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VITAMIN A STATUS OF HEALTHY INFANTS IN ANKARA, TURKEY*

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SUMMARY: Hatun Ş, Teziç T. (Department of Endocrinology, Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Vitamin A status of healthy infants in Ankara, Turkey. Turk J Pediatr 1995; 37: 187-192.

Vitamin A deficiency is considered widespread health problem among children in developing countries. There are a limited number of studies related to the vitamin A status of children in Turkey. We studied serum vitamin A levels in 80 healthy children less than 2 years of age admitted to Dr. Sami Ulus Children's Hospital for measles immunization. Vitamin A levels were determined by high performance liquid chromatography, and ranged from 8.5 to 34 µg/dl (mean 23.54 ± 6.86 µg/dl). We have shown that subclinical vitamin A deficiency is an important public health problem in Ankara, as approximately 30 percent of the children examined were found to have low levels of serum vitamin A (< 20 µg/dl).
Key words: vitamin A deficiency, child health, infant, Turkey.

Vitamin A, discovered in 1913, has such metabolic functions in the human organism as ensuring the integration of epithelial cells, growth, reproduction, vision and adjuvant actions of the immune system[1]. Vitamin A deficiency is one of the important nutritional deficiencies in developing countries and plays an important role in the vicious infection-malnutrition cycle (Fig. 1)[2].

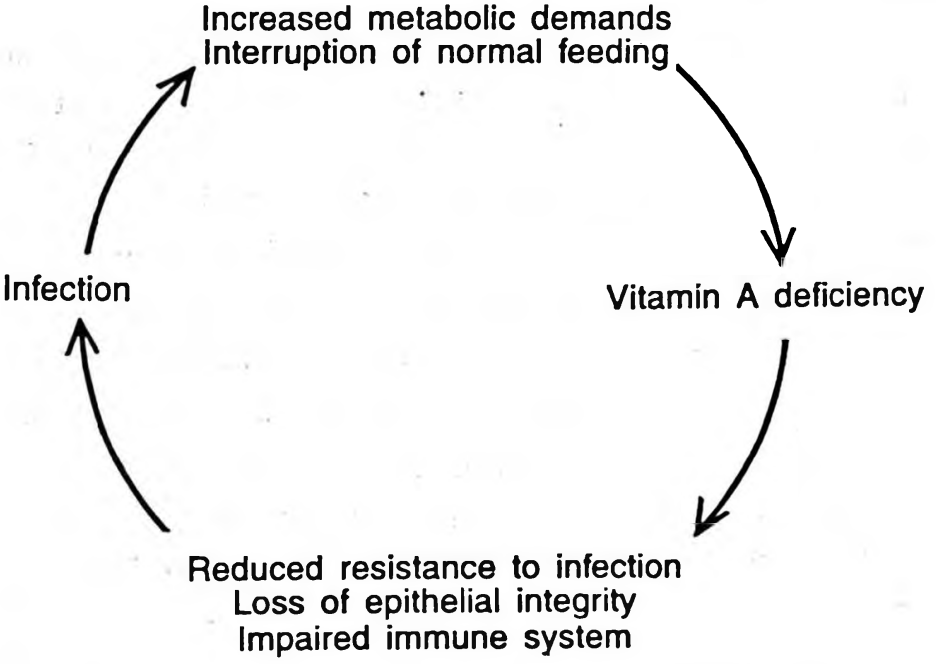

Fig. 1: Cycle of disease and vitamin A deficiency (2).

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Following the attention drawn to its anti-infective effects as early as 1928[3], vitamin A has once more become the focal point with the work in the early 1980s of Alfred Sommer et al[4,5]. Subsequent studies have revealed that deficiency of vitamin A resulted in respiratory and gastrointestinal infections[4], and that administration of this vitamin in cases of deficiency reduced the one-to five-year-old child mortality by as much as 35 percent[5]. These studies have contributed to the development of a significant nutritional initiative program with vitamin A during the childhood period.

According to World Health Organization (WHO) criteria, when the serum vitamin A level is less than 10 µg/dl in more than five percent of the population, there is a serious public health problem[6]. As for Pan-American Health Organization (PAHO) criteria, a public health problem arises when 15 percent or more of the population display serum vitamin A levels of 20 µg/dl or less[6]. These criteria suggest that many parts of the world, particularly African and Southeast Asian countries, suffer serious problems arising from vitamin A deficiency[4,5].

In Turkey, there have been a few studies related to vitamin A deficiency, most of which have been done on children with malnutrition[7-10]. Our hospital plans to provide vitamin A to healthy children also residing in the slum area in the immediate vicinity. This study aims to examine the vitamin A levels of children under two years of age to determine whether vitamin A deficiency constitutes a problem in our area.

Material and Methods

Eighty infants who were brought to Dr. Sami Ulus Children's Hospital for measles immunization were considered for enrollment in this study. Date of birth, sex, home area, education of the mother, number of children in the family, whether they were breast-fed at the time of reporting to the hospital and whether they received vitamin support and had an infection during the last three months were recorded.

A complete physical examination was done on all infants, and their weight percentiles by age were calculated according to Neyzi et al. Standards for Turkish Children[11].

Five milliliter venous blood samples were taken from all infants, and serum obtained by centrifugation was stored at -30 °C. The samples were kept away from sunlight during all procedures. Serum vitamin A levels (as retinol) were determined by the high-pressure liquid chromatography method (Beckmann Instruments, Inc., Altex Scientific Operations, California 94710, USA).

The determined serum vitamin A levels were classified according to sex, living environment (slum or residential area), maternal education (primary school, junior or senior high school and university), those who received vitamin support and had previous infections, and the results were compared. An inquiry was then made into the relations of the above parameters with groups in which the serum vitamin A levels were < 10 µg/dl and < 20 µg/dl.

All values are reported as meas ± SD. Chi square and Fisher exact chi square tests were used for the comparison of group ratios. Differences in the means of the two groups were compared using the Student's t test; the means of more than two groups were compared by one-way analysis of variance. The Pearson correlation analysis was used for determining the relation between the number of infants and vitamin A levels. Statistical analyses were performed with an SPSS for Windows V 5.01.

Results

The ages of the 80 infants included in the study ranged from 9 to 17 months, with a mean of 10.36 ± 1.40 months. The weight percentile mean was 24.2 ± 14.3, and none of the children had malnutrition according to weight percentile. The male/female ratio was 1.2. Thirty-six (45%) infants were from families living in slum areas, 32 (40%) received vitamin support and 30 (37.5%) had at least one respiratory tract infection during the previous three months. Ten percent of the mothers were illiterate, 46 percent had primary and 44 percent had senior high school or university educations. Eighty-five percent of the families had one or two children.

The mean serum vitamin A level was 23.54 ± 6.86 µg/dl (range 8.5-34.0 µg/dl). Thirty percent of the infants (24 infants) had serum vitamin A levels of less than 20 µgm/dl, while 1.3 percent (one infant) had a level < 10 µg/dl. The relations of serum vitamin A levels to various other parameters are given in Table I.

Table I: Vitamin A Status of Children According to Various Parameters

	Serum Retinol Level < 10 µg/dl	P*	No.with Retinol Level (µg/dl)	P*	No.with Retinol < 20 µg/dl	P*
Male (n: 44)	23.15±6.63	NS	15 (34.1%)	NS	0	NS
Female (n: 36)	23.98±7.11		9 (25%)		2 (2.8%)	
Slum areas (n: 36)	22.67±6.71	NS	12 (33.3%)	NS	1 (2.5%)	NS
Residential areas (n: 44)	24.22±6.94		12 (24.0%)		0	
Infections during the previous three months (n: 30)	22.57±7.56	NS	10 (33.3%)	NS	1 (28%)	NS
No. infections during the previous three months (n: 50)	24.10±6.35		14 (28.0%)		0	
Those receiving vitamin support (n: 92)	26.20±7.12	0.004	6 (15.8%)	0.07	0	NS
Those not receiving vitamin support (n: 48)	21.75±6.05		18 (37.5%)		1 (2.8%)	
Total (n: 80)	23.54±6.86		24 (30%)		1 (1.3%)	

$p < 0.05$ was considered significant; NS: not significant.

When the relationship of serum vitamin A levels with the above parameters were analyzed, only the group who received vitamin A support had significantly higher levels than those who did not. The other parameters did not display significant differences in serum vitamin A levels. There was no correlation between serum vitamin A level and the number of children in the family ($r = 0.2030$: $p = 0.07$).

Discussion

Vitamin A deficiency occurs as a result of low dietary intake, absorption disorders, problems related to the conversion of carotene into vitamin A and its transportation within the body, and rapid losses of vitamin A[1]. As a general rule, vitamin A deficiency occurs more frequently among preschool-age children; however, studies done in Asia and Africa suggest that the weaning period is a period of special risk[6]. WHO defines two main groups among those considered to be at high risk from the viewpoint of vitamin A deficiency[6]. The countries in the first group where xerophthalmia and nutritional blindness constitute serious public health problems are Tanzania, India and Indonesia, while the second group comprises countries where vitamin A deficiency does not constitute a significant health problem, though a continuous monitoring of its eventual consequences is recommended. According to WHO, Turkey is among the countries in the second group.

In our study, the vitamin A deficiency rate (< 20 µg/dl) in children under two years of age having no acute infections or malnutrition was found to be 30 percent. As for those having serum vitamin A levels of less than 10 µg/dl, the rate was 1.3 percent. Considering the criteria established by PAHO, vitamin A deficiency appears to be a problem in this country, although the WHO criteria do not corroborate this statement. A recent study, carried out in the semi-urban areas of Ankara on children with recurrent diarrhea and/or respiratory tract infections, revealed that 60.7 percent of the population have serum vitamin A levels of less than 20 µg/dl, while rates below 10 µg/dl were found in 3.7 percent of children[10]. Another study discovered 9.3 percent vitamin A deficiency (< 20 µg/dl) among healthy school-age (7 to 17 years of age) children[12]. Our study is the first of its kind on healthy infants and suggests that vitamin A deficency is a problem which should be considered.

The results of this study indicate that there is no correlation between vitamin A deficency and sex, inhabited area and infections suffered during the previous three months. Though a statistically significant difference was not noted, the vitamin A deficiency rate (< 20 µg/dl) was higher among those inhabiting slum areas and not receiving vitamin A support. These results suggest that a nutritional initiative program should be a priority in the slum areas.

Several previous studies revealed that subclinical vitamin A deficiency (< 20 µg/dl) constitutes a major risk to infant health[13-15]. Similarly, vitamin A support given

to children at risk significantly reduces infant mortality[16]. A recent study done in Sudan indicates that the rate of diarrhea is reduced among children to whom vitamin A support is provided[17].

In conclusion, our study and the previous studies done in this country show that vitamin A deficiency is an important child health problem. For this reason, initiation of vitamin A support programs must be considered without delay, preferably integrated into immunization programs similar to those introduced in countries where vitamin A deficiency is a public health problem. Otherwise, "One child will die needlessy from vitamin A deficiency every minute we will wait"[18].

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VITAMIN A LEVELS OF CHILDREN WITH MEASLES IN ANKARA, TURKEY*

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SUMMARY: Hatun Ş, Teziç T, Kunak B, Cengiz AB. (Department of Pediatrics, Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Vitamin A levels of children with measles in Ankara, Turkey. Turk J Pediatr 1995; 37: 193-200.

Recent studies show that vitamin A levels decrease during measles and that vitamin A therapy can improve measles outcome in children in the developing world. Vitamin A levels of children with measles have not been studied before in Turkey. Therefore we measured serum vitamin A levels in 21 children with measles and compared the results with "sick" and "healthy" control groups. The mean vitamin A levels in children with measles were markedly lower than in the "sick" and "healthy" control groups (p: 0.001). Vitamin A levels in children with measles ranged from 1.3 to 32 µg/dl; 11 (52%) were vitamin A deficient (< 10 µg/dl). This frequency among Turkish children supports evaluation of vitamin A status as a part of acute management of measles in Turkey. Clinicians may wish to consider vitamin A therapy for children with measles according to WHO recommendations. *Key words: vitamin A, measles, vitamin A deficiency, Turkey.*

The anti-infectious effect of vitamin A was pointed out by Green and Mellanby in 1928[1], and four years later Ellison[2] showed the potential benefit of vitamin A in measles treatment. Vitamin A, which has not drawn the attention of research thereafter, became popular again in the 1980s with the efforts of Alfred Sommer et al[3, 4]. Studies done for the last fifteen years have showed that vitamin A support may have a significant role both in reducing child mortality and in measles treatment[5-8].

Research investigating the relationship between measles and Vitamin A can be classified into three groups:

1. The first group of research points out that xerophthalmia usually follows measles, and measles is the precipitating factor for half of childhood blindness cases in Africa[9, 10].
2. The second group of research draws attention to the fact that during measles infection, the serum vitamin A level is low, leading to increased mortality and morbidity from measles[11-13].
3. In the third group of research it is shown that administering high-dose vitamin A to children with measles decreases mortality up to 50 percent[14, 15].

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As a result, the World Health Organization (WHO) and UNICEF published a report about vitamin A therapy in measles in 1987[16]. This report admits that vitamin A deficiency is a public health problem, and for those communities where mortality related to measles is greater than one percent, recommends routine vitamin A therapy, for children with measles (100,000 IU for children less than 12 months of age, and 200,000 IU for those older than 12 months). After this recommendation, vitamin A levels were investigated in several developing countries, and vitamin A therapy for measles has been initiated.

Measles is still a major child health problem in our country. According to the Ministry of Health data, 35,000 children were reported as having measles in 1993[17]. The measles mortality rate is not exactly known in our country. Despite the report published by WHO/UNICEF in 1987, vitamin A therapy is not widespread in Turkey. Very few studies have examined vitamin A deficiency in children, and there is a lack of research on the vitamin A status of children with measles[18]. In this study, the objective was to determine the vitamin A status in children with measles in Ankara and then to assess the necessity of vitamin A therapy in our country.

Material and Methods

Twenty-one patients seen at Dr. Sami Ulus Children's Hospital with a diagnosis of measles from November 1993 through March 1994 were considered for enrollment. The diagnosis of measles was made on clinical grounds. Children receiving vitamin A supplements in an amount greater than twice the recommended daily allowance were excluded from the study. Anthropometric values at enrollment included weight for age and height for age according to Neyzi et al. Standards for Turkish Children[19].

After completing the informed consent form, 5 ml of blood was drawn by venipuncture within 72 hours of the onset of a rash. Serum was obtained by centrifugation and stored at -30 °C until analyzed (within two months). During all procedures, blood samples were protected from sunlight to prevent photodestruction of vitamin A. Vitamin A (as retinol) was measured by normal phase high-pressure liquid chromatography (Beckman Instruments, Inc Altex Scientific Operations, California 94710, USA) at Düzen Laboratory, Ankara.

Two control populations were also studied. Fourteen children without acute infections and twenty-one children with documented infections other than measles (five with purulent meningitis, seven with pneumonia, and two with urinary tract infection) were enrolled as "healthy" and "sick" control groups, respectively.

All values are reported as mean ± SD. Differences in proportions in the data were examined by chi square and Fisher exact chi square tests. Differences in the means were examined by student's two-tailed t test. The Turkey studentized range method

within a one-way analysis of variance was used to perform pair-wise comparisons. The homogeneity of variances was examined by Levene test. A two-way analysis of variance was performed with age as covariate, because an age effect was observed. All statistical analyses were performed using SPSS for Windows V 5.01.

Results

A total of 56 children were included in the study; 21 had measles, 14 had acute infections other than measles and 21 were healthy. The characteristics of these children are given in Table I. Sixty-two percent of the children with measles were younger than 24 months of age. According to anthropometric measurements, none of them was identified as having malnutrition. Age variation was significant between children with measles and the "healthy" control group (p: 0.03).

Table I: Characteristics of Children with Measles and Control Children

	Measles Group	Sick Control Group	Healthy Control Group	ANOVA *p*
n	21	14	21	
Age (months)	42.5 ± 38.7	35.2 ± 30.9	10 ± 1.8	0.01 (KW)
% Male	66.7	50	52.4	NS
Weight Percentile for age	27.2 ± 21.1	28.1 ± 23.2	35.2 ± 20.2	NS
Height Percentile for age	33.7 ± 22.8	36.4 ± 26.5	40.5 ± 14.8	NS
Retinol (µg/dl)	11.5 ± 6.5	22.1 ± 6.5	26.9 ± 6.4	0.001
No. with retinol < 20 µg/dl	19 (90.5%)	6 (42.9%)	2 (9.5%)	0.00001
No. with retinol < 10 µg/dl	11 (52%)	1 (7.2%)	0	0.00006

ANOVA: analysis of variance; KW: Kruskal-Wallis; NS: not significant.

In children with measles, 19 out of 21 (90.5%), in children with acute infections other than measles (sick control group), six out of 14 (42.9%) and in the healthy control group, two out of 21 (9.5%) serum retinol levels were measured to be less than 20 µg/dl. In 11 children with measles (52%) and one child in the sick control group (7.2%), serum retinol levels were measured as less than 10 µg/dl. All of the children in the healthy control group had serum retinol levels greater than 10 µg/dl. The age variation between children with measles and the healthy control group did not affect the variation in serum retinol levels (p: 0.001 after the effect of age variation is eliminated).

Twelve children with measles were diagnosed with pneumonia (Table II). There was no significant difference between the serum retinol levels of children with and without pneumonia (p: 0.33); however, while 75 percent of children with pneumonia had serum retinol levels of less than 10 µg/dl, this low level was measured in only 22.2 percent of those without pneumonia. The number of children

having pneumonia with serum retinol levels of less than 10 µg/dl was significantly higher than the number of children in the other group (p: 0.02). Of the 12 children with pneumonia, four had severe clinical symptoms and very low retinol levels (1.3, 4.0, 7,0 and 8.2 µg/dl). One of these four children died of respiratory arrest.

Table II: Vitamin A Levels in Children With Measles With and Without Pneumonia

	Retinol (µg/dl)	No.with Retinol < 20 µg/dl	No.with Retinol < 10 µg/dl
With pneumonia (n: 12)	10.3 ± 7.7	11 (91.7%)	9 (75%)
Without pneumonia (n: 9)	13.3 ± 4.4	8 (88.9%)	2 (22.2%)
p*	0.33	0.69	0.02

(*) Fisher exact chi square test.

Discussion

In recent years, the studies done particularly in Africa and Asia show that serum retinol levels are low (< 20 µg/dl) in children with measles[11-13]. In a longitudinal study undertaken in India including 32 children with measles, low levels of the vitamin were shown to be specific to the acute phase of the infection, returning to normal at the end of eight weeks[12]. In another study published recently, low levels of retinol measured in the acute phase increased during convalescence[20]. Low serum retinol levels were first considered to be a result of malnutrition, thus more a problem of developing[21]. But surprisingly, in a recent study done in three different regions of the United States (U.S.) the serum retinol level was found to be low even in well-nourished children with measles[20, 22, 23]. Hence, the American Academy of Pediatrics suggested vitamin A therapy in accordance with WHO's recommendation[24]. Serum retinol levels of children with measles from various countries are given in Table III.

Table III: Vitamin A Status of Children With Measles in Various Countries

Country	n	Retinol (µg/dl)	No.with Retinol < 20 µg/dl	No.with Retinol < 10 µg/dl	References
Long Beach, USA	20	24.06 ± 12.03	10 (50%)	?	Arrieta CA et al[22].
Wisconsin, USA	114	16.61 ± 5.15	82 (72%)	?	Butler CJ et al[23].
Thailand	25	12 ± 0.9	(?)	8 (32%)	Varavithya W et al[11].
South Africa	31	11.73 ± 1.05	?	?	Coutsoudis A et al[34].
Zaire	283	5-63 (median, 8)	?	164 (58%)	Markowitz LE et al[13].
India	153	11.5 ± 0.44	?	?	Reddy V et al[12].
Ankara, Turkey	21	11.5 ± 6.5	19 (90.5%)	11 (52%)	

In our study, serum retinol levels were measured during the acute phase of measles and were found to be less than 20 µg/dl in 90.5 percent patients, and less than 10 µg/dl in 52 percent. Mean retinol levels of our patients and the degree of low levels are similar to the results of studies done in Africa and Asia (Table III). It is well known that vitamin A deficiency is a major public health problem in many countries of Africa and Asia. In a recent study done in our country, serum retinol levels were measured as low (< 20 µg/dl) in 60.7 percent of children with recurrent lower respiratory tract infections and/or diarrhea[25]. In another study done in the Sivas region including 100 children with malnutrition, 15 percent were found to have some kind of visual defect due to hypovitaminosis A[26]. Considering this information, a general vitamin A deficiency in the child population may be an important component of the very low levels of vitamin A measured in our study. However, as pre-measles levels of vitamin A were not measured in this study, it is not possible to draw conclusions. According to a study done in Zaire on 283 children with measles, a vitamin A level of less than 10 µg/dl significantly increases mortality, especially for children under the age of two[13]. But, as our study group was small and there was only one death, we cannot correctly discuss the impact of vitamin A deficiency on mortality.

The reason for low serum retinol levels in children with measles is unclear. This low level was previously explained by the exacerbation of the deficiency state due to the disease. However, in the study done in the U.S., serum retinol levels were measured as low even in well-nourished children with measles, and this low level was attributed to an acute decrease in the level of proteins (prealbumin and retinol binding protein) which mobilize retinol from the liver[24]. This view is supported by the fact that during convalescence, serum retinol levels return to normal without vitamin A administration[12, 22]. The finding of low retinol levels in other acute infections leads us to consider retinol as having a role of negative acute phase reactant in infections[27]. However, the finding that retinol levels are significantly lower during measles compared to other infections signifies that low levels are specific for measles[22]. Whatever the reason may be, during the acute phase of measles, serum retinol levels decrease independent of the nutritional status of the child, and the low level affects the outcome of the infection[21].

In our study, serum retinol levels of children with measles were significantly lower than those with other infections and healthy children. This result supports the idea that a low level of vitamin A is associated with a mechanism specific to measles, rather than being a general effect of infections[21]. However, it is worth mentioning that the children in the sick control group had significantly lower vitamin A levels than those of healthy children. Similar results have been published in the U.S.[22]. These findings point to the need for further research regarding the levels of vitamin A in infections other than measles and their clinical significance.

The clinical significance of low serum retinol levels and measles outcome with vitamin A therapy has been stressed by previous research[21, 24]. It is well known that children with measles frequently develop xerophthalmia. Studies from Asia and Africa show that measles plays an important role in childhood blindness[9, 10]. In addition to studies which have uncovered the association between measles and xerophthalmia, recent studies have shown that low levels of serum retinol are associated with the severity of measles. Markowitz et al.[13], in their Zaire study, showed that vitamin A deficiency significantly increases the mortality of children with measles, particularly for those under the age of 24 months. Similarly, in two studies from the U.S., low levels of vitamin A were shown to cause increased severity and morbidity of measles[20, 23]. The mechanism by which vitamin A depletion exacerbates measles infection is unknown. In experimental models, vitamin A deficiency impairs cellular immunity[28], delayed type hypersensitivity[29] and antibody production[30, 31]. Animal experiments indicate that vitamin A deficiency is associated with thymus atrophy and antibody production defects[32, 33]. In a study done in Indonesia, the ratio of CD4/CD8 was found to be low, and this low level could be corrected by vitamin A support[32]. Additionally, in recent studies done in the U.S. and South Africa on children with measles, it was pointed out that in children with low vitamin A levels, measles-specific antibodies were also in low levels, and could be restored by giving vitamin A[20, 34].

In our study, the presence or absence of pneumonia was considered to be a measure of the severity of measles. Despite the fact that serum retinol levels of children with pneumonia were not significantly different from those without pneumonia, 75 percent of the children with pneumonia had serum levels of less than 10 µg/dl. Although the number of cases is low, these findings still show an association between the severity of measles and serum retinol levels of less than 10 µg/dl (Table II). In one study done recently in the U.S., the mean level of serum retinol was lower in children with measles who were hospitalized and had pneumonia[23].

The effect of vitamin A therapy on mortality and morbidity in children with measles has been assessed with controlled studies. Barclay et al.[14], in a double-blind study, compared the effect of high-dose vitamin A (200,000 IU two days in a row) with that of a placebo[14]. In this study, measles mortality was reduced by vitamin A therapy, particularly for children under two years old. Vitamin A therapy was shown to reduce measles mortality by Hussey and Klein[15] in a 1990 study, and to reduce measles morbidity by Coutsoudis et al.[34] in a 1992 study. Hence, the American Academy of Pediatrics is now recommending vitamin A therapy for measles[24].

In conclusion, serum vitamin A levels are significantly low in children with measles in our country, and this low level is associated with the severity of disease. When recommendations from both WHO and the American Academy of Pediatrics are

taken into consideration, vitamin A therapy should be given routinely to children with measles in our country.

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CAUSES OF FETAL AND NEONATAL DEATH*

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SUMMARY: Taşdelen E, Aksoy F, Arvas A, Berk Y, Ataoğlu N, Dervişoğlu S, İlter Ö. (Neonatology Unit, Department of Gynecology and Obstetrics, and Department of Pathology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey). Causes of fetal and neonatal death. Turk J Pediatr 1995; 37: 201-207.

Autopsy was performed on 601 out of 654 (91.9%) fetus and newborn cases of death which occurred during a four-year period between 1988-1991 at İstanbul University Cerrahpaşa Faculty of Medicine, Gynecology Department and Neonatal Unit. According to autopsy findings, among the main causes of death in newborns were infection, hyaline membrane disease, congenital anomalies, perinatal hypoxia and immaturity, and in the fetal period, perinatal hypoxia, asphyxia and congenital anomalies. In these cases, when pathologic and clinical findings were examined, it was observed that in 204 out of 301 newborn cases (67.8%) the clinical findings were well correlated with the autopsy findings; in 97 (32.2%) of the remaining cases the main disease and primary causes of death could not be determined through clinical findings; in 69 (23%) cases, in addition to the clinical diagnosis on autopsy, minor defects were determined on autopsy which were not directly related to death. When clinical and autopsy findings were compared, diagnoses with the highest discordance were pulmonary hemorrhage infection and intracranial hemorrhage. *Key words: neonatal death, intrauterine death, neonatal autopsy.*

In recent years the number of autopsies performed has significantly declined; however in many studies conducted by clinicians and other researchers, the importance of autopsy is emphasized because of its contribution to scientific research, understanding differences during various phases of diseases, determining specific case characteristics, and educating doctors and patients[1-10]. Studies on newborn autopsy findings are limited compared to adult cases[11].

However, the results of fetal and neonatal autopsies may provide significant information for subsequent pregnancy decisions and genetic counseling[1].

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We have retrospectively studied autopsy cases in a four-year period in order to determine the autopsy percentage of our unit, see the correlation between clinical and pathological findings, and emphasize the importance of fetal-neonatal autopsy.

Material and Methods

Clinical and pathological records of fetal and neonatal death cases in our unit during the four-year period between January 1988 and December 1991 were studied to determine the number of autopsies and rate of discordance between clinical and pathological findings. The pathological features of diseases in different phases and the personal differences in the same disease in various infants were also investigated.

Results

During the four-year period there were a total of 15,510 births in our unit. The number of deaths in this period was 654 (318 fetal deaths). Out of 654 cases, autopsy was performed on 601 (91.9%). The distributions of the number of births, deaths and autopsies are shown in Table I. Ninety-five percent of these (n = 550) were preterm and 8.5 percent (n = 51) were term babies.

Table I: Yearly Distributions of Birth, Death, Autopsy Cases and Autopsy Rates

Year	Number of Births	Number of Deaths	Number of Autopsies	Autopsy/Death Rate (%)
1988	3565	141	109	77.3
1989	4640	191	187	97.9
1990	3985	166	154	92.8
1991	3320	156	151	96.8

One hundred and fifty-eight of 301 (52.5%) neonatal deaths occurred in the first 24 hours of life. The causes of death occurring during the first 24 hours after birth were hyaline membrane disease in 66 cases (41.8%), hypoxia-asphyxia in 35 cases (22.1%), infection in 31 cases (19.6%), and congenital anomalies in 14 cases (8.8%). The number of deaths recorded after 72 hours was 54 (17.9%) (Table II). When the clinical findings of the 302 neonatal deaths were studied in the order of frequency of occurrence, 67 cases involved hyaline membrane disease (22.3%), 54 cases infection (17.9%), 51 cases congenital anomalies (16.9%), 44 cases hypoxia-asphyxia (14.6%), 29 cases severe immaturity (9.6%), 20 cases intracranial hemorrhage (6.7%), three cases hydrops fetalis (1%), and one case pulmonary hemorrhage (0.4%). Thirty-two cases were lost due to twin pregnancy complications (10.6%) (Table III).

Table II: Distribution of Cases According to Age at Death

Death Age (Hours)	Number of Cases	Percentage (%)
< 24	158	52.5
24-48	68	22.6
49-72	21	7.0
> 72	54	17.9

Table III: Clinical Diagnoses of 301 Neonatal Death Cases

Clinical Diagnosis	Number of Cases	Percentage (%)
Hyaline Membrane Disease	67	22.3
Infection	54	17.9
Congenital Anomalies	51	16.9
Perinatal hypoxia-asphyxia	44	14.6
Twin pregnancy complications	32	10.6
Immaturity	29	9.6
Intracranial hemorrhage	20	6.7
Hydrops fetalis	3	1.0
Pulmonary hemorrhage	1	0.4
	301	100.0

Eighteen out of 54 cases of infection revealed positive culture results. Infecting agents were determined as Echerichia coli (n = 5, 25.7%), Streptococcus epidermidis (n = 3, 16.7%), Klebsiella pneumoniae (n = 3, 16.7%), Pseudomonas aeruginosa (n = 3, 16.7%), Enterobacter aerogenes (n = 2, 11.1%), and Staphylococcus aureus (n = 2, 11.1%). Since most of the autopsies were performed 12 hours after death, bacteriologic examination could not be done due to contamination from the environment. In the limited number of autopsies (3.5%) in which bacteriologic examination was performed, parallel findings with clinical culture results were observed.

The autopsy diagnoses from highest to lowest rate of occurrence were infection, hyaline membrane disease, congenital anomalies, perinatal hypoxia-asphyxia and severe immaturity (Table IV).

Table IV: Autopsy Diagnoses of 301 Neonatal Death Cases (1988-1991)

Autopsy Diagnosis	Number of Cases	Percentage (%)
Infection	74	24.7
Hyaline Membrane Disease	73	24.3
Congenital Anomalies	58	19.3
Hypoxia-Asphyxia	40	13.4
Intracranial Hemorrhage	24	8.0
Immaturity	24	8.0
Pulmonary Hemorrhage	4	1.3
Hydrops Fetalis	3	1.0
	301	100.0

In the 300 fetal death cases on which autopsy was performed, the main diagnoses were 138 cases of anoxia (46%), 61 cases of congenital anomalies (20.3%), 16 cases of intracranial hemorrhage (5.3%), 13 cases of infection (4.4%), and seven cases of pulmonary hemorrhage (2.4%) (Table V).

Table V: Autopsy Diagnoses of 300 Fetal Deaths

Autopsy Diagnosis	Number of Cases	Percentage (%)
Anoxia	138	46.0
Congenital Anomalies	61	20.3
Intracranial Hemorrhage	16	5.3
Infection	13	4.4
Pulmonary Hemorrhage	7	2.4
Hydrops Fetalis	6	2.0
Twin Pregnancy Complications	3	1.0
Immaturity	1	0.3
Coagulation Anomalies	1	0.3
Nondiagnostic due to Autolysis	54	18.0
	300	100.0

When clinical and autopsy diagnoses were compared in 301 newborn cases, in 204 of them the findings correlated well (67.8%), while in 97 cases the disease and the primary cause of death could not be found clinically but were diagnosed through autopsy. The discordance rate between the clinical and pathological diagnoses was 32.2 percent. In 69 cases (23%), in addition to clinical diagnoses the autopsies revealed some additional findings which did not lead to death.

Among the main diagnoses with the highest discordance rates were pulmonary hemorrhage, infection and intracranial hemorrhage (Table VI).

Table VI: Comparison Between Clinical and Autopsy Diagnoses of 301 Neonatal Deaths

Diagnosis	Number of Cases		Discordance Rate (%)
	Clinic	Autopsy	
Pulmonary Hemorrhage	4	1	75.0
Infection	74	54	27.0
Intracranial Hemorrhage	24	20	16.7
Immaturity	24	20	16.7
Congenital Anomalies	58	51	12.1
Hyaline Membrane Disease	73	67	8.2
Hydrops Fetalis	3	3	0.0

Discussion

Autopsy was performed in our unit in 91.9 percent of cases overall, rising from a low of 77.3 percent in 1988 to 96.8 percent in 1991 (Table I).

In the United States, the hospital autopsy rate, which was greater than 50 percent in the 1940s, dropped to 15 percent by 1985[11]. In Germany this percentage is 8-10[12]. Graft et al.[11] reported the neonatal autopsy rate in the first three years as 63 percent based on the records of a tertiary newborn intensive care unit. In Belgium, Wals et al.[13] reported the neonatal autopsy rate ase 51 percent, and in India, Singh et al.[14] reported the rate as 43.9 percent. The main reasons for the high autopsy rate in our unit include: the special emphasis placed on this method, the possibility of obtaining easier permission for autopsy from families through emphasizing the importance of this method in reaching a correct diagnosis and in determining the precautions that need to be taken in subsequent pregnancies, and the provision of financial support towards the cost of autopsy by the Pathology Department of our Faculty. Another important reason for the high autopsy rate is the effective collaboration between our unit and the Pathology Department. In this way, the important obstacle that caused significant reductions in the autopsy rates mentioned in the literature has been successfully avoided[11, 15-23].

More than half of the 301 newborns (52.5%) were lost in the first 24 hours of life (Table II). Mattos et al.[24] determined in a study in Brasil over a five-year period that the percentage of deaths in the first 24 hours was 42 percent.

Examination of the clinical findings of the autopsies performed on 301 newborns revealed that the major causes of death were, in descending order of frequency, hyaline membrane disease, infection, congenital anomalies and perinatal hypoxia-asphyxia (Table III). In India, Singh et al.[14], in their study on 755 newborn autopsy cases, determined that the primary causes of death were infections (27.2%), hyaline membrane disease (20.2%) congenital anomalies (19.6%) perinatal hypoxia-asphyxia (14.5%), immaturity (5.1%) and birth trauma (2.7%). Craft et al.'s[11] findings on 71 newborn autopsies listed diagnoses as congenital anomalies (16 cases), infections (nine cases), iatrogenic complications (five cases) and others (11 cases). In Agapitos et al.'s[25] work, the causes were listed as hyaline membrane disease, infection, congenital anomalies, anoxia and immaturity.

In our study, the first five primary diagnoses determined through autopsy were infection (24.7%), hyaline membrane disease (24.3%), congenital anomalies (19.3%), perinatal hypoxia-asphyxia (13.4%) and immaturity (8%). These results correlated with Singh et al.'s[14] results. The above diagnoses were followed by 24 cases of intracranial hemorrhage (6%), four cases of pulmonary hemorrhage (1.3%) and three cases of hydrops fetalis (1%) (Tables IV, V).

The fact that infection is the primary autopsy diagnosis highlights an important problem in our unit. The infection of the newborn during the antepartum, intrapartum and postpartum periods cannot be avoided in our unit since regular antenatal follow-up of the mothers cannot be done and aseptic conditions in the labor room, operation room and neonatal unit cannot be properly implemented due to a personnel shortage.

In our unit, asphyxia remains an important perinatal problem. In order to minimize the asphyxia risk, prenatal follow-up should be done properly, the neccessary obstetric procedures should be timely and adequately chosen, and appropriate resuscitation along with effective neonatal care should be provided. However, under even optimum conditions, the asphyxia rate can be as high as 10 percent[26].

When clinical and autopsy findings were compared in 204 out of 301 newborn cases according to the primary cause of death, clinical and autopsy diagnoses correlated well (67.8%). In 97 cases, however, the main disease and the primary cause of death could not be determined clinically but could be found through autopsy. Thus, the discordance rate between the clinical and pathologic diagnoses was found to be 32.2 percent. In 69 cases (23%), in addition to the major cause, additional diagnoses which did not lead to death were determined through autopsy. Most of these causes were genetic anomalies. Among the diagnoses in which the discordance rate was highest were pulmonary hemorrhage (75%), infection (27.2%) and intracranial hemorrhage (16.6%).

In the literature, the discordance rate reported between clinical and pathologic diagnoses ranges between five and 40 percent[3]. Among the diagnoses with the highest discordance rates are cardiovascular system diseases, infections and tumors[27,28]. The fact that pulmonary hemorrhage and infections were the causes with the highest discordance rates in our series could be explained by the inefficient and delayed applications of some diagnostic methods such as radiographic examination and microbiological tests, since most of the cases were lost within the first 24 hours. A further explanation would be that an exact diagnosis could not be derived because in newborns, the infection's clinical and laboratory findings were not specific.

Despite all technical means, the high discordance rate between the clinical and pathologic diagnoses again emphasizes the importance and necessity of autopsy. Fetal and neonatal autopsy findings not only provide the correct diagnosis, but they also help in subsequent pregnancies to decide on genetic counseling and other methods that should be applied.

We believe that efficient collaboration is necessary between perinatologist, neonatologist and pathologist to emphasize the importance of newborn and fetal autopsies and to increase the autopsy rates.

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ANALYSIS OF PATIENTS ADMITTED TO THE EMERGENCY UNIT OF A UNIVERSITY CHILDREN'S HOSPITAL IN TURKEY*

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SUMMARY: Karaböcüoğlu M, Kartoğlu Ü, Molzan J, Uğur S, Uzel N, Neyzi O. (Institute of Child Health, İstanbul University, İstanbul, Turkey). Analysis of patients admitted to the emergency unit of a university children's hospital in Turkey. J Turk Pediatr 1995; 37: 209-216.

A retrospective analysis of the computerized data of patients admitted to our Emergency Unit Inpatient Service in 1991 was conducted to obtain data about age, sex, referred sources, admission period, monthly admission rates, diagnoses and eventual outcome. More than 47% of patients were younger than one year of age. The most common causes for hospital admission were infectious, respiratory and neurological diseases. The mean hospitalization period was 3.26 days. More than 60% of patients were treated by the Emergency Unit staff. The net mortality rate was 2.9%, infectious diseases being the most common cause of mortality. We conclude that demographic and diagnostic data regarding admissions to the Emergency Unit can be utilized to develop new strategies for patient care and to reorganize education programs for pediatric residents. *Key words: pediatric emergency unit, hospital admissions, demographic and diagnostic data.*

Although studies based on hospital data do not reflect general population characteristics, they are important for the development of new strategies and retrospective evaluation of hospital utility[1,2]. In the case of a teaching hospital, these data gain importance beyond patient care.

İstanbul University Faculty of Medicine Children's Hospital in Çapa has been running a Pediatric Emergency Unit (PEU) since 1980. This PEU is one of the largest emergency referral centers in Turkey, serving a population of 3.5 million people. Information about PEU patients and the procedures to which they were exposed have been loaded into a computer system for the last four years. In order to encourage proper collection of more reliable and complete data, the documentation has been evaluated periodically.

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The purpose of this study was to evaluate the patient data with regard to demographic and diagnostic variables in order to develop new strategies for efficient utilization of the PEU and to establish a more suitable training curriculum for residents there.

Material and Methods

This study consisted of an analysis of computerized data regarding patients admitted to the PEU of İstanbul University Faculty of Medicine Children's Hospital in Çapa in 1991.

Patient information was coded on a special data card called an "inpatient card" which could then be loaded into a computer file. The patient's name, date of birth, sex, referred sources, diagnosis and outcome were recorded on the inpatient card. Diagnostic information on the card was coded by a resident under the heading 999 in accordance with the ICD-79 version.

Control and analysis of the data were done using Foxpro and SPSS/PC computer programs.

Results

The total number of patients admitted to the PEU in 1991 was 1958. Of these admissions, 60.1 percent were male and 39.5 percent were female, a ratio of 1.5:1 ($p < 0.05$). No data as to gender were available for five patients (Table I). Data about the diseases were evaluated under separate headings.

Table I: Frequency of visits to the PEU by Demographic Variables

Sex	Number of Patients	% of Patients
Male	961	60.1
Female	632	39.5
Unrecorded	5	0.4
Total	1598	100.0
Age		
1-29 days	192	12.0
1-12 months	568	35.5
1-3 years	382	23.9
4-7 years	222	13.9
8-11 years	137	8.6
12-15 years	78	4.9
> 16 years	6	0.4
Unrecorded	13	0.8
Total	1598	100.0

Distribution by Age

Age-related data were not available for 13 patients (Table I). Overall, 12 percent were 1-11 months in age, 47.5 percent were less than one year old and more than 85 percent of patients were younger than seven years of age.

Distribution by Months

Seasonal distribution of patients admitted to the PEU in 1991 is shown in Fig. 1. If the distribution of patients were homogenous, 8.3 percent of patients would be admitted each month; however, there were five months (January, March, May, June, July), when the admittance rate exceeded 8.3 percent ($p > 0.05$).

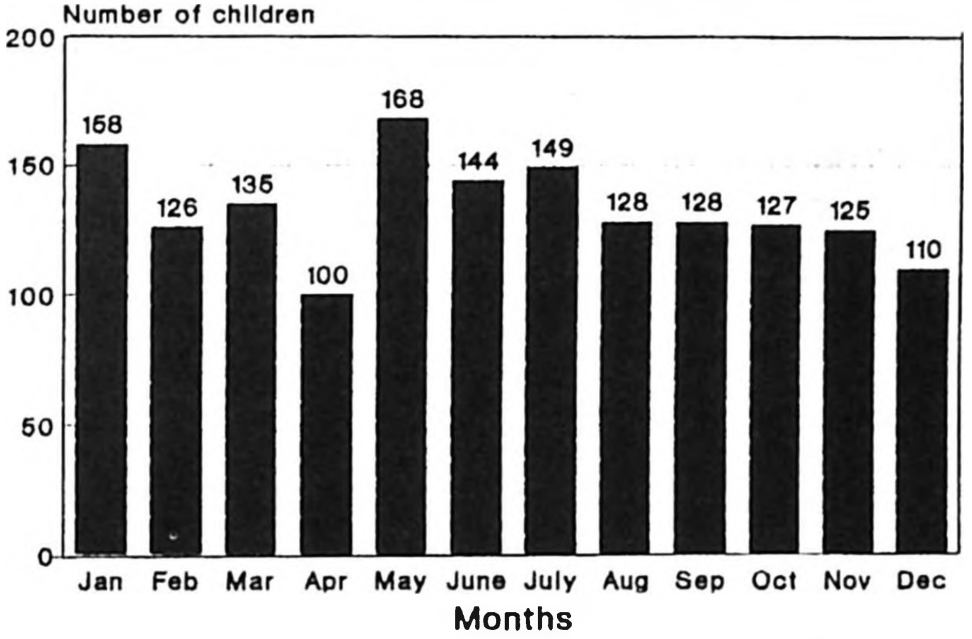

Fig. 1: Rate of visits to the PEU by month in 1991.

Hospitalization Period

Distribution of patients with regard to hospitalization period is shown in Fig. 2. The mean hospitalization period was 3.26 days, and ranged from one to 4 days for 50 percent of patients.

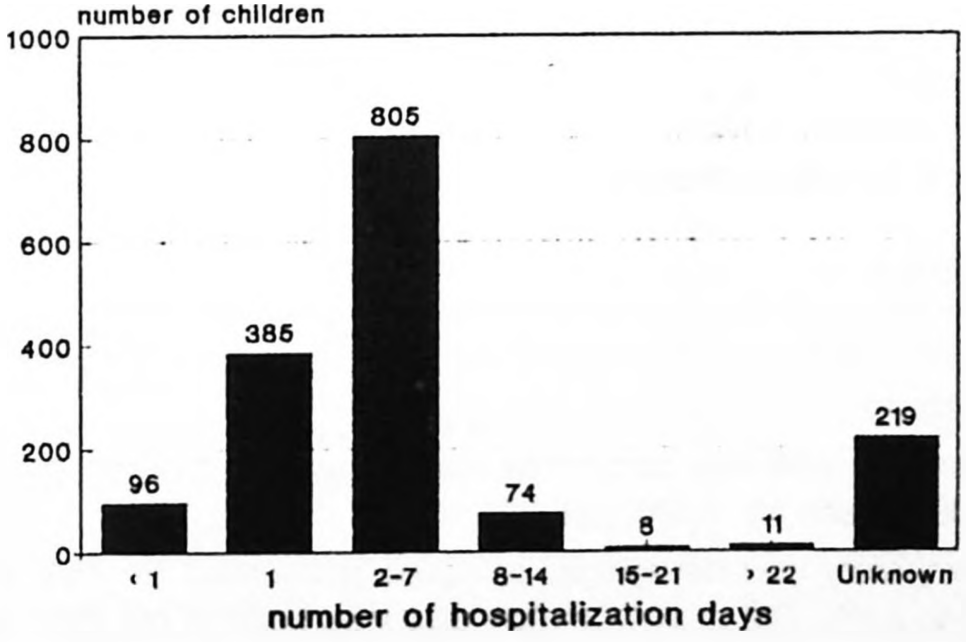

Fig. 2: Distribution of patients by hospitalization period.

Referred Patients (Sources)

The geographical orientation of patients is shown in Table II. Although patients from 36 cities in all geographic areas of Turkey were admitted to the PEU in 1991, most patients were from İstanbul. Since the hospital is located in the area of Marmara, this region contributed the highest number of patients. Of the counties within İstanbul, patients came mostly from Bakırköy, Fatih, Gaziosmanpaşa, Küçükçekmece and Bayrampaşa (31.8%, 8.9%, 8.3%, 8.0%, and 6.4%, respectively), the counties nearest to the hospital.

Table II: Rate of Visits According to Patients' Cities of Origin

City Name	Number of Patients	% of Patients
İstanbul	1392	87.1
Kocaeli	50	3.1
Tekirdağ	27	1.7
Adapazarı	26	1.3
Other Cities	103	6.8
Total	1598	100.0

Distribution by Outcome

The outcome of patients is shown in Table III. There was no significant difference in outcome between males and females ($p > 0.05$). The overall death rate was 7.8 percent (125 patients), with 39 patients (31.2% of deaths) dying within 24 hours and 42 patients (33.6%) dying between the 25^{th} and 48^{th} hours after admission.

Table III: Outcome of Patients Admitted to the PEU

Outcome	Number of Patients	% of Patients
Transport to another hospital	197	12.3
Discharged	628	39.3
Against medical advice	73	4.6
Transport to subspecialties	354	22.2
Died	125	7.8
Unrecorded	221	13.8
Total	1598	100.0

Diagnostic Groups

Since between one and five diagnoses were assigned to each patient, there were 2,259 diagnoses for 1,598 patients.

Infectious respiratory and neurologic diseases accounted for 45.8 percent of diagnoses (Table IV). The most common diseases seen in our PEU are shown in Table V.

Table IV: Distribution by Diagnostic Groups

Diagnostic Groups	Number of Patients	% of Patients
Infectious Diseases	415	18.4
Respiratory Diseases	366	16.2
Neurologic	255	11.3
Intoxications	167	7.4
Unidentified Diseases	161	7.1
Congenital Anomalies	140	6.2
Perinatal Morbidities	127	5.6
Metabolic Diseases	110	4.9
Genitourinary Diseases	103	4.6
Cardiovascular Diseases	102	4.5
Hematologic Diseases	99	4.4
Gastrointestinal Diseases	58	2.6
Oncological Diseases	53	2.3
Connective Tissue Diseases	26	1.2
Endocrine Diseases	23	1.0
Nutritional Diseases	23	1.0
Dermatologic Diseases	12	0.5
Mental Diseases	12	0.5
Immunologic Diseases	6	0.4
Complications of Pregnancy	1	0.0
Total	2259	100.0

Table V: Common Diagnoses at the PEU

Diagnosis	Number of Patients	% of Patients
Pneumonia	227	10.0
Septicemia	188	8.3
Intestinal Infections	154	6.8
Intoxications	126	5.5
Neonatal diseases*	124	5.4
Bacterial meningitis	97	4.3
Acid-base and Electrolyte Disturbance	76	3.3
Congenital cardiac anomalies	73	3.2
Coagulation anomalies	72	3.1

* This group includes prematurity, SGA, birth injury, asphyxia, respiratory difficulties, infections, bleeding, isoimmunization, hyperbilirubinemia and thermoregulation disturbances. The majority consisted of infectious disease (18.5%), hyperbilirubinemia (18.5%) and prematurity (12.9%).

Among causes of death, infectious diseases accounted for the greatest percentage (25.6%) (Table VI). Perinatal and unknown diseases ranked second and third at 16.8 and 14.4 percent, respectively. Regarding main diagnostic groups, sepsis was the most common cause of death (18.4%). Unidentified diseases and prematurity were second and third at 12 and 6.4 percent, respectively.

Table VI: Diagnostic Categories of Mortality at the PEU

Diagnostic Groups	Number of Patients	% of Total Mortality
Infectious Disease	32	25.6
Perinatal Diseases	21	16.8
Unidentified Diseases	18	14.4
Congenital Anomalies	11	8.8
Respiratory Diseases	10	8.0
Cardiovascular Diseases	7	5.6
Oncologic Diseases	7	5.6
Neurologic Diseases	5	5.5
Gastrointestinal Diseases	4	3.2
Metabolic Diseases	3	2.4
Genitourinary Diseases	2	1.6
Hematologic Diseases	2	1.6
Dermatologic Diseases	1	0.8
Connective Tissue Diseases	1	0.8
Nutritional Diseases	1	0.8
Total	125	100.0

Discussion

Although there has been a dramatic increase in the use of emergency department facilities since 1950[3,4], there is very little information in the pediatric literature documenting the age, diagnoses, time spent in PEU and outcomes of these children[5]. These data will be very useful and may also assist in plans to allocate resources appropriately and in organizing educational programs with relevant emphasis[2,6].

The current study showed that there was a clear majority of males (60.1%) over females (39.5%) seen in the PEU. Since the same result was seen in the study by Rothschild et al.[7] and yet no difference has been reported in the frequency of admission of the two sexes among patients seen in studies of PEUs western countries[1,3,8], we believe that this result reflects a difference in the attitudes of parents toward illness in boys and girls in Middle Eastern countries.

More than 47 percent of our patients were younger than one year old. Our data support earlier observations that PEU usage was related to age, with distribution

skewed to the younger ranges (infants and toddlers)[2,6]. Since resuscitation and treatment are most difficult in younger patients, we share the ideas of Kisson et al.[2] that educational programs should place greater emphasis on the needs of the very young. PEUs should also be supplied with equipment necessary for younger patients (e.g. infant mask, infant blood pressure cuffs, smaller catheters, etc.).

In the present study, though monthly admission rates did not differ significantly, the highest rate of visits to the PEU occurred in January, May, June and July. We speculated that increased frequency of respiratory infections in winter and gastroenteritis in summer may be reasons for these slight increases in admission rate.

Since we do not have an intensive care unit, we use our PEU as an inpatient facility for critically ill patients. We also provide inpatient care for patients whose diagnoses have yet to be established, and who must be stabilized until their transfer to the appropriate subspecialty ward. Thus, length of stay in our PEU is longer than that reported in the literature[2,9].

Though patients were referred from all regions of Turkey, there was an inverse relationship between the distance from the patient's home to the hospital and rate of visits to the PEU similar to that reported previously in the literature[3,7,8]. The rate of visits to the PEU from Marmara, the area where the hospital is located, was highest. The same was also valid for inner-city visits with the nearest five counties sharing the first five ranks for visits to the PEU.

In this study the evaluation of outcomes showed that more than half of the patients admitted to the PEU were treated by PEU staff. Transfer to other hospitals was mainly due to social factors (economic, parental wish, high turn-over rate at the PEU, etc.) and lack of bed availability. Twenty-two percent of patients were admitted to subspecialty divisions; this group of patients included those who were stabilized or who were diagnosed in the PEU, as suggested by Medina et al[10].

Our results show, that patients with all sorts of diseases were admitted to our PEU, with the greatest percentages having infectious diseases (18%), respiratory system diseases (16%) and neurological problems (11.3%). These figures are similar to Kissoon's results[2]. Infectious diseases are also the most common cause for PEU utilization in the literature[2,6,7].

One interesting finding in our study, in contrast to other studies[2,3,7], was that upper airway pathology, such as viral croup, was not commonly seen in our patient population. We believe that the reason for this difference is that only the inpatient records were reviewed in this study, while other studies have included outpatient charts. Also, since trauma patients are also treated by the Department of Surgery, our results did not include these patients either.

As would be expected in a developing country, the most common cause for mortality was infectious disease in our PEU. Perinatal diseases play an important role in infant mortality in both developing and developed countries[11].

Analysis of these data permitted us to reach several conclusions:

1. Pediatric Emergency Medicine, a new and developing subspecialty of pediatrics in our country, is an important component of the medical services provided by the hospital. 2. Our data collection system has some handicaps, and we have made appropriate changes in that system in order to encourage proper collection of more reliable and complete data. 3. Since the majority of our patient population was less than one year old and nearly half had infectious, respiratory or neurologic diseases, we may reorganize our pediatric resident training curriculum to ensure education in the above subspecialities before emergency rotation.

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SERUM AND URINE TOTAL, FREE AND ACYLCARNITINE LEVELS RELATED TO AGE: ASSESSMENT OF RENAL HANDLING OF CARNITINE*

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SUMMARY: Güneral F. (Central Laboratory, Department of Clinical Chemistry, University of Lausanne, Lausanne, Switzerland, and the Nutrition-Metabolism Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Serum and urine total, free and acylcarnitine levels related to age: assessment of renal handling of carnitine. 1995; 37: 217-222.

Control ranges of free, total and esterified carnitine in serum and spot urine samples of a healthy population of children and adults were established by radio-enzymatic assay. Children were divided into three groups according to age: six months to two years (n = 15), three to five years (n = 19), and six to ten years (n = 16). The adult group ranged in age from 20 to 35 years (n = 18). Serum free and total carnitine displayed a significant increase up to ten years of age, while acylcarnitines and the acylcarnitine/free carnitine ratio decreased until five years of age. Urinary free carnitine increased significantly up to five years of age. The overall increase in urinary total carnitine was insignificant. Urinary acylcarnitines and the acylcarnitine/free carnitine ratio decreased significantly in the three- to five-years age- group, increased significantly in the six- to ten-years age-group and remained constant afterwards. Renal handling of carnitine was assessed by evaluation of the renal reabsorption rate for free carnitine (RRFC) and the acylcarnitine/free carnitine clearance ratio (RAFCC), both of which were found to increase significantly up to five years of age. These data suggest that a balance in carnitine metabolism and excretion seems to be reached only after five years of age. The establishment of reference ranges in different population groups is critical for the investigation of children suspected to suffer from inherited metabolic disorders. *Key words: free carnitine, acylcarnitines, children, carnitine reabsorption, reference ranges, creatinine.*

L-Carnitine has a basal role in the facilitation and modulation of the transport of long-chain fatty acyl moieties across the inner mitochondrial membrane via a carnitine acetyltransferase system. In the last decade, clinical investigations have demonstrated that the prevalence of carnitine deficiency is relatively high, occurring as both primary[2] and secondary to other disorders[3,4] and organic acidurias[5]. Decreased carnitine concentrations have also been reported in children with Reye-like syndrome[6] and in those treated with valproic acid[7]. However, information about free, total and acylcarnitine serum and urine levels in healthy children and adults is scarce and unsatisfactory[8-12]. Some studies

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have been concerned only with free carnitine[12-14] or total carnitine[15, 16] others have not specified whether the values given refer to free or total carnitine and used less sensitive methods[12]. The relationships between esterified and free carnitine in serum and urine (AC/FC ratio) are sensitive indicators of metabolic derangement. In addition, the acylcarnitine/free carnitine clearance ratio (RAFCC) and the renal reabsorption rate for free carnitine (RFCC) are essential for the evaluation of the renal handling of carnitine. Data concerning the normal values of these parameters is lacking[9]. In this study we aimed to establish the normal ranges of free, total and acylcarnitines in both the serum and urine of healthy Turkish children and adults, and to assess carnitine metabolism and excretion during growth.

Material and Methods

The study group consisted of: a) 50 children aged six months to ten years who were referred for minor disturbances such as frequent infections, abdominal pain, minor injuries or enuresis; and b) 18 adult volunteers, 20 to 35 years of age. All subjects were metabolically healthy, with no cardiac, renal, gastrointestinal, hematologic or myopathic disease. Informed consent was obtained from the children's parents and from the adults. Children were divided into three groups according to age: 1. six months to two years (n = 15), three to five years (n = 19), and six to ten years (n = 16). All blood samples were drawn in the morning after an overnight fast. Samples of single voids of urine were obtained simultaneously. Serum was separated by centrifugation and, along with urine samples, stored at -20 °C until analysis. Serum and urine free, total and acylcarnitine determinations were made using a modified radio-enzymatic assay[8]. RRFC and RAFCC were calculated by the following equations:

RRFC = (1-UFCxSCr/SFCxUCr) x 100%; RAFCC = UACxSFC/SACxUFC (SFC is serum free carnitine, SAC is serum acylcarnitine, SCr is serum creatinine, UFC is urine free carnitine, UAC is urine acylcarnitine and UCr is urine creatinine).

Serum and urine creatinine concentrations were determined using an automated Jaffe method.

Statistical Analysis: For means, standard deviations and ranges, descriptive statistics were applied. One-way ANOVA and hypothesis tests for means were used to test the statistical significance between means. Linear regression was used to evaluate the relationship between age and carnitine concentrations. All statistical analyses were computed using the Microsta software program.

Results

Table I summarizes the serum data. Serum free and total carnitine were found to increase significantly until ten years of age. Serum AC and the AC/FC ratio reached adult values by the age of five years.

Table I: Serum Free, Total, Acylcarnitine and AC/FC ratios in Healthy Children and Adults

Age Groups	1	2	3	4
Age	6 months-2 years	3-5 years	6-10 years	20-35 years
SFC (μM)	35.02 ± 9.2[a] (21.3-46.1)	43.63 ± 11.9[b] (25.1-58.6)	52.8 ± 11.1[c] (31.8-66.2)	52.2 ± 11.9 (33.5-67.1)
STC (μM)	44.5 ± 11.3[d] (27.1-58.4)	52.4 ± 13.1[e] (31.9-68.6)	60.2 ± 11.0[f] (38.2-73.1)	59.6 ± 11.9 (40.9-74.5)
SAC (μM)	9.4 ± 2.1[g] (5.8-12.4)	8.3 ± 1.4[h] (6.6-10.6)	7.8 ± 1.0 (6.4-9.5)	7.6 ± 0.6 (7.4-9.3)
SAC/SFC	0.27 ± 0.02[i] (0.25-0.3)	0.21 ± 0.04[j] (0.17-0.27)	0.20 ± 0.02 (0.15-0.21)	0.19 ± 0.03 (0.14-0.22)
n	15	19	16	18

The values are expressed as mean ± SD. The ranges are shown in brackets.
Significantly lower ($p < 0.01$) a vs. b, b vs. c; Significantly lower ($p < 0.05$) d vs. e, e vs. f; Significantly higher ($p < 0.05$) g vs. h; Significantly higher ($p < 0.001$) i vs. j.

Urinary excretion of carnitines displayed a different pattern (Table II).

Table II: Urinary Distribution of Carnitines and AC/FC Ratios in Healthy Children and Adults

Age Groups	1	2	3	4
Age	6 months-2 years	3-5 years	6-10 years	20-35 years
UFC (μmol/g Cr)	35.8 ± 22.6[a] (2.4-60.2)	68.5 ± 42.4[b] (15.0-140.7)	70.6 ± 33.5 (12.6-156.1)	75.0 ± 38.6 (16.2-160.0)
UTC (μmol/g Cr)	146.6 ± 91.3 (11.0-284.6)	158.0 ± 68.6 (53.6-295.8)	175.5 ± 70.1 (48.2-331.2)	204.8 ± 66.0 (107.5-346.0)
UAC (μmol/g Cr)	110.8 ± 69.3[c] (5.8-12.4)	104.5 ± 39.4[d] (6.6-10.6)	126.8 ± 40.4[e] (6.4-9.5)	144.8 ± 35.1 (7.4-9.3)
UAC/UFC	3.2 ± 0.4[f] (2.7-3.8)	1.9 ± 0.77[g] (1.1-3.3)	2.6 ± 0.8[h] (1.1-3.5)	2.7 ± 0.7 (1.1-3.3)
n	15	19	16	18

The values are expressed as mean ± SD. The ranges are shown in brackets.
Significantly lower ($p < 0.01$) a vs. b; Significantly higher ($p < 0.05$) c vs. d; Significantly lower ($p < 0.05$) d vs. e; Significantly higher ($p < 0.001$) f vs. g; Significantly lower ($p < 0.01$) g vs. h.

Urinary free carnitine increased significantly up to five years, and a slight increase was noted thereafter. Urinary total carnitine increased insignificantly in all groups. A statistically significant decrease in urinary acylcarnitines and urinary AC/FC ratios was observed in the three- to five-years group, followed by a significant

increase in the six-to ten-years group. RRFC and RAFCC were both observed to increase significantly until five years of age. A slight increase was found in the older group up to adulthood (Table III).

Table III: Renal Reabsorption Rate for Free Carnitine (RRFC), AC/FC Clearance Ratio (RAFCC), Serum and Urine Creatinine Ranges in Healthy Children and Adults

Age Groups	1	2	3	4
Age	6 months-2 years	3-5 years	6-10 years	20-35 years
RRFC (%)	98.5 ± 0.94[a] (96.5-99.7)	99.1 ± 0.79[b] (96.3-99.7)	99.4 ± 0.31 (98.8-99.8)	99.5 ± 0.33 (98.6-99.9)
RAFCC (µmol/g Cr)	11.7 ± 1.4[c] (10.1-15.2)	15.6 ± 2.7[d] (10.7-20.6)	17.9 ± 6.0 (10.9-34.5)	18.1 ± 7.3 (10.5-41.9)
SCr (mg dl)	0.18 ± 0.07[e] (0.18-0.39)	0.32 ± 0.06[f] (0.2-0.39)	0.41 ± 0.11[g] (0.25-0.6)	0.5 ± 0.1[h] (0.3-0.65)
UCr (mg/dl)	18.1 ± 6.7[i] (8.0-29.1)	69.6 ± 49.2[j] (18.0-165.0)	76.2 ± 28.7[k] (28.0-120.0)	112.8 ± 41.0[l] (55.0-163.0)
n	15	19	16	18

The values are expressed as mean ± SD. The ranges are shown in brackets.
Significantly lower ($p < 0.05$) a vs. b, g vs. h; Significantly lower ($p < 0.001$) c vs. d, e vs. f, f vs. g, i vs. j, k vs. l.

Serum creatinine (SCr) showed a statistically significant increase in all age groups.Urine creatinine (UCr) displayed the same pattern, except in the three to five-years and six-to ten-years groups, where only a slight increase was present (Table III).

Discussion

The serum free, total and acylcarnitine concentrations corresponded well with the findings of other studies[10-12]. (Table I). Discrepancies with some reports in regard to ranges[8, 12, 17-19] may be due to methodological differences and variation in the selection of age groups. A positive correlation was observed between total ($r = 0.51$) and free carnitine ($r = 0.63$) serum concentrations and the age of children. We observed free and total carnitine values to reach adult values in the six to ten-years group. This finding corroborates that of Sousa et al.[8], who reported plasma free carnitine to increase significantly in the five- to 12-year age group; this increase may be explained by the activation of hormones, maturity in hepatic synthesis or reduced oral intake of carnitine in younger age groups.

The AC/FC ratio and acylcarnitines were negatively correlated with age ($r = -0.46$). Adult values were found to be reached by five years of age. The decrease in

plasma acylcarnitines and AC/FC ratios with age has also been mentioned by other authors[8, 10]. The reason may be higher fatty acid oxidation and ketogenesis at earlier ages.

The urinary total, free and acylcarnitine concentrations compared well with those of other studies[8, 9, 19] (Table II). An age-related increase in urinary total or free carnitine excretion has been reported in previous studies [8, 12, 13, 17, 20]. We found urinary free carnitine to increase significantly up to five years of age ($r = 0.59$). Battistella et al.[12] reported free carnitine excretion to be low in the first three years of life. In the literature, a sex-related difference in the urinary free carnitine excretion pattern has been reported after adolescence, and a hormonal factor suggested[21]. The increased urinary output of free carnitine in older ages may be due to endocrine factors or to a quantitatively different muscular activity[22].

Urinary total carnitine increased slightly throughout childhood up to adult ages. Acylcarnitine excretion and the urinary. AC/FC ratio followed a different pattern (Table II), decreasing significantly in the three- to five-years group and increasing to adult values in the six- to ten-years group.

In this study, the observed RRFC in children aged three to five years (99.1 ± 0.79) (Table III) was comparable to that of Matsuda et al.[9] The relatively decreased RRFC in the younger age group, with lower serum free carnitine levels, suggests a decreased renal threshold for free carnitine. The reabsorption rate for free carnitine could be influenced by the AC/FC ratio and the amount of acylcarnitines in serum[9]. No report has mentioned the variation in RFCC andd RAFCC throughout childhood. In this study, a statistically significant increase in these two parameters was observed until five years, followed by a slight increase in the older age groups.

According to the results of this report, carnitine homeostasis seems to be restored in the age range of five to ten years. More detailed studies are needed to test this finding.

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FOLLOW-UP RESULTS OF SYNTHETIC VASCULAR GRAFTS IN CHILDREN UNDERGOING HEMODIALYSIS*

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SUMMARY: Nayır A, Sönmez Y, Şirin A, Emre S, Aydoğan Ü (Nephrology Unit, Department of Pediatrics, İstanbul University Faculty of Medicine, İstanbul, Turkey). Follow-up results of synthetic vascular grafts in children undergoing hemodialysis. Turk J Pediatr 1995; 37: 223-228.

Polytetrafluoroethylene (PTFE) grafts were inserted in the thigh of 14 children (7 boys and 7 girls, age 12 ± 1.8 years) who were undergoing chronic hemodialysis for end-stage renal disease. Removal of grafts was necessary in three patients within three months of implantation. In a fourth case it was indicated in the fifteenth month. In two cases thrombectomy was necessary. Echocardiography was performed in 10 patients before and three and 12 months after surgery. Cardiac performance followed by echocardiography did not change after one year. After two years the survival of grafts was 71%. It appears that synthetic grafts offer advantages for pediatric hemodialysis petients with arteriovenous fistula failure. On the other hand, this technique entails serious risks. *Key words: hemodialysis, children, polytetrafluoroethylene grafts, echocardiography.*

The increasing number of surviving hemodialysis patients and the demand for vascular access requires different shunting procedures in patients with arteriovenous fistula failure[1]. Synthetic or biological vascular grafts interposed subcutaneously between artery and vein provide a very important second choice for these patients[2,3]. However, while there are advantages, there are also disadvantages[4]. The most common complications of synthetic grafts are thrombosis, infection, false aneurysms and a "vascular steal" phenomenon. Patients with a vascular graft may also develop symptoms of excessive cardiac output. The aim of this paper is to present kinds of material, sites of implantation and complications of grafts used for some of our pediatric patients and to determine the long-term effects of polytetrafluoroethylene (PTFE) grafts on cardiac performance using echocardiography.

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Material and Methods

During the period from May 1989 to June 1990, 86 surgeries to create vascular accesses were performed on 48 children undergoing chronic hemodialysis (mean: 1.8 arteriovenous fistulas/patient). Twenty-six of the patients were female and 22 were male, with an age range of six to 16 years. Fourteen patients, seven boys and seven girls aged eight to 15 years (mean ± SD: 12 ± 1.8 years), with failed arteriovenous fistulas received access grafts. They had been on dialysis for an average of 12 months (range 1-32 months) (Table I). The location and type of access were PTFE grafts in the shape of a loop between the superficial femoral artery and the saphenofemoral junction. Vascular anastomoses were made using CV 7 Gore-tex sutures in running fashion. All PTFE grafts of 6 mm diameter were thin-walled and full-ringed. All patients received a prophylactic antibiotic (ceftazidime) preoperatively and postoperatively for five days. Anticoagulants were not used.

Table I: Clinical Data of Patients Who Received PTFE Grafts

Case No.	Age (years)	Sex	Underlying Renal Disease	Duration of Hemodialysis (months)	Weight (kg)	Serum Albumin (g/dl)	Removal of the Graft
1	8	F	CGN	8	28	3.2	no
2	11	F	LMM	2	2.5	3.6	no
3	13	F	PCKD	12	36	4.6	no
4	12	F	RH	12	34	4	no
5	14	F	VUR	18	52	3.9	no
6	13	M	Amyloidosis	22	28	2.3	no
7	11	F	Urolithiasis	12	32	3.6	no
8	10	M	OU	1	32	3.4	no
9	14	M	CGN +NS	32	30	2.2	3rd month (hemorrhage)
10	12	M	Alport's syndrome	20	28	3.4	2nd month (pericarditis)
11	15	M	OU	6	34	4.1	15th month (hemorrhage)
12	14	M	CGN + NS	1	30	2	1st month (hemorrhage)
13	13	F	LMM	6	46	3.4	no
14	12	M	CGN	10	36	3.6	no
mean ± SD	12 ± 1.8	7 F		12 ± 9	33.6 ± 7.3	3.37 ± 0.74	
range	(8-15)	7 M		(1-32)	(25-52)	(2-4.6)	

CGN : Chronic glomerulonephritis.
PCKD: Polycystic kidney disease.
VUR : Vesicoureteral reflux.
OU : Obstructive uropathy.
LMM : Lumbar myelocele.
RH : Renal hypoplasia.
NS : Nephrotic syndrome.

Four operations were performed under ketamine anesthesia, while topical anesthesia was used for the remainder. The PTFE grafts were used for hemodialysis two weeks after implantation for the first time. Immediately prior to, three months and one year after surgery, blood samples were obtained before a hemodialysis session for hematocrit, blood urea, serum creatinine and albumin measurements.

On these days an M-mode echocardiographic tracing of the left atrium and left ventricle was obtained on ten children two hours after the hemodialysis session on a Hitachi EUB-40 ultrasonography apparatus on long-axis view. Left ventricular wall thickness, chamber size, left atrial and aortic diameters were measured by the standard technique from the m-mode echocardiogram[5]. Ventricular volume measurements were calculated using the Teichholz method[5].

Standard laboratory methods were used for blood urea, plasma creatinine, albumin and hematocrit measurements. All data were presented as mean and standard deviation. Wilcoxon signed rank test for paired data was used for statistical analysis.

Results

Removal of grafts was necessary in three patients within three months of implantation. In one patient a serious hemorrhage at the arterial anastomosis site occurred in the first month. A subclavian catheter was inserted and remained for a month; the patient was then switched to Continuous Ambulatory Peritoneal Dialysis (CAPD). In another patient, secondary infection after pericarditis was observed in the second month. He continued hemodialysis with the aid of a subclavian catheter, and a fistula was created. In a third patient, infection of the hematoma occurred in the third month at the puncture site. A Tenchoff catheter was implanted and the patient was switched to CAPD. In the first and third cases (cases 9 and 12), the primary disease was nephrotic syndrome. In the second, infection resulted in graft removal. In a fourth case, removal was required at 15 months due to hemorrhage at the anastomosis site. The patient continued hemodialysis for three months with a Permcath subclavian catheter, and a kidney transplant from her mother was then performed. In the remaining ten patients neither false aneurysm nor infectious complications were encountered. Two PTFE grafts thrombosed and required reoperation at 15 and 18 months. In two cases, moderate swelling of the leg resolved after two weeks of conservative therapy. One child developed ipsilateral limb hypertrophy with no gait abnormality.

Blood urea, serum creatinine, serum albumin and hematocrit values did not change significantly during the study (Table II). Heart rates increased slightly, but the increase was not statistically significant. Systolic and diastolic blood pressure values remained at the same levels. M-mode and two-dimensional echocardiographic measurements of left ventricular size did not change significantly between: 1. the initial and third months; 2. the initial and twelfth months; and 3. the third and twelfth months ($p > 0.05$, Table III). None of the patients showed evidence of high-output cardiac failure. Ten of the 14 grafts were still functioning after two years.

Table II: Patient Characteristics During Follow-up

	Before Surgery	3 Months Later	1 Year Later
Weight (kg)	33.6 ± 7.3		34.07 ± 7.09
Hematocrit (%)	25.07 ± 3.7	24.2 ± 3.2	25 ± 2.9
Blood urea (mg/dl)	215.3 ± 28	220 ± 25	214 ± 22.7
Serum creatinine (mg/dl)	5.7 ± 0.56	5.8 ± 0.8	5.68 ± 0.6
Serum albumin (g/dl)	3.37 ± 0.74	3.26 ± 0.81	3.41 ± 0.7
Systolic blood pressure (mm Hg)	115 ± 24	117 ± 25	107 ± 24
Diastolic blood pressure (mm Hg)	69 ± 21	75 ± 18	70 ± 22

Table III: M-mode and Two-dimensional Echocardiographic Measures Before and After PTFE Graft Implantation

	Before	3rd Month	12th Month
EDD (mm)	43.9 ± 7.5	43.8 ± 4.9	44.2 ± 8.2
ESD (mm)	29 ± 6.28	31 ± 4.28	32 ± 8.5
PWDT (mm)	10.2 ± 2.97	9.8 ± 2.6	9.6 ± 2.75
PWST (mm)	15.5 ± 3.5	13.7 ± 3.4	13.7 ± 3.2
IVSDT (mm)	9.4 ± 1.83	8.9 ± 1.3	9.5 ± 1.35
IVSST (mm)	12.6 ± 2.8	11.2 ± 2.34	12.1 ± 2.28
HR (beats/min)	87.1 ± 22.07	99.7 ± 12	104.4 ± 15.7
LVDV (ml)	107.4 ± 44.7	102 ± 25.7	108 ± 48
LVSV (ml)	35.4 ± 17.3	33.3 ± 10.4	34.4 ± 9
SV (ml)	66.8 ± 27.4	66.1 ± 18.3	69.1 ± 20.6
EF (%)	66.6 ± 8.48	63.9 ± 6.33	65.4 ± 4.9
CO (l/min)	6.46 ± 1.64	6.43 ± 1.78	6.6 ± 1.65
SF (%)	33.16 ± 7.03	29.17 ± 5.27	29.65 ± 5.39
AOD/LAD ratio	0.83 ± 0.07	0.8 ± 0.1	0.83 ± 0.09

EDD : Left ventricular dimension in diastole.
ESD : Left ventricular dimension in systole.
PWDT : Left ventricular posterior wall thickness in diastole.
PWST : Left ventricular posterior wall thickness in systole.
IVSDT : Interventricular septum diastolic thickness.
IVSST : Interventricular septum systolic thickness.
HR : Heart rate.
LVDV : Left ventricular diastolic volume.
LVSV : Left ventricular systolic volume.
SV : Stroke volume.
EF : Ejection fraction.
CO : Cardiac output.
SF : Shortening fraction.
AOD/LAD ratio : Aortic diameter/left atrial diameter ratio.

Discussion

The difficulty in maintaining vascular access in patients on long-term hemodialysis is a serious problem[6]. This problem is exacerbated in children because of the

diameter of the vasculature[1]. Improvements in synthetic materials have made the use of PTFE an attractive alternative for hemodialysis access when the autogenous vessels are of inadequate size[2].

Guzzetta et al.[7] observed in their series that femoral artery to femoral vein PTFE grafts led to either limb hypertrophy or excessive flow through the fistula, and they did not recommend this technique for children. Some references consider forearm grafts more suitable than thigh grafts because of cardiac overload[1]. The PTFE grafts cause a circuit of low vascular resistance resulting in a decrease in circulation transmit time and an increase in venous return, stroke volume and heart rate. Echocardiography, which provides a direct means for noninvasive visualization of cardiac structure and function, is a good tool for follow-up. The results of this study using echocardiography show that thigh grafts have no clinically important side effects. Cardiac functions stroke volume, cardiac output, ejection fraction and fractional shortening), cardiac dimensions (left atrium/aorta ratio, left ventricular systolic and end-diastolic dimensions) and muscular mass are not impaired after thigh graft implantation. These findings show that a circulatory shunt through a 6 mm thigh graft does not affect cardiac functions, with the exception of a slight increase in heart rate which is statistically insignificant. On the other hand, in younger patients weighing less than the study group (less than 25 kg), the ratio of shunting to total blood volume may be significant.

In children, thigh grafts are preferable to forearm grafts because the larger vessels are more suitable for surgery and blood flow is greater in this region. Long-term follow-up of patients with these grafts is imperative since these children may develop cardiac problems due to a chronic output state.

It appears that synthetic grafts offer great advantages for pediatric hemodialysis patients, especially if the waiting time for transplantation is prolonged[8]. On the other hand, this technique entails serious risks[9]. Acute thrombosis of PTFE grafts can occur at any time after insertion. Sudden occlusion of large-caliber, PTFE thigh grafts in children, through which a large percentage of total cardiac output may be diverted, may result in hypertensive encephalopathy[10]. Early graft thrombosis (within the first postoperative month) may be due to transient hypotension, an imperfectly chosen or performed operative procedure or unusually elevated resistance in the outflow bed[11]. Late graft thrombosis (more than one month postoperatively) may be due to intimal hyperplasia or progression of atherosclerosis, although some grafts can thrombose with no apparent explanation[12, 13]. In our series thrombectomy was indicated in two cases.

An infection of a prosthetic vascular graft placed electively under sterile conditions is a rare event. However, if graft infection does occur, there are limb- and life-threatening consequences[14, 15]. During systemic infections, secondary graft colonization may also arise, as seen in our follow-up.

For patients with hypoproteinemia, PTFE grafts involve even greater risks due to delayed wound healing, increased incidence of thrombosis and infection. In two of our patients with nephrotic syndrome and hypoproteinemia, graft failure occurred. In hemodialysis patients with hypoproteinemia, insertion of synthetic grafts should be avoided when possible.

Even when a technically perfect anastomosis has been performed, significant bleeding can still result[16]. Hemorrhage may be life-threatening and can occur in both the early and late phases. After hemodialysis, perigraft hematoma at the site of puncture can cause serious complications. These complications can be remedied simply by applying pressure at the puncture site.

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PROGNOSTIC FACTORS IN SALMONELLA TYPHIMURIUM SEPTICEMIA

A 10 - Year Retrospective Study*

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SUMMARY: Seçmeer G, Kanra G, Cemeroğlu AP, Özen H, Ceyhan M, Ecevit Z. (Infectious Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Prognostic factors in Salmonella typhimurium septicemia: a 10-year retrospective study. Turk J Pediatr 1995; 37: 229-233.

In this study, 74 S.typhimurium septicemia cases were evaluated retrospectively from their records, and the age and sex distribution, presence of underlying disease, signs and symptoms, complete blood count, liver function tests and case fatality rate were documented and prognostic factors determined. It has been shown that S.typhimurium is the most common strain causing Salmonella septicemia, which is more fatal in the newborn period and in the presence of an associated disease, while hemoglobin and leukocyte counts do not play an important role in the prognosis. In Salmonella septicemia, congenital heart disease was the second-most common associated disease, which may be attributed to probable underlying immunodeficiency. *Key words: Salmonella typhimurium, septicemia.*

Non-typhoidal Salmonella infections (NTS) are still a major health problem in children, particularly those with certain underlying diseases[1-8]. Two-thirds of NTS infections present with gastroenteritis and fever, but septicemia occurs only in approximately 5-18 percent of cases[2, 3]. S.typhimurium is the most common strain isolated as the cause of Salmonella septicemia in many countries[1, 2].

S.typhimurium septicemia is frequently encountered in patients with underlying disease, especially when cellular immunity is compromised, such as in Hodgkin's disease, renal transplantation, acquired immune deficiency syndrome (AIDS), leukemia and malnutrition[4-8]. Salmonella typhimurium septicemia is still quite fatal in these patients and in newborns[4-9].

In this study, we investigated the clinical and laboratory findings of S.typhimurium septicemia retrospectively to determine the course and prognostic factors for the past ten years. Antibiotic therapy used in these patients was not taken into consideration.

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Material and Methods

Between August 1982 and September 1992, Salmonella species was isolated from the blood cultures of 105 cases at Hacettepe Children's Hospital. The clinical and laboratory features of 74 S.typhimurium blood isolates were documented retrospectively from the records, and the prognostic factors were determined.

Cultures and serotyping were performed by the Microbiology Laboratory of Hacettepe Children's Hospital. Information was obtained from each patient's medical records. The age and sex distribution, presence of underlying disease, signs and symptoms, complete blood count (CBC), liver function tests and case fatality rate were evaluated retrospectively for S.typhimurium septicemia cases. The blood isolates were accepted as septicemic when the patients had additional signs and symptoms such as fever, convulsion, stupor, malaise, vomiting, irritability, hepatosplenomegaly or elevated liver enzymes. According to these criteria, all of the patients with S.typhimurium infection were found to be septicemic.

Statistical analyses were performed using student's t-test, chi-square test and exact chi-square test.

Results

Salmonella species was isolated from the blood cultures of 105 inpatient cases. Seventy-four (70.5%) were S.typhimurium, 27 (25.7%) were S.typhi, three (2.9%) were S.paratyphi and one (0.9%) was S.choleraesuis. In addition to blood cultures, stool cultures of 18 (out of 46, 39.1%), bone marrow cultures of two (out of two) and cerebrospinal fluid (CSF) cultures of one (out of four) patient also revealed S.typhimurium.

Of 74 patients with S.typhimurium septicemia, nine (12.15%) were newborns, 35 (47.3%) were between one and 12 months of age, nine (12.15%) were between 13 and 24 months, and 21 (28.4%) were more than two years old (Table I). Thirty-three (44.6%) were female and 41 (55.4%) were male.

Table I: Age Distribution of Salmonella Typhimurium Septicemia Cases

Age (months)	No. of Patients	(%)
0-1	9	12.15
1-6	23	31.1
7-12	12	16.2
13-24	9	12.15
> 24	21	28.4
Total	74	100.0

In the S.typhimurium septicemia cases, 39 (52.7%) had an associated disease, such as malnutrition (16.2%), congenital heart disease (9.5%), malignancy (8.1%), mental retardation (2.7%) or other miscellaneous diseases (Table II).

Table II: Distribution of Patients with an Associated Disease

Disease	No. of Patients	(%)
Malnutrition*	12	16.2
Congenital heart disease	7	9.5
Malignancy	6	8.1
Mental retardation	2	2.7
Miscellaneous**	12	16.2
Total	39	52.7

* Four third-degree, two second-degree and six first-degree.

** Trisomy 13, prematurity, congenital immunodeficiency, aplastic anemia, Leiner's disease, nephrotic syndrome, polyarteritis nodosa, hemophilia, thalassemia major, congenital adrenal insufficiency, miliary tuberculosis and measles; one in each group.

The most common signs and symptoms were fever (70.2%), diarrhea (56.8%), vomiting (29.7%), cough (18.9%) convulsions (12.2%), stupor (9.5%) and hepatosplenomegaly (28.4%). In 38 patients, liver enzymes were measured; 20 (52.6%) had elevated SGOT (> 50 IU), 13 (34.2%) had elevated SGPT (50 IU) and 13 had elevated levels of both liver enzymes. When the patients with hematologic diseases (six patients) were excluded, 23 (33.8%) had leukocytosis, four (5.9%) had leukopenia and 29 (42%) had anemia according to the normal age standards[10].

Complications included meningitis (three patients), hemolytic anemia (one patient) and subdural effusion (one patient).

Of 74 patients with S.typhimurium septicemia, 39 (52.7%) died. Among 39 deaths, nine (23.1%) were newborns, 25 (64.1%) were between one and 12 months of age, three (7.7%) were between 13 and 24 months and two (5.1%) were more than two years old.

There was a striking difference between the fatality rates of each age group (Table III). In the newborn period, none of the blood isolates survived, but the fatality rate in the group older than two years of age was 9.5%. The fatality rate was also found to be significantly higher in patients with an associated disease than in those without (64.2% versus 23.1%, $p < 0.01$). When hematologic parameters were evaluated, neither hemoglobin (41.4% versus 65.0%, $p > 0.05$) nor leukocyte counts had a statistically significant effect on prognosis. Patients with leukocytosis, leukopenia and normal leukocyte counts had similar fatality rates (58.5%, 50.0% and 56.5% respectively, $p > 0.05$, Table IV).

Table III: Age Versus Fatality Rates of S.typhimurium Septicemia

Age (months)	No. of Patients		Fatality Rate (%)
	Total	Deaths	
0-1	9	9	100.0
1-6	23	15	65.2
7-12	12	10	83.3
13-24	9	3	33.3
> 24	21	2	9.5
Total	74	39	52.7

Table IV: White Blood Cell (WBC) and Hemoglobin (Hb) Counts Versus Fatality Rates in S.typhimurium Septicemia

Hematologic Parameters*	Total	Deaths
Normal WBC	41 (60.3%)	25 (58.5%)
Leukocytosis	23 (33.8%)	19 (56.5%)
Leukopenia	4 (5.9%)	2 (50.0%)
Anemia	29 (42%)	12 (41.4%)
Normal Hb	40 (58%)	26 (65.0%)

* Patients with hematologic disease (six patients for WBC and five for Hb counts) were excluded.

Discussion

Recently, it has been reported that S.typhimurium is the most common blood isolate among the other strains of salmonellae[2, 8, 9, 11], as confirmed (70.5%) in this study. Thus, it is important to determine the clinical and laboratory properties and the prognostic factors of S.typhimurium septicemia for better management.

In this study, 50.5 percent of S.typhimurium septicemia cases had an associated disease, most commonly malnutrition, followed by congenital heart disease. We could not find any report in the literature on the association between congenital heart disease Salmonella septicemia. However, it has been shown that the total T cell percentage, T helper cells, Immunoglobulins A and G, complement C3 and C4 levels were low and there was a high frequency of infections in the clinical records of patients with congenital heart disease[12, 13]. Although there were no laboratory data regarding the immunologic status of our patients with congenital heart disease, the high frequency of Salmonella septicemia may be attributed to underlying immunodeficiency.

It has also been shown that patients with an associated disease had a higher fatality rate than those without (64.2% versus 23.1%, $p < 0.01$).

In S.typhimurium septicemia, age is another important determinant for the prognosis[2, 3, 9]. In this study, the fatality rate was 100% in the newborn period, decreasing to 9.5% in the above-two age group.

On the other hand, hemoglobin and leukocyte counts were not significant factors for the fatality rate in S.typhimurium septicemia ($p > 0.05$). It is well known that leukopenia is a poor prognostic factor in patients with septicemia[14], which was contrary to our findings.

In conclusion, S.typhimurium was the most common strain causing Salmonella septicemia, which is more fatal in the newborn period and in the presence of an associated disease, while hemoglobin and/or leukocyte counts do not play an important role in the prognosis. Furthermore, S.typhimurium septicemia is commonly encountered in patients with congenital heart disease.

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VARIOUS CLINICAL ASPECTS OF DIDMOAD (WOLFRAM) SYNDROME*

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SUMMARY: Ökten A, Gedik Y, Demirci A, Mocan H, Erduran E, Aslan Y (Departments of Pediatrics and Radiology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Various clinical aspects of DIDMOAD (Wolfram) syndrome. Turk J Pediatr 1995; 37: 235-240.

The association of juvenile diabetes mellitus (DM), diabetes insipidus (DI), optic atrophy (OA) and sensorineural deafness (D) is known as DIDMOAD or Wolfram syndrome. Aside from these four cardinal features, a wide variety of abnormalities of the nervous system, urinary tract and endocrine glands have been described in this syndrome.

In this report, the clinical features of six patients with DIDMOAD syndrome are presented. All six patients had DM. Five of the six patients had DI, five OA and five displayed abnormal audiogram findings. In addition, two had goiter, two delayed puberty, one seizure and one mental retardation with depression attacks. Urinary tract dilatation was recorded in five patients.

Four patients developed typical complications of DM. One of them had overt nephropathy and arthropathy despite the short duration of DM. In addition, this patient had diabetic retinopathy, which is considered to be rare in this syndrome. *Key words: diabetes mellitus, diabetes insipidus, optic atrophy, deafness.*

The association of juvenile diabetes mellitus (DM), diabetes insipidus (DI), optic atrophy (OA) and sensorineural deafness (D), known as DIDMOAD syndrome, was first described by Wolfram in 1938[1,2]. Aside from these four cardinal features, the clinical picture may be accompanied by a wide variety of other abnormalities affecting the nervous system, urinary tract and endocrine glands[2].

An autosomal recessive mode of inheritance has been well documented in DIDMOAD syndrome[2,3]. However, recently it has been shown that some cases may have mitochondrial-mediated inheritance[4].

In this report, various features of the disease are discussed in six cases with DIDMOAD syndrome.

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Material and Methods

To date, DIDMOAD syndrome has been diagnosed in six cases at Karadeniz Technical University Faculty of Medicine. Venous blood samples were drawn from these six patients to evaluate serum glucose, urea, creatinine, electrolytes and HbA_{1c} levels. In addition, urinary output was measured and creatinine clearance was claculated at three-month intervals.

The thyroid functions, antithyroid antibodies, daily albuminuria and β_2 microglobinuria were measured at six-month intervals.

The following tests were performed in all patients annually: chest radiogram, ultrasonography of the kidney and bladder, intravenous pyelography (IVP), audiography, electromyography (EMG), electrocardiography, echocardiography, electroencephalography (EEG) and cranial magnetic resonance imaging (MRI).

Results

Age, sex, age at onset of DM, DI, various clinical features of patients, and parents' consanguinity are summarized in Table I.

Table I: Clinical Presentation

Case	1	2	3	4	5	6
Sex	F	F	M	F	F	F
Age when last seen (years)	15	13	19	18	15	9
Age at onset of:						
Diabetes mellitus	14	4	6	7	7	9
Diabetes insipidus	14	8	—	10	12	9
Optic atrophy	—	+	—	+	+	+
Abnormal audiogram	+	+	+	+	+	—
Dilatation of urinary tract	—	+	—	+	+	+
Additional endocrine disorders	Goiter	Delayed puberty	—	—	Goiter Delayed puberty	—
Neurologic, pyschiatric status	UR	UR	Seizure	Depression Mental retardation	UR	UR
Parents' consanguinity	—	+	+	+	—	+

UR: Unremarkable.

All six patients had DM and required treatment with insulin. DI was diagnosed in five o six patients and treated with desmopressin. In the patients with DI, the normal hyperintensity of the posterior hypophysis, which shows antidiuretic hormone supply, was absent on MRI (Fig. 1a). Although OA was determined in four patients and abnormal audiogram findings in five, only one case had

decreased visual acuity and hearing loss. As shown in figures 1a and 1b, OA was demonstrated on MRI. Dilatation of the urinary tract was determined in four of six patients, as shown in Figures 2a and 2b.

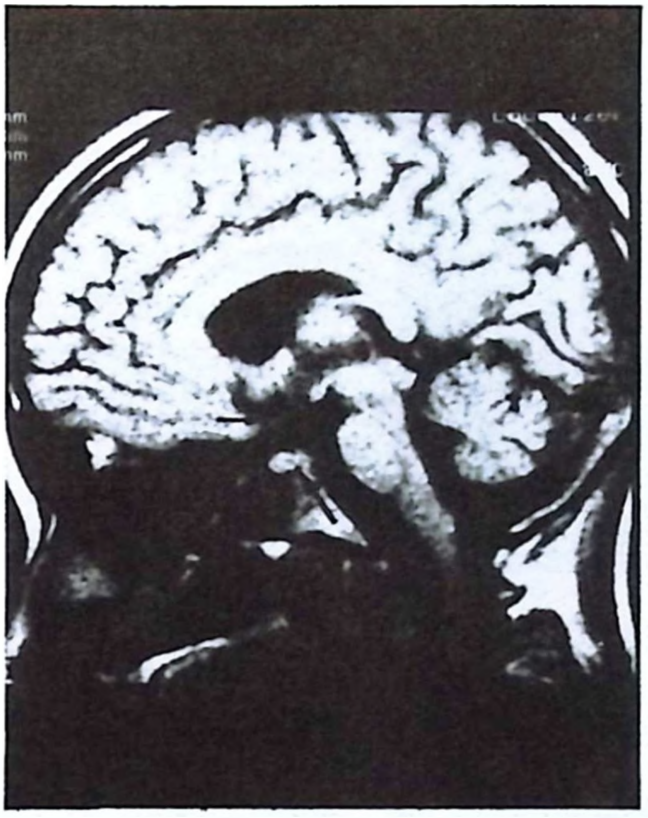

Fig. 1a: Sagittal T_1-weighted (TR/TE 400/20) image shows absence of hyperintense signal in the posterior hypophysial gland (large arrow) and atrophic prechiasmatic optic nerve (small arrow).

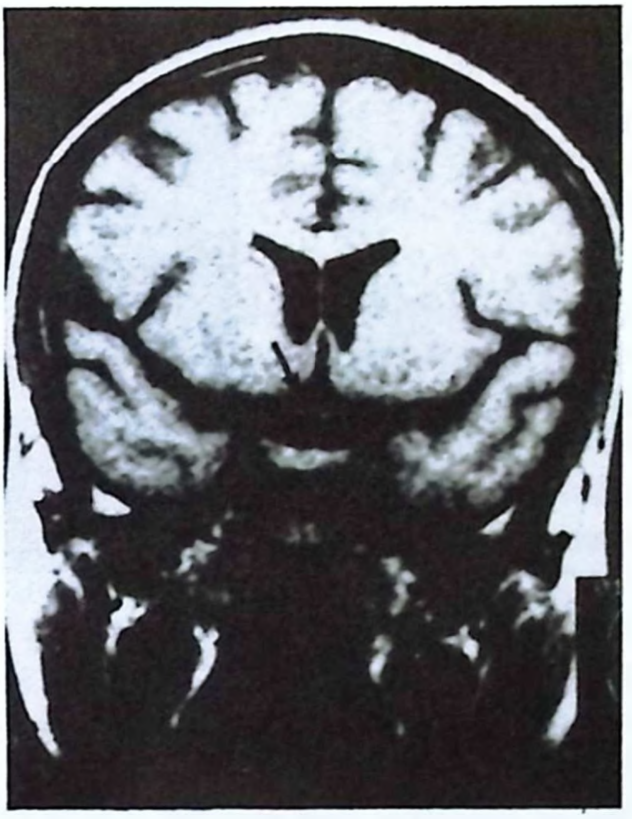

Fig. 1b: Coronal T_1-weighted (TR/TE 400/20) image shows atrophy in the optic chiasm (arrow).

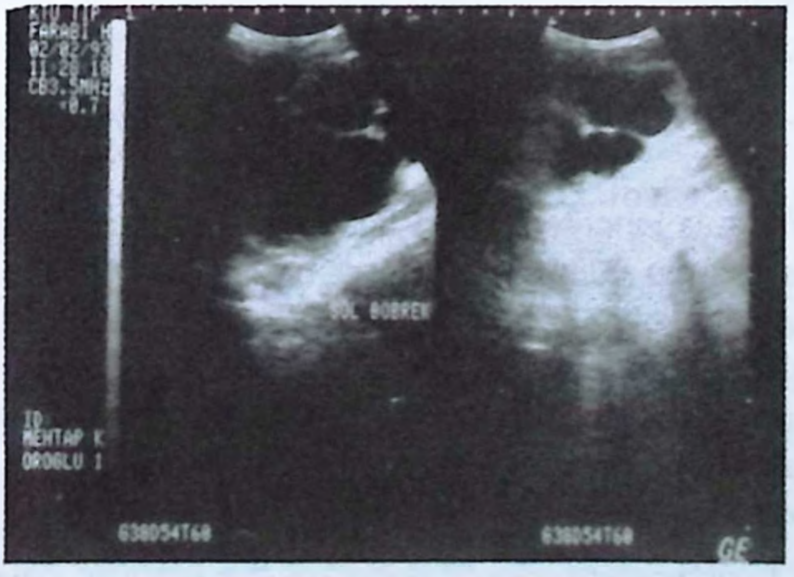

Fig. 2a: Ultrasonography shows hydronephrosis.

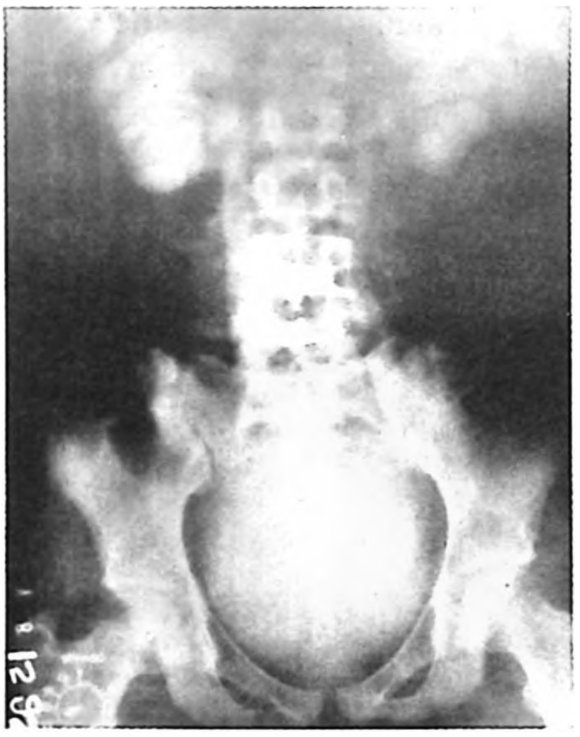

Fig. 2b: IVP shows bilateral, dilated urinary tract.

Long-term complications of DM in our patients are listed in Table II.

Table II: Diabetes Mellitus Complications in Six Patients with DIDMOAD Syndrome

Case	1	2	3	4	5	6
Retinopathy	+	–	–	–	–	–
Neuropathic changes on ENMG	+	+	–	+	+	–
Microalbuminuria	+	+	—	+	—	—
Overt nephropathy	+	—	—	—	—	—
Arthropathy	+	—	—	+	—	—
Cardiomyopathy	—	—	—	—	—	—

Discussion

DIDMOAD syndrome is inherited as an autosomal recessive pattern, and many but not all cases are the offspring of consanguineous parents[3]. In our series, four patients were the offspring of consanguineous parents, and two cases siblings. Although the frequency of DIDMOAD syndrome has been reported as one in 150, we diagnosed six patients out of 148 juvenile diabetics in our clinic. The high prevalence of this syndrome can be expected in our country, with its high rate of consanguineous marriages[5, 6].

Hydronephrosis, hydroureters and dilatation of the bladder have been reported as associated findings in this syndrome. The dilatation of the urinary tract is

considered to be a consequence of high diuresis associated with DI. Indeed, an improvement of the urinary tract is often noted with decreased urinary output by desmopressin treatment. However, it has been suggested that since dilatation may occur in the absence of DI, degeneration of the nerve supply to the ureters and bladder may be the primary cause[7, 8]. In our series, four patients had urinary tract dilatation, and all had DI. Although all patients responded to treatment with desmopressin and urinary output decreased from 4-6 L to 1.2-2 L daily, urinary tract dilatation improved in only one patient, the one case with no neuropathy (Case 6). This observation emphasizes the role of a degenerative process affecting the central and peripheral nervous system.

In addition to neurogenic bladder, a wide variety of neurologic features including ataxia, nystagmus, mental retardation and seizures have been reported in DIDMOAD syndrome[9, 10]. Atrophic changes with neuronal loss, gliosis and demyelination in the cerebellum and brainstem, and myelin pallor in the spinal cord tract have been described in autopsies[10, 11]. MRI studies have showed specific abnormalities that correlated with the cardinal neurologic features[10, 12]. According to its progressive clinical course and pathologic and radiologic findings, DIDMOAD syndrome may be considered a diffuse neurodegenerative disease[9-11]. One of our patients had seizures with pathologic changes on EEG, and another was mentally retarded and had episodes of severe depression. A prevalence of severe psychiatric illness is remarkable in DIDMOAD syndrome. The behavioral abnormalities could be related to widespread neuropathological changes, or the Wolfram syndrome gene itself may predispose to psychiatric episodes[13].

Endocrine abnormalities include delayed sexual maturation, growth retardation and hypothyroidism[2, 14]. We diagnosed an euthyroid goiter in two patients, but it is difficult to claim as a symptom associated ith DIDMOAD syndrome because the northern Black-Sea region of Turkey, where the patient is living is a well-known area of endemic goiter. Delayed puberty, recognized in two patients, might be a feature of the syndrome or may be explained by poor metabolic control and long duration of DM (8-9 years).

Four of our patients developed typical diabetic complications of longstanding DM, as in the common Type I variant. These findings correlate with previous reports[15], except in Case 1, who displayed a different clinical course of disease. She had overt nephropathy and arthropathy despite the short duration of DM (one year) and good metabolic control. Diabetic retinopathy, which is considered rare in this syndrome even in DM of long duration, was also found on fundoscopic examination[16].

An unexplained association of symptoms with an early onset and rapidly progressive course of this syndrome is consistent with an ATP-supply defect, which is so often seen in mitochondrial-mediated disorders[4]. In addition, different mitochondrial DNA mutations have been identified recently[17, 18]. These findings suggest that this syndrome also has a mitochondrial origin, at least in some

cases. Since mitochondrial dysfunction may explain the rapidly progressive course of disease, further genetic investigation should be done to evaluate these patients.

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The Turkish Journal of Pediatrics 1995; 37: 241-246

CONGENITAL GENERALIZED LIPODYSTROPHY: BERARDINELLI SYNDROME*

Report of Two Siblings

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SUMMARY: Gürakan F, Koçak N, Yüce A. (Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Congenital generalized lipodystrophy: Berardinelli syndrome. Report of two siblings. Turk J Pediatr 1995; 37: 241-246.

Two successively born infants with Berardinelli syndrome, an unusual lipodystrophic disease, are reported. In addition to hepatomegaly, accelerated growth, muscle hypertrophy, lack of adipose tissue, hirsutism and hypertriglyceridemia, which are the characteristics of the syndrome, these brothers demonstrated bilateral, symmetrical, renal medullary hyperechogenicity, which has not before been reported in association with generalized lipodystrophy. Although more than 25 cases have been recorded, the metabolic defect responsible for this inborn error of metabolism has not yet been determined. *Key words: Berardinelli syndrome, lipodystrophy.*

Congenital generalized lipodystrophy (CGL), also known as Berardinelli syndrome, is a rare genetic disorder transmitted as an autosomal recessive trait and characterized by extreme paucity of fat in adipose tissue from birth. Berardinelli first reported this unusual syndrome in 1954 in two children with acromegaloid gigantism, hepatosplenomegaly, fatty infiltration of the liver, hyperlipidemia, hyperproteinemia and disturbed carbohydrate metabolism[1]. Coarse and hyperpigmented skin, hirsutism with curly scalp hair, large superficial veins, phallic enlargement, hypertrophy of muscle with excess glycogen, acanthosis nigricans, cardiomegaly, corneal opacities and variable mental deficiency are the other features of the disease. While accelerated growth and hypertriglyceridemia are most prominent in early childhood, diabetes mellitus, insulin-resistant non-ketotic hyperglycemia, hyperinsulinism and cirrhosis may develop in later childhood or adulthood[2]. Here we report two brothers who are believed to have CGL with specific clinical findings.

Case Reports

Case 1

A seven-month-old boy was admitted to the hospital with a prominent abdomen and failure to gain weight. The child was the first product of a third-degree

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consanguineous marriage. The baby was born after an uncomplicated pregnancy, weighing 2700 g. On admission, physical examination revealed a weight of 5600 g (5^{th} percentile), height of 68 cm (50^{th}-75^{th} percentile) and head circumference of 42 cm (10^{th} percentile). The patient displayed marked abdominal protrusion with a palpable liver having soft, regular borders approximately 7 cm below the right costal margin and 8 cm below the xiphoid. The spleen was palpable 1 cm below the left costal margin. He had a peculiar, cachectic face with the appearance of an old man. Psychomotor development was normal. Special mention should be made of the advanced muscular development of the limbs and lack of subcutaneous fat. The muscles were bulky, firm and well-shaped with thick, large superficial veins. The skin was also thick and dry with little fat or turgor. The child had large hands, feet and joints. Although his back and limbs were covered with fine hair, the pubis and axillae were free of hypertrichosis. He had well-developed genitalia.

Routine laboratory tests were normal, including blood cell counts, electrolytes, glucose, creatinine, urea nitrogen, aspartate amino transferase, alanine amino transferase, alkaline phosphatase, uric acid, albumin, cholesterol, pH and blood gases. Prothrombin and partial thromboplastin times were also normal. Serum total protein, calcium and phosphorus levels were high (11.6 g/dl, 11.7 mg/dl and 6.2 mg/dl, respectively). The triglyceride level was much higher than normal (1715 mg/dl). Lipid electrophoresis revealed an increase in the pre-beta region that corresponded to type IV hyperlipidemia. His parents' biochemical tests were normal. Urinalysis, daily urine oxalate excretion, ratio of calcium to creatinine in spot urine, serum parathormone, and complement 3 and 4 levels were within normal limits. Plasma and urinary aminoacid chromatography revealed relatively high glycine, serine, glutamine and basic amino acids. Abdominal ultrasonography revealed hepatosplenomegaly with diffuse steatosis of the liver, bilateral renomegaly with increased parenchymal echogenicity and medullary enlargement together with hyperechogenic, symmetrical lesions. Histopathologic examination of the liver obtained by needle aspiration biopsy indicated diffuse, large, vacuolated steatosis. Mild radiographic cardiomegaly was evident, but the electrocardiogram and echo-cardiogram were normal as well as the cardiac sounds. His bone age was five months older than his chronological age. Neither hyperinsulinism nor hyperglycemia was noted during follow-up. At 16 months of age, his weight was 10.6 kg and his height was 83 cm (25^{th}-50^{th}, and 75^{th} percentiles, respectively). The parents complained of frequent respiratory tract infections. Serum total protein and calcium levels were normalized and the triglyceride level lowered (656 mg/dl) without any medication.

Case 2

A three-month-old infant, the brother of the first patient, displayed the same clinical findings of the disease. His weight was 5 kg and height 61 cm (10^{th}-25^{th} and

50th percentiles, respectively). Subcutaneous fat was absent on his face and in the gluteal region, his liver was palpable 4 cm below the costal margin, and his muscles were hypertrophic. Hypertriglyceridemia (620 mg/dl), advanced bone age (6-9 months), ultrasonographic findings of hepatomegaly and renal medullary hyperechogenicity revealed the syndrome. Blood cell counts, glucose, creatinine, urea nitrogen, aspartate and alanine aminotransferases, alkaline phospatase, uric acid, total protein, albumin, cholesterol, calcium and phosphorus levels of serum, as well as urinalysis and the ratio of calcium to creatinine in spot urine were in the normal ranges.

Discussion

The patients' findings suggested Berardinelli syndrome (Figs. 1-4). This very rare syndrome was first reported from Brasil[1]. Later several cases were reported from the United States, Norway, Great Britain, Germany and France[3,4]. Autosomal recessive inheritance is suggested for this syndrome.

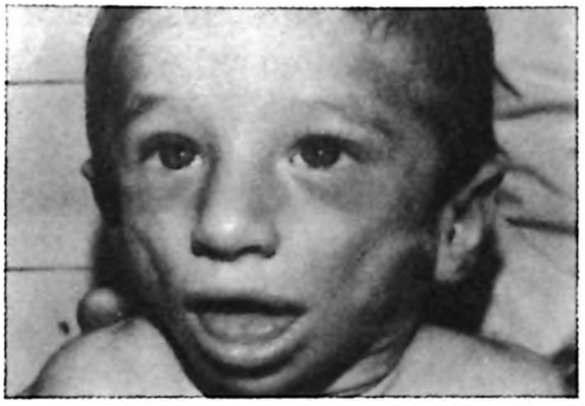

Fig. 1: Cachectic face of Case 1 (nine months old).

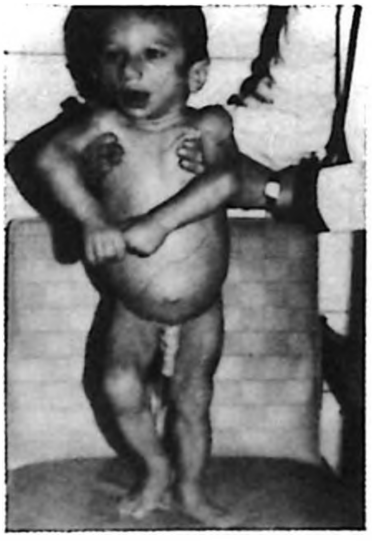

Fig. 2: Muscle hypertrophy, hepatomegaly and hirsutism of Case 1 (nine months old).

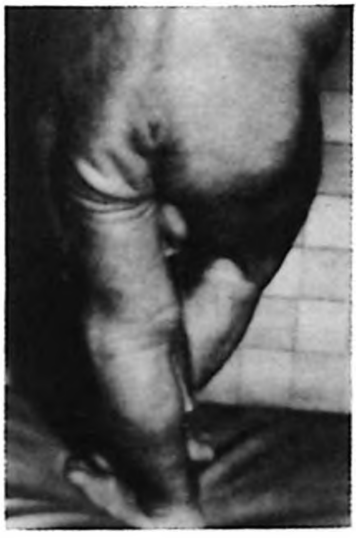

Fig. 3: Lack of adipose tissue in gluteal region of Case 1 (nine months old).

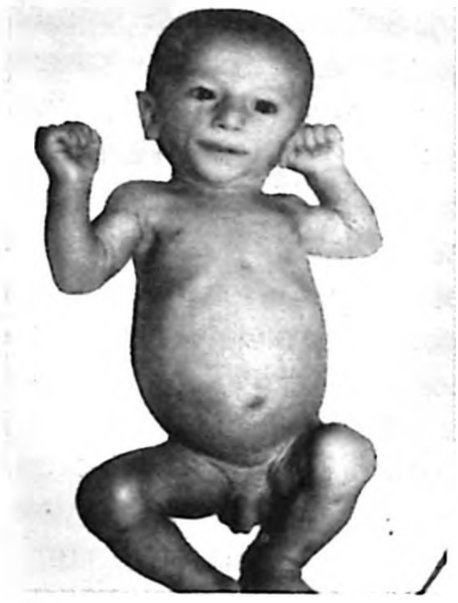

Fig. 4: Note the cachectic face and muscle hypertrophy of Case 2, three months old.

In total generalized lipodystrophy, there is said to be a complete loss of adipose tissue, either evident at birth or appearing later in life, together with a number of associated features, commonly including hepatomegaly, hyperglycemia and hyperlipidemia. The liver is affected in all patients. Histology reveals combinations of periportal foci of round cell infiltration, nuclear syncytial formation, fatty infiltration, glycogen deposition and fibrosis. Fibrosis seems progressive, and some patients have died of hepatic failure or bleeding esophageal varices[3]. One of our patients underwent liver biopsy, which revealed steatosis but no fibrosis.

Hyperglycemia is commonly considered a major and constant component of CGL. All adults have been affected, but this has not been evident in several of the younger patients[4]. In fact, our patients' glucose levels were normal. Generalized lipoatrophy may also occur as an acquired condition, often combined with diabetes (lipoatrophic diabetes)[5].

Partial lipodystrophy is more frequent, particularly affects females, and is characterized by loss of facial fat alone or with involvement of the neck, arms, chest and abdomen; however, fat deposition over the legs is normal or even increased. In addition to the strikingly cadaverous appearance, these patients usually have renal and liver involvement with complement abnormalities[6]. In contrast, patients with Berardinelli syndrome have displayed normal complement levels[7], as did our older patient.

Hyperlipidemia, which is most notable during the first years of life, has been present in most reported patients, and the increase confined almost solely to the triglyceride moiety. In accordance with this, our patients revealed high triglyceride levels. Although the triglyceride levels of some patients' parents have

been found to be higher than normal, we could not demonstrate this. A substantial portion of such patients exhibit disorders of the kidneys (nephrotic syndrome or nephromegaly). Our patients had nephromegaly and medullary hyperechogenity, findings which have not been reported before. Central nervous system anomalies, including ventricular dilatation and mental retardation, have been reported[8]; however, the neurological findings of our cases were normal. Cardiomegaly, another component of the syndrome, has been found to be more pronounced with increasing age. Among adult patients, mild hypertension and nonobstructive hypertrophic cardiomyopathy have also been reported[9].

Gang et al.[10] recently showed with whole-body magnetic resonance imaging (MRI) in three patients with CGL that fat was present in areas where it might be serving mainly a mechanical function, such as in the orbits, palms, soles, periauricular and epidural regions; and to a lesser extent in the tongue, breasts, vulva and buccal area, but not in other subcutaneous areas, in the intraabdominal and intrathoracic regions or the bone marrow. These researchers believe that the genetic defect in CGL results in poor growth and development of metabolically active adipose tissue.

Although accelerated growth and maturation plus muscular hypertrophy and enlargement of the phallus are suggestive of an androgen effect, neither and rogens nor gonadotropins are elevated[11], and hirsutism does not include pubic and axillary hair, as in our elder patient.

The pathogenesis is quite obscure, and no ready hypothesis suggests itself to explain satisfactorily so many diverse features. A primary disorder of the fat-storing cells might lead to hyperlipidemia, hyperglycemia and a fatty liver as a consequence of loss of the major storage organ for calories. However, accelerated growth, bone maturation, pigmentation, hirsutism, genital enlargement and increase of muscle mass are not easily explicable. One postulate is that absence of an important target organ, adipose tissue, might result in oversecretion of hormones. There is another postulate of a hypothalamic disorder causing release of a fat-mobilizing agent. This regulation of normal adipose tissue function might also result in lipoatrophy. Another explanation is the increased activity of the adrenergic nervous system resulting in lipoatrophy because of the lipolytic effects of the catecholamines. Guanfacine, a supressor of adrenergic activity, however, did not yield any increase in the adipose tissue of a partial lipodystrophy patient[12].

A factor contributing to the variability of the features of the syndrome is the age at which the patient is observed. As hyperglycemia and cardiac changes are the features of older ages, our patients will be carefully observed for those symptoms throughout their lives.

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The Turkish Journal of Pediatrics 1995; 37: 247-252

AMPHOTERICIN B IN THE TREATMENT OF CANDIDA MENINGITIS IN THREE NEONATES*

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SUMMARY: Aydın M, Küçüködük Ş, Yalın T, Çetinkaya F, Gürses N. (Departments of Pediatrics and Radiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey). Amphotericin B in the treatment of candida meningitis in three neonates. Turk J Pediatr 1995; 37: 247-252.

Candidiasis is an opportunistic infection and may result in significant morbidity and mortality in neonates. Cerebral candidiasis is rare and usually associated with systemic candidiasis. Information concerning the toxicity and efficacy of antifungal therapy for neonates is limited. In this report, we present three neonates with candidiasis. All of the patients were premature with low birth weights, and received antibiotic therapy for one to four weeks before the onset of candidiasis. Candida albicans was isolated from cerebrospinal fluid cultures. Amphotericin B was given administered at an initial dose of 0.25 mg/kg/day intravenously (IV) and increased to a dosage of 2 mg/kg/day, and therapy was continued for three to four weeks. A transient and mild elevation in hepatic enzyme concentration was observed in two patients, and transient thrombocytopenia occurred in all of them. *Key words: candida meningitis, amphotericin B, neonate.*

Candida infections appear to be an increasing problem among neonates, and may result in serious neonatal morbidity including meningitis, cerebritis, osteomyelitis, endocarditis and abscesses[1]. The risk factors include low birth weight, aggressive chemotherapy, parenteral hyperalimentation, corticosteroids, venous catheters, endotracheal tubes and ventriculo-peritoneal or ventriculo-atrial shunts[2].

Although amphotericin B is the drug of choice in the treatment of candidiasis, little is known about its toxicity and efficacy in neonates[3]. In this paper, we report three neonates with candida meningitis treated with amphotericin B and review the relevant literature.

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Case Reports

Case 1

A premature (34-week gestation) male infant was delivered by caesarean section due to vaginal bleeding of his mother. He was admitted to the hospital with the diagnosis of respiratory distress syndrome. On day three, his general condition was deteriorating, and the clinical and laboratory findings were compatible with sepsis. Ceftriaxone and amikacin were given for sepsis. On day six, a lumbar puncture was performed and cerebrospinal fluid (CSF) examination revealed meningitis. After the isolation of Candida albicans from the CSF, treatment with amphotericin B was started (initially 0.25 mg/kg/day and increasing to 2 mg/kg/day). Transfontanelle ultrasonography revealed bilateral dilated ventricles and multiple echogenic areas. Cranial computed tomography (CT) was suggestive of multiple cerebral abscesses (Figs. 1, 2). Nonspecific antibiotic administration was stopped by the tenth day of treatment. A mild and transient thrombocytopenia was determined during antifungal treatment. CSF findings improved on the twentieth day of treatment. Administration of amphotericin B was continued for four weeks and stopped after clinical improvement was sufficient. The patient was discharged within eight weeks. After six months, physical examination revealed motor and mental retardation. Cranial CT displayed hydrocephalus and multiple calcified lesions in both hemispheres (Fig. 3).

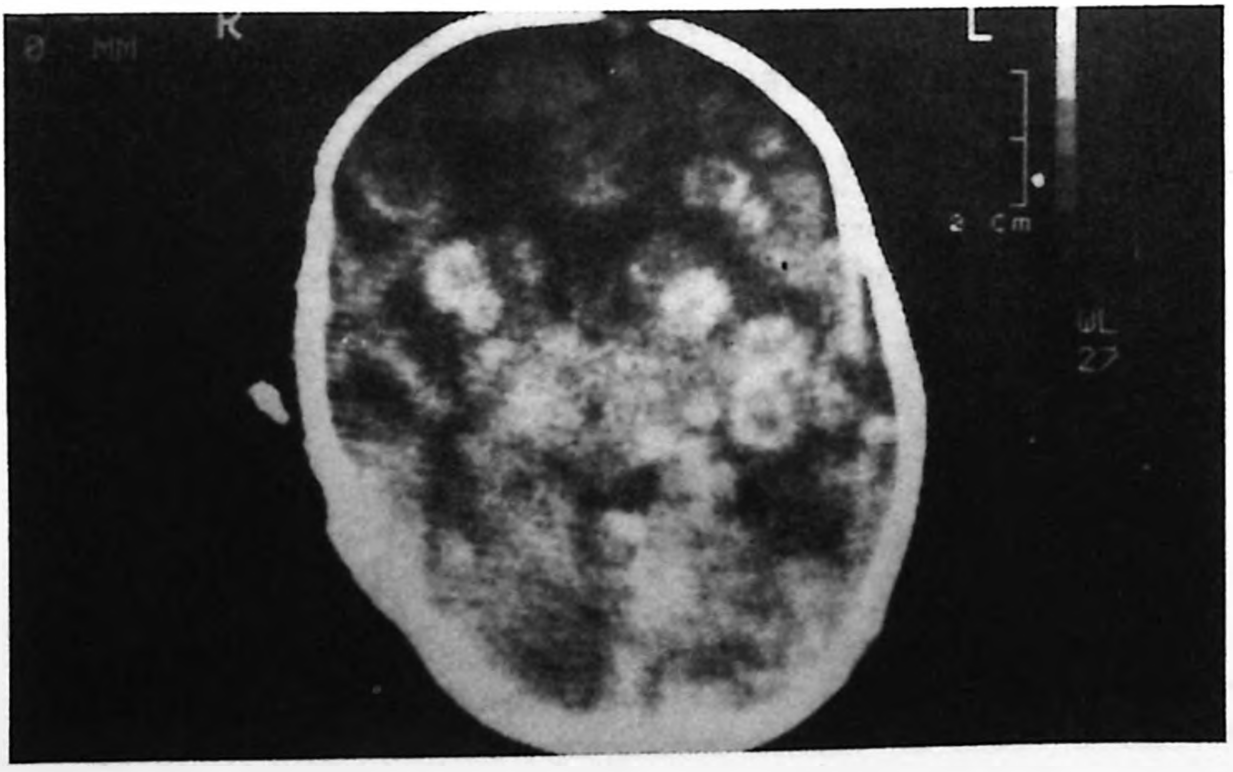

Fig. 1: Initial contrast-enhanced computed tomography (CECT) scan showing multiple nodular lesions of different sizes with good enhancement (Case 1).

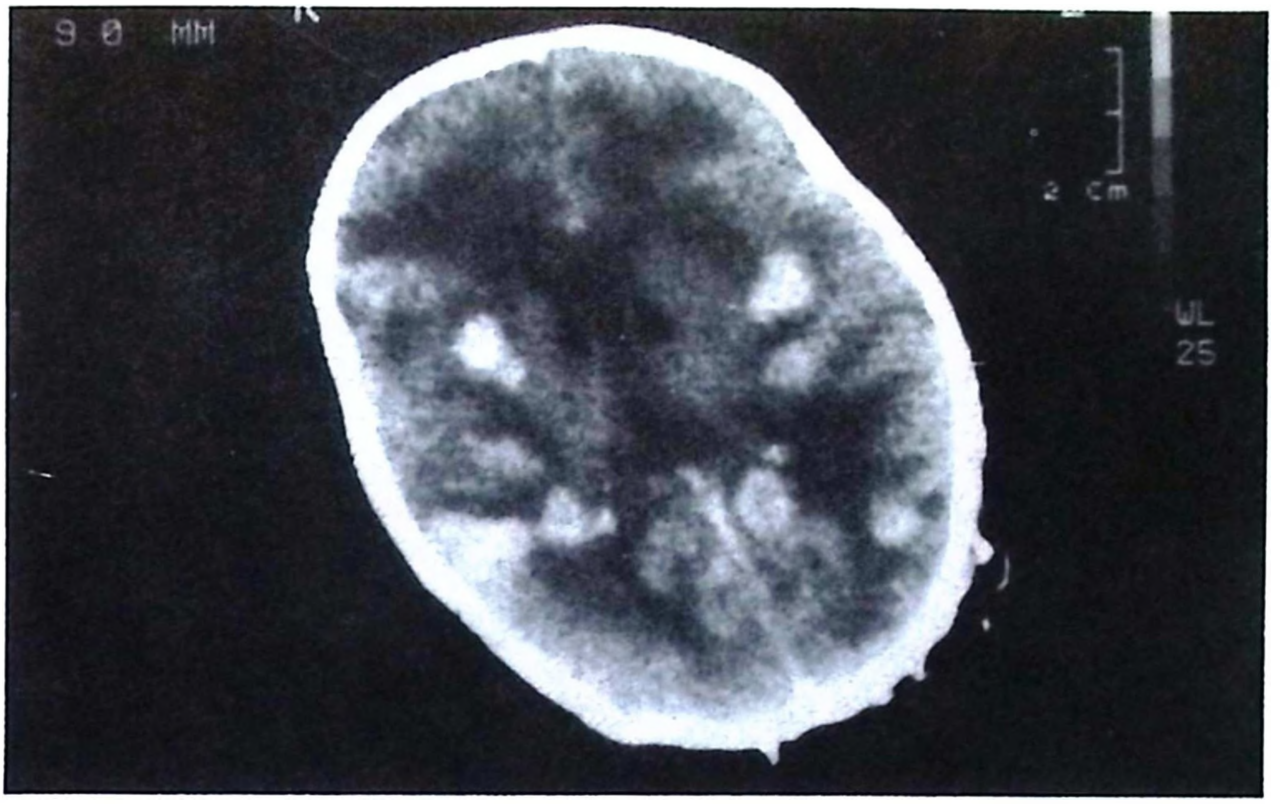

Fig. 2: CECT on the fifteenth day, illustrating marked resolution of lesions with respect to size and quantity (Case 1).

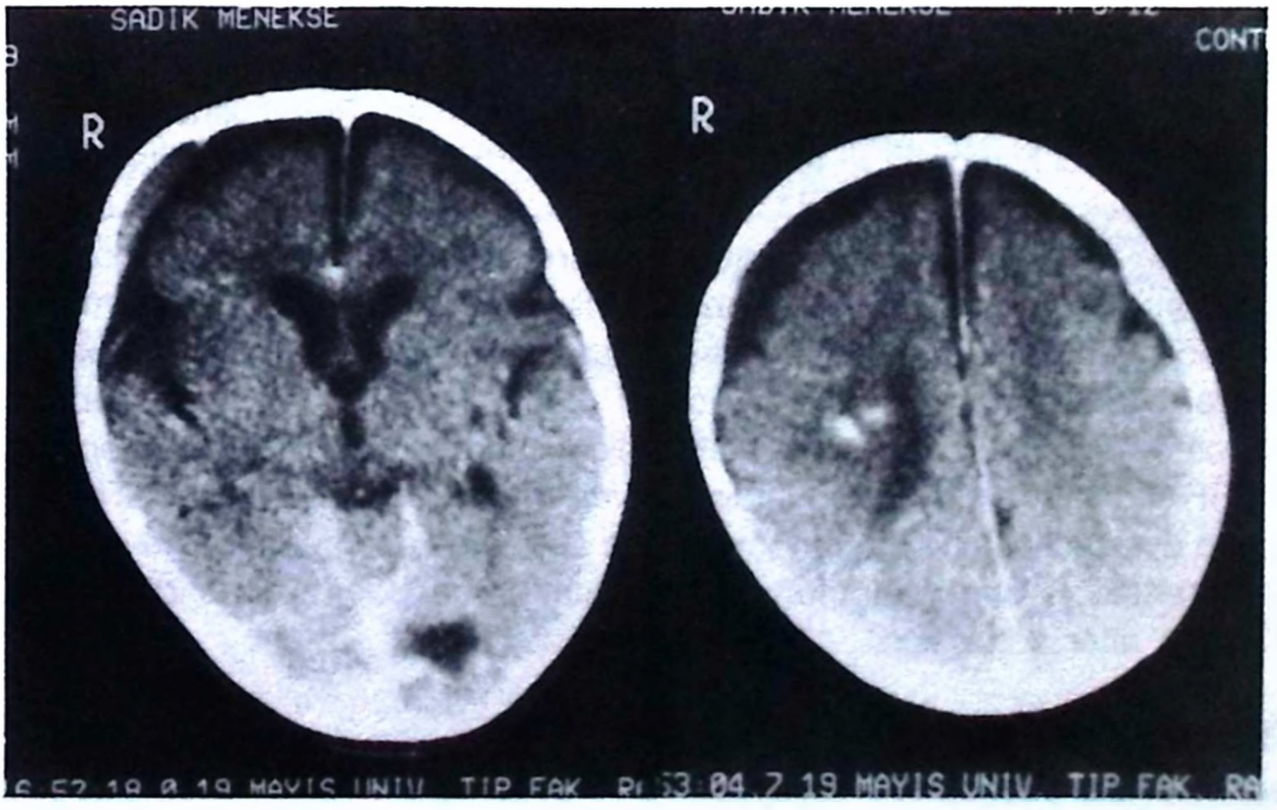

Fig. 3: Post-contrast CT at five months, demonstrating small hyperdense lesions in the right paraventricular white matter, encephalomalacic focus in the left occipital lobe, and minimal subdural effusion (Case 1).

Case 2

A premature female baby was delivered at 33 weeks gestation by cesarean section weighing 1800 g. Jaundice was observed on the first day and phototherapy begun. Because of increasing serum bilirubin levels, two exchange transfusions were performed. After these procedures, clinical and laboratory findings were suggestive of sepsis, and ceftazidime and amikacin were started empirically. Later, cefotaxime was substituted for ceftazidime due to isolation of ceftazidime-resistant enterobacter from the blood on the twelfth day of treatment. Clinical findings did not improve sufficiently during antibiotic therapy. On day 32, Candida albicans was isolated from CSF. At that point the treatment regimen was reevaluated; antibiotic administration was stopped and treatment with amphotericin B initiated. Transfontanelle ultrasonography and cranial CT findings were normal. Seven days after the start of antifungal treatment the patient had improved moderately, and amphotericin B was stopped at the end of the third week. A transient increase in hepatic enzymes was observed from the second to third weeks of treatment. She was discharged nine weeks after admission. Good neurological development was noted at a clinic visit three months later.

Case 3

A preterm female infant was delivered by cesarean section for maternal preeclampsia at 35 weeks gestation. Her birth weight was 1900 g. She was diagnosed with neonatal sepsis on the third day of life, and received ceftriaxone and amikacin. Five days later, oligoanuria was observed. Renal ultrasonography showed adrenal hemorrhage and papillary hypertrophy. Peritoneal dialysis was performed twice for acute renal failure, and the antibiotics were changed. In the fourth week of broad-spectrum antibiotics administration, Candida albicans was isolated from the blood, CSF, urine and joint fluid of the left wrist. CSF examination revealed meningitis. Transfontanelle ultrasonography and cranial CT showed bilateral hydrocephaly. Administration of other antibiotics was stopped, and amphotericin B was commenced with clinical improvement and improvement in the CSF and affected joint fluid findings over the course of four weeks. Transient hepatic dysfunction and thrombocytopenia appeared, caused by side effects of amphotericin B during antifungal treatment. The patient was discharged 10 weeks after admission.

Discussion

Neonates are susceptible to systemic infection because of less adequate anatomic barriers, low serum immunoglobulins and complement levels, deficient cell-mediated immunity, impaired opsonic ability and defective phagocytic function, such as chemotaxis, intracellular killing and oxidative burst[4].

Coupled with chronic antibiotic use, which suppresses normal bacterial flora thus allowing Candida and other nosocomial pathogens to flourish, the neonate becomes a prime candidate for fungal invasion[5,6].

Candida species cause late-onset systemic infection in neonates, especially in premature infants[3]. Common signs and symptoms of systemic candidiasis include respiratory deterioration (an increase in oxygen requirement or ventilatory support), acidosis, apnea and bradycardia, carbohydrate intolerance, abdominal distention, guaiac-positive stools, lethargy, hypotension, hepatosplenomegaly and nonspecific maculopapular rashes[2,3]. These nonspecific signs do not allow for distinction of bacterial from fungal infection. Involvement of the central nervous system is not uncommon, and cerebral candidiasis is frequently secondary to systemic candidiasis. In all three of our patients, the clinical picture resembled nonspecific meningitis. Only the culture results demonstrated Candida albicans as the responsible microorganism.

For the treatment of systemic candidiasis, amphotericin B, flucytosine, itraconazole, fluconazole and ketoconazole are the recommended drugs; however, neither the optimal dosage nor duration of therapy with these drugs is known in neonates. Recent reports suggest that amphotericin B and flucytosine should be used in neonates, although they have also been reported as potentially toxic agents[2,7]. Butler et al.[3] and other researchers[2,8] have suggested that amphotericin B might be a contributing factor in the morbidity and mortality of neonates with systemic candidiasis. Azotemia, hepatotoxicity and thrombocytopenia have been reported with amphotericin B therapy[3,8-10]. In our patients, no significant side effects were observed other than a transient elevation in liver enzymes in two of them, and transient thrombocytopenia in all three (Table I).

Table I: Laboratory Findings at the Onset, During and at the End of Amphotericin B Treatment

							Cerebrospinal Fluid			
	SGOT (U/L)	SGPT (U/L)	GGT (U/L)	BUN (mg/dl)	Cr (mg/dl)	Thromb (/mm3)	Prot (mg/dl)	Gluc (mg/dl)	PNL (/mm3)	Lymp (/mm3)
Case 1										
OT	37	40	131	5	0.4	365,000	201	34	200	10
DT	40	52	375	10	0.4	147,000	740	46	270	140
ET	18	23	92	15	0.6	350,000	414	43	10	10
Case 2										
OT	28	14	116	23	0.5	300,000	310	57	330	10
DT	85	104	246	36	1.1	65,000	157	57	0	0
ET	50	55	187	21	0.8	380,000	110	70	0	0
Case 3										
OT	28	19	—	27	1.2	110,000	264	19	140	150
DT	66	82	1665	54	2.4	34,000	180	14	60	30
ET	30	40	160	12	0.5	370,000	124	84	5	

OT: At onset of therapy; DT: At any time during therapy; ET: At end of therapy; ALT: Alanine aminotransferase; AST: Aspartate aminotranasferase; GGT: Gamma glutamyl transferase; BUN: Blood urea nitrogen; Cr: Creatinine; Thromb: Thrombocytes; Prot: Protein; Gluc: Glucose; PNL: Polymorphonuclear leukocytes; Lymp: Lymphocytes.

In conclusion, amphotericin B may be used as a single drug in candidal infections of neonates, but because of its toxicity caution should be used in prescribing and administering this drug.

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LYMPHANGIOMA TREATMENT WITH Nd-YAG LASER*

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*Kemal Şençift Dt******

SUMMARY: Taşar F, Tümer C, Şener BC, Şençift K. (Department of Oral Surgery, Hacettepe University Faculty of Dentistry, Ankara, Turkey). Lymphangioma treatment with Nd-YAG laser. Turk J Pediatr 1995; 37: 253-256.

In the oral cavity, lymphangioma is a rare, non-odontogenic, benign neoplasm which originates from lymph vessels. This lesion is common in the first decade of life and mostly occurs on the dorsal surface and lateral border of the tongue and rarely arises on the palate, gingiva, buccal mucosa and lips. Treatment of the lesion is surgical excision, however in recent years Neodymium Yitrium Aluminum Garnet (Nd-YAG) laser surgery has become favorable due to its many advantages. This case report presents the treatment of a buccal lymphangioma in a 10-year-old girl by Nd-YAG laser. *Key words: lymphangioma, laser surgery.*

Lymphangioma, which has some similarities to cavernous hemangioma, is a benign tumor of lymphatic vessels[1]. Most lymphangioma cases, similar to hemangioma, present at birth so it should be considered congenital[2]. Ninety-five percent of the lesions arise before the age of 10 in the oral cavity. Lymphangioma occurs most commonly on the dorsal surface and lateral border of the tongue, and rarely arises on the palate, gingiva buccal mucosa and lips. Histologically, simple lymphangioma consists of numerous dilated lymphatic channels which are lined by endothelial cells and contain lymph fluid.

Neodymium Yitrium Aluminum Garnet (Nd-YAG) laser, which is used as a surgical tool in medicine and oral surgery, is suggested as an alternative treatment method to the conventional methods, such as scalpel surgery, electrocautery and cryosurgery, for the treatment of some lesions[3,4]. Lasers may be used for evaporation and hemostasis because they create thermal changes and are applicable for sharp dissection due to adjustable spot size[5,6]. This case report presents the treatment of a rare buccal lymphangioma in a 10-year-old girl with Nd-YAG laser, which recurred after conventional surgery.

Case Report

In December 1988, a 10-year-old girl was referred to our clinic with the complaint of vesicular lesions in her mouth. Her parents stated that these lesions had been

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present for five years and occasionally would flare up. Her medical history was not remarkable, and physical examination revealed bilateral chronic submandibular lymphadenopathy. In the intra-oral examination, translucent, pink-bluish vesicular lesions especially on the right buccal mucosa and alveolar ridge and minimally on the right lower labial mucosa were noticed (Fig. 1). A biopsy was taken from the right alveolar ridge and buccal mucosa. The result of the histological examination was reported as lymphangioma. Pathological examination of the specimen exhibited dilated vascular structures lined with thinned endothelial cells and containing serous fluid (Fig. 2). In February 1989, surgical excision and electrocautery of the lesion were performed under general anesthesia. Due to recurrence of the lesions after one month, the same surgical approaches were repeated. After 10 months, the treatment course was changed because of another recurrence, and Nd-YAG laser (20 watt) was used with 2-3 seconds of exposure under general anesthesia. The patient was followed up clinically on the second, fifth, seventh and fifteenth postoperative days. Epithelialization of the operative site was completed in three weeks. Lack of postoperative pain and edema was notable. Additionally, wound healing was better and scar tissue formation less than after electrocautery. Eighteen months after laser surgery, the clinical examination revealed no recurrence, and the operative site was healthy (Fig. 3).

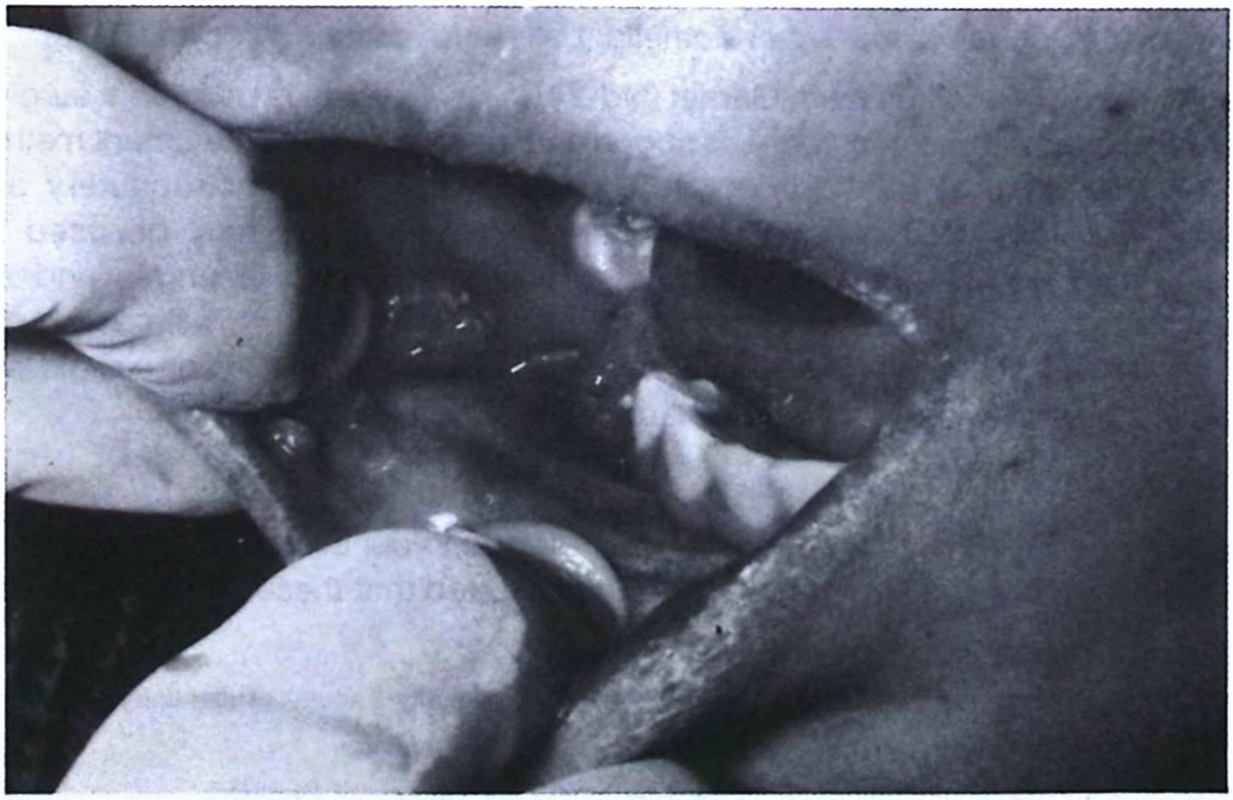

Fig. 1: Preoperative intraoral view of lymphangioma.

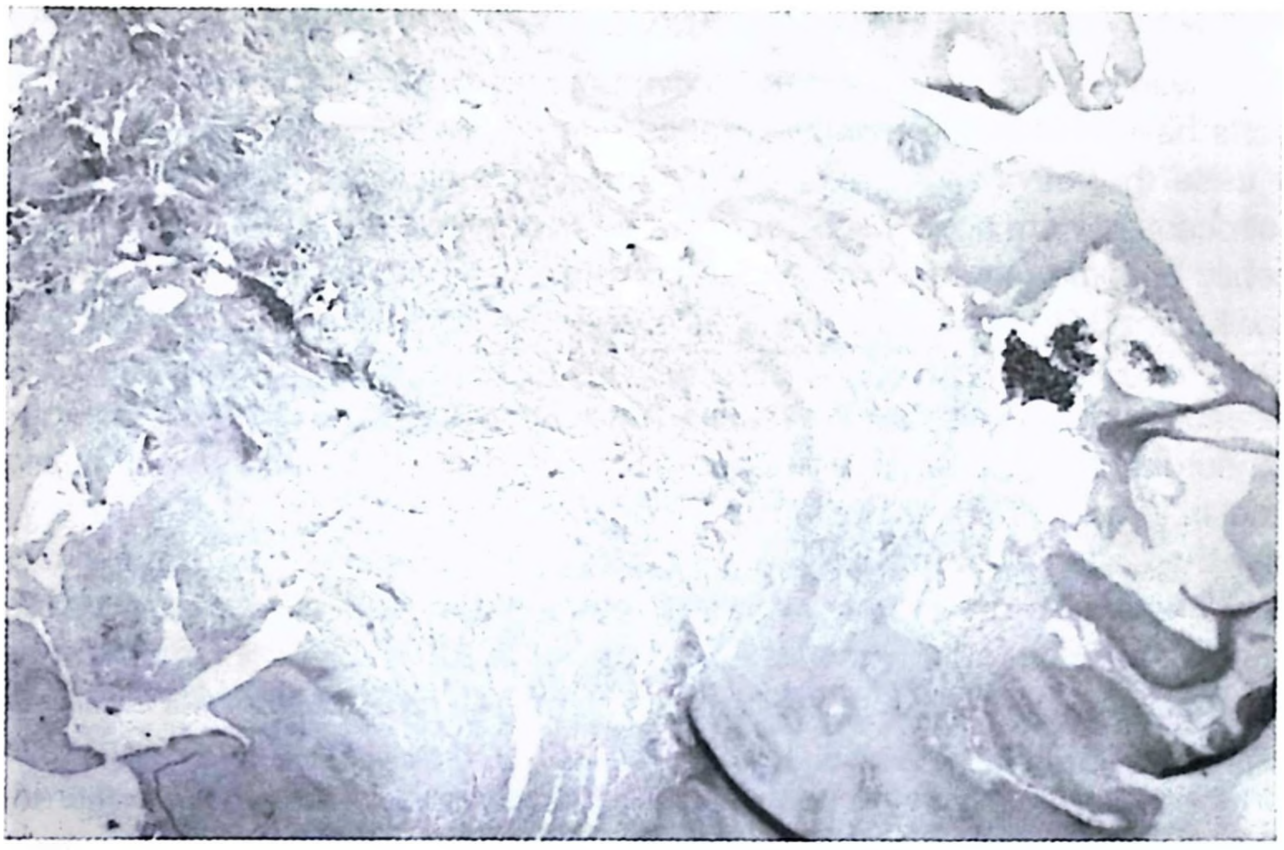

Fig. 2: Histopathologic appearance of the lesion.

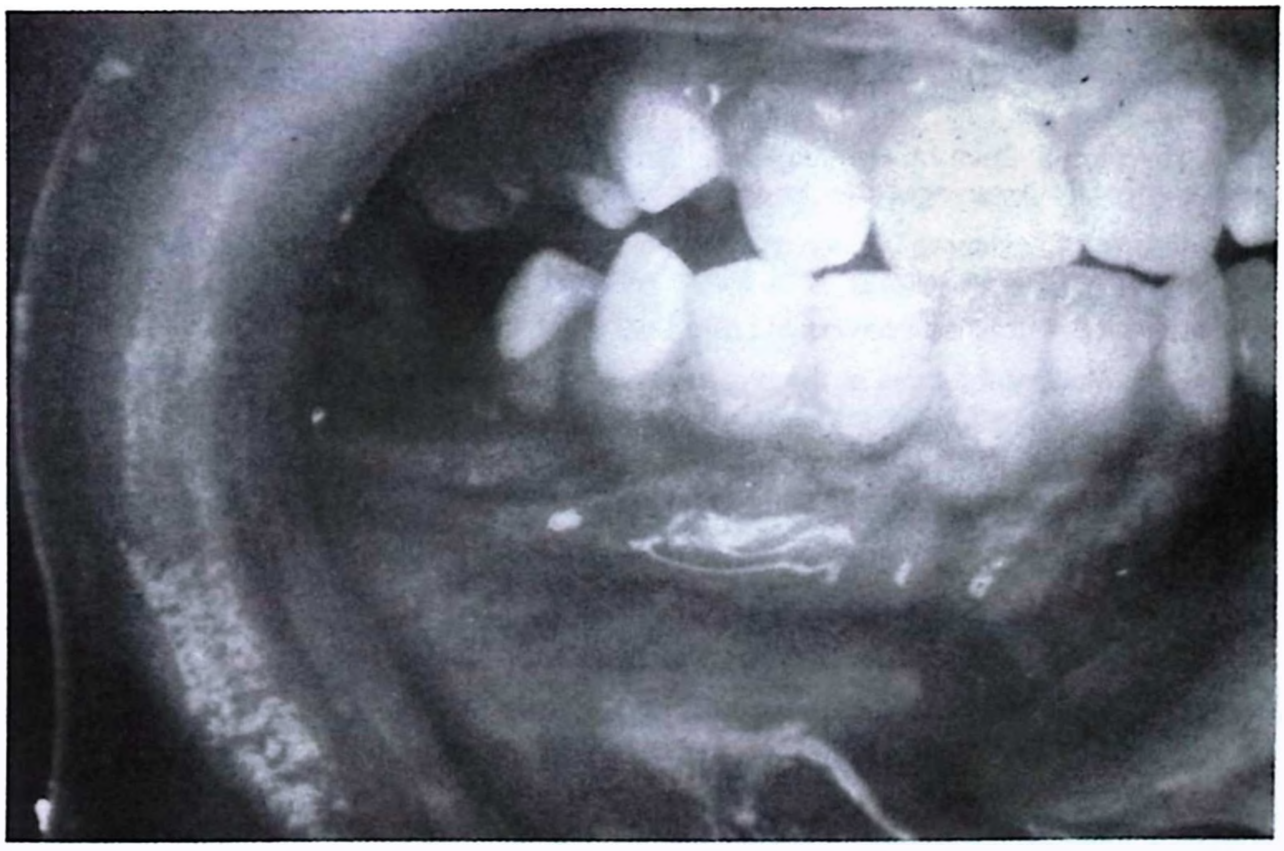

Fig. 3: Intraoral appearance in the postoperative 18th month.

Discussion

The conventional treatment course of lymphangioma is surgical excision. Case reports have revealed a high recurrence rate (41%) of this lesion[1]. Similarly, in our case the lesions recurred even though extensive surgical excision and electrocautery were done. In oral surgery, carbondioxide and Nd-YAG lasers have recently become more favorable than conventional methods for the treatment of some lesions[3]. Studies have shown that laser application seals the blood and lymph vessels and yields superior wound healing[4,7]. These properties of laser were noticeable in our case as well. Pecaro and Garehime[8] claim the advantage of laser surgery in postoperative findings, such as edema, pain and wound healing, in the treatment of some benign oral lesions. In our case, wound healing was faster than after electrocautery and complaint-free. Bradley[5] and Paulsen and Fibaek[6] have also described certain features of laser surgery, such as excellent hemostasis, instant sterilization of the operative site and less contamination risk, as its most important advantages. In our case, the features of Nd-YAG laser, such as deep tissue penetration, sealing of the lymph vessels and ease of application, shortened the operative time and prevented recurrence. The healthy appearance of the operative sites in the postoperative 18th month show that Nd-YAG laser is an alternative and/or preferable method to conventional treatment for lymphangioma, which has traditionally been associated with a high recurrence rate.

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CARDIAC RHABDOMYOSARCOMA DIAGNOSED BY ECHOCARDIOGRAPHY*

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SUMMARY: Paç FA, Akçören Z, Çağlar M, Özkutlu S. (Cardiology and Pathology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Cardiac rhabdomyosarcoma diagnosed by echocardiography. Turk J Pediatr 1995; 37: 257-261.

Primary, malignant, cardiac tumors are extremely rare in infants and children. Only a few cases of cardiac rhabdomyosarcoma have been reported in childhood. Echocardiography greatly increases the rate of correct diagnosis of cardiac tumors. There are some cases in the literature which were diagnosed by echocardiography and confirmed histopathologically.

In this report, a 13-year-old girl with the clinical findings of cardiac tamponade and who was diagnosed as having a cardiac tumor by two-dimensional echocardiogram is presented An echodense, solid tumor with irregular borders extending especially toward the left ventricular cavity from the apex was demonstrated on echocardiography. The diagnosis was confirmed histopathologically on postmortem examination. *Key words: cardiac tumor, rhabdomyosarcoma, echocardiography.*

Primary, malignant, cardiac tumors are extremely rare in infants and children. Only a few cases of cardiac rhabdomyosarcoma have been reported in children[1-4].

Echocardiography greatly increases the possibility of correctly diagnosing cardiac tumors. There have been some reported cases which were diagnosed by echocardiography and confirmed histopathologically[5, 6].

In this report, we present a 13-year-old girl with a malignant, cardiac tumor diagnosed by echocardiography which proved to be rhabdomyosarcoma on histopathologic examination.

Case Report

A 13-year-old girl was admitted to Hacettepe Children's Hospital with a two-month history dyspnea, fatique and edema. The physical examination revealed tachycardia, tachypnea, orthopnea, cyanosis, jugular venous distension,

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edema in the extremities, and hepatomegaly. On auscultation, the heart sounds were muffled. The pulse rate was 120/min with marked pulsus paradoxus. The arterial blood pressure was 100/75 mmHg. The chest roentgenogram showed marked enlargement of the cardiac silhouette. There were low voltage QRS complexes in the EKG, which also displayed massive pericardial effusion. Emergency pericardiocentesis was performed with the diagnosis of cardiac tamponade, and 600 ml serosanguinous fluid was drained. The subsequent echocardiogram revealed the presence of an echodense mass in the ventricular apexes with irregular borders and extending to both ventricular cavities, especially to the left (Fig. 1). Minimal pericardial fluid was detected in the apical portion. B-bump mitral valve was demonstrated by M-mode echocardiography.

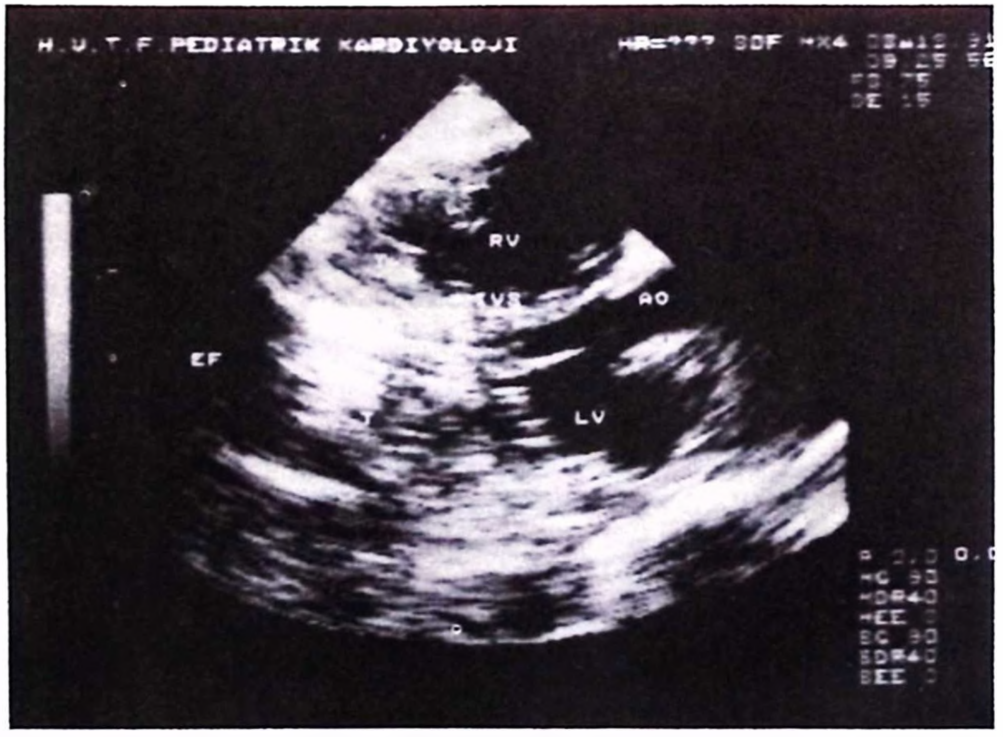

Fig. 1: Two-dimensional echocardiogram showed an echodense mass with irregular borders in the ventricular apexes and pericardial effusion. T: tumor, LV: left ventricle, RV: right ventricle, Ao: aorta, EF: effusion.

Congestive heart failure, pericardial effusion and the echocardiographic appearance suggested a cardiac tumor. The patient underwent tube drainage and pericardial biopsy. She was given digoxin for heart failure. She died two days after admission. Neither chemotherapy nor any further radiologic evaluation could be applied.

Postmortem examination revealed thickening of the myocardium, especially of the left ventricle, irregularity of the endocardium and budlike appearance of the visceral pericardium. Histopathologic study of the specimens showed hypertrophy

of the myocardial fibers and diffuse infiltration of the myocardium and pericardium by tumor cells. The tumor seemed to arise from the base of the left ventricular cavity and was mostly composed of undifferentiated round cells and spindle-shaped rhabdomyoblasts (Fig. 2). There were few strap-shaped cells. No cross-striation was identified even with phosphotungstic-acid hematoxylin stain. These microscopic findings were all compatible with embryonic-type rhabdomyosarcoma. Although the other organs could not be evaluated on postmortem examination, all histopathological and clinical findings strongly suggested that the tumor was a primary rahbdomyosarcoma of the heart.

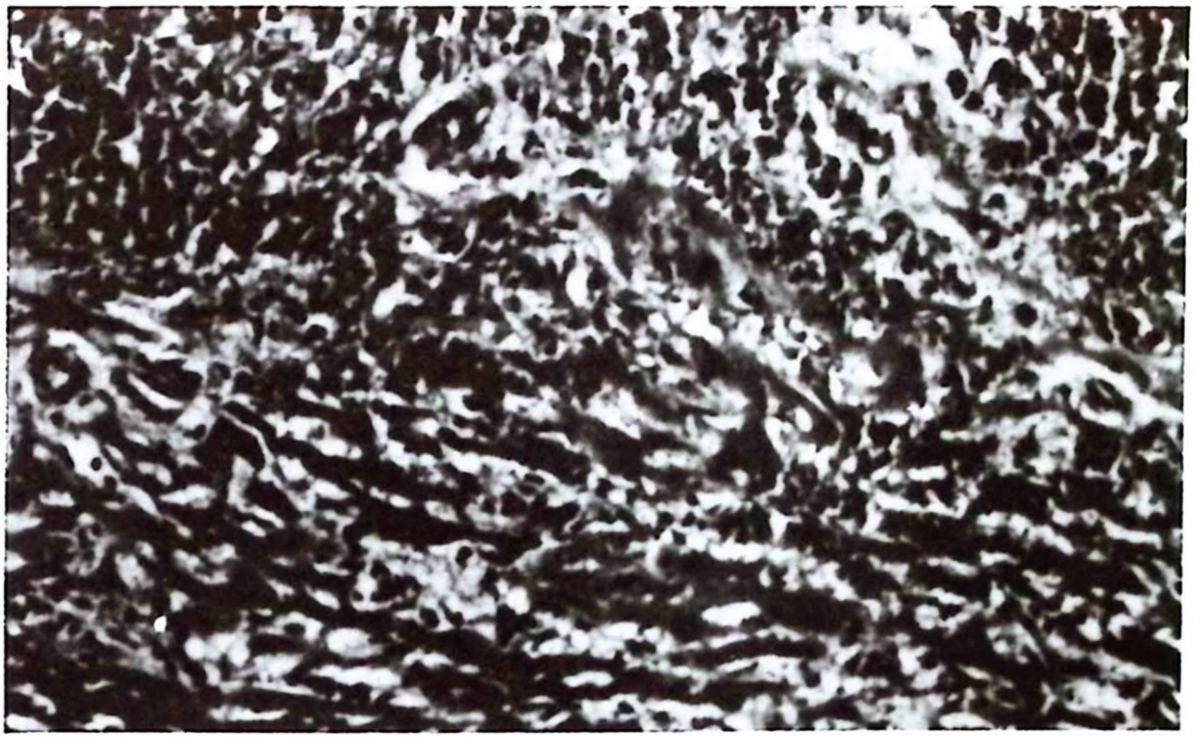

Fig. 2: Infiltration of the myocardium by round and a few spindle-shaped tumor cells (HE, x33).

Discussion

The incidence of primary cardiac tumors on autopsy is reported to be 0.0017-0.28 percent in children[1]. Only nine cases of primary cardiac tumor were described in 11,000 (0.08%) postmortem examinations[7]. Malignant, primary cardiac tumors account for approximately 25 percent of all primary cardiac tumors reported in the literature. In this rare entity, rhabdomyosarcoma is the second-most common neoplasm representing five percent of all heart tumors, but only 2.2 percent in children under 15 years of age[1]. Over a 62-year period, 16 children with primary cardiac tumors were seen at the Hospital for Sick Children in Toronto, and only one of these was rhabdomyosarcoma[3]. Putnam et al.[2] reported 21 primary cardiac sarcoma cases that underwent surgical resection in a 25-year period; two of these patients were children with rhabdomyosarcoma.

Cardiac rhabdomyosarcoma may arise in any cardiac chamber and with nearly equal frequency on the left and right sides of the heart[1,8]. In autopsy series, multiple cardiac sides were found to be involved in 60 percent of the patients, as in our case[9]. The pericardium was also involved in 50 percent of patients, usually by direct extension of the tumor[8].

Clinically the diagnosis is difficult to establish, not only due to its rarity but also because of its varied presentation[1]. The clinical manifestations vary considerably depending upon the histologic type, size and location of the tumor and the degree of involvement of the myocardium[7].

Pericardial effusion seen in primary or secondary malignant heart tumors may cause cardiac tamponade[7]. Pericardial effusion is rarely the first finding in extracardiac tumors[10]. The massive pericardial effusion of our case led us to consider malignant tumor. On the other hand, when pericardial effusion is minimal the echocardiographic diagnosis of cardiac tumor is suspicious, but surgery or necropsy reveals the diagnosis[11].

Rhythm disturbances, ST and T changes, and voltage supression, as in our case, may also be present.

Primary cardiac tumors with non-specific clinical manifestations, and telemetry findings often remain undetected during life, and the diagnosis is made at autopsy[3,5,11]. Cardiac catheterization and angiography, echocardiography, nuclear imaging, computerized tomography and magnetic resonance imaging (MRI) are diagnostic tools in cardiac tumors. Methods such as catheterization and angiography are not preferred because of the risk o rhythm disturbance and embolisation[6].

Echocardiography has become the definitive imaging method for the diagnosis of cardiac tumors in children; in most cases it has eliminated the need for further invasive studies in establishing the diagnosis[7]. Recently, cardiac-gated MRI has been used for the evaluation of cardiac tumors[12]. We could not use MRI for our patient because of her fast demise. In our patient, two-dimensional echocardiography revealed a noncapsulated solid tumor, protruding irregularly, especially toward the left ventricular cavity from the apex. These echocardiographic findings led us to a diagnosis of malignant cardiac tumor. Despite the absence of a full autopsy, microscopic findings such as infiltration of the myocardium and involvement of the pericardium by direct extension of tumor cells suggested primary cardiac rhabdomyosarcoma.

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ANGIOMYOLIPOMA LOCATED IN THE LUMBAR REGION OF A NEWBORN*

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*Zuhal Akçören MD*****, Nebil Büyükpamukçu MD******

SUMMARY: Gündoğdu ZH, Kale G, Tanyel FG, Akçören Z, Büyükpamukçu N. (Department of Pediatric Surgery and Pathology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Angiomyolipoma located in the lumbar region of a newborn. A case report. Turk J Pediatr 1995; 37: 263-267.

An unusual example of angiomyolipoma, which presented as a bulging mass on the right lumbar region of a newborn baby, is presented. The case described is the first report of a newborn with an unusually located angiomyolipoma. The most common predilection sites are the renal parenchyma and the retroperitoneum. However, most of the patients described are adults, and to the best of our knowledge no newborn patient has previously been reported in the literature. *Key words: angiomyolipoma, lumbar region mass.*

Angiomyolipomas are hamartomatous lesions composed of a variable mixture of smooth muscle, blood vessels and fat. They are usually discovered either during routine examination, in patients with tuberous sclerosis, or in cases of hemorrhage into or from a tumor[1,2]. The most common predilection sites are the renal parenchyma and the retroperitoneum[3,5]. Unusual examples of angiomyolipomas have also been reported in the mediastinum, liver and spleen[4,6,7]. However, most of the patients described are adults, and to the best of our knowledge no newborn patients have previously been reported in the literature.

The case described is the first newborn with an unusually located angiomyolipoma.

Case Report

A five-day-old baby was admitted with a bulging mass in the left lumbar region which was first noticed at birth. The physical examination revealed a soft, regular, immobile mass, 6x4 cm in diameter, originating from the abdominal wall in the left lumbar region (Fig. 1). The laboratory findings, which included routine hematological and biochemical investigations, were within normal limits.

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Intravenous pyelography (IVP) was normal (Fig. 2). Ultrasonographic examination revealed a solid mass 10x6 cm in diameter within the abdominal wall. Computerized tomography (CT) revealed a mass at the L1-L5 vertebral level, extending from the right paravertebral area within the paraspinal and quadratus lumborum muscles to the retroperitoneal space, 10x7.5x6 cm in diameter and composed of low-density lipoid material (Fig. 3).

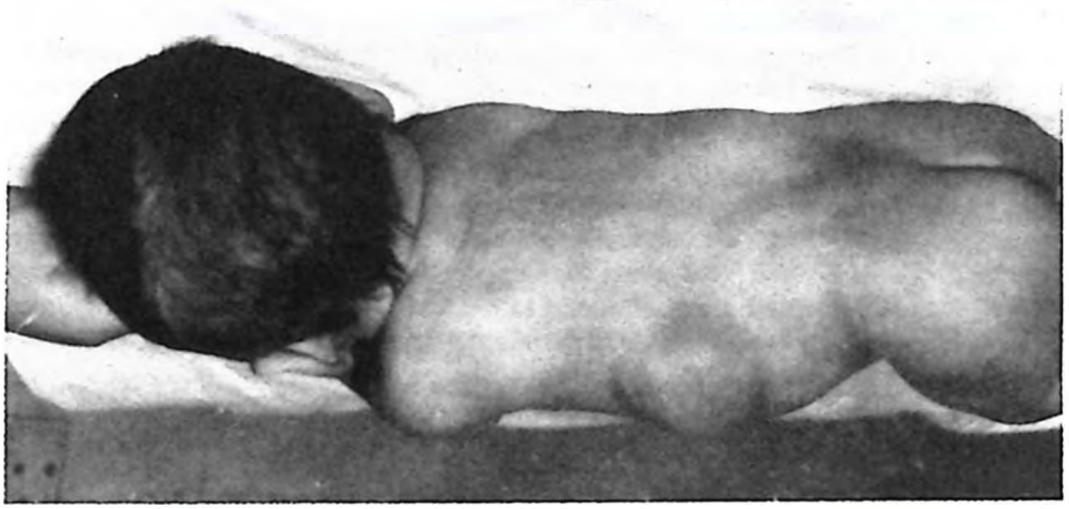

Fig. 1: A five-day-old baby with a bulging mass in the left lumbar region.

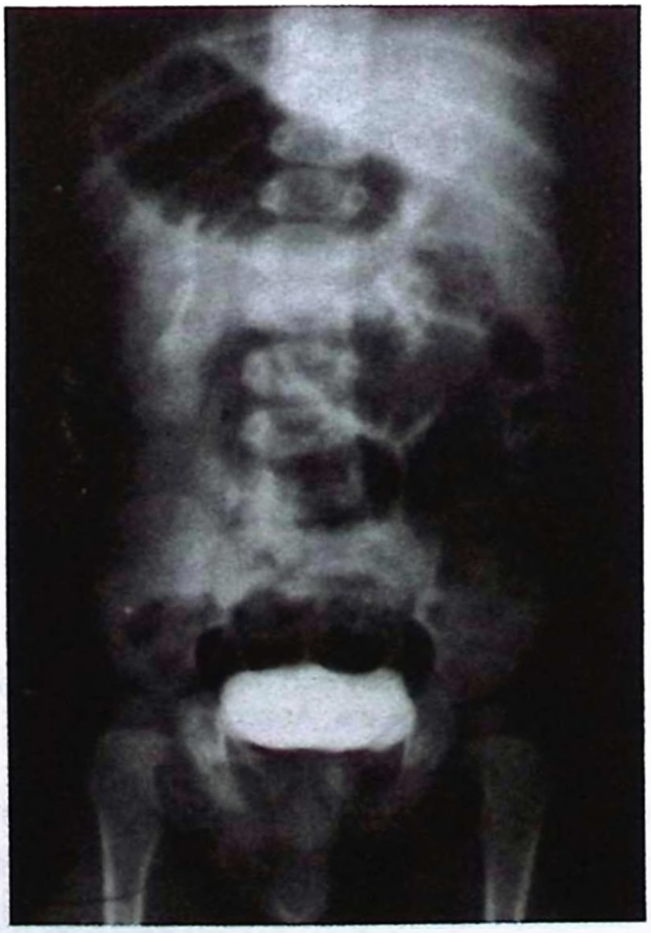

Fig. 2: Normal intravenous pyelogram.

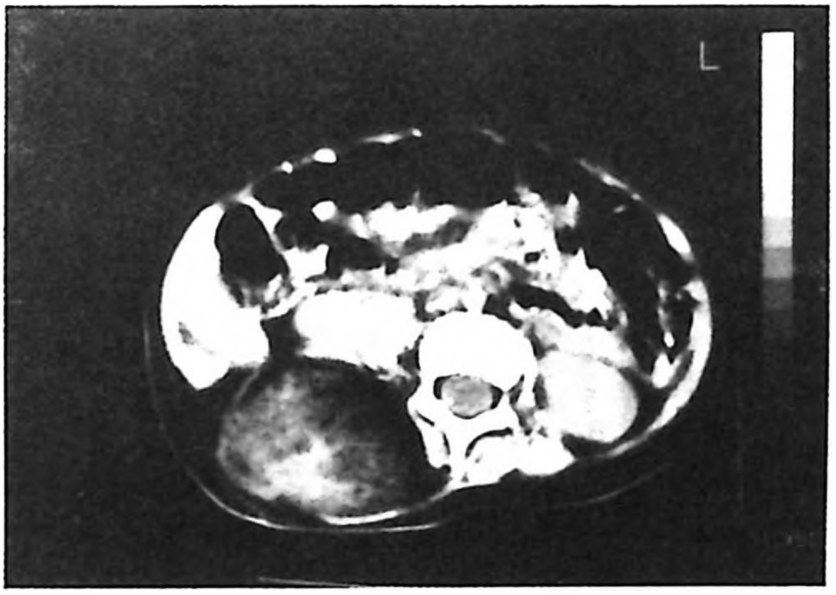

Fig. 3: Computerized tomography showing a mass at L1-L5 vertebral level extending from the right paravertebral area within the paraspinal and quadratus lumborum muscles to the retroperitoneal space 10x7.5x6 cm in diameter and composed of low-density lipoid material.

Surgery was performed to excise the mass through a vertical incision over it. During surgery, an easily bleeding mass with no surrounding capsule was found. A biopsy was performed from the mass. The histopathological examination revealed that the specimen consisted of bundles of smooth muscle cells, thick-walled, hyalinized blood vessels and mature adipose tissue, which were consistent with angiomyolipoma (Fig. 4).

No treatment was given postoperatively. During follow-up examinations extending one year postoperatively, the patient was symptom-free and the mass was found to be of the same dimensions.

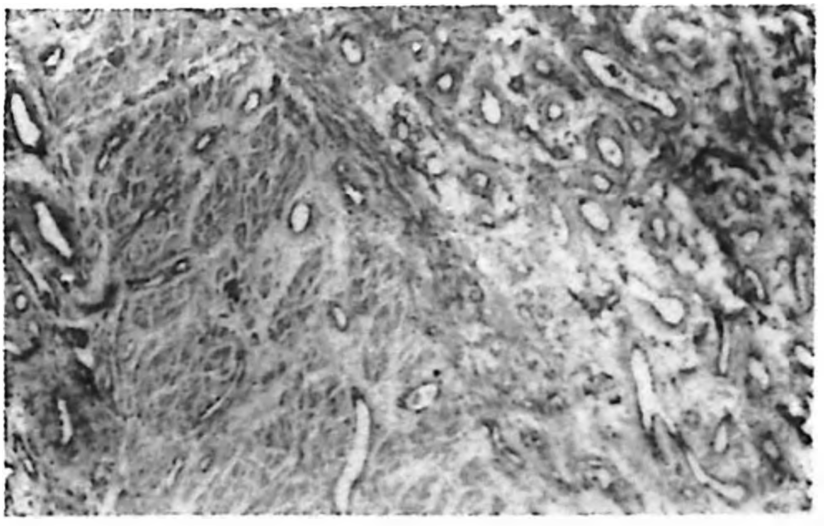

Fig. 4: The histopathological examination revealed that the specimen consisted of bundles of smooth muscle cells, thick-walled hyalinized blood vessels and mature adipose tissue, which were consistent with angiomyolipoma.

Discussion

Angiomyolipoma is not a very rare tumor, with more than 300 patients described in the literature[8], but it is not mentioned among the masses encountered in newborn children. However, the presented case reveals the possibility of angiomyolipoma even in newborns.

Additionally, most reported angiomyolipomas originated from the renal parenchyma[3, 4, 5] and the retroperitoneum. Although some involvements, such as the liver, spleen, head, neck, spinal cord and penis[1, 6, 7, 9, 10], are reported, abdominal wall involvement has not previously been encountered. To the best of our knowledge, this is the first reported case with abdominal wall involvement.

Angiomyolipoma is a benign tumor, but some reviews have found mitotic figures in 50 percent and renal capsular invasion in 25 percent of cases[4, 11, 12]. A single case of recurrence following partial surgical resection of a renal angiomyolipoma was also reported[11]. In our case, total excision was not considered to be passible, and a biopsy for histopathological diagnosis was performed. This histopathological examination did not reveal mitotic figures. Since some angiomyolipomas can be more harmful than it is generally believed, we observed the case closely with monthly check-ups. During one year of follow-up, there was no change in the dimensions of the mass, and the child's growth was found to be within normal limits.

In conclusion, angiomyolipoma can indeed be found in very young children, and can also involve the abdominal wall musculature.

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KAWASAKI DISEASE ASSOCIATED WITH GALLBLADDER HYDROPS*

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SUMMARY: Coşkun Y, Bayraktaroğlu Z, Gökalp A, Çil A, Özkutlu S. (Departments of Pediatrics and Surgery, Gaziantep University Faculty of Medicine, Gaziantep, and Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Kawasaki disease associated with gallbladder hydrops. Turk J Pediatr 1995; 37: 269-273.

Kawasaki disease is an acute, febrile, systemic syndrome of unknown etiology which principally affects young children. We present a five-year-old boy, who developed an unusual finding, acute hydrops of the gallbladder, in addition to the characteristic signs and symptoms of Kawasaki disease. Clinical features of the disease and treatment regimens, including early administration of intravenous gamma globulin (IVGG), which prevents cardiac complications, are discussed. *Key words: Kawasaki disease, gallbladder hydrops.*

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute, febrile, systemic syndrome of unknown etiology seen in early childhood. Although diagnostic tests for KD are lacking, the diagnosis of the disease is not difficult in patients with full expression of clinical features of the disease. The main clinical features of KD are: 1. fever lasting more than five days and unresponsive to antibiotics; 2. bilateral conjunctival hyperemia; 3. nonsuppurative cervical lymphadenopathy; 4. a non-vesicular exanthem, usually truncal; 5. one or more signs of oropharyngeal mucosa, including "strawberry tongue", pharyngeal hyperemia, and dry, fissured or injected lips; and 6. erythema and desquamation of the hands and feet[1].

This syndrome has rarely been reported in Turkey[2,3]. Here we present an unusual case of KD associated with gallbladder hydrops.

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Case Report

A five-year-old boy was admitted to the pediatric department of Gaziantep University Hospital with the complaints of a three-day history of fever, cervical bilateral lymphadenopathy, rash, abdominal pain, vomiting, dark urine and jaundice (Fig. 1a).

Clinical examination revealed a well-developed child with a body weight of 18 kg. His body temperature was 40 °C. The main physical findings were: diffuse erythematous maculopapular rash, bilateral cervical lymphadenopathy a diameter of with 3 cm; dry, red, fissured lips; "strawberry tongue"; hyperemia in the pharynx; bilateral hyperemic conjunctivitis; icteric sclera; abdominal discomfort and irritability with conspicuous neck stiffness; and Kernig and Brudzenski signs (Fig. 1b). Laboratory investigations initially revealed a hemoglobin level of 7.4 g/dl and white blood count of 16,600/mm^3, with a distribution of 81% segmented neutrophis, 5% juvenile neutrophils, 2% monocytes, 12% lymphocytes and 305,000/mm^3 platelets, The sedimentation rate was 120 mm/h. Urine analysis showed marked bilirubinuria and trace proteinuria. Blood electrolytes, BUN and creatinine were within normal limits. Liver function tests were abnormal: total protein 45 g/L, albumin 25 g/L, total bilirubin 122.4 µmol/L, direct bilirubin 95.2 µmol/L, alkaline phosphatase 49.6 nmol/L, ALT 1.1 µmol/L and AST 1.3 µmol/L.

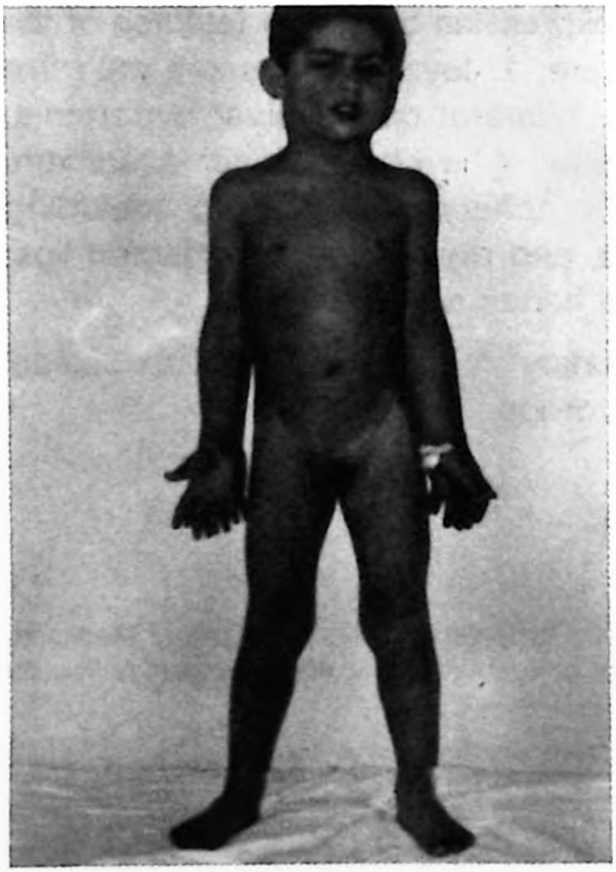

Fig. 1a: Non-vesicular exanthem and cervical lymphadenopathy.

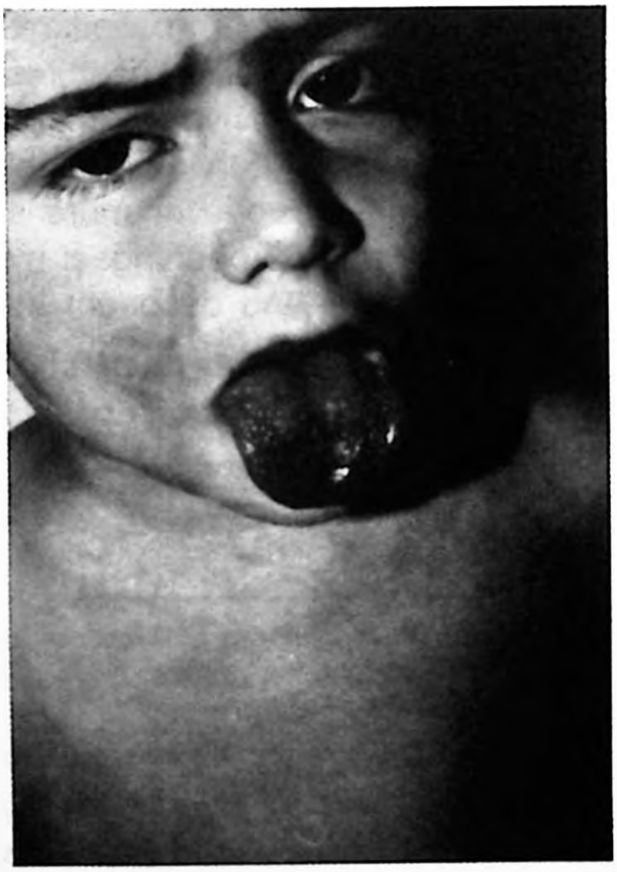

Fig. 1b: Injected lips and strawberry tongue of the patient.

Other laboratory studies, including blood, throat and feces cultures, Brucella and Salmonella agglutination tests, HBsAg and anti-HBsAg, serum immunoglobulin levels (IgG, IgM, IgA, IgE), C3, C4, RF and ASO titers, were negative or within normal limits. Hydropic gallbladder was discovered by abdominal ultrasonography (USG) (Fig. 2). Cardiomegaly was not detected on chest x-ray. At first, electrocardiogram (EKG) revealed no abnormality except sinus tachycardia. Echocardiographic examination in the first and eleventh months were normal.

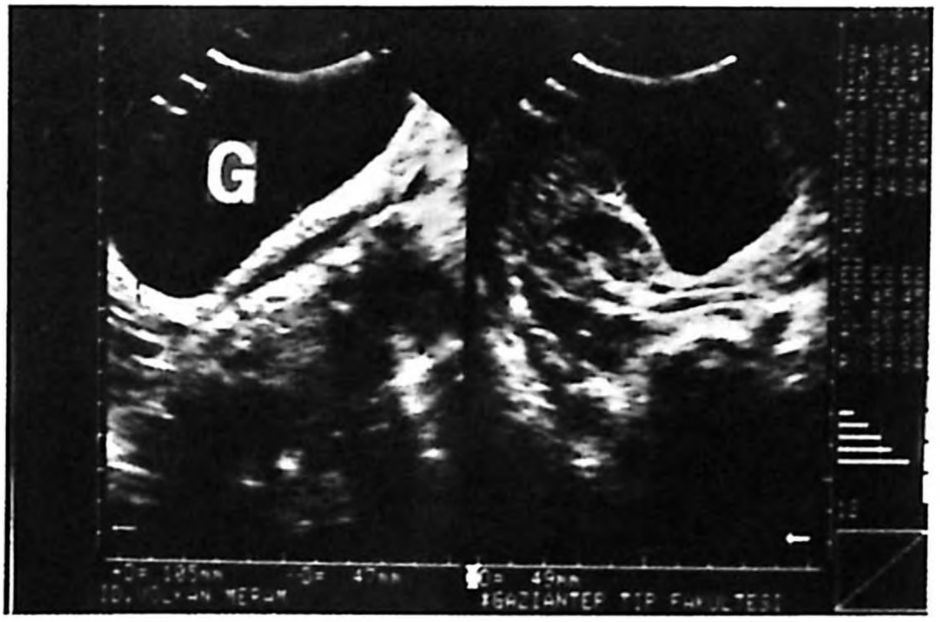

Fig. 2: The appearance of hydropic gallbladder in ultrasonography. G: gallbladder.

On the first day of hospitalization, intravenous (IV) potassium penicillin G administration was initiated at 300,000 units/kg/24h in six divided doses. Then on the fourth day, administration of penicillin G was stopped and ceftriaxone at a dose of 2 g/24h was started and given for ten days. On the second day, in addition to antibiotherapy, acetylsalycylic acid at a dose of 100 mg/kg24h and IV immunoglobulin (400 mg/kg/24h) were commenced and given for three weeks and seven days, respectively. The patient had daily fevers as high as 39-40 °C for ten days. The rash gradually increased, and then desquamation was observed mainly on the trunk, spreading to the extremities; in addition, marked abdominal pain and discomfort continued during the first month of the disease.

The hydrops of the gallbladder recovered according to ultrasound findings, and serum bilirubin levels returned to normal at the end of the fourth week. At the beginning of the second week of the disease, thrombocytosis up to one million/mm^3 and slight ST depression and prolonged PR interval on EKG were detected; thus, dipyridamole 3 mg/kg/24h was added as an anticoagulant therapy and continued until the end of the second month when thrombocytosis subsided. The patient received acetylsalycylic acid at a dose of 30 mg/kg/24h for one month and then 5 mg/kg/24h for approximately one year.

Discussion

In our patient we observed high fever lasting ten days; bilateral cervical lymphadenopathy; dry, red, fissured lips; "strawberry tongue"; pharyngeal hyperemia; hyperemic conjunctivitis; diffuse maculopapular rash and desquamation on the trunk and extremities. With these well-known diagnostic criteria, the diagnosis of KD was not difficult to make, and the typical clinical course of the patient confirmed our diagnosis.

Although meningeal signs are uncommon in KD they may be seen as in our patient, suggesting central nervous system involvement. The other main finding in the patient was jaundice. This finding is not usual in KD, although mild abdominal pain and discomfort are occasionally seen in KD as a sign of hepatic involvement. Marked abdominal pain particularly in the right upper quadrant of the abdomen and associated with jaundice in our case suggested a hepatobiliary complication of Kawasaki syndrome[4]. Then, in the ultrasound examination we detected profound hydropic gallbladder, which is an unusual finding of the disease. Hydrops of the gallbladder did not resolve before one month, and the patient had slight abdominal discomfort lasting for several months. The cause and incidence of this rare complication is not exactly known. Some explanations for the occurrence of gallbladder hydrops, such as regional lymph node compression in the porta hepaticus, have not been well documented[5].

Electrocardiographic changes and cardiac omplications are commonly seen in KD, with frequencies of 74 percent and 25-30 percent, respectively[5-7]. We found PR prolongation and slight ST depression on EKG with no abnormal finding in echocardiography in the acute phase of the disease. The EKG changes resolved within two months, and no abnormality was demonstrated by echocardiography in long-term follow-up (12 months). The other main feature that occurs in almost all patients is thrombocytosis that usually appears in the second week of the disease; thus, management of platelet aggregation is an important issue for decreasing the risk of cardiovascular complications.

Previous reports have strongly demonstrated that early administration of high dose intravenous gammaglobulin (IVGG) plus acetylsalycylic acid will prevent cardiac complications of this syndrome[8]. We started administering IVGG plus acetylsalycylic acid on the second day of hospitalization and added dipyridamole at the end of the second week when the thrombocytosis was profound.

Prevention of cardiac complications was most likely due to early administration of IVGG and long-term use of acetylsalycylic acid and dipyridamole in the thrombocytotic state. Whether IVGG administration was effective in the early resolution of gallbladder hydrops is not clear.

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METHOTREXATE – INDUCED LEUKOENCEPHALOPATHY
A Case Report*

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SUMMARY: İlhan İ, Cila A, Büyükpamukçu M, Akyüz C, Kutluk T, Berberoğlu S. (Oncology Unit, Department of Pediatrics, and the Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Methotrexate-induced leukoencephalopathy: a case report. Turk J Pediatr 1995; 37: 275-278.

A six-year-old girl with non-Hodgkin's lymphoma who was treated with both intravenous (IV) and intrathecal (IT) methotrexate and developed brain damage secondary to the cytostatic drug is described. This patient displayed hypertension, hypothermia/ hyperthermia, lethargy, deterioration and coma as clinical findings, and bilateral, focal white matter hyperintensities in the occipital lobes were seen in her magnetic resonance imaging (MRI). Treatment-related leukoencephalopathy is one such adverse effect of IT methotrexate administration on the central nervous system and usually appears in a generalized form. *Key words: leukoencephalopathy, intrathecal methotrexate, non-Hodgkin's lymphoma.*

Methotrexate (MTX) is one of the most commonly used cytostatic drugs in both children and adults with malignant disease[1,2]. Methotrexate can be given intrathecally (IT) either for therapeutic or prophylactic purposes, but it can cause several central nervous system (CNS) complications which can be difficult to differentiate from the original disease.

The aim of this study was to present a case of focal leukoencephalopathy developed due to IT methotrexate administration, as leukoencephalopathy is usually seen in a generalized form.

Case Report

A six-year-old girl was admitted to Hacettepe Children's Hospital with an abdominal mass and right-sided pleural effusion. A diagnosis of non-Hodgkin's

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lymphoma was made on the basis of cytological findings from pleural effusion. Bone marrow aspiration was normal. She was in stage III according to Murphy's staging system[3]. She was given chemotherapy with the BFM-B cell NHL protocol[4]. After six courses of chemotherapy she had only a 20 x 15 mm lymphadenopathy in front of the pancreas, as detected by ultrasonography. After the COMP protocol[5] was started, she developed dysuria, constipation, cramps and weakness in both legs within two days of her last intravenous (IV, 500 mg/m^2) and IT MTX (12 mg/m^2) administration. A chest wall mass and hilar lymphadenopathy displayed L3-type blastic infiltration. Hypertension and hypothermia-hyperthermia attacks were followed by lethargy, generalized convulsions and deterioration of consciousness. The cerebrospinal fluid (CSF) pressure was 18 cm H_20, with a protein content of 39 mg/dl. Cerebrospinal fluid virus cultures and serum antibody tests were all negative. Electroencephalography (EEG) was within normal limits. Computerized tomography (CT) showed minimal brain atrophy (Fig. 1). High-dose methylprednisolone (30 mg/kg/day) administration was started. One week later magnetic resonance imaging (MRI) revealed bilateral, asymmetric, occipital, white matter hyperintensities which extended into the U-fibers. T1-weighted images showed the lesion only on the right side, which was hypointense relative to the white matter, and no enhancement occurred after Gd-DTPA infusion (Fig. 2).

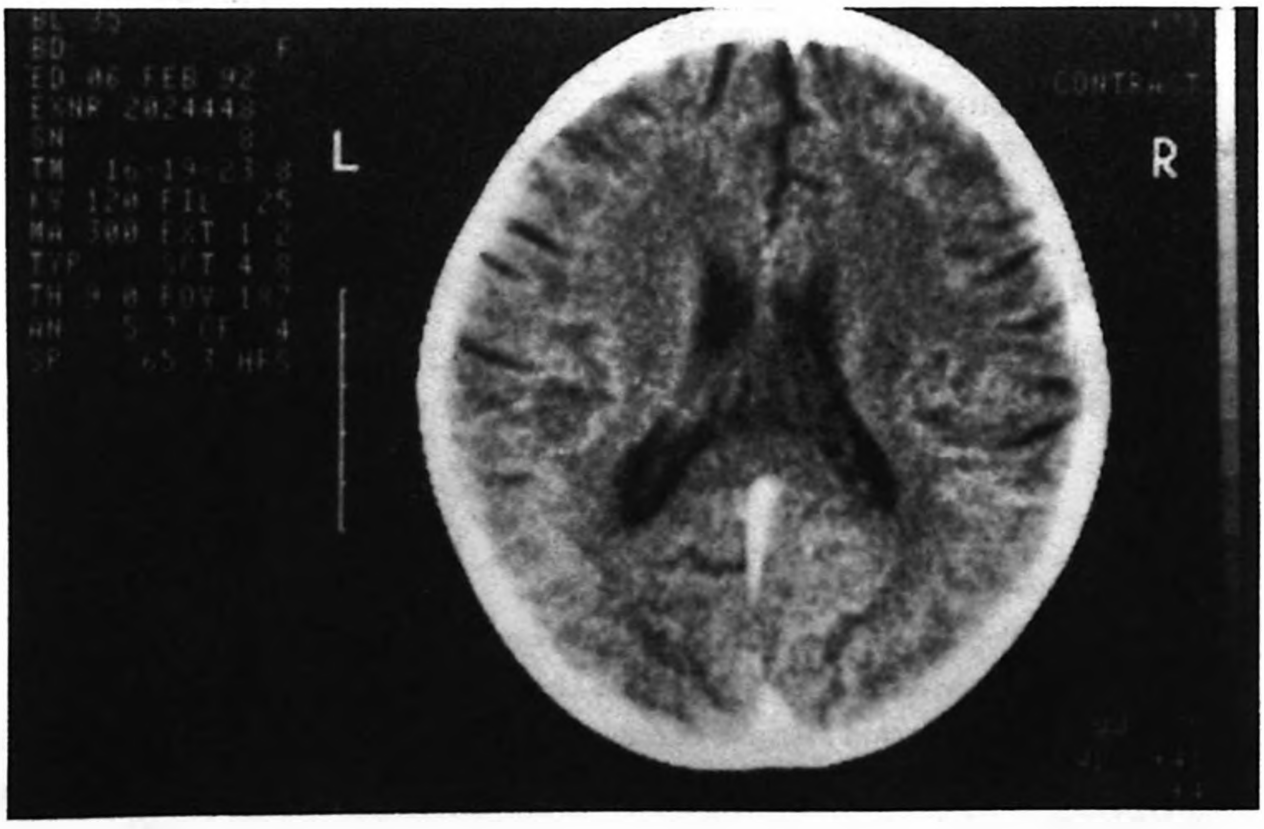

Fig. 1: CT scan. The white matter density is normal in both of the occipital lobes.

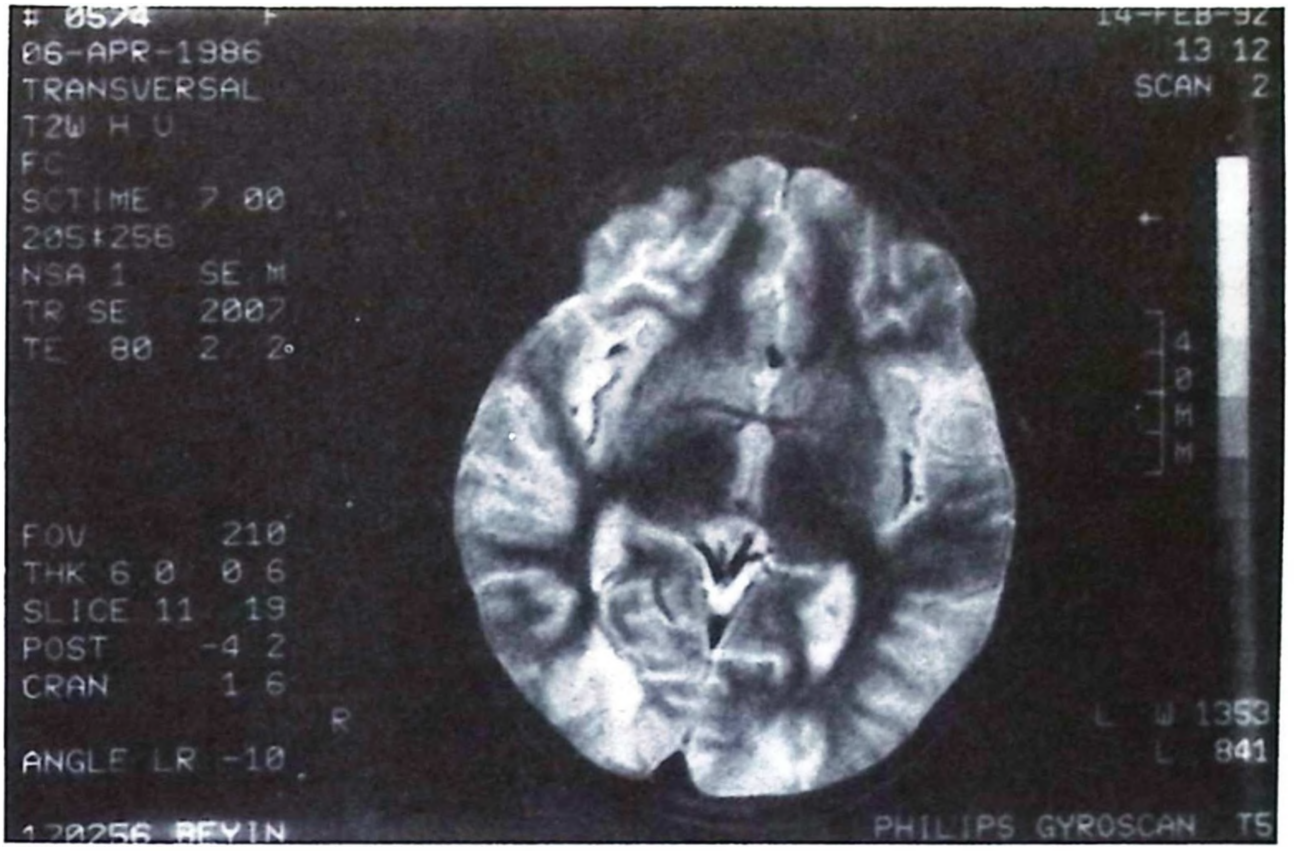

Fig. 2: MRI performed one week later shows bilateral white matter hyperintensities in the occipital lobes extending into the U-fibers.

Two days later, the patient developed a maculo-vesicular rash which was later diagnosed as varicella. Bone marrow aspiration as positive for L3-type blastic infiltration for the first time during the course of her disease. Although acyclovir treatment was started, she died on the third day of her varicella infection.

Discussion

Treatment-related leukoencephalopathy is defined as an entity in which acute or delayed changes in white matter secondary to chemotherapy and/or radiotherapy produce CNS dysfunction[6]. Necrotizing encephalopathy and subacute leukoencephalopathy are terms used to define the same pathology[7]. The chemotherapeutic agents most commonly implicated in its pathogenesis are MTX, Ara-C, BCNU, cisplatin and thio-TEPA. High-dose IV (8-20 g/m^2) and IT/intraventricular injection of MTX is a common cause of leukoencephalopathy[1,8]. Our patient received 12 mg MTX at each IT administration (total 84 mg), and her total IV dose was 3000 mg.

Neurologic symptoms may appear during the treatment (acute), within a few weeks to months after the treatment (early delayed) or several years later (late delayed)[7]. The disease must be distinguished by specific laboratory tests from several other clinical entities such as tumoral infiltration, infection, toxic-metabolic encephalopathy, disseminated intravascular coagulopathy, arteritis and

progressive multifocal encephalopathy. Computerized tomography may show diffuse, white matter hypodensity[9]. Biti et al.[10] reported that MRI showed an abnormal focus in all patients with normal CT findings. We performed imaging studies such as CT, MRI, biochemical and viral studies to establish the etiology of encephalopathy and concluded that it may be treatment-related acute-type leukoencephalopathy. Our patient's CT showed no focal lesion, while the MRI demonstrated abnormal white matter changes. Although there are some reports of generalized leukoencephalopathy due to IT MTX administration, our report is important because her MRI showed focal leukoencephalopathic changes[1, 4, 7]. Since our patient received both IV and IT MTX, it is difficult to distinguish whether the leukoencephalopathy was related to one or both. High-dose steroids and folinic acid is the treatment of choice, but it may be complicated by a superimposing infection, such as varicella in our patient.

In summary, IT MTX administration has been useful in prophylactic treatment of leukemia and lymphoma, but it may cause neurotoxicity as well. Serious and life-threatening forms are rare; thus the effectiveness of prophylactic therapy outweighs the risks.

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SECONDARY ACUTE MYELOBLASTIC LEUKEMIA IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH EPIPODOPHYLLOTOXINS*

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SUMMARY: Özbek N, Çetin M, Tuncer AM, Yetgin S. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Secondary acute myeloblastic leukemia in a child with acute lymphoblastic leukemia treated with epipodophyllotoxins. Turk J Pediatr 1995; 37: 279-282.

Etoposide is a semi-synthetic, topoisomerase active podophyllotoxin derivative which frequently causes deletions and rearrangements on chromosomes 11q23 and 11q22. It can cause therapy-related, acute myeloblastic leukemia in patients receiving the drug in a schedule-dependent manner. Here we present a case with acute lymphoblastic leukemia who developed secondary acute myeloblastic leukemia 28 months after the beginning of therapy which contained etoposide on an every-other-week schedule.
Key words: acute lymphoblastic leukemia, etoposide, secondary acute myeloblastic leukemia.

Etoposide (VP-16), a semi-synthetic podophyllotoxin derivative, is a phase-specific drug which blocks cell cycle progression in the late S and early G2 phase and causes single and double-stranded breaks in DNA. This action is due to inhibition of topoisomerase II, an enzyme which reseals the DNA breaks[1]. Etoposide has been used in malignant diseases such as acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma and some solid tumors of children. In recent reports, the leukemogenic potential of etoposide has been extensively reviewed[2,3]. This drug frequently causes chromosomal deletions and rearrangements, especially on chromosomes 11q23 and 11q22[4,5]. Mixed lymphoma leukemia (MLL) locus, a unique gene that is associated with both ALL and acute myeloblastic leukemia (AML), is usually fractured as a result of rearrangement of chromosome 11q23[6,7].

In Hacettepe University's Pediatric Hematology Unit, etoposide has been used in modified St. Jude's Total XI protocol (Table I) since 1991 in children with ALL. This is the first case with secondary acute myelocytic leukemia (AML) in three years of follow-up of 151 ALL patients.

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Table I: Modified St. Jude's Total XI Protocol For Patients with Acute Lymphoblastic Leukemia

Remission Induction (6 weeks)			
Prednisolone (Pred)		: 2 mg/kg	p.o d 1-29
Vincristine		: 0.05 mg/kg	i.v d 1, 8, 15, 22
L-Asparaginase		: 200 U/kg	i.vi.m d 3, 4, 6, 8, 10, 12
Daunorubicine		: 1 mg/kg	i.v d 1, 8
Cytosine Arabinoside (Ara-C)		: 10 mg/kg	i.v d 22, 25, 29
Cyclophosphamide		: 10 mg/kg	i.v d 36, 43
VP-16		: 3-6 mg/kg	i.v d 36, 43
Intrathecal therapy (MTX + Ara-C + Pred)			: d 2, 22, 43
Consolidation (2 weeks): High-dose methotrexate (1.5 g/m²) d 50, 57			
Maintenance (120 weeks, repeated every 4 weeks)			
	1st week	VP-16	i.v 300 mg/m²d 1
		Ara-C	i.v 300 mg/m²d 1
	2nd week	Vincristine	i.v 1.5 mg/m²d1
		Prednisolone	p.o 40 mg/m²d 1-7
	3rd week	VP-16	i.v 300 mg/m²d 1
		Cyclophosphamide	i.v 300 mg/m²d 1
	4th week	Methotrexate (MTX)	i.m 40 mg/m²d 1
		6-Mercaptopurin	p.o 75 mg/m²d 1-7

p.o.; per os, i.v.; intravenous, d; day.

Case Report

A $2^1/_2$-year-old girl was admitted to the hospital with complaints of paleness, failure to thrive and restlessness. The physical examination was normal, and neither hepatosplenomegaly nor lymphadenopathy was evident. The patient's initial complete blood count results were as follows: hemoglobin 3.86 g/dl, hematocrit 10%, white blood cell count (WBC) 5300/mm³ and the peripheral smear revealed 94% lymphoblasts with prominent thrombocytopenia. The chest radiogram displayed mediastinal enlargement. The bone marrow aspiration smear revealed 95% of FAB L2 lymphoblasts. In immunophenotypic studies using the peroxidase antiperoxidase technique (PAP), CD19 was 80%, CD34 was 10%, CD14 was 8% positive and CALLA, CD2 and CD33 were negative. PAS was positive and myeloperoxidase was negative. She was diagnosed with high-risk ALL-L2 and given St.Jude's modified total XI protocol Group A. Bone marrow aspiration performed on day 15 was not in remission. Complete remission was able to be achieved at the end of the remission induction therapy. After remission induction, high-dose methotrexate (MTX) and radiotherapy were administered without complication, and maintenance therapy was started. She was doing well

during maintenance therapy except for bronchopneumonia, which was treated successfully. After 28 months of maintenance therapy consisting of etoposide administration every other week she developed bone marrow relapse. The bone marrow smear showed 95 percent of FAB M2-type blastic infiltration. In immunophenotypic studies, CD13 was 100 percent CD33 was 70 percent, CD5 was five percent positive and CALLA, CD19, CD14, Tdt and Gp IIb/IIIa were negative. Myeloperoxidase was positive and PAS was negative. Chromosomal analysis revealed 46 XX genotype with no additional abnormality. A second remission induction protocol with high-dose methylprednisolone, mitoxantrone and cytosine arabinoside (ara-C) was started. Due to sepsis the therapy could not be completed, and her WBC count gradually increased to 112,000/mm^3. She died because of sepsis one and one-half months after the beginning of the second remission induction therapy.

Discussion

Therapy-related AML accounts for up to 20 percent of AML. Its incidence in recent years has increased due to longer survival and more intensive chemotherapy and irradiation protocols. Pui et al.[8] reported therapy-related AML in 13 out of 733 ALL patients. In this series, the cumulative risk of AML was significantly higher in T-cell ALL patients. The same author reported results of 21 secondary AML patients and demonstrated a schedule-dependent rather than dose-dependent relationship to etoposide exposure[3]. Patients receiving weekly or twice-weekly etoposide had a 12.3 percent cumulative risk of acquiring AML compared to 1.6 percent for those patients who receive etoposide on an every-other-week schedule. Cytogenetic abnormalities of chromosomes 11q and 11q22 were frequently detected in this form of disease. Duration of leukemia treatment before second relapse (treatment-leukemia interval) was usually short (mean 33 months) and response to therapy was poor[5]. Secondary AML due to epipodophyllotoxins usually presented with FAB M4 subgroup.

Our patient was diagnosed with secondary AML by morphological and immunophenotypic studies. The treatment-leukemia interval was similar to that associated with etoposide-related AML[5]. The patient's response to therapy was poor. These findings suggested that etoposide could have been the cause of secondary AML in this patient. In our case, we could not detect any cytogenetic abnormality, and the AML subgroup was diagnosed as M2 type. However, in the literature there are cases reported with different types of AML and cases without any cytogenetic abnormality[2]. This is the first case of AML in our unit suspected to be related to etoposide. Our incidence is still lower than that in the literature, but the mean follow-up of ALL patients in this chemotherapy protocol is shorter than the series in the literature.

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THE ROLE OF HIGH-DOSE METHYLPREDNISOLONE THERAPY IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA*

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SUMMARY: Erduran E, Aslan Y, Gedik Y, Mocan H, Ökten A (Department of Pediatrics, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). The role of high-dose methylprednisolone therapy in paroxysmal nocturnal hemoglobinuria. Turk J Pediatr 1995; 37: 283-287.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder characterized by intermittent hemolytic anemia. High-dose methylprednisolone (HDMP) was administered in two patients, eight- and 16-year-old females, with PNH. This drug produced a dramatic improvement in the hemoglobin level, leukocyte and platelet counts. No side effect was observed in either patient during the treatment period. The patients were followed up on an outpatient basis for six and 16 months. In conclusion, HDMP therapy for PNH appears to be more effective and safe than previously reported therapies. *Key words: high-dose methylprednisolone, paroxysmal nocturnal hemoglobinuria.*

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, clonal hematologic disorder characterized by hemoglobinuria, thrombosis, infection and a tendency toward bone marrow aplasia[1].

The cause of hemolytic anemia seen in PNH is complement-mediated hemolysis[2]. Blood cells from patient with PNH contain an abnormal cell that lacks two complement regulatory proteins, Decay Accelerating Factor, (DAF) and CD59, both of which protect host cells from the action of complement. DAF and CD59 are phosphatidylinositolglycan (PIG)-anchored surface molecules[2,3]. The cause of PIG-anchored surface molecule deficiencies is defective synthesis of the molecules of glycosylphosphatidylinositol[4,5]. This mutant gene is termed PIG-A (phosphatidylinositol glycan class A)[5]. The localization of the PIG-A gene is found on p22.1 of the X-chromosome[5]. Therefore, pancytopenia may occur in patients with PNH[1,6].

Various treatment modalities, such as danazol, high-dose recombinant human erythropoietin (r-Hu EPO), corticosteroids and/or anabolic agents, and bone marrow transplantation have been used in PNH[1,7-11]. High-dose

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methylprednisolone (HDMP) was used in our two patients with PNH. Complete correction of hematological findings was observed in both patients following HDMP therapy.

Case Reports

Case 1

An eight-year-old girl came to the pediatric clinic with complaints of right hemiplegia and paleness for two days. She had a four-year history of recurrent jaundice, dark urine and paleness.

Physical examination revealed normal vital signs. Paleness, cutaneous petechiae, right hemiplegia and positive Babinski sign were found.

Laboratory examination: hemoglobin 6.4 g/dl; leukocyte 5,400/µl; mean corpuscular volume (MCV) 96.6 fl; thrombocyte 5,400/µl; reticulocytes 6%; differential count: 68% neutrophils, 24% lymphocytes, 8% band neutrophils and 2% normoblasts. Spherocytes were seen on peripheral smear. Direct Coombs was negative. Clotting time, prothrombin time, partial thromboplastin time, protein-C, protein-S, anti-thrombin-III, antinuclear antibody (ANA), anti DNA, C_3, C_4, antistreptolysin-O (ASO), osmotic fragility test, autohemolysis test and biochemical analyses were all within normal limits. Haptoglobulin was 16 g/dl and no microorganism was determined to grow in the throat culture. Lupus erythematosus (LE) cells were negative. Total bilirubin and direct bilirubin were 6.4 mg/dl and 0.8 mg/dl, respectively. Serum iron was 50 µg/dl, serum iron binding capacity 360 µg/dl and transferrin saturation 14%. Urine hemoglobin and acid-Ham test were positive. Hemoglobin electrophoresis was normal. Erythroid hyperplasia and hypocellularity were seen on the bone marrow smear. Multiple infarcts on the left parieto-occipital region were seen on cranial CT-scan.

High-dose methylprednisolone therapy was administered orally at doses of 30 mg/kg/day for three days, 20 mg/kg/day for four days, 10, 5, 2 mg/kg/d for one week, and 1 mg/kg/day according to hematological findings. Elevations in hemoglobin level (8.2-11.2 g/dl), leukocyte count (7,500-9,800/µl) and thrombocyte count (116,000-316,000/µl) were observed on the first and third weeks of treatment, respectively. Subcutaneous heparin therapy (50 u/kg/d) was supplemented. The patient has been followed on an outpatient basis for 16 months.

Case 2

A sixteen-year-old girl came to the pediatric clinic with complaints of vaginal bleeding, epistaxis and skin bruises for seven days. The patient had received a blood transfusion 25 days before coming to our clinic.

Physical examination revealed normal vital signs. Paleness, ecchymotic and purpuric lesions on her skin, epistaxis and vaginal bleeding were noted.

Laboratory examination: hemoglobin 8.2 g/dl, leukocytes 4,600/μl, thrombocytes 4,000/μl, MCV 71.3 fl, reticulocytes 6%, and differential count: 58% neutrophils, 40% lymphocytes and 2% monocytes. Anisocytosis was noted on the peripheral smear.

Biochemical analyses, direct Coombs test, partial thromboplastin time, prothrombin time, clotting time, ASO, C3, C4, ANA and anti-DNA were within normal limits, and LE-cells were negative. No microorganism was determined to grow in the throat swab culture. Total bilirubin and direct bilirubin were 4.3 mg/dl and 0.2 mg/dl, respectively. Serum iron was 34 μg/dl, serum iron binding capacity 335 μg/dl and transferrin saturation 10%. Haptoglobulin was 20 mg/dl, while the acid-Ham test and urine hemoglobin were positive. Erythroid hyperplasia was detected on the bone marrow smear.

High-dose methylprednisolone therapy was administered in a schedule similar to that in the previous case. Elevations in hemoglobin level (10.4-11.6 g/dl), leukoctyte count (7,400-10,200/μl) and thrombocyte count (64,000-230,000/μl) were observed in the first and third weeks of treatment, respectively. Ferrous iron (6 mg/kg/day) was also supplemented. The patient has been followed on an outpatient basis for six months.

Discussion

Paroxysmal nocturnal hemoglobinuria is now generally accepted as a disease in which bone-marrow-derived cells have deficient PIG-anchored surface molecules[2, 3]. Furthermore, Miyata et al.[5] suggested that these surface molecules are defective. DAF and CD59, which are PIG-anchored surface molecules, ameliorate the complement sensitivity of PNH red blood cell[12].

Paroxysmal nocturnal hemoglobinuria can arise from or evolve into aplastic anemia, sideroblastic anemia and myelofibrosis[11]. Iron-deficiency anemia may occur due to urinary loss of iron during intravascular hemolysis[13]. Iron-deficiency anemia also occurred in one of our patients (Case 2).

The precise mechanism of thrombosis in PNH is unknown. However, the platelets and leukocytes in patients with PNH are also abnormally sensitive to complement-mediated lysis. Certain aspects of complement-platelet interaction may predispose a patient to thrombosis[13]. Thrombosis was also been determined in one of our patients (Case 1).

Danazol has been used in patients with PNH. This drug has reportedly produced a dramatic improvement in hemoglobin levels and platelet counts, but was associated with a few androgenic side effects[7]. High dose r-Hu Epo for the treatment of anemia in two patients with PNH was administered. In one patient,

a relapse of severe aplastic anemia occurred and r-Hu Epo therapy was discontinued. Another patient showed too great an increase in hemoglobin, and monthly phlebotomies were done to reduce his iron overload. However, an increase in leukocytes and thrombocytes was not observed[8].

It has been suggested that glucocorticoid and androgen therapy is moderately effective in PNH. However, both are poorly tolerated, particularly by women[8, 14]. Marrow transplantation for aplastic complications of PNH has been found to be successful and well-tolerated. For patients without aplasia, the complication risk of transplantation as well as the life-threatening nature of thrombotic episodes and hemolysis have been reported[11].

Blood transfusions are valuable in the treatment of anemia, but they must be given in the form of saline-washed, or frozen-thawed, deglycerolized red cells. Transfusion of other preparations, especially fresh blood, may precipitate or accelerate the hemolytic process either by supplying components of complement or by inducing the formation of antibodies that activate early components of complement[15].

High-dose methylprednisolone therapy has succesfully been used in various hematologic disorders such as aplastic anemia, idiopathic thrombocytopenic purpura, myelofibrosis, acute leukemia and osteopetrosis instead of conventional prednisolone therapy[16].

HDMP therapy has been used previously in two adolescent patients with PNH[16]. In this study, HDMP therapy was administered to two adolescents with PNH. HDMP therapy has been observed to be successful and well-tolerated in patients with PNH. No side effects were noted during HDMP treatment. Patients' blood cells began to increase on the 7th day and reached normal levels on the 21st day of therapy. Recurrence was not seen in our patients within six and 16 months of HDMP therapy. Finally, we believe that PNH may be treated successfully with HDMP.

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IMMUNE THROMBOCYTOPENIC PURPURA IN A CHILD WITH HODGKIN'S DISEASE*

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SUMMARY: Berberoğlu S, Sarıalioğlu F, Akyüz C, Kutluk T, Büyükpamukçu M. (Oncology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Immune thrombocytopenic purpura in a child with Hodgkin's disease. Turk J Pediatr 1995; 37: 289-292.

The occurrence of immune thrombocytopenic purpura (ITP) in Hodgkin's disease is uncommon. This report describes a patient who developed ITP twice before splenectomy, and for the third time several years later, preceding an abdominal relapse of the disease. We suggest that patients with a history of Hodgkin's disease undergo diligent searches for active disease when ITP is diagnosed. ITP may be the only manifestation of active disease and may preceed histologic documentation of Hodgkin's disease by months or years. *Key words: Hodgkin's disease, immune thrombocytopenic purpura.*

Thrombocytopenic purpura is commonly seen in Hodgkin's disease as a result of bone marrow failure due to the disease or secondary to treatment with chemotherapy or radiation therapy[1,2]. On the other hand, immune thrombocytopenic purpura (ITP) is less common[3]. It is unusual in young children, but seen more often in adolescents[4]. Some patients present with ITP at initial diagnosis, whereas others are diagnosed in the course of the disease. This report describes a child with Hodgkin's disease who had three episodes of profound thrombocytopenic purpura unrelated to bone marrow failure.

Case Report

A twelve-year-old boy was admitted to Hacettepe Children's Hospital with a mass in the left cervical area. A diagnosis of clinical IVA, mixed, cellular Hodgkin's disease was made on the basis of clinical and laboratory findings. According to our sandwich therapy protocol, combined COPP chemotherapy was initiated.

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Three courses of chemotherapy and low-dose, involved field radiation therapy (2000 cGy) and then three more courses of COPP chemotherapy were administered with no major problem. He was in complete remission in August 1987. Chemotherapy was stopped in October 1987, and the patient was followed until March 1990 with no evidence of disease.

In March 1990, the patient presented with easy bruising. On physical examination the only pathological finding was petechial lesions. The platelet count was 50,000/mm^3. In the peripheral blood smear, platelets were rare with no clumps. Bone marrow aspiration showed a marked increase of megacaryocytes. Abdominal ultrasonography demonstrated a hypoechoic lesion with a diameter of 8 mm in the parenchyma of the splenic hilum. Bone marrow biopsy was normal, no treatment was given. One week later, thrombocytopenia disappeared spontaneously.

In August 1990 the patient presented with epistaxis and multiple petechiae. He also complained of night sweats, itching and fever. Physical examination revealed multiple bilateral, cervical microlymphadenopathies. On peripheral blood smear no platelet clumps were seen and single platelets were common. The platelet count was 60,000/mm^3. Bone marrow biopsy was normal. Abdominal ultrasonography demonstrated multiple hypoechoic areas in the spleen. Prednisone administration at a daily dose of 40 mg/m^2 was initiated and continued for one month. One month later, the platelet count rose to 300,000/mm^3 and the steroid was stopped. Splenectomy was then performed and histological examination revealed active Hodgkin's disease in the spleen. Intensive investigations revealed no residual disease. The decision was made to follow the patient with no treatment.

Nearly two years later, in February 1992, the patient was readmitted to the hospital with nose bleeding and multiple petechiae all over the body. There was no evidence of Hodgkin's disease. The platelet count was 6,000/mm^3. The prothrombin time and partial-thromboplastin time were normal. Direct Coombs test, antinuclear antibody (ANA) and lupus erythematosus (LE) cell were negative. IgA, IgG and IgM were normal. The throat culture was negative, and there was no recent infection or drug administration history. On the basis of clinical and laboratory findings, a diagnosis of immune thrombocytopenic purpura was made. Prednisolone at a dose of 40 mg/m^2 was initiated. In the first week, the thrombocyte count increased to 60,000/mm^3 and the petechiae disappeared. Steroid therapy was continued for one month, yielding normal thrombocyte counts.

In September 1992 the patient was readmitted to the hospital because of fatigue and weight loss. Multiple paraaortic and parailiac lymph nodes were noted on abdominal ultrasonography. All other laboratory tests were normal. A diagnosis of relapsed Hodgkin's disease was made, and ABVD combination chemotherapy

was started. Six courses of chemotherapy were given with no problem. At his last follow-up in February 1994, the patient was well and free of disease.

Discussion

ITP associated with certain malignant lymphoproliferative diseases, such as chronic lymphocytic leukemia and non-Hodgkin's lymphoma, has been well documented[5]. However, ITP associated with Hodgkin's disease is unsual. As of 1979, 30 patients had been reported in the English literature[6]. In seven cases, the data were not sufficient to characterize ITP syndrome, except that in at least three cases it preceded Hodgkin's disease[7-9]. In the remaining 23 patients, ITP syndrome appeared at the time of or subsequent to the diagnosis of Hodgkin's disease[6]. In a recent report, a 37-year-old woman with treated Hodgkin's disease in remission was admitted to the hospital with ITP and recurrent Hodgkin's disease involving the stomach and paragastric lymph nodes[10]. Two patients with Hodgkin's disease who developed severe ITP with negative platelet antibody studies very soon after splenectomy have also been reported[6].

Our patient experienced three attacks of ITP. In the first two episodes, the patient was believed to have ITP and Hodgkin's disease, apparently limited to the spleen, which was docmented by splenectomy. After a two-year period of remission, the patient again presented with an ITP picture, and after therapy with corticosteroids his thrombocytopenia recovered but Hodgkin's disease reappeared within a period of seven months.

The incidence of ITP in Hodgkin's disease has been reported as two percent in the literature[6]. Between 1972 and 1992, 629 patients were diagnosed with Hodgkin's disease in our department. This case is the only patient with ITP and Hodgkin's disease in our series.

Rudders et al.[1] reported three patients with Hodgkin's disease who exhibited marked thrombocytopenic purpura without marrow replacement by tumor or fibrosis. Initially the patients presented with thrombocytopeniae. After extensive evaluation, they were diagnosed as having Hodgkin's disease with localized splenic involvement. The authors discussed the issue that patients with Hodgkin's disease who peresent with this picture could be easily confused with patients who have true ITP, may have an occult recurrence, and were likely to have involvement of the spleen which could be best managed by splenectomy. In the majority of the reported cases of immune thrombocytopenia complicating Hodgkin's disease or other lymphomas, the occurrence of thrombocytopenia has preceded the appearance or reccurrence of active malignancy. Most authors conclude that an aggressive search for the underlying malignancy must be undertaken[5, 11, 12]. In our patient ITP was present at the time of occurrence of disease in the spleen. The third time, ITP preceded the occurrence of relapse. Thus it can be concluded that ITP in our patient signalled the recurrence of Hodgkin's disease.

Our observation on the association of ITP and Hodgkin's disease is in general agreement with previous reports[1, 12]. It is recommended that patients with a history of Hodgkin's disease undergo a diligent search for active disease when ITP is diagnosed. It should be remembered that ITP may be the only manifestation of active disease and may preceed histologic documentation of lymphoma by months or years[1, 6, 12].

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