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CONTENTS

Discovery of the Rett syndrome gene and its function*

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Rett syndrome (RTT) is a neurodevelopmental disorder which affects approximately 1/15,000 liveborn females. Normal development for the first 6-18 months of life is followed by progressive neurological deterioration, such as loss of communication skills and purposeful hand use, the appearance of stereotypic hand wringing movements, seizures, acquired microcephaly, and mental retardation. The majority of cases are sporadic, but a few families with multiple affected females related through females suggested a genetic defect, in particular, an X-linked dominant mutation that may be lethal in hemizygous males.

Work on the identification of the RTT gene was done in collaboration with the laboratory of Huda Zoghbi at Baylor College of Medicine. First, the RTT gene was assigned to chromosome band Xq28 by exclusion mapping studies of the few available families. Candidate genes in this region were systematically tested for any changes in individuals affected with RTT, and a number of them were excluded. In 1999, our search was successful: we identified mutations in the MECP2 gene[1] MECP2 encodes a ubiquitously expressed abundant chromosomal protein, methyl-CpG-binding protein 2, which binds specifically to methylated DNA and is thought to inhibit the expression of other genes. Loss of MECP2 function in RTT patients could lead to inappropriate expression or over-expression of those genes in specific tissues. Missense or truncating mutations in the MECP2 gene have now been found in over 70 percent of classic RTT patients, as well as in some altypical RTT patients and in a male with congenital encephalopathy[2]. We have developed a molecular diagnostic test to confirm the clinical diagnosis of RTT. Genotype/phenotype correlations, however, are not straight-forward, they need to take into account the modulating influence of X chromosome inactivation mosaicism. Attempts to discover the targets of MeCP2-mediated gene silencing and their role in RTT pathogenesis are under way by using gene expression microarray technology.

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* This is a summary of the paper presented at an Honorary İhsan Doğramacı Conference on 5 June 2000.

Neonatal tetanus in the southeast of Turkey: risk factors, and clinical and prognostic aspects Review of 73 cases, 1990-1999

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SUMMARY: Yaramış A, Taş MA. Neonatal tetanus in the southeast of Turkey: risk factors, and clinical and prognostic aspects-a review of 73 cases, 1990-1999. Turk J Pediatr 2000; 42: 272-274.

Although neonatal tetanus (NT) can be prevented by immunization of expectant mothers and by good hygiene and asepsis during delivery, it is still a common cause of neonatal mortality in developing countries. The objective of this study was to determine indicators in NT. We reviewed the clinical records of 73 neonates admitted to the Pediatric Infectious Diseases Ward of Dicle University Hospital, Diyarbakır, Turkey, with the diagnosis of NT.

Delivery had occurred at home by untrained traditional birth attendants in all cases. None of the mothers had immunization with tetanus toxoid during pregnancy. The median age of infants at presentation was 7.3 days and the mean age at onset of symptoms was 5.6 ± 2.8 days. The overall mortality was found to be 52 percent. Mortality was significantly associated with an incubation period of 4.3 days or less and fever.

The incidence of NT in Turkey is on the decline due to widespread tetanus toxoid use in pregnant women, but in some regions, especially in the so-called rural poor areas, there is still risk of preventable diseases. Hygienic deliveries and immunization of pregnant women are very important for the prevention of NT deaths, and universal prenatal care, including education programs on appropriate perinatal and cord care, can significantly reduce NT incidence and mortality in developing countries.

Key words: neonatal tetanus, prognostic factors, Turkish children.

Neonatal tetanus (NT), which can be effectively prevented through immunization and clean delivery practices, continues to be a serious threat to public health in many parts of the world. Community-based NT mortality surveys helped to determine the true incidence of NT and revealed that, before immunization and clean delivery programs were well established, approximately one million children contracted NT each year, of which 800.000 died. Mortality rates varied markedly by locality, ranging from 0 to 70 NT deaths per 1.000 live births[1].

Unfortunately, NT continues to occur in Turkey, despite the nationwide anti-tetanus immunization policy. In this article, hospital records of 73 cases of NT were evaluated to identify the possible factors affecting prognosis and the clinical features.

Material and Methods

The study population consisted of 73 cases of NT who had been admitted to the Infectious Diseases Ward of Dicle University Hospital, Diyarbakır, Turkey, from February 1990 through May 1999. There were 52 males and 21 females. Untrained traditional birth attendants delivered all patients at home, and none of the mothers had immunization with tetanus toxoid or healthcare services during pregnancy. All of the families were of low socioeconomic level. Most parents were either illiterate or had only attended primary school.

Results

The mean age of infants at admission was 7.3 ± 8.9 days (range 3-5), and the mean incubation period was 5.6 ± 2.8 days. All

families were aware of their baby's poor sucking and excessive crying, but only brought their infant to the hospital when spasms occurred. On admission, sustained tonic contractions and spasms were observed in most patients and diagnosis was based on clinical findings. Razor blade (48%), scissors (30%), and knife (22%) were the instruments used to cut the cord in non-hygienic conditions. Spasticity (78%), lack of sucking (73%), trismus (67%), fever (45%), omphalitis (38%), risus sardonicus (18%) and opisthotonus (12%) were the most common presenting signs and symptoms. High fever was present in 24 of the 38 patients that died and in only 13 of 35 survivors ($p < 0.05$). The mean incubation period was 4.7 ± 2.9 days for the fatal cases and 6.5 ± 1 days for the survivors ($p < 0.05$). The median hospitalization period was 6.3 days for the fatal cases and 27.8 days for the survivors. Conventional treatment consisted of diazepam for sedation, tetanus antitoxin and benzylpenicillin, Subsequent infections were treated using the appropriate antibiotic. All patients were kept in quiet, darkened rooms, and movement was kept to a minimum. The Student's t test was used for statistical analysis.

Discussion

Neonatal tetanus (NT) is a major cause of mortality in developing countries, with over 800,000 deaths estimated to occur annually. It is endemic in 90 countries throughout the world[1]. The incidence of NT in Turkey is on the decline due to widespread tetanus toxoid use in pregnant women, an increasing number of hospital births and improvements in postpartum hygiene[2], but the population of some regions, especially the so-called rural poor, is still at risk for preventable diseases.

In most parts of the world, particularly in developing countries, reported NT cases appear to be more common in males than in females[3]. In our study, most cases (71%) were males. The incubation period, severity of illness, preterm birth, infant's weight, secondary infections, age at onset, fever, risus sardonicus, opisthotonus, and mode of treatment all affect survival in NT[4-8]. In this study, mortality was significantly associated with an incubation period of 4.3 days or less and presence of fever. High fever was present in 24 of the 38 patients that died and in only 13 of the 35 survivors ($p < 0.05$). Age at onset of symptoms was found to be 5.6 ± 2.8 (mean) days, and the fatal cases showed a significantly shorter mean incubation period (4.3 ± 8.6) than the survivors, which is in accordance with results from other studies[4,5,7,9,10]. The case fatality rate of neonatal tetanus ranges between 25-90 percent with therapy, depending on the intensity of supportive care[11]. In this study, this rate was determined to be 52 percent, which substantiates the reports of other centers in our country[2,5,6,12,13].

In the present study, razor blade (48%), scissors (30%), and knife (22%) were the instruments used to cut the cord in non-hygienic conditions. Spasticity (78%), lack of sucking (73%), trismus (67%), fever (45%), omphalitis (38%), risus sardonicus (18%) and opisthotonus (12%) were the most common presenting signs and symptoms. The mean incubation period was 4.7 ± 2.9 days for the fatal cases and 6.5 ± 1 days for the survivors ($p < 0.05$). The median hospitalization period was 6.3 days for the fatal cases and 27.8 days for the survivors. All patients studied were products of unhygienic home deliveries and none of the patients were delivered with a midwife in attendance. Inexperienced persons delivered most of the patients. Demographic characteristics of all patients are shown in Table I.

Table I. Demographic Characteristic of All Patients

Number in group	73
Mean age at admission (range)	7.3 ± 8.9 days (3-25)
Mean incubation period	5.6 ± 2.8 days
Fatal cases	4.7 ± 2.9 days
Survivors	6.5 ± 1 days
Sex (M/F)	51/22
Birth weight	
Mean	3.433 ± 70 g
Range	2.800-4.750 g
Instruments used to cut the cord	
Razor blade (%)	48
Scissors (%)	30
Knife (%)	22
Number of unhygienic home deliveries (5)	100
Prenatal tetanus immunization (%)	0
Most common presenting signs and symptoms	
Spasticity (%)	78
Lack of sucking (%)	73
Trismus (%)	67
Fever (%)	45
Omphalitis (%)	38
Risus sardonicus (%)	18
Opisthotonus (%)	12
Median hospitalization period (days)	
Fatal cases	6.3
Survivors	27.8
Deaths (%)	52

Epidemiological studies in Turkey show that the majority of infants with neonatal tetanus are born to mothers not previously immunized for tetanus, which is in accordance with our present study and studies reported from other countries[2,11]. Tetanus is a totally preventable disease. Risk factors in NT are reduced by the birth attendant washing his/her hands using a cleaned cord-cutting tool, by the education of mothers, promotion of hospital delivery (particularly in rural areas), prenatal tetanus immunization of all pregnant women, and by topical antimicrobials against neonatal tetanus applied to the umbilical cord wound during the first several days of life[14-16].

The prevention of NT is important not only because of the high mortality rate associated with the disease, but also because sequelae in survivors are not uncommon[17]. The World Health Organization has adopted the goal of eliminating NT worldwide, and a major strategy for its prevention is the administration of at least two properly spaced doses of tetanus toxoid (TT) to women of childbearing age in high-risk areas to passively protect their newborns at birth[18].

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Reactogenicity and immunogicity of a new measles-mumps-rubella vaccine containing RIT 4385 mumps virus strain in healthy Turkish children

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SUMMARY: Kanra G, Ceyhan M, Özmert E. Reactogenicity and immunogenicity of a new measles-mumps-rubella vaccine containing RIT 4385 mumps virus strain in healthy Turkish children. Turk J Pediatr 2000; 42: 275-277.

A total of 44 children aged between 15-18 months were randomly vaccinated either with a new measles-mumps-rubella (MMR) vaccine (Priorix®, SmithKline Beecham) or a commercially available MMR vaccine (MMR-II®, Merck) to compare the reactogenicity and immunogenicity. No local symptoms or fever was reported. Seroconversion rates of the study vaccine were 100, 95 and 100 percent for measles, mumps and rubella, respectively. The seroconversion rates for the control vaccine were 100, 94.7 and 95.5 percent, respectively. The geometric mean titers (GMT's) for the study and control groups were 1695, 95, 58; and 2198, 1183 and 47; respectively.

In conclusion, the new MMR vaccine containing RIT 4385 mumps strain derived from the Jeryl Lynn strain was shown to be immunogenic and safe in healthy Turkish children. Further post-marketing surveillance should be conducted.

Key words: measles, mumps, rubella, immunization, Jeryl Lynn strain.

Vaccination is the most effective method for prevention of mumps[1]. The Jeryl Lynn and Urabe Am 9 mumps virus strains have been most commonly used for the production of the live attenuated mumps vaccine. Both have been shown to be immunogenic and to protect against mumps infection, although the Jerly Lynn strain has seemed less immunogenic[2,3]. Cases of vaccine-associated meningitis have been reported, especially with the Urabe strain[4,5].

A new mumps strain, indistinguishable from the Jeryl Lynn strain in terms of post-vaccinal meningitis, was combined with Schwarz measles and rubella 27/3 strains in a new measles-mumps-rubella (MMR) vaccination (Priorix®, SmithKline Beecham). The presented study was conducted to compare the reactogenicity and immunogenicity of the new measles-mumps-rubella vaccine with the commercially available MMR-II (Merck) vaccine in healthy Turkish children.

Material and Methods

This single blind, randomized, controlled study was conducted between 1 December 1993-19 January 1994 at the Etimesgut Health Center. A total of 44 healthy children between 15-18 months of age were enrolled and randomly assigned to one of the two vaccine groups. Written informed consent was obtained from all parents. Children with any of the following were excluded from the study: clear history of clinical measles infection or vaccination against measles, significant exposure to mumps within the previous four weeks, administration of immunoglobulin during the last three months, history of allergic reactions to any previous vaccination, neomycin and/or egg allergy, history of seizure or encephalopathy, episode of acute febrile illness at the time of vaccination, any continued chronic drug therapy, administration of other parenteral vaccines during the study or within the previous four weeks, or simultaneous participation in any other study.

Monodose vials of vaccines were coded according to a randomization list. Children received either the new MMR vaccine [SKB, Lot MJR111D42 containing per dose a mean titer of $10^{3.8}$ 50% cell-culture infectious dose

($CCID_{50}$) of Schwarz measles strain, $10^{4.4}$ $CCID_{50}$ of RIT 4385 mumps strain and $10^{4.1}$ $CCID_{50}$ of RA 27/3 rubella strain) as study vaccine or MMRI-II (Merck Sharp Dohme Lot 80391OU containing per dose $\geq 10^3$ $CCID_{50}$ of Edmonston Enders measles strain, $\geq 10^{3.7}$ $CCID_{50}$ of Jeryl Lynn mumps strain and $\geq 10^{3.0}$ $CCID_{50}$ of RA 27/3 rubella strain] as the control vaccine. Each vaccine was reconstituted with an individual ampule of water for injection, and a 0.5 ml dose was administered subcutaneously in the left upper arm.

This study was conducted according to the Declaration of Helsinki and Good Clinical Practice. On day 0 of the study all previously screened subjects underwent a complete physical examination, including palpation of the parotid gland and recording of rectal temperature. A prevaccination blood sample was collected and a dose of vaccine injected. At 15 and 30 minutes after injection, swelling or pain at the injection site, or any other symptom, was recorded on a diary card.

On days 7, 14, 21 and 28 postvaccination, a nurse visited the child at home to evaluate the presence of any adverse reactions, especially parotid gland swelling. On day 42 a complete physical examination was performed and a post-vaccination blood sample was collected.

Separated pre- and post-vaccination serum samples were stored at -20 °C until they were titrated at SmithKline Beecham Biological Laboratory in Belgium. Antibody titers against measles, mumps and rubella were determined by commercial kits: Enzygost anti-measles virus/IgG (Behringwerke AG, Marburg, Germany) and expressed as mIU/ml; Enzygost anti-parotitis virus/IgG (Behring) and expressed as U/ml; and Enzygost anti-rubella virus/IgG (Behring) and expressed as U/ml, respectively.

Serconversion was defined as the appearance of a detectable level of antibodies in the serum of subjects who were seronegative before vaccination: for measles < 180 to ≥ 180 mIU/ml, mumps < 230 to ≥ 230 U/ml and for rubella < 4 to ≥ 4 IU/ml[6,7] A booster response was defined as a four-fold or greater increase of a previously positive titer. Subjects with parotid/salivary gland enlargement were examined as soon as possible by the investigator.

Statistical analyses were performed by SAS computer programs. Geometric mean titers (GMT) of antibodies against mumps, measles and rubella and their 95% confidence intervals were calculated in all pre- and post-vaccination sera. GMTs were calculated by taking the anti-log of the mean of the log transformation of non-zero titers. The seroconversion rate in initially seronegative subjects and the percentage of initially seropositive subjects demonstrating a booster response against measles, mumps and rubella on day 42 after vaccination were determined. The seroconversion rates in the two groups were compared using chi-square test.

Results

All subjects were included in the analysis of reactogenicity and immunogenicity. Mean age of subjects was 16.3 ± 0.84 months in the study group and 16.2 ± 0.81 months in the control group. The male to female ratio was 1:0.69 in both groups.

Safety and Reactogenicity

Neither fever nor local symptoms were reported in any case. Parotid gland swelling was reported in one case in the study group on the first day postvaccination. A viral study was not performed but the swelling occurred following exposure to natural mumps infection in the sibling.

There were no unsolicited signs or symptoms reported during the 42 day follow-up period nor any serious adverse events.

Immunogenicity

All subjects were included in the analysis. The seroconversion rate and the GMT values of each group are shown in Table I.

Table I. Serconversion* Rates and GMTs of the Two Vaccine Groups for Measles, Mumps and Rubella

Antibody	Priorix group	MMR-II group
Anti-measles		
Sreconversion rate (%)	100	100
$GMT_{[95\% CI]}$	$1695_{[1163-2468]}$	$2198_{[1532-3153]}$
Anti-mumps		
Seroconversion rate (%)	95	94.7
$GMT_{[95\% CI]}$	$1359_{[934-1978]}$	$1183_{[786-1781]}$
Anti-rubella		
Seroconversion rate (%)	100	95.5
$GMT_{[95\% CI]}$	$58_{[42-80]}$	$47_{[33-69]}$

* Seroconversion was defined as either appearance of antibodies (i.e.titer ≥ cut-off) or in prevaccination seropositive subjects as a four-fold or greater rise in the prevaccination titer. $p < 0.05$ for seroconversion rate of all three antibodies.

GMT: geometric mean titer; 95% CI: 95% confidence interval.

Discussion

This study indicates that Priorix®, containing the new RIT 4385 mumps strain, is safe and immunogenic. No difference could be found between the groups. In eight other recent single blind, randomized, controlled studies conducted in Chile, the Czech Republic, Germany, Lithuania, Switzerland and Taiwan, where 4.702 children were vaccinated either with Priorix or MMR-II, results were similar to those of our study[6,7]. In those studies, local symptoms were reported less frequently after Priorix as compared to after MMR-II. General symptoms and all other events were similar in both groups. The GMTs for all three antibodies were higher for MMR-II, but the clinical significance was not determined. Aseptic meningitis is a rare complication, and was not detected in any of the vaccinees.

The new SmithKline Beecham Biologicals MMR vaccine Priorix® was well tolerated; no local reactions, fever or serious adverse event was reported. The seroconversion rates were similar. Although the study sample was small, still this study points to the safe alternative use of the new vaccine in Turkish children. Further safety studies should be conducted to determine rare events post-marketing.

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Carnitinuria in rickets due to vitamin D deficiency

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SUMMARY: Dursun A, Aliefendioğlu D, Özkan B, Coşkun T. Carnitiuria in rickets due to vitamin D deficiency. Turk J Pediatr 2000; 42: 278-280.

In this study, we measured the serum-urine total carnitine levels and PTH levels before and after treatment in 18 patients with nutritional rickets. The urine and blood samples were taken on the first (pretreatment) and the 15th day of the study (post-treatment). The total carnitine levels of serum and urine somples, serum PTH and serum-urine creatinine concentrations were determined. We found that the levels of carnitine excreted in the urine on the first (pre-treatment) and on the 15th day (post-treatment) were higher than the reference levels. Decrease in carnitine excretion on the 15th day seemed to be correlated with decrease in aminoaciduria at that time. The study showed a significant correlation between urinary carnitine excretion and serum PTH levels. In our study we did not find any significant difference between the serum total carnitine levels on the first (pre-treatment) and the 15th day (post-treatment), and both values were lower than the reference values for the same age group. We observed that the total serum carnitine levels did not change on the 15th day of the post-treatment period in spite of a decrease in urinary carnitine excretion. The results of the present study indicated that carnitine metabolism is disturbed in nutritional rickets. Further evaluation of rickets cases and new studies will probably lead to a better understanding of carnitine metabolism in nutritional rickets.

Key words: carnitine, nutritional rickets, carnitinuria, hypocarnitinemia, cardiomyopathy.

Rickets due to vitamin D deficiency is often encountered during the period of rapid growth between three months and two years of age. In recent years rickets cases due to vitamin D deficiency with accompanying cardiomyopathy have been reported[1-3]. The exact mechanism of cardiomyopathy in these cases has not been completely understood although it has been observed that cardiomyopathy resolves completely after vitamin D and calcium replacement therapy. Carnitine, the deficiency of which causes cardiomyopathy, has an essential role in the oxidation of long chain fatty acids. It has been shown that Fanconi's syndrome is one of the causes of secondary carnitine deficiency in which the amount of carnitine excreted correlates with the severity of aminoaciduria[4,5].

The fact that aminoaciduria is also one of the main laboratory findings in rickets due to vitamin D deficiency led us to postulate that cardiomyopathy in rickets is related to increased carnitine excretion, with accompanying aminoaciduria. In this study, we aimed to clarify the carnitine status in rickets cases caused by vitamin D deficiency. For this reason, serum and urine total carnitine levels before and after treatment with vitamin D and calcium were measured.

Material and Methods

A total of 18 patients aged between four and 10 months diagnosed as having nutritional rickets according to clinical, biochemical and radiological findings were included in this study. Reasons for secondary carnitine deficiency such as renal dysfunction, hepatic problems and metabolic disorders which could cause primary carnitine deficiency were excluded. Nutritional status of the patients was evaluated according to the Gomez classification[6]. All the patients were given calcium lactate (75 mg/kg/day as elementary calcium for 10 days) and vitamin D

(300,000 units i.m. as a single dose) for treatment. Urine and blood samples were taken on the first (pre-treatment) and 15th day of the study (post-treatment). The samples were stored at -20 °C until they were assayed. Total carnitine levels in serum and urine were measured using a modified radio-enzymatic assay[7]. The serum PTH level was measured with the chemiluminescence method. Serum and urine creatinine concentrations were determined using an automated Jaffe method. The presence of aminoaciduria was evaluated by paper chromatography. Cardiomyopathy was investigated in only eight of the 16 patients before treatment by echocardiography. Informed consent was obtained from the parents before the study. Mean pre-treatment and post-treatment serum and urine carnitine levels were compared with reference values by the unpaired t-test; the relation of these values with serum PTH levels and other biochemical parameters was evaluated by linear regression analysis.

Results

The study showed that there was no significant difference between serum total carnitine levels measured on the first (pre-treatment) and the 15th day of the study (post-treatment). Both values were lower than the reference values for the same age group. The levels of carnitine excreted in the urine on the first (pre-treatment) and on the 15th day (post-treatment) were higher than the reference levels (Table I)[8]. A significant correlation between the amount of urinary carnitine excreted and serum PTH levels was found ($p = 0.003$). No findings of cardiomyopathy were detected in the eight patients who were examined by echocardiography. We detected a decrease in aminoaciduria on the 15th day of the treatment in all patients. Eight of the 16 patients were suffering from first-degree malnutrition with a body weight ranging from 76 to 90 percent of the standard; the remaining patients were of normal weight.

Discussion

Carnitine deficiency may develop due to a primary defect (e.g., carnitine transport disorders, carnitine palmitoyltransferase I and II deficiency) or to a secondary cause (e.g., Fanconi's syndrome, organic acidemias, hemodialysis, malnutrition). A relationship between the degree of aminoaciduria and that of carnitinuria in patients with Fanconi's syndrome has been reported, and it was proposed that the similarity between the mass and electrical charge of carnitine and amino acids could explain this relationship[4]. We found that the levels of carnitine excreted in the urine both on the first (pre-treatment) and on the 15th day (post-treatment) were higher than the reference levels; a significant difference between the pre- and post-treatment urine total carnitine level was also found ($p < 0.001$) (Table I). Decrease in carnitine excretion on the 15th day correlated with a decrease in aminoaciduria.

Table I. The Total Serum and Urine Carnitine, Serum Parathyroid Hormone (PTH), Serum Calcium (Ca), Serum Phosphorus (P) and Serum Alkaline Phosphatase (AP) Levels of the Patients on the First (Pre-Treatment) and on the 15th Day (Post-Treatment) of the Treatment

	1st day	15st day	Normal values	P value
Urinary carnitine (µmol/g Cr)	n = 18 370 ± 160.9 (193.9-799.5)	n = 17 207.2 ± 98.9 (86.5-460.8)	146.6 ± 91.3[6]	0.001
Serum carnitine (µmol/L)	n = 18 24.2 ± 13.3 (6.9-55.5)	n = 16 26.9 ± 12.3 (11.3-52.4)	44.5 ± 11.3[6]	NS
PTH (ng/ml)	n = 15 366.7 ± 111.5 0	n = 14 111.9 ± 44.1 0	0.2-0.7	0.04
Ca (mg/dl)	n = 18 6.7 ± 1.1 (4-8.8)	n = 17 8.9 ± 0.5 (8-10.1)	8.8-10.8	0.000
P (mg/dl)	n = 18 4.1 ± 1.4 (2.1-7.0)	n = 17 5.3 ± 0.7 (4.5-7.1)	4-7	0.003
AP (IU/L)	n = 18 987.0 ± 381.3 (618-2191)	n = 16 606.8 ± 166.5 (294-847)	200-420	0.001

* expressed as: mean ± SD, NS: not significant, Cr: creatinine.

We found a significant correlation between urinary carnitine excretion and serum PTH levels ($p = 0.003$). Previous studies have indicated that aminoaciduria in vitamin D deficiency is not related with elevated levels of PTH, but with calcium status and dietary intake of phosphate[9-11]. The obvious correlation between urinary carnitine excretion and the serum PTH level led us to hypothesize that PTH may play a role in renal carnitine loss. However, further studies should be carried out for a detailed understanding of the PTH effect on carnitinuria in nutritional rickets cases.

In this study, no significant difference between the pre- and post-treatment serum total carnitine levels was found. Both values were lower than the reference values for the same age group (Table I). Although carnitine can be synthesized by the human body, most of the daily requirement has to be gained from food. Therefore, an inadequate supply can easily lead to carnitine deficiency. Malnutrition is known to be one of the causes of low serum carnitine levels. However, we believe that carnitinuria might be an important contributing factor for the low serum carnitine level in our patients as well as malnutrition.

Previous studies have indicated that total serum carnitine level is closely related with urinary carnitine excretion and may not accurately reflect the tissue carnitine level[12]. Although the tissue carnitine level was not measured in our study, we would expect low tissue carnitine levels due to malnutrition and carnitinuria in our cases. We observed that the serum total carnitine levels did not change on the 15th day of the post-treatment period, but decreased significantly in urinary carnitine excretion in the same period. Therefore, we postulated that even though more carnitine was supplied to the blood due to decreased carnitine excretion, it was immediately withdrawn from circulation by the carnitine-depleted tissues, thereby resulting in a pre-treatment serum carnitine level similar to that seen in the post-treatment period. In conclusion, it can be expected that the serum total carnitine levels would return to normal as urinary carnitine loss decreased and malnutrition was cured completely.

In recent years, rickets cases accompanied by cardiomyopathy have been published under the heading of "rickets cardiomyopathy" in which the pathogenesis is not known[8-12]. We detected neither clinical nor echocardiographic findings of cardiomyopathy in eight rickets patients studied. The results of the present study indicate that carnitine metabolism is disturbed in nutritional rickets. However, we failed to establish a "cause and result" relationship between cardiomyopathy and disturbed carnitine metabolism in nutritional rickets. Further evaluation of rickets cases and new studies will probably lead to a better understanding of carnitine metabolism in nutritional rickets.

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The relationship between osteocalcin levels and sexual stages of puberty in male children

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SUMMARY: Şen TA, Derman O, Kınık E. The relationship between osteocalcin levels and sexual stages of puberty in male children. Turk J Pediatr 2000; 42: 281-285.

Osteocalcin is a specific and reliable marker which increases with rapid bone turnover and gives data about bone metabolism. The pubertal growth spurt is also known as a good example of rapid bone turnover.

The aim of this study was to determine whether osteocalcin is a useful marker for the pubertal growth spurt period. In this study, osteocalcin levels in male adolescents were examined in relation to their sexual maturation stage and age. The osteocalcin levels and alkaline phosphatase levels were compared during the pubertal growth spurt. Serum osteocalcin and alkaline phosphatase levels were evaluated in 100 eligible healthy male children and adolescents (aged 10 to 17 years). Five groups (n: 20 each) of children and adolescents were formed according to their sexual maturation stages. Finally, the subjects were divided into three main groups in relation to the pubertal growth spurt and sexual maturation stages.

Data were evaluated and compared among these three groups:

First group = Stage 1 (prepuberty) + Stage 2 (early puberty) consisted of 40 (20+20) children and adolescents. Their mean osteocalcin value was 17.2 ± 6.3 ng/ml and alkaline phosphatase 573.8 ± 143.9 IU/L.

Second group: Stage 3 + Stage 4 consisted of 40 (20+20) children and adolescents. These groups were known as the pubertal growth spurt groups. Their mean osteocalcin value was 29.4 ± 10.6 ng/ml and alkaline phosphatase 728.4 ± 233.9 IU/L.

Third group: In this group, there were 20 children and adolescents who reached Stage 5 of sexual maturation and whose pubertal growth spurt was slowing. Their mean osteocalcin value was 15.3 ± 5.8 ng/ml and alkaline phosphatase 435.8 ± 184.8 IU/L.

During the pubertal growth spurt, there is a relationship between bone remodelling and increasing osteocalcin and alkaline phosphatase levels. When sexual maturation reaches Stage 4 at 14 years old, osteocalcin and alkaline phosphatase levels make a peak, associated with the rapid growth in height. As sexual maturation reaches Stage 5, osteocalcin and alkaline phosphatase levels gradually decrease with growth maturation and their levels decline to the level of adults at the completion of this period.

Our study showed that osteocalcin and alkaline phosphatase levels can be used as markers for evaluation of the growth spurt period.

Key words: osteocalcin, pubertal growth, male children.

During bone remodelling, osteocalcin is produced by osteoblasts and its level increases during the events characterized by yrapid bone turnover[1-4]. Osteocalcin is known as a gamma carboxy glutamic acid protein binding calcium. It is rich in bone dentin and other mineralized tissues. Although serum alkaline phosphatase activities and urine hydroxyproline levels are routinely used for evaluating bone metabolism, they are affected by other nonosseous metabolic

events. They are not reliable markers in cases of systemic disorders. Osteocalcin is a bone matrix protein which is specific for bone metabolism and it is not influenced by metabolic bone disorders. In adolescents, the pubertal growth spurt is accompanied very closely by sexual maturation[1,4,5]. During childhood, the rate of gain in height is approximately 5 cm per year; it shows a slow decrease just before the puberty period and after that rapidly increases. It is known as growth blowing or the growth spurt of adolescents[6]. During this period, adolescents gain 15 percent of their adult height, 40 percent of total body mineralization 50 percent of weight and 54 percent of body muscular mass. During the growth spurt, the increase in bone turnover correlates with osteocalcin and alkaline phosphatase levels. There are some diseases which influence bone turnover. For example, osteocalcin levels are increased in primary hyperparathyroidism, hyperthyroidism, with gonadotropin releasing hormone, in chronic renal disease, Paget's disease, rickets, malignant disease, osteoporosis and especially under hemodialysis, and are decreased in liver disease, with estrogen, and in pregnancy, hypothyroidism and hypoparathyroidism. Three vitamins (K, D and C) play an important role in this pathway. Vitamin K plays a major role in glutamic acid production. Vitamin C plays a role in conversion of proline to hydroxyproline, and vitamin D regulates osteocalcin gene transcription[7-8]. Serum osteocalcin plays an important role in the growth of the skeleton correlating with insulin-like growth factor 1 (IGF-1), and it is shown that osteocalcin synthesis in the rat is stimulated by IGF-1. Osteocalcin levels are in correlation with IGF-1 levels[9-10].

The aim of the study was to examine osteocalcin levels in relation with the growth spurt.

Material and Methods

One hundred healthy male children aged between 10 and 17 years who were admitted to the adolescent outpatient clinic were included in the study.

They were chosen according to the following criteria:

1. Absence of growth retardation.
2. No restriction of their normal (physical) activity.
3. Skeletal age appropriate for chronological age.
4. Absence of systemic disease.
5. No medication.

Greulich and Pyle's radiographic atlas of skeletal development of the hand and wrist was used for determination of skeletal ages. Alkaline phosphatase levels were measured using spectrophotometric method measuring products of the alkaline phosphatase enzyme and p-nitrophenyl phosphatase reaction. All results were expressed in international unit/litre (IU/L) (BM/Hitochi 917 Systems Pack) All osteocalcin samples were taken after fasting between 8 cm and 9 cm and preserved 30 minutes at room temperature before centrifuge. Osteocalcin levels were measured using ELISA kits (Novo Calcin Metro Biosystems) and results were expressed as ng/ml (nanogram/milliliter). J.M. Tanner's classification[11] was used for sexual maturation staging in the male children. Testicular volumes were evaluated by Proder's orchidometer. Children were divided into five groups according to their sexual maturation stages. Each group consisted of 20 children. At first, clinical and laboratory findings were collected and evaluated in these five groups. Later, some groups were combined according to sexual maturation stages and findings; three groups were formed. Statistical analyses were performed using one way variance analysis ANOVA + Tukey HSD test to compare the osteocalcin levels with the alkaline phosphatase activities in each group. Spearmen correlation test was used to show the relationship between osteocalcin levels and alkaline phosphatase activities.

Results

According to the sexual maturation stages, all data were evaluated and compared in three groups:

Group 1:
Stage 1 (prepuberty) + Stage 2 (early puberty);

Group 2:
Stage 3 + Stage 4 (pubertal growth spurt); and

Group 3:
Stage 5 (late puberty).

The peak levels of osteocalcin and alkaline phosphatase that were determined in Group 2 are given in Table I. Mean alkaline phosphatase levels in Group 2 were significantly higher than in Groups 1 and 3. (728.4 IU/L, 573.8 IU/L, 435.7 IU/L, respectively, $p < 0.05$). Mean osteocalcin level in Group 2 was significantly higher than in Groups 1 and 3 (29.4 ng/ml, 17.2 ng/ml, 15.3 ng/ml, respectively, $P < 0.05$).

There was a significant difference between Groups 1 and 2 and also between Groups 2 and 3, but there was no significant difference between Groups 1 and 3. There was a positive correlation between osteocalcin and alkaline phosphatase levels (Fig. 1), and between osteocalcin levels and sexual maturation stages. Mean osteocalcin levels and sexual maturation stages. Mean osteocalcin levels were highest in the fourth stage (36.3 ng/ml) versus the others: stage 1 18.1 ng/ml; stage 2 16.4 ng/ml; stage 3 22.6 ng/ml; stage 5 15.0 ng/ml, $p < 0.05$. Osteocalcin in adolescents began to rise at about 12 years of age (stage 3), peaked about two years later (stage 4) and then declined toward adult levels at 15 to 16 years of age (stage 5) (Fig. 2).

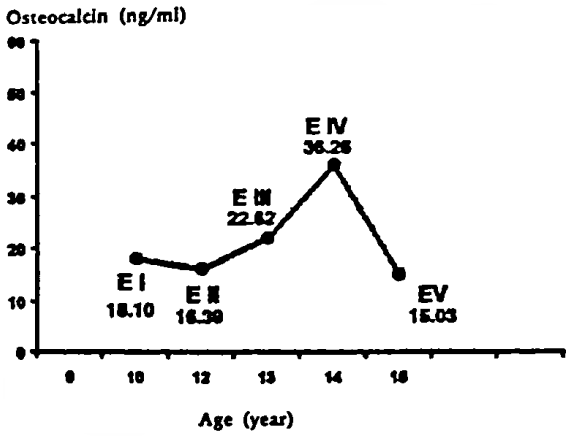

Fig. 2. The changes in mean osteocalcin levels of sexual stages by ages ($p < 0.05$).

Table I. Evaluation of All Results in Relation to Sexual Growth Stage

Variables	Mean values	Standard deviation	Standard error	Number of cases
Group 1 (Sexual Growth Stages 1 and 2)				
Osteocalcin	17.2	6.3	1.0	40
Alkaline phosphatase	573.8	143.9	22.8	40
Testicular volume	4.1	1.1	0.2	40
Skeletal age	135.1	10.0	1.6	40
Chronological age	136.9	10.1	1.6	40
Group 2 (Sexual Growth Stages 3 and 4)				
Osteocalcin	29.4	10.6	1.7	40
Alkaline phosphatase	728.4	233.2	36.9	40
Testicular volume	11.6	4.1	0.6	40
Skeletal age	162.0	10.9	1.7	40
Chronological age	162.6	10.6	1.7	40
Group 3 (Sexual Growth Stage 5)				
Osteocalcin	15.3	5.8	1.3	20
Alkaline	435.7	184.8	41.3	20
Testicular volume	18.2	3.4	0.8	20
Skeletal age	186.3	10.7	2.4	20
Chronological age	186.4	9.4	2.1	20

Osteocalcin (ng/ml); alkaline phosphatase (IU/L); testicular volume (ml); skeletal age and chronological age (month).

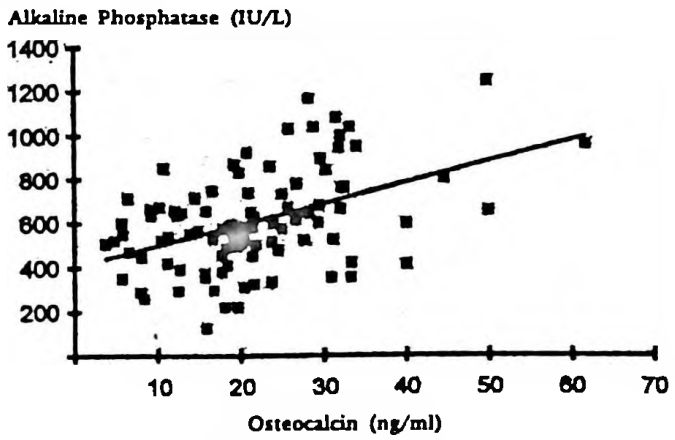

Fig. 1. The relationship between osteocalcin and alkaline phosphatase levels ($r: 0.4187$, $p < 0.001$).

Discussion

The pubertal growth spurt is one of the most prominent signs of puberty. It is characterized by a sharp acceleration in linear growth velocity, a peak period of growth (peak height velocity) and a sharp decline in the yearly growth increment. The growth spurt begins in male adolescents at approximately 12 years of age. The increase in height reaches peak levels at 14 years of age, then declines gradually to the end of puberty. Serum osteocalcin levels parallel physical maturation periods, especially during the first year of life and during the pubertal growth spurt. In neonates, osteocalcin levels

reach 40-60 ng/ml at the end of the first month. These levels are maintained between six and 12 months of age. After the first year, the mean osteocalcin level is 18 ng/ml. It then reaches 25-39 ng/ml during puberty, and declines to adult levels between 17 and 20 years of age in male children. Osteocalcin is the lowest in the morning, gradually increases in the afternoon and reaches its highest level at night. This diurnal rhythm is not influenced by sex, age or season.

Osteocalcin peak levels in the literature reach Stage 4 at 14 years and their relation to the growth spurt is very close. Magnusson et al.[12] reported that osteocalcin levels in male children reached the highest level at 14 years. In other words, osteocalcin achieved its peak level at the peak of height velocity. After 15-16 years of age, osteocalcin levels declined to adult levels with slow growth rate. Magnusson classified cases according to sexual stages: Group 1 = Stage 1 Prepuberty, Group 2 = Stage 2 Early puberty + Stage 3 Pubertal Growth Spurt, Group 3 = Stage 4 Pubertal Growth Spurt + Stage 5 Late Puberty. He did not find any significant correlation of osteocalcin levels and pubertal stage. In that study, the beginning of the pubertal growth spurt (Stage 2) and the decline of the pubertal growth rate (Stage 5) were joined with the pubertal growth spurt periods (Stages 3 and 4), so osteocalcin levels decreased and the expected difference was not found between the groups. This may be due to their having combined the periods of pubertal growth spurt with the beginning and declining growth rate periods, which may have masked any significant changes. Indeed, their study was to have classified sexual stages of puberty as Group 1 = Stage 1 Prepuberty + Stage 2 Early Puberty, Group 2 = Stage 3 + Stage 4 Pubertal Growth Spurt, and Group 3 = Stage 5 Late Puberty, which may explain the lack of significant differences in osteocalcin levels between stages. In the literature, studies of osteocalcin use age, instead of sexual maturation stage, as a criteria, but age does not show correct results due to the relation of different sexual stages. Using the sexual maturation stage was much more suitable than the chronological age for these other studies[5]. Osteocalcin peak levels reached Stages 3 and 4 at 14 years of age[13,14,15]. A relationship between osteocalcin levels and the growth spurt was shown in some studies[16]. A correlation between osteocalcin levels and alkaline phosphatase activities has also been reported in childhood[17]. It is now well established that there is a link between alkaline phosphatase activity and sexual maturity[18-22], which was also confirmed by our results. In conclusion, osteocalcin levels increase with the pubertal growth spurt as do alkaline phosphatase levels. They reach a peak at 14 years of age at Stages 3 and 4, then decrease to the level of adults. There is a very close correlation between the growth spurt and osteocalcin levels. According to our findings, the follow up of osteocalcin levels in relation to sexual maturation stages could be a new method to determine the phase of the pubertal growth spurt. An increase or decrease in osteocalcin levels on consecutive measurements may indicate the child's entering the accelerated or decelerated stages of the growth spurt, respectively. We emphasize that the follow up of adolescent growth is made by the determination of the sexual maturation stage, and not by age. Osteocalcin is a highly specific, reliable and useful marker for evaluation of the growth spurt and is not influenced by nonosseous disorders.

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Analysis of 2017 Holter records in pediatric patients

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SUMMARY: Ayabakan C, Özer S, Çeliker A, Özme Ş. Analysis of 2017 Holter records in pediatric patients. Turk J Pediatr 2000; 42: 286-293.

Holter monitoring (HM) is widely used in arrhythmic disorders of adult patients; however, studies in the pediatric age group are limited. This study aims to determine the value of HM in diagnosis and treatment of disorders related to arrhythmias in pediatric patients.

We examined 2,017 Holter records of 1,500 children who applied to our institution between November 1994 and October 1998. The age ranged from 0-24 years (52% male, 48% female). The indications for HM were screening for arrhythmic symptoms (palpitation, chest pain, syncope) in 67 percent, monitoring dysrhythmic therapy in 17 percent, postoperative control in five percent, and pacemaker control in four percent. Palpitation is the leading presenting symptom, with more frequent findings of supraventricular extrasystole (SVE), supraventricular tachycardia (SVT), ventricular extrasystole (VE) and complete heart block (CHB) whem compared to other symptoms. Only 5.3 percent of the patients had arrhythmic symptoms during monitoring and asymptomatic patients had more frequent arrhythmias. SVT, VE, and CHB are more frequent findings in the abnormal heart with previous cardiac operations.

The diagnostic yield is low with arrhythmic symptoms in the pediatric age group; however, HM enables cumulative evaluation of heart rhythm and rhythm variability, which is important in diagnosing silent arrhythmias in high risk groups (abnormal heart, postoperative heart).

Key words: childhood arrhythmia, Holter monitoring.

In 1961, Holter[1] used a portable electrocardiorecorder that could record electrocardiogram (ECG) continuously for 10 hours. Since then, ambulatory ECG monitoring has been widely used for many clinical purposes[2,3]. Improvement of the recording quality over the next 10 years, and the diminished size and weight of the recording devices rendered the technique feasible for the pediatric age group as well[3].

Holter monitoring (HM) is one of the most specific and sensitive tools in diagnosis and follow-up of arrhythmias[4]. There are numerous studies on HM concerning adult patients; however, studies in the pediatric age group are limited. Rhythm and conduction disturbances differ in quality and quantity in different age groups. Clinical utility of HM may differ in pediatric and adult patients. We examined the Holter data of our department to investigate the arrhythmia spectrum of the pediatric patients and to determine the value of HM in diagnosis and treatment of these dysrhythmic disorders.

Material and Methods

In this study, 1,500 consecutive pediatric patients with 24-hour Holter records who applied to our institution between November 1994 and October 1998 are included; 2,017 Holter records of these 1,500 patients are reviewed. Del-Mar Avionics™ "Model 459, 3 channel cardiocarder" was used for 24-hour ambulatory ECG recording. The results were interpreted by two experienced pediatric cardiologists, using a computerized analysis program developed by Del-Mar Avionics Holter Systems (Del-Mar Avionics™ Irvine, California, USA). The presenting complaint, physical examination, chest x-ray, ECG, and echocardiographic findings were also studied. Any cardiac catheterization or surgery was especially noted, if present. The patients were

classified into subgroups according to age (newborn-infant: < 2 years; preschool age: ≥ 2 and < 5 years; school age: ≥ 5 and < 10 years; adolescent: ≥ 10 years), and cardiac pathology (patients with normal heart; preoperative congenital heart defect; postoperative congenital heart defect).

The patients or the parents noted any symptoms during HM, specifying in a diary the time and the activity accompanying the symptom.

Computerized statistical analysis program, "SPSS for Windows, version 6" was used for the non-parametric frequency analysis and chi-square tests.

Results

Fifty-two percent of the patients were male, 48 percent female. The age ranged from 0-24 years (mean = 9.96 years, median = 10 years). Only 18 records belonged to patients older than 18 years old (0.09%). The distribution of the patients according to age groups is given in Figure 1. Holter recording time ranged from 8-24 hours (mean = 22.7 hours, standard deviation SD = 2.6).

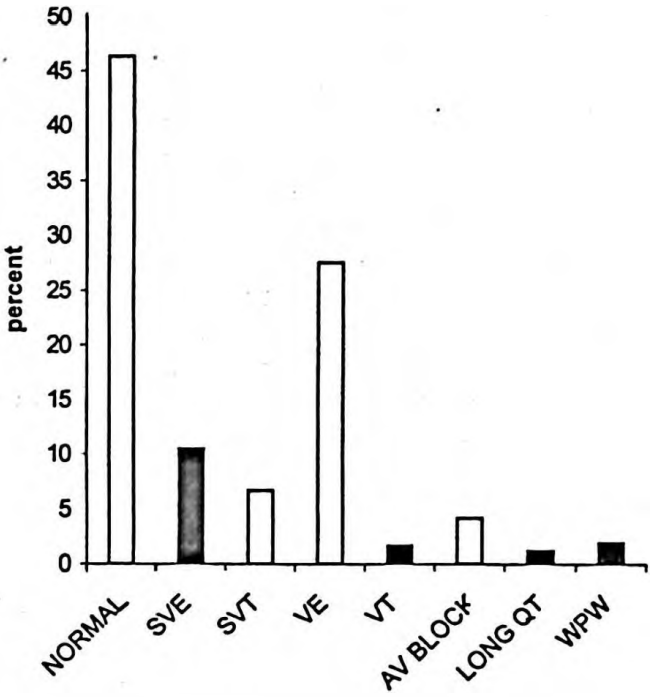

Fig. 2. Results of Holter records.
SVE: supraventricular extrasystole; SVT: supraventricular tachycardia; VE: ventricular extrasystole; VT: ventricular tachycardia; WPW: Wolff-Parkinson-White syndrome.

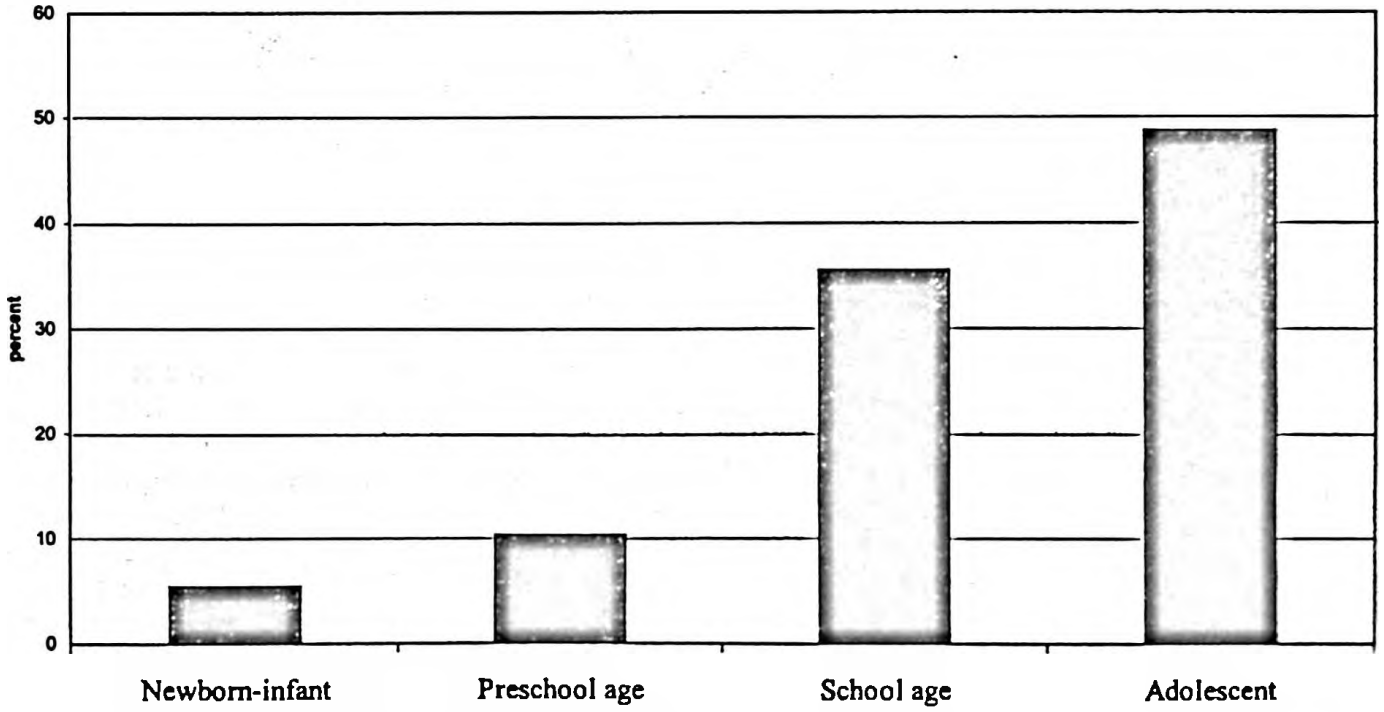

Fig. 1. Distribution of patients according to age groups.

Nearly half of the records were normal (45%). Ventricular extrasystole (VE) was the most frequent arrhythmia (28%), followed by supraventricular extrasystole (SVE) (11%), supraventricular tachycardia (SVT) (7%), and complete heart block (CHB) (4%) in decreasing frequency (Fig. 2).

Presenting Complaint/Clinical Indication for Holter Monitoring

Palpitation, chest pain, and syncope were the symptoms considered as major clinical indications for HM. Other indications included follow-up for pacemaker (PM) functions, known arrhythmias, or cardiac operation. Palpitation

was the leading single presenting complaint in our study group (22%), followed by syncope (10%) and chest pain (9%) (Fig. 3). Girls (50.1%) complained of palpitation more than boys (41.9%) ($p < 0.01$). Frequencies of other complaints were similar in both sexes ($p > 0.05$). More than one complaint refers to having at least two of three main complaints, namely chest pain, palpitation, and syncope. Palpitation was the most frequent postoperative symptom as well (22.1%). Among the postoperative patients, 33.3 percent were asymptomatic after cardiac operation.

Table I. Holter Findings and Associated Presenting Symptom

Holter findings	Associated presenting symptom
SVE	Palpitation
SVT	Palpitation
VE	Palpitation
Complete Heart Block	Palpitation
Long QT Syndrome	Syncope
WPW Syndrome	Not associated
VT	Not associated

SVE : supraventricular extrasystole.
SVT : supraventricular tachycardia.
VE : ventricular extrasystole.
WPW : Wolff-Parkinson-White syndrome.
VT : ventricular tachycardia.

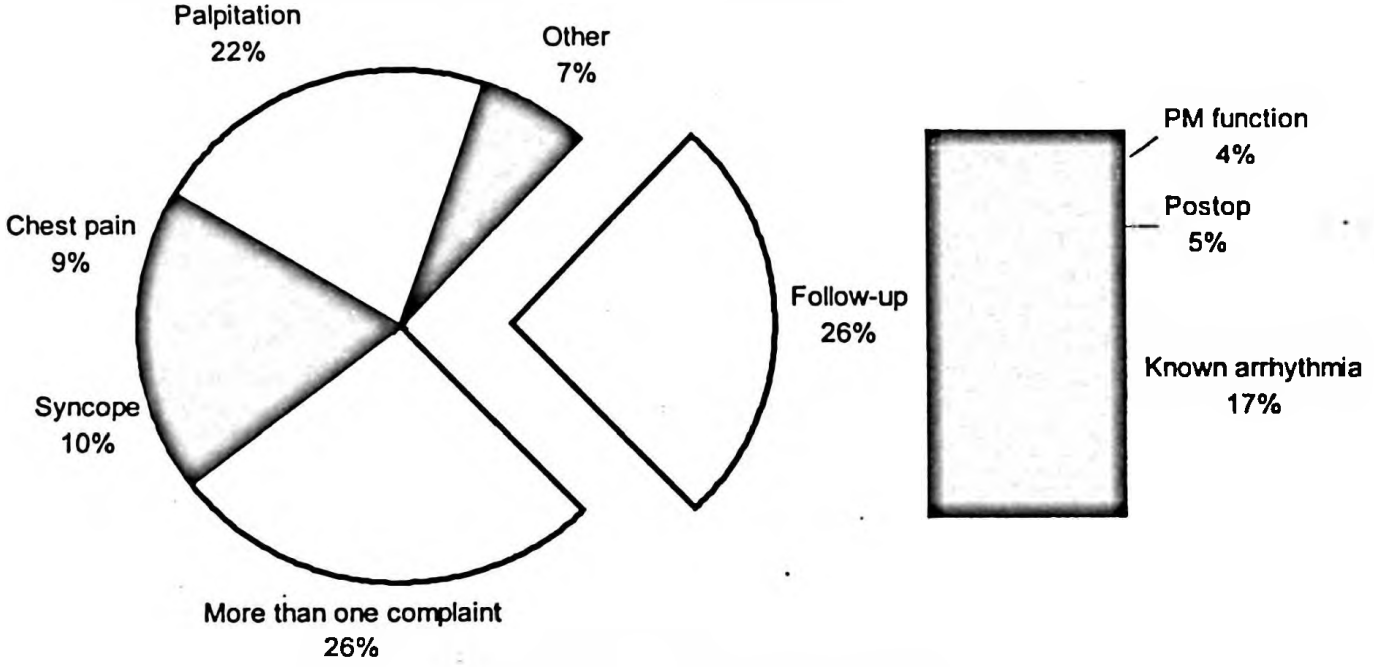

Fig. 3. Presenting complaints. Pm: pacemaker.

Among the patients presenting with palpitation, 71 percent had arrhythmia in their Holter records, whereas the frequencies of arrhythmia in Holter records of patients with syncope and chest pain were 601 and 51.5 percent, respectively. Patients having palpitation had significantly more dysrhythmic findings in their Holter record ($p = 0.012$). The least frequent dysrhythmic findings were noted in Holter records of those with chest pain ($p < 0.01$). SVE, SVT, VE, and CHB were significantly associated with palpitation ($p < 0.019$). Frequencies of these arrhythmias increased when palpitation was associated with syncope ($p < 0.01$). Long QT syndrome (LQTS) was significantly associated with syncope ($p < 0.01$). Wolff-Parkinson-White (WPW) syndrome had ventricular tachycardia (VT) were not significantly associated with any presenting complaint ($p > 0.05$) (Table I).

Patients presenting with symptoms like palpitation, chest pain and/or palpitation, but who did not have known arrhythmia or postoperative heart disease comprised 67 percent of the whole group (1,105 patients). Only 5.3 percent of these had similar complaints during HM, and only 34.8 percent of the 5.3 percent had arrhythmia in their Holter records. The majority of dysrhythmic patients in our study group were asymptomatic (54%) compared to the ones presenting with symptoms (46%). Ninety-one percent of the patients who had symptoms during HM were over eight years old.

Twenty-six percent of our patients (390 patients) did not have any complaint before having a Holter monitoring. HM was done to follow-up known arrhythmias, pm functions, or postoperative patients.

Age Groups

Supraventricular extrasystole (SVE), SVT, VT and CHB were observed most frequently in the newborn-infant age group. The frequencies of these arrhythmias significantly decreased with age ($p < 0.01$). VE was most frequently observed in adolescents. Its frequency increased with age; however, the difference was statistically non-significant ($p = 0.33$) (Fig. 4).

The newborn-infant age group was unique in terms of presenting complaint because this group was comprised of children who were unable to talk or express their complaints; therefore, this group had to be considered separately. Figure 5 summarizes the presenting complaints in newborn-infant group. Children < 2 years old represented only 5.2 percent of the whole group.

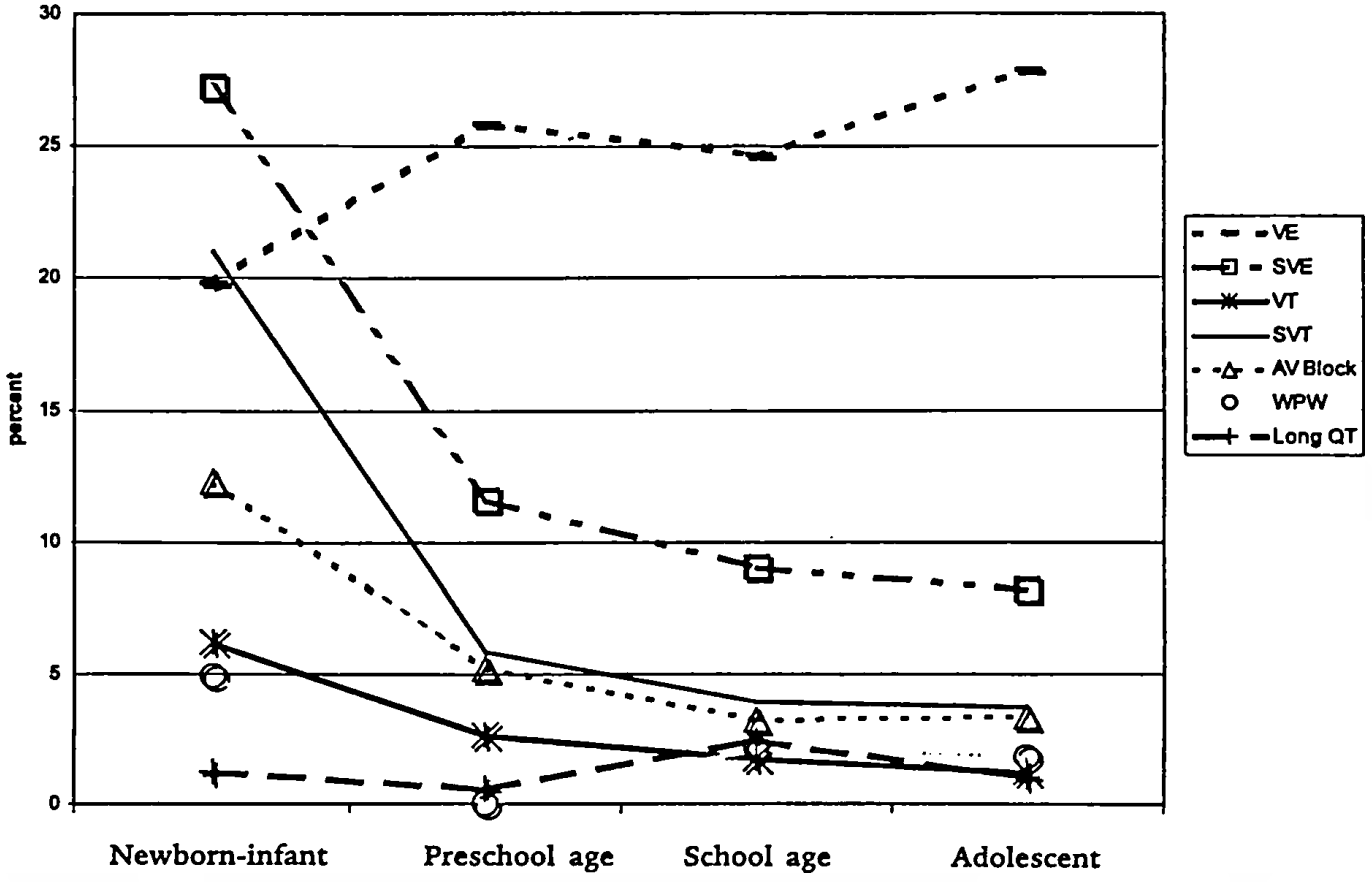

Fig. 4. Holter findings according to age groups.
VE: ventricular extrasystole; SVE: supraventricular extrasystole; VT: ventricular tachycardia; SVT: supraventricular tachycardia; WPW: Wolff-Parkinson-White syndrome.

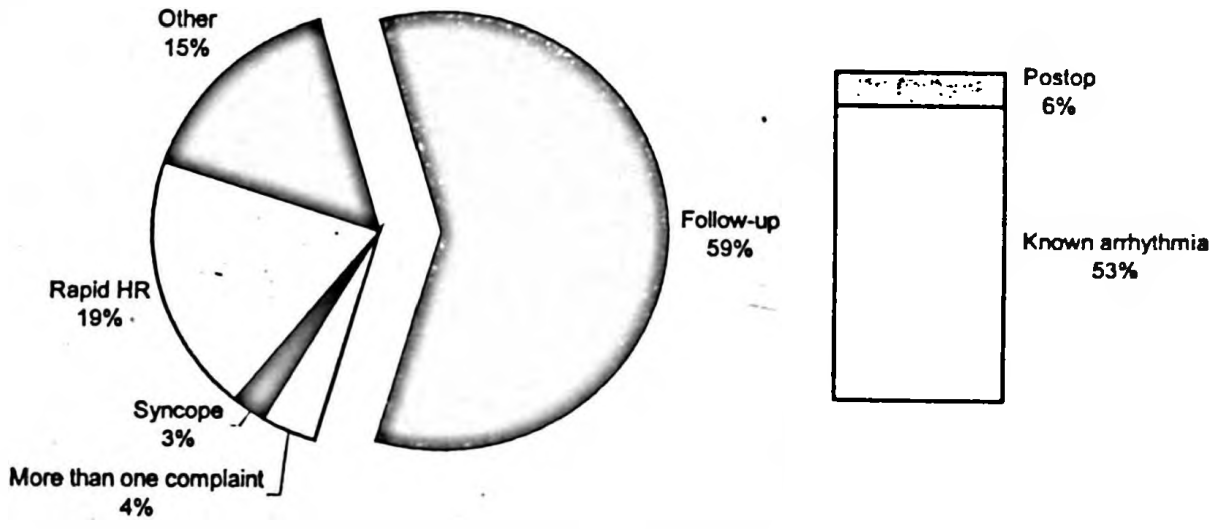

Fig. 5. Presenting complaints in newborn-infant group. HR: heart rate.

Cardiac Pathology

Table II summarizes the Holter finding of our study group in relation to cardiac pathology. VE was the most frequent arrhythmia in all three groups regarding cardiac pathology (normal heart-24.5%, preoperative abnormal heart-31.7%, or postoperative abnormal heart-34.3%). Its frequency was not significantly different in any of the groups. SVT was the most frequent arrhythmia requiring treatment in the normal heart (4.4%). It was observed more frequently in the preoperative abnormal heart (11.6%) than in the normal heart. It was most frequently seen in the postoperative abnormal heart (16.8%) ($p < 0.05$) among all the groups. SVT, VE, and CHB were statistically more frequent findings in the abnormal heart with previous cardiac operations ($p < 0.05$). Although VT was expected to be more frequent in the postoperative abnormal heart, the difference was not significant in any of these groups.

Table II. Holter Findings in Relation to Cardiac Pathology

	Frequency (%)		
Holter findings	Normal heart	Preoperative abnormal heart	Postoperative abnormal heart
SVE	9.6	10.9	13.3
SVT	4.4	11.6	16.8
VE	24.5	31.7	34.3
VT	1.7	3.4	1.5
AV Block	2.9	5.5	8.8
WPW Syndrome	2.1	2.4	0.2
LQT Syndrome	1.5	1.7	0
PM Rhythm	1.5	6.1	25.2
PM Dysfunction	0.1	0.3	8.0

SVE: supraventricular extrasystole; SVT: supraventricular tachycardia; VE: ventricular extrasystole; VT: ventricular tachycardia; AV: atrioventricular; WPW: Wolff-Parkinson-White; LQT: Long-QT; PM: pacemaker.

Postoperative Patients

In our study group, 231 of 1,500 patients had a cardiac operation before a HM. These patients had more frequent SVE, SVT, VE and CHB in Holter records than the ones without cardiac operations ($p < 0.05$) (Table II). On the other hand, WPW syndrome and LQTS were less frequent in this group ($p < 0.05$), and the frequency of VT was similar in both groups ($p > 0.05$). The frequency of arrhythmias was similar between the types of operation, namely atriotomy, ventriculotomy, atrioventriculotomy, aortotomy, and pulmonary arteriotomy, with the exception of the left ventriculotomy, which as more frequently associated with VT (statistically insignificant; $p = 0.23$).

Among the postoperative patients, those who were younger and without symptoms, and those who presented in the early postoperative period had more dysrhythmic findings in their Holter records ($p < 0.05$) (data not shown). CHB was observed mostly in the first 15 days postoperatively (before the patient was discharged from the hospital). Its frequency decreased as the follow-up period increased ($p < 0.05$). SVE was observed least frequently in the first 15 days postoperatively, and its frequency increased as the follow-up period increased ($p < 0.05$) (Table III).

Table III. Holter Findings in Postoperative Period

	Frequency (%)			
Holter findings	1st 15 days	1st 15 days-1st month	1st month-1st Year	>1 Year
SVE	4.5	9.7	18.9	22.5
SVT	8.1	3.2	14.7	20.7
VE	32	25.8	27.3	45.9
VT	0.9	0	4.2	0.9
AV Block	16.1	9.7	8.4	2.7
WPW Syndrome	0	0	0	0
LQT syndrome	0	0	0	0
PM Rhythm	57.5	25.8	33.3	7.2
PM Dysfunction	18.6	19.4	6.3	0

SVE: supraventricular extrasystole; SVT: supraventricular tachycardia; VE: ventricular extrasystole; VT: ventricular tachycardia; AV: atrioventricular; WPW: Wolff-Parkinson-White; LQT: Long-QT; PM: pacemaker.

Discussion

Clinical indications for Holter monitoring are different in pediatric and adult patients; however, the most frequent and common indication in both groups is the investigation of arrhythmic symptoms like palpitation, chest pain, and syncope[5]. In many clinical studies it is difficult to associate symptoms with arrhythmias, since serious arrhythmias are frequently observed in asymptomatic patients[6,7]. HM has a low diagnostic yield in explaining arrhythmic symptoms of adult patients[2,8-12]. If the symptoms occur every day, the possibility of recording arrhythmia during HM is very high; however, if they occur less frequently, transtelephonic ECG (TTECG) or electrophysiological study (EPS)

may be necessary. Especially TTECG has an advantage over HM since it selectively records the time of the event and therefore the overall recording time is longer than with HM. There are a few studies in literature comparing the results of HM and EPS; practically, the data obtained via these procedures are complementary[13,14].

Although patients with symptoms like palpitation, chest pain and/or syncope comprised the majority (67%) of our study group, only a small portion (5.3%) of these had similar complaints during HM. Less than half (34.8%) of the patients complaining of palpitation, chest pain, or syncope during HM had arrhythmia in Holter records. This suggests that the intervals of arrhythmic symptoms are widely set apart in pediatric patients. Therefore, HM has a low diagnostic yield in pediatric patients. Young children are usually unable to describe subjective symptoms like palpitation and chest pain. In our study group, patients having no arrhythmic symptoms before or during HM had more frequent arrhythmias than the ones with symptoms. HM enables cumulative evaluation of heart rhythm, which is important in diagnosing silent arrhythmias in high-risk groups like patients with abnormal heart or in postoperative patients.

The frequency and the type of rhythm and conduction disturbances vary with the age of the patient. Cardiac arrhythmias, especially VE, increases with age[3,15,16]. Although statistically insignificant, the frequency of VE increased with age in our group. On the other hand, SVE, SVT, VT, CHB are observed most frequently in the newborn-infant group and frequency of these arrhythmias significantly decreases with age. SVT and WPW syndrome are self-limited in the newborn period. The first dysrhythmic episode may be observed shortly after birth and even if left untreated, no further episodes may be observed at older age. WPW syndrome may be asymptomatic until the 6th decade, and asymptomatic WPW syndrome is frequent in family members of symptomatic patients[17,18]. Since the first symptom of WPW syndrome may be sudden death, it is appropriate to screen the asymptomatic members of the family whenever a patient with WPW syndrome is identified.

The diagnostic value of HM is not well known in asymptomatic arrhythmia[2]. The "premature ventricular contraction hypothesis" briefly proposes that certain frequencies and forms of VE, even if the patient is asymptomatic, predict the occurrence of sustained ventricular arrhythmias. The corollary to this hypothesis is that suppression of these VE's will protect patients from episodes of sustained arrhythmia, and prolong life[19]. Non-sustained VT and sinus pause may stay asymptomatic for a long time[20,21]. In a study concerning healthy middle aged adults, death within five years was more frequent in those having more than 10 VE per 1,000 beats; however, the reason of death was not stated in the study[15]. In another study of adults over 65 years old, patients having more than 100 VE per day, multifocal VE's, or more than 1.5 second sinus pause had higher risk of dying due to cardiac reasons[16]. These two studies seem to support the "premature ventricular contraction hypothesis". There is no randomized controlled study in the pediatric age group verifying this hypothesis. Furthermore, many other studies have shown that medical treatment of asymptomatic patients does not increase survival, and that cases of frequent or complex SVE or VE have a relatively good prognosis in the long-term follow-up if they are not associated with cardiac disorders[2,15]. The negative inotropic and proarrhythmic effects of many antiarrhythmic drugs are well known. In our study group, as VE increased with age, VT was most frequently observed in the newborn-infant age group and decreased with age. This finding conflicts with the "premature ventricular contraction hypothesis"; before, the asymptomatic arrhythmias must be treated in otherwise healthy people, considering the severity of arrhythmia, associated cardiac pathology, and frequency of similar arrhythmias[2].

In the pediatric age group, VT is not frequent and is usually associated with congenital cardiac anomalies, cardiac tumors, cardiomyopathy, or myocarditis. When VT is seen in an anatomically normal heart, it is referred to as "idiopathic VT"[22]. The most frequent arrhythmia requiring treatment in a normal heart is SVT[23,24]. This was true for the patients in our study group as well. SVT, VE and CHB are more frequent in structural heart disease compared to normal heart ($p < 0.01$). However, the frequency of VT is not different in the normal or abnormal heart ($p > 0.05$).

Early and late arrhythmias seen in patients undergoing cardiac surgery impose important

problems. During intracardiac repair cannulation, ventriculotomy/atriotomy incision and sutures may damage the conduction system, or the scar tissue may act as a focus of increased automaticity. Atrial switch operations like Senning and Mustard, total correction for tetralogy of Fallot and Fontan operations carry high-risk for postoperative arrhythmias. The frequency of arrhythmia and the risk of sudden death increase with older age at operation, residual hemodynamic disorder, symptoms suggesting arrhythmia, and in the late postoperative period[25,26].

Postoperatively, 33 percent of the patients are asymptomatic. Those having symptoms mostly presented in the late postoperative period with palpitation. In our patient group, those who were asymptomatic had more frequent abnormal Holter records ($p < 0.01$). In our institution, routine repeated HM is done after procedures like total correction of tetrology of Fallot, Senning and Mustard operations for transposition of the great arteries, or palliation for complex cardiac pathologies during follow-up of postoperative patients, even if the patient is asymptomatic. Therefore, the asymptomatic arrhythmias are recognized earlier and more frequently. CHB is more frequenct in the immediate postoperative period and its frequency decreases as the follow-up period increases. Most of the CHB seen after cardiac operations are transient; the permanent ones are treated with pacemakers. Therefore, the frequency of CHB decreases in the follow-up period. Postoperative syncope is most frequently associated with abnormal Holter findings (100%). The least frequent arrhythmia-associated symptom is chest pain (60%) ($p = 0.01$).

Holter monitoring has not been used for risk evaluation or to determine myocardial ischemia in children with arrhythmias. Our retrospective study was not informative in this field. On the other hand, HM is effective in investigating asymptomatic arrhythmias in high-risk pediatric patients (congenital heart disease and postoperative patients). It is useful in monitoring antiarrhythmic therapy and pacemaker functions. HM has a low diagnostic yield in associating symptoms like palpitation, syncope and chest pain with arrhythmia in children.

Holter monitoring (HM) is a non invasive technique with no complications, is a relatively cheap procedure compared to other procedures like EPS or TTECG, and it can be applied in out patient settings to patients of any age. Since HM enables cumulative analysis of heart rhythm and rhythm variability, it has advantages over other techniques. It should be the first line diagnostic tool in investigating known and suspected arrhythmias of children.

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Complications of pediatric cardiac catheterization: 18 - month study*

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SUMMARY: Tavlı V, Kayhan B, Okur FF, Kırman M, Tekdoğan M. Complications of pediatric cardiac catheterization: 18-month study. Turk J Pediatr 2000; 42: 294-297.

Pediatric cardiac catheterization may be indicated under certain conditions, but is associated with some risk. The purpose of the study was to evaluate the complications associated with diagnostic and interventional catheterization procedures done over an 18-month period in our laboratory. Of the 230 cardiac catheterizations, 204 were solely diagnostic in nature. Eleven percent were interventional catheterizations including aortic and pulmonary valvuloplasties and balloon atrial septostomy. Six percent of the patients constituted grown-up congenital heart disease (GUCH). The median age was 34 months excluding the GUCH group. There was one death below one year of age (0.4% mortality) occurring six hours after the diagnostic catheterization; it was attributed to the underlying disease. There were eight complications (3.4%) that we would consider serious, including atrial flutter, ventricular tachycardia, severe hypercyanotic spell, seizure, transient complete heart block, peripheral vascular injury which resulted in pseudoaneurysm formation of the femoral artery requiring surgical intervention, and transient pulse loss. When catheterization is necessary, it should be carried out as efficiently as possible with awareness of conditions that probably increase the risk of a clinically important event. Although patients undergoing cardiac catheterization are now younger and have more complex cardiac abnormalities, the procedure seems to have become safer when compared to previous literature.

Key words: catheterization, interventional, pediatric, complications.

Despite advances in noninvasive evaluation, cardiac catheterization and angiocardiography continue to be essential for patients with congenital heart disease, but they are associated with some risk. The risks leading to complication may be reduced with appropriate patient selection and pericatheterization medical management[1-6,10]. The incidence of major complications and death associated with pediatric cardiac catheterization is reported to have decreased markedly compared to the results a few decades ago[2]. The majority of the complications are either successfully treated or are self limited. However, interventional catheterization has been reported to introduce a small number of new complications[7-10], although technological advances seem to contribute significantly to the reduction of the risks. The aim of the present study was to describe the complications and treatment and prevention techniques in a relatively new pediatric catheterization laboratory.

Material and Methods

We report the complication rate among 230 pediatric cardiac catheterizations and angiocardiographies performed from December 1996 until July 1998. The files of these cases were reviewed retrospectively and analyzed. The diagnoses and complications are displayed in Tables I and II, respectively. Eleven percent of procedures were interventional, including pulmonary valvuloplasty, peripheral pulmonary angioplasty, aortic valvuloplasty and balloon atrial septostomy. Seven neonates aged five to 11 days underwent balloon atrial septostomy (Table III). Twelve patients with an age range

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of 2.5 to 15 years (mean 7.1 years) underwent pulmonary balloon valvuloplasty, one of whom had tetralogy of Fallot and left pulmonary artery cut-off following left-sided modified Blalock-Taussig shunt (Table IV). Seven patients, aged two months to eight years (mean: 4.5 years) underwent aortic balloon valvuloplasty (Table V). Two patients, aged 20 months and three years, underwent peripheral pulmonary angioplasty. Seven percent of the patients were in the grown-up congenital heart disease (GUCH) group. Totally, the age range was one day to 39 years (mean: 7.5 years). Excluding the GUCH group, the age range was one day to 17 years (mean: 34 months). Three-and-a-half percent of the patients were under one month. Twenty-two percent were between the ages of one month and two years. Twenty percent were between the ages of two and five years. Forty-seven-and-a-half percent were between five and 17 years. Pulmonary hypertension was present in 6.9 percent of the patients with left-to-right shunting lesions (age range: 26 months-11 years, mean: 6 years). Eisenmenger's syndrome was present in three patients (age range: 3-12 years), two of whom were Down's syndrome and atrioventricular septal defect. In the third, aorto-pulmonary window with a ventricular septal defect (VSD) was present. Persistent left superior vena cava was present in three patients with VSD, and in three patients with tetralogy of Fallot (TF), coronary sinus type atrial septal defect (ASD) and aortic coarctation. Interrupted inferior vena cava with azygos continuation accompanied tricuspid atresia, dextro-transposition of the great arteries, pulmonary stenosis (PS) and common atrium associated with polysplenia syndrome. Nine patients in the GUCH group had ASD, two PS, two TF, one VSD and PS, one patent ductus arteriosus, one aortic coarctation, and one corrected transposition of the great arteries and ASD.

Catheretizations were performed by previously described techniques[1]. Patients under one year of age were usually sedated by administration of oral chloral hydrate (50 mg/kg). A mixture of demoral, thorazine, phenergan (0.1 ml/kg, max: 2 mg) or 0.1 mg/kg subcutaneous morphine HCl was administered to older patients. Heparin (50-100 U/kg/dose) was given based on cardiologist's preference. Cineangiography was performed in nearly all patients. Nonionic, low osmolality contrast material was used at a maximum dose of 5-6 ml/kg/catheterization.

Table I. Frequency of Congenital Heart Lesions

Lesions	% of All lesions
Ventricular septal defect	26
Atrial septal defect	16
Tetralogy of Fallot	15
Pulmonary stenosis	9
Coarctation of aorta	7
Aortic valve stenosis	6
Patent ductus arteriosus	5
Post-operative	4
Double-outlet right ventricle	3.5
Dextrocardia	2
Atrioventricular septal defect	2
Dextro-transposition of the great arteries	1.7
Others*	2.8

* Tricuspid atresia, corrected transposition of the great arteries, total abnormal pulmonary venous return, subaortic stenosis, pulmonary atresia, cor triatriatum, Shone's complex, aorto-pulmonary window, double arcus aorta.

Table II. Complications of 230 Diagnostic and Interventional Pediatric Cardiac Catheterizations

Major	Number of patients	Minor	Number of patients
A) Death within 24h of catheterization	1	A) Arrhythmias	
B) Arrhythmias		a) Supraventricular tachycardia	7
a) Ventricular tachycardia	1	b) Atrial flutter	1
b) SVT	1	c) Sinus bradycardia	3
C) Catheter problems		d) 3° AV-block	1
a) Breakage or kinking	1	B) Arterial	4
D) Hypoxic spells	2	a) Weak or absent pulses after catheterization with good capillary refill	2
E) Hypothermia	1	b) Pseudoaneurysm formation surgical exploration and repair	2
F) CNS seizure	1	C) Myocardial staining with or without ST-T changes but without perforation	2
		D) Blood loss not requiring transfusion	3
Total	8 (3.4%)		25 (10.9%)

(SVT: supraventricular tachycardia, CNS: central nervous system, AV: atrioventricular).

Table III. Immediate Results of Balloon Atrial Septostomy

	Before	After
Aortic oxygen saturation	17.5 ± 4.4%	74 ± 18%
Serum bicarbonate	5.5 ± 1.6	14 ± 2.2
Mean RA pressure (mmHg)	4.7 ± 1.1	5.7 ± 0.9
Mean LA pressure (mmHg)	10 ± 1.5	5.75 ± 1.2

(RA: right atrium, LA: left atrium).

Table IV. Immediate Results of Pulmonary Balloon Valvuloplasty

	Before	After
Systolic RV pressure (mmHg)	132 ± 58	59 ± 36
Systolic PA pressure (mmHg)	21 ± 9	32 ± 8
Gradient (RV-PA)	110 ± 46	37 ± 22

(RV: right ventricle, PA: pulmonary artery).

Table V. Immediate Results of Aortic Balloon Valvuloplasty

	Before	After
Systolic left ventricular pressure (mmHg)	173 ± 25	117 ± 37
Systolic aortic pressure (mmHg)	96 ± 14	80 ± 19
Left ventricular-aortic gradient (mmHg)	85 ± 10	34 ± 16

(RV: right ventricle, PA: pulmonary artery).

Balloon atrial septostomy was performed using Edwards-Miller catheter in seven neonates with the diagnosis of transposition of the great arteries. Arterial blood gases were obtained before and after the procedure. The indication for pulmonary balloon valvuloplasty was a peak Doppler echocardiographic gradient of 50 mmHg or more. Mean annulus to balloon ratio was 59 ± 16 percent. Aortic balloon valvuloplasty was performed in patients with peak instantaneous Doppler gradient of 50 mmHg or more and mild aortic regurgitation at most. The ratio of the annulus to balloon size was 1 ± 0.08 in our patients.

A life-threatening event requiring immediate treatment was considered a major complication. A transient event that had no long-term ill effect on the patients and was resolved with specific treatment was considered a minor complication.

Results

There were eight major (3.4%) and 25 minor (10.9%) complications in our study group (Table II). Eighty-seven-and-a-half percent of the major complications occurred in patients less than five years of age. The complication rate in the GUCH group was zero. Two of the major (0.86%) and five of the minor complications (2.1%) occurred in the interventional catheterization group.

Death: There was one death below one year of age (0.4% mortality) occurring six hours after the diagnostic catheterization which was attributed to the underlying disease. This patient, who was a six-month-old male with truncus arteriosus, developed high fever and febrile seizures within six hours of the procedure. During a seizure he developed cardiopulmonary arrest which did not respond to resuscitation.

Arrhythmias: A serious episode of ventricular tachycardia occurred in a five-month-old patient with tricuspid atresia, hypoplastic right ventricle and systemic venous return abnormality during contrast material injection into the presumed hypoplastic ventricle. Following intravenous lidocaine bolus, ventricular tachycardia (VT) subsided immediately and continued in the form of 2:1 ventricular ectopic beats within several minutes of lidocaine infusion.

2:1 atrial flutter followed by VT occurred and resolved spontaneously in an eight-month-old patient with single ventricle physiology and heterotaxy syndrome.

Spontaneously resolving supraventricular tachycardia was noted in seven patients (3%). Intravenous administration of verapamil was necessary in only one patient. Sinus bradycardia accompanied pulmonary balloon valvuloplasty in three cases. Spontaneously resolving transient complete heart block occurred in an eight-year-old patient with Down's syndrome, atrioventricular septal defect, Eisenmenger's syndrome and alternating 2:1 and 3:1 block.

Arterial Complications: Four arterial complications were noted (1.7%). Two patients, aged 35 days and 2.5 months, had decreased pulses in the limb; an arterial catheter had been placed beyond two hours in both. Decreased pulses returned to normal following intravenous heparinization at a dose of 1 ml/kg bolus followed by 20 U/kg/hr for a mean period of 36 hours[4]. None required thrombolytic therapy or surgical thrombectomy[5,6]. In two cases, pseudoaneurysm of the femoral artery developed and was surgically repaired approximately two weeks after the catheterization.

Catheter Problems: Kinking of the balloon catheter occurred during the pulmonary balloon valvuloplasty, but it was successfully with drawn through the introducer sheath.

Hypercyanotic Spells: Hypoxic spells occurred in two patients, aged six months and 18 months. The latter patient was a tetralogy of Fallot who had undergone left modified Blalock-Taussig shunt. He manifested with the symptoms approximately 12 hours after the procedure. Both patients responded well to medical treatment.

Seizure : A 12-year-old boy with pulmonary stenosis and suprasystemic right ventricular pressure developed seizure during the first episode of balloon inflation and deflation.

Bleeding : Prolonged bleeding from the entry site at the groin occurred in three infants who were severely cyanotic and manifested elevated hematocrit levels.

Discussion

Current risk of pediatric catheterization is reported to have decreased significantly when compared to previous results within the same institution[1]. The incidence of major complications was 3.4 percent and of minor complications 10.9 percent in all age groups in our study population. Cassidy et al.[2] reported an incidence of 1.4 percent for major and 6.8 percent for minor complications, lower compared to our results. Yet, our results may be assumed reasonable considering the reported data reflects our initial experience in a new unit. In this study, the majority of complications occurred in patients less than two years of age. Seventy-one percent of the major and 47 percent of the minor complications were seen in the infant group (Table II).

The risk of perforation is also greater in newborns and infants. Therefore, infants should be considered a high risk group regarding all aspects of catheterization procedures. Arterial problems are reported to be as high as 15 percent in the neonatal group, as was the case in our study group[4-6]. However, prophylactic use of heparin in prolonged procedures should decrease the incidence of such complications. Cyanotic patients constitute another group of major complications. Arrhythmias, bleeding at the entry site, hypoxic spells and major events such as death have been shown to occur more commonly in the cyanotic infant group. Hypoxic spells may be prevented with administration of intravenous fluids to avoid dehydration in the pre-catheterization period, use of low osmolality, nonionic contrast material and with careful manipulation at the right ventricular outflow tract. Mean hematocrit and arterial oxygen saturation of the cyanotic patients who manifested minor complications were 55 ± 9 and 77 ± 10 percent, respectively.

In this study, only two major complications occurred during interventional catheterizations. Arterial problems were seen in none of the patients undergoing aortic balloon valvuloplasty[5,6].

It may be stated that interventional catheterizations introduced a small number of new complications when compared to previous literature[1-3,7,8,11].

In conclusion, the majority of the catheterization complications were successfully treated or were self limited. Careful planning and keeping the duration of the procedure short as far as possible, supervision of relatively inexperienced personnel and recognition of high risk procedures should certainly result in decreased possibility of complications.

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Thymic enlargement in childhood

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Thymic masses constitute one of the least common mediastinal masses in childhood. While producing symptoms of airway compromise, they also raise the suspicion of malignancy when detected. Radiological, operative and pathological findings of patients that have been operated for thymic masses in our instituion is presented in this paper. Nine patients were operated in our institution during a 12-year-period between 1985-1997 for thymic masses. Ages of the patients ranged from four months to 13 years. With the exception of one, who was diagnosed with a routine chest x-ray, all the patients had respiratory complaints. All the patients had been evaluated with computed tomography preoperatively. In total, seven sternotomies and four thoracotomies were performed to reach the anterior mediastinum. The distribution of masses was as follows two malignant thymomas, three thymic hyperplasia, one lymphocyte-rich thymoma, one epithelial thymoma, one cystic thymoma and one lymphoblastic lymphoma. Although rare, thymic enlargement may be a cause of intractable respiratory complaints in childhood. Because of the high incidence of primary malignancy of the mediastinal neoplasms in childhood, thymic enlargement requires accurate pathological diagnosis and treatment. Median sternotomy with intensive anesthetical care allows proper tumoral exposure.

Key words: thymus, anterior-superior mediastinal mass, respiratory distress.

The thymus normally occupies the anterior and superior mediastinum. Great vessels, a network of lymphatic structures as well as connective and adipose tissue are the other structures found in the anterosuperior mediastinum[1]. Embryologically, the thymus develops as sacculations from the ventral aspect of the third pharyngeal pouch during the sixth week of intrauterine life. Migrational defects during embryogenesis may cause ectopic thymic localization[2].

The thymus is composed of lymphatic tissue, with the characteristic Hassall's corpuscles of epithelial origin. The mean weight of the thymus at birth is 22 ± 13 g. It reaches the maximal weight of 30-40 g at puberty, but when the percentage ratio of thymus to body weight is taken into account, it is greatest at birth with a percentage of 0.76 which declines to 0.19 at one to six years of age[3,4].

It has long been known that thymocytes play an important role in the immune mechanism. The thymus is also related with myasthenia gravis; a thymectomy has been shown to relieve the symptoms of the myasthenic patients. Thymic neoplasms are also associated with some conditions which are called thymic syndromes, like pure red cell aplasia, pemphigus, lupus erythematosis, and Sjögren's syndrome[3]. Unlike the situation in adults, myasthenia gravis and other thymus-related disorders are very uncommon in childhood[5].

Twenty-six percent of the primary childhood mediastinal neoplasms are anteriorly[6] located. Thymic lesions constitute 2.5 percent of overall mediastinal neoplasms[1]. Because of the high incidence of malignancy in mediastinal lesions in the pediatric age group, thymic enlargement requires prompt assessment of pathological diagnosis. The low incidence and the relative inexperience with thymus-related masses in childhood may create a diagnostic dilemma. For these reasons patients with anterior mediastinal

masses require general anesthesia for diagnostic and therapeutic procedures in which fatal or life-threatening complications can occur both during and after its application. Compression of the major airway, pulmonary artery and/or the superior vena cava can occur unexpectedly at any time during anesthesia and surgery including induction, intubation, positioning or extubation[7,8]. Therefore, we evaluated the medical records of patients operated for thymic masses in our institution to find preoperative, peroperative and postoperative surgical and anesthetical clues for thymic enlargement in childhood.

Material and Methods

During a 12-year period between 1985 and 1997, nine patients were operated for thymic masses in our institution. All the patients had complete blood count, peripheral smear, blood biochemistry, urinalysis, bone marrow aspiration, posteroanterior and lateral x-ray projections of the chest, and computed tomography of the thorax routinely before the operation.

Venous access was secured with a 20 or 22 gauge cannula in a peripheral arm vein. No premedication was commenced. All patients received an anticholinergic and standard monitoring consisting of electrocardiogram, blood pressure cuff and pulse oximeter. After confirming preparation and presentation of the pediatric rigid bronchoscope, anesthesia was induced with an intravenous opioid (1 mg/kg fentanyl citrate) and sodium thiopental (4-5 mg/kg). After ventilation of the lungs, tracheal intubation was facilitated with succinylcholine (1-2 mg/kg). Anesthesia was maintained with halothane or isoflurane and increments of fentanyl and vecuronium as required.

As the first surgical intervention, seven complete midline sternotomies and two antero-lateral thoracotomies were performed under general anesthesia to expose the mediastinum. Additionally, two second-look thoracotomies and one emergent sternotomy because of massive bleeding were later required. The clinical data of the patients are summarized in Table I.

Table I. Summary of Clinical Data

Case No.	Sex	Age at operation	Incision and procedure	Complication	Diagnosis	Result
1	M	13 yr	Sternotomy biopsy	–	Malignant thymoma	Alive
2	M	5 yr	Sternotomy thymectomy	–	Lymphocyte-rich thymoma	Alive
3	M	5 yr	Thoracotomy thymectomy	–	Thymic hyperplasia	Alive
4	M	13 yr	Thoracotomy biopsy	–	Malignant thymoma	Alive
5	F	14 mo	Sternotomy thymectomy	Pneumothorax	Thymic hyperplasia	Alive
6	M	5 yr	Sternotomy thymectomy	–	Epithelial thymoma	Alive
7	M	4 mo	Sternotomy thymectomy	Bleeding	Thymic hyperplasia	Alive
8	M	6 yr	Sternotomy thymectomy	–	Lymphoblastic lymphoma	Alive
9	M	12 yr	Sternotomy thymectomy	Pneumothorax	Cystic thymoma	Alive

Results

The sex distribution of the patients were eight males and a female. The ages ranged from four months to 13 years. Except for the 9th case who was on follow-up with a diagnosis of systemic lupus erythematosus (SLE), all the other patients had symptoms associated with the respiratory system. Common symptoms were coughing and dyspnea. Duration of symptoms ranged from 20 days to 1.5 years. Most of the patients received some courses of antibiotic therapies. Case 2 received asthma therapy for one year in another institution.

After obtaining chest x-rays (Fig. 1), all patients were evaluated by computed thoracic tomograms. In all patients, computed tomography revealed masses filling the anterior mediastinum with heterogeneous density enhancement (Fig. 2). In Cases 6 and 8, which were an epithelial thymoma and a lymphoblastic type lymphoma, the trachea was found deviated in tomograms. In Case 7, who was a four-month-old boy with severe respiratory symptoms, the upper lobe of the right lung revealed marked atelectasis. Other laboratory work-up peripheral blood smear, blood biochemistry, urinalysis and bone marrow aspiration provided no additional information for the diagnosis.

While seven patients underwent complete midline sternotomy, antero-lateral thoracotomy was chosen as the surgical approach in two patients. No adverse hemodynamic and

respiratory events occurred in either patient as a result of their peroperative anesthetic experience. All patients were extubated successfully. Total excision of the tumoral mass was possible in six of the seven patients who underwent midline sternotomy. In Case 1, the biopsy obtained by sternotomy from the irregular, large solid gray mass adherent to the right pleura revealed malignant thymoma. The case was considered as stage III and received 4400 rad irradiation to the mediastinum with 3000 rad to the pericardium. After one year of radiotherapy with a chemotherapy course of vincristine, adriamycin and prednisone, total excision of the mass was managed by right antero-lateral thoracotmy.

Fig. 1. Postero-anterior chest x-ray showing a mediastinal mass projecting from superior to left hemithorax.

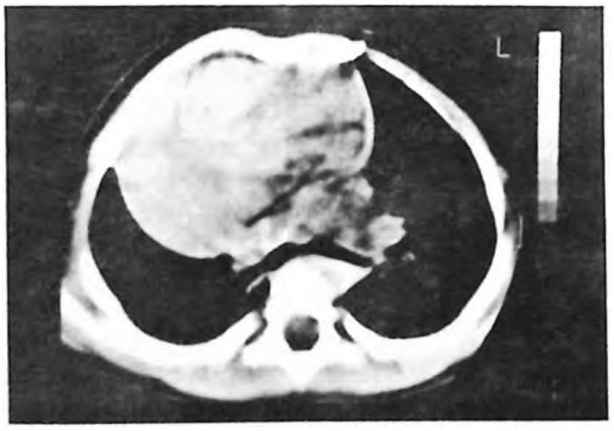

Fig. 2. CT scan showing anterior mediastinal mass with heterogeneous density enhancement.

In Cases 3 and 4, right and left antero-lateral thoracotomies were preferred because the mediastinal masses were mainly occupying the right and left hemithorax, respectively. Total excision was possible in Case 3, a thymic hyperplasia weighing 371 grams, in which a reversible atelectasis of the right upper lobe was observed. In Case 4, the tumor was densely adherent to the pericardium and pleura, in which small nodular, metastatic-like lesions were observed, making total excision impossible. The pathological diagnosis of the specimen that could be obtained was malignant thymoma. The case was considered as stage III. After receiving a total irradiation of 4400 rad to the mediastinum, 2000 rad to the left lung, and 3000 rad to the pericardium, re-exploration through the same incision revealed a necrotic mass which was totally excised after seven months of radiotherapy and chemotherapy course. No complication was observed after thoracotomies.

Pleural tears occurred in Case 5, a mass of thymic hyperplasia weighing 360 grams and in Case 9 who was a cystic thymoma. They healed in a few days by underwater chest tube drainage.

Massive bleeding, which required re-exploration the same night of the surgery, was observed in Case 7, in whom a very large mass, beginning from the anterior mediastinum and extending to the posterior, compressing the right upper lung, and weighing 278 grams, was excised (Figs. 3-4). Oozing from the tumoral bed was controlled in the emergency sternotomy.

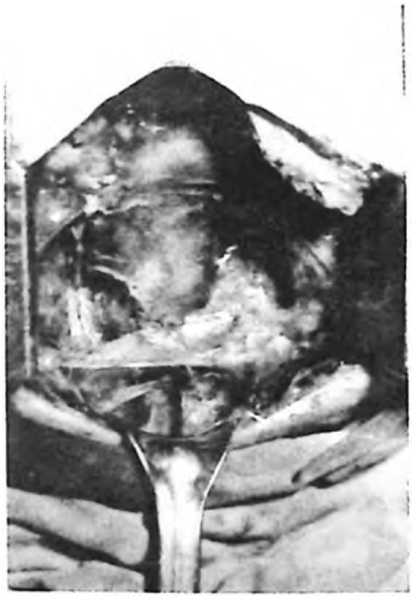

Fig. 3. Peroperative view of the thymic mass (hyperplasia) compressing the adjacent lobe.

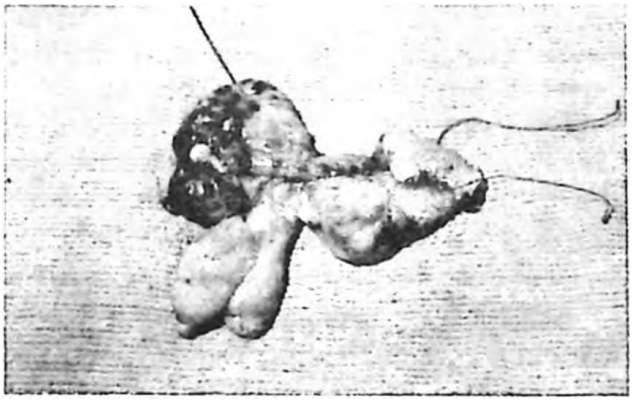

Fig. 4. Operating room gross photograph of the true thymic hyperplasia involving both lobes of the thymus.

Case 7, considering his age and severity of respiratory symptoms, and Cases 6 and 8 due to tracheal deviation, received 2 mg/kg of prednisolone preoperatively for one week. No improvement of respiratory distress was obtained in any of the cases.

Although myasthenia gravis was not encountered in any patient, Case 9 was in follow-up for systemic lupus erythematosus, which is considered as one of the thymic syndromes. This case, a cystic thymoma, also had a history of idiopathic thrombocytopenic purpura which healed after corticosteroid therapy.

Discussion

Although the thymus is recognizable on chest radiograms up to two to three years of age, tumors and tumor-like enlargement of the thymus are among the least frequent lesions in childhood[5]. After four years of age, enlarged thymic shadow is rarely encountered in radiograms.

Thymic lesions constitute 2.5 percent of all childhood mediastinal lesions[1]. Because of the rarity of thymic lesions in childhood, most of the reports about the thymus are single cases[4,9-11]. Welch et al.[3] reported their experience on 17 patients with thymic cysts and neoplasms, excluding thymic hyperplasia and lymphomas, located in the anterior mediastinum. However, considering the similarity of the preoperative radiographic findings and need for the same surgical approach as required for thymic lesions, we included lymphoma of the thymus in our series.

Thymic hyperplasia can be considered as one of the rare conditions of abnormal thymic growth. Recent studies have shown that histological and immunohistochemical staining patterns of thymic hyperplasia are similar to those of normal thymic tissue occurring in immunologically normal children, exhibiting rapid growth of both thymocyte and epithelial elements with normal thymic architecture. Thymic hyperplasia grows no differently in long term culture and responds no differently to cytokine than does normal thymic tissue[9]. These data suggest that thymic hyperplasia can be considered as a benign hypertrophy of the thymus. On the other hand, quantitative and comparative cytoenzymatic studies suggest that massive thymic hyperplasia represents an intrathymic accumulation of immature T cells, a condition which may be related with a failure of cell differentiation connected with some thymic hormonal activity[12]. Massive hyperplasia of the thymus should be differentiated from "lymphoid", "follicular", or "germinal center" hyperplasia of the thymus, which are encountered in adulthood and most often are associated with myasthenia gravis. Such an association is a very unique condition in childhood[13].

Although Rice et al.[9] proposed that thymic hyperplasia is usually an asymptomatic lesion, Ricci et al.[14] emphasized the presence of respiratory distress in a clinicopathological study of four patients[14]. Quite similar to that report, all three patients with thymic hyperplasia in our series expressed the most severe respiratory distress, particularly four-and 14-month-old infants. While steroid administration failed to relieve respiratory distress, total excision of the lesions provided a prompt relief in symptoms. The surgical approach has both diagnostic and therapeutic roles for thymic hyperplasia in childhood. Grossly, true thymic hyperplasia involves the whole thymus, whereas thymoma may involve either one or both thymic lobes, always presenting with some unaffected thymus tissue[15].

Thymoma has been defined as a neoplasm of thymic epithelial cells that differentiate towards either the slender, long branching epithelial cells that characterize the normal thymic cortex or the more rounded epithelial cells of the thymic medulla[16]. While thymomas represent approximately 20 percent of all mediastinal tumors in all age groups, it has been estimated that only one percent of them occur in childhood. Like thymic hyperplasia, no association has been demonstrated between myasthenia gravis and childhood thymomas[17].

The distinction between benign and malignant thymoma for a pediatric surgeon can be made by the finding of an encapsulated versus truly invasive lesion during surgery. Encapsulated thymoma can be treated by surgery alone. While not being uniformly practiced, a multimodal treatment has been recommended for thymomas. The obvious treatment of choice accepted by all authors is complete resection of the tumor. Debulking procedures have been implied to have no value on prognosis. Aggressive surgical intervention has been advised for all tumors of the thymus[3,18-20]. To achieve this goal, pleura-pneumonectomy, lobectomy, resection of the pericardium, diaphragm, both innominate veins or superiof vena cava may be required. It has been speculated that thymomas should be considered adherent rather than truly invasive, and complete resection has been advised even with the anterior pericardium[3]. As the tumoral masses were found densely adherent to pleura and pericardium, only a limited surgical intervention was performed in Cases 1 and 4, both malignant thymomas. In such a circumstance, a large patch of anterior pericardial resection has been recommended to establish a plane of dissection. Limited experience about the nature of thymic neoplasms probably led to the less invasive surgery, in those cases.

Operative complications during resection of the thymus include resection of the phrenic nerve, vocal cord paralysis, Horner's syndrome, and bleeding from the tumoral bed, as in our Case 7, and severe pneumothorax, as in our Cases 5 and 9. Superior vena cava and the aortic arch can be found adherent to the lesion, which could handicap establishing a clean removal plane. Similarly, segmental resection and reanastomosis or bridging by an intercostal nerve graft of the phrenic nerve may be needed if it is found enveloped by the thymic mass[3,19]. Airway obstruction may occur due to relaxation of the tracheal musculature, causing collapse and complete obstruction with fatal consequences. Cardiovascular involvement may be related to the direct compression of the heart or of the great vessels. If the child has arrhythmias, pulsus paradoxus, hypotension or superior vena cava syndrome, the risk of general anesthesia increases dramatically. So the site and the degree of airway obstruction must be assessed preoperatively[21].

Although the association of thymoma and myasthenia gravis is extremely rare in childhood, a tension test has been suggested before any surgical intervention for all patients presenting with an anterior mediastinal mass and a history compatible with muscle weakness to prevent postoperative respiratory failure[22].

Lymphomas of the thymus should be mentioned while speculating on thymic lesions. The most common lesion is the lymphoblastic lymphoma of the thymus, which is most often encountered in males, usually in the second decade[18]. Although rare it can be seen in children, as in our Case 8, who was a six-year-old boy with respiratory complaints for 1.5 months. His preoperative diagnostic studies revealed nothing other than an anterior mediastinal mass which could not be distinguished from a thymic mass.

Another group of lymphoma, histiocytic type, may present as an anterior mediastinal mass, which is usually encountered in the third to fourth decades. Hodgkin's disease may also arise primarily from the thymus and is regarded as a variety of thymoma by some authors (granulomatous lymphoma). However, lymphomas of the thymus seldom create problems in the differential diagnosis of thymic lesions for pathologists[16].

Thymolipoma is another rare cause of thymic enlargement that should be listed in the differential diagnosis of thymic lesions. Histologically there is a prevalence of mature fatty tissue with a moderate lipomatous involution, but the main component is the normal hyperplastic thymic tissue[16,23].

In conclusion, thymic enlargement can be a rare cause of respiratory distress and intractable respiratory tract symptoms in childhood. The symptoms may be due to the direct compression of the airway or to the atelectasis of the compressed lung segments, and the patient can still be receiving doses of antibiotics or even asthma therapy. Lack of thymic markers, similarity of the radiological findings, high malignancy risk of mediastinal lesions, and presence of airway compression symptoms require a dynamic surgical approach to the thymic lesions. The anesthesiologist must stay alert for the development of severe airway obstruction and cardiovascular complications during the anesthesia of symptomatic or

asymptomatic patients with anterior mediastinal masses. A rigid bronchoscope must be available in the operating room in case of a possible complication. If airway obstruction occurs, the position of the patient must be changed rapidly to lateral and/or prone.

The pathological evaluation of the lesion does not create as much confusion as the preoperative work-up. Thus, a radical surgical intervention with total excision of the thymic lesion and intensive anesthetical care are the most important means of managing thymic lesions of childhood.

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The clinical outcome of childhood masturbation

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This study was performed to investigate the clinical outcome of childhood masturbation. For this purpose 50 children (mean age = 48.7 ± 24.5 months, 34 girls females and 16 boys males) with masturbation symptoms were examined at first visit to the Department of Child Psychiatry and two years thereafter with psychiatric interviews. The mean masturbation frequency at the initial interview was significantly decreased after two years. It was noted that 39 children (78%) were completely recovered and 11 children (22%) continued to masturbate after two years. Children who did not recover were significantly younger, began to masturbate earlier and masturbated more frequently than others at the time of initial evaluation. It was concluded that the findings about the beneficial effect of sedative drugs in combination with parental guidance, education and means for behavior modification were promising.

Key words: masturbation, child, longitudinal study.

Childhood masturbation (CM) is defined as self-stimulation of the genitalia in a prepubertal child, frequently accompanied by symptoms like sweating, flushing and tachypnea[1,2]. In spite of the fact that CM is not a rare condition[3,4], and causes parental distress of various degrees in different societies[3,5]; it is not included in DSM-IV[6]. The ICD-10[7] placed this problem under the title 'Other Specified Behavioral and Emotional Disorders with Onset Usually Occurring in Childhood and Adolescence' (F98.8) without any detailed description.

Although CM is frequently a confusing problem both for the pediatrician and for the child psychiatrist, the clinical data about CM is based merely on case studies[1,8-13] and general observations[14-16] which also constitute the main source of information in the few review articles about CM[1,2,17]. Systematic reports about this condition are limited to some studies about electroencephalogram (EEG) findings[18-20], or parental attitudes in CM[3]. Sedative drugs[1] and some aversive behavioral methods were reported to be useful in a few children[21,22]; however, there is a remarkable lack of information about the course of CM. Thus, the main purpose of this study was to investigate the clinical outcome and associated clinical variables in CM.

Material and Methods

The 50 children participating in this study were referred to the Department of Child Psychiatry of Hacettepe University Hospital in 1995 and 1996. Children with the symptom of genital self-stimulation interfering with home and/or school functioning and/or strongly disturbing the parents were assessed. After evaluation by at least two physicians to determine that the symptoms were not due to a medical disorder, and that the symptom severity was sufficient to diagnose CM, children with genital self-stimulation and accompanying symptoms like sweating, flushing and tachypnea were included in the study. Children whose parents could not give sufficient information; who masturbated infrequently or simply 'played' with their genitalia for a short while without the accompanying symptoms listed above; those with mental or motor retardation, psychotic disorders, pervasive developmental disorders, or medical or neurological diseases; and children who showed signs of puberty were excluded.

The initial evaluation, performed by a pediatrician, consisted of physical examination, routine blood, urine and stool analyses, routine sleep EEG and consultations with a pediatric neurologist, urologist or a dermatologist when

necessary. Children without positive medical findings were referred to the Department of Child Psychiatry with an initial diagnosis of CM. A child psychiatrist interviewed the family and observed the children in appropriate settings. Age-appropriate intelligence tests, the Stanford-Binet[23] or Wechsler Intelligence Scale for Children-Revised[24] were applied by a psychologist.

The subjects of this longitudinal study were recruited from a larger sample of 61 children described in another article[25]. To recruit the sample, it was attempted to locate 61 children two years after the initial interview. It was possible to get into contact with 57 (93.4%) families and 87.7 percent (n = 50) of them agreed to participate in the longitudinal study. Children whose parents agreed to participate in the follow-up study and children whose parents declined did not differ in age, gender, or masturbation frequency.

As it was not the intent to control the treatment variables, CM and comorbid disorders were treated according to the protocols of the Department of Child Psychiatry; thus, no attempt to randomize the therapy alternatives was made. Parents were informed about the normal sexual development and clinical characteristics of CM, misbeliefs and unrealistic worries were eliminated and various behavior modifications were discussed, depending on the frequency and timing of masturbation. Distracting the child during masturbation, preventing isolation or creating an alternative activity that would take the place of masturbation were among these recommendations. In addition, psychoactive medications were administered to 26 (52%) children who frequently (more than twice a day) masturbated and/or had comorbid psychiatric disorders. Eighteen (36%) children used hydroxyzine (1 mg/kg/day), four (8%) children used thioridazine (1 mg/kg/day), and four (8%) children used imipramine (1 mg/kg/day).

All 50 children were assessed approximately two years (± 6 weeks) after their initial examination, by the same child psychiatrist. Clinical progress of CM and comorbid disorders, and compliance to the treatment were the framework of this interview.

Statistical analysis was performed with a computer package program. Chi-square test and Mann-Whitney U test were used with non-parametric data, and t-test with parametric data. Fisher's exact test was applied when necessary. All tests were two-tailed.

Results

The sample of the present study consisted of 34 girls (68%) and 16 (32%) boys, with an age range of eight to 132 months (mean = 48.7 ± 24.5 months, median ± 24.5 months, median = 38.5 months) at the initial interview. The beginning age of masturbation was 32.4 ± 23.3 months (range = 3-105 months, median = 26.5 months) and was not different among boys and girls. Most of the children came from middle class nuclear families with moderate-income level. Mean schooling time was 8.5 ± 3.7 years for mothers and 10.7 ± 3.3 for fathers.

Twenty-six (52%) patients received at least one additional diagnosis in the initial evaluation according to the DSM-IV diagnostic criteria. These comorbid diagnoses were as follows (because of multiple comorbid diagnoses, the cumulative rates were listed): oppositional defiant disorder (20%, n = 10), nocturnal enuresis (16%, n = 8), sleep terror disorder (8%, n = 4), pica (8%, n = 4), attention deficit hyperactivity disorder (8%, n = 4), nightmare disorder (6%, n = 2), conduct disorder (2%, n = 1), encopresis (2%, n = 1).

The mean masturbation frequency at the initial interview (13.8 ± 14.1 per week) was decreased after two years (1.9 ± 3.8 per week) significantly ($t = 6.248$, $p < 0.0001$). It was noticed that most of the children (62%, n = 31) were completely recovered after six months; eight (16%) other children showed a relapsing course in the first year but were also recovered after two years. Eleven children (22%) continued to masturbate after two years, but at a lower frequency (8.5 ± 3.1 per week).

It was recongnized that the compliance to pharmacotherapy was poor except for the first three months. Most of the parents discontinued the drug therapy after the recovery. The parents of the children who continued to masturbate also discontinued pharmacotherapy without recommendation. Only four (8%) children were using drugs for comorbid disorders after two years. However, it was interesting to learn that most of the behavior modifications were successfully carried out, and worries about this symptom completely disappeared, even in parents whose children did not recover.

Sixteen (32%) children persevered in their comorbid diagnoses after two years. These disorders were as follows (cumulative rates):

oppositional defiant disorder (12%, n = 6), nocturnal enuresis (6%, n = 3), sleep terror disorder (4%, n = 2), pica (4%, n = 2), attention deficit hyperactivity disorder (8%, n = 4), and conduct disorder (2%, n = 1).

The associations between clinical outcome and various clinical variables were examined. It was observed that children who did not recover were significantly younger, and began to masturbate earlier and masturbated more frequently than others (Table I). These children did not differ in terms of other demographic and clinical variables.

Table I. Associations Between Clinical Outcome and Various Clinical Variables

	Recovered (n = 39, 78%)	Not recovered (n = 11, 22%)	Mann-Whitney U	p
Age at the initial evulation (months)	53.9 ± 28.8	30.0 ± 17.8		
Mean rank	28.6	14.5	93.5	0.005
Age when masturbation started (months)	36.1 ± 24.2	19.4 ± 14.0		
Mean rank	28.1	16.4	114.5	0.019
Masturbation frequency at the initial evaluation (weekly)	10.4 ± 10.0	25.6 ± 19.9		
Mean rank	22.6	35.7	102.0	0.008

Discussion

The female to male ratio for CM was about 2:1 in our clinical population. Although girls with CM were more frequently the subjects of case reports[8-11,12], there was also a study in which boys were reported to be prevalent[3]. It is not possible to claim that the rate of masturbation is higher in girls with clinico-epidemiological information alone. It could be assumed that masturbation in boys would create less worry as compared to girls and may be handled at home without any request for medical help.

One of the interesting findings of this study was that masturbation began in most of the children before two years of age. In the literature, the youngest case is a one-month old infant[1]. Bradley[8] also reported two five month-old children. In our study, there were 11 children (22%) who began masturbation between three to 12 months. These findings show that interest toward the genital area begins earlier than expected.

When comorbid features are reviewed, certain clues about the psychopathology and outcome of CM may be detected. Whereas the comorbidity with oppositional defiant disorder, pica, and encopresis may reflect the association of CM with environmental factors, nocturnal enuresis, sleep disorders, and attention deficit hyperactivity disorder suggest the developmental aspects of the symptom. The improvement in the comorbid disorders in two years may also demonstrate both the developmental and the environmental progress. In other words, behavior modifications that provide a more satisfactory relationship and pharmacotherapy may lead to the treatment of CM and some comorbid disorders like oppositional defiant disorder or encopresis. It is also possible that spontaneously, the developmental process itself may play a significant role in the improvement of CM in some patients, as is the fact in some children with comorbid disorders like nocturnal enuresis or sleep disturbances.

The results of this study showed three different clusters of outcome possibilities in the course of CM. Most of the children completely recovered within six months after the first examination with the help of some behavior modification techniques and/or pharmacotherapy, a few children recovered later after a relapsing course, and some children continued to masturbate after two years. However, there are few data to determine these clusters. Even if the children are evaluated in two groups (those who recovered and those who could not), significant associations about the outcome are limited to variables such as age and masturbation frequency. Nevertheless, it can be claimed that children who begin to masturbate early in infancy or who have a high daily frequency of masturbation will have a poor outcome.

This is the first study with a naturalistic design investigating the clinical outcome of CM in a large series of children. Thus, the effects of various treatments on the outcome were not controlled. Despite this limitation, the findings of this study may give us a preliminary opinion about different treatment possibilities and

outcome measures. The findings about the beneficial effect of sedative drugs combined with parental guidance, education and behavior modification techniques seem to be promising. However, it is necessary to investigate various treatment alternatives for CM in a controlled setting.

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Neonatal morbidity and mortality associated with maternal HELLP syndrome

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SUMMARY: Aliefendioğlu D, Yurdakök M, Oran O, Erdem G, Tekinalp G, Önderoğlu L. Neonatal morbidity and mortality associated with maternal HELLP syndrome. Turk J Pediatr 2000; 42: 308-311.

The syndrome of hemolysis, elevated liver enzymes and low platelet count (HELLP syndrome) is a severe form of preeclampsia and eclampsia. To compare the impact of HELLP syndrome and hypertension in pregnancy (HIP) on neonatal morbidity and mortality, 11 infants born to mothers with HELLP syndrome were recruited between 1993 and 1997 from neonatal records. They were compared to 11 infants born to mothers with HIP and 11 control infants born to healthy mothers matched for gestational age, postnatal age and gender. Cesarean section rate was higher in the HELLP group than in the controls ($p < 0.05$). HELLP group infants had lower Apgar scores (54.5% < 1 at 5th min), than controls (9.1%) ($p < 0.05$). Both HELLP and HIP group infants showed a higher incidence of intrauterine growth retardation (63.6% and 54.5%, respectively) than the controls (9.1%) ($p < 0.05$). The incidence of respiratory distress syndrome (RDS) was similar in HELLP and HIP groups and was greater than that in controls (p = NS). Additionally, the neonatal death rate was the highest in the HELLP group (p = NS).

Key words: HELLP syndrome, infant, premature.

The syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP syndrome) is a severe form of preeclampsia and eclampsia. It is a major cause of maternal and perinatal morbidity and mortality. Maternal mortality ranges from 0 to 24 percent and perinatal mortality from 6.6 to 60 percent in the literature[1-3]. The pathogenesis of this syndrome is still unclear. Deterioration of the mother's condition is a major determinant of the management of these pregnancies and often leads to premature delivery. Detailed information on the neonatal manifestations of maternal HELLP syndrome is scarce even though an increased morbidity and mortality has been observed[1,2]. This retrospective study was aimed to compare the outcomes of infants born to mothers with HELLP syndrome and hypertension in pregnancy (HIP).

Material and Methods

We recruited 33 infants born from 1 November 1993 to 30 October 1997 from Hacettepe University Hospital medical records. Infants were grouped (each group included 11 infants) as born to mothers with HELLP syndrome, born to mothers with HIP, and born to healthy mothers. For each HELLP infant, a neonate of a hypertensive mother and a control infant with similar gestational age and, if possible, sex were selected by checking accumulated obstetric records. The selected infant had the birth date closest to the HELLP neonate. Infants of diabetic mothers, infants born to multiple pregnancies, and infants with intrauterine infections and congenital anomalies were excluded. The diagnosis of HELLP syndrome required the presence of thrombocytopenia (< 150000/μl), hepatic dysfunction (increased SGOT, SGPT) and hemolysis (hyperbilirubinemia, and anemia)[3].

Gestational age was determined on the basis of maternal history, early pregnancy ultrasound data and on the Ballard maturity score of the neonate[4]. Small for gestational age (SGA) was

defined as any infant whose birth weight was at the 10th percentile or less for gestational age[5]. The ponderal index was used to detect asymmetric or symmetric SGA. Asymmetric SGA was defined in a newborn whose ponderal index

$$\left(\frac{\text{weight}}{\text{length}^3} \times 100 \left[\frac{\text{gr}}{\text{cm}^3}\right]\right)$$

was below the 3rd percentile[6]. Sepsis was diagnosed based on a positive blood culture and clinical findings, while respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) were diagnosed based on clinical and/or radiological findings. Periventricular-intraventricular hemorrhage (PV-IVH) was diagnosed by cranial ultrasonography.

Results

Maternal and neonatal data are summarized in Tables I and II. Cesarean section rate was the highest in the HELLP group, and the difference between this group and controls was statistically significant; otherwise, the difference between the HELLP and HIP groups was statistically insignificant.

The figures related with the incidence of HELLP syndrome (n = 11) in toxemia (n = 224) and in all pregnancies (n = 9276) was obtained from obstetric records of our hospital from 1 November 1993 to 30 October 1997. Their percentages were 4.9 and 0.12, respectively.

All three groups were similar with respect to gestational age and gender. The control group had the highest birthweight among the other groups. Percentages of SGA infants in the HELLP and HIP groups were close to each other and higher than in controls, and the difference was statistically significant. Apgar scores were less than seven at the 5th minute in six infants in the HELLP group, while the control group had only one infant with a lower Apgar score; the difference was statistically significant.

In the HELLP group two infants (18.2%) died on the 2nd day from RDS, one infant (9.1%) died on the 6th day from sepsis and one infant died on the 15th day from NEC. In the HIP group one infant (9.1%) died on the 2nd day from RDS and one infant died on the 6th day from sepsis. In the control group, only one infant died on the 11th day from sepsis.

Table I. Maternal Characteristics

	HELLP syndrome n = 11	Hypertension in pregnancy (HIP) n = 11	Control n = 11
Maternal age*	26.1 ± 4.1	28.8 ± 4.9	28.9 ± 6.7
Multiparity	7	9	8
Cesarean section**	11	8	5
Antenatal steroid	6	5	5
Mortality	0	0	0

* (Mean ± SD).
** $p < 0.05$ HELLP syndrome versus control.
$p > 0.05$ in all comparison groups by chi square test.

Table II. Demographic Characteristics, Neonatal Morbidity and Mortality

	HELLP syndrome n = 11	Hypertension in pregnancy (HIP) n = 11	Control n = 11
Gestational age (w)*	31 ± 3.7	31.4 ± 3.8	31.0 ± 3.4
Birth weight (g)*	1217 ± 512.7	1285 ± 584	1526 ± 646
Male/Female	4/7	4/7	4/7
Apgar score < 7 at 5th min.**	6	3	1
Neonatal mortality			
Early (< 1 week)	3	2	–
Late (≥ 1 week)	1	–	1
Total	4	2	1
SGA***	7	6	1
Symmetric	4	3	–
Asymmetric	3	3	1
Hypoglycemia	4	2	–
RDS	5	4	1
Sepsis	3	5	2
NEC	1	–	1
Pulmonary hemorrhage	1	–	1
PV-IVH	1	2	1
ROP	1	–	1
BPD	1	–	1

SGA : small for gestational age.
RDS : respiratory distress syndrome.
NEC : necrotizing enterocolitis.
PV-IVH: periventricular-intraventricular hemorrhage.
ROP : retinopathy of prematurity. BPD: bronchopulmonary dysplasia.

* Mean ± SD.
** $p < 0.05$ (HELLP group versus control).
*** $p < 0.05$ (HELLP and HIP group versus control).
$p > 0.05$ in all comparison groups by chi-square test.

Discussion

Although described by several investigators for a number of years[7,8], this variant of preeclampsia was described by the acronym HELLP by Weinstein[3]. The disorder is characterized primarily by microangiopathic hemolytic anemia that progresses to low grade disseminated intravascular coagulation in proportion to the primary process[9]. The pathogenesis of HIP and

HELLP syndrome is attributed to vasoactive agents causing endothelial damage and platelet activation. It is still unknown whether these agents may affect the fetus[10].

Deterioration of the mother's condition is a major determinant in the management of these pregnancies. The termination of the pregnancy results in an increase of the number of thrombocytes and a normalization of the liver enzymes within a few days[11]; therefore, an immediate delivery has been recommended after the diagnosis is made. In our study, cesarean section was the primary mode of delivery in accordance with other reports[1,12].

HELLP syndrome may occur in five to 15 percent of patients with toxemia and the overall incidence is 0.12-0.85 percent for all pregnancies[13,14]. These figures were 4.9 percent and 0.12 percent, respectively, in our study. Pregnancies complicated by the HELLP syndrome have been associated with both poor maternal and neonatal outcome in several publications. While maternal mortality has been reported as between 0-24 percent in literature[1-3], there was no maternal death in our series.

Most of the cases of this study were multipara, as reported by Barlas et al.[15] The gestational ages of infants ranged from 27 to 37 weeks, with a mean of 31.2 (Table II), while it is around 32 to 34 weeks in literature[1,2].

The use of antenatal steroid was not different among the groups. The incidence of RDS was greater in HELLP and HIP groups (36.3%) than in the controls (9.1%), but the difference was not statistically significant. The role of hypertension in pregnancy as a risk factor for neonatal respiratory morbidity is well known. The increased incidence of RDS in babies of hypertensive mothers may be due to the absence of labor before delivery because of the greater likelihood of cesarean section[16]. However, in another study it was observed that after adjustment for labor and mode of delivery, hypertensive disease remained associated with an increase in RDS incidence. The authors concluded that, if the hypertensive disease had not resulted in abnormal antepartum tests, the protective effect would not have developed, and furthermore, the risk of RDS would have increased[17]. In a recent comparative study it was reported that incidence of severe RDS is higher in the HELLP group than in the HIP and control groups[18].

As seen from Table II, SGA proportions for HELLP and HIP groups were close to each other and were significantly higher than those of the control group. Intrauterine growth retardation is a well known consequence of placental insufficiency in babies of mothers with hypertension in pregnancy. Insignificant differences in the HELLP and HIP groups led us to suggest that the growth retardation is basically related to hypertension which begins at earlier or later periods of gestation and that it is not aggravated with maternal HELLP syndrome.

Furthermore, the percentage of lower Apgar scores at the 5th minute was significantly higher in the HELLP group than in the control group, in accordance with other studies[14,19]. Finally, the incidence of neonatal death was greater in the HELLP group but the difference was not statistically significant.

In summary, considering the limitations of its retrospective character, our study suggests an increased morbidity and mortality in infants born to mothers with HELLP syndrome that can be basically related to maternal hypertension.

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Clinicopathological conference: An 11-year-old boy with recurrent infections, hypertension, skin rash, and nephritic syndrome

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SUMMARY: Tınaztepe K, Göçer Ş, Bakkaloğlu A. An 11-year-old boy with recurrent infections, hypertension, skin rash, and nephritic syndrome. Turk J Pediatr 2000; 42: 312-318.

In this clinicopathological conference, an 11-year old boy who presented with recurrent pyogenic infections, hypertension, malar rash, various skin lesions and nephritic syndrome since five years of age is discussed. He was hospitalized for clinical investigation with skin and renal biopsies at 10 years of age. Using clinicopathological data obtained from his last admission, a clinical diagnosis was reached, and the disorders of the complement system causing patients to show these signs or symptoms are emphasized. At the end of the discussion, a clinicopathological correlation is given for making the diagnosis.

Key words: hereditary complement deficiency, childhood, systemic lupus erythematosus, lupus nephritis.

An 11-year old boy was admitted to the hospital with the complaints of fever, rash, shortness of breath and edema. His past medical history revealed that he had been experiencing desquamative, erythematous, crusted skin lesions over the face and extremities, recurrent aphthous ulcers of oral mucosa and purulent otitis media for five years. His pyodermic skin lesions responded well to local or systemic applications of antibiotics but his malar rash and other cutaneous manifestations persisted during his follow-up. He also had a history of recurrent attacks of bronchopneumonia.

Three years after his initial admission to the hospital when he was first noted to have findings of a glomerular disease (hematuria and oliguria), he was put on oral prednisone medication. Three months later, he was hospitalized because of respiratory infection, hypervolemia and heart failure. A lesional skin biopsy revealed microvasculitis and a weak band formation with complement C3 [Lupus Band Test (LBT)] at the dermoepidermal junction, while renal biopsy showed chronic progressive sclerosing glomerulonephritis with a weak but granular staining of C3 and IgG in the glomerular basement membrane and mesangium. Cyclophosphamide and azathioprine were added to the treatment and he was discharged. Five months later, he was readmitted to the hospital with a five-day history of fever, diarrhea, shortness of breath and periodic loss of consciousness.

His parents were unrelated and healthy; no similar complaints were found in one sister (asymptomatic) and two brothers. Family investigation for serology of complement components is discussed later in the text. He was born to a first gravida mother following an uneventful pregnancy.

On physical examination, his general condition was poor. He was pale, irritable and dyspneic with a body temperature of 37 °C, regular pulse of 92/min, respiration rate of 56/min and blood pressure of 155/110 mm Hg. The femoral artery pulses were bilaterally palpable. His height was 136 cm (5^{th}-10^{th} percentile) and weight 28 kg (5^{th}-10^{th} percentile). There were small ecchymotic areas, petechia on the trunk and erythematous and pyodermic skin lesions on the face and whole body, (Fig. 1). A slight edema was noted on eyelids and lips. Fine rales were widely heard on auscultation of lungs. The liver was palpable 10 cm below the right costal margin. There was also ++ pitting edema of legs. The rest of the physical examination was unremarkable.

Laboratory investigation revealed hemoglobin (Hb) 7.5 g/dl, white blood cell (WBC) 3,000/mm^3

with abundant thrombocytes, and no toxic granulation or hypochromia. Urinalysis demonstrated 1012 of specific gravity, 3 (+) proteinuria, no glucose, abundant erythrocytes and 8-10 WBC per high power field in the sediment. Blood urea nitrogen (BUN) was 98 mg /dl (creatinine 8.6 mg/dl, Na 137 mEq/L, K 6 mEq/L, Cl 100 mEq/L, total albumin 4.2 g/dl, albumin 2.2 g/dl, calcium 7.4 mg/dl, phosphorus 4.0 mg/dl, ALT 14 U/L, AST 21 U/L, uric acid 3.5 mg/dl, and creatinine clearance 17 ml/min/ 1.73 m^2. Tests for ASO, CRP, cellular and humoral immunity (blastogenesis, skin tests, T-cell markers, immunoglobulins) were all in normal ranges. Serum total hemolytic activity (CH50) was zero. Complement C3 and C4 levels were normal. Direct Coombs test, LE cell, cryoglobulins, Latex test, HBsAg and antiHBs were negative. Initial antinuclear, anti-DNA, anti-extractable nuclear antigens (anti-ENA), anti-mitochondrial and anti-smooth muscle antibodies were negative. However, anti-DNA antibody became positive during his follow-up. Serum immune complex assays remained persistently elevated.

The patient was treated for lung infection, hypervolemia and hypertension. Fresh frozen plasma given on two occasions was of no benefit. Renal functions progressively deteriorated and a peritoneal dialysis was performed. However, it was ineffective and the patient died of renal failure six days after hospital admission.

CLINICAL DISCUSSION

Based on the medical history, and physical and laboratory findings, it was clearly understood that this patient had experienced recurrent and chronic infections of various organs and systems since early childhood. He also had additional signs and symptoms indicating renal involvement for three years. In childhood,

a) a history of systemic bacterial infections on two or more occasions.
b) three episodes of severe respiratory infection or bacterial infection like cellulitis, or purulent otitis media documented by cultures.
c) development of an infection in unusual sites like liver or brain abscess.
d) development of an infection with uncommon pathogens, i.e. Aspergillus infection and,
e) presence of more severe infections than expected by common pathogens.

indicate a necessity for a thorough investigation of the immune system[1]. In this context, this patient should first have been thought to have an immune deficiency state because of the recurrent infections occurring in the respiratory system, ears and skin.

The initial step to work-up the immunodeficiency disorders is routine screening for complete blood count (CBC), peripheral blood smear and erythrocyte sedimentation rate (ESR), with tests for B and T cell functions and CH50 for the complement system. Afterwards, more sophisticated molecular, biologic and other specific tests may be needed in light of obtained data[1]. The present case showed nearly normal results for T and B cell functions for his age. On the other hand, it was a notable finding that the value of CH50 was zero, while serum levels of complement C3 and C4 were normal. Therefore, a functional and quantitative measurement of other components of the complement system, particularly the early ones like C1q and C2, should be determined.

This case revealed capillaritis, a weakly positive lupus band test (LBT), anemia, leukopenia, and biochemical data and urinary findings, such as proteinuria, hematuria and granular casts in the sediment, suggesting a renal involvement. Renal biopsy performed six months prior to his death also confirmed the latter, yielding a diagnosis of chronic sclerosing progressive glomerulonephritis (GN). In view of the combined data, a systemic disease, particularly systemic lupus erythematosus (SLE), should be strongly suspected[2,3]. LBT is known to be positive in 90 percent of lesional skin in cases with SLE[4]. It is also detected in 60 percent of non-lesional skin in these cases, providing a rather specific and diagnostic finding in making the diagnosis of SLE. On the other hand, an initially negative anti-DNA antibody test became positive during the course of the disease with simultaneous deterioration of renal functions. Though a small percentage of patients with SLE may show a negative ANA test, especially in the state of antigen excess, it is wellknown that ANA and anti-DNA antibody may be completely undetectable in cases with SLE or SLE-like illnesses associated with primary deficiency of the complement components[2]. The present case could be considered deficient for the early components of the complement system since he had undetectable CH50 with all these findings and in view of results of family

investigation on serum complement levels. Deficiency of early complement components should be remembered because our patient was a male child with clinical findings and serology mimicking SLE, and with an elevated level of circulating immune complexes, and his initial complaints started in the preschool period. Development of SLE is unusual in a male child of this age. Therefore, SLE accompanying a hereditary deficiency of early complement components is most likely. This underlines the value of evaluation of age and gender in these conditions.

In fact, SLE or SLE-like illnesses may develop in hereditary complement deficiency states, particularly of the early components like C1q, C2, C3 or C4[5-10]. These patients have an increased risk of autoimmunity and of serious bacterial infections, particularly with pneumococcus. Deficiencies of terminal components are associated with a high incidence of Neisseria infections. SLE or other collagen vascular diseases may also be seen in these cases, though to a lesser extent (Table I)[5]. In addition to SLE, recurrent skin lesions, discoid lupus or SLE-like illnesses, patients with C1q deficiency have been reported in association with various types of glomerular diseases such as lupus GN, membranoproliferative GN, mesangioproliferative GN and IgA nephropathy[7-10]. Renal biopsy done six months before death in our case revealed a diagnosis of chronic progressive sclerosing glomerulonephritis. However, the needle biopsy could reflect only this aspect of lupus nephritis with a highly pleomorphic nature varying from one glomerulus to another. Immunohistology revealed evidence of an immune complex-mediated disease. The demonstration of granular deposition of immune reactants in glomeruli with LBT positivity in skin by immunofluorescence microscopy confirmed the diagnosis of SLE. Additionally, both glomeruli and skin revealed C3 deposition but no C1q, suggesting a disorder of complement system components especially when the CH50 value was found to be zero. These immunohistological findings also indicated the progressive nature of the chronic sclerosing glomerulonephritis. The persistence of high levels of circulating immune complexes indirectly supported this. Hypertension is considered as a natural consequence of chronic

Table I. Primary Deficiencies of Complement Components and Associated Clinical Findings

Deficient component	Infection type	Renal and/or rheumatologic findings
Classical pathway		
C1q, r, s	Pneumococcal sepsis, meningitis, other pyogenic	SLE*, GN, cutaneous vasculitis
C4	Other pyogenic	SLE, GN, collagen tissue disease
C2	Other pyogenic, pneumococcal sepsis, meningitis, meningococcal meningitis	SLE, GN, collagen tissue disease cutaneous vasculitis, discoid lupus
C3	Other pyogenic, pneumococcal sepsis, meningitis, meningococcal meningitis	GN, cutaneous vasculitis, SLE, discoid lupus
C5-9	Meningococcal, gonococcal infections	SLE, GN, collagen tissue disease
Alternative pathway		
Factor D	Rarely gonococcal infections	
Factor B	Frequent meningococcal infections	
Control proteins		
C1 esterase INH	Hereditatry angioedema	
Factor I	Other pyogenic meningococcal, meningococcal meningitis	
Factor H	Meningococcal meningitis, Other pyogenic	GN, cutaneous vasculitis, SLE, discoid lupus, membranoproliferative GN type 11, hemolytic, uremic syndrome
Properdin	Meningococcal meningitis Pneumococcal sepsis	Cutaneous vasculitis, discoid lupus Collagen tissue disease excluding SLE

SLE: systemic lupus erythematosus; GN: glomerulonephritis.

parenchymatous disease leading to chronic renal failure.

In conclusion, a primary deficiency of one of the early complement components (C1q or C2) in our case was likely and SLE and/or SLE-like disease might develop with this genetic background. The manifestations associated with renal involvement may reflect morphologically the lupus nephritis since all types of GN with immune complex deposition may be encountered in patients with SLE.

Clinical Diagnoses

I. Primary (hereditary) complement deficiency
   a) Deficiency of early components, C1q or C2?
   b) SLE or SLE-like disease
      1. Lupus nephritis (renal biopsy diagnosis) (Class IV WHO classification)
         Chronic progressive sclerosing glomerulonephritis
         (with granular immune complex deposition)
      2. A weak LBT positivity (lesional skin)
      3. Malar rash, oral and nasal mucosal ulcers and various types of skin lesions
      4. A history of frequent chronic active suppurative infections such as bronchopneumonia, otitis and bacterial dermatitis

II. Chronic renal failure and its related hypertension

III. Failure to thrive

Additional Tests for Evaluation of the Complement System

These studies were performed by Berkel et al.[8] Immunohistochemical and functional tests of all complement components were within normal values except for C1q. The alternative pathway activity was normal. A sister was found to be asymptomatic with undetectable CH50 and no C1q activity, suggesting a hereditary, (primary) complement deficiency. The father had a normal CH50 and the mother had intermediate values of CH50. A retrospective study was initiated to find any known mutations for the genes of C1q in the family members. Unfortunately, no specimen was available to extract chromosomal DNA of the present case. However, a point mutation at amino acid position 186 in the C1q A chain gene was identified in the asymptomatic sister with C1q deficiency by polymerase chain reaction of amplified C1q A chain gene and restriction with endonuclease PvuII. This finding confirmed the diagnosis of a hereditary deficiency of C1q.

Pathological Findings and Clinicopathological Correlation

Histopathological and Immunohistological Findings: Renal and skin biopsies together with micronecropsies of right whole kidney, skin, muscle, liver and small intestine were examined. On light microscopy, when comparing the renal biopsy done six months prior to death, glomeruli and interstitial tissue revealed more severe involvement. There were various types of injury in almost all glomeruli. (Fig. 2). Mesangial proliferation, mesangial matrix increment, basement membrane thickening (as wire-loop lesions in some areas), segmental or global sclerosis in some glomeruli, subepithelial spikes and focal membranous changes resembling chain-like structures, double-contour appearance and focal extracapillary proliferation were noted (Figs. 3-6). Additionally, polymorphonuclear leukocyte infiltration, karyorrhexis, focal areas of necrosis and intraluminal thrombosis in some glomeruli were also observed (active lesions). Tubuli showed prominent atrophy with hyalin and cellular casts in their lumina (Fig. 2). Vessels seemed to be unaffected while the interstitial tissue revealed focal areas of fibrosis, minute calcifications and mononuclear cell infiltration. All these chronic and acute pleomorphic findings were compatible with lupus nephritis. On immunohistology, a weak granular staining with C3, C4, IgG, and IgM was demonstrated in the glomerular basement membrane zone (BMZ), but no C1q deposition. A diagnosis of "diffuse active, segmentally proliferative, focal membranous and sclerosing and extracapillary proliferative lupus glomerulonephritis" (WHO Class IV) was made. Lesional skin biopsy revealed microvasculitis and a weakly positive LBT. Liver necropsy revealed congestion and non-specific triaditis. There were no remarkable findings on histological examination of skin, muscle or small intestine micronecropsies.

Final Pathologic Diagnoses

1. Pimary C1q deficiency(clinicopathological diagnosis)
   SLE or SLE-like illness (Clinicopathological correlative diagnosis)

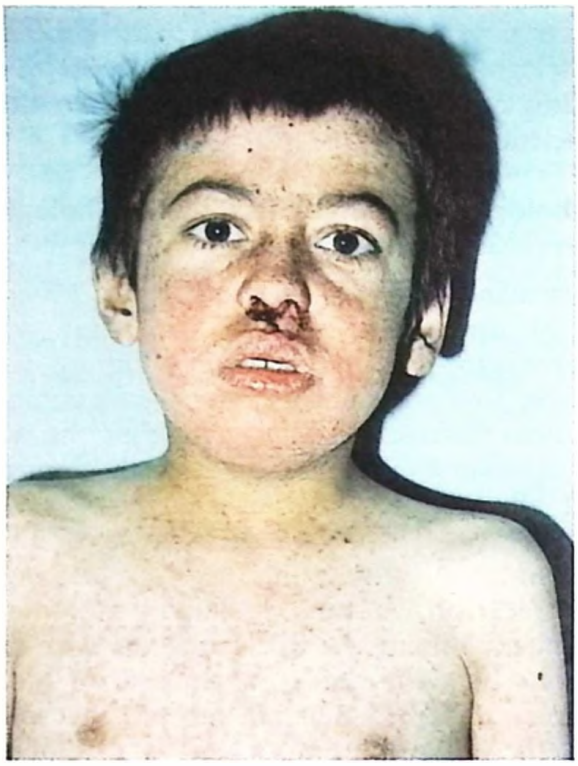

Fig. 1. Butterfly rash on the face, maculopapular lesions covering whole face and upper part of the trunk, and epistaxis (recalling ulcerative lesions of nasal mucosa).

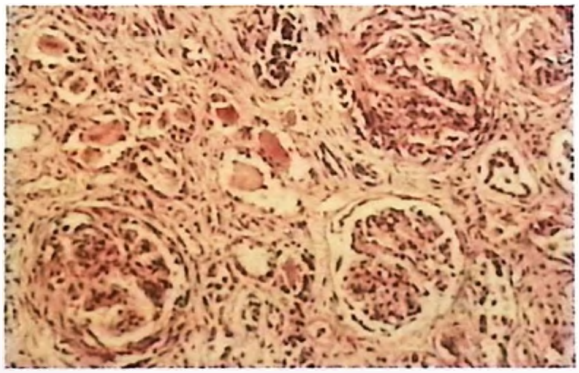

Fig. 2. Renal necropsy under lower magnification. Glomerular lesions (diffuse proliferative, crescentic, lobular) varying from one glomerulus to another, even from one segment to another in a single glomerulus. Variable tubular atrophy, interstitial and periglomerular fibrosis, are also seen. (HE x 200).

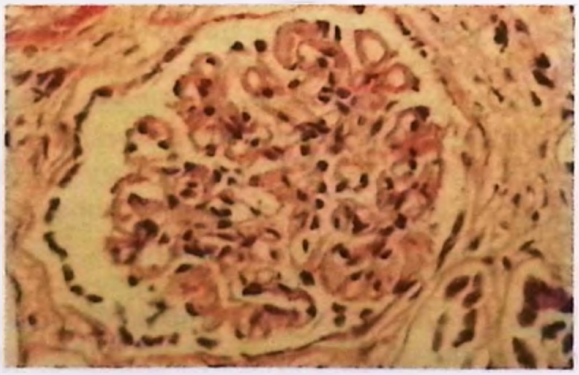

Fig. 3. A glomerulus with focal endocapillary proliferation and basement membrane thickening are seen, (HE x 400).

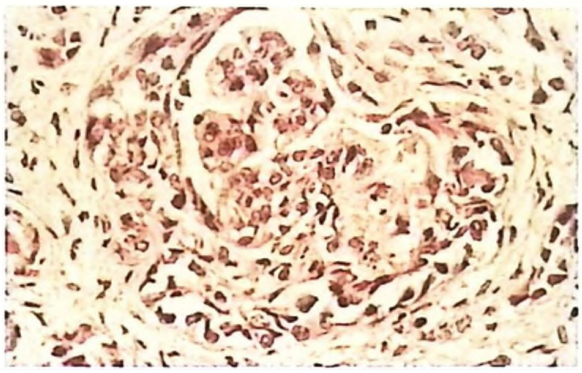

Fig. 4. This microphoto depicts a glomerulus with endo- and extracapillary proliferation. The crescent is mostly epithelial covering two-thirds of the glomerular thuft. (HE x 400).

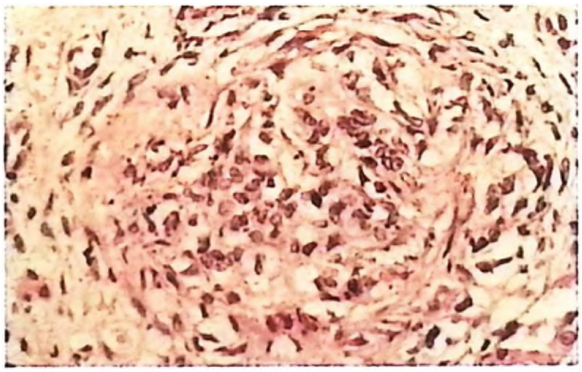

Fig. 5. Bowman's capsule space in a glomerulus is completely obliterated by crescent consisting of mostly fibrous and a few cellular components. Endocapillary proliferation is still prominent in the middle of the glomerulus (chronic active) (HE x 320).

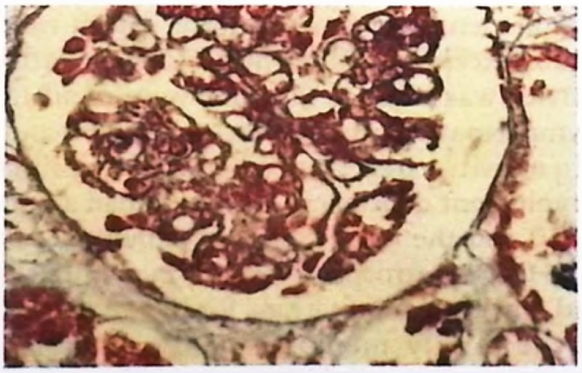

Fig. 6. Focal 'wire-looping' appearance due to thickening of the glomerular basement membrane. On close examination, reddish immune complexes can be seen in the thickened segments of the glomerular basement membrane, (thrichrome stain x 400).

1. Lupus nephritis (Class IV)

   Diffuse proliferative chronic progressive lupus glomerulonephritis (WHO Class IV)
2. LBT positivity (lesional skin)
3. Dermal vasculitis, lupus dermatitis (clinicopathological diagnosis)

Clinicopathological Correlation

Glomerular lesions in this 10-year-old boy were both histopathologically and immunohistologically consistent with diffuse lupus nephritis. Lupus nephritis develops in two-thirds of patients with SLE[2,3], and the diffuse type indicates a poor prognosis. Systemic lupus erythematosus is a rare disease in childhood and is seen mostly in adolescent girls. Male:female ratio is 1:9 in this age group and reduces to 1:3 below 10 years of age. It is notable that the patient was male and that his complaints started before the age of 10. In such a case, primary complement deficiency should be kept in mind when SLE or an SLE-like disease is encountered[7-9].

The complement system is one of the most important components of humoral immunity[5]. This biomolecular system plays a role in virus neutralization, opsonization, release of histamine and, other mediators and most importantly, solubilization of immune complexes. The complement system describes early components of classical (C1423) and alternative (C3, Factors B and D) activation pathways, the membrane attack complex (C5b-9), seven serum and five membrane regulatory proteins, one serosal regulatory protein and eight membrane receptor binding components and their fragments. These 20 components are all proteins and make up 10 percent of the serum globulin fraction. They are made mainly in the liver but are also produced by monocytes and adipose tissue. Complement components interact like a cascade which is known to be activated in two different pathways, the classical and alternate pathways (Fig. 7). In the classical pathway, the sequence of interaction of complements is antigen-antibody-C142356789, and in the alternate pathway, activator (antibody)-C3BD-C356789.

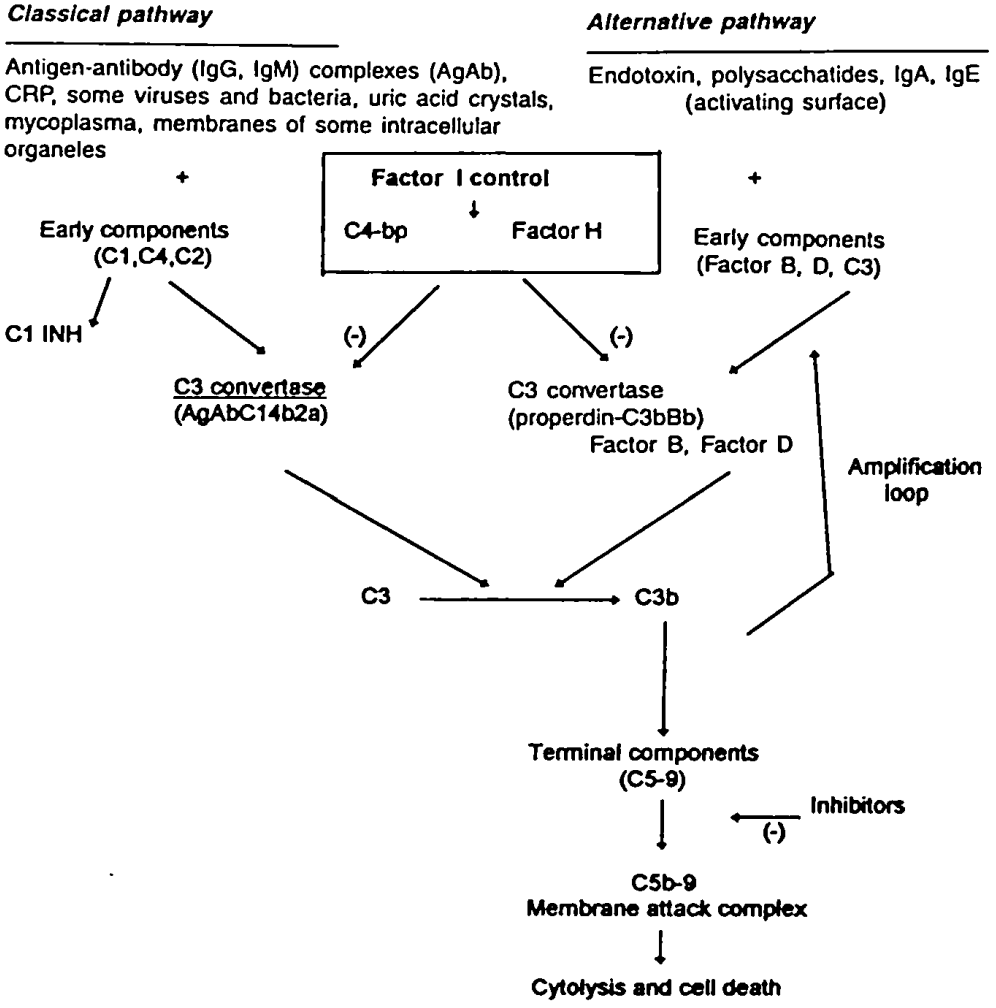

Fig. 7. Complement system and its activation cascade.

Patients with hereditary complement deficiencies have an increased risk of autoimmunity and of development of life-threatening infections such as sepsis or meningitis[5]. This is because of defective clearance of immune complexes by the mononuclear phagocytic system due to failure of their opsonization caused by the complement deficiency. These insoluble immune complexes can aggregate in the tissues resulting in initiation of the inflammatory reaction and the release of autoantibodies[5,6]. Studies on C1q deficiency suggest that C1q-C1q receptor interactions may play an important part in cleaning the apoptotic cells. In deficiency states, this residual apoptotic material may trigger the autoimmune response[9,11].

Clinical and laboratory findings of patients with SLE associated with primary complement deficiencies differ somewhat from those of cases without primary complement deficiency. For instance, renal disease might not be evident and could be identified only by biopsy (Lupus nephritis Class I, WHO classification). In addition, tests for ANA and anti-DNA antibody can be negative or appear weakly positive later in most of the patients, as in the present case.

C1q deficiency is a rare complement deficiency[10,11]. The disease is usually associated with recurrent pyogenic skin and mucosal lesions, glomerulonephritis accompanying SLE or SLE-like diseases (Fig. 1). The number of cases with C1q deficiency reported so far is now over 40. Many cases with complete C1q deficiency (both functionally and antigenically) may present with SLE-like disease, infectious complications and mesangioproliferative GN, whereas those with only functionally deficient C1q may show severe SLE and lupus nephritis[8].

In conclusion, this rare complement defect should be insistently investigated in male patients who are under 10 years of age presenting with SLE or SLE-like diseases with recurrent infections, erythematous desquamative skin lesions, malar rash, and oral and nasal aphthous lesions.

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Triosephosphate isomerase deficiency with elevated sweat chloride test: report of a case

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A 15-month-old girl with severe hemolytic anemia and progressive respiratory failure is presented. She was well until the age of six months when she developed a pulmonary infection. During the next six months, she had frequent respiratory infections and her paleness became evident. At the age of 12 months, she was observed to have easy fatigability and muscle weakness, and she received her first blood transfusion. She was referred to our hospital at the age of 15 months. The physical examination revealed a malnourished girl with hypotonia, nystagmus, generalized muscle weakness and severe breathing difficulty requiring ventilatory support The hemoglobin (Hb) was 9.7 g/dl; hematocrit (Hct) 29%, mean corpuscular volume (MCV) 101 fl and reticulocyte count 15%. Peripheral blood smear revealed macrocytosis and stomatocytosis (30% of the red cells) and polychromasia. Sweat chloride test was 90 and 94 mEq/L on two separate occasions. The serum vitamin E level was 0.26 mg/dl (N: 0.44-0.68). She was found to be heterozygous for factor V Leiden mutation. Although malnutrition, low serum vitamin E and elevated sweat chloride test were suggestive of cystic fibrosis, this diagnosis failed to account for all the findings in the patient. A search for a red cell enzyme deficiency revealed that the red cell triosephosphate isomerase (TPI) activity was low. DNA analysis showed the 315 G-C (105 Glu-Asp) TPI mutation, thus confirming the diagnosis of TPI deficiency.

Key words: triosephosphate isomerase deficiency, elevated sweat chloride.

Triosephosphate isomerase (TPI) enzyme catalyzes the interconversion of dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3 phosphate in the energy-generating glycolytic pathway. Although the enzymatic defect can be partially bypassed via the hexose monophosphate shunt, its deficiency results in a rare autosomal recessive disease characterized by markedly reduced enzyme activity in all tissues accompanied by metabolic block in glycolysis with accumulation of intracellular DHAP, particularly in red cells. Clinically, patients present with hemolytic anemia, increased susceptibility to infections and progressive and severe neuromuscular symptoms. As yet, there is no promising treatment and the disease usually culminates in death[1]. We report a new case with TPI deficiency who, in addition to the characteristic findings of TPI, had a greatly elevated sweat chloride test and low vitamin E levels and was prone to develop thrombosis. Implications of these findings in the differential diagnosis are discussed. The patient also had heterozygosity for factor V Leiden mutation.

Case Report

A 15-month-old girl was admitted to the intensive care unit because of progressive respiratory failure. Her parents were first cousins and she had a seven-year-old healthy sister. Her past history revealed that she was well and had normal developmental milestones

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until six months of age when she was diagnosed to have anemia and pulmonary infection. After this point, respiratory infections recurred frequently. She was transfused at another facility once at 12 months of age when she also started to have easy fatigability and muscle weakness. She was never able to sit without support or to crawl. Physical examination in this hospital at 15 months of age showed a severely malnourished girl weighing 6.9 kg (< 3rd percentile). She had striking hypotonia, generalized muscle weakness and prominent breathing difficulty with patchy infiltrates on both lungs. Blood gas determination showed carbon dioxide retention, whereupon she was intubated for ventilatory support. The hemoglobin (Hb) was 9.7 g/dl: hematocrit (Hct) 29%, white blood cell count 12,000/mm^3; mean corpuscular volume (MCV) 101 fl; platelets 314,000/mm^3; and reticulocytes 15%. Peripheral blood smear showed macrocytosis, polychromasia and marked basophilic stippling. It was remarkable in addition for the presence of stomatocytosis (30%) of the red cells). Hb electrophoresis, direct and indirect Coombs tests, autohemolysis, osmotic fragility, serum B12 and folic acid levels and urinary orotic acid excretion were normal. Red cell G6PD, pyruvate kinase, and pyrimidine 5'-nucleotidase levels were within normal limits. Of note, however, was an abnormal hydrogen peroxide hemolysis test and a low α-tocopherol level, 0.26 mg/dl (N: 0.44-0.68), which prompted a search for cystic fibrosis (CF). Sweat chloride was 90 and 94 mEq/L on two occasions with a two week interval. Steatocrit was negative and an ultrasonographic examination of the pancreas was normal. In order to have definitive evidence to affirm or refute the diagnosis, a mutation analysis was undertaken and exons of cystic fibrosis transmembrane regulator (CFTR) on chromosome 7 were analyzed. A large part of the CFTR gene, including exons 3, 7, 9, 10, 11, 14a, 14b, 17b, 18, 19, 20, 21 and 22, were screened and no mutation was detected. Immunologic evaluation, including immunoglobulin levels, lymphocyte subsets, blastic transformation, and neutrophil chemotaxis, was normal. Similarly, a search for a mitochondrial DNA abnormality was negative.

A diagnosis of TPI deficiency was entertained on clinical grounds and was confirmed by an enzymatic assy showing a significantly low TPI level (459.7 IU/g Hb N: 1317.0-2905.0). The mutation on chromosome 12p13 was at cDNA 315 G-C and had the amino acid chain designation 105 Glu-Asp.

Interestingly, the patient was noted to have thrombosis at venipuncture sites, and she was found to be heterozygous for factor V Leiden mutation. The patient was unable to be fed orally and total parenteral nutrition (TPN) was instituted at the second month of hospital stay.

Sweat chloride test was repeated at four week intervals, and a final sweat chloride test two months after the first one was 20 mEq/L. On the fifth month of admission, the patient died of respiratory failure.

Discussion

Our patient exhibited all the characteristic features of TPI deficiency, and the diagnosis was confirmed by enzymatic assay and mutation analysis. The exact mechanism leading to clinical manifestations in TPI deficiency remains obscure. Although accumulation of DHAP was claimed to be responsible[2], other enzymatic deficiencies associated with increased concentrations of DHAP do not result in a similar clinical picture[3].

The most interesting features in our patient with respect to the previously published patient were the high sweat chloride test, marked stomatocytosis and the incidental finding of heterozygosity for factor V Leiden mutation. Many of the findings, including parental consanguinity, recurrent pulmonary infections, low vitamin E levels and hemolytic anemia[4,5], suggested the diagnosis of CF. As the diagnosis of TPI deficiency was confirmed by biochemical and molecular analysis, the question then arose whether the elevated sweat chloride was a sign of coexisting CF, even though the absence of chronic diarrhea and chronic changes in the chest X-ray did not support this diagnosis.

The extensive molecular search that was performed failed to detect any mutations. The final low sweat chloride determination also supports the notion that the elevation in sweat chloride was probably not due to CF. Yet another possibility is that the elevated sweat chloride might have been due to the presence of severe malnutrition, as sweat chloride normalized, probably because of TPN[4,5].

Another interesting finding in our patient was marked and persistent stomatocytosis in the peripheral blood smear. We introduce this pathology as one of the features of the hemolytic components of the disease. However, this finding needs to be supported by other observations in the future.

Presence of factor V Leiden mutation, which is the most common pathology underlying the hypercoagulable state in Turkish patients, with a frequency of 32 percent in children with thrombosis versus 7.1 percent normal controls[7,8], shows that even in patients with known pathologies, a search for this distinct entity should be instituted.

The case presented in this report, in addition to being another example of a very rare autosomal recessive deficiency, implies that some cases, especially those with hemolytic anemia due to vitamin E malabsorption, may have been misdiagnosed as CF. Therefore, we suggest that, especially in cases where molecular analysis fails to detect any mutation and where hemolytic anemia and stomatocytosis are part of the clinical picture, TPI level should be determined in order to rule out this rare deficiency.

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Familial Müllerian agenesis

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SUMMARY: Tiker F, Yıldırım SV, Barutçu Ö, Bağış T. Familial Müllerian agenesis. Turk J Pediatr 2000; 42: 322-324.

Müllerian agenesis is characterized by the absence of the fallopian tubes, uterus and internal portion of the vagina. Patients have normal female phenotype and genotype, with normal secondary sex characteristics but with amenorrhea. We report a family in which müllerian agenesis was diagnosed in three siblings and their two paternal aunts. This family was ascertained when the proband was evaluated for primary amenorrhea. She had normal secondary sexual development. Her karyotype was 46, XX. Ultrasound examination and magnetic resonance imaging of the pelvis revealed absence of the uterus and vagina. The proband had three sisters and two of them showed similar physical and radiological findings. Two of the proband's paternal aunts had no uterus. Although the pathogenesis of müllerian agenesis is well understood, the etiology and genetics are still unknown. Various forms of inheritance patterns have been suggested by several authors. In conclusion, it would appear that müllerian agenesis is influenced by multifactorial inheritance and polygenic and familial factors.

Key words: müllerian agenesis, familial, genetics.

The normal development of the female reproductive system depends on complete interaction between genetic, hormonal and environmental factors to produce the differentiation of the müllerian and wolffian ducts and urogenital sinus. The female reproductive system develops from the pair of müllerian ducts, which subsequently, in the absence of müllerian inhibiting factor, secreted by the testis, fuse to create the fallopian tubes, the uterus and the upper four-fifths of the vagina[1,2].

Müllerian abnormalities range from minor anatomic changes to total aplasia[1,3]. Müllerian agenesis, also known as Mayer-Rokitansky-Küster-Hauser syndrome, is a syndrome involving the absence of müllerian structures including the fallopian tubes, the uterus and the internal portion of the vagina. The disorder may be associated with other somatic anomalies, most frequently involving the urological and skeletal systems, and rarely the eye and middle ear.

Although the pathogenesis of müllerian abnormalities is well understood, the etiology and the genetics of müllerian agenesis are still unknown. Familial aggregates of müllerian agenesis have been reported[4,5]. But a genetic study of 23 families by Carson et al.[6] revealed no affected relative of the proband. Shokeir[7] concluded that müllerian aplasia was a female-limited autosomal dominant trait.

The syndrome is usually diagnosed in adolescence because of primary amenorrhea. The karyotype is usually 46, XX.

We report a family in which müllerian agenesis was diagnosed in three siblings and their two paternal aunts, and review the literature.

Case Report

This family was ascertained when the proband, 14-years-old, was evaluated for primary amenorrhea. She had the normal onset of thelarche and adrenarche at the age of 11 years. On physical examination she had normal secondary sexual development. Her vaginal introitus appeared rudimentary with a depth of 0.5 cm and a hypoplasia of the hymenal ring. Her karyotype was 46, XX. Ultrasound examination and magnetic resonance imaging of the pelvis revealed absence of the uterus and vagina (Fig. 1). Both ovaries were present and normally located (Fig. 2). Radiographic findings of the spine were normal. Intravenous

pyelogram showed normal renal system. The odiogram and ear examination were normal.

The proband had three sisters, two of whom showed similar findings. Genital examination showed blind vaginal pouch. Their karyotypes were 46, XX. Ultrasound examination and magnetic resonance imaging of the pelves of the two sisters showed absence of the uterus and vagina (Figs. 3, 4). Intravenous pyelogram and spine radiograms were normal.

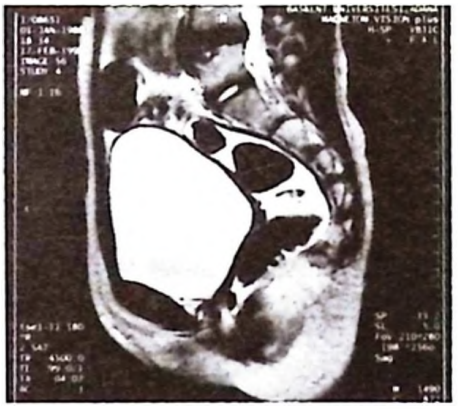

Fig. 1. Midline sagittal section with T2W reveals the absence of the uterus.

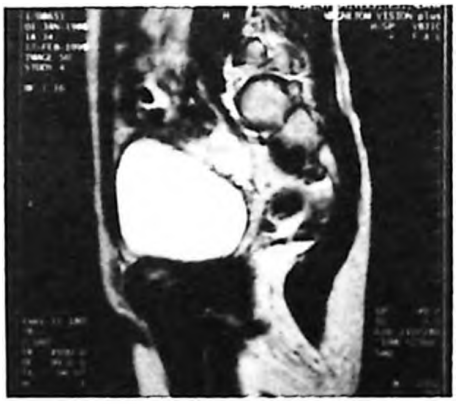

Fig. 2. Right parasagittal T2W image demonstrates the right ovary containing several follicles.

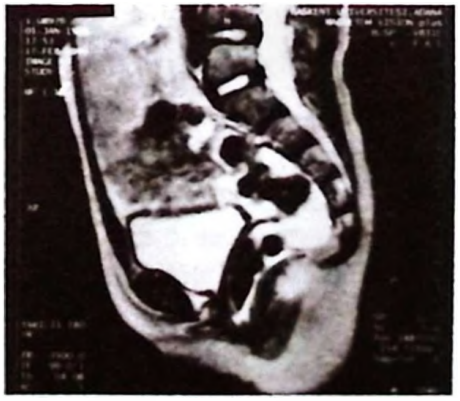

Fig. 3. T2W midline sagittal image demonstrates the bladder and rectum. The uterus is absent.

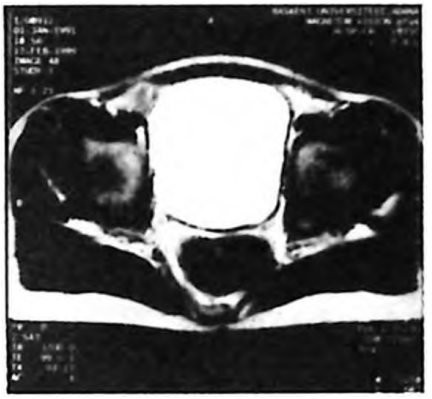

Fig. 4. T2W transverse image reveals the absence of the uterus between the bladder and rectum.

The pedigree of the family is shown in Fig. 5. The mother and father were second-degree relatives. The father had eight siblings and the mother ten. Two of the proband's paternal aunts were infertile and had been told by their gynecologist that they had no uterus. The paternal grandfather and grandmother were not relatives. There were seven other female cousins, but the family refused to bring them in for diagnostic investigations.

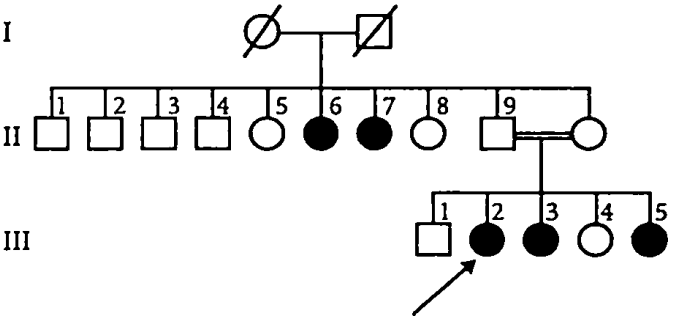

Fig. 5. The pedigree of the family.

Discussion

Müllerian agenesis is characterized by the absence of the fallopian tubes, uterus, and internal portion of the vagina. Patients have normal female phenotype and genotype and normal secondary sex characteristics, but with amenorrhea.

Müllerian agenesis is accompanied by renal abnormalities in approximately one-third of the cases[8-11]. Spinal and skeletal anomalies may occur with a frequency ranging from 10 to 12 percent[12,13]. Anomalies involving the eye and middle ear can also occur[14,15].

Strubbe et al.[16], in a study including 100 women with congenital absence of the vagina and uterus, performed various diagnostic investigations to

establish whether there were any associated congenital anomalies. His findings suggested that there might be two different syndromes in this patient group, namely an isolated form of congenital agenesis of the vagina and uterus and a more generalized condition. In the family we report here no other abnormalities involving the other systems were detected, thus suggesting an isolated form of congenital absence of the vagina and uterus.

The etiology and genetics of müllerian agenesis is unknown. Activating mutations of either the gene for antimüllerian hormone or of the gene for the antimüllerian hormone receptor are proposed as possible factors[17].

Familial aggregates of müllerian aplasia have been reported by Sarto and Simpson[5,18] and suggested a polygenic or a multifactorial inheritance. Families with affected siblings have been documented by several investigators[19]. These familial aggregates raise the formal possibility of an autosomal recessive gene. But Lischke et al.[20] observed three affected individuals who each had a normal monozygotic twin. Thus, autosomal recessive inheritance is an unlikely explanation for all cases. In this study, Schokeir[7] believed that a sex limited autosomal dominant gene might be responsible for some of the cases of müllerian aplasia. The study of Petrozza et al.[21] suggested that congenital absence of the uterus and vagina is not inherited commonly in a dominant fashion and that it is likely a polygenic, multifactorial, or possibly a recessive trait.

Although the family we report here and other reports of families characterized by multiple affected siblings and relatives raise the possibility of an autosomal recessive gene or female limited autosomal dominant inheritance, other earlier reports in the literature suggested various forms of inheritance. In conclusion, it would appear that müllerian agenesis is influenced by multifactorial inheritance and polygenic and familial factors.

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Dilatation of a restrictive interatrial communication using a balloon angioplasty catheter

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SUMMARY: Ayabakan C, Karagöz T, Çeliker A. Dilatation of a restrictive interatrial communication using a balloon angioplasty catheter. Turk J Pediatr 2000; 42: 325-327.

Balloon atrioseptostomy is a life-saving procedure palliating certain congenital heart defects like transposition of the great arteries, right or left atrioventricular valve atresia, hypoplastic left heart syndrome, and pulmonary hypertension. Occasionally the Rashkind balloon septostomy technique may be ineffective in creating an adequate interatrial communication. We performed balloon dilatation of a restricted atrial septal defect using a balloon angioplasty catheter in a three-month-old infant.

Key words: atrioseptostomy, balloon dilatation, transposition of the great arteries.

The survival of infants with certain congenital cardiac defects depends on the presence of an adequate interatrial communication[1]. Balloon atrial septostomy is one of the most commonly performed palliative procedures for neonates[2,3]. Occasionally, an adequate communication at the atrial level is present at birth but becomes restrictive with increasing age, and a communication then has to be made. The Rashkind balloon septostomy is usually successful in neonates, but may be ineffective in older children with a thickened atrial septum[1,4]. Blade atrial septostomy may be an alternative for such patients; however, it has its limitations[1,4,5]. Technically it is harder to perform and may have increased risk of complications. We performed balloon dilatation of a restricted atrial septal defect in a three-month-old infant.

Case Report

A three-month-old female infant was referred to our hospital. She had cyanosis since birth. On admission she had tachycardia (156/min) and tachypnea (52/min). Her blood pressure was 90/45 mmHg. She had hepatomegaly, palpated 4 cm below the costal margin. The first and second heart sounds were normal; a systolic ejection murmur of grade 1 was heard at the second left intercostal area. All the pulses were symmetrically palpated, including the femoral pulses. The other physical examination findings were normal.

On telecardiogram the cardiothoracic ratio was 56 percent with a narrow base of the cardiac silhouette. Pulmonary vascular markings appeared normal. The electrocardiography revealed right axis deviation (+10°) and right ventricular hypertrophy. The white blood cell count, hemoglobin and arterial oxygen saturation were 9,200/mm^3, 16.7 g/dl, and 29 percent, respectively.

The transthoracic echocardiography revealed transposition of the great arteries with a small patent foramen ovale. There was no patent ductus arteriosus or ventricular septal defect. A balloon atrial septostomy was performed via the right femoral vein with fluoroscopic guidance. Initially a 5F Nu-med Z-5' ® balloon atrioseptostomy catheter was used for the procedure. The balloon was inflated with a maximum 2 ml saline in the left atrium and was retracted to the right atrium. The oxygen saturation of the right ventricle before and after this procedure was 29 and 38 percent, respectively. The small increment in the oxygen saturation suggested insufficient mixture at the atrial level after the balloon atrial septostomy. Therefore, we inflated a Tayshack balloon angioplasty catheter of 7x3 mm twice at the interatrial septal level (Fig. 1). The oxygen saturation increased to 54 percent. On the transthoracic echocardiography, 7 mm of atrial septal defect was measured after the procedure. The patient is now clinically well awaiting an atrial switch operation.

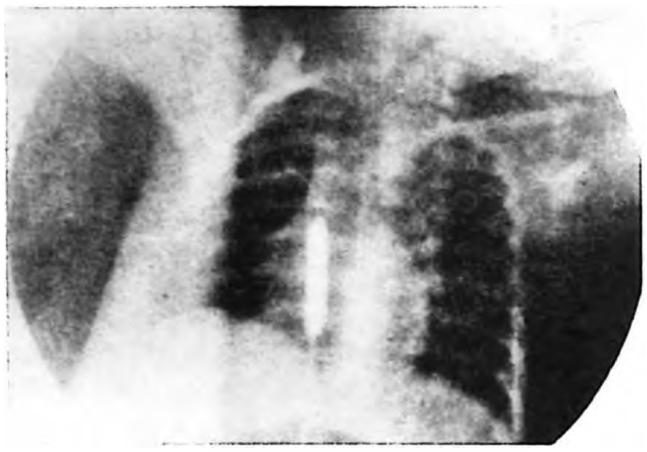

Fig. 1. Dilatation of the atrial septum using balloon angioplasty catheter.

Discussion

Many patients with certain forms of congenital heart defects require an adequate interatrial communication for survival. The transposition of the great arteries usually presents in the neonatal period, and a balloon atrial septostomy is life saving for these patients. However, some patients, as in the case presented here, may need this procedure after the neonatal period. There are other congenital heart diseases that usually present after the neonatal period, namely right or left atrioventricular valve atresia. Recently, an atrial septostomy has been used to palliate infants with hypoplastic left heart syndrome and older patients with primary pulmonary hypertension[1,6]. Rashkind balloon atrial septostomy procedure may not be successful for many patients, especially beyond the neonatal period. Even when the balloon septostomy is performed in the neonatal period, progressive restriction of the interatrial communication often develops[7]. These patients have been palliated surgically with Blalock-Hanlon atrial septectomy or non-surgically with Park's blade septostomy procedure for many years. Both techniques may be quite hazardous for a critically ill neonate or infant. Furthermore, not all the cardiologists are familiar with the blade atrial septostomy procedure.

There is limited experience in literature regarding balloon dilatation of the atrial septal defect; therefore, comparing the effectiveness as well as the security of this procedure with blade septostomy is not possible. In all the cases presented in the literature so far, this procedure was very successful without many serious complications[1,6,8-11]. Creating a large interatrial defect through a small introducer sheath (5-6 F) is a clear advantage of this procedure. Any palliation achieved may be of short duration, which may also be a restriction of other procedures. Mitchell et al.[8] showed that stationary angioplasty balloon atrial septostomy is effective in producing interatrial communications which remained patent for four to 14 weeks in animals. Although experimental studies in animals have demonstrated that balloon dilatation of the atrial septum produced defects within the fossa ovalis without causing tears that extended to the adjacent septum, excessive tearing of the atrial septum beyond the fossa ovalis is a possible risk, especially when large balloons are used for small infants.

Balloon dilatation of an atrial septal defect is a procedure that is safe and easy to perform. It is an alternative technique that can produce larger atrial defects than the Rashkind balloon atrial septostomy procedure. Further reports of clinical experience are needed to determine the efficacy and safety of this procedure in relation to blade septostomy.

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Pseudomonas sepsis with neutrophagocytosis in a premature newborn

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SUMMARY: Aliefendioğlu D, Aslan D, Tekinalp G, Gürgey A. Pseudomonas sepsis with neutrophagocytosis in a premature newborn. Turk J Pediatr 2000; 42: 328-330.

Secondary hemophagocytic syndrome may develop during certain severe infections commonly due to viral infections, but is rarely associated with bacterial infections, and its appearance in a premature newborn is uncommon. We present a case of hemophagocytosis during Pseudomonas aeruginosa septicemia in a premature infant. After sepsis treatment with imipenem-cilastatin and aminoglycoside, remission of hemophagocytosis was achieved.

Key words: hemophagocytosis, newborn, Pseudomonas.

Secondary hemophagocytic lymphohistiocytosis (HLH) is more often associated with an infectious episode, particularly with viruses of the herpes group, and tends to occur in older individuals who may have received immunosuppressive therapies. Secondary HLH is also referred to as infection associated hemophagocytosis[1] .

The association of hemophagocytic syndrome with bacterial infection is rare[2] and its appearance in a premature newborn is uncommon. We present a premature infant with bacterial sepsis due to Pseudomonas. Her clinical picture and findings were consistent with secondary hemophagocytosis. She was treated only with antibacterial therapy and remission was obtained.

Case Report

A female infant was born to a 40-year-old healthy mother by spontaneous vaginal delivery at 31 weeks of gestation. The pregnancy was complicated by premature rupture of membranes and chorioamnionitis. The mother had neither a family history for hemophagocytic syndrome nor was there parental consanguinity.

Her clinical and radiological findings were compatible with respiratory distress syndrome (RDS) and she was given surfactant therapy. Her clinical status deteriorated and she developed sclerema and jaundice on the 2nd day of life. She was diagnosed as having clinical sepsis; a single blood volume exchange transfusion was performed and empirical antibiotic therapy was started immediately. On the 7th day of life, hepatosplenomegaly was noted (the liver was palpable 5 cm below the right costal margin and the spleen was palpable 3 cm below the left costal margin). Later, liver and spleen sizes increased further, and on the 15th day the liver and spleen were palpable at 7 cm and 8 cm below the costal margins, respectively. Laboratory investigation showed hemoglobin 10.5 g/dl, platelets 9,000/mm^3, and leukocyte count 15,500/mm^3. On the peripheral blood smear neutrophils were 67%, and lymphocytes 33%, and vacuolated blood cells were seen. Plasma triglyceride and transaminating enzymes were increased. Coagulation test results were within normal ranges. Bone marrow aspiration revealed proliferation of histiocytes and hemophagocytosis; neutrophagocytosis was especially prominent. Viral investigation showed no exposure to Epstein-Barr virus (EBV), cytomegalovirus (CMV), rubella, herpes simplex virus (HSV), toxoplasma, hepatitis B and C, or parvoviruses. Lymphocyte subset analysis revealed no abnormality. Metabolic investigation (galactosemia spot test, amino acid chromatography) was normal.

Tracheal aspirate, bronchoalveolar lavage, and blood cultures revealed Pseudomonas aeruginosa. According to the antibiogram, broad spectrum antibiotic regimen (imipenem-cilastatin and

aminoglycoside combined therapy) was started on the 15th day. Hepatosplenomegaly regressed and platelet count normalized within ten days. The treatment was discontinued and the patient was discharged on the 39th day of life.

Discussion

Hemophagocytic lymphohistiocytosis is a reactive disorder of the histiocytes, characterized by their increased hemophagocytic and proliferative activity against erythrocytes, leukocytes and platelets in the liver, spleen, lymph nodes and bone marrow. The main features of HLH are persistent fever, cytopenia, liver dysfunction, hepatosplenomegaly, jaundice, coagulopathy and sometimes central nervous system symptoms. Bone marrow examination permits diagnosis with characteristic presence of macrophages with signs of active hemophagocytosis[3]. Although phagocytosis of only erythrocytes is a common process[4], neutrophagocytosis was prominent in our patient (Fig. 1).

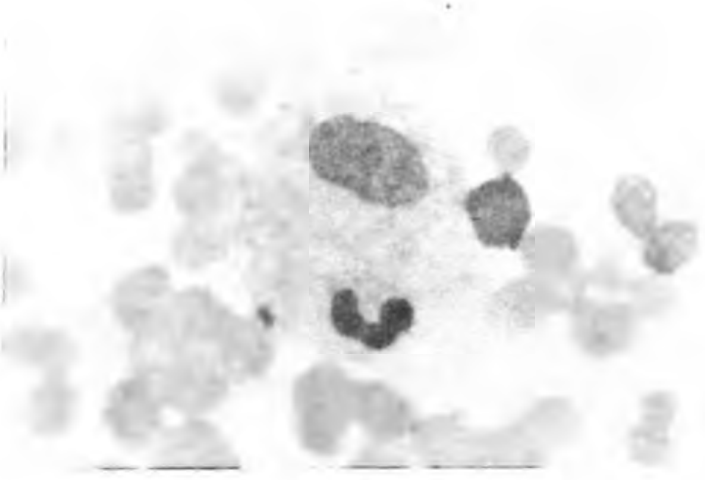

Fig. 1. Histiocyte with neutrophagocytosis.

The pathophysiology is thought to be mediated through a defect in the immunomodulation, resulting in an unrestricted release of inflammatory cytokines. The clinical and laboratory findings are consistent with these cytokines[5] . The clinical findings of our case were compatible with HLH, except for the absence of fever. The febrile response is believed to reflect enhanced metabolic activity and to be related to the release of endogenous pyrogens (i.e. cytokines, interleukin-1 and TNF) from the host's leukocytes, which then trigger a hypothalamic response. Because these pathways are not particularly well developed in the neonate, fever is not a valuable sign of infection[6] nor probably of HLH in this age group.

Patients with congenital or acquired immunodeficiency are at risk of having hemophagocytosis and of developing a hemophagocytic syndrome with or without associated infection. Acquired immunity in the newborn is affected by qualitative and quantitative deficiencies and, as newborn infants are at increased risk of serious infections, this situation may cause the newborn to be vulnerable to HLH.

This syndrome encompasses both primary (familial) and secondary HLH, which are frequently difficult to distinguish from each other[4]. The clinical course and the prognosis of secondary HLH are more favorable than in familial HLH. A previously affected sibling and/or history of consanguinity and an early onset may reveal a familial basis. In our case, there was neither a family history for HLH nor parental consanguinity, and the disease was self limited with the treatment of underlying bacterial sepsis. These findings led us to the diagnosis of secondary HLH in this patient.

Secondary HLH is more often associated with an infectious episode. Viral infections probably play a major role in secondary HLH; however, bacterial infections (tuberculosis, Leishmania, brucellosis, syphilis)[7] have rarely been reported. We were unable to find any other report of Pseudomonas infection associated with HLH.

In conclusion, hepatosplenomegaly, cytopenia, liver dysfunction, jaundice, coagulopathy, and

central nervous system symptoms exist in patients with both HLH and neonatal sepsis. In patients where hepatosplenomegaly and cytopenia resist appropriate antibiotic and supportive treatment, HLH should be kept in mind, and bone marrow aspiration should be performed for the diagnosis. In addition, in patients where neutrophagocytosis predominates, bacterial infection should be suspected as the cause of secondary HLH.

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Double meningocele Case Report

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SUMMARY: Durmaz R, Arslantaş A, Özön YH, Tel E. Double meningocele: case report. Turk J Pediatr 2000; 42: 331-333.

The coexistence of two distinct meningoceles of the spine is a very unusual event. We report a three-day-old boy with double meningoceles at the thoracic and lumbar levels. The connection between the stalk of the thoracic meningocele and the spinal cord, as seen on magnetic resonance imaging, showed a neurological involvement in this lesion. Our case is only the third without association of congenital anomalies or neurofibromatosis to be reported to date.

Key words: double meningocele, tethered cord.

The occurrence of double meningocele and/or myelomeningocele in different regions of the spine is an exceedingly rare event. Apart from cases with an association of congenital anomalies or neurofibromatosis, only two cases are reported in the literature[1,2]. We present a case with double meningoceles, of which one was connected to the spinal cord.

Case Report

The patient, a three-day-old male, was admitted to the Neurosurgical Department of Osmangazi University Hospital with two cysts located on the spine. He was born by cesarean section to a 30-year-old mother at 40 weeks of gestation. He weighed 4000 g at birth (90th percentile) and was 51 cm in length. He was the third child of non-consanguineous parents. His mother's second pregnancy was terminated due to congenital hydrocephalus at 28 weeks of gestation.

Physical examination revealed two celes in the midline, one in the thoracic and the other in the lumbar area (Fig. 1). The one overlying the upper thoracic region was 6x7 cm and appeared more tense than the lumbar cele, which was 3x2 cm in diameter. Both lesions were widely covered by skin but only partly by an opaque membrane at the top of the fundus. The patient's head circumference was 37 cm (over 90th percentile) and no congenital anomaly was found. There was no sign of neurofibromatosis, and the neurological examination was normal. There were no numerical or structural anomalies in the GTG-banding chromosome karyotype analysis of blood samples taken from the patient or from his parents.

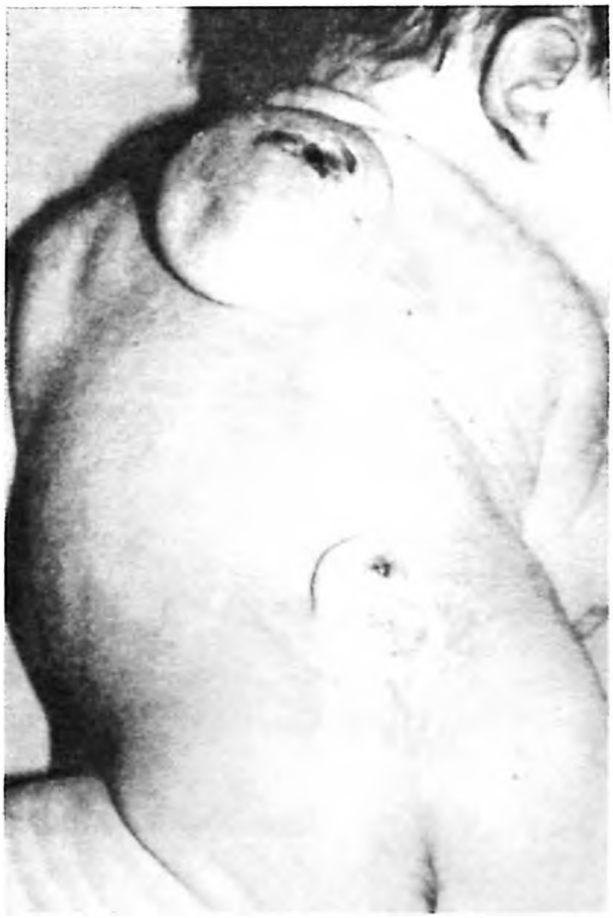
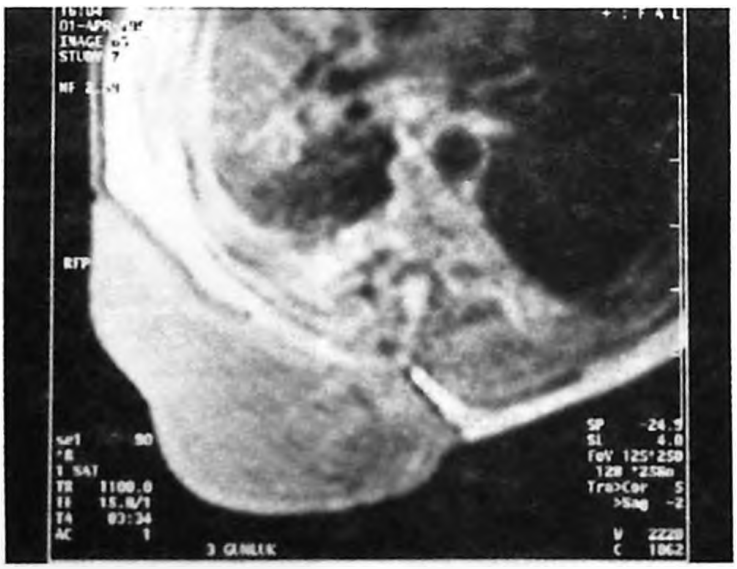


Fig. 1. The patient with double meningomyelocele at the dorsal and lumbar areas of the spine

An X-ray radiogram of the spine was normal. On magnetic resonance imaging (MRI) the thoracic sac was shown to be covered by skin and connective tissue, and there was a connection between the spinal cord and the neck of the lesion (Fig. 2).

Both lesions were explored at the same time through a circumferential incision. Both sacs contained clear cerebrospinal fluid but no neural tissue; however, neural elements were seen attached to the stalk of the thoracic sac. A partial laminectomy was performed on the bony

(a)



(b)

Fig. 2. a) The sagittal T1-weighted MRI shows two distinct sacs and also a neural connection between spinal cord and the stalk of the thoracic meningocele. b) A neural attachment to the neck of the lesion on the axial T1-weighted MRI of the thoracic cele.

structure surrounding the neck of the lesion and the neural elements were released as far as possible. Both defects were repaired with subcutaneous fascia and normal skin.

The patient developed no neurological deficits nor hydrocephalus over the duration of a one-year follow-up.

Discussion

The incidence of meningoceles in Turkey is reported to be high[3]: seven cases were found among a total of 41,785 deliveries[4]. The coexistence of meningocele and/or myelomeningocele in different regions of the spine is very unusual; to the best of our knowledge, only six cases of such an occurrence have been reported to date. Unfortunately, two cases with thoracic and lumbar meningoceles were associated with neurofibromatosis type 1[5]. Potter[2] noted two such occurrences, one of which was associated with hydrocephalus and Arnold-Chiari malformation. Bertan and Wilson[6] also reported a similar case of a patient who underwent operation for double myelomeningocele and died from bronchopneumonia as a result of a ventriculo-pleural shunt complication. Bailey[1] reported a case of double meningocele of which one contained neural elements. Following the first case of Potter and the second case of Bailey, our case is only the third without congenital anomalies or neurofibromatosis to be published to date.

Etiological factors responsible for spinal dysraphism are not known. Dietary causes and vitamin deficiency, such as of folic acid, especially during the critical period of neurolation between 18 and 21 days of gestation, may play a role in its development[7]. In addition, karyotype analysis of chromosomes was performed on blood samples from our patient and from his parents, but no abnormality was found.

The MRI findings of dysraphic thoracic cele may disclose cord involvement in our case, which showed a connection between the stalk of the cele and spinal cord. The term "meningocele with tethered cord" has been coined for this type of lesion, and found in nearly 50 percent of patients with meningocele[8].

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Congenital generalized infantile myofibromatosis and neonatal hemochromatosis
An autopsy case report

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SUMMARY: Aksoy F, Göksel S, İlvan Ş, Dervişoğlu S, Ramazanoğlu R. Congenital generalized infantile myofibromatosis and neonatal hemochromatosis: an autopsy case report. Türk J Pediatr 2000; 42: 334-337.

An autopsy case of congenital infantile myofibromatosis and neonatal hemochromatosis is reported. A thirty-six-hour-old baby girl had multiple subcutaneous nodules in addition to multiple visceral involvement of heart, lungs, pharynx, larynx, stomach, small bowel, large bowel, pancreas, kidneys, spleen, thyroid, adrenal glands, lymph nodes, peripheral nerves, meninges and soft tissues. In these tumoral nodules, three types of histological patterns were observed: 1-hemangiopericytoma-like, 2-mixed, and 3-pure spindle cell. Tumor cells were immunohistochemically positive for actin, and negative for desmin, muscle-specific antigen, and estrogen, related protein. The histological and immunohistochemical findings of the case suggested that a close relationship may exist between infantile myofibromatosis and infantile hemangiopericytoma. In addition to infantile myofibromatosis, neonatal hemochromatosis characterized by iron deposition in parenchymatous organs such as liver, pancreas, lungs, thyroid, and adrenal glands was another important characteristic of the case.

Key words: infantile myofibromatosis, neonatal hemochromatosis, congenital fibromatosis infantile hemangiopericytoma.

Congenital generalized infantile fibromatosis is a rare entity characterized by the formation of multiple tumoral nodules or masses localized in the viscera, musculoskeletal system and subcutaneous tissues[1-4]. Infantile myofibromatosis may also arise postnatally or in adolescence[2,3]. After its first recognition by William and Schrum[5] ind 1951 as a congenital fibrosarcoma, Stout[5] indicated that this tumor is benign and denoted it as congenital generalized fibromatosis. Chung and Enzinger[3] renamed it as infantile myofibromatosis (IMF)[3]. It has been reported that IMF can be of multicentric, solitary or generalized types, with the solitary type being the most common[1,36-11].

Neonatal hemochromatosis (NHC) is also a rare and specific entity in the spectrum of childhood liver diseases[12,13]. Three cases of IMF with iron deposition in the liver have been reported in the literature[6,9,14]. To our knowledge, however, there is no reported case of IMF together with NHC. We present an autopsy case of generalized congenital IMF with NHC in a 36-hour-old baby girl.

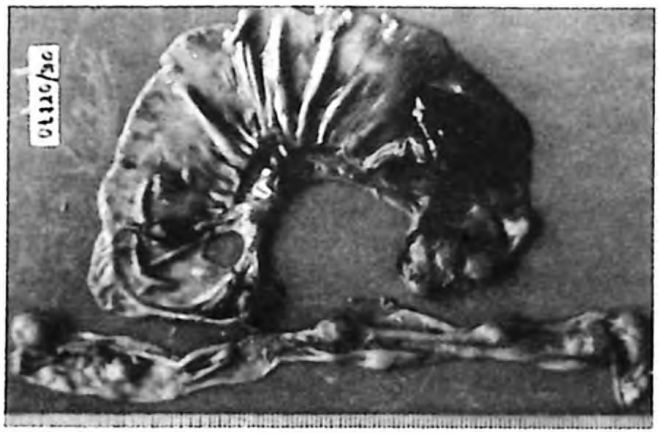
Case Report

The infant, who weighed 2,250 g at birth, was the second child of a 19-year-old multigravida, and was born after 36 weeks of gestation. The first pregnancy of the mother had ended during the first trimester by spontaneous abortion. The infant died in 36 hours as a result of cardiopulmonary insufficiency. There was no kinship between mother and father, no history of disease and no use of drugs before or during pregnancy.

Autopsy Findings: Multiple subcutaneous, polypoid nodules ranging between 0.5 to 1.5 cm in diameter were seen all around the body (face, scalp, trunk and extremities) upon gross examination. Similar types of nodular lesions were seen in many visceral organs such as heart, lungs, gastrointestinal tract, gall bladder,

pancreas, spleen, tongue, pharynx, larynx, adrenal glands, kidneys and meninges (Figs. 1, 2). The same nodules were located in diaphragma and the soft tissues of the body cavities as well. Extrahepatic bile ducts were not obstructed. The internal organs appeared normal both in shape and position, except for these nodules.

(1)



(2)

Figs. 1, 2: Multiple visceral nodules, some of which are hemorrhagic, are seen in heart, kidneys, adrenal glands, and small and large intestines.

Three types of histological patterns of the nodules were observed: 1-centrally located endothelial-lined vascular clefts surrounded by spindle cells (Fig. 3), as revealed by Gomori's reticulum silver staining (hemangiopericytoma-like pattern), 2-centrally located hemangiopericytoma-like pattern surrounded by spindle cells resembling fibroblasts or smooth muscle cells (mixed pattern), and 3-entire nodule composed of fusiform cells arranged in fascicular pattern (pure spindle-cell pattern). All three tumor patterns showed secondary changes such as hyalinization, hemorrhage, necrosis, and calcification.

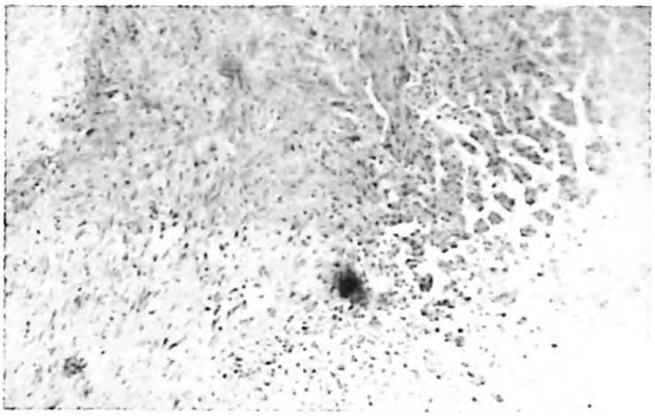


Fig. 3. These well circumscribed nodules exhibit fasicles of spindle-shaped cells in the periphery and prominent vascular features in the center, (hemangiopericytoma-like) (HxE 200).

Immunohistochemically, fusiform cells reacted positively with actin (BioGenex), and negatively with desmin, muscle-specific antigen and estrogen-related protein (BioGenex).

Sections from the liver showed atrophy of hepatocytes and a pseudoacinary arrangement with giant-cell formation. Fibrosis of the sinusoidal walls and portal areas were additional features revealed by silver stain (Gomori's reticulum). Moderate extramedullary hemopoiesis was observed (Fig. 4). Almost all hepatocytes contained accumulation of yellowish-brown pigments in their cytoplasms. Bile thrombi were detected in the intrahepatic bile canaliculi. The heavy accumulation of iron was demonstrated by the application of Lillie's iron staining (Fig. 5). While it was limited to the hepatocytes, no such accumulation was detected in Kupffer cells. Fouchet's bile staining was positive only in intracanalicular bile thrombi. In addition to the liver, the pancreas also showed heavy iron accumulation. Other parenchymatous organs such as lungs, kidneys, and the thyroid gland, contained moderate amounts of iron. Deposition of iron in the tumoral nodules located adjacent to the necrotic and vascular-rich areas was a striking feature. Pathological diagnosis was congenital generalized infantile myofibromatosis with neonatal hemochromatosis.

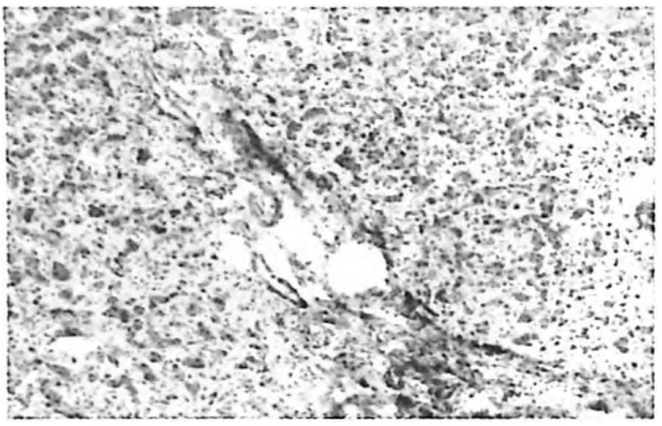


Fig. 4. Atrophy of hepatocytes and pseudoacinary arrangement with giant cell formation is shown (HxE 100).

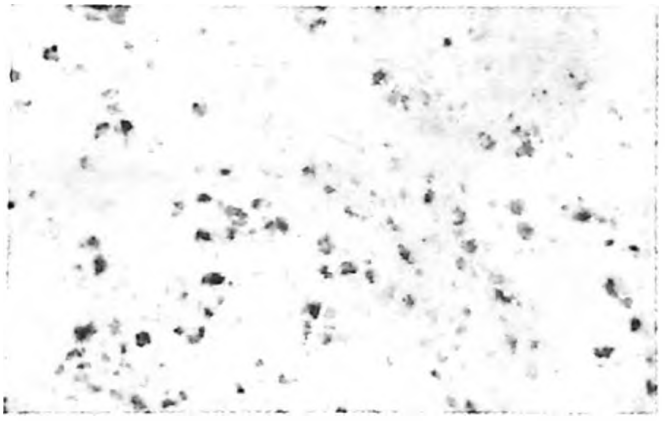


Fig. 5. Lillies's iron staining demonstrating iron accumulation in the liver (Lillies's iron x 200).

Discussion

Infantile myofibromatosis is a rare childhood soft-tissue tumor. Coffin and Dehner[2] reported a large series of infantile myofibromatosis with an incidence of 12 percent in childhood soft tissue tumors and of 22 percent in childhood fibromatosis[2,5,16]. Ünüvar et al.[17] and Kotiloğlu et al.[18] reported two cases of infantile myofibromatosis, one in a 14-day-old neonate, the other in a three-month-old infant, respectively. Our case was a baby born at the 36th week of gestation who lived for 36 hours.

There are some debatable points on the histogenesis of the tumors. Their marked resemblance to smooth muscle and staining reaction specific to smooth muscle were noticed by some authors[6,21]. However, because of the desmin negativity with actin positivity, the possibility of myofibroblastic origin was considered[3,7,9,15,19]. In our case, the fusiform tumor cells were positive for actin, but negative for desmin and muscle-specific antigen. Kotiloğlu et al.[18], in their case of the three-month-old infant with multicentric infantile myofibromatosis, showed the same type of staining patterns in the tumor cell. These findings are not specific for either myofibroblastic or for smooth muscle origin. Chung and Enzinger[3] indicated that infantile hemangiopericytoma should be included in the differential diagnosis of these tumors, and emphasized that the presence of myofibroblasts is a differentiating feature between these two entities[3]. On the other hand, Coffin and Dehner[16] suggested that IMF and infantile hemangiopericytoma are identical tumors[2,20,22]. Ultrastructurally, the tumor cells in IMF have fibroblastic features such as dilated cisternae of rough endoplasmic reticulum, prominent Golgi apparatus, mitochondria and peripheral micropinocytotic vesicles. Furthermore, these tumor cells have the smooth muscle features as well, including irregularly margined nuclear membranes with deep infoldings, abundant longitudinal bundles of parallel cytoplasmic microfilaments, intracytoplasmic dense bodies along microfilaments and basement membrane-like material[7-9].

The above features have also been observed in the ultrastructural examinations of the tumor cells in hemangiopericytoma, and some similarities between pericytes and fibroblasts/ smooth muscle cells have been noted in the literature[14,21,22,24,25]. As a parallel finding, the tumor cells of adult hemangiopericytoma react positively with actin and vimentin, and negatively with desmin and myoglobulin, as in IMF[22-26]. In view of the above, it can either be concluded that pericytic and myofibroblastic cells cannot be differentiated by ultrastructural and immunohistochemical methods, or that these are identical tumor cells. In our case, early lesions determined by light microscopy were in a hemangiopericytoma-like pattern. With this observation and with the observations of the other authors, we suggest that IMF is the same tumor as infantile hemangiopericytoma.

Neonatal hemochromatosis is a rare autopsy finding of the neonatal period with an unknown etiology. The pathologic chances in the liver are the same as with adult type hemochromatosis, containing iron depositions in the hepatocytes

with fibrosis and bile stasis. Iron deposition in the other parenchymatous organs of the body is a constant feature[10,11].

Three cases of IMF associated with iron deposition in the liver are reported in the literature (one is dense, the other is moderate, and the third is slightly higher than normal range)[6,10]. These findings are considered coincidental and not related to IMF[1,15]. Excess iron intake by the mother is a suspected etiologic agent in the development of neonatal hemochromatosis. However, various experimental studies showed that the placenta controls iron transportation and that excess iron in the mother does not affect the fetus in utero. Therefore, maternal iron overload alone is not responsible for the abnormalities seen in NHC[12]. In our case, due to secondary changes like hemorrhage and necrosis of the tumors, excessive free iron and its compounds from the degenerated cells caused hemochromatosis.

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Congenital sick sinus syndrome with breath holding and severe syncope episodes during infancy A case report

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SUMMARY: Karagöz T, Çeliker A, Özer S, Özme Ş, Saraçlar M. Congenital sick sinus syndrome with breath holding and severe syncope episodes during infancy: a case report Turk J Pediatr 2000; 42: 338-340.

Sick sinus syndrome is a rare cause of bradycardia in children without structural heart disease. A case of profound sinus bradycardia, sinus arrest with junctional escape, and pauses in a two-year-old infant with breath-holding and syncope episodes is presented. As a result of these clinical symptoms and elecrocardiographic findings, the patient with sick sinus syndrome underwent implantation of transvenous ventricular pacemaker. He has been well and asymptomatic since the insertion of the pacemaker. In the differential diagnosis of an infant with breath-holding and syncope episodes, when these symptoms in particular cannot be explained by other common reasons, sick sinus syndrome should be kept in mind. This case also illustrates the importance of electrocardiographic studies for the diagnosis.

Key words: sick sinus syndrome, breath holding, syncope, infancy.

Although sick sinus syndrome (SSS) is usually a disease of the elderly produced by idiopathic degeneration of the sinoatrial node, it can be seen in children after extensive cardiac surgery, particularly involving the atria, such as the Mustard or Senning procedure, and after operations for tetralogy of Fallot or tricuspid atresia[1]. SSS occurs infrequently in children who have not undergone cardiac surgery, otherwise involving a normal heart without structural defect[1]. The reason sometimes can be a focal myocarditis or arteritis[1].

Its initial manifestations range from asymptomatic to nonspecific symptoms including palpitation, fatigue, dizziness, chest pain, syncope, congestive heart failure and even sudden death[1]. Although SSS rarely occurs, considering its serious consequences, for example severe syncopes and sudden death, it should be borne in mind in the differential diagnosis of an infant with breath holding and severe syncope episodes.

Case Reports

A two-year-old male infant was referred for evaluation of breath holding and syncope. He was born at term, the first pregnancy of a 23-year-old healthy mother. His birth weight was 3000 g. The parents were first cousins. A slow fetal heart rate was detected by a Doppler recording at the prenatal routine examination at 32 weeks of gestation. Then fetal echocardiography was performed which revealed bradycardia with normal anatomy. Because of the poor cultural and economic level, the woman gave birth in another center without informing us and did not bring her baby for a check-up after the delivery for two years. His medical history included four breath-holding episodes lasting about 20 seconds and three syncope episodes lasting about 3-10 minutes, noticed by the parents over the two years.

Physical examination revealed only bradycardia (45 beats per minute). His weight was 12,000 g (25^{th}-50^{th} percentile); and head circumference, 49 cm (50^{th} percentile). Otherwise the physical examination was normal.

Electrocardiography (ECG), ambulatory ECG analysis and echocardiographic study were performed. A standard 12-lead electrocardiogram revealed profound sinus bradycardia less than

50 beats per minute (Fig. 1). Echocardiographic study showed normal cardiac anatomy. On 24-hour electrocardiography, his rate ranged from 33 to 77 (average 45) beats per minute (bpm). Also, it represented frequently occurring sinus arrest with junctional escape and pauses above two seconds (Fig. 2).

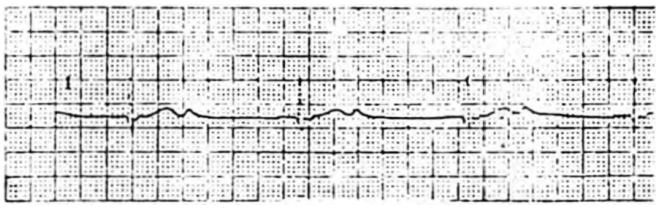
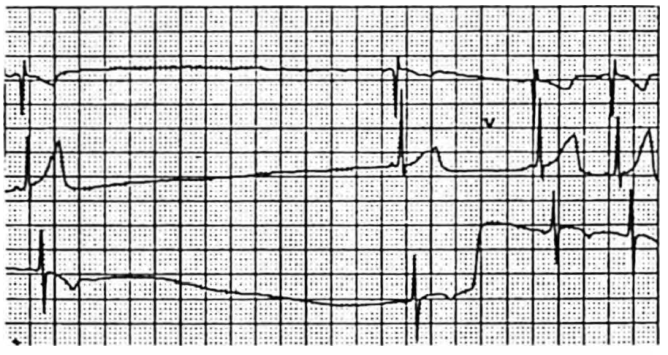


Fig. 1. Standard electrocardiogram of patient with profound sinus bradycardia.



Fg. 2. Ambulatory electrocardiography of patient with sinus pauses above two seconds.

Because of severe syncope episodes and profound bradycardia, we decided to implant a permanent pacemaker, and immediately inserted a "Pacesetter Microny SR+ 2425T S/N: 732501994 VVIR" pacemaker (ventricular). Since the insertion of the pacemaker, he has been well and asymptomatic. He is now three-years-old and his growth and development are normal.

We investigated the other members of the family for SSS and found no evidence of sinus node disorders.

Discussion

The underlying pathologic abnormality in patients who have undergone extensive cardiac surgery is probably sinus node damage because of hemorrhage, necrosis, and injury during operation with placemant of sutures through the sinus node[1]. However, the underlying pathologic process and causes in young patients with normal cardiac anatomy are unknown. There is not enough information about pathologic features of sinus node dysfunction in the medical literature. Thus, to describe SSS when no other cause is found, the terms "idiopathic, primary, and congenital" are commonly used. Familial occurrences have been described in a few reports but are probably rare, and these reports revealed an autosomal dominant mode of inheritance[1,4]. For this reason we investigated the parents of our case, but they showed no evidence of sinus node disorders.

The diagnosis of SSS in children often depends on the clinical setting. The clinical manifestation of SSS is related directly to age, the function of the remaining conduction system and the underlying hemodynamic state. In infants, poor feedings, lethargy or signs and symptoms of congestive heart failure may be associated with severe bradycardia. In older children bradycardia may manifest as general fatigue, and increased sleep requirement. Dizziness and syncope are difficult to detect in infants and young children. In this age group, seizures may be secondary to unwitnessed syncope. Furthermore, unless these young patients have noticeable syncope episodes and seizures, the disease is unlikely to be detected. Some reports are indicating that SSS may frequently be undiagnosed in young patients who have this syndrome and a normal cardiac anatomy[1]. The incidence of such dysfunction in children without associated cardiac defects may be higher than the reported values in the literature. We thus believe that any complaints of "breath-holding spells", syncopes, dizziness or light-headedness, unexplained seizures, or any observation of palpitation with a fast or slow heart rate should be investigated further by ambulatory or exercise electrocardiography, or both. In some cases, an electrophysiologic study may be used for the diagnosis.

The diagnosis of sick sinus syndrome is based on the following electrocardiographic findings: sinus arrest (pauses) for more than two seconds, sinus bradycardia (less than 60 beats/min during sleeping), marked sinus arrhythmia, slow escape rhythms, sinoatrial exit blocks, bradyarrhythmias, tachyarrhythmias, sinus node re-entry tachycardia, or atrial muscle re-entry tachycardia (atrial flutter or fibrillation)[1,5]. Patients may have any one or a combination of these arrhythmias[1]. But atrial muscle re-entry tachycardia may also exist without accompanying sinus node

dysfunction[1]. We diagnosed the sinus node dysfunction in our patient who met at least three surface ECG criteria for sinus node dysfunction.

When severe sinus or junctional bradycardia and frequent sinus arrest result in loss of consciousness, acute medical treatment is indicated. Regardless of causes, intravenous atropine 0.04 mg/kg and/or isoproterenol 0.05-0.5 ug/kg/min usually increases the heart rate[1]. But chronic medical treatment is not accepted as standard treatment for SSS. Treatment in asymptomatic patients with SSS is controversial. When there are life-threatening symptoms such as near-syncope or syncope episodes associated with arrhythmias, like in our patient, the accepted mode of treatment is permanent pacemaker implantation[1,5,6]. The prognosis in patients with congenital SSS is good. To our knowledge, sudden death from sinus node dysfunction after pacemaker implantation has not been reported[1,5].

In order to obtain a diagnosis in infants with breath-holding and syncope episodes, the following are important: detailed investigation of medical history, performance of complete physical examination and electrocardiographic studies. Finally, due to life-threatening symptoms and sudden death, early detection and treatment are valuable for symptomatic children.

Thus, in the differential diagnosis of an infant with breath-holding and syncope episodes, particularly when these symptoms cannot be explained by other common reasons, sick sinus syndrome should be kept in mind.

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Intraabdominal lymphangiomyoma in an infant with protein-losing enteropathy and hemihypertrophy

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SUMMARY: Koltuksuz U, Özgen Ü, Özen S, Saraç K, Gürsoy MH. Intraabdominal lymphangiomyoma in an infant with protein-losing enteropathy and hemihypertrophy. Turk J Pediatr 2000; 42: 341-343.

Lymphangiomyoma is an extremely rare tumor occurring exclusively in women of reproductive age. The tumor is characterized by proliferation of immature smooth muscle along the lymphatic vessels of the abdomen, thorax and lung. Although lymphangiomyoma has been reported in a young girl and a girl infant, none has been reported in boys. We report herein a case of lympangiomyoma in a two-year-old boy. The unusual presentation in this patient was that the tumor arose from the small bowel mesentery without any evidence of lung involvement. The tumor was extirpated and lymphangiomyomatosis was confirmed pathologically.

Key words: lymphangiomyoma, protein-losing enteropathy, hemihypertrophy.

Lymphangiomyoma is an extremely rare tumor occurring exclusively in women of reproductive age. The tumor is characterized by proliferation of immature smooth muscle along the lymphatic vessels of the abdomen, thorax and lung. The most frequent symptoms are usually due to diffuse pulmonary involvement, which may cause severe ventilation/perfusion problems. Progression in the disease may cause death from these conditions[1,2]. Although lymphangiomyoma has been reported in a young girl and a girl infant, none has been reported in males in the pediatric age group[3,4]. We report the first male infant with lymphangiomyoma in the literature, also having protein-losing enteropathy and hemihypertrophy.

Case Report

The patient, a two-year-old boy, was admitted to the Department of Pediatric Surgery with the complaints of abdominal distention, vomiting and diarrhea beginning two months before admission. Physical examination revealed a swelling of the right arm and leg that was present at birth. He previously had undergone a laparotomy, and a mass, 6 cm in diameter, was excised. Pathological examination of the mass revealed a lymphangioma. In addition to the swelling of the extremities, he had right scrotal hydrocele and edema of preputial and scrotal skin. The abdomen was distended. There was neither hepatosplenomegaly nor a palpable intraabdominal mass. There was no evidence of venous dilatation or varicose changes in either the right leg or the arm.

Laboratory studies showed a serum albumin of 1.2 g/dl and total serum protein of 3.4 g/dl. Protein-losing enteropathy was confirmed by α_1-antitrypsin level of 17 mg/g in dry feces which was much higher than normal (normal < 2 mg/g). Chest roentgenogram revealed no abnormal shadow or pleural effusions. The computed tomographic scan (Fig. 1) of the abdomen showed a mass in the left abdomen between the intestinal loops adjacent to the mesentery, measuring 5.5x4 cm. Intravenous urography was normal. On the barium enema, the contrast medium flowed freely through the colon into the distal ileum. The contrast survey of the gastrointestinal tract revealed intestinal irregularity in a few small bowel segments, but isotope lymphangiogram was normal. These physical and laboratory findings led us to a preoperative diagnosis of the mass as intraabdominal lymphangioma.

Since normal diet and formulas were not tolerated, total parenteral nutrition was started.

After the protein levels reached normal levels, the patient was taken to the operating room. At the laparotomy, milky and slightly hemorrhagic fluid was present in the abdominal cavity. A mass measuring about 10x15 cm that arose from the small bowel mesentery was present. Adjacent portions of the small bowel and mesentery were edematous and had a milky appearance. About 15 cm of small bowel segment was resected together with the mass by preserving main mesenteric vessels and an end-to-end anastomosis was performed on both ends. A milky fluid was seen oozing from the mass during the resection. There were multiple lymph nodes on the mesentery. Other intraabdominal and retroperitoneal organs were apparently normal.

The histopathological evaluations of the specimen revealed lymphangiomyoma showing smooth muscle proliferation surrounding lymphatic spaces and lymphoid aggregates (Fig. 2). To investigate cause of the swelling of the right extremities, skin muscle biopsies were obtained from the right leg, but no pathological change was detected.

No postoperative complications were encountered. His diarrhea disappeared and α_1-antitrypsin decreased to normal levels. The serum albumin and total serum protein increased to normal levels. The scrotal and preputial edema resolved. But the swelling of the right extremities remained unchanged during the postoperative period.

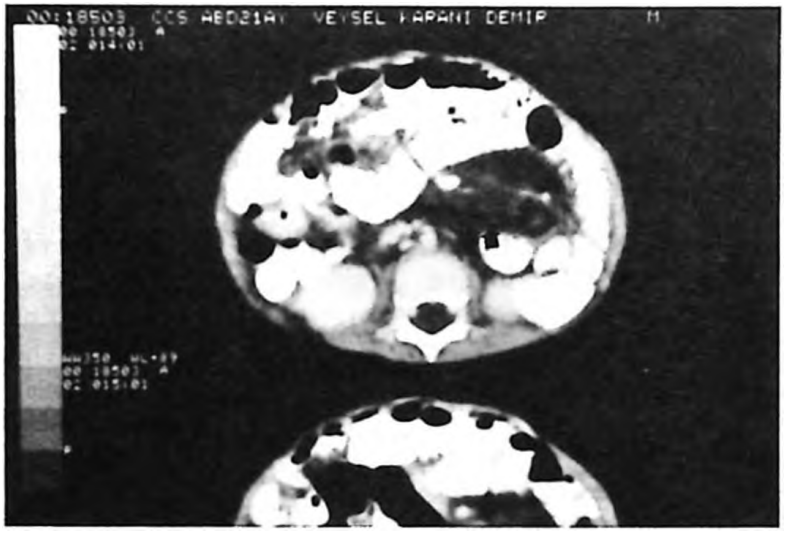

Fig. 1. Lymphangiomyoma showing smooth muscle proliferation (arrow) surrounding lymphatic spaces and lymphoid aggregates (hematoxylin and eosin x 20).

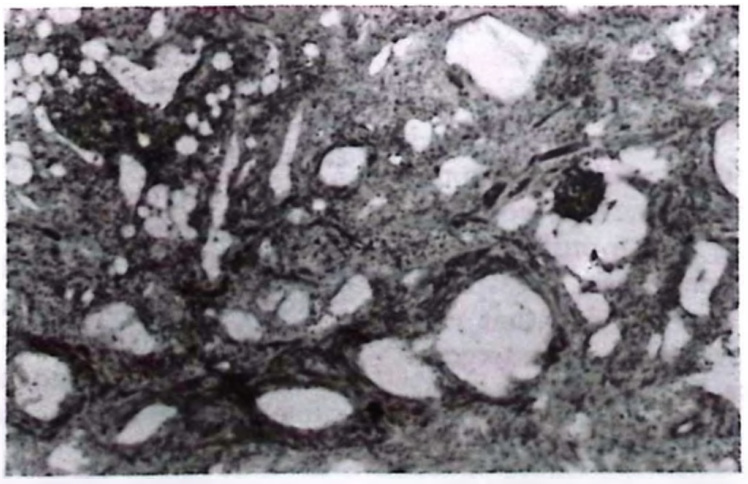

Fig. 2. Abdominal CT scan showing the intraabdominal mass (arrow).

Discussion

Lymphangiomyoma is a rare disease of women occurring almost exclusively during reproductive life and in an age range from 18-69 years. Jacobs et al[5] reported the first case of renal lymphangiomyoma in a male, 79 years old. Although two atients have been previously reported in the pediatric age group, both were female[3,4]. We report a case of intraabdominal lymphangiomyoma in a boy with protein-losing enteropathy. In addition, our patient had no pulmonary symptoms.

Lymphangiomyoma is described as a benign proliferation of smooth muscle involving the abdomen and/or thoracic lymphatics. The site of lymphangiomyoma is usually in the mediastinum and/or the retroperitoneum[6]. The most common complaints refer to the presence of chylous pleural effusion or to pulmonary involvement as well as dyspnea, cyanosis, cough, chest pain, hemoptysis and pneumothorax. Other symptoms include weight loss, abdominal mass, chylous ascites, abdominal pain and abdominal swelling[1]. In the present case, the first symptom was the swelling of the right extremities and face. There was an obvious asymmetry between right and left sides of the body, but without any venous dilatations or varicose changes in organs. Skin and muscle biopsies of the right leg revealed no extra findings. We thus could not find any relation between the swelling and the tumor, and suspected that hemihypertrophy and lymphangiomyoma developed independently.

Although the causes of the vomiting and diarrhea were not clear, we believe that the obsturction which occurred at the tumor level on the small lymphatic branches caused lymphatic leakage and consequently enteric protein loss. This mechanism may have occurred in the present case. Because the tumor invaded mesenteric and lymphatic vessels. There was no sign of mechanical pressure present on the bowels, caused by the tumor. Protein loss disappeared immediately after surgery.

The patient is now four years old, and protein-losing enteropathy did not recur. The follow-up for the intraabdominal mass did not reveal any evident mass. Because of the lack of a similar case reported in the literature, we cannot make any statistical suggestions about the prognosis. However, the regression of the clinical symptoms tends to indicate a favorable outcome.

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Polysplenia syndrome with hepatic artery of superior mesenteric artery origin and a circumaortic renal vein

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SUMMARY: Tarhan NÇ, Ağıldere AM, Boyvat F, Coşkun M, Ersoy H. Polysplenia syndrome with hepatic artery of superior mesenteric artery origin and a circumaortic renal vein. Turk J Pediatr 2000; 42: 344-347.

An $8^1/_2$-month-old girl with biliary atresia and polysplenia syndrome having multiple vascular anomalies without cardiac anomalies is reported. Interruption of the inferior vena cava with azygous continuation, which is a common anomaly, was seen in conjunction with origin of the common hepatic artery from the superior mesenteric artery and with a circumaortic renal vein. The case has particular importance in that no hepatic artery or renal vein variations have been described with biliary atresia and polysplenia syndrome in the literature thus far to our knowledge. The anomalies were shown using different radiological examinations including computed tomography, echocardiography, angiography, venography and magnetic resonance imaging.

Key words: polysplenia syndrome, biliary atresia, vascular anomalies.

Polysplenia syndrome involving biliary atresia is a rare phenomenon to occur in conjunction with other congenital anomalies[1-2]. The most commonly associated anomalies are cardiovascular, but the syndrome is also seen coupled with intestinal and respiratory malformations[1]. The vascular anomaly most frequently noted in polysplenia syndrome is interruption of the inferior vena cava (IVC) with azygous or hemiazygous continuation, seen in 50-85 percent of patients[2]. Cardiac anomalies are common, but the other vascular abnormalities described as part of this syndrome are rare[3].

The patient described here, with polysplenia syndrome and biliary atresia, had not only the common anomalies such as IVC interruption with azygous continuation, but unusual vascular variations as well. The common hepatic artery originated from the superior mesenteric artery (SMA), and the left renal vein was circumaortic. We present these malformations in this report, with special attention given to the computerized tomography (CT), magnetic resonance imaging (MRI), and angiography findings.

Case Report

An $8^1/_2$-month-old girl was admitted to hospital with jaundice and failure to thrive. She had jaundice since birth and had undergone a liver biopsy which was consistent with biliary atresia. Physical examination revealed icteric skin, hepatomegaly, a high-arched palate, ascites, and abdominal venous collaterals. Blood test results were consistent with anemia. Other laboratory tests indicated abnormal liver function. A chest x-ray showed cardiomegaly and increased bronchovascular markings in the hilar region. The right main bronchus was longer and had a wider angle than normal which was symmetric with the left bronchus.

On CT, the liver was located slightly to the left side and had irregular contours with hypodense nodules in the parenchyma (Fig. 1). Multiple, rounded splenules of variable size were situated in the right hypochondrium (Fig. 2). The stomach was located on the right side, and the cardiac apex was shifted to the left. These findings were consistent with abdominal situs inversus and left isomerism. The intrahepatic segment of the IVC was not visible, and an enlarged azygous vein was identified to the right of the aorta (Fig. 1). The left renal vein (Fig. 2) could be seen in a circumaortic configuration.

Echocardiography showed left atrial isomerism and narrowed hepatic veins draining directly into the right atrium (Fig. 3a). MRI demonstrated narrowed hepatic veins in cirrhotic liver as well (Fig. 3b).

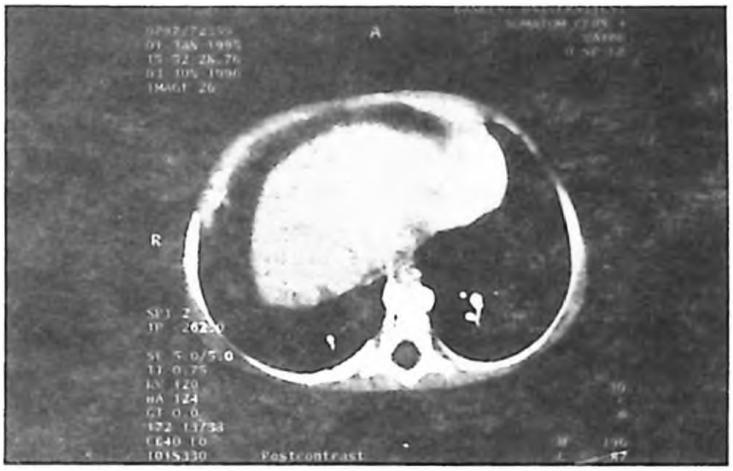

Fig. 1. Contrast-enhanced CT scan of the upper abdomen shows an enlarged liver with irregular contours and hypodense nodules. Also note the absence of the intrahepatic segment of the IVC and the dilated azygous vein (arrow) to the right of the aorta.

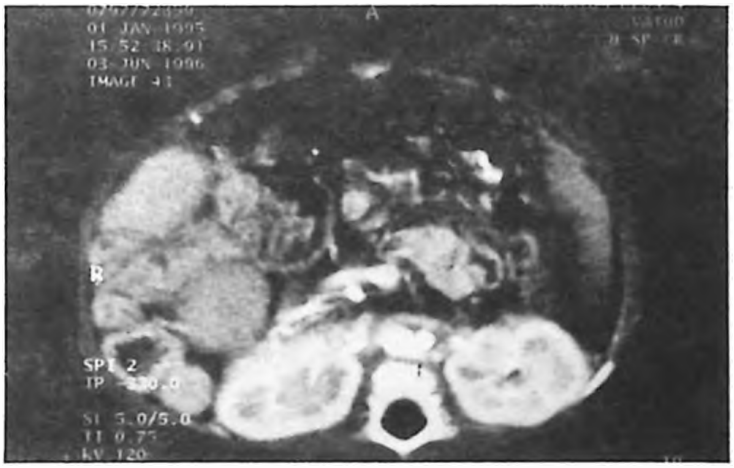

Fig. 2. Contrast-enhanced CT scan of the upper abdomen shows multiple, rounded splenules of variable size located in the right hypochondrium. The circumaortic left renal vein (arrow) is also visible.

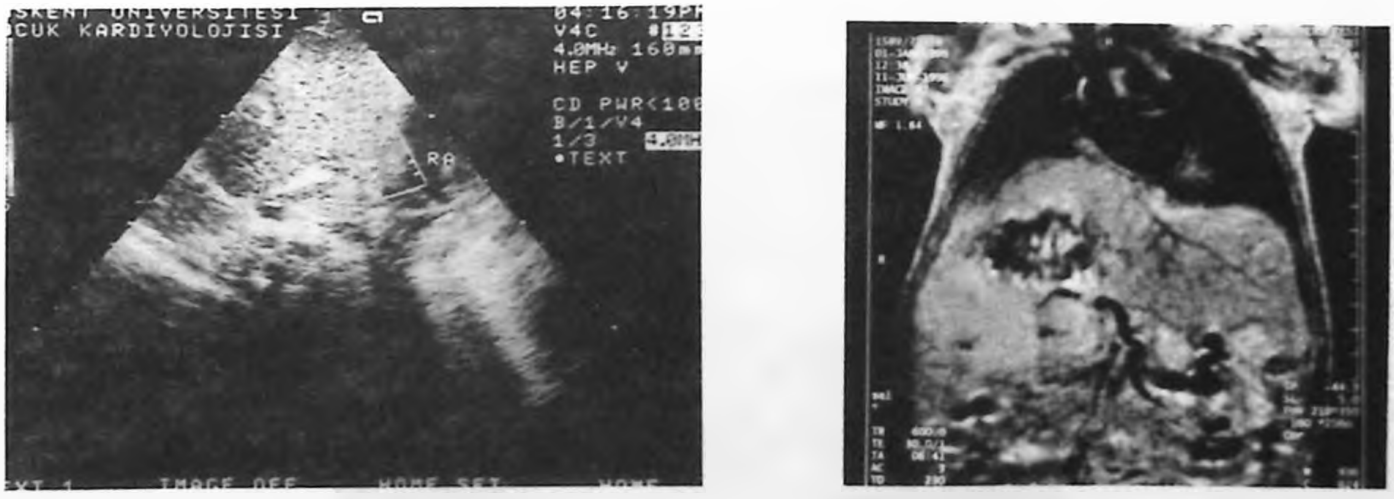

Fig. 3. Echocardiography shows one of the narrowed hepatic veins draining into the right atrium (a). Narrowed hepatic veins also noted on MRI [TR: 600 msec, TE: 30 msec, Acq: 3] (b).

Inferior vena cavography and visceral angiography were performed in order to confirm the vascular anomalies seen on CT, and to identify whether additional vascular anomalies were present. Vena cavography demonstrated interruption of the IVC at the level of the right renal vein, as well as azygous continuation. The azygous vein was dilated and was observed to be draining into the superior vena cava (Fig. 4). Visceral angiography examinations revealed that the common hepatic artery originated from the SMA, which was not demonstrated on CT (Fig. 5). MRI also showed the enlarged azygous vein, and bilateral bronchial symmetry with a longer right main bronchus, traits also consistent with left isomerism.

Discussion

Polysplenia syndrome describes a condition wherein more than two spleens of variable size are present, and where visceral heterotaxia and bilateral left sidedness are involved[1-2]. Polysplenia syndrome in conjunction with biliary atresia is a rare phenomenon, with only 10-20 percent of biliary atresia cases having such an association[2,3]. A condition seen more commonly with the syndrome is abdominal situs inversus, which usually includes cardiovascular, intestinal, and respiratory anomalies[1-3]. Recent studies have labeled polysplenia syndrome an acquired intrauterine anomaly of unknown etiology, stating that it

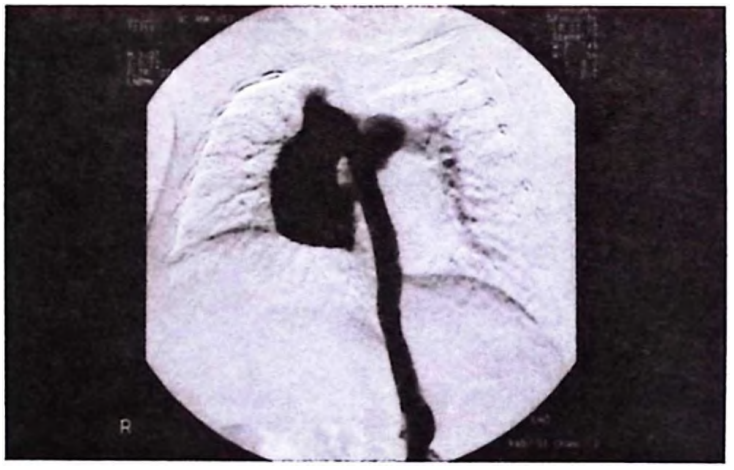

Fig. 4. Left anterior oblique inferior vena cavography showing dilated azygous vein continuation and drainage into the superior vena cava.

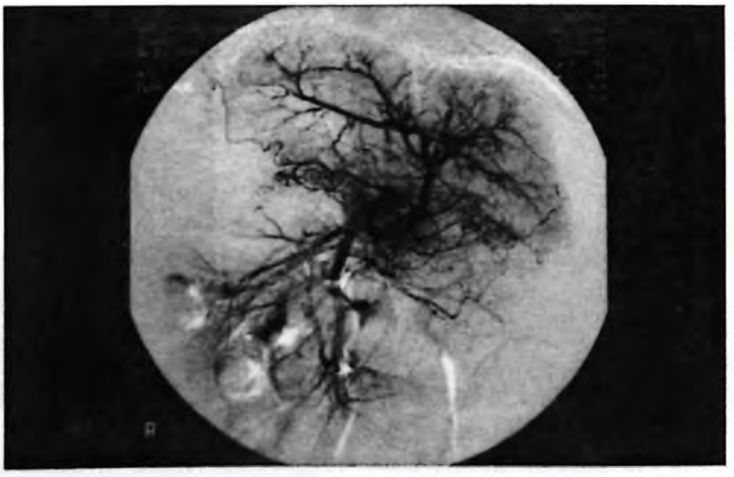

Fig. 5. Selective superior mesenteric artery (SMA) angiography shows the common hepatic artery originating from the SMA. Notice the slightly left-sided orientation of the liver.

occurs due to defective lateralization of abdominal organs and duplication of the left-sided ones[2,3]. The condition is thought to be the result of an intrauterine insult since no known cases of biliary atresia and polysplenia syndrome have been documented in autopsied stillborn infants[1]. It is also known that embryogenesis of the bile ducts, spleen, bronchial tree, cardiac septa and endocardial cushions, and formation of the IVC through the union of the subcardinal and hepatic veins occurs at roughly the fifth week of gestation[2,3].

Cardiac anomalies are more common than vascular types in polysplenia syndrome[1]. The most frequently seen vascular anomaly is interruption of the IVC with azygous continuation[2]. Other, less commonly described, vascular anomalies include preduodenal portal vein, bilateral superior vena cava[1,2], hepatic veins draining directly into the right atrium[2], pulmonary venous anomalies and anomalous origin of the right subclavian artery[3]. Anomalous hepatic arterial supply was mentioned in the study of Karrer and his collegues[3], but it was neither described in detail nor shown in any case.

Circumaortic renal vein is a vascular variation in which a two-limbed renal vein is present. The upper limb passes as normal in front of the aorta to join the IVC, and the lower limb passes behind the aorta. This malformation is seen in up to 17 percent of otherwise normal individuals[4]. Renal veins develop around the fifth to seventh week of gestation, which is around the same time as embryogenesis of the structures mentioned above[5]. The midline anastomosis of the supracardinal vein with the left renal vein when persists can be at the level of the left renal vein or more caudally located. In our case, the circumaortic renal vein was at the same level, with one limb passing in front of the aorta and the other passing behind (Fig. 2). Hepatic artery variations are also seen in normal individuals, at an incidence of 10 percent. In only 2.5 percent of these cases, the common hepatic artery originates entirely from the SMA[4]. To our knowledge, a case where the common hepatic artery originates at the SMA and a circumaortic renal vein is present as not been identified to date in connection with polysplenia syndrome. The case presented here included some of the more common anomalies of polysplenia syndrome: abdominal situs inversus, polysplenia, bilateral bronchial symmetry, and IVC interruption with azygous continuation. However, unique in terms of the literature were the patient's other vascular anomalies. Together with hepatic and renal vein variations, polysplenia syndrome and biliary atresia, being an uncommon anomaly as mentioned above, become more distinct as a case. These vascular anomalies were suspected on CT scans, and were confirmed by echocardiography, MRI, venacavography and abdominal angiography.

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Preoperative diagnosis of bronchial atresia presenting with recurrent respiratory symptoms in an infant

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SUMMARY: Yüksel H, Demir E, Tanaç R, Savaş R, Alper H. Preoperative diagnosis of bronchial atresia presenting with recurrent respiratory symptoms in an infant. Turk J Pediatr 2000; 42: 348-351.

Bronchial atresia (BA) is a rare respiratory malformation that may be diagnosed from infancy to adulthood. A typical feature of the disease is involvement of the left upper lobe and a mass-like lesion surrounded by a hyperlucent and nondeflating zone. We present a six-month-old male infant who was diagnosed by contrast-enhanced spiral computed tomography (CT) with three-dimensional (3D) technology, and by Tc-99m-macroalbumin aggregate (Tc99m-MAA) radionuclide scintigraphy. We stress that early diagnosis of BA can be made noninvasively using contrast-enhanced spiral CT and radionuclide scintigraphy. 3D computed tomographic reformation allows a more accurate diagnosis as well as a more specific approach to management and follow-up.

Key words: bronchial atresia, children, computed tomography, spiral.

Congenital bronchial atresia (BA) is a rare anomaly consisting of atresia or stenosis of a lobar or segmental bronchus, a mucocele formation behind the atretic area and a nondeflating hyperlucent segment of the lung[1]. The apicoposterior bronchus of the left upper lobe is almost always affected. However, right upper, right middle and, rarely, lower lobe involvement have been reported[2]. Although BA is a congenital malformation, it produces minimal symptoms and therefore may not become apparent until late childhood or even in adult hood[1-3].

So far, approximately fifty children have been reported in the literature. The incidence of BA has been reported as approximately two percent among children undergoing evaluation for bronchopulmonary malformation[4]. BA rarely causes recurrent respiratory problems. This anomaly is usually discovered on a routine chest roentgenogram[1]. We present an infant with BA presenting with recurrent respiratory symptoms, such as persistent cough, moderate respiratory distress, high fever and a persistent mass-like appearance at the left upper lobe of the lung.

Case Report

A six-month-old male infant was admitted to our clinic with persistent cough, moderate respiratory distress and persistent mass-like appearance at the left upper lobe of the lung on chest roentgenogram. His family had noticed these symptoms three months previously. Postero-anterior chest roentgenogram showed a mass-like lesion in the inspiratory phase, and an ipsilateral hyperlucent lung in the expiratory phase of breathing (Fig. 1). A finger-like mass produced by a mucus plug or mucocele at the apicoposterior segmental bronchus of the left upper lobe was detected with spiral computed tomography (CT) volumetric acquisition (using 3-mm collimation and a pitch of 1). This mucus plug was surrounded by multiple air-filled cysts and hyperlucent and oligemic lung tissue (Fig. 2). Three-dimensional (3D) surface rendering of the left upper lobe showed that it extended from the thoracic wall to the hilum at the apicoposterior segment of the left upper lobe (Fig. 3). Adjacent normal parenchyma was displaced away from the affected segment, and this pathological appearance extended down to the lower lobe of the left lung. Tc99m-macroalbumin aggregate (Tc99m-MAA) radionuclide lung perfusion scintigraphy revealed a total perfusion defect at the left apicoposterior segment of the lung (Fig. 4). The infant was treated with appropriate antibiotics

and supportive therapy. Left upper lobectomy was performed, and pathological examination of operation material revealed a segmental blind bronchus and a cyst-like intrabronchial plug, which was formed by inspissated mucus; the bronchial tree peripheral to the point of obliteration was patent and normal. Histological examination of the blind bronchus showed thinning of the bronchial wall and cartilage and a decreased number of alveoli, which were distended by inspissated mucus secretion.

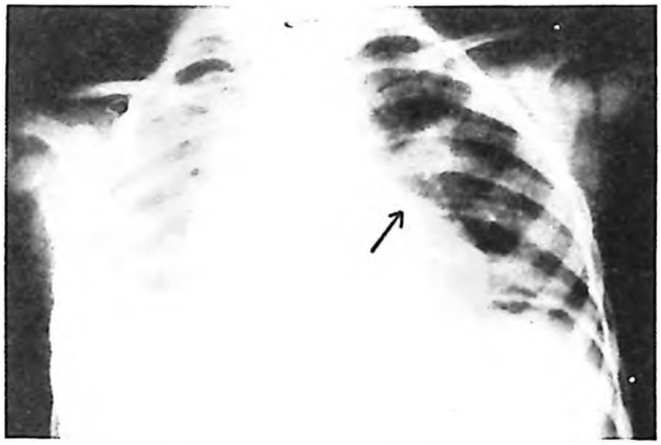

Fig. 1. Postero-anterior chest roentgenogram at expiration shows a mass-like lesion adjacent to the left hilum. The lung is hyperlucent and overinflated (note increased intercostal spaces on the left).

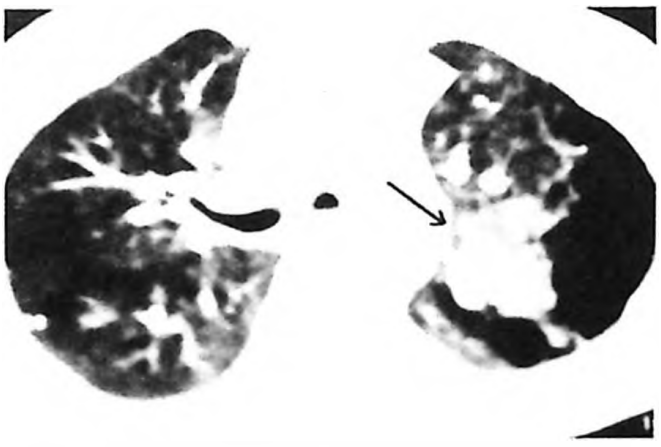

Fig. 2. Axial computed tomography (CT) scan shows mucoid impaction (arrow) with a hyperinflated apicoposterior segment of the left upper lobe.

Discussion

Bronchial atresia is a rare congenital malformation diagnosed in childhood[1,4]. The incidence of BA has been reported as approximately two percent among children under

Fig. 3. Three-dimensional (3D) surface rendering of the left upper lobe shows mucoid impaction clearly.

Fig. 4. Tc99m-macroalbumin aggregate (Tc99m-MAA) perfusion scintigraphy shows hypoattenuation in the left upper lobe (arrow).

going evaluation for bronchopulmonary malformation. Most of the reported patients are young children or adults because most affected infants or children have no significant clinical or recurrent symptoms showing respiratory problems[2,5,6]. Many patients having BA are diagnosed on routine chest roentgenogram without specific clinical symptoms. Thus, it may not become apparent until later childhood or even in adult hood. The involvement of the apicoposterior segment of the left upper lobe is the most characteristic feature[7]. The etiopathological origin is unknown. However, two theories have been postulated. The first is that the bronchial abnormality is probably developmental in origin. This theory was supported by some cases which were reported in early childhood, occasionally at birth, and with the concomitant presence of other congenital anomalies[8-10]. The second theory suggests that

a localized intrauterine interruption of the bronchial artery produces bronchial wall ischemia and secondary luminal obstruction[11].

Our patient had significant recurrent respiratory symptoms and moderate respiratory distress since birth. As mentioned above, rare cases are symptomatic in early childhood and thus can be diagnosed with a chest roentgenogram. A typical chest roentgenogram shows a mass-like appearance produced by a mucus plug, mucocele, and a hyperlucent, overexpended and nondeflating perimucocele zone. Adjacent normal parenchyma is compressed and depressed[1,2,12]. The inspiratory and expiratory roentgenograms reveal air-trapping behind the atretic segment. In our patient, routine images showed only a mass-like lesion (mucocele) in inspiratory images; expiratory roentgenogram showed nondeflating hyperlucent hemithorax typically. CT findings included multiple air-filled cysts, oligemia, a finger-like shadow demonstrating the mucus plug, mucocele, and hyperinflation in the affected segment[1,2,10,12].

Spiral CT is superior for showing mucus plug configuration, the finger-like shadow and the atretic segmental bronchus. Spiral CT images of our patient, obtained using reformatted images and enhanced 3D technology, showed that the finger-like shadow extended to the thoracic wall and was associated with a hyperinflated and hypoattenuated apicoposterior segment of the left upper lobe. The origin of the left apicoposterior segmental bronchus was not visible.

The mechanism of mucus plug formation is that retained fetal fluid and/or mucus secreted within patent airways distal to the point of atresia cannot pass the stenosis, and accumulate in the form of a plug[12]. The typical hyperlucent appearance points to the fact that the air can enter the affected segments only via collateral channels, creating an air draft between obstructed and adjacent normal ventilated segments and causing overinflation, expiratory air trapping and nondeflation[13]. Oligemia and hypoperfusion can be demonstrated using radionuclide perfusion scanning, as in our patient. We suggest that oligemia may be secondary to two causes. The first may be interruption of arterial supply as mentioned above. The other reason might be overinflation and displacement of the normal adjacent parenchyma, which may cause pressure on the pulmonary vessels and disruption in capillary circulation. This may affect the development of periatretic normal parenchyma and vasculature. Thus, early diagnosis and surgical treatment may help the normal development of the adjacent normal parenchyma. Our patient had a left upper lobectomy which improved his clinical condition. Respiratory symptoms did not recur for six months after surgery and he has been doing well since that time.

Bronchial atresia may be associated with bronchogenic cysts, anomalous pulmonary venous drainage and pectus excavatum[5,14]. Our patient had no other pulmonary or extrapulmonary malformations. Early surgical treatment should be considered especially in this situation.

Our experience showed that early diagnosis and approach to BA may be possible using both spiral CT and radionuclide perfusion scintigraphy before invasive procedures like bronchography and bronchoscopy. Spiral CT of the tracheobronchial tree with reformatted images, such as 3D technique, allows a more accurate diagnosis, and a more specific approach to surgical applications and follow-up of the cases. Therefore, evaluation of the tracheobronchial status of children with BA and associated respiratory anomalies might be possible using the above-mentioned technologies. Also, invasive procedures for demonstration of the tracheobronchial tree in children, especially in infants, may cause life-threatening complications and result in unsuccessful imaging. Thus, our proposed methods may lead to significant modification and selection of patient management, lower complications and also cost effectiveness.

In conclusion, BA should be considered in infants and children with a mass lesion, especially at the left upper lobe of the lung. Early diagnosis may be possible using enhanced spiral CT with secondary reformation and radionuclide perfusion scintigraphy. Spiral CT with secondary reformations may provide a more accurate approach to the medical and surgical management.

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Are ferric compounds useful in treatment of iron deficiency anemia?

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SUMMARY: Arvas A, Gür E. Are ferric compounds useful in treatment of iron deficiency anemia? Turk J Pediatr 2000; 42: 352-353.

The effect of ferric compounds in therapy of iron deficiency anemia is doubtful; however, the absorption of iron is not affected negatively by food or drugs. In our Well Baby Clinic, ferric polymaltose (6 mg/kg/d) was given to 59 infants (Group 1) and ferrous sulphate (same doses) was given to 64 infants (Gorup 2) (74 ± 9 d, 70 ± 7 d, respectively). These infants had iron deficiency anemia, and their therapy was continuous. Ferric polymaltose was not as effective as ferrous sulphate, although it increased hemoglobin and serum iron. Mean corpuscular volume and serum ferritin were not significantly changed after therapy. For this reason, we prefer to use only ferrous salts in therapy.

Key words: ferric polymaltose, ferrous sulphate, iron deficiency anemia.

Iron deficiency anemia (IDA) is a common problem in infancy, especially in developing countries[1]. Iron compounds are given perorally for ease, low price and low adverse reactions. ferrous compounds are usually preferred because they are more bioavailable. Also the therapeutic value of ferric compounds are disputable. In our study, we wanted to compare ferric polymaltose with ferrous sulphate in the therapy of IDA. Ferric polymaltose (6 mg/kg/d elementary Fe+3, p.o., b.i.d.) was given to 59 anemic infants (27 girls, 32 boys) (Group 1) and ferrous sulphate (same doses elementary Fe+2) was given to 64 anemic infants (33 girls, 31 boys) (Group 2). These infants were followed between April 1997-January 1999 at the Children's Hospital's Well Babay Clinic, and their therapy was continuous. Babies were separated into groups according to a record book. They were born at term and had no infection during therapy. All the infants in each group were fed the same complementary foods following the same time schedule after four months (vegetable purees, yoghurt, fruit, cereal, meat, eggs, respectively). Hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), serum ferritin (SF), serum iron (SI) and total iron binding capacity (TIBC) were measured for the diagnosis of IDA. Hb: 11 g/dl, MCV: 70 fl and ferritin: 12 ng/ml were accepted as a cut-off level[2]. Hemogram was made by cell counter analysis method (Counter Micro Diff 18, Miami, US). SI and TIBC were measured by colorimetric method (Iron/TIBC reagent set-pointer Scientific Inc.). SF was measured by radioimmunoassay method (Active TM Ferritin, Diagnostic Systems Laboratories 3000, Inc. US). Student's-t test was used for statistical analysis in the program of SPSS for 5.0 Windows. The age of infants in Group 1 was 235 ± 82 days, the period of therapy was 74 ± 9 days, birth weights were 3297.5 ± 401.5 g, weights before therapy were 8210 ± 1245 g and exclusive breast-feeding period was 87 ± 28 days. In Group 2, these values were 252 ± 90 days, 70 ± 7 days, 3269.8 ± 403.6 g, 8503 ± 1531 g, and 72 ± 35 days, respectively. Only breast-feeding time in Group 1 was higher than in Group 2 ($p < 0.001$); there was no significant difference between birth weight and therapeutic periods between the two groups ($p > 0.05$). Hematological values of groups before and after therapy shown in Table I. In Group 2, Hb, MCV SI and SF values after therapy compared to before therapy and to Group 1 values were significantly increased ($p < 0.001$). TIBC was not different before and after therapy in the two groups ($p > 0.05$). In Group 1, only Hb and SI values were increased after therapy ($p < 0.01$). It has been known that ferrous salts are most useful in the therapy of IDA, but the therapeutic importance of ferric compounds is doubtful. There is no recent literature on this subject. Geisser[3] reported that ferric polymaltose has a

Table I. Hematological Findings

	Ferric polymaltose (Gorup 1, n = 59)	Ferrous sulphate (Gorup 2, n = 64)	p values
Hb (g/dl)			
b.t.*	9.7 ± 0.7***	10.0 ± 0.6	0.021
a.t.**	10.5 ± 1.0	11.3 ± 0.6	0.0001
p	0.0001	0.0001	
MCV (fl)			
b.t.	69.9 ± 5.6	70.4 ± 5.4	0.116
a.t.	70.9 ± 6.4	75.7 ± 5.0	0.0001
p	0.130	0.0001	
SF (ng/ml)			
b.t.	11.4 ± 9.5	11.7 ± 7.7	0.460
a.t.	14.5 ± 9.8	29.1 ± 19.0	0.0001
p	0.090	0.0001	
SI (µg/dl)			
b.t.	35.1 ± 18.7	38.8 ± 16.2	0.239
a.t.	45.2 ± 23.2	63.2 ± 25.9	0.0001
p	0.002	0.0001	
TIBC (µg/dl)			
b.t.	354.2 ± 48.6	360.3 ± 55.8	0.523
a.t.	349.4 ± 69.6	329.0 ± 53.4	0.070
p	0.563	0.0001	

* before therapy.
** after therapy.
*** Mean ± SD.

Hb : hemoglobin.
MCV: mean corpuscular volume.
SF : serum ferritin.
SI : serum iron.
TIBC: total iron binding capacity.

different absorption mechanism and that its elementary Fe+3 was not affected by intestinal pH, food or drugs. Sas et al.[4] stated that ferrous and ferric compounds have comparable effects in IDA[4]. Also, Jacobs[5] found that ferrous sulphate and ferric polymaltose have the same iron absorption and the same therapeutic effects[5]. In IDA, two to four months are usually sufficient for treatment. In our study, we found that ferric polymaltose is not effective in therapy of IDA when compared to ferrous sulphate, even though it increased Hb and SI values. Nielsen[6] and Özsoylu et al.[7] also found comparable results[6,7]. In conclusion, it can be shown that ferric compounds are not as effective as ferrous sulphate in the therapy of IDA, which is in accordance with the opinion available in literature.

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