saunders Co; 1996: 661-670.
3. Ewer AK, Darbyshire PJ, Southwood TR. Systemic-onset juvenile chronic arthritis and bone marrow hypoplasia. Br J Rheumatol 1993; 32: 78-80.

4. Reid MM. Bone marrow examination before steroids in thrombocytopenic purpura or arthritis. Acta Paediatr 1992; 81: 1052-1053.

5. Scopelitis E, Perez M, Biundo JJ. Leukopenia in Still's disease. JAMA 1984; 252: 2450-2452.

6. Brugnara C. Reference ranges for leukocyte counts in children. In: Nathan DG, Orkin SH (eds). Hematology of Infancy and Childhood (5th ed). Philadelphia: WB Saunders Co; 1998: Appendix 28.

7. Beardsley DS. Quantitative platelet abnormalities. In: Nathan DG, Orkin SH (eds). Hematology of Infancy and Childhood (5th ed). Philadelphia: WB Saunders Co; 1998: 2586-1607.

8. Schaller JG. Systemic lupus erythamatosus. In: Behrman RE, Kliegman RM, Arvin AM (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: WB Saunders; 1996; 661-670.

9. Abshire TC. The anemia of inflammation. A common cause of childhood anemia. Pediatr Clin North Am 1996; 43: 623-637.

10. Sherry DD, Kredich DW. Transient thrombocytopenia in systemic onset juvenile rheumatoid arthritis. Pediatrics 1985; 76: 600-603.

11. Bray VJ, Singleton JD. Disseminated intravascular coagulation in Still's disease. Semin Arthritis Rheum 1994; 24: 222-229.

12. Silverman ED, Miller JJ, Bernstein B, et al. Consumption coagulapathy associated with systemic juvenile rheumatoid arthritis. J Pediatr 1983; 103: 872-876.

13. Pelton SI. Fever of unknown origin. In: Stockman JA (ed). Difficult Diagnosis in Pediatrics. Philadelphia: WB Saunders Co; 1990: 175-182.

A case of primary chylous ascites resolved within 4 months by exclusive breast-feeding

Zafer Kurugöl, Özgür Çoğulu, Kaan Kavaklı

Department of Pediatrics, Ege University Faculty of Medicine, İzmir, Turkey

SUMMARY: Kurugöl Z, Çoğulu Ö, Kavaklı K. A case of primary chylous ascites resolved within 4 months by exclusive breast-feeding. Turk J Pediatr 2000; 42: 165-167.

Chylous ascites is a rare disease in infancy. A two-month-old male infant was admitted to the Department of Pediatrics with chylous ascites. No cause was found throughout the investigation period. The baby recovered spontaneously through breast-feeding without any specific treatment and chylous ascites disappeared at the age of six months.

Key words: chylous ascites, infant, human milk, medium-chain triglycerides, breast-feeding.

Ascites is an accumulation of fluid within the peritoneal cavity. If milky ascitic fluid is obtained via paracentesis after a fat-containing feeding, it is called chylous ascites. Chyloùs ascites is a rare and sometimes subclinical condition in infants[1]. It can result from a congenital abnormality, which is classified as primary chylous ascites. Secondary reasons such as aortic surgery, penetrating abdominal trauma, and malignancy or obstruction of the intraabdominal portion of the thoracic duct can cause chylous ascites. Treatment includes a low-fat diet supplemented with medium-chain triglycerides, diuretics, total parenteral nutrition, surgical exploration and intestinal shunting[2]. Paracentesis should be repeated if abdominal distension causes respiratory distress. Here we present an infant with chylous ascites who healed without any treatment schedule by being exclusively breast-fed.

Case Report

A two-month-old boy was referred to our department with a history of abdominal distension and decrease in diuresis. His birth weight was 3800 g and length was 52 cm. He was the second child of non-consanguineous parents. There was no history of tuberculosis in the family. This patient was noted to have abdominal distension, bilateral inguinal hernia and hydrocele when he was 25 days old and abdominal ultrasonography demonstrated ascites. Gross ascites was demonstrated in abdominal computed tomography.

When the patient was two months old, his weight was 5050 g (50th percentile), length was 58 cm (50th percentile) and head circumference was 39 cm (50th percentile). Abdominal circumference was 47.5 cm (Table I). Pallor, abdominal distension, bilateral inguinal hernia and hydrocele were determined. Tuberculin skin test was negative.

Table I. Some Findings of Our Patient on Admission and After 2 and 4 Months

	On admission (2 months of age)	After 2 months (4 months of age)	After 4 months (6 months of age)
Weight (g)	5050	6000	7550
Length (cm)	58	62	65
Abdominal circumference (cm)	47.5	45	43
Hb (g/dl)	10.2	10	9.4
Hct (%)	28.9	31	29.6
MCV (fl)	71.4	70	60.9
AFP (ng/ml)	630.7	180	32.5
Ferritin (ng/ml)	448	130	19
Ultrasonography	Gross ascites	Minimal ascites	Normal
Lymphoscintigraphy	Lymph accumulation	Normal accumulation	—

Hb Hemoglobin; MCV: Mean corpuscular volume; Hct: Hematocrit; AFP: α-fetoprotein.

Complete blood count was normal except for hemoglobin and mean corpuscular volume (Table I). Blood biochemical (Na, K, Ca, P, Mg, glucose, uric acid), renal and liver function tests (urea, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-gultamyl-transpeptidase, total bilirubin, total protein, albumin, prothrombin time), lactate dehydrogenase and vanilmandelic acid were in normal range. Alpha-fetoprotein (AFP) and ferritin levels were 630.7 ng/ml and 448 ng/ml, respectively.

Abdominal paracentesis revealed the presence of chylous fluid (Table II). Cytological and microbiological analysis of chylous fluid did not show any abnormal result.

Table II. Chylous Ascites Fluid Analysis

Total lipid (mg/dl)	1950
Triglycerides (mg/dl)	921
Cholesterol (mg/dl)	652
Protein (g/dl)	3.08
Lymphocytes (mm^3)	3080
Atypical cell	(-)

Serologic tests for cytomegalovirus, rubella, hepatitis A virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, and parvovirus were negative.

Abdominal Doppler ultrasonography and computed tomography demonstrated massive ascites but no enlarged lymph nodes or mass. Thorax volume was decreased because of gross ascites in X-ray examination. Voiding cystoureterography was normal. There was abnormal finding in double contrast barium meal. Lymphoscintigraphy revealed the presence of chyle accumulation.

Paracentesis was performed only twice. No diet therapy was given and the patient was fed only with breast milk. When the patient was four months old, abdominal circumference had receded from 47.5 cm to 45 cm (Table I). Abdominal ultrasonographic examination demonstrated minimal ascites and lymphoscintigraphy was normal.

The patient was clinically normal, and his abdominal circumference was 43 cm when reviewed at six months of age. His growth was normal. No ascites was noted with abdominal ultrasonographic examination. Alpha-fetoprotein (AFP) and ferritin levels were 32.5 ng/ml and 19 ng/ml respectively, when the patient was six months old.

Discussion

Chylous ascites is an uncommon problem in children. The incidence is between 1/50,000 and 1/100,000 hospital admissions[3]. Abdominal distension occurred in 83% percent of chylous ascites cases[4]. Our case was admitted to the hospital when he was two months old because of abdominal distension. Other symptoms and signs such as inguinal hernia, hydrocele and respiratory insufficiency are secondary to abdominal distension as in our case, whose first sign was abdominal distension noticed at the age of 25 days.

The diagnosis of chylous ascites depends on the character of the fluid. When it is diagnosed, differential diagnosis should be made to assess other possible reasons for this cliical problem. The reasons for chylous ascites are neoplasms, abdominal lymphatic vessels, infections, cirrhosis, mesenteric adenitis and congenital abnormalities[5,6]. While abdominal neoplasms comprise the majority of adult cases, congenital lymphatic abnormalities are more common in children. Unger et al.[4] classified the causes of chylous ascites in infants and children, and the majority of the cases were congenital and idiopathic (43%), followed by leaking lymphatics (12%), and lymphangioma and mesenteric cyst (10%). Among the others were: lymphadenopathy, obstructive lesion of mesentery, trauma, appendicitis, liver disease, incarcerated hernia and tuberculosis.

Since malignancy is an extremely rare cause of chylous ascites in children, it may be disregarded after blood and cytological analyses. There was no atypical cell line in the cytological examination of the fluid in our patient. Abdominal ultrasonography and computed tomography scan did not show any mass in the abdomen. VMA for neuroblastoma, LDH and ferritin as tumor markers were in normal ranges. Alpha-fetoprotein (AFP) level was higher than normal as is expected in ascites and, as ascites disappeared, AFP level decreased to the normal level (Table I). There was no history of aortic surgery or penetrating abdominal trauma.

Tuberculosis has been reported as a prominent cause of chylous ascites in children[3]. PPD skin test in our patient was negative and there was no history of tuberculosis in the family. Acid-fast bacilli were not found in the direct examination of the ascites fluid and cultures of the fluid were negative.

Hepatic enzyme levels, computed tomography (CT) scanning, and abdominal ultrasonography gave no clue for a hepatic origin.

Congenital defects of the lymphatic system such as lymphoperitoneal fistula and leaking bowel are primary causes of chylous ascites. Browse et al.[1] proposed three principal mechanisms for chylous ascites: direct leakage of chyle through a lymphoperitoneal fistula, exudation through the walls of retroperitoneal megalymphatics and exudation from the bowel. The mechanism of chylous ascites formation is usually caused by obstruction in the mesenteric or thoracic lymph nodes. Abdominal ultrasonography and computerized tomographic scanning did not show any mass lesion in our case. There was no pathologic finding in voiding cystoureterography. Barium meal revealed no remarkable result which might explain the cause of chylous ascites. Lymphangiography is claimed to be the most important diagnostic and prognostic tool before surgery[1]. However, lymphoscintigraphy can also be used in these patients as a diagnostic procedure, and in the case of our patient detected chyle accumulation.

Surgery is not advised as a primary therapy for chylous ascites unless it is secondary to an incarcerated hernia, appendicitis, or intussusception. Some authors in the treatment of chylous ascites suggest low-fat, high-protein diets and repetitive paracentesis. Cure was achieved within one month of commencing therapy, hence, at least one month of nonoperative therapy is suggested for all patients to stop the accumulation of chyle in the peritoneum[4].

In light of the investigations done for the presented case, primary chylous ascites was thought to be the only explanation, caused by a lymphatic leakage from the small bowel or mesenteric lymph nodes. No specific treatment was given to our patient and he was fed only with human milk. Paracentesis was performed only twice. Ascites gradually subsided and disappeared in four months. Abdominal circumference receded from 47.5 to 43 cm within that time. The patient was clinically normal when reviewed at six months of age. Substituting medium-chain triglycerides (MCT) for a usual diet has been suggested by some authors because medium-chain fatty acids are absorbed directly into the portal venous blood and delivered to the target tissues more quickly[7,8]. However, the intestinal absorption of medium-chain fatty acids is affected by the structure and by the type of fat in the diet. It was suggested that intestinal absorption was enhanced by the administration to rats of medium-chain fatty acids in a mixture of MCT containing molecules of C:8 fatty acids and long-chain triglycerides containing molecules of C:18 fatty acids[9]. Human milk contains 98-99% percent of its lipid composition in the form of triglycerides. Although the triglycerides in human milk are composed of 167 different fatty acids, 10 of them, with 8 to 18 carbons present, are found in larger quantities than the others[10]. Therefore, triglycerides in human milk are more readily absorbed by the intestine. Cure without using any treatment schedule in our patient may be related to the better absorption of MCT in human milk. Furthermore, complete substitution of MCT for all fat in the diet exposes the patient to the hazards of essential fatty acid deficiency[4]. For this reason, the hazards of essential fatty acid deficiency can be avoided and appropriate nutrition provided by breast-feeding. In conclusion, we point out the importance of breast-feeding as not only essential for normal infants but also as useful in the management of infants with primary chylous ascites for which mortality rates of 8 to 24 percent have been reported in children by some authors[3,7,11].

REFERENCES

1. Browse NL, Wilson NM, Russo M, Al-Hasan H, Allen DR. Aetiology and treatment of chylous ascites. Br J Surg 1992; 79: 1145-1150.
2. Rector FE, Whittlesey G. Effective control of chylous ascites: an alternative approach. J Ped Surg 1993; 28: 76-77.
3. Vasko JS, Tapper RI. The surgical significance of chylous ascites. Arch Surg 1967; 95: 355-368.
4. Unger SW, Chandler JG. Chylous ascites in infants and children. Surgery 1983; 93: 455-461.
5. Press OW, Ottman Press N, Kaufman SD. Evaluation and management of chylous ascites. Ann Intern Med 1982; 96: 358-364.
6. Hyams JS. Ascites. In: Behrman RE, Kliegman RM, Arvin AM (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: WB Saunders Company; 1996: 1159.
7. Chye JK, Lim CT, Van der Heuvel M. Neonatal chylous ascites-report of three cases and review of the literature. Pediatr Surg Int 1997; 12: 296-298.
8. Borum PR. Medium-chain triglycerides. Annales Nestle 1997; 55: 73-78.
9. Jensen MM, Christensen MS, Hoy CE. Intestinal absorption of octanoic, decanoic, linolenic acids: effect of triglyceride structure. Ann Nutr Metab 1994; 38: 104-116.
10. Özalp I. Besleyici olarak anne sütü. Katkı Pediatri Dergisi 1991; 12: 510-520.
11. Man DW, Spitz L. The management of chylous ascites in children. J Ped Surgery 1985; 20: 72-75.

Successful treatment of reactive hemophagocytic syndrome with cyclosporin A and intravenous immunoglobulin

Erol Erduran, Yusuf Gedik, Yaşar Şen, Alişan Yıldıran

Department of Pediatrics, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey

SUMMARY: Erduran E. Gedik Y, Şen Y, Yıldıran A. Successful treatment of reactive hemophagocytic syndrome with cyclosporin A and intravenous immunoglobulin. Turk J Pediatr 2000; 42: 168-170.

Infection-associated hemophagocytic syndrome (IAHS) is a form of the reactive hemophagocytic syndrome. IAHS is associated with viral, bacterial, fungal, mycobacterial, rickettsial and protozoal infections and with various malignant neoplasms. A more accurate designation for this acquired form of the syndrome is reactive hemophagocytic syndrome (HS). Reactive HS is characterized by malaise, fever, hepatosplenomegaly, lymphadenopathy, cytopenia, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis. Cyclosporin A, VP-16, high-dose steroids, and intravenous immunoglobulin (IVIG) have been used in the treatment of IAHS. Here, a 10-year-old girl with reactive HS due to possible viral infection was treated successfully with cyclosporin A and IVIG. Fever disappeared on the third day, complete blood count reached normal levels on the sixth day and hepatosplenomegaly disappeared on the ninth day after treatment.

We believe cyclosporin A and IVIG may be used in the treatment of reactive HS, at least in selected patients. Further studies are required to confirm its role as first-line therapy for children with IAHS.

Key words: reactive hemophagocytic syndrome, intravenous immunoglobulin, cyclosporin A.

Two forms of hemophagocytic syndrome (HS) have been characterized: infection-associated HS (IAHS) and familial erythrophagocytic lymphohistiocytosis (FEL). Because IAHS is not always infection induced, with many cases associated with a variety of malignant neoplasms, a more accurate designation for this acquired form of the syndrome is reactive HS[1].

Common presenting features of this syndrome are fever, malaise, weight loss, hepatosplenomegaly, lymphadenopathy, profound cytopenia involving two or more cell lines, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis[2]. The clinical course is generally fulminant and may be complicated with hepatic dysfunction and renal failure[2].

Cyclosporin A, high-dose steroids, intravenous immunoglobulin (IVIG), and VP-16 have been used in the treatment of IAHS; however, the treatment of IAHS has still not been standardized[3-6].

Here, we present a case of reactive HS showing a very favorable clinical course following treatment with cyclosporin A and IVIG.

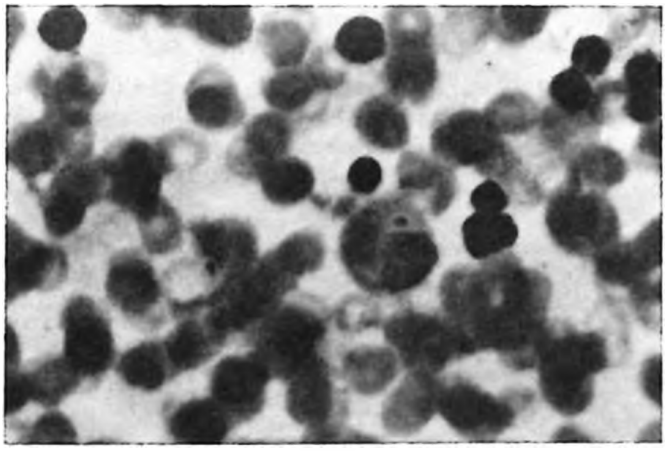
Case Report

A 10-year-old girl was admitted to our clinic with complaints of fever and weakness for five days. She was the product of a consanguineous marriage and had two healthy siblings. On admission, the patient appeared severely pale and ill with a body temperature of 38.5 °C. Physical examination revealed tonsillopharyngitis, maculopapular eruptions on her trunk and extremities, and cervical, axillary and inguinal microlymphadenopathies. The liver and spleen were palpable 6 and 5 cm below the costal margins, respectively. Clinical findings related to malignant lymphoma and connective tissue disorders such as systemic lupus erythematosus were not determined. The rest of the physical findings were unremarkable.

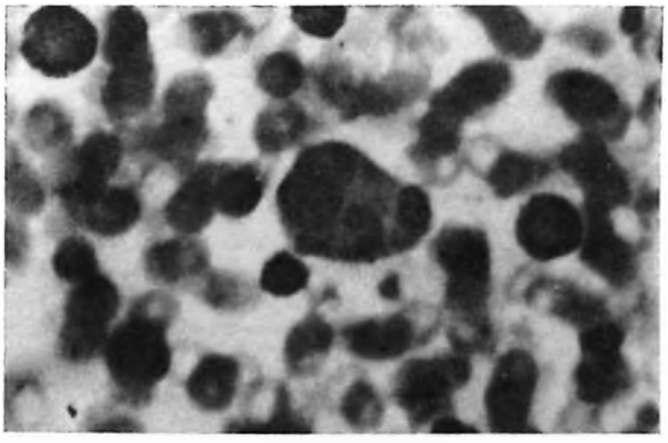
Laboratory tests revealed erythrocyte sedimentation rate (ESR) of 45 mm/h; hemoglobin (Hb) 9.4 g/dl, leukocytes 3.4×10^9/L with 63% lymphocytes (4% atypical lymphocytes), 34% neutrophils, 3% monocytes and platelets 52×10^9/L.

The activated partial thromboplastin time (aPTT) was 29.4 seconds, prothrombin time (PT) 12.2 seconds and the plasma fibrinogen levels 220 mg/dl. LDH was 2250 U/L, ALT 91 U/L, AST 164 U/L, GGT 369 U/L, triglyceride 204 mg/dl, cholesterol 104 mg/dl, and ferritin 629 mg/ml. Other biochemical test results were within normal limits. Immunoglobulin levels were IgG 1206 mg/dl, IgA 161.7 mg/dl, and IgM 168 mg/dl. Flow-cytometric analysis of peripheral blood lymphocytes indicated CD_4 34%, CD_8 25% and CD_4/CD_8: 1.4. Serology, including Epstein-Barr virus (EBV), parvovirus B_{19} and cytomegalovirus (CMV), was negative. Throat swab and blood cultures were negative. A plain chest radiograph was normal..

Examination of bone marrow aspiration showed an increased number of histiocytes with erythrocytes, thrombocytes, leukocytes and lymphophagocytosis, and no evidence of malignant cells (Fig. 1a, 1b).



(a)



(b)

Fig. 1. Photomicrograph of the bone marrow aspirate demonstrating histiocytic phagocytosis of erythrocytes and thromboycles (Fig. 1a), leukocytes and lymphocytes (Fig. 1b).

The patient was treated with IVIG (0.4 g/kg/d) for five days and cyclosporin A (5 mg/kg/d) for 10 days. The patient became afebrile on the third day, blood cell count returned to normal on the sixth day and hepatosplenomegaly disappeared on the ninth day of therapy.

The patient has been in good health for two months.

Discussion

A diagnosis of reactive HS should be considered if a patient has fever of unknown origin, a variable degree of pancytopenia, the progressive development of multiorgan dysfunction, coagulopathy, and the presence of an increased number of phagocytic histiocytes in bone marrow[1]. Based on these criteria our patient was considered to have reactive HS.

Reactive HS has been known to occur in association with infections by many different microorganisms such as viral, bacterial, fungal, mycobacterial, rickettsial and protozoal, in addition to a wide spectrum of malignant neoplasms[2,7-10]. Therefore, the hemophagocytosis in our patient might have been related to viral infection according to the physical signs and peripheral smear findings, although serology, including EBV, CMV and parvovirus B_{19}, was negative.

The mechanism responsible for the hemophagocytic activity of reactive histiocytosis is unclear. Oyama et al.[3] presented data indicating that there is an alteration in T cell function in hemophagocytosis with uncontrolled secretion of T cell producing interferon (IFN)-γ and other lymphokines. Elevated levels of IFN-γ, soluble interleukin (IL)-2 receptor (sIL-2R), soluble CD_8, and macrophage colony-stimulating factor (M-CSF) have been found in patients with hemophagocytosis[4,5,11]. Uncontrolled IFN-γ and M-CSF can lead macrophages to a hemophagocytosing and tumor necrosis factor-α (TNF-α) and IL-6 secreting state[3,12].

There is no specific treatment for IAHS. Various drugs such as cyclosporin A, VP-16, high-dose steroids, and IVIG have been used[3-5]. Fort and Buchanan[6] reported a child treated successfully with acyclovir, VP-16 and dmultiple doses of IVIG. Yao et al.[13] described high-dose IVIG plus corticosteroid therapy in two adult patients with hemophagocytic syndrome. The action mechanisms of IVIG are blockage of Fc-receptor-mediated phagocytosis in the mononuclear/

phagocyte system, anti-idiotype effects and possibly down-regulation of immunoglobulin synthesis[14,15]. In addition, IVIG may exert its therapeutic effect by modulating T cell response and associated changes in mediator release[15].

Sixty percent of children with IAHS treated with immunosuppressive drugs, mostly steroids and etoposide or both, showed a response[19]. It was emphasized that only etoposide or immunoglobulin treatment or combination of both led to remarkable improvement in the prognosis of the usually fatal EBV-related HS[17]. In addition, an adolescent patient with IAHS was treated successfully with cyclosporin A[16]. Therefore, we used cyclosporin A in our patient with reactive HS due to possible viral infection although a triggering viral agent could not be determined. The action mechanism of cyclosporin A is suggested to be inhibition of T cell activation due to blockade of IL-2 secretion from CD_4^+ lymphocytes[4,17,18]. However, the use of immunosuppressive agents needs special consideration because of their adverse effects in increasing the progression of and mortality rate of IAHS during the acute infection. Here, we report a child with reactive HS due to possible viral infection treated successfully with cyclosporin A and IVIG. Although clinical findings of the patient were not very severe, we decided to use cyclosporin A in addition to IVIG treatment to prevent the progression of the clinical findings. We believe cyclosporin A and IVIG may be used in the treatment of reactive HS. However, further studies are necessary to confirm that this treatment combination is always effective.

REFERENCES

1. Hess CE. Hemophagocytic syndromes. In: Lee GC, Bithell TC, Foerster J. Athens JW, Lukens JN, (eds). Wintrobe's Clinical Hematology (2nd ed) Vol.2. Pennsylvania: Lea and Febiger; 1993: 2189-2190.
2. Reiner AP, Spivak JL. Hematophagic histiocytosis: a report of 23 new patients and a review of the literature. Medicine 1988; 67: 369-388.
3. Oyama Y, Amano T, Hirakawa S, Hironaka K, Suzuki S, Ota Z. Haemophagocytic syndrome treated with cyclosporin A: a T-cell disorder? Br J Haematol 1989; 73: 276-278.
4. Imashuku S, Hibi S. Cytokines in hemophagocytic syndrome. Br J Haematol 1991; 77: 438-439.
5. Monier B, Fauroux B, Chevalier JY, et al. Miliary tuberculosis with acute respiratory failure and histiocytic hemophagocytosis: successful treatment with extracorporeal lung support and epidophyllotoxin VP-16-213. Acta Paediatr 1992; 81: 725-727.
6. Fort DW, Buchaman GR. Treatment of infection-associated hemophagocytic syndrome with immunoglobulin. J Pediatr 1994; 124: 332.
7. Sullivan JL, Woda BA. Lymphohistiocytic disorders. In: Nathan and Oski (eds). Hematology of Infancy and Childhood (4th ed) Vol.2. Philadelphia: W.B. Saunders Co; 1993; 1354-1374.
8. Noma T, Kou K, Yoshizawa I, et al. Monoclonal proliferation of Epstein-Barr virus-infected T-cell in a patient with virus associated hemophagocytic syndrome. Eur J Pediatr 1994: 153: 73-738.
9. Zucker JM, Cailloux JM, Vanel D, Gerard MR. Malignant histiocytosis in childhood clinical study and therapeutic in 22 cases. Cancer 1980; 45: 2821-2830.
10. Risdall RJ, McKenna RW, Nesbit ME, et al. Virus-associated hemophagocytic syndrome. A benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 1979; 44: 993-1002.
11. Imashuku S, Ikushima S, Esumi N, Toda S, Saito M. Serum levels of interferon-gamma, cytotoxic factor and soluble interleukin-2 receptor in childhood hemophagocytic syndromes. Leuk Lymphoma 1991; 3: 287-292.
12. Akashi K, Hayashi S, Goudo H, et al. Involvement of interferon-γ and macrophage colony-stimulating factor in pathogenesis of haemophagocytic lymphohistiocytosis in adults. Br J Haematol 1994; 87: 243-250.
13. Yao M, Cheng AL, Su IJ, et al. Clinicopathological spectrum of haemophagocytic syndrome in Epstein-Barr virus-associated peripheral T-cell lymphoma. Br J Haematol 1994; 87: 535-543.
14. Fujiwara F, Hibi S, Imashuku S. Hypercytokinemia in hemophagocytic syndrome. Am J Pediatr Hematol Oncol 1993; 15: 92-98.
15. Imbach P, Barandum S, Cottier H, et al. Immunomodulation by intravenous immunoglobulin. Am J Pediatr Hematol Oncol 1990; 12: 134-140.
16. Watson HG, Goulden NJ, Manson LM, McDormid G, Gray JA, Parker AC. Virus-associated haemophagocytic syndrome: further evidence for T cell mediated disorder. Br J Haematol 1994; 86: 213-215.
17. Chen RL, Lin KH, Lin DT, et al. Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 1995; 89: 282-290.
18. Pawelec G, Rehbein A, Katrilaka K, Balko I, Busch FW. Prevention of human helper T-cell clone activation by cyclosporin A also block secretion of granulocyte/macrophage colony stimulating activity. Immunopharmacol 1988; 16: 207-216.
19. Janka G, Imashuku S, Elindar G, Schneider M, Henter J-I. Infection- and malignancy-associated hemophagocytic syndromes. Hematol/Oncol Clin North Am 1998; 12: 435-443.

Triplets with growth failure, microcephaly, mental retardation, nail hypoplasia and corpus callosum agenesis: is it a variant of Coffin-Siris or a new syndrome?

Birgül Kırel[1], Nurdan Kural[1], Ayten Yakut[1], Baki Adapınar[2]

Departments of [1]Pediatrics, and [2]Radiology, Osmangazi University Faculty of Medicine, Eskişehir, Turkey

SUMMARY: Kırel B, Kural N, Yakut A. Adapınar B. Triplets with growth failure, microcephaly, mental retardation, nail hypoplasia and corpus callosum agenesis: is it a variant of Coffin-Siris or a new syndrome? Turk J Pediatr 2000; 42: 171-176.

We report eight-year-old triplet girls whose clinical features included microcephaly, severe mental retardation, hypoplasia of distal phalanges of both fifth and second fingers and nail hypoplasia on second fingers, dysmorphic facial features, and partial corpus callosum agenesis. During infancy, a Pavlik harness was used for congenital hip dislocation, and they had difficulty in feeding. One had been operated for patent ductus arteriosus. To our knowledge, this rare combination has not been previously reported in triplets whose clinical features closely resemble those of Coffin-Siris syndrome. The other diagnostic possibilities are also reviewed.

Key words: Coffin-Siris syndrome, growth failure, microcephaly, mental retardation, nail hypoplasia.

We describe eight-year-old triplet girls with microcephaly, severe mental retardation, hypoplasia of distal phalanges of both fifth and second fingers and nail hypoplasia on second fingers, dysmorphic facial features and partial corpus callosum agenesis. These reatures closely resemble the abnormalities seen in Coffin-Siris syndrome. Coffin and Siris[1] first described three unrelated girls with severe mental and developmental retardation, absence of nails and distal phalanges of their fifth fingers and toes, and lax joints. They had coarse facial features with bushy eyebrows, wide mouth, and thick lips. New additional cases were reported later[2]. Our triplets had some differences regarding the facial and skeletal characteristics in previously reported cases of Coffin-Siris syndrome and these are discussed below.

Case Reports

The triplet girls were first admitted to our hospital at six years of age when one of them (Case 1) presented with generalized edema due to nephrotic syndrome. The girls had similar growth and developmental history and physical dysmorphic characteristics (Table I). They were products of an uncomplicated 37 week pregnancy and of an uneventful normal delivery. At birth, weight and length were both below the 10th percentile for all three, and head circumferences were below the -2 standard deviation. They had a history of feeding difficulty during infancy, of using Pavlik harness for congenital hip dislocation and of delayed neuromotor development. Case 2 had been operated for patent ductus arteriosus at 18 months of age. Their parents were nonconsanguineous. They had one older healthy brother and one older healthy sister. Physical examinations of the parents and two older siblings were normal. There was no family history of similar characteristics. On admission, weight and height were both below the 5th percentile and their head circumference were below the -2 standard deviation. Physical examination revealed mental retardation, hypoplastic distal phalanges and nails of second fingers, slightly hypoplastic distal phalanges of fifth fingers (Fig. 1), microcephaly and dysmorphic features such as bushy eyebrows, short, broad nose, hypertelorism, micrognathia,

Table I: Clinical Features of The Triplets

	Case 1	Case 2	Case 3
Low birth weight	+	+	+
Body weight (kg)	15	15	16
Height (cm)	102	105	107
Head circumference (cm)	44	45	45
IQ score	46	44	42
Microcephaly	+	+	+
Dysmorphic facial features	+	+	+
Partial corpus callosum agenesis	+	+	+
Feeding difficulty	+	+	+
Congenital hip dislocation	+	+	+
Severe myopia	+	+	+
Second nail hypoplasia	+	+	+
Fifth finger hypoplasia	+	+	+
Distal phalanges hypoplasia of 2^{nd} and 5^{th} fingers and all toes*	+		
Pseudoepiphysis of distal phalanges of hallux*	+		
Retarded bone age*	+		
Patent ductus arteriosus		+	
Nephrotic syndrome	+		

* Radiographs were only available in Case 1.

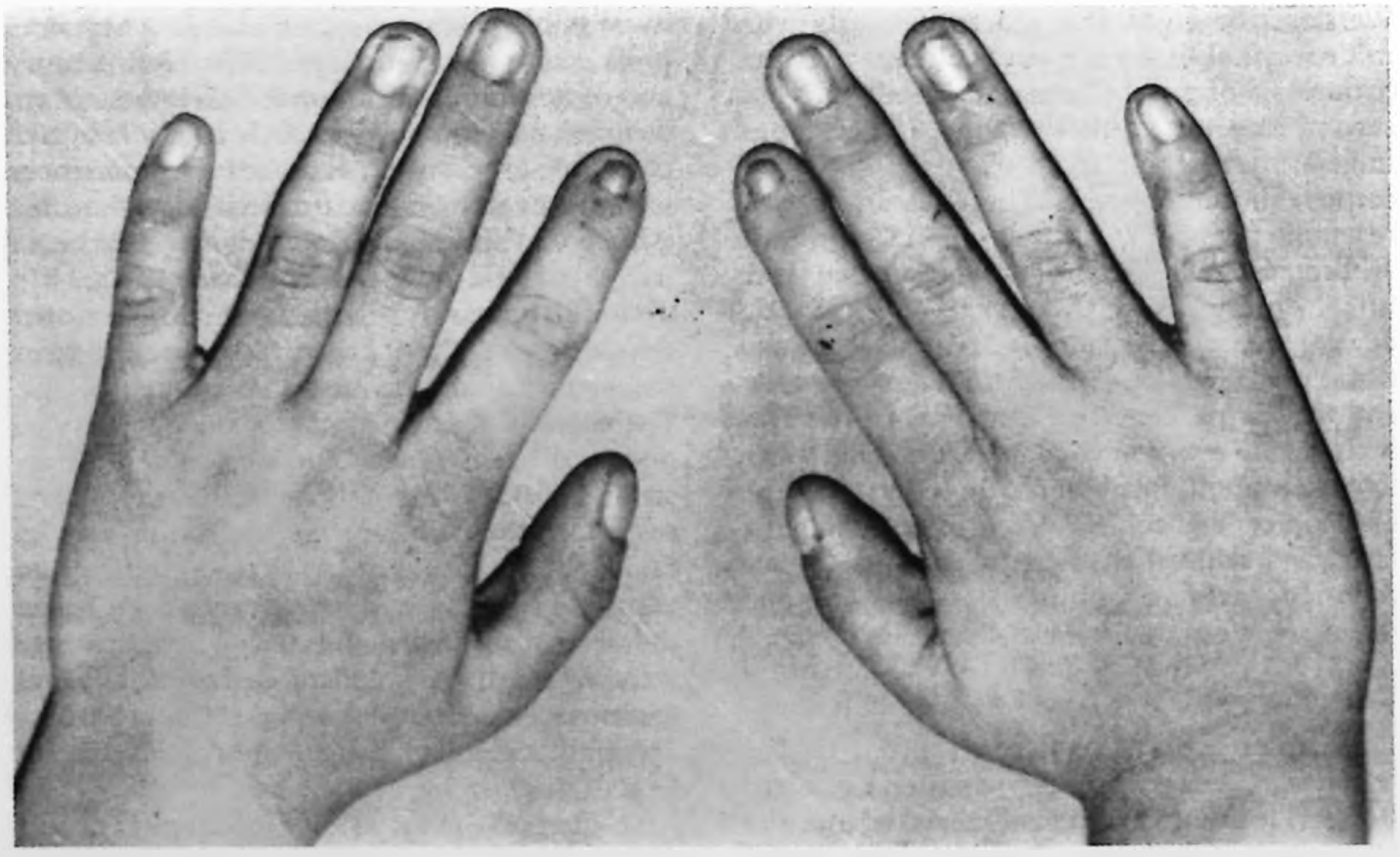


Fig. 1. Hypoplastic nails on the 2^{nd} fingers and hypoplastic distal phalanges of 2^{nd} and 5^{th} fingers.

fish mouth, low anterior hairline and left preauricular skin tag and normal scalp hair (Figs. 2-4). Other systems and neurologic examination were normal. Magnetic resonance imaging of brain demonstrated partial corpus callosum agenesis in all triplets (Fig. 5). Other laboratory investigations of Case 1 were as follows: urine and blood biochemical analysis, immunologic study and abdominal ultrasonography were compatible with nephrotic syndrome. Radiographs that were available at eight years of age showed hypoplasia as well as widened epiphysial distances and thick epiphysis on the distal phalanges of the second fingers (Fig. 6). Both fifth fingers demonstrated similar epiphysial findings on distal phalanges but no conspicuous hypoplasia (Fig. 7). There were hypoplasia of distal phalanges of all toes and radiolucencies on the middle part of distal phalanges of the first toe, which is compatible with pseudoepiphysis (Fig. 8). Bone age was compatible with 6.5 years of age. Only bilateral acetabular hypoplasia was demonstrated on the pelvic radiography. Chromosomal analysis of blood showed normal

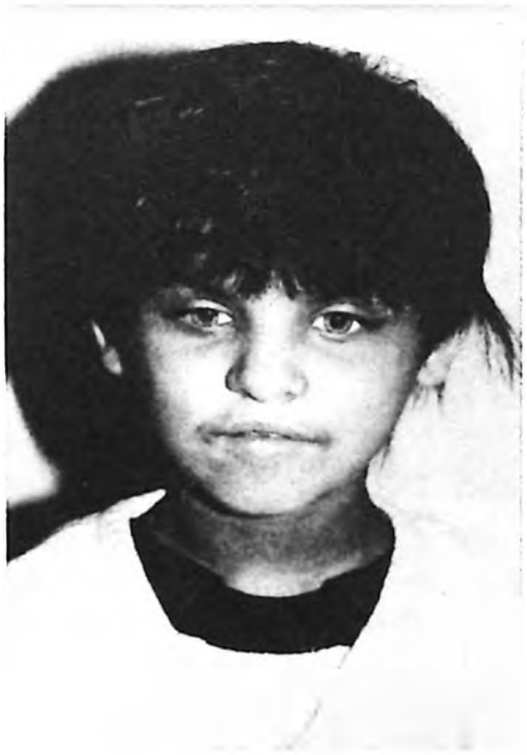


Fig. 2.

Fig. 3.

Fig. 4.

Figs. 2, 3, 4. Facial characteristics of the cases.

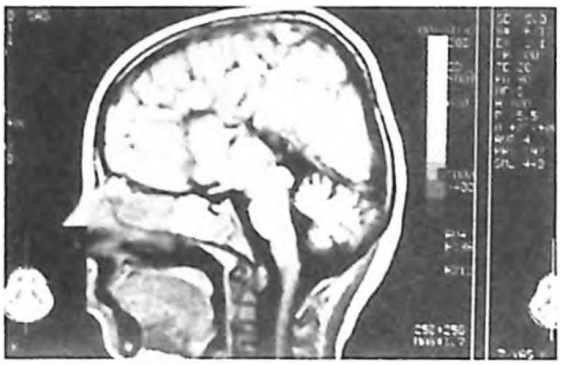


Fig. 5. Partial corpus callosum agenesis on MR imaging.

Fig. 6. Hypoplastic distal phalanges with epiphysial abnormality of 2nd fingers.

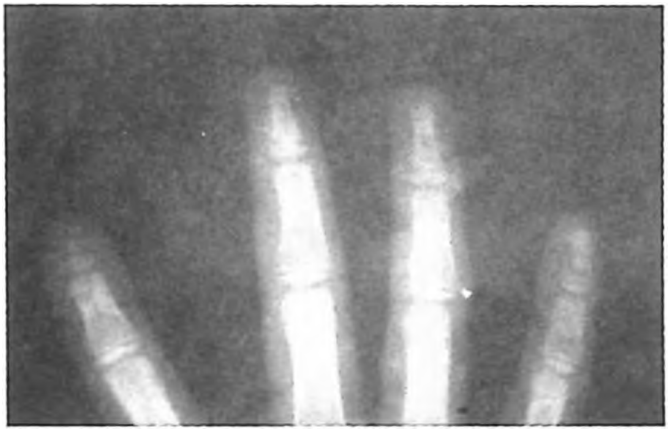


Fig. 7. Slightly hypoplastic distal phalanges with epiphysial abnormality of 5th finger on right hand.

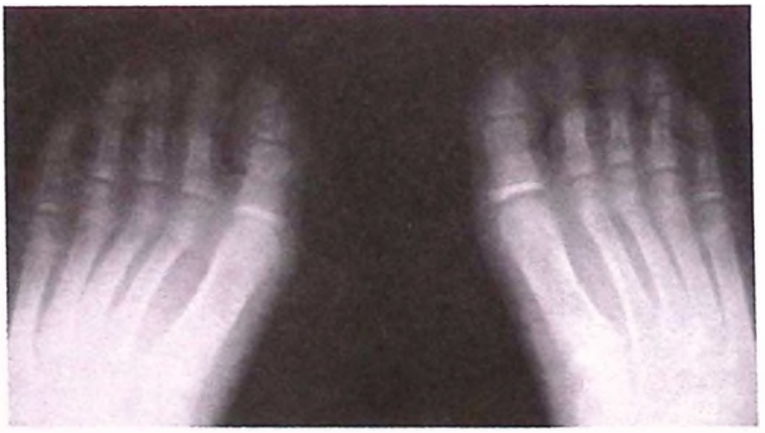


Fig. 8. Hypoplasia of distal phalanges of toes and pseudoepiphysis of distal phalanges of 1st toes.

karyotype. Nail-patella syndrome was ruled out because of presence of bilateral normal platellae and the pelvic findings on radiography. The nephrotic syndrome was steroid sensitive and still in remission after three years.

Discussion

In addition to microcephaly, mental retardation and growth failure, our triplets had dysmorphic facial characteristics and hypoplastic second nails and distal phalanges, which are more

impressive characteristics for the diagnosis. Hypoplastic nails are reported as a feature of several syndromes which are listed in Smith's Recognizable Patterns of Human Malformation[3]. Review of these syndromes showed that they had other quite different clinical characteristics and laboratory findings from our triplets.

Shortened distal phalanges and hypoplastic or aplastic nails of fingers have also been reported in anticonvulsant embryopathy. The triplets had dysmorphic facial features including short, broad, more or less turned-up nose, broad, low nasal bridge and hypertelorism[4-6]. Our triplets' facial features were very similar to the patients of anticonvulsant embryopathy seen in an atlas of characteristic syndromes[5]. But, our cases had no history of epilepsy, nor did the mother receive anticonvulsant therapy during gestation.

The features of the triplets also closely resembled Coffin-Siris syndrome, the main features of which are growth and developmental retardation, hypoplasia or absence of nail and distal phalanges with predominantly fifth digit involvement, hypotonia, infancy feeding problems, retarded bone age and craniofacial abnormalities. These features were present in variable frequency (Table II)[7-12]. The absent or hypoplastic nails and terminal phalanges of the fifth fingers and toes are constant features[7-12]. The other digits are also affected in Coffin-Siris syndrome[6-9]. Recently, this syndrome has also been defined as fifth digit syndrome by McKusick[2]. Our triplets' fifth digits were less involved than the other digits in contrast to the syndrome's definition.

Table II. Comparison of the Features of Our Cases with the Features of Coffin-Siris Syndrome

	Total cases*	Our cases
Sex: F/M	26/7	3/3
Low birth weight	17/32	+
Delayed growth postnatal	19/23	+
Developmental delay	31/31	+
Mental retardation	21/21	+
Retarded bone age	11/16	+
Microcephaly	21/31	+
Sparse scalp hair	23/28	–
Coarse face	27/31	–
Bushy eyebrows	23/31	–
Broad nose/nasal tip	24/29	–
Wide mouth	23/27	–
Thick/prominent lips	28/32	–
Hypoplastic/absent nails on 5th digits	33/33	–
Generalized hirsutism	25/30	–
Feeding problems	25/30	+
Recurrent respiratory infections	15/23	–
CNS defects	6	+
Cardiac defects	9/22	+
Renal defects	3/12	–
Scoliosis	6/15	–

* These frequencies adapted from Levy and Baraitser[7].

Body hirsutism is one of the most frequent features of Coffin-Siris syndrome. But, the second case reported by Weiswasser et al.[12], the third case of Coffin and Siris[1] and the case of Balcı, et al.[10] did not reflect body hirsutism, as was the case with our triplets.

Craniofacial abnormalities of Coffin-Siris syndrome include microcephaly, sparse scalp hair, coarse face, flat nasal bridge, bushy eyebrows, wide mouth, prominent lips. However, there are some cases without coarse face and bushy eyebrows reported[7]. Our triplets also had dysmorphic face, but it was not similar to previously described cases in this syndrome.

Central nervous system malformations associated with Coffin-Siris syndrome are Dandy-Walker malformation, partial corpus callosum agenesis, abnormal olive and arcuate nuclei and cerebellar heterotopias[1,13,14]. On the other hand, cardiac and renal defects and lax joints have also been described[1,6-10]. Our sibs had partial corpus callosum agenesis and congenital hip dislocation, and the second case had patent ductus arteriosus.

Although our triplets had some main and occasional features of Coffin-Siris syndrome, they had some skeletal and facial findings different from those seen in this syndrome, and they had no body hirsutism. Since the differential diagnosis did not lead us to another convincing diagnosis, we considered the triplets as having a variant of Coffin-Siris syndrome or a new syndrome.

Chromosomal analysis was available in only one of the triplets, and showed normal karyotype. The parents were nonconsanguineous, and there was no one resembling the triplets in the family, so we could not make any interpretation about the inheritance of these multiple and similar developmental abnormalities in the triplets.

In conclusion, to our knowledge, this is the first report of this combination in triplets. It might be a variant of Cofin-Siris syndrome or a new syndrome.

REFERENCES

1. Coffin GS, Siris E. Mental retardation with absent fifth fingernail and terminal phalanx. Am J Dis Child 1970; 119: 4332.
2. McKusick VA. Mendelian Inheritance in Man. Baltimore and London: The Johns Hopkins University Press; 1992: 396.
3. Jones KL. Smith's Recognizable Patterns of Human Malformation. Philadelphia: WB Saunders Co.; 1997: 818-819.

4. Hanson JW, Smith DW. The fetal hydantoin syndrome. J Pediatr 1975; 87: 285-288.
5. Widemann K, Grosse KR, Dibbern H. An Atlas of Characteristic Syndromes. A Usual Aid to Diagnosis. London: Wolfe Med Publications Ltd; 1985: 344.
6. Jones KL. Smith's Recognizable Patterns of Human Malformation. Philadelphia: WB Saunders Co; 1997: 582-583.
7. Levy P, Baraitser M. Coffin-Siris syndrome. J Med Genet 1991; 28: 338-341.
8. Lucaya J, Garcia-Conesa JA, Bosch-Banyeras JM, Pons-Peradejordi G. The Coffin-Siris syndrome: a report of four cases and review of the literature. Pediatr Radiol 1981; 11: 35-38.
9. Schinzel A. The Coffin-Siris syndrome. Acta Paediatr Scand 1979; 68: 449-452.
10. Balcı S, Erçal MD, Tokgözoğlu N, et al. Coffin-Siris Syndrome. Çocuk Sağlığı ve Hastalıkları Dergisi 1990; 33: 59-66.
11. Carey JC, Hall BD. The Coffin-Siris syndrome: five new cases including two siblings. Am J Dis Child 1978; 132: 667-671.
12. Weiswasser WH, Hall BD, Delavan GW, Smith DW. Coffin-Siris syndrome: two new cases. Am J Dis Child 1973; 125: 838-840.
13. DeJong G, Nelson MM. Choanal atresia in two unrelated patients with the Coffin-Siris syndrome. Clin Genet 1992; 42: 320-322.
14. DeBassio WA, Kemper TL, Knoefel JE. Coffin-Siris syndrome: neuropathologic findings. Arch Neurol 1985; 42: 350-353.

Occurrence of an aortic arch anomaly in two siblings born to a diabetic mother

Kürşad Tokel, Gonca Yılmaz, Berkan Gürakan

Department of Pediatrics, Başkent University Faculty of Medicine, Ankara, Turkey

SUMMARY: Tokel K, Yılmaz G, Gürakan B. Occurrence of an aortic arch anomaly in two siblings born to a diabetic mother. Turk J Pediatr 2000; 42: 177-179.

A patient with interruption of aortic arch type A, born to a diabetic mother, is described. The patient, a male infant, was the fourth child of a 29-year-old mother, and had a sibling with coarctation of the aorta. The mother had been treated for insulin-dependent diabetes mellitus for the previous 10 years. The infant died on the 3rd day of life after symptoms of cardiogenic shock. To our knowledge, interruption of aortic arch type A has not been previously described in infants of diabetic mothers. The relevance of the case is discussed and the literature reviewed.

Key words: infants of diabetic mothers, interruption of the aortic arch type A, aortic arch anomalies.

The incidence of congenital heart disease in infants of diabetic mothers is about four to five times higher than that observed in the normal population[1,2]. Conotruncal anomalies (tetralogy of Fallot, truncus arteriosus, double outlet right ventricle) and ventricular septal defects are among the most common cardiac defects found in infants of these women[3-6]. Interruption of the aortic arch (IAA), especially type B, has been discussed within the realm of conotruncal anomalies. The literature lacks any reports of IAA type A and B in infants of diabetic mothers.

We report a patient with IAA type A born to a diabetic mother. Interestingly, one of the patient's siblings had coarctation of the aorta.

Case Report

A male infant, the fourth child of a 29-year-old mother, was delivered by cesarean section at the 37th week of gestation, and weighed 3740 g (Apgar score 8) at birth. The mother had been treated for insulin-dependent diabetes mellitus for the past 10 years.

The family's first child, who is presently 10 years old, was afflicted with meningomyelocele at the lumbosacral region. The second child is healthy at eight years of age. The third child, born with coarctation of the aorta, ventricular septal defect, and atrial septal defect, died at one month of age after an attempt at resection and end-to-end anastomosis at another hospital.

At the 20th week of gestation in the fourth pregnancy, fetal echocardiography revealed muscular ventricular septal defect. Because of the mother's extreme obesity, the fetal aortic arch could not be demonstrated.

At birth, the physical examination revealed a pale tachypneic neonate weighing 3740 g and measuring 52 cm in length. His facial appearance was normal. His heart rate was 130 beats per minute, and respiratory rate was 56 breaths per minute. There was evidence of peripheral, but not central, cyanosis. No murmur was detected on auscultation and both femoral pulses were palpable. Other physical findings were within normal limits.

The chest X-ray revealed enlargement of the heart and prominent pulmonary vasculature (cardiothoracic index was 0.67). Thymus shadow was apparent. An electrocardiogram showed sinus rhythm and hypertrophy of the right ventricle.

Laboratory findings showed normal levels of serum Na^+ and K^+, and transient hypoglycemia and hypocalcemia. Pulse-oxymeter of the upper extremities showed O_2 saturation of 96-98

percent, while umbilical arterial blood gas analysis indicated PO_2 = 46 mmHg, O_2 saturation 70 percent, and PCO_2 = 47 mmHg.

Two dimensional echocardiographic examination demonstrated the presence of muscular, trabecular ventricular septal defect, thick interventricular septum and aortic interruption. Angiography, which was performed after PGE_1 treatment, indicated the presence of ventricular septal defect, patent ductus arteriosus, aortic interruption (distal to the left subclavian artery) and pulmonary hypertension (pulmonary artery pressure was 42/25 mmHg) (Fig. 1).

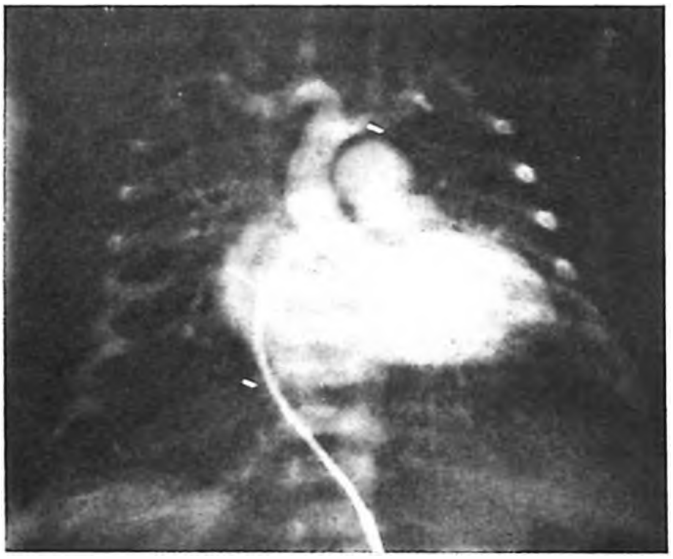


Fig. 1. Contrast injection of the left ventricle demonstrating the interruption of the aortic arch after the left subclavian artery.

During follow-up his general condition gradually worsened, and progressive acidosis developed. Despite therapy for heart failure, he developed severe bradycardia and symptoms of cardiogenic shock. The infant died on the 3rd day after birth. Permission for autopsy could not be obtained. No chromosomal abnormality could be demonstrated.

The fifth child of this family had a small muscular ventricular septal defect on echocardiography and his arcus aorta was normal.

Discussion

The teratogenicity of diabetes mellitus is complex, and arises due to a combination of various genetic, environmental and toxic factors. Diabetes dictates a fetal genetic susceptibility to abnormal development and may induce a maternal factor which can alter neural crest ectomesenchymal cell migration and growth in the fetus or directly cause fetal cardiomyopathy[4].

In itself, insulin or insulin analogue therapy for diabetes neither decreases nor increases the risk of malformation in the fetus, but a longer duration of diabetes has been shown to be significantly associated with higher risk for such abnormalities. Chung et al.[7] suggest that mothers who have had the disease longer have a higher incidence of fetal malformations. Because the mother's diabetes was under control, the prolonged duration of disease might have been a factor in our case.

Interruption of the aortic arch is estimated to occur in three of 100,000 live births, accounting for approximately one percent of congenital heart disease cases in infancy[8]. Since IAA type B is closely related to neural crest abnormality, it can be expected to occur more frequently in infants of diabetic mothers than type A. However, we could find no reports of either abnormality in infants of diabetic mothers.

Coarctation of the aorta, as seen in our patient's sibling, has been listed as one of the common cardiac defects seen in fetuses of diabetic women[8]. Furthermore, the coexistence of IAA type A and coarctation of the aorta in two children of a diabetic mother is particularly interesting, since Pierpont et al.[10] found no congenital cardiac malformations in siblings of children with IAA type A.

Interruption of the aortic arch is clearly not due to an involution or atresia of any of the aortic arches, because the interruption is located between the origin of the left subclavian artery and the ductus arteriosus, i.e. at the aortic isthmus. In preductal coarctation of the aorta, the obstruction also involves the isthmus. Both IAA type A and coarctation of the aorta therefore must manifest themselves relatively late in development, after the seventh cervical intersegmental artery has completed its proximal migration[11].

The similarity between the pathogenesis of IAA type A and coarctation of the aorta may partially explain their existence in the siblings in our case.

In conclusion, despite the well controlled maternal diabetes mellitus in the case presented, the presence of IAA type A and coarctation of the aorta in two siblings and the meningomyelocele in another sibling suggest diabetes mellitus as a common etiologic factor in these disorders.

REFERENCES

1. Fraser R. Diabetes in pregnancy. Arch Dis Child 1994; 71: 224-230.
2. Ramos-Arroya MA, Rodriguez-Pinilla E, Cordero JF. Maternal diabetes: the risk for specific birth defects. Eur J Epidemiol 1992; 8: 503-508.
3. Adams MM, Mulinare J, Dooley K. Risk factors for conotruncal cardiac defects in Atlanta. J Am Cardiol 1989; 14: 432-442.
4. Ferencz C, Rubin JD, McCarter RJ. Maternal diabetes and cardiovascular malformations: predominance of double outlet right ventricle and truncus arteriosus. Teratology 1990; 41: 319-326.
5. Smith RS, Comstock CH, Lorenz RP, Kirk JS, Lee W. Maternal diabetes mellitus: which views are essential for fetal echocardiography? Obstet Gynecol 1997; 90: 575-579.
6. Öztunç F, Özer S, Saraçlar M, Özkutlu S, Bilgiç A. Kesintili "interrupted" arkus aorta. Türk Kardiyoloji Derneği Arşivi 1991; 19: 244-248.
7. Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations. II. Effect of maternal diabetes on congenital malformations. Birth Defects 1975; 11: 23-28.
8. Morris MJ, McNamara DG. Coarctation of the aorta and interrupted aortic arch. In: Garson A. Bricker JT, McNamara DG (eds). The Science and Practice of Pediatric Cardiology. Philadelphia: Lea and Febiger; 1990: 1373-1376.
9. Reece EA, Hobbins JC. Diabetic embryopathy: pathogenesis, prenatal diagnosis and prevention. Obstet Gynecol Surv 1986; 41: 325-335.
10. Pierpont ME, Gobel JW, Moller JH, Edwards JE. Cardiac malformations in relatives of children with truncus arteriosus or interruption of the aortic arch. Am J Cardiol 1988; 61: 423-427.
11. Van Mierop L, Kutsche LM. Interruption of the aortic arch and coarctation of the aorta: pathogenetic relations. Am J Cardiol 1984; 54: 824-834.

ANNOUNCEMENTS

JERUSALEM 9-13 APRIL 2000
THE SECOND INTERNATIONAL CONGRESS ON PEDIATRICS IN THE COMMUNITY (SIPCC) 2000+
Inquiries to : Congress Secretariat
ORTRA Ltd.
1 Nirim St.
PO Box 9352
Tel Aviv 61092
ISRAEL
Phone : +972 3 638 4444
Fax : +972 3 638 4445
e-mail : pediat@ortra.co.il
website: www.ortra.com/pediatrics

BEIRUT, 30 MARCH - 2 APRIL 2000
THE FIRST INTERNATIONAL SYMPOSIUM IN PEDIATRICS UPDATE
Inquiries to : Dr. Mohammadd Mikati
Department of Pediatrics
American University of Beirut
Medical Center
Room C-660, P.O. Box: 113-6044/B52
Beirut
LEBANON
Phone : 961-1-754500 or
961-1-353465/6
extensions 5521/2
Fax : 961-1-744464 or 739268
e-mail : gj01@aub.edu.lb

ANKARA, 12-15 APRIL 2000
IIIrd INTERNATIONAL CONGRESS OF NUTRITION AND DIETETICS
Inquiries to : Flap Tour
Cinnah Caddesi, No: 42
06690 Çankaya
Ankara
TURKEY
Phone : +90 (312) 442 07 00
+90 (312) 438 21 21-22-23
Fax : +90 (312) 440 77 99
e-mail : flaptour@flaptour.com.tr
website: www.flaptour.com.tr

İZMİR, 20-22 APRIL 2000
FIRST WORLD CONGRESS OF PEDIATRIC THORACIC DISCIPLINES
Inquiries to : Prof. Oktay Mutaf
Ege University
Faculty of Medicine
Department of Pediatric Surgery
35100 Bornova
İzmir
TURKEY
Fax : +90 232 375 12 88
e-mail : omutaf@med.ege.edu.tr

İZMİR, 26-29 APRIL 2000
ADOLESCENT AND YOUNG ADULT TUMORS
Inquiries to : Funda Çorapçıoğlu
Dokuz Eylül University
Institute of Oncology
35340 İnciraltı
İzmir
TURKEY
Phone: +90 (232) 277 96 66
Fax : +90 (232) 277 96 66
e-mail: fundacp@cs.med.deu.edu.tr
website : turkpog.kongresi.gen.tr

ANTALYA, 3-7 MAY 2000
FAMILIAL MEDITERRANEAN FEVER
IInd INTERNATIONAL CONFERENCE
Inquiries to : Figür Turizm ve Organizasyon Ltd.
Nişantaşı Ihlamur Yolu
Yonca Apt., No: 40/3 80200 Topağacı
İstanbul
TURKEY
Phone : +90 (212) 232 52 19
Fax : +90 (212) 231 12 62 -
246 18 69
e-mail : figumorth@ticaretnet.com

ANKARA, 14-16 MAY 2000
IInd NATIONAL CONGRESS OF PEDIATRIC NEUROLOGY
Inquiries to : Congress Secretariat
Hacettepe University
Faculty of Medicine
Department of Pediatrics
Neurology Unit 06100 Hacettepe
Ankara
TURKEY
Phone: +90 312 311 37 11 or
305 11 65
Fax : +90 312 311 62 62
e-mail: mtopcu@gen.hun.edu.tr

LONDON, 3-25 MAY 2000
IMPERIAL COLLEGE SCHOOL OF MEDICINE DIVISION OF PAEDIATRICS, OBSTETRICS AND GYNAECOLOGY COURSES AND SYMPOSIA OF INTEREST TO PAEDIATRICIANS

Code (please use for reference)

12 Recent advances in genetics (for paediatricians)	3 May 2000
16 Revision course for DCH	15-19 May 2000
17 Update in neuromuscular disorders	17-19 May 2000
18 Advanced course in fetal medicine	22-24 May 2000
19 Paediatric endocrinology	25 May 2000

Inquiries to : Symposium office
Imperial College of Medicine
Queen Charlotte's & Chelsea Hospital
Goldhawk Road London W6 0xG
UNITED KINGDOM
Phone: +44 (0) 20 8383 3904
Fax : +44 (0) 20 8383 8555
e-mail: sympreg@ic.ac.uk
website: http://www.med.ic.ac.uk/dp/dpsh

İSTANBUL, 29 MAY - 2 JUNE 2000
XXXVIth TURKISH PEDIATRICS CONGRESS
TURKISH PEDIATRICS AND OUR CHILDREN IN THE BEGINNING OF THE THIRD MILLENIUM
Inquiries to : Congress Secretariat
İstanbul University
Cerrahpaşa Faculty of Medicine
Department of Pediatrics
P.K. 2 34303 Cerrahpaşa
İstanbul
TURKEY
Phone: +90 (212) 530 03 31
Fax : +90 (212) 586 15 95
588 49 18

STOCKHOLM 4-8 JUNE 2000
XIIIth INTERNATIONAL CYSTIC FIBROSIS CONGRESS
Inquiries to : Congress Secretariat
Stockholm Convention Bureau
XIIIth International Cystic
Fibrosis Congress
P.O. Box 6911, SE-102 39
Stockholm
SWEDEN
Phone: +46 8 736 15 00
Fax : +46 8 34 84 41
e-mail: cf@stocon.se

BURSA, 4-8 SEPTEMBER 2000
44th NATIONAL PEDIATRIC CONGRESS WITH INTERNATIONAL PARTICIPATION CHILD HEALTH IN THE 2000s
Inquiries to : Prof. Dr. Nihat Sapan
Congress Secretariat
Milli Pediatri Derneği Bursa Şubesi
Bursa
TURKEY
Phone: +90 224 442 85 62
Fax : +90 224 442 85 82
e-mail: nsapan@uludag.edu.tr

CAMBRIDGE, 13-17 SEPTEMBER 2000
VIIIth INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM
Inquiries to : Congress Secretariat
VIII ICIEM
42 Dvonshire Road
Cambridge CB1 2BL
United Kingdom
Phone : +44 (1223) 323437
Fax : +44 (1223) 460396
e-mail : cc@confcon.demon.co.uk
website: www.ssiem.org.uk

LONDON 14-15 SEPTEMBER 2000
ASSOCIATION FOR PEDIATRIC EDUCATION IN EUROPE (APEE) 30th ANNUAL CONGRESS NEONATOLOGY FOR THE NON-SPECIALIST: TEACHING, TRAINING AND CONTINUING EDUCATION
Inquiries to : Secretariat APEE 2000
P.O. Box 3219 Barnes
London SW13 9XR
UNITED KINGDOM
Phone: +44 (0) 20 8741 1311
Fax : +44 (0) 20 8741 0611
e-mail: CourseRegs@aol.com
web site: http://www.
altinternet.com/apee

ANTALYA 18-22 SEPTEMBER 2000
7th ASIAN EUROPEAN WORKSHOP ON INBORN ERRORS OF METABOLISM (AEWIEM)
Inquiries to : Prof. Dr. Turgay Coşkun
Scientific Secretariat
Cinnah Cad., 24/13
06600 Kavaklıdere
Ankara
TURKEY
Phone: +90 312 305 11 23
Fax : +90 312 467 60 72
e-mail: turgay@gen.hun.edu.tr
mgurbuz@serenas.com.tr

PORTOROZ, 4-6 OCTOBER 2000
26th CONGRESS OF THE UNION OF MIDDLE EASTERN AND MEDITERRANEAN PEDIATRIC SOCIETIES (UMEMPS)
Inquiries to : UMEMPS
Dr. Ivan Vidmar
Klinicni oddelek za otrosko kirurgijo
in intenzivno terapijo
1525 Ljubljana
SLOVENIA
Phone: +368 61 130 17 14
Fax : +368 61 130 17 14
e-mail: Ivan.Vidman@kclj.si

ANTALYA, 8-11 OCTOBER 2000
IX. NATIONAL ALLERGY AND CLINICAL IMMUNOLOGY CONGRESS WITH INTERNATIONAL PARTICIPATION
Inquiries to : Dicle Güç, MD
Ömer Kalaycı, MD
Hacettepe University
Faculty of Medicine
Department of Pediatrics
Pediatric Allergy and dAsthma Unit
06100 Hacettepe, Ankara
TURKEY
Phone: +90 312 324 25 11 or
305 17 00
Fax : +90 312 311 23 57
e-mail: allergy@gen.hun.edu.tr

BEIJING, 9-14 SEPTEMBER 2001
THE 23rd INTERNATIONAL CONGRESS OF PEDIATRICS (The IPA World Congress of Pediatrics)
The 2nd INTERNATIONAL CONGRESS ON PEDIATRIC NURSING
Inquiries to : Secretariat
23rd ICP
International Convention Services
Chinese Medical Association
42 Dongsi Xidajie
Beijing 100710
CHINA
Phone: +86 10 6525 0394
Fax : +86 10 6512 3754
website: http://www.
chinamed.com.cn/pediatrics

NOTICE TO AUTHORS

The Turkish Journal of Pediatrics is an English publication of original articles, case reports, reviews of the literature, case of the month, short communications, clinicopathological exercises and letter to the editor in the field of pediatrics, and will consider papers from authors of all countries. Original articles should report scientific findings within the pediatric field of interest. Case reports should contain accounts of rare syndromes, new diagnostic tools and methods, new kinds of treatment and laboratory research with foreseeable practical application. Review articles should contain an objective account of different points of view and an internationally representative bibliography. Authors considering submission of review articles of medical progress are encouraged to consult with the Editor before submission. Papers should in general not exceed 15 written pages for original articles or 7 for case reports and reviews of the literature, including tables, figures and illustrations. All papers are subject to editorial revision for the purpose of conformity to the style adopted by *The Turkish Journal of Pediatrics,* and authors may be requested to shorten or revise their papers.

Statements and opinions expressed in the articles are those of the author(s) and not necessarily those of the Editor or publisher; the Editor and publisher disclaim any responsibility or liability for such material. Neither the Editor nor the publisher guarantees, warrants, or endorses any product or service advertised in this publication; neither do they guarantee any claim made by the manufacturer of such product or service.

We recommend that all manuscripts be approved for submission by the department chairman or head of the institution in which the study has been done. All manuscripts must be accompanied by the following **written statement,** signed by the author(s): "The author(s) transfer(s) all copyright ownership of the manuscript entitled (title of article) to *The Turkish Journal of Pediatrics* in the event the work is buplished. The author(s) warrant(s) that the article is original, is not for consideration by another journal, has not been previously published (except in a congress report), and has been prepared according to the manuscript rules" (as described below). Papers describing research involving human subjects should indicate that informed consent was obtained from the parents or guardians of the children who served as subjects and, when appropriate, from the subjects themselves.

Preparation of Manuscript

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles and may result in rejection of otherwise acceptable manuscripts. Manuscripts should be sent in triplicate (original and two photocopies acceptable) to the Editorial Secretary, *Turkish Journal of Pediatrics,* P.K. 66, 06240 Samanpazarı, Ankara, Turkey. Manuscripts, whether rejected or published, are not returned to the authors, but original illustrations which are rejected are returned upon request of the author.

Format Manuscripts should be typed, double-spaced, on one side of the paper only, with wide margins.

Title Page A separate title page should include authors' names and academic degrees; departmental and institutional affiliations of each author, and sources of financial assistance, if any. Designate one author as the correspondent, and provide an address as well as business and home telephone numbers. Galley proofs and order forms for reprints will be sent to the corresponding author, at a later date.

Contents Each original article should contain the following sections: Introduction, Material and Methods, Results, Discussion and Summary, and each Case Report should contain an Introduction, Case Report, Discussion and Summary.

Abbreviations Abbreviations must conform to accepted standards. Laboratory slang, clinical jargon and colloquialisms must be avoided.

Tables Tables should be numbered with Roman numerals according to the order of mention in the text. Each table must be typed double-spaced on a separate sheet of paper, and a concise title supplied for each. Tables should be self-explanatory and supplement, not duplicate the text. If a table or any data therein have been previously published, a footnote must give full credit to the original source.

Figures Figures and illustrations should be of direct interest to the subject of the paper and numbered with Arabic numerals according to order of reference in the text. Figures should be drawn on white paper and photographs must be clear prints. The name of the first author and the number of the figure or illustration must be written in pencil on the back of each, with an arrow indicating the top side. Original drawings or graphs should be prepared in black India ink or typographic (press-apply) lettering. Typewritten or freehand lettering is unacceptable. All lettering must be professional and in proportion to the drawing, graph, or photograph. Do not send original art work, x-ray films or ECG strips. A list of legends for the figures and illustrations must be provided on a separate page.

Summary / Abstract An informative summary not exceeding 150 words must accompany each manuscript, typed on a separate sheet. Unexplained abbreviations and references are not allowed.

References References to the literature should be limited to those cited by the author, arranged and numbered according to order of mention in the text. All authors of an article or book should be listed where there are six or fewer. If more than six, the first three names should be given followed by the indication "et al". In a manuscript underlining indicates italics.

References to journal articles:

Example : 1. Bier DM, Fulginiti VA, Garfunkel JM, et al. Duplicate publication and related problems. Pediatrics 1990; 86: 997-998.

Names of journals are to be abbreviated in accordance with the style of *Index Medicus.*

References to books:

Example : 2. Praat RTC. *The Genetics of Neurological Disorders.* London: Oxford University Press; 1967: 173-174.

References to chapters in books:

Example : 3. Kissane JM. Development of the kidney and congenital malformations. In: Heptinstall RH (ed). Pathology of the Kidney (2nd ed) Vol. 1. Boston: Little, Brown and Co; 1974: 69-109.

Key Words Authors are requested to list on a separate sheet of paper key words related to their article. These will bu used in compiling an index for the volume of the journal in which the article appears.

Proofs and Reprints Galley proofs will be sent to the corresponding (or principal) author by the editor. The master proof should be returned to the Managing Editor together with the manuscript within two days, and by air mail if received by air mail.

Announcements Announcements of scheduled meetings, symposia, or postgraduate courses may be sent to the publisher for consideration at least 5 months in advance of the meeting date.

Books for Review Books and monographs, domestic or foreign, may be sent to the Editor for consideration for review. No books are returned, nor acknowledgement made of books received.

Advertising Communications of a business nature and all advertising communications should be addressed to the Journal's Editor.

Checklist

Please check your article as described below before sending it to the Editor.

- Letter of submission
- Signed "Statement" (which is written on a separate paper) as described above
- Three copies of article (one original and two photocopies will be acceptable).
- Title page
  - Title of article
  - Short running title
  - Name(s), academic degrees, and affiliations of author(s)
  - Name, address, and business and home telephone numbers of corresponding author
- Article proper
  - Original articles: Introduction, Material and Methods, Results, Discussion, Summary
  - Case Reports: Introduction, Case Report, Discussion, Summary
  - Key words
- References on a separate sheet
- Tables on separate sheets
- Legends on separate sheets
- Illustrations properly labelled (one set of glossy prints and one set of photocopies).