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A PEDIATRICIAN AND HIS MOTHERS AND INFANTS*

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SUMMARY: Gracey M. (Elected President of the International Pediatric Association). A pediatrician and his mothers and infants. Turk J Pediatr 1997; 39: 1-5.

Pediatricians are in a unique place in society by being able not only to care for the health and well-being of mothers and which, are their clinical responsibility, but also by being able to act as advocates for those patients who are often among the most vulnerable of our population. This article illustrates some of these points by referring to Australian Aboriginals from the vast desert areas of Westerns Australia. In remote areas of Western Australia, Aboriginal infants have high rates of low birth weight, failure to thrive and undernutrition. They also have high rates of respiratory, gastrointestinal and other infections. Aboriginal infant mortality has improved significantly over recent years, but Aboriginal health and mortality rates are still much worse than those of non-Aboriginal children and tend to be worst in more remote parts of the state. Overall, Aboriginal infants less than one year in age were hospitalized 9.5 times more frequently than non-Aboriginal infants for respiratory diseases (such as pneumonia, acute bronchiolitis and asthma); diarrheal diseases and skin infections were other very important causes of hospitalization for Aboriginal infants. Another poorly understood aspect of Aboriginal health is their widespread proneness to urinary tract infections. This is very important now in Australian Aboriginals in whom end-stage renal failure is becoming very prevalent. Rapid social and lifesyle changes have been very important in the poor health status of Aboriginals. They are also subject to severe socio-economic discrimination, underemployment, limited education, overcrowding, social depression and severely depressed housing conditions, relative inaccessibility to adequate and nutritious foodstuffs, and limited access to clinical services. Aboriginal people are prone to obesity, hypertension, type-2 diabetes mellitus and cardiovascular diseases. Overuse of alcohol and tobacco smoking have also become important challenges, particularly among adolescents and young adults. For the past twenty years or so, special programs have been developed to help overcome some of these problems; these include immunization programs, an extensive child health care program, special childhood screening programs, and oral rehydration therapy to reduce the high rates of mortality and morbidity associated with diarrheal diseases. These improvements have been achieved despite a set of socio-economic circumstances that face Aboriginal infants and children who live with adverse social factors. This was termed "Down and Out in 1996" in an editorial in The New Scientist (27 January 1996). A strategy that Australian Aboriginals are using now is to increase their own role through Aboriginal-controlled health and medical services including child health programs. *Key words: Aboriginals, Australia, children, pediatrician.*

Pediatricians are in a unique place in society by being able not only to care for the health and well-being of mothers and babies who are their clinical responsibility, but also to act as advocates for those patients who are often among

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the most vulnerable sections of our populations. This may be done by arguing for better clinical services and facilities locally, by providing independent facilities and resources for women's indigenous groups and by assisting with local farming, banking and small business enterprises. Female pediatricians are often much more effective in these roles despite initial resistance from males in their entrenched positions of power. This essay will illustrate some of these points by referring to Australian Aboriginals from the vast desert areas of Western Australia.

Maternal and Infant Health Among Australian Aboriginals

It may come as a surprise to this audience to learn that in the 1960's and 1970's the health standards of the Aboriginals, Australia's original inhabitants, were considered to be worse than in any other identifiable groups of Australians, although official census figures were not widely available until the 1970's, when Aborigines were for the first time included in the national census figures. Because the total aboriginal population of Western Australia (WA) is so small and because its population distribution is so sparse and uneven, it is difficult and rather dangerous to generalize about demographic distribution and patterns of health and disease. The following, however, can be stated.

The total land mass of WA (2.4 million square kilometres) is very large and mostly very dry; most of the human population (1.7 million) lives in its coastal capital city (Perth) and the port of Fremantle, and in the closely settled south west part of the state where agriculture, dairying, fishing, forestry and tourism are among the main commercial activities.

Much of the rest of WA is sparsely populated but is wealthy because of its mineral deposits; mining of gold, nickel, iron ore, titanium, mineral sands, zinc, diamonds and the culture of pearls is very active in many parts of the state. Generally speaking, in remote parts of WA, Aboriginal infants have high rates of low birthweight (LBW), growth faltering, failure-to-thrive and undernutrition, particularly from 6 to 36 months of age. They also have high rates of respiratory, gastrointestinal and other infections. Aboriginal infant mortality has improved significantly over recent years (Table I) but Aboriginal health and mortality rates are still much worse than for non-Aboriginal children and tend to be worse in the more remote parts of the state.

The age-standardized (all ages) mortality rate ratios (Aboriginal versus non-Aboriginal) were 2.6 for males and 3.0 for females. The five leading causes of death for Aboriginal males were I. cardiovascular diseases, II. injury and poisoning. III. respiratory diseases, IV. neoplasms, and V. diseases of the digestive system. For Aboriginal females the five main causes of death vere I. cardiovascular diseases; II. neoplasms; III. endocrine, nutritional, metabolic and immune diseases (overwhelmingly diabetes); IV. respiratory diseases; and V. injury and poisoning.

Table I: Infant Mortality Rates in Western Australia

Year	Aboriginal (Rate/Thousand/Year)	Non - Aboriginal (Rate/Thousand/Year)	Relative Rate (Aboriginal: non - Aboriginal)
1976	45.6	12.2	3.7
1977	29.6	11.8	2.5
1978	27.5	10.7	2.6
1979	29.7	10.3	2.9
1980	31.1	8.1	3.8
1981	19.2	7.9	2.4
1982	25.2	8.1	3.1
1983	24.7	7.2	3.4
1984	24.7	8.1	3.0
1985	25.9	7	3.7
1986	20.3	7.8	2.6
1987	18.8	7.1	2.6
1988	28.7	6.2	4.6
1989	22.4	6.9	3.2
1990	16.3	6.1	2.7
1991	19.2	5	3.8
1992	22	5.3	4.2
1993	14.7	4	3.7

Overall, Aboriginal infants (i.e., up to 12 months of age) were hospitalized in WA 9.5 times as frequently as non-Aboriginal infants for respiratory diseases; diarrheal diseases and skin infections were other very important causes of hospitalization for Aboriginal infants. The main causes of hospitalization of Aboriginal infants for respiratory conditions were acute respiratory tract infections (such as acute bronchiolitis and bronchitis), pneumonia and asthma.

The relative rates of hospital admissions (Aboriginal: non-Aboriginal) for respiratory tract disorders in 1 to 4 year-old and 5 to 14 year-old children were 4.8 and 2.2, respectively. At these ages, asthma and pneumonia were major causes of hospital admissions in Aboriginal children; "other respiratory tract diseases" were also prominent. Diarrheal diseases and skin infections became much less prevalent and serious in the older children.

Among 15 to 24 year-olds, the relative rate of hospital respiratory admissions in Aboriginals compared to non-Aboriginals was 2.9. Pneumonia, asthma and "other respiratory tract diseases" were the major causes of respiratory admissions in Aboriginal patients.

Another poorly understood aspect of Aboriginal health is their widespread proneness to urinary tract disease, much more evident in females than in males. This is often detectable in clinically symptomless children and teenagers, years

before clinical disease or its complications are evident. This is very important now in Australian Aboriginals in whom end-stage renal failure is becoming very prevalent, problematical and expensive in terms of screening programs (that are almost non-existent) as well as planning for dietary, clinical and sociological management and, for some patients, regular dialysis or transplantation.

Rapid sociological lifestyle changes have been very important in the poor health status of Aboriginals, and Aboriginal Health Worker involvement is crucial in overcoming some of these problems, particularly the social and rapid lifestyle changes. This includes access to alcohol and store and processed foods (e.g. refined flour and sugar), which are available to many of these people for the first time. As a result, and because of a rapid change from "hunter gatherer" to a remarkably sedentary lifestyle over a very short period of time, these people are particularly prone to a group of "lifestyle" diseases. They are also subject to severe socio-economic discrimination, underemployment, social depression and severely depressed housing conditions. Inappropriate use and overuse of drugs of addiction, including tobacco smoking, have also become important challenges, particularly among adolescents and young adults. General gasoline has been available widely in desert areas for many years. When inhaled, this can cause serious neurological damage; the use of aviation gasoline instead of standard gasoline has had a very beneficial effect on the health of these young children. Aboriginal people are also prone to obesity, hypertension, type-2 diabetes mellitus and cardiovascular disease. Dietary programs, exercise, a healthy lifestyle and avoidance of noxious substances, including cigarette smoke, and control of alcohol consumption, will all need to become components in the development of successful future health plans for groups of vulnerable infants and children like these.

The inequalities in Aboriginal child health are due to many inter-related factors, among which environmental factors are very important. These include inadequate housing, overcrowding, microbiological contamination of living environments, high-risk individual and community hygiene behaviors, difficulties in maintaining basic infrastructure services (e.g., water supplies, sewage and waste disposal) in remote areas, and inadequate domestic skills and hardware.

These factors are complicated by low educational attainment and very limited employment opportunities. Limited access to adequate and nutritious foodstuffs in remote areas is a very important and complex issue that brings in the huge problems of vast distances from food suppliers, the deficiencies of foodstores in remote Aboriginal communities and the much higher prices of basic food items as environmental factors that affect the nutritional health of Australian Aboriginal individuals and communities.

For the past 20 years or so, special programs have been developed to help overcome some of these problems. These include immunization programs, an

extensive 0-5 year child health program, special childhood screening programs, and oral rehydration therapy (ORT) to reduce the high rates of mortality and morbidity associated with diarrheal disease.

There have been some significant improvements in these figures since the early 1970's. These include the decline in rates of gastroenteritis and respiratory tract infections. These improvements have been achieved despite a set of socio-economic circumstances that face Aboriginal infants and children who live with adverse social factors-overcrowding, discrimination, limited educational and employment opportunities, relative inaccessibility to nutritious food and limited access to cilincal services. This was termed "Down and Out in 1996" in an Editorial in The New Scientist (27 January 1996). A strategy that Australian Aboriginals are using now is to increase their own role through Aboriginal-controlled health and medical services including child health programs. These are becoming increasingly involved in planning, in the delivery of health infrastructure training of their own indigenous staff and increasing collaboration with mainstream government health services. Our work is at the forefront of such activities in WA (e.g., Aboriginal Environmental Health Worker Training and Support). There is scope for many more Aboriginal initiatives in such areas in the future.

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ANTIBIOTIC SUSCEPTIBILITIES OF SALMONELLA SEROGROUPS ISOLATED FROM TURKISH CHILDREN*

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SUMMARY: Akan Ö, Kanra G, Seçmeer G, Ceyhan M, Ecevit Z, Berkman E. (Infectious Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Antibiotic susceptibilities of Salmonella serogroups isolated from Turkish children. Turk J Pediatr 1997; 39: 7-11.

This study is performed to show the serogroup distribution and in-vitro antibiotic susceptibilities of Salmonella species that cause either gastroenteritis with/without bacteremia or enteric fever at Hacettepe University İhsan Doğramacı Children's Hospital. Of the 309 Salmonella strains evaluated, serogroup B was the most common isolate (56%) followed by serogroup D (33%). Antibiotic susceptibility tests using the disk diffusion technique revealed resistance rates of 43 percent for ampicillin, 41 percent for chloramphenicol, 29 percent for trimethoprim-sulfamethoxazole (SXT) and 32 percent for ceftriaxone among Salmonella serogroup B. The same rates were 10, eight, seven and zero percent for Salmonella serogroup D, and seven, 14, and zero percent for serogroup C, respectively. S.thypi strains susceptible to all antibiotics studied except tetracycline (33% resistant). No resistance was detected against the quinolones. The antibiotic resistance of Salmonella species isolated from children seems to be important, especially in serogroup B. Susceptibility tests should be considered in the antimicrobial therapy of Salmonella infections where indicated. *Key words: Salmonella species, antibiotic susceptibility.*

Salmonella infections continue to be one of the important health problems among adults and children in Turkey, especially in the warm seasons[1,2]. Use of antibiotics mainly depends on the type of infection. Chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole have been considered to be the standard agents for therapy in view of their efficacy and low cost. However, since resistance to each of these standard antibiotics has become common in many parts of the world, the antibiotic susceptibility pattern of the involved pathogen should be considered during the therapy[3,4]. This study was performed to show the serotype distribution and in-vitro antibiotic susceptibilities of Salmonella species that cause either gastroenteritis with/without bacteremia or enteric fever at Hacettepe Children's Hospital.

Material and Methods

Strains: Salmonella strains isolated from stools or blood cultures of children admitted to Hacettepe University İhsan Doğramacı Children's Hospital between January 1994 and June 1995 with complaints of diarrhea and/or fever, were

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included in the study. All strains were acquired outside the hospital, and special attention was given not to include more than one isolate from the same child. Identification of the strains were done first by using biochemical and then serological tests. Serogroups were determined by slide agglutination technique using standard polyvalent and group specific antisera (Difco)[5,6].

Antibiotic Susceptibility Tests: The antibiotic susceptibility to eight antibiotics using the disk diffusion technique was determined according to the recommendations of the National Committee for Laboratory Standards[7]. The antibiotic disks were as follows: ampicillin (10 µg/ml), chloramphenicol (30 µg/ml), tetracycline (30 µg/ml), trimethoprim-sulfamethoxazole (1.25,23.75 µg/ml), sulbactam-ampicillin (10/10 µg/ml), ceftriaxone (30 µg/ml), ofloxacin (5 µg/ml), and ciprofloxacin (5 µg/ml) (Oxoid, BBL).

Results

A total of 309 Salmonella strains were included in the study. The types of specimens and the serogroups of Salmonella species are shown in Table I.

Table I: The Types of Specimens and the Serogroups of the Salmonella species

Salmonella Serogroup	Blood	Stool	Total
B	9	154	173
C	0	14	14
D	1	101	102
S.typhi	4	16	20
Total	14	285	309

One hundred and seventythree (56%) of the strains belonged to Salmonella serogroup B, followed by serogroup D (102 strains, 33%). The isolates of serogroup B were more resistant to the antibiotics studied. The quinolones and ceftriaxone were the most effective antibiotics with the lowest resistance rates. The antibiotic resistance rates of Salmonella isolates according to their serogroup is shown in Table II. S.typhi isolates were more sensitive than non-typhoid Salmonella to the antibiotics studied (Table III).

Table II: Antibiotic Resistance Rates of Salmonella Species

Salmonella Serogroup	AMP R%	CHL R%	SXT R%	SAM R%	Tet R%	CRO R%	OF R%	CIP R%
B	43	41	29	39	53	32	0	0
C	7	14	14	7	14	0	0	0
D	10	8	7	7	33	0	0	0
S.typhi	0	0	0	0	21	0	0	0

Table III: Antibiotic Resistance Rates of S.typhi and nontyphoid Salmonella

	n	AMP R%	CHL R%	SXT R%	SAM R%	TET R%	CRO R%	OF R%	CIP R%
nontyphoid Salm.**	289	30	28	20	26	46	20	0	0
S.typhi	20	0	0	0	0	21	0	0	0

* R% includes both resistant and intermediately resistant strains. AMP: ampicillin, CHL: chloramphenicol, SXT: trimethoprim-sulfamethoxazole, SAM: sulbactam-ampicillin, TET: tetracycline, CRO: ceftriaxone, OF: ofloxacin, CIP: ciprofloxacin.

** nontyphoid salmonella.

Discussion

Antimicrobial therapy in Salmonella infections is only indicated in patients with bacteremia or enteric fever. The use of antibiotics in non-typhoid Salmonella gastroenteritis remains controversial[8]. Studies have shown no clinical improvement with antimicrobial therapy, and both clinical and/or bacteriological failure or relapse has been demonstrated in Salmonella gastroenteritis. There is also the risk of emergence of drug-resistant strains, so antibiotic therapy in the gastroenteritis form should be limited to neonates, young infants and immunosuppressed patients[3, 9].

The choice of antibiotics has been complicated by the emergence of Salmonella strains resistant to the commonly used antimicrobials such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (SXT). Increasing multiple-resistant strains have been a problem in many parts of the world[10]. In Turkey several studies about the antibiotic susceptibility of Salmonella spp. show antibiotic resistance rates of 27 to 95.8 percent for ampicillin, 27 to 94.3 percent for chloramphenicol, and 18 to 88.8 percent for SXT[11-15]. The wide range among the rates reported from different parts of Turkey may be due to lack of differentiation of hospital and non-hospital isolates. Hospital-acquired Salmonella spp. tend to be more resistant to the antibiotics studied[15]. In general S.typhi has remained susceptible to antimicrobial agents, especially compared to non-typhoid Salmonella[16]. Though multiple resistant S.typhi isolates have been reported in some parts of the world, it is not yet a problem for Turkish isolates[13, 17, 18]. Our isolates of S.typhi also showed no resistance to the antibiotics studied except tetracycline.

The difference in resistance rates among non-typhoid Solmonella and S.typhi may be because of the distinct sources of the species. The only reservoir for S.typhi is man, whereas animals constitute the principal source of non-typhoid Salmonella strains that infect man[19]. Multiple resistant Salmonella strains are generally transmitted on plasmids, an the widespread use of antimicrobials in animals directly affects the resistance rates of Salmonella spp. present in the environment[3, 20]. Resistance of the Salmonella spp. to commonly used antibiotics

has brought about the search for new effective antibiotics. Third-generation cephalosporins have been used successfully in enteric fever of children[21], but the resistance rate of 32 percent for ceftriaxone in our Salmonella serogroup B strains should be taken into account in the decision of empirical use. Our high rate of cephalosporin resistance may be due to extended spectrum beta-lactamases seen in such isolates[22]. The quinolones have been found to be effective against enteric pathogens. Their spectrum of activity, high fecal levels, good intracellular and bowel penetration properties, and high lymph node and systemic drug concentrations have made them the drug of choice in enteric fever of adults[23]. However, their usage in children is controversial. In some pediatric trials, good to excellent efficacy has been reported with mild and reversible adverse effects. They may be promising in enteric infections in childhood if they are approved for children[24].

Antibiotic resistance of Salmonella species isolated from children seems to be important, especially in isolates belonging to serogroup B. In addition to antibiotic susceptibility results, the clinical efficacy of the antimicrobials, duration of excretion of the pathogen, relapse rates and the development of Salmonella carrier state are important factors that must be considered in the selection of the antibiotic. Further studies regarding clinical and laboratory findings should be performed to construct a protocol about rational antibiotic usage in Salmonella infections among children.

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ANTIBIOTIC SUSCEPTIBILITIES OF ENTEROCOCCI ISOLATED FROM TURKISH CHILDREN*

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SUMMARY: Akan Ö, Kanra G, Ecevit Z, Ceyhan M, Seçmeer G, Berkman E. (Infectious Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine. Ankara, Turkey). Antibiotic susceptibilities of enterococci isolated from Turkish children. Turk J Pediatr 1997; 39: 13-17.

To evaluate the antibiotic resistance rates of enterococci isolated at Hacettepe Children's Hospital, in vitro antibiotic susceptibility tests were performed in 77 enterococci (32 hospital, 45 nonhospital strains) isolated from various clinical specimens in 1994. Microbroth dilution tests against ampicillin, vancomycin, gentamicin and streptomycin were performed according to the NCCLS standards. High-level resistance to aminoglycosides was investigated. Ampicillin resistance rates were 21.9 percent and 2.2 percent for hospital and nonhospital strains, respectively ($p < 0.01$). The same rates were 46.9 and 13.3 percent for gentamicin ($p < 0.01$), and 15.6 and 13.3 percent for streptomycin ($p = 0.25$). No resistance was detected against vancomycin. Six strains (7.8%) showed high-level resistance to both aminoglycosides studied. Special attention should be paid to enterococci isolated from hospitalized patients. Appropriate antibiotic use in serious infections can only be achieved by choosing an appropriate regimen according to antibiotic susceptibility tests. Periodic evaluation of the antibiotic susceptibility patterns of enterococci is necessary for the empirical treatment of infections due to these microorganisms. *Key words: enterococci, antibiotic susceptibility, high-level aminoglycoside resistance.*

For years enterococci have been considered as harmless inhabitants of the gastrointestinal tracts of humans and animals. Despite their low virulence, recent studies have documented that enterococci are increasing as significant nosocomial pathogens[1]. Enterococci do not possess the common virulence factors found in many other bacteria. Their intrinsic and acquired resistance against various antimicrobials explain the pathogenic potential of these microorganisms. Because of the diverse antimicrobial resistance mechanisms, successful treatment of enterococcal infections with current antimicrobial agents is becoming difficult, especially in serious infections[2]. This study was performed to show the antibiotic resistance rates of enterococci isolated in Hacettepe University Children's Hospital in order to give information to clinicians about the antibiotic therapy of enterococcal infections until susceptibility results are available.

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Material and Methods

Seventy-seven enterococci isolated in 1954 from urine (49), wound (23) and blood (5) specimens were evaluated in this study. All isolates were identified by colony morphology, hemolytic properties on sheep blood agar plates, Gram stain, negative catalase reactions, bile-esculin hydrolysis and growth in 6.5 percent NaCl. Streptococcal group antigens were also detected using group D antisera (Slidex Strepto-Kit, bio-Merieux-France). Biochemical reactions (mannitol, lactose, sorbitol fermentations) were used for differentiation of the species, and some of the strains were identified using API 20 Strep kit (bio-Merieux-France)[3].

The antibiotic susceptibility tests using ampicillin, vancomycin, streptomycin and gentamicin powders were performed using the microbroth dilution technique according to NCCLS standards[4]. High-level resistance against aminoglycosides (MIC's > 500 mcg/ml and > 2000 mcg/ml for gentamicin and streptomicin, respectively) was detected. Statistical analysis was performed using Fisher's exact test.

Results

Forty-five of the 77 total strains were isolated from outpatient clinics, and 32 were hospital isolates. Seventy-three of them were identified as E.fecalis, three E. faecium and one was E. durans. The antibiotic resistance rates for the hospital and nonhospital isolates are shown in Table I. The hospital isolates were more resistant to ampicillin and gentamicin ($p < 0.01$). Four of the seven ampicillin-resistant, and 11 of the 15 high-level gentamicin-resistant hospital strains were from pediatric surgical wards. All of the patients had histories of broad-spectrum antibiotic usage. MIC50 values for ampicillin and vancomycin were 0.50 mcg/ml, while MIC90 values were 2 mcg/ml and 8 mcg/ml, respectively. Four strains were resistant to all antibiotics studied except vancomycin. Six (7.8%) strains showed high-level resistance to both aminoglycosides studied.

Table I: Antibiotic Resistance Rates of Hospital and Nonhospital Strains

	Hospital Strains n: 32		Nonhospital Strains n: 45		
	n	R%	n	R%	p value
Antibiotic					
Ampicillin	7	21.9	1	2.2	$p < 0.01$
Vancomycin	0	0	0	0	
Gentamicin*	15	46.9	6	13.3	$p < 0.01$
Streptomycin*	5	15.6	6	13.3	$p = 0.25$

* Highly resistant strains.
n: number of cases.
R: Antibiotic resistance rate.

Discussion

Enterococci cause mostly urinary tract and intraabdominal or pelvic wound infections[5]. They can also cause bacteremia with high mortality[6]. Enterococcal infections of all types have been thought to be acquired from patients' own flora; however, in recent years the spread of these microorganisms among hospitalized patients has been observed. Hospital personnel and nurses can carry these bacteria to their patients[1,5]. In the USA, enterococci are reported to be the second-most common cause of nosocomial infections. They are also capable of causing a variety of community-acquired infections. E.fecalis is the most common isolate (85-90%), followed by E. faecium (5-10%)[1,7]. In our series, urinary tract specimens were most common, followed by wound and blood isolates. E. fecalis was the most common isolate.

In addition to their intrinsic resistance to a wide variety of antimicrobials, such as antistaphylococcal penicillins and most cephalosporins, increasing resistance of enterococci to the limited number of antibiotics used in therapy was become a worldwide problem[2]. Prolonged hospital stays, hospitalization in surgical wards and prior treatment with antimicrobials have been found as predisposing factors for acquisition of resistant strains[5,8]. Our resistance rate was higher in hospital isolates, and the majority of strains were from surgical wards.

Ampicillin is the preferred β-lactam for the treatment of nonserious infections such as urinary tract infections; however, some strains, especially E. faecium isolates, are resistant because of the changes in penicillin-binding proteins. PBP5 is the responsible protein[9]. Since 1983 β-lactamase-producing strains have been reported[10]. Infections caused by these strains can be treated with combinations of β-lactamase inhibitors or with vancomycin[2]. Our ampicillin-resistant strains were mostly E. faecium. Our resistance rate (2.2%) of outpatient isolates was not high, but resistance among hospital isolates (21.9%) was remarkable. A similar resistance rate (22%) was detected in 100 pediatric urine specimens studied in İstanbul[11]. No β-lactamase-producing strains have been found in Turkey yet[11,12]. β-lactamase production in our strains was not evaulated. In serious infections the combination of an aminoglycoside with penicillin/ampicillin or a glycopeptide is used to obtain a synergistic bactericidal effect[13]. However, strains that are highly resistant to aminoglycosides are no longer susceptible to the combination therapy[1]. High-level resistance to streptomycin was first reported in the early 1970's, and at the end of the same decade high-level gentamicin resistance was described[8,14]. Ribosomal resistance and aminoglycoside-modifying enzymes coding on self-transferable plasmids cause high-level aminoglycoside resistance[2,15]. Enterococci with high-level gentamicin resistance are increasing in prevalence and are generally resistant to all aminoglycosides with the exception of streptomycin[14]. Our gentamicin resistance was higher than

in previous reports from Turkey[11, 12]. It may be because no distinction was made between hospital and non-hospital strains in those studies. The fact that high-level streptomycin resistance was less common among our isolates may be due to limited use of this agent in our hospital.

Clinically important infections by enterococci resistant to glycopeptides were first described in France in 1986[16], and have been reported from various parts of the world in both adult and pediatric populations[2, 17]. The alarming point about the spreading potential of resistance is that vancomycin-resistant genes could be transferred among enterococci and from enterococci to staphylococcus species[2]. Although vancomycin-resistant enterococci have not yet been isolated in Turkey, with the wide use of such antimicrobials it may become a problem.

Clinical isolates of enterococci, especially isolated from hospitalized patients, should be screened for ampicillin, vancomycin and high-level aminoglycoside resistance. should be emphasized, especially in surgical wards. Suitable therapy for empirical treatment can only be chosen on the basis of susceptibility studies.

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EXPERIENCE WITH ORAL REHYDRATION THERAPY IN MODERATELY DEHYDRATED CHILDREN DUE TO DIARRHEA*

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SUMMARY: Yurdakök K, Yalçın SS, Özmert E. (Department of Social Pediatrics, Hacettepe University Institute of Child Health, Ankara, Turkey). Experience with oral rehydration therapy in moderately dehydrated children due to diarrhea. Turk J Pediatr 1997; 39: 19-25.

Additional reports on oral rehydration therapy (ORT) in the management of moderately dehydrated patients may convince practitioners to convert from high-cost intravenous treatment to low-cost and efficient ORT in moderately dehydrated patients. Therefore, the failure rate and its association with admission serum sodium, potassium and bicarbonate levels of 162 moderately dehydrated children with diarrhea treated with ORT were analyzed retrospectively. The overall failure rate was found to be 17.6 percent. This rate did not differ significantly among normonatremic, hyponatremic and hypernatremic patients (16%, 25% and 28%, respectively; $p > 0.05$), nor did the rate differ among normokalemic, hypokalemic and hyperkalemic patients (16%, 33% and 25%, respectively; $p > 0.05$). Only moderately and severely acidotic patients had higher failure rates than non-acidotic and mildly acidotic cases (21%, 38%, 4% and 14% respectively; $p < 0.05$). Severely acidotic patients were also rehydrated over a longer time (10.4 ± 6.6 hours) than were nonacidotic patients (6.7 ± 2.3 hours, $p < 0.001$). Thus the degree of acidosis, which is closely related to the clinical severity of dehydration, was found to be much more predictive of ORT failure and the duration of rehydration than were other electrolyte disturbances. Besides correcting dehydration, ORT was safe and effective in treating various electrolyte disturbances. *Key words: G-ORS treatment, initial electrolyte levels, outcome.*

The Control of Diarrheal Diseases Programme was first established in 1986 in Turkey. Since then, WHO-recommended oral rehydration salts (ORS) have been distributed free-of-charge to all government health facilities. Despite the wide avalibility of ORS and intensive training programs, in-patient treatment of diarrheal cases does not correspond to the standard WHO management guidelines[1]. A survey reported in 1992 revealed a high rate of unneccesary hospitalizations for intravenous (IV) treatment in diarrheal cases[2]. Underuse of oral rehydration therapy (ORT) has also been reported from other countries. A recent study from the United States has shown that almost one-third of pediatric practitioners consider moderate dehydration to be a contraindication of ORT[3]. The presumption that moderately dehydrated children will have electrolyte and acid-base disturbances is one of the reasons for the preference of IV treatment in these cases.

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A second contributing factor to the underuse of ORT in moderate dehydration is the emphasis on IV treatment in fluid, electrolyte and acid-base disturbances in medical schools[4]. This results in a discrepancy between what is taught and what should be practiced. More reports on routine ORT experience in various electrolyte and acid-base disturbances may help to convince practitioners to change their practice from high-cost IV treatment to low-cost, highly efficient ORT. Therefore, we present the outcome of who were treated with standard WHO glucose oral rehydration solution (G-ORS) according to their initial serum electrolyte and acid-base levels.

Material and Methods

This study was done at Hacettepe University İhsan Doğramacı Children's Hospital Diarrhea Training and Treatment Center. Among 3,611 cases of diarrheal disease admitted to the center between September 1, 1992 and April 30, 1994, 162 cases of moderate dehydration were treated with G-ORS. The files of these cases were reviewed retrospectively and analyzed.

The clinical history and detailed physical examination were recorded in all cases. The diagnosis of moderate dehydration and management of the patients were based on standard WHO criteria[5]. Blood samples were obtained from all patients with moderate dehydration on admission for the assessment of serum electrolyte, pH and bicarbonate levels. G-ORS 100 ml/kg was administered to all cases for four to six hours. During this period the patients were observed closely for vital signs, vomiting, purging rate, abdominal distention and signs of dehydration. At the end of the first four to six hours, the patients were either re-administered G-ORS, hospitalized or discharged, depending on the clinical and laboratory assessments. Treatment failure was defined as deterioration in the clinical signs of dehydration after two hours of treatment, persistent frequent vomiting (more than 3/h), high purging rate (stool output exceeding 10 ml/kg/h during treatment) or no improvement in electrolyte and acid-base disturbance after two subsequent rehydration periods. Glucose malabsorption was considered to be present if the stool glucose strip test was positive (a color reaction corresponding to > 0.1 g/dl). in association with ORT failure related to a high purging rate. This test was performed in all patients with ORT failure and a high purging rate. Cases who had diarrhea for longer than 14 days were considered to have persistent diarhea. Patients hospitalized for associated diseases were not considered as treatment failures.

Patients were grouped according to their admission serum electrolyte and acid-base levels. Hyponatremic dehydration was defined by a serum sodium concentration of less than 130 mEq/L. Serum sodium levels greater than 150 mEq/L were considered as hypernatremia. Patients with serum potassium levels of less than 3 mEq/L and greater than 5.5 mEq/L were considered as hypokalemic and hyperkalemic, respectively. Patients were grouped according

to blood pH levels as normal (blood pH level of 7.35-7.40), midly acidotic (blood pH level of 7.30-7.34), moderately acidotic (blood pH level of 7.29-7.20) and severely acidotic (blood pH level less than 7.20).

Two outcome parameters, the hospitalization rate and the mean rehydration time of the patients, were analyzed accounting the patient groups according to their initial serum sodium, potassium and blood pH levels.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 5.0. One way ANOVA, Chi-square and Student's t test were used to compare the groups.

Results

Among 3,611 diarrhea admissions, 162 patients (4.5%) had moderate dehydration and were treated with G-ORS. Selected characteristics of all patients are shown in Table I. The mean age of the patients was 10.4 ± 8.8 months. The mean duration

Table I: Characteristics of Moderately Dehydrated Patients

Number of patients	162
Mean age (months)	104 ± 8.8
Male / Female	102 / 60
Mean weight (kg)	7.8 ± 2.6
Mean days before admission	6.9 ± 10.1
Mean serum electrolytes (mEq/L)	
Na^+	143 ± 10
K^+	4.5 ± 0.9
Cl^-	109 ± 12
HCO_3^-	13.3 ± 3.7
Number (%) of patients with $Na^+ < 130$ mEq/L	8 (5)
$Na^+ > 150$ mEq/L	32 (20)
$K^+ < 3.5$ mEq/L	15 (9)
$K^+ > 5.5$ mEq/L	20 (12)
$HCO_3^- < 15$ mEq/L	113 (70)
Mean blood pH	7.27 ± 0.08
Number (%) of patients with blood pH	
7.30 - 7.735	37 (23)
7.20 - 7.29	80 (49)
< 7.20	21 (13)
Number (%) of patients with coexisting diseases	
Bronchopneumonia	1 (0.6)
Acute Otitis Media	6 (4)
Urinary Tract Infection	14 (9)
Sepsis	3 (2)
Mean rehydration time (hours)	8.4 ± 4.6

of diarrhea was 6.9 ± 10.1 days on admission, 89.5 percent of the cases having acute diarrhea and 10.5 percent persistent diarrhea. On admission 32 patients (20%) had hypernatremia, eight patients (5%) had hyponatremia and 15 patients (9%) had hypokalemia. Serum bicarbonate levels were less than 15 mmol/L in 113 (70%) patients. According to blood pH levels, 37 (20%) patients had mild, 80 (49%) patients had moderate 21 (13%) patients had severe acidosis. Overall 138 (85%) patients had some degree of acidosis. The mean blood pH of all cases was within the moderate acidosis range (7.27 ± 0.08).

The characteristics and outcome of patients according to their initial serum sodium levels are shown in Table II. The age of patients with hypernatremia was significantly younger than that of normonatremic and hyponatremic patients (6.3 ± 3.2 months, 11.4 ± 9.6 months, respectively, $p < 0.05$). As shown in Table II,

Table II: Characteristics and Outcome of Patients According to Serum Sodium Levels on Admission

	Normonatremic	Hyponatremic	Hypernatremic
No. of patients (%)	122 (75)	8 (5)	32 (20)
Age (months)	11.4 ± 9.6*	13.5 ± 10.2	6.3 ± 3.2*
Body weight on admission (kg)	7.9 ± 2.7	7.8 ± 3.0	7.0 ± 1.6
Mean pH	7.28 ± 0.07	7.29 ± 0.10	7.26 ± 0.07
Serum electrolytes (mEq/L)			
Na^+	141 ± 5.0[a]	124 ± 7.1[a]	157 ± 6.7[a]
K^+	4.4 ± 0.7[b]	4.0 ± 0.8[c]	5.1 ± 0.7[b,c]
HCO_3^-	13.5 ± 3.7	13.0 ± 3.5	12.3 ± 2.7
Mean rehydration time (hours)	8.0 ± 4.0	8.3 ± 6.9	10.3 ± 5.6
No. of hospitalized patients (%)	20 (16)	2 (25)	9 (28)

Values are mean ± SD

*: $p < 0.05$

a, b, c: For all comparisons $p < 0.001$

the mean rehydration time and the rate of hospitalization were not significantly different among groups. Hyperkalemic patients were younger than hypokalemic patients (6.6 ± 3.9 months, 15.8 ± 9.6 months, respectively, $p < 0.05$, Table III). Neither the rehydration time nor the hospitalization rate varied significantly among the patients with different initial serum potassium levels.

Table III: Characteristics and Outcome of Patients According to Serum Potassium Levels on Admission

	Normakalemic	Hypokalemic	Hyperkalemic
No. of patients (%)	127 (78)	15 (9)	20 (12)
Age (months)	10.5 ± 9.2	15.8 ± 9.6*	6.6 ± 3.9*
Body weight on admission (kg)	7.9 ± 2.6	8.4 ± 2.7	6.7 ± 2.0
Mean pH	7.28 ± 0.07	7.29 ± 0.7	7.27 ± 0.08
Serum electrolytes (mEq/L)			
Na^+	143 ± 9.0[a, b]	135 ± 6.2[a, c]	149 ± 9.1[b, c]
K^+	4.5 ± 0.5[d]	3.1 ± 0.4[d]	6.0 ± 0.5[d]
HCO_3^-	13.2 ± 3.6	13.1 ± 3.5	13.4 ± 3.4
Mean rehydration time (hours)	8.3 ± 4.3	8.5 ± 5.7	8.3 ± 6.4
No. of hospitalized patients (%)	21 (16)	5 (33)	5 (25)

Values are mean ± SD
*: $p < 0.05$
a, b, c: For all comparisons $p < 0.001$

Children with moderate acidosis on admission had a longer rehydration time than non-acidotic or mildly acidotic children (9.6 ± 4.7, 6.7 ± 2.3, 6.2 ± 2.7 hours, respectively; $p < 0.001$; Table IV). Children with severe acidosis on admission had a longer rehydration time compared with nonacidotic and mildly acidotic children (10.4 ± 6.6, 6.7 ± 2.3, 6.2 ± 2.7 hours, respectively; $p < 0.001$; Table IV).

Table IV: Characteristics and Outcome of Patients According to Blood pH Levels on Admission

	Normal	Milld Acidosis	Moderate Acidosis	Severe Acidosis
No. of patients (%)	24 (15)	37 (23)	80 (49)	21 (13)
Age (months)	9.5 ± 6.4	12.9 ± 9.1	10.6 ± 8.1	6.6 ± 4.8
Body weight on admission (kg)	7.3 ± 1.8	8.4 ± 3.1	7.6 ± 2.2	6.7 ± 2.9
Mean pH	7.40 ± 0.04*	7.32 ± 0.01*	7.25 ± 0.3*	7.16 ± 0.02*
Serum electrolytes (mEq/L)				
Na^+	141 ± 8.9	142 ± 6.9	144 ± 8.9	145 ± 12.8
K^+	4.5 ± 0.7	4.5 ± 0.8	4.5 ± 0.8	4.7 ± 1.0
HCO_3^-	17.2 ± 3.9*	15.0 ± 3.5*	12.2 ± 2.2*	10.0 ± 2.2*
Mean rehydration time (hours)	6.7 ± 2.3[a, b]	6.2 ± 2.7[c, d]	9.6 ± 4.7[a, c]	10.4 ± 6.6[b, d]
No. of hospitalized patients (%)	1 (4)[e, f]	5 (14)[g]	17 (21)[e]	8 (38)[f, g]

Values are mean ± SD
*: For all comparisons between groups $p < 0.001$
Comparisons for a, b, c, d: $p < 0.001$
Comparisons for e, f, g: $p < 0.05$

There was no significant difference between the mean rehydration time of moderately and severely acidotic patients. The hospitalization rate was significantly

higher among severely acidotic children than non-acidotic and mildly acidotic children (38%, 4% and 14%, respectively; $p < 0.05$). Moderately acidotic cases were also more likely to be hospitalized than were non-acidotic, moderately dehydrated children (21% and 4%, respectively, $p < 0.05$).

One hundred and thirty-one cases (82.4%) were treated successfully with G-ORS, the failure rate being 17.6 percent (28 cases Table V). The reasons for treatment failure are given in Table V. The main reasons for failure in order of decreasing frequency were high purging rate, persistent acidosis, glucose malabsorption, persistent vomiting, persistent hypernatremia, persistent hypokalemia and paralytic ileus with abdominal distention. Persistent acidosis constituted 25 percent and electrolyte disturbances constituted only 10.5 percent of the failures. Three patients were hospitalized due to sepsis.

Table V: Reasons for ORT Failure

	n	%
High purging rate	9	32
Persistent acidosis	7	25
Glucose malabsorption	5	18
Persistent vomiting	3	11
Electrolyte disturbances		
Persistent hypernatremia	2	7
Persistent hypokalemia	1	3.5
Abdominal distention, paralytic ileus	1	3.5
Total	28	100

Discussion

The overall ORT failure rate is reported by WHO to be five percent among all diarrheal dehydration cases[6]. An earlier report from Turkey has revealed a failure rate of 8.5 percent among moderately dehydrated cases, which is compatible with the literature[7]. In this study we found the failure rate to be 17.6 percent. Our failure rate seems to be higher than those reported earlier. This may be explained by the low initial blood pH levels and the long duration of diarrhea of our patients before admission, both of which criteria are correlated to the severity of dehydration. Although the WHO criteria were used for assessment of the degree of dehydration, we may have underestimated the degree of dehydration in some of our cases that were borderline severe dehydration.

Failure was mostly due to a high purging rate, persistent acidosis and glucose malabsorption. These are the major leading causes of ORT failure according to WHO. Initial serum sodium and potassium levels were not predictive of ORT

failure. On the contrary, the initial blood pH and bicarbonate levels could be significant in predicting ORT failure. The failure rate increased significantly with the degree of acidosis. In our study the overall failure rate in initially acidotic patients was 21 percent; the rate was five percent in mildly acidotic and 17 percent in moderately acidotic patients, and the rate increased significantly to 38 percent in severely acidotic patients. Thus, not only the presence but also the degree of acidosis is important in determining the final outcome.

The overall mean rehydration time was found to be longer than the four to six hours established by WHO[5]. Most of the patients admitted to our center required twice as much time as recommended by WHO for adequate rehydration. Although the time seems to have been prolonged in all cases, the only significant association with the mean rehydration time could be found in moderately and severely acidotic cases. Non-acidotic and mildly acidotic patients had a mean rehydration time of approximately six hours, which may be compatible with the WHO recommendations. The mean rehydration time did not change significantly with various initial serum sodium and potassium levels. Thus, the overall, prolonged, mean rehydration time may only be related to the moderate or severe acidosis present in most of our patients.

In conclusion, in this study it has been shown that the initial level of metabolic acidosis is the only parameter that determines ORT failure and the necessary duration of rehydration. Low-cost and highly efficient ORT can be used safely and successfully even in patients with severe acidosis and various electrolyte disturbances. However, the mean duration of rehydration should be longer for acidotic patients than nonacidotic patients.

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THE ANGIOCARDIOGRAPHIC ANALYSIS OF 73 PATIENTS WITH DOUBLE-OUTLET RIGHT VENTRICLE*

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Alpay Çeliker MD[****]

SUMMARY: Çil E, Özme Ş, Saraçlar M, Bilgiç A, Özkutlu S, Özer S, Çeliker A. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The angiocardiographic analysis of 73 patients with double-outlet right ventricle. Turk J Pediatr 1997; 39: 27-33.

The purpose of this study was to determine the cardiac anatomy of patients with double-outlet right ventricle by angiocardiography. A total of 73 patients between the ages of one day and 11 years were examined. The aorta was on the right side of the pulmonary artery in 23 cases (32%), right anterior in 20 (27%) and right posterior in 17 cases (23%). Pulmonary stenosis was found in 53 patients (73%) and subaortic stenosis in six cases. Ventricular septal defect (VSD) was subaortic in 39 cases (52%), remote type in 17 (23%), doubly committed in 10 (13%), and subpulmonic in 9 (12%). Double VSD was noted in two patients. Pulmonary hypertension was more frequent in subpulmonic ventricular septal defect (78%). The most common associated anomalies were atrial septal defect (34%), anomalous coronary arteries (12%) and endocardial cushion defect (10%). Aortic root angiography was not satisfactory in half of the cases with coronary arterial anomaly. In conclusion, double-outlet right ventricle is a complex anomaly, all of whose cardiac features can be successfully demonstrated in detail by echocardiography and angiocardiography. However, in order to determine the anatomy of the coronary arteries, selective coronary angiography may be necessary in some patients. *Key words: double-outlet right ventricle, echocardiography, angiocardiography, cardiac catheterization, coronary artery.*

Double-outlet right ventricle (DORV) is an uncommon, congenital, cardiac anomaly in which the aorta and pulmonary artery reside predominantly above the morphologic right ventricle[1,2]. The natural history and clinical spectrum vary depending on the location of the ventricular septal defect (VSD), the presence or absence of pulmonary stenosis (PS), and other associated cardiac anomalies[3-7]. The feasibility of anatomic repair of DORV malformation has been reported with low mortality and morbidity rates[3,8,9]. To provide optimal surgical results, one must know the anatomy of the heart, great vessels and coronary arteries. The purpose of this study was to determine the entire cardiac anatomy by angiocardiography in 73 patients with the diagnosis of DORV.

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Material and Methods

The clinical records of the 234 patients who were diagnosed with DORV between January 1980 and September 1993 at Hacettepe Children's Hospital were reviewed. Of these patients, 73 cases with the following criteria were included the study: 1. only the patients whose clinical follow-up records were sufficient, 2. patients who had a satisfactory echocardiographic record, and 3. cases whose cineangiography was sufficient to depict all the cardiac anatomy.

For the purposes of this study, a patient was considered to have DORV when echocardiography, angiocardiography or direct inspection at operation demonstrated the origin of both great arteries to be the morphologic right ventricle, or the origin of one great artery and most of the other from the right ventricle with discontinuity of a great artery and mitral valves and with a bilateral subarterial conus[3, 10-12]. The diagnosis of DORV was made in all patients by both echocardiography and angiocardiography, and was confirmed intraoperatively in controversial cases. The categorization into morphologic subsets was made according to the commitment of the VSD to the great arteries as described by Lev et al.[2]. The relation of the great arteries was classified as in the study of Sridaromont et al.[1].

In all patients, the following parameters were evaluated: a) the position of the great arteries with respect to each other at the valvar level, b) the relationship of the ventricular septal defect and semilunar valves, c) the presence of subarterial stenosis, d) the anatomy of the coronary arteries, and e) the presence of associated defects.

Results

Seventy-three cases (45 boys and 28 girls) with the defined criteria were included the study. The ages of the patients at the time of diagnosis ranged from one day to 11 years (mean 2.8 ± 2.7 years, median 1.2 years). The mean age of the patients was 1.1 years at the time of palliative surgery and 4.5 years at corrective surgery.

The position of the semilunar valves with respect to each other is shown on Table I. The pulmonary outflow tract was devoid of obtruction in only 20 patients, while 53 (73%) had various forms of pulmonary stenosis. The pulmonary stenosis was valvar in eight patients, subvalvar (or infundibular) in 34 (Fig. 1) and both valvar and subvalvar in 11. The aortic outflow tract was obstructed in six patients. All of them had mild stenosis due to subvalvar hypertrophy. The location of the VSD was subaortic in 39 patients (52%), remote type in 17 {inlet in 11 (Fig. 2) and muscular in 6}, doubly committed in 10 and subpulmonic in nine cases. Two cases had double VSD, both perimembranous, subaortic and muscular.

Table I: Relation of the Aorta to the Pulmonary Artery

Relation	No. of Cases	%
Aorta on the right side	60	82
Side-by-side	23	32
Anterior (dextromalposition)	20	27
Posterior (normal relation)	17	23
Aorta on the left side	11	15
Anterior (levomalposition)	9	12
Side-by-side	2	3
Aorta in front of the pulmonary artery	2	3

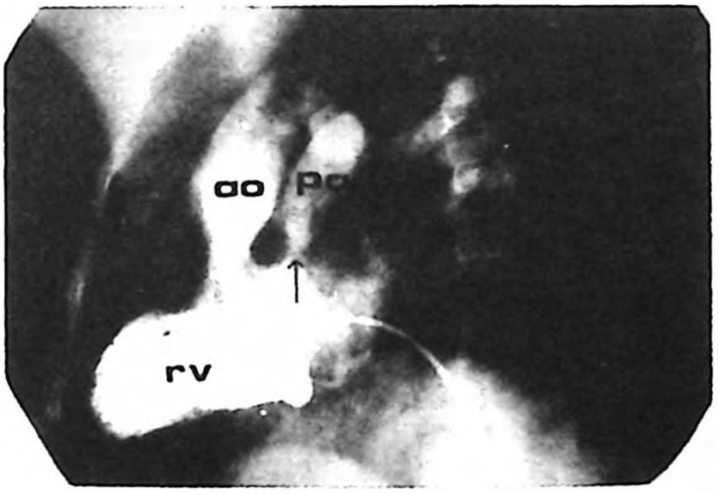

Fig. 1: Right ventriculagraphy (in lateral position) in a patient with double-outlet right ventricle. Aorta is anterior to the pulmonary artery and there is subvalvar pulmonary stenosis (arrow). ao: aorta, pa: pulmonary artery, rv: right ventricle.

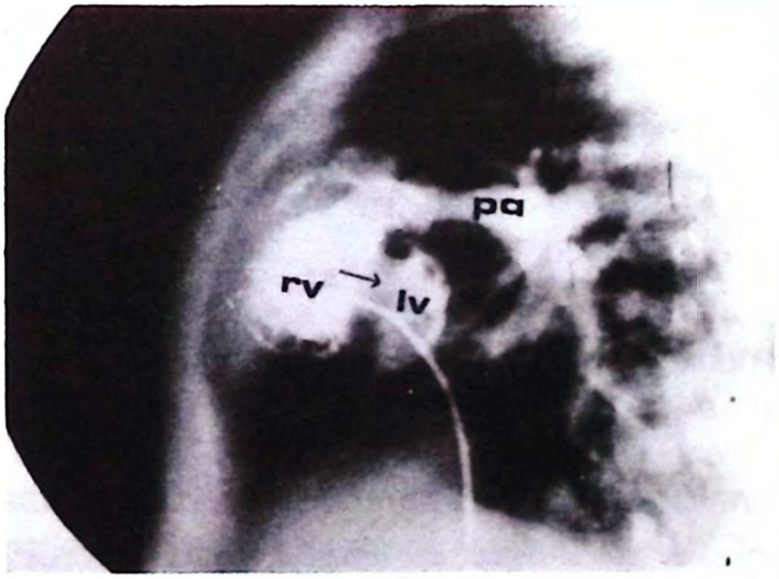

Fig. 2: The remote type (inlet muscular) of ventricular septal defect on right ventriculography (in lateral postion). lv: left ventricle, pa: pulmonary artery, rv: right ventricle, arrow: ventricular septal defect.

Pulmonary hypertension (PH) was present in 20 patients, and was severe in 14 cases. In the patients with PH, VSD was subpulmonic in seven cases, subaortic in five, remote type in four and doubly committed in four. The occurrence rate of pH according to the types of VSD was 78 percent in subpulmonic, 40 percent in doubly committed, 18 percent in remote type and 14 percent in subaortic (Table II).

Table II: The Rate of Occurrence of Pulmonary Hypertension by Type of VSD

VSD Type	PH/Patients	Rate (%)
Subpulmonic	7/9	78
Doubly committed	4/10	40
Remote type	4/17	18
Subaortic	5/39	13
Total	20/75*	27

* Double VSD was present in two patients. PH: pulmonary hypertension. VSD: ventricular septal defect.

Associated anomalies: All of the patients had at least one VSD. Atrial septal defect was the second-most common associated anomaly after VSD, while 18 patients had an ostium secundum defect. In addition, four paients had common atrium and three had ostium primum defect as part of the endocardial cushion defect. In six patients, a common atrioventricular valve was present. Patent ductus arteriosus was also present in seven cases. The position of the ventricles was abnormal in five patients: in four of them, the ventricles were in the side-by-side position (Fig. 3), and in one, they were superior-and-inferior. Anomalies of the coronary arteries were found in nine patients (12%). In five of them, the left anterior descending artery was originated from the right coronary artery. A single origin of the coronary arterial system (left) was present in two cases, with the right coronary artery coursed immediately beneath the pulmonary annulus; in two cases with levomalposition of the aorta, the right coronary artery coursed inferior to the pulmonary annulus.

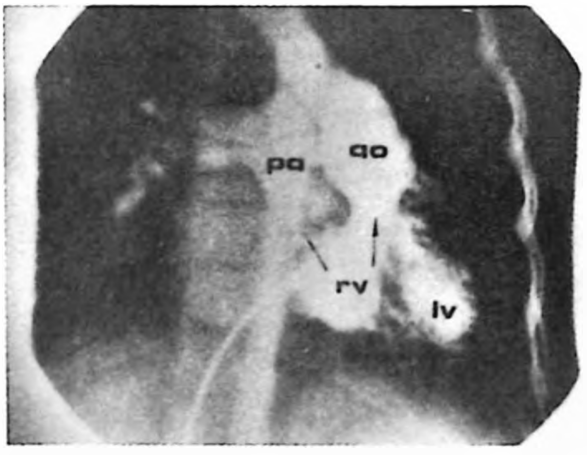

Fig. 3: Subaortic ventricular septal defect and bilateral subarterial conus (arrows) in a case with double-outlet right ventricle. note the side-by-side position of the ventricles. (Right ventriculography was performed in antero-posterior position).
ao: aorta, lv: left ventricle, pa: pulmonary artery, rv: right ventricle.

Discussion

Double-outlet right ventricle is a rare, congenital, cardiac anomaly that includes a diverse group of malformations sharing the common feature that both great arteries arise primarily from the right ventricle. The overall outlook for patients with DORV has improved greatly since the improvement of corrective procedures. However, surgical repair of DORV is complicated by the great variability in intracardiac and extracardiac morphology evidenced by these hearts. Complete correction of DORV mainly depends on the complexity of the cardiac anatomy. It is essential to obtain full detail of intracardiac anatomy and extracardiac anomalies before corrective surgery. Most of the previous series of cases with DORV have been reported by cardiac pathologists or cardiac surgeons, with pathologists tending to see patients with associated severe abnormalities, and surgeons tending to see patients free of such lesions[13]. Therefore, we analyzed the angiocardiographic data on all patients with DORV with or without surgical treatment.

In the present study, the median age of the patients (1.2 years) was greater than that in similar studies, since the patients from underdeveloped, rural regions of this country are generally older. In all cases, both great arteries were observed to originate predominantly from the morphologic right ventricle. In 82 percent of patients, the aorta was to the right of the pulmonary artery. The aorta and pulmonary artery were located side-by-side in 23 patients (32%); the side-by-side relation of the great arteries was also most common in previous studies[1, 5, 6, 11]. Dextromalposition (aorta on the right and in front of the pulmonary artery) was the second-most frequent type. The aortic levoposition was relatively uncommon, seen only in 15 percent of patients. The relation of the great arteries in the present study was nearly the same as in previous studies[1, 2, 5, 11]. However the location of the aorta in front of the pulmonary artery or to the left of the pulmonary artery (reverse side-by-side) was extremely uncommon in the medical literature[1, 6, 10, 11]. In the present study, the aorta was in front of the pulmonary artery in two patients and was on the left of the pulmonary artery (reverse side-by-side) in two patients.

The position of the great arteries must be defined clearly before corrective surgery because reconstruction of the pulmonary outflow tract is complicated when the pulmonary artery is behind the aorta. The location of the VSD is also important in patients with DORV. Remote-type (noncommitted) VSD and multiple VSDs in particular must be determined before surgery. Recognition of these types of defects is extremely important for the performance of a safe and complete repair. In the present study, noncommitted VSD was more common (23%) than in most of the previous studies. Judson et al.[11] reported three patients with remote-type VSD out of 62 patients (5%). The rate of remote-type VSD was 19 percent in the study by Macartney et al.[5], 17 percent in that of Hagler et al.[10], 10 percent in that of Sondheimer et al.[13] and 20 percent in that of Kirklin et al.[3].

Pulmonary hypertension is an anticipated outcome in patients with DORV without PS. Sondheimer et al.[13] reported that PS was present in 39 perecent of their patients with DORV. In the study of Judson et al.[11], PS was present in 74 percent of cases. The occurrence rate of PS was 61 percent in the study by Luber et al.[4]. In the present study PS was diagnosed in 73 percent of patients, and the remaining patients had PH of various severities. When the patients with PH were classified according to the site of VSD, it was observed that the majority of the VSDs were the subpulmonic type. The incidene of PH in the subpulmonic type of VSD was 78 percent; however, this rate was 40 percent in doubly committed VSD, and 13 percent in subaortic VSD. Therefore, early surgical treatment is compulsory in the subpulmonic type of VSD where the development of PH was extremely frequent.

The coronary arterial anatomy was drastically important in patients with DORV for both the arterial switch operation and pulmonary outflow reconstruction. There have been few studies examining the coronary anatomy in patients with DORV. Judson et al.[10] and Stellin et al.[14] reported high prevalences of anomalous coronary artery (28% and 22%, respectively); however, Luber et al.[4] reported only one patient (2%) with a coronary arterial anomaly out of a total of 57 cases. In the study presented, anomalous anatomy of the coronary arteries was determined in 12 percent of the patients. In all of these patients PS was accompanied by DORV. In spite of cardiac catheterization and angiography being performed in these patients, four of the coronary arterial anomalies were not diagnosed pre-operatively. Retrospectively it was perceived that aortic root angiography could not demonstrate the full coronary arterial anatomy in some patients because of the relatively inadequate amount of contrast material in the enormously enlarged aortic root. Therefore selective coronary angiography may be necessary in some patients.

In conclusion, double-outlet right ventricle is a complex anomaly in which all the cardiac features could be successfully demonstrated in detail by echocardiography and angiocardiography. However, to determine the anatomy of coronary arteries correctly, selective coronary angiography may be required in some patients.

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SURGICAL MANAGEMENT OF CONGENITAL LOBAR EMPHYSEMA*

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SUMMARY: Doğan R, Demircin M, Sarıgül A, Paşaoğlu İ, Göçmen A, Bozer AY. (Department of Thoracic and Cardiovascular Surgery, and the Chest Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara Turkey). Surgical management of congenital lobar emphysema. Turk J Pediatr 1997; 39: 35-44.

Here in nine patients with congenital lobar emphysema who had been treated surgically in the previous 10 years are reported. The ages of the patients at diagnosis ranged from 26 days to 11 months. The six patients whose symptoms started in the neonatal period had more severe dyspnea, cyanosis and respiratory distress. Tube thoracostomy was performed in two of three patients who had been misdiagnosed initially. The affected side was the left upper lobe in five patients, the right upper lobe in three, and the right middle and upper lobes in one patient. Lobectomy was performed in all cases. Dysplasia of the bronchial cartilage was found in six patients and bronchial atresia of the left upper lobe was found in another infant as the etiologic cause of the condition. Although the possibility of conservative management in congenital lobar emphysema has been reported recently, we believe that surgery is the treatment of choice in patients who have persistent or progressive, severe respiratory distress in spite of medical treatment. *Key words: congenital lobar emphysema, pulmonary emphysema, respiratory tract.*

Congenital lobar emphysema is an uncommon condition in which overinflation of the involved lobe can cause severe respiratory distress. Since the first report on the successful treatment of lobar emphysema by lobectomy by Gross[1] in 1945, the condition of lobar emphysema in infancy and childhood has been recognized with increasing frequency.

Clinically the condition may present with varying severity. In approximately one-third of cases, severe respiratory distress occurs soon after birth, and rapid deterioration may follow[2-4]. The remaining two-thirds of patients have a slower onset, usually at one or two months of age, often coinciding with a respiratory infection. Occasionally asymptomatic or stable cases have been reported, but characteristically in patients who were not symptomatic until they were older than six months of age[3-6]. This may be confusing to the physician faced with the problem of diagnosing this rare condition.

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The natural history of the disease is unknown for the most part, since surgery to remove the overinflated lobe has been performed in the majority of patients. Only a few isolated case reports of nonsurgical treatment were recorded in the literature before 1990[7-10]. More recently, Kennedy[11] and Stigers[12] showed that most patients with congenital lobar emphysema could be managed medically with good results. However, the treatment of choice is surgical removal of the affected lobe in patients who have persistent or progressive, severe respiratory distress that does not respond to medical treatment.

In the past 10 years, nine patients with congenital lobar emphysema were surgically treated at the Thoracic and Cardiovascular Surgery Department. Here in we present our experience with the diagnosis, etiology, prognosis and treatment of this condition.

Material and Methods

In this study, nine children with congenital lobar emphysema who had undergone surgical treatment in our department between 1985 and 1995 were analyzed. Of the nine patients, two were diagnosed at Dr. Sami Ulus Children's Hospital. The remaining seven children were diagnosed at Hacettepe Children's Hospital.

Six of the nine patients were boys and three were girls. Their ages ranged from 26 days to 11 months (Table I). The history was typical in most, with dyspnea dating from early infancy and intermittent attacks of cyanosis. On admission all were severely ill. Chest x-rays showed a markedly emphysematous lobe of the lung causing compression atelectasis of the adjacent lobes and shifting of the mediastinum to the opposite side of the thorax (Figs. 1-4). The affected side was the left upper lobe in five patients, the right upper lobe in three, and the right middle and upper lobes in one patient. In all patients, physical examination revealed tachypnea, cyanosis, intercostal retraction, and decreased breath sounds over the involved hemithorax. Chest radiographs of Cases 5, 6 and 8 were initially interpreted as pneumothorax, and diagnostic aspiration was performed at another institution. Tension pneumothorax developed with a marked increase in respiratory distress with cyanosis. A chest drain was inserted with no further air drainage and no clinical improvement (Cases 5 and 8).

To exclude any associated cardiac defect or vascular abnormalities that could accompany congenital lobar emphysema, two-dimensional echocardiography was performed in all patients. Except for patent foramen ovale in Cases 3, 7 and 9, no additional anomaly was found. Time-consuming examinations requiring sedation and intubation, such as angiography and computed tomography, could not be done. However, in order to determine the presence or absence of abnormalities of the bronchial tree mucous plug or a foreign body, bronchoscopy was performed in all cases with Starz (Karl-Starz Endocopy 6MB and Co, Tuttlingen, West Germany) pediatric rigid bronchoscopy equipment under general anesthesia with controlled ventilation. No foreign body aspiration or mucous plaque was found. However, in Case 3, the left upper lobe bronchus was found to be a blind-ended pouch filled with a small amount of mucoid material.

Table I: Patients with Congenital Lobar Emphysema Symptomatology, Management and Results

No.	Patients	Sex	Age of onset of symptoms	Age at operation	Presenting features	Additional anomalies	Affected lobe	Treatment	Results
1 SA	1638116	F	2.5 months	3 months	Tachypnea Cyanosis	–	RUL	Lobectomy	Well at 3 years
2 RB	1671903	M	2 months	2.5 months	Tachypnea Cyanosis	–	RUL	Lobectomy	Lost to follow-up after first check-up
3 ÇÖ	1671830	M	10 months	11 months	Cough, fever, wheeze	PFO, CPD	LUL	Lobectomy	Well at 3 years
4 AA	1690080	M	10 days	2 months	Cough, cyanosis, dyspnea, congestive heart failure, fever	–	RUL RML	Bilobectoy	Died on 8th day with sepsis
5 CA	1865479	M	15 days	2 months	Fever, cough, tachypnea	–	LUL	Tube thorocostomy Lobectomy	Well at 6 years
6 ÖT	1877143	F	4 days	10 days	Respiratory distress, cyanosis, iatrogenic pneumothorax	–	LUL	Lobectomy	Well at 3 months
7 MÖD	1896478	F	2 days	26 days	Respiratory distress, tachypnea, cyanosis	PFO	LUL	Lobectomy	Well at 1 year
8 EÜ	2065800	M	15 days	1 month	Cyanosis Tachypnea, tube thoracostomy	–	RUL	Lobectomy	Well at 2 years
9 MÇ	2037484	M	2 days	2 months	Tachypnea	PFO	LUL	Lobectomy	Well at 3 years

RUL : Right Upper Lobe.
LUL : Left Upper Lobe.
RML : Right Middle Lobe.
PFO : Patent Foramen Ovale.
CPD : Congenital Pericardial Defect.

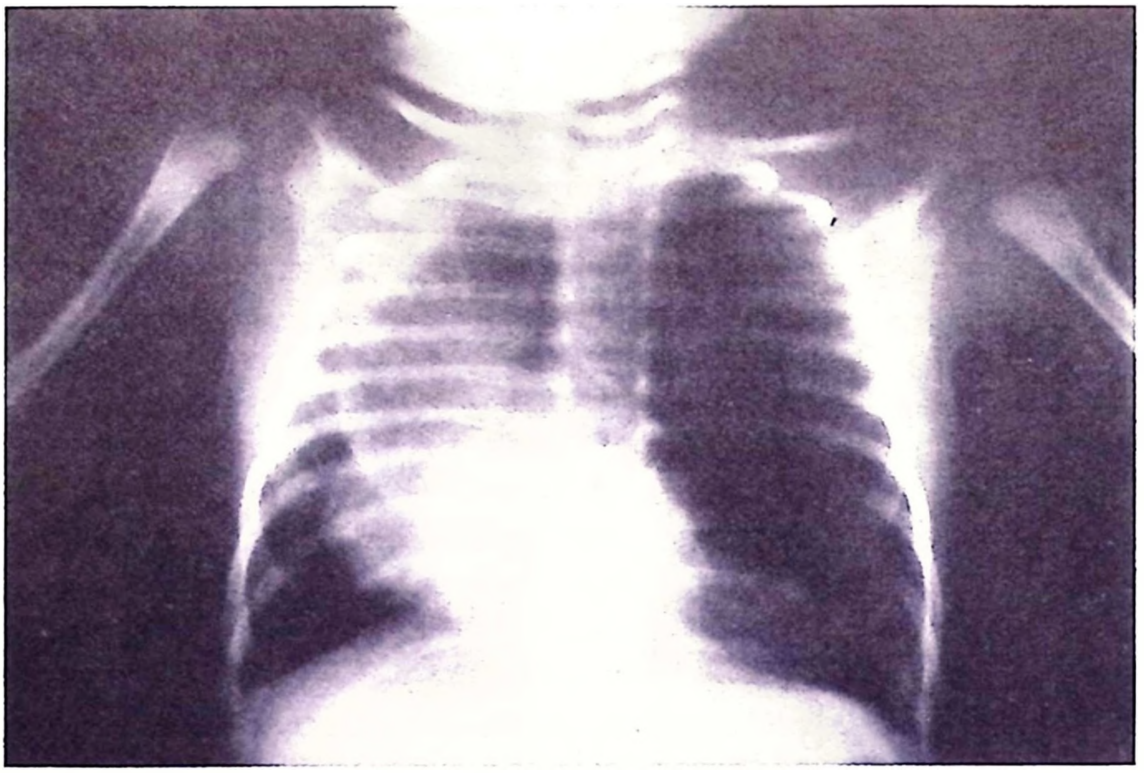

Fig. 1: The emphysematous left upper lobe is herniated across the mediastinum into the right side. Note the mediastinal shift to the right (Case 7).

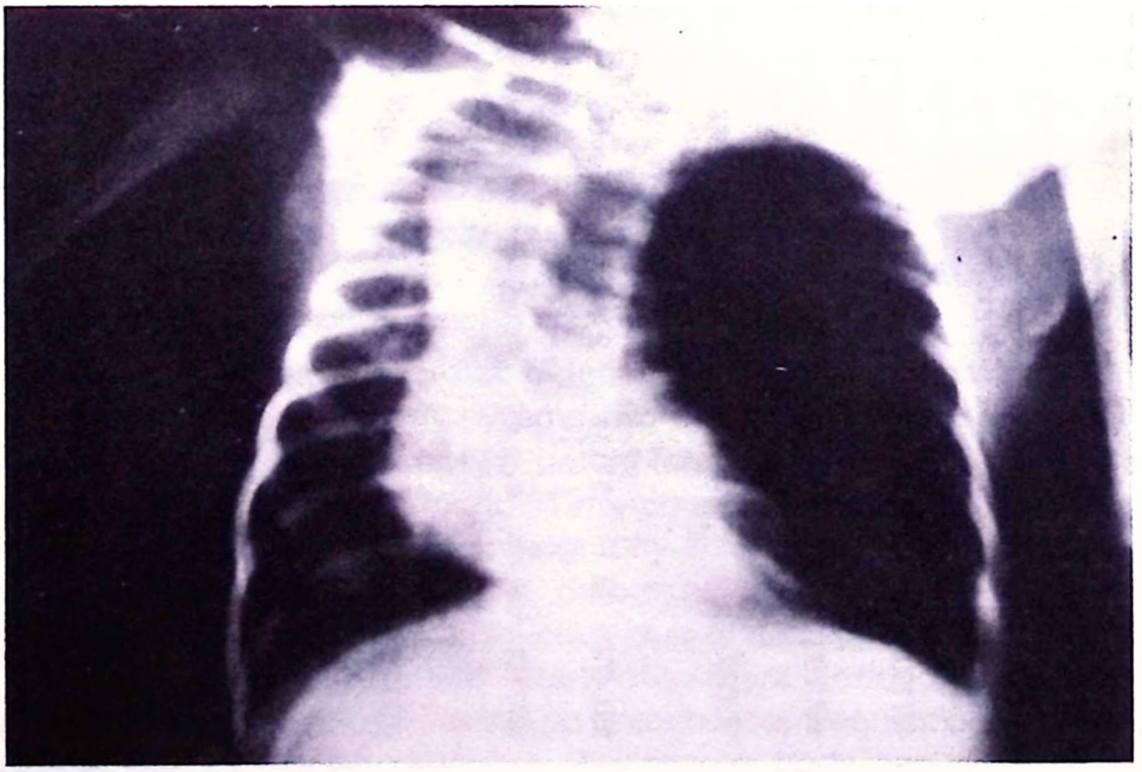

Fig. 2: Hypertanslucent left chest. Initial diagnosis was tension pneumothorax (Case 6). Congenital left upper lobe emphysema.

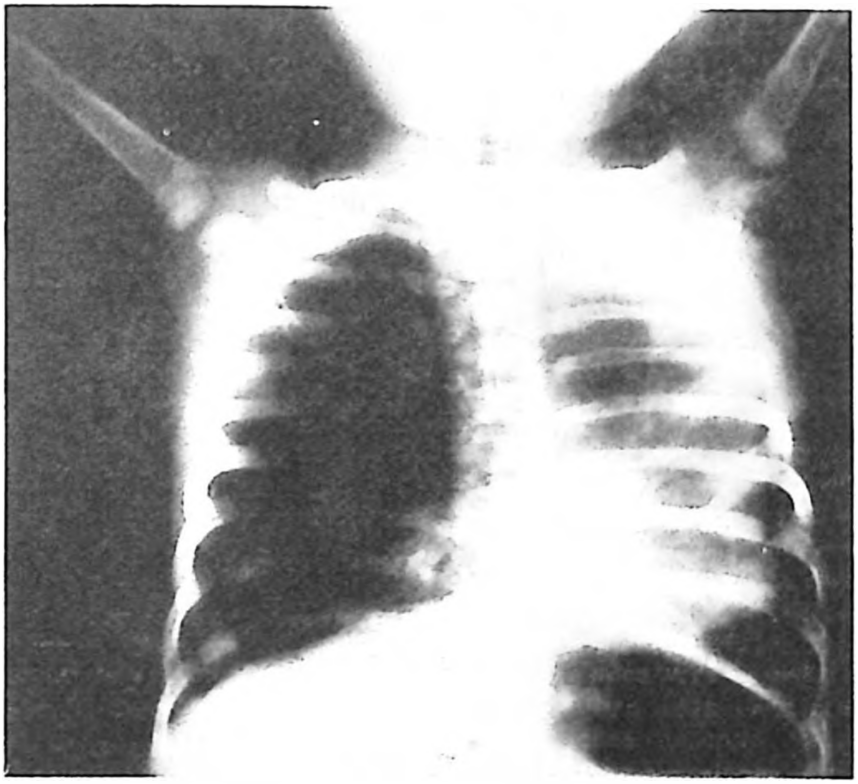

Fig. 3: Infant with congenital lobar emphysema of the right upper lobe. The involved lobe is hyper-aerated and has crossed the mediastinum into the left hemithorax. The right lower lobe is compressed (Case 8).

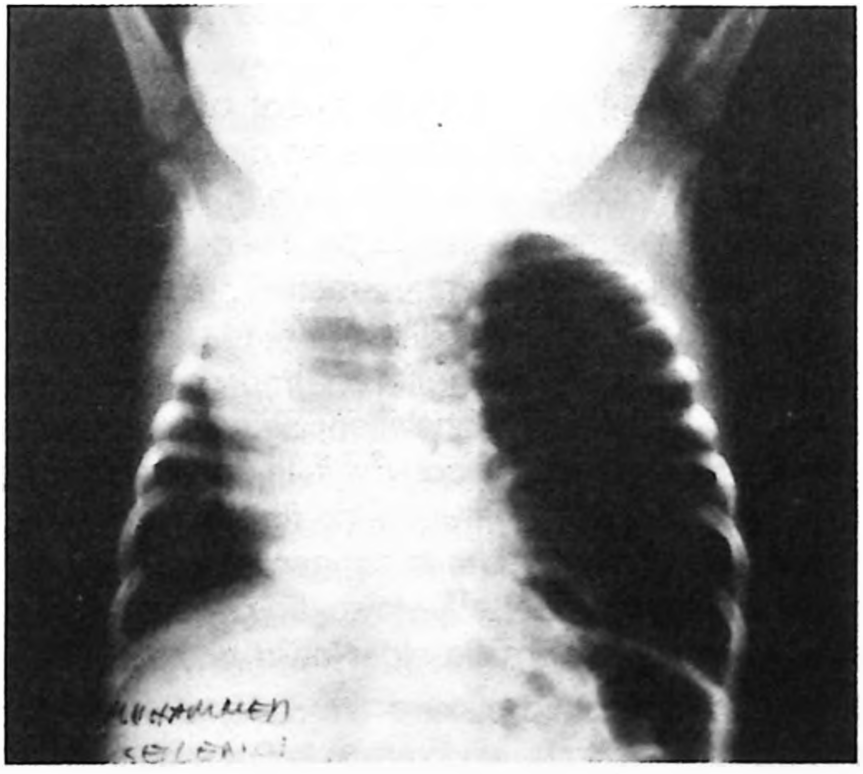

Fig. 4: Infant with overdistended left upper lobe due to congenital lobar emphysema, with displacement of the heart and mediastinum to the right (Case 9).

Following bronchoscopy, which was performed in the operating room, the children were intubated. At the time of anesthetic induction, positive pressure ventilation, which may precipitate air trapping and cardiorespiratory collapse, was avoided. Thereafter the chest was opened as quickly as possible. Grossly, the affected lobes seemed like sponge rubber, not deflating bouncing back into shape after being compressed. The remaining lung tissue was atelectatic. Before resection, the mediastinum was carefully examined for lesions that could have obstructed the bronchus. Lobectomy was performed in all patients. On histopathological examination of the resected lobes, sponge-like lung structure and emphysematous alveoli were detected. Although the gross appearance of the bronchial cartliages was found to be dysplastic in six patients at operation, the operative findings were not confirmed pathologically. In Case 3, the proximal bronchial cartilage of the left upper lobe was found to be absent after ligation of the pulmonary artery and veins. The left upper lobe bronchus ended with a blind pouch containing fetal mucoid secretions. A congenital pericardial defect measuring 2 x 1 cm was also seen in this case.

One patient died on the eighth postoperative day. This patient who had been severely ill preoperatively, developed sepsis and, despite antibiotic and resuscitative measures, suffered a cardiac arrest and died. The survivors were followed up by the Pediatric Chest Diseases Division. One patient was lost to follow-up after the first postoperative check-up. The remaining seven patients were found to be well at regular follow-up visits.

Discussion

Infantile congenital emphysema is an infrequent but progressive variety of obstructive emphysema leading to uniform massive distension of the involved lobe. Severe respiratory distress occurs soon after birth in approximately one-third of patients. The severity of dyspnea depends on the degree of over-inflation the affected lobe. Cyanosis, wheezing and rib retraction are common. Approximately 12 percent of patients are in critical condition prior to treatment[5]. The symptoms can progress rapidly with crying and agitation. Improvement is rarely achieved with medical treatment, i.e., oxygen inhalation, airway humidification, antibiotic administration, suctioning and bronchoscopy[2, 3, 6]. In approximately half of patients, symptoms develop later, sometime between the first week of life and six months of age[2, 13]. Only five percent of cases with congenital lobar emphysema present with symptoms after six months of age[14]. However, congenital lobar emphysema may be diagnosed in an asymptomatic older child or adult[13, 15].

Approximately two-thirds of reported patients are male, and almost all patients are white. The condition is reported to be uncommon in black and premature infants[6, 14]. Murray[5] reported a 14 percent incidence of associated congenital heart lesions and lack of familial incidence. Although it is rare, some cases have bilateral involvement[16, 17].

In the present series the onset of the symptoms was typically in early infancy. The symptoms are those of respiratory distress. The seven neonates who presented with severe respiratory distress supported the hypothesis that the earlier the presentation the more severe the symptoms. Our male/female ratio (2/1) was similar to that reported in the literature. Congenital lobar emphysema usually affects the left upper lobe, followed by the right middle lobe. However, in our series the left upper lobe was most often affected. (5/10), followed by the right upper lobe (4/10). Right-middle-lobe involvement was seen in only one infant.

The cardinal radiographic sign of congenital lobar emphysema is expansion of the involved lobe. During the first few days of life, bronchial obstruction often results in delayed clearance of fetal lung fluid from the affected lobe. During this period the affected lobe may be seen to be opaque. This radiologic finding occurs in two-thirds of patients who present with symptoms at birth[12, 13, 18]. In infants with progressive respiratory distress and the characteristic x-ray findings of lobar hyperinflation, mediastinal displacement away from the emphysematous side, and controlateral atelectasis, congenital lobar emphysema should be suspected[3, 5, 19]. The diaphragm is depressed and flattened on the affected side. There may be anterior herniation of the lobe through the mediastinum, with consequent posterior displacement of the heart. In severe cases the over-expanded lung may herniate into the opposite hemithorax. These radiological findings and the clinical picture of an infant in respiratory distress are generally diagnostic, and no further examination is necessary. Congenital lobar emphysema should be differentiated from giant air cysts of the upper lobes, diaphragmatic hernia and pneumothorax. A mistake in diagnosis can be avoided by careful interpretation of the chest x-ray, fluoroscopy, lung isotope scanning and barium swallowing[2, 16, 19].

Fluoroscopy helps to establish the diagnosis in an older child with less severe clinical signs or when there are atypical radiologic features; compensatory emphysema and other causes of non-obstructive emphysema should also be considered. When other causes of obstructive emphysema are suspected, a barium swallow may exclude extrinsic compression to a bronchus such as aberrant vessels, bronchogenic cyst, etc[19]. Bronchography may help to identify the obstructed bronchus and show either an intrinsic or extrinsic obstruction. It must be noted that these investigative procedures are not indicated and may be dangerous for an infant with respiratory distress[6, 12, 19]. More invasive investigative procedures such as arteriography may occasionally be required to show anomalous vessels causing extrinsic compression of a bronchus[20, 21]. Bronchoscopy may be valuable to rule out the presence of a mucous plug, mucosal fold or foreign bodies causing either obstructive emphysema or atelectasis with compensatory emphysema, but it would be hazardous for an infant in severe respiratory distress[17, 19]. In an older child with an acute onset of symptoms, bronchoscopy is indicated to rule out an endobronchial mass or an aspirated foreign body, and should be planned to precede immediate thoracotomy.

Radionuclide ventilation/perfusion scintigraphy is useful in evaluating the function of the affected and compressed lobes, and is safe with a minimal absorbed radiation dose[11, 12, 19, 22, 23]. Perfusion studies are accomplished by intravenous injection of ^{99m}Tc-MAA[11, 12, 19, 23]. Ventilation studies may be performed in infants utilizing Krypton 81-m or submicronic aerosols containing either ^{99m}Tc-DTPA or ^{99m}Tc-SC[11, 23]. In case in which plain radiographs or CT indicate congenital lobar emphysema, the scintigraphic demonstration of a reduction in both ventilation and perfusion to the affected lobe can confirm the diagnosis of congenital lobar emphysema; however, CT and ventilation/perfusion scintigraphy are difficult to perform in a small infant. Each of these studies takes approximately six minutes. Although Kr-81m ventilation/perfusion scans are obtained during continuous breathing in an acceptable period of time (1-3 minutes), they have not been used in our center. Moreover, Kr-81m has some disadvantages, such as it is not conveniently available on a regular basis, and it may not be as effective as Xe-133 (the agent routinely used in our center) in the assessment of air trapping.

The etiology of congenital lobar emphysema has not been clearly defined. It has been suggested that several mechanisms may be involved: infection damaging the alveoli, developmental abnormality of alveoli[24], an obstruction of the lobar bronchus perhaps from inspissated secretion[25], bronchomalasia resulting from undue flexibility or absence of cartilage[26], or the most recently described pathologic entity-polyalveolar lobe[27]. In polyalveolar lobe the alveolar number is increased fivefold. The airways and arteries are normal for age in number, size and structure, suggesting that the condition represents gigantism of the alveolar region[28]. Although it is rare, the clinical features of congenital lobar emphysema may arise from bronchial atresia of the left upper lobe[29]. However, most authors now agree that in approximately one-half of cases no definite causes could be found[3, 14, 20].

In the past, congenital lobar emphysema was considered to be strictly a surgically treatable disease. This point of view was based on the belief that removal of the affected lobe would improve pulmonary function by releasing compressed normal lung parenchyma, and prevent recurrent infection and sudden distention of the affected lobe. Most trials of medical treatment have not been encouraging and have been associated with high mortality rates[3, 5, 6, 17, 26, 30]. When treated by medical therapy alone, 50 percent of patients died from progressive respiratory distress, and 75 percent of the survivors had persistent emphysema[6].

Conservative treatment for lobar emphysema has been recommended by some authors. Korngold[7] reported two surviving cases treated by needle aspiration. Later, Roghair[8] reported two cases of long-term follow-up of medically treated infants with infantile lobar emphysema. Eigen et al.[9] suggested that lung growth and function in patients with congenital lobar emphysema who were treated conservatively were not different from those of children treated surgically.

Observation of these authors shows that the medically treated patients did not have an increased incidence of pulmonary infection and did not experience sudden deterioration. In 1977 Shannon et al.[10] reported 16 patients treated medically. Two of these patients died from bronchopulmonary dysplasia; surgical resection was required in three of the 14 surviving patients, and the remaining 11 were successfully managed medically. In 1991 Kennedy et al.[11] reported 12 children with congenital lobar emphysema who were managed medically with long-term follow-up. More recently Stigers et al.[12] also reported eight infants with congenital lobar emphysema. Three patients required surgical resection for progressive worsening of respiratory distress; the remaining five patients were managed medically with eventual remission of symptoms. However, it would not be appropriate for us to enter a discussion about the conservative treatment and follow-up of such patients because we do not have patients treated this way in our clinic.

Based on the reports in the literature and our own experience, it can be concluded that patients with congenital lobar emphysema can be managed medically. The urgency of treatment and the treatment modality depends on the severity of the patient's respiratory disease. Attempts at needle aspiration must be avoided, for this almost always results in a tension pneumothorax that can be fatal. Conservative treatment may be considered in selected infants and older children with mild symptoms. In patients who have persistent or progressive, severe respiratory distress that does not respond to medical therapy, the treatment of choice is surgical removal of the affected lobe.

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TRANSTELEPHONIC ECG VERSUS ELECTROPHYSIOLOGIC STUDY IN CHILDREN WITH RECURRENT PALPITATION ATTACKS*

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SUMMARY: Çeliker A, Tokel K, Medikoğlu M, Özme Ş. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Transtelephonic ECG versus electrophysiologic study in children with recurrent palpitation attacks. Turk J Pediatr 1997; 39: 45-50.

Palpitation may be a terrifying event for children and pose diagnostic problems for pediatric cardiologists. Routine methods often fail to document episodic arrhythmia because the episodes may be brief or infrequent or both.

The purpose of this study was to evaluate and compare values of non-invasive and invasive techniques. Twenty-three children (mean age 11.7 ± 2 years, range 7-16 years) with recurrent palpitation attacks (> 2 times), who had normal physical examinations, ECG, echocardiography, 24 hour ambulatory ECG monitoring and treadmill exercise tests, were included in the study. Rediline[R] Model CG 4000 TTE recorders were given to patients for 10 or 20 days. We performed an intracardiac electrophysiologic study (EPS) on 14 patients. The mean number of palpitation attacks was 11.3 ± 7.4 (median: 5), lasting 9.6 ± 7 (median 3) minutes. The number of transmitting records was 2 ± 1.4 (1-20). Of the 23 patients, only 15 (65%) transmitted during the palpitation attacks. Twenty-four-hour ambulatory ECG monitoring findings were normal in all patients. One patient had a wide QRS tachycardia attack in the TTE records. We stimulated ventricular tachycardia in the same patient in the EPS. Among the other patients who transmitted TTE records during palpitation attacks, we diagnosed two cases of concealed accessory pathway and eight cases of dual AV nodal pathway in the EPS. In conclusion, TTE is a sensitive and accurate method for diagnosis and follow-up of patients with cardiac arrhythmia. It can be used before invasive studies in children with recurrent palpitation attacks.
Key words: transtelephonic ECG, palpitation, electrophysiologic study, children.

Palpitations are forceful pulsations of the heart that are perceptible to the patient, usually accompanied by an increase in rate and sometimes by irregularity in rhythm. The complaint of palpitations does not necessarily imply the presence of heart disease or a specific arrhythmia[1]. Children without previous evidence of heart disease are frequently referred to a pediatric cardiologist for evaluation of symptoms of palpitations. It is sometimes difficult to evaluate the cause of this symptom. Electrocardiographic documentation during symptoms may be of considerable diagnostic value in patients with suspected paroxysmal arrhythmias.

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There may be no finding on physical examination, routine 12-lead electrocardiography (ECG) records or 24-hour ambulatory ECG monitoring if symptoms are infrequent[1-3]. For these reasons, new diagnostic tools are being used for the evaluation of recurrent palpitation attacks. Transtelephonic monitoring may be helpful in certain situations, as the monitoring period may be extended indefinitely[4-6]. Invasive studies, such as trans-esophageal atrial pacing and intracardiac electrophysiologic studies (EPS), have proved valuable in the diagnosis and treatment of cardiac rhythm disturbances[2,7]. The purpose of this study was to evaluate and compare the values of non-invasive and invasive techniques.

Material and Methods

Twenty-three children with recurrent palpitation attacks (> two times) were evaluated between February 1993 and March 1994. All patients had normal physical examinations, complete blood count, routine 12-lead ECG recordings, echocardiography, treadmill exercise testing, serum T3, T4 and TSH, and 24-hour ambulatory ECG monitoring (Table I).

Table I: Epidemiologic Data of Patients

Age of patients	11.7 ± 2 years (range 7-16)
No. of palpitation attacks	11.3 ± 7.4 (median 5 attacks)
Duration of palpitation attacks	9.6 ± 7 (median 3) minutes
Ten-day TTM	13 cases
Twenty-day TTM	10 cases
No. of transmissions	2 ± 1.4 (range 1-10, median 2)

TTM: transtelephonic monitoring.

Transtelephonic ECG Monitoring

Each patient was provided with a transmitter (Redline Model CG 4000 TTM). The system consisted of a small, clip-on, portable recorder unit attached to under-arm electrodes placed at the time of symptoms. The patients or their parents were asked to transmit their electrocardiograms during typical palpitation episodes. All transmitted electrocardiograms were reviewed by a physician for evidence of arrhythmia at the time of transmission. If any abnormality was detected, the referring physician (A.Ç. or K.T.) was contacted immediately for further evaluation.

The monitoring period was 10 days if a transmission was possible during palpitation attacks. If the patient did not transmit electrocardiograms, the recorder was kept for 20 days.

Electrophysiological Study

We performed intracardiac EPS on 14 patients whose parents agreed. Diazepam (0.01 mg/kg) was administered intravenously to each patient two minutes before

cardiac catheterization. Three bipolar or quadripolar catheters were inserted percutaneously into one or both femoral veins and were positioned in two or three of the following areas: 1. the high right atrium near the sinoatrial node, 2. across the tricuspid valve orifice to record the low septal right atrial and His depolarizations, and 3. the right ventricular apex.

At the beginning of the study, sinus node functions (sinus node recovery time, and sinoatrial conduction time), atrioventricular conduction (the duration between atrial electrocardiogram and His bundle deflection: AH; the duration between His bundle deflection to the beginning of ventricular activation: HV; and the Wenckebach point) and ventriculoatrial conduction were determined. Atrial and ventricular programmed stimulation was performed at 600, 500, and 430 msec pacing lengths for eight beats with one and two extra stimuli. Then we tried to stimulate tachycardia with burst stimulation. All of these studies were repeated after an intravenous atropine bolus (0.04 mg/kg) if supraventricular tachycardia had not been induced.

Results

During a 13-month period, 23 children and adolescents suffering from recurrent palpitation attacks were evaluated. Their ages ranged from seven to 16 years (mean: 11.7 ± 2). The mean number of palpitation attacks was 11.3 ± 7.4 (range 3-22). We noted more than five attacks in nine patients (Table I). The duration of palpitation attacks was 9.6 ± 7 minutes (median 3 minutes).

Of the 23 patients who received transtelephonic monitors, 15 (65%) attempted to record and transmit during their monitoring period. Fifteen patients who transmitted records during a palpitation attack had normal 24-hour ambulatory monitoring records. One patient had a wide QRS tachycardia attack in the TTE record (Table II).

Table II: Twenty Four Hour Ambulatory Monitoring and TTE Record Findings in Patients' Transmitting Records During Palpitation Attacks

Findings	24 h Ambulatory Monitoring n = 23	TTE records n = 15
Sinus rhythm	11	10
Sinus tachycardia	4	4
Wide QRS tachycardia	–	1

The findings of the intracardiac electrophysiologic study are shown in Table III. Eight patients had dual atrioventricular nodal physiology, and we could not induce supraventricular tachycardia (SVT). Two patients with concealed atrioventricular conduction were followed without SVT attacks for 15 and 17 months. These patients were monitored very closely with frequent 24-hour ambulatory ECG monitoring. Eight patients who transmitted records during palpitation attacks were evaluated by intracardiac electrophysiologic study (Table IV). Ventricular tachycardia was induced in one patient with wide QRS tachycardia in the TTE record.

Table III: Electrophysiologic Findings in Children with Recurrent Palpitation Attacks

Findings	n	%
Dual AV nodal pathway	8	57.0
Concealed atrioventricular conduction	2	14.3
Induced ventricular tachycardia	1	7.1
Wenckebach point decreased	1	7.1
Normal EPS	3	21.3

Table IV: TTE and EPS Findings of Patients with Transmitting Records During Palpitation Attacks

Age	No. of palpitation attacks	TTE findings	EPS findings
10	8-10	Wide QRS tachycardia	Induced ventricular tachycardia
9	4	Sinus rhythm	Concealed accessory pathway
14	5-6	Sinus tachycardia	Concealed accessory pathway
14	20-25	Sinus rhythm	Dual AV nodal pathway
16	20-25	Sinus rhythm	Dual AV nodal pathway
16	5-6	Sinus rhythm	Normal EPS
12	3-4	Sinus rhythm	Normal EPS
7	20	Sinus tachycardia	Normal EPS

Discussion

Documentation of paroxysmal, brief and/or infrequent cardiac arrhythmias with palpitation attacks presents a frustrating problem to the pediatric cardiologist. The specific diagnosis and appropriate management depend on electrocardiographic confirmation[5]. Although the treadmill exercise test and 24-hour ambulatory monitoring have been used to detect arrhythmias, their sensitivities are low in patients without documented tachycardia[8,9]. In our study we did not detect any arrhythmia in patients with palpitation during 24-hour ambulatory monitoring. During the monitoring period, only three patients (13%) experienced palpitation attacks, all of which were sinus tachycardia. There is consensus that the greatest utility of ambulatory electrocardiography is in the area of arrhythmia assessment[9]. Twenty-four-hour ambulatory monitoring was also more effective in detecting nonsense and asymptomatic events among high-risk children such as postoperative patients and known cardiac arrhythmias related to congenital heart disease[10].

Outpatient transtelephonic electrocardiographic monitoring for transient event recording has been recommended for the evaluation of both adult and pediatric patients with infrequent symptoms[4-6,10]. Sixty-five percent of our patients succeeded in sending TTE transmissions during their clinical symptoms, which is comparable to previously reported rates[4-6,10]. We found that transtelephonic monitoring often provides reassurance of the absence of an arrhythmia during

symptoms. Four patients (26.6%) transmitted ECG records during symptoms, and these were sinus tachycardia. The most important data we obtained was a wide QRS tachycardia in a patient's TTE records, but his 24-hour ambulatory monitoring was normal.

In a previous report, the utility of transesophageal pacing in the evaluation of young patients with palpitations has been demonstrated[2, 11]. Pongiglione et al.[2] demonstrated that transesophageal atrial pacing frequently (71%) induced a short bout of tachycardia, which may be the cause of symptoms in young patients with a history of palpitations and other evidence of heart disease. They did not induce any sustained tachycardia lasting more than one minute. We did not find any article about intracardiac EPS in children with recurrent palpitations and no documented arrhythmia. We induced ventricular tachycardia in only one patient who had wide QRS tachycardia in the TTE during a palpitation attack. Compared to previous studies, our supraventricular tachycardia induction results seem low. This may be partially explained by the lack of isoproterenol infusion during atrial pacing. We found dual atrioventricular nodal physiology in eight patients, which is a common finding in the normal population[11]. Two patients with concealed atrioventricular conduction excluding the atrioventricular node did not experience any supraventricular tachycardia attacks during follow-up. However, there was no arrhythmia in these patients' TTE records. We did not induce tachycardia in the other seven patients with transmitting records during palpitation attacks, nor in the six patients without records during palpitation attacks.

In conclusion, 24-hour ambulatory monitoring is insufficient in children with recurrent palpitation attacks, while TTE monitoring is a sensitive and accurate method for diagnosis of arrhythmia. Transtelephonic monitoring may be valuable in demonstrating the absence of an arrhythmic basis for a patient's palpitation as well as in documenting the arrhythmia responsible for those palpitation attacks. Transtelephonic ECG can be used before invasive studies in children with recurrent palpitation attacks. If the palpitation attacks originate from sinus tachycardia and if here is no arrhythmia, invasive evaluation of the patient is unnecessary.

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EAR, NOSE AND THROAT FINDINGS IN CYSTIC FIBROSIS PATIENTS*

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SUMMARY: Özçelik T, Özgirgin N, Özçelik U, Göçmen A, Gürcan B, Kiper N. (Department of Otolaryngology, Bayındır Medical Center, and the Chest Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Ear, nose and throat findings in cystic fibrosis patients. Turk J Pediatr 1997; 39: 51-54.

An ear-nose-throat survey was carried out on 30 children with cystic fibrosis (CF) between two and 17 years of age. There were three (10%) confirmed cases of secretory otitis media. One child had previous surgery for polyps. Ten children had chronic pansinusitis mildly responsive to medical therapy. Hypertrophy of the nasal conchae was detected in eight cases. The data showed that the risk of ear-nose-and-throat disease was increased in CF patients, but audiologic problems are not very common in CF patients. CF should be kept in mind in children who have nasal polyps, hypertrophied turbinates or sinusitis unresponsive to medical therapy. *Key words: cystic fibrosis, paranasal sinuses, nasal polyposis, ear problems.*

Cystic fibrosis (CF) is characterized by a defect in cyclic adenosine monophosphate (cAMP)-regulated chloride conductance, and is caused by mutations in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR)[1]. The exocrine dysfunction of the acinotubular glands is manifested by abnormalities in the composition and physiochemical behavior of the secretions. The mucus produced is 30 to 60 times more viscid than normal.

Clinical symptoms commonly affect the gastrointestinal, upper and lower respiratory systems. The otolaryngological aspects of CF are dominated by involvement of the paranasal sinuses. This involvement is manifested as delayed development of the frontal sinus and opacification of the maxillary, sphenoid and ethmoid sinuses, as well as nasal polyposis. Middle ear problems can also be seen[2].

In this study we assessed the incidence of upper respiratory disease, in particular middle ear problems, in a group of CF children. In addition to clinical assessment, impedancemetry was used to estimate the incidence of secretory otitis media.

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Material and Methods

The study included 30 patients between ages two and 17. Patients diagnosed with CF had at least two sweat chloride values greater than 60 mEq/L and clinical and other radiological findings[3]. The patients were selected upon referral to the ear, nose and throat (ENT) department. The prerequisite for the patient to be included in the study was that he was free of acute illness and able to cooperate in an impedancemetric evaluation.

Each patient's parents completed a questionnaire on ENT symptoms, family history, recent respiratory symptoms and treatment. A full ENT examination, including bilateral otoscopy using operating microscope and pneumatic otoscope, rhinoscopy and endoscopic evaluation of the nasopharynx in cooperative patients, was carried out. Secretory otitis media was diagnosed clinically when fluid was suspected behind a dull or yellowish drum; drum retraction or reduced mobility on pneumatic otoscopy has also accepted as suggestive. The diagnosis of sinusitis was confirmed by x-ray.

Results

Three cases (10%) were clinically suspected of having secretory otitis media. Negative middle ear pressure and the absence of acoustic reflexes suggested the presence of effusion. Two cases resolved at the end of medical treatment. Ventilation tube insertion was planned for the third case.

One case (3%) had previous surgery for bilateral nasal polyps. Eight other cases (26%) were considered to have an abnormal nose with either purulent nasal discharge, congested mucosa or polypoid nasal conchae.

Ten (33%) cases had sinusitis symptoms such as facial pain, sinus headache or nasal obstruction sinusitis was confirmed by the detection of opacification of the paranasal sinuses on radiographs (Fig. 1).

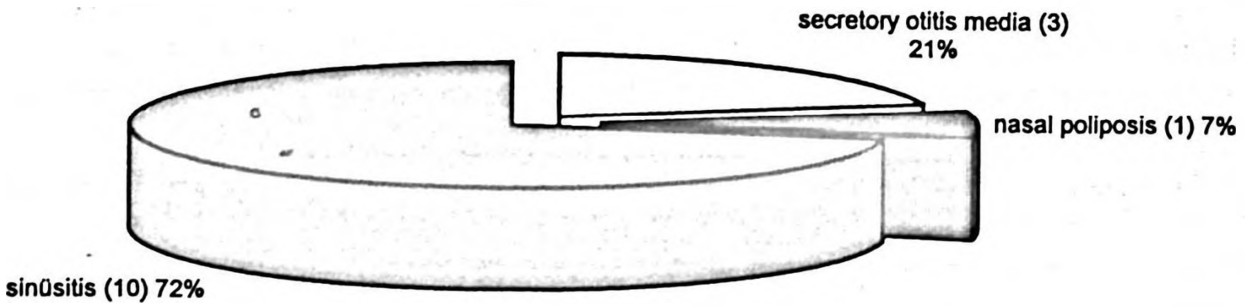

Fig. 1: Main ear nose and throat pathologies in CF patients.

Discussion

The literature is conflicting on whether there is an increased incidence of conductive deafness in CF, while an increased incidence of eustachian tube dysfunction and serious otitis media have been suggested[4]. The mucosal epithelium of the middle ear and the eustachian tube are in direct continuity with the upper respiratory tract. Thus it might be assumed that children with CF would have a higher than usual incidence of middle ear disease. Kulczycki et al.[5] reported a 26 percent incidence of conductive hearing loss in 70 children with CF. Jerger and Neely[6] observed a six percent incidence and Taylor et al.[7] found none. Kramer[2] indicated that the incidence of otologic disease in CF patients did not appear to be statistically greater than in the general population. Local experience does not suggest a significant increase in hearing problems in CF, although it could be argued that since we do not routinely perform audiograms, cases with hearing impairment could be missed. In our series, we found a 10 percent incidence of conductive hearing loss. The low incidence of serous otitis media in our own series may be attributable to the use of antibiotics for the slightest respiratory infection.

Nasal polyposis in cystic fibrosis children has been studied by several authors. six to 10 percent of cystic fibrosis patients have been found to have nasal polyps, most of which were bilateral[7]. Nasal polyposis was the first sign in one case (3.3%), and CF was diagnosed afterwards. Also, a hypertrophied, purplish turbinate accompanied by purulent rhinitis are features of CF that we found in eight (26%) children. The appearance is claimed to differ from that of the engorged turbinates of allergic rhinitis. Rulon et al.[8] reported that approximately 28 percent of the patients they studied had nasal polyps. However, to date there is no information as to why children with cystic fibrosis develop nasal polyps. It must be noted that nasal polyps in children without cystic fibrosis are rare, so in the presence of nasal polyps cystic fibrosis should always be considered in the differential diagnosis. Recurrence after surgery is the rule rather than the exception; spontaneous resolution may occur, many cases are asymptomatic, and the symptoms are tolerated with minimal discomfort in others. Nasal corticosteroids may be used in the treatment of nasal polyps and in order to prevent recurrences after the removal of the polyps[9].

Opacity of the paranasal sinuses on radiographs is an almost universal finding in cystic fibrosis; however, only rarely do symptoms arise from the sinuses. The symptoms described are sinus headache, facial pain and swelling. The possible causes of sinus involvement are excessive or unusually viscid mucus, infection and allergy[10]. Surgery is frequently unsuccessful and is best avoided[11]. In ten of our cases (33%), infection was detected clinically and radiologically in one or more sinuses and was mildly responsive to medical therapy.

In conclusion, the present data suggest that despite frequent involvement of the upper airways, audiological problems are not as common in CF patients as one would expect.

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A RETROSPECTIVE STUDY ON 16 COLLODION BABIES*

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SUMMARY: Öztürk A, Çaksen H, Çetin N, Kurtoğlu S. (Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey). A retrospective study on 16 collodion babies. Turk J Pediatr 1997; 39: 55-59.

Sixteen collodion babies followed in the Neonatal Care Unit between January 1982 and December 1994 were evaluated retrospectively. The preterm/term ratio was 1.6, and complete shedding of the collodion membrane took an average of 21.9 days (range 18-46 days). Problems noted were marked temperature instability, defective barrier function, increased insensible water loss predisposing to hypernatremic dehydration, cutaneous infections and septicemia. Hypernatremia was observed in 11 (68.7%) and septic infection in seven patients (43.7%). All the infants were treated topically with vaseline containing five percent lactic acid. In the hypernatremic infants, intravenous fluid was administered for rehydration. In the septic infants, antibiotics were used according to the antibiogram. Four of the infants died due to septicemia. The mortality rate was 25 percent, and the major complications included hypernatremia, cutaneous infection and sepsis. *Key words: collodion babies.*

Collodion baby is a rare congenital disorder that resembles harlequin fetus but is milder in degree[1]. The infant is born tightly encased in a shiny membrane resembling parchment or oiled silk, which is perforated by scalp and lanugo hair[1-3]. Collotion babies are often born prematurely[2, 4]. Because of the presence of ectropion, eclabium and flattening of the ears and nose as well as fixation of the lips in an O-shaped configuration, these infants resemble one another in the first few days of life[1-3]. Motion of the limbs is restricted[1]. Soon after birth the collodion membrane peels off, leaving reddish skin which can very easily become infected and may result in pyoderma, causing fatal sepsis and pulmonary infections within the first days or weeks of life. Complete shedding of the collodion membrane may take several weeks[2, 3].

Occasionally, an affected infant is observed to have normal skin subsequent to shedding of the membrane[1, 2]. The collodion baby probably represents a phenotype for several genotypes[1-3]. Complications include marked temperature instability, skin irritation, water loss via the epidermis predisposing to hypernatremic dehydration, pyodermia, septicemia and pneumonia secondary to aspiration of squamous material in the amniotic fluid[1-4, 6]. Cutaneous infections from gram-positive organisms, candida albicans and milk aspiration are common problems[1].

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Supportive care is of primary importance for management of the collodion baby. The encasing membrane should not be manually removed. In the treatment of collodion babies, application of topical antikeratinogenic agents have been used, and measures have been taken to prevent other complications[4-6].

Material and Methods

A total of 16 collodion babies were retrospectively evaluated. All patients were treated in the Neonatal Care Unit at Erciyes University Faculty of Medicine between January 1982 and December 1994. Physical examination, whole blood count and blood chemistry (except in the 1st and 3rd patients) were performed for clinical evaliation. Blood, urine and/or cerebrospinal fluid cultures were taken from patients who had a septic appearance. All patients were diagnosed according to clinical findings. Histopathological examination of the skin was not performed in all patients. Four of the 12 patients who lived were reexaminated when they were two, five, eight and ten years old.

All the infants were treated topically with vaseline containing five percent lactic acid. In the hypernatremic infants, intravenous fluid was administered for rehydration. In the septic infants, antibiotics were used according to the antibiogram, The hyperbilirubinemic infants received phototherapy. An exchange transfusion was given to one infant in addition to phototherapy. In one hypoglycemic infant who had sepsis, concentrated glucose fluid was administered.

Results

The mean age of patients at the time of diagnosis was 17 hours (range 1-62 hours). Ten of the 16 patients were preterm, with a preterm/term ratio of 1.6. The mean age of the preterm infants was 36.1 weeks (range 35-37 weeks). The male/female ratio was 2.2 (Table I). In all but one case the parents were first-degree relatives. Five patients had a family member with the clinical appearance of a collodion baby. Patients were followed for one to 41 days (average 14.7 days). Hyperbilirubinemia complicated the course in eight patients and was managed with phototherapy. One patient needed an exchange transfusion.

Hypernatremia was a frequent complication, observed in eleven patients (68.7%), and improved within the first month of life. Complete shedding of the collodion membrane took an average of 21.9 days (range: 18-46 days, Table I).

Infection occurred in seven patients (43.7%) four of whom were preterm. These infections included sepsis, cutaneous infection and urinary tract infection. Sepsis occurred in five patients, while cutaneous infection due to Staphylococcus albus accompanied sepsis in two cases. In two cases, cutaneous infection and urinary tract infection were the only presenting symptoms. A case who had hypoglycemia,

consumption coagulopathy and cutaneous infection was considered to be septic in spite of the fact that no microorganism was isolated in the blood culture. Microorganisms isolated from blood cultures were proteus and enterococcus in two patients and candida albicans in two other patients with sepsis. Four patients died, yielding a mortality rate of 25 percent.

Table I: Cases of Collodion Baby

Case no/Age (hours)/Sex	Gestational age (Weeks)	Initial serum Na^+ values (mEg/L)	Complete shedding of collodion membrane (days)	Outcome
1/05/B	40	–	–	Exitus
2/19/B	36	132	18	Unknown
3/24/B	40	–	–	Exitus
4/36/B	36	143	25	Unknown
5/05/B	35	168	23	Unknown
6/48/B	37	161	26	CNBIE
7/48/G	38	158	21	CNBIE
8/12/G	36	138	19	Unknown
9/04/G	36	157	21	Unknown
10/24/B	40	159	25	Unknown
11/07/B	36	144	–	Exitus
12/48/G	36	141	37	CNBIE
13/03/B	38	144	–	Exitus
14/03/G	36	160	28	CNBIE
15/62/B	37	148	46	Unknown
16/17/B	40	138	31	Unknown

B: Boy, G: Girl, CNBIE: Congenital non-bullous ichthyosiform erythroderma.

Four of the 12 patients who survived were reexaminated later in their lives. Normal physical and neurological development, but mild ichthyotic scaling was observed in all patients. There was no information about the outcome in the other eight patients.

Discussion

Collodion babies are seen rarely. This condition often eventuates in lamellar ichthyosis or congenital ichthyosiform erythroderma but may evolve into other disorders, such as Netherton's and Conradi's syndrome, ichthyosis vulgaris, recessive X-linked ichthyosis and Sjögren-Larsson syndrome[2,4,7]. Van Scott[8] suggested a classification for ichthyosis with four groups based on anatomical, cellular, kinetic and genetic observations, which seem to provide the best framework for approaching these disorders.

The presence of positive family histories, the absence of congenital abnormalites, and normal motor and mental development led us to conclude that the collodion

appearances in the four patients who were reexaminated later in their lives were manifestations of the autosomal-recessive form of lamellar ichthyosis (congenital non-bullous ichthyosiform erythroderma).

Light microscopically the neonatal collodion skin is characterized by a thick compact stratum corneum which was PAS positive in its upper two thirds, a thin stratum granulosum, and a non-acanthotic stratum spinosum with normal mitotic activity[9].

Two siblings with Netherton's syndrome complicated by neonatal hypernatremia have recently been reported[6]. It is known that hypernatremia may occur when there is a considerable increase in the area of thin erythematous skin or increased skin loss (burn, phototherapy, preterm or generalized dermatoses)[6].

In the presented cases, histopathological examination of the skin was not performed. In eleven of our patients, serum sodium (Na^+) levels were greater than 140 mEq/L in the absence of symptoms such as vomiting, tachypnea, polyuria, fever and ambient temperature, suggesting transepidermal water loss. Moreover, the hypernatremia was improved within the first month of the life in all patients. In one study, transepidermal water loss values four days after birth were shown to be abnormally high compared with those of normal infants of the same age. The transepidermal water loss measurements returned to normal within the first month, parallel to the improvement of both the skin signs and the electrolyte and fluid balance[10].

Loricrin and involucrin are major precursor proteins to the cornified cell envelope expressed late in epidermal differentiation[11]. Involucrin represents 25 percent of the living epidermis in normal humans and 38 percent in collordion babies.

Kanitakis et al.[12] demonstrated altered involucrin expression in a variety of keratinization disorders including collodion babies, and suggested that in such conditions, cellular functions other than keratin metabolism are also affected.

Larreque et al.[13] showed in 267 collodion babies that the mortality rate was 33 percent in 1976 and 11 percent in 1984. Skin infection with systemic spread was the major complication. Larreque et al[14] in another study showed that the collodion membrane in 198 collodion babies spontaneously desquamated between the 15th day and the third month of life, and during the neonatal period one-third of the infants died due to pulmonary complications or infection.

Topical preparations containing alphahydroxy acids and closely related compounds have been found to exert profound antikeratinogenic effects on ichthyosis or other forms of epidermal keratinization[8, 15]. A topical preparation containing five percent lactic acid, an alphahydroxy acid, has been firstly exerted in the treatment of collodion babies in Turkey and by Erdem[5, 16]. He reported that shedding of the collodion membrane took an average of 16 days (range

11-22 days) on five collodion babies. In addition, he observed decreased mortality with this compound. In our study, this duration was longer in spite of using the same therapy. Its cause may be related to supportive care, the occurrence of cutaneous infections and prematurity.

In this study, the mortality rate was 25 percent and the major complications were hypernatremia, cutaneous infection and sepsis. Four of the seven patients with infections were preterm. Aside from the primary disorder, prematurity can also a predisposing factor for infection and mortality.

Supportive care is of primary importance in the management of the collodion baby. These patients are best managed in a humidified incubator, with special attention given to the prevention of temperature instability, cutaneous infection, sepsis, and fluid and electrolyte imbalance. The skin should be covered with vaseline and gauze to prevent irritation and water loss.

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ADENOSINE – SENSITIVE RIGHT VENTRICULAR TACHYCARDIA IN CHILDREN*

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SUMMARY: Çeliker A, Alehan D, Koçak G, Özme Ş, Özer S. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Adenosine-sensitive right ventricular tachycardia in children. Turk J Pediatr 1997; 39: 61-67.

Right ventricular outflow tachycardia is a distinct subgroup of idiopathic ventricular tachycardia (VT) with characteristic clinical and electrophysiologic properties. This study was planned to evaluate the effects of adenosine on idiopathic right ventricular tachycardia in children, and to assess the long-term efficacy of verapamil treatment. Diagnostic tests including electrocardiogram, chest roentgenogram, echocardiogram, exercise stress test and 24-hour ambulatory electrocardiographic monitoring were performed in each patient. Adenosine was administered in increasing amounts until an effective dose or a maximal dose of 300 μg/kg was reached. In adenosine-sensitive patients verapamil was given orally (3-10 mg/kg/day) for long-term suppression of arrhythmia.

Seven patients with a mean age of 10.2 ± 4.7 years were enrolled in the study. There were five male and two female patients. Six patients had VT, and one patient had frequent ventricular ectopic beats. Arrhythmia originated from the right ventricle in all patients. Adenosine was effective in terminating the arrhythmia in all patients, with a mean effective dose of 183 ± 75 μg/kg. Favorable long-term results (mean follow-up period 17 ± 8 months) were obtained with verapamil treatment at an average dose of 6.3 ± 2.2 mg/kg.

In conclusion, adenosine can be used effectively for termination of VT originating from the right ventricular outflow tract in children. In these patients verapamil may be considered as the drug of choice for long-term therapy. *Key words: adenosine, right ventricular tachycardia, children.*

Ventricular tachycardia (VT) in the absence of apparent structural heart disease is an uncommon but well-recognized entity[1]. Various descriptive terminologies, including benign, repetitive, functional, and idiopathic, have been used for this form of VT. The mechanisms underlying VT in patients with no demostrable cardiac abnormality are still not clear, and may involve triggered activity, reentry, or catecholamine-sensitive automaticity[2]. One form of idiopathic VT is characterized by a right bundle branch block morphology, suppressed by verapamil, and is considered to be caused most commonly by reentry. The second type of idiopathic VT typically originates from the right ventricle, has a left bundle branch

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block morphology, requires adrenergic stimulation for initiation and can be terminated by adenosine and verapamil administration. Suppression or termination of the arrhythmia with adenosine suggests a cyclic adenosine monophosphate (c-AMP)-mediated, triggered activity as the arrhythmia mechanism[3].

Several studies have demonstrated the effects of adenosine on idiopathic VT in adult patients, however there is little information concerning pediatric patients. The purpose of this study was to evaluate the effects of adenosine on idiopathic right ventricular tachycardia in children and to examine the long-term results of verapamil treatment in these patients.

Material and Methods

The study population comprised seven consecutive patients with recurrent episodes of idiopathic, monomorphic, right ventricular tachycardia or frequent ventricular ectopic beats originating from the right ventricle, admitted to Hacettepe University Pediatric Cardiology Unit between March 1993 and April 1995.

After a thorough physical examination, several diagnostic tests including 12-lead surface electrocardiogram (ECG); chest roentgenogram; M-mode, two-dimensional and Doppler echocardiogram; exercise stress test with modified Bruce Protocol; and 24-hour ambulatory electrocardiographic monitoring were performed in each patient.

During VT, adenosine was administered as a rapid bolus through a peripheral vein, followed by a rapid flush of normal saline solution. The initial dose was 100 µg/kg, with each subsequent dose increased by 50 µg/kg until the desired effect was obtained or a maximal dose of 300 µg/kg was reached. Surface ECG monitoring was used for continuous recording of three leads during adenosine administration. If VT was terminated by adenosine administration, verapamil was given orally to asses its efficacy in the suppression of ventricular arrhythmia.

Results

There were five male and two female patients with a mean age of 10.2 ± 4.7 years. Four patients had sustained incessant VT, two patients (Cases 1 and 7) had short runs of VT, and one patient (Case 6) had frequent ventricular ectopic beats (Table I). Ventricular arrhythmia originated in the right ventricle (a left bundle branch block configuration and an inferior axis) in all patients (Fig. 1). Physical examination, chest roentgenogram and echocardiogram were normal in each patient, and no one had evidence of structural heart disease. VT was associated with chest pain in five patients, four of whom had palpitations as well. Two patients were asymptomatic and none of the patients experienced syncope. Previous antiarrhythmic therapy had been given to three patients for several months without success. Two patients had received propranolol or propafenone, and one patient had been treated with propafenone and mexiletine.

Table I: Clinical and Laboratory Findings of Patients

Patient	Age/Sex (year)	Symptom	QRS morphology	Exercise	Effective adenosine dose	Effective verapamil dose	Prior drug therapy	Holter
1	6/M	chest pain, palpitation	LBBB, inferior axis	VEB (+)	300 µg/kg	10 mg/kg	Propranolol	VT (nonsustained)
2	7/M	chest pain, palpitation	LBBB, inferior axis	VEB (+)	200 µg/kg	8 mg/kg	–	VT (sustained)
3	4/M	chest pain, palpitation	LBBB, inferior axis	VEB (+)	200 µg/kg	5 mg/kg	–	VT (sustained)
4	12/F	–	LBBB, inferior axis	VEB (+)	100 µg/kg	6 mg/kg	Mexiletine Propafenone	VT (sustained)
5	16/F	–	LBBB, inferior axis	VEB (+)	100 µg/kg	3 mg/kg	Propafenone	VT (sustained)
6	16/M	chest pain, palpitation	LBBB, inferior axis	VEB (-)	200 µg/kg	5 mg/kg		Frequent VEB's (couplets)
7	11/M	chest pain	LBBB, inferior axis	VEB (-)	100 µg/kg	8 mg/kg		VT (nonsustained)

F : Female.
M : Male.
LBBB : Left bundle branch block.
VEB : Ventricular ectopic beat.
VT : ventricular tachycardia.

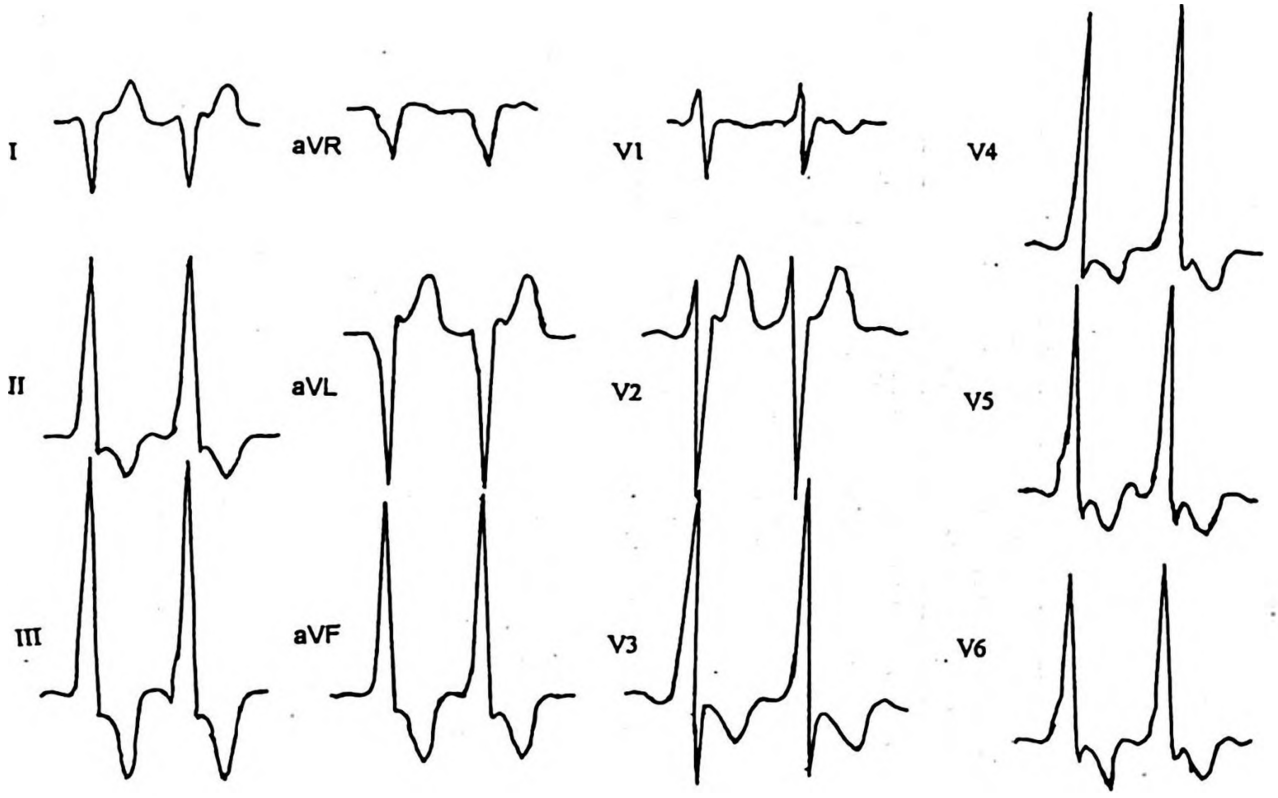

Fig. 1: Surface electrocardiogram recorded during ventricular tachycardia. The typical left bundle branch block-inferior axis morphology suggests that ventricular tachycardia originates from the right ventricular outflow tract.

Five patients had exertion-related VT, and tachycardia could be induced with an exercise stress test. However, in two patients (Cases 6 and 7) episodes of tachycardia were unrelated to exercise, and could not be initiated with an exercise stress test. Twenty-four-hour ambulatory electrocardiographic monitoring demonstrated repetitive monomorphic VT in six patients, and spontaneous ventricular premature complexes with a similar QRS configuration in all patients, usually increasing during periods of exercise.

Drug Therapy: Adenosine was effective in terminating the arrhythmia in all seven patients (Fig. 2). The mean effective dose was 183 ± 75 μg/kg (range 100-300 μg/kg), and the average time to terminate VT after a rapid bolus through a peripheral vein was 20 seconds. Afterwards, oral verapamil was given to all patients. Verapamil was effective in the suppression of arrhythmia in each patient with an average dose of 6.3 ± 2.2 mg/kg (range 3-10 mg/kg), proved with 24-hour ambulatory ECG monitoring.

Follow-up: During a mean follow-up period of 17 ± 8 months (range 5-31 months), no patient had sustained palpitations or chest pain. Verapamil-related side effects were not observed in any patient. Repeated control electrocardiograms and ambulatory monitoring revealed significant improvement of arrhythmia, with occasional premature ventricular complexes.

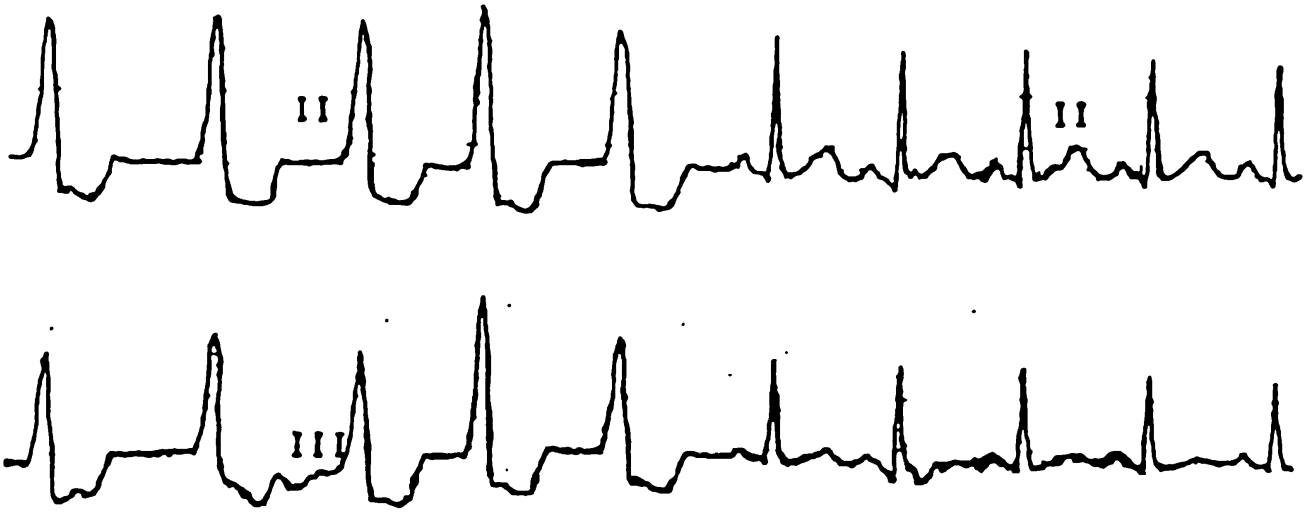

Fig. 2: Termination of ventricular tachycardia with adenosine administration. After a bolus injection of adenosine, ventricular tachycardia terminates and sinus rhythm is restored.

Discussion

Ventricular tachycardia in children, although uncommon, has received increasing attention in recent years. In the absence of structural heart disease, VT could be either right ventricular or left ventricular in origin. Right ventricular outflow tract tachycardia is a distinct subgroup of idiopathic VT, with characteristic clinical and electrophysiologic properties. Recently Lerman et al.[3] demonstrated that this form of VT is nonreentrant, nonautomatic, catecholamine-mediated, and sensitive to exogenous adenosine.

Based on the cellular mechanism of adenosine and other related electrophysiologic findings, it has been suggested that the mechanism of VT is triggered activity dependent on delayed afterdepolarizations (DADs). DADs arise during phase 4 of the action potential and are dependent on intracellular calcium (Ca^{++}) overload. Elevated Ca^{++} activates the oscillatory release of Ca^{++} from the sarcoplasmic reticulum that alters cell membrane permeability, allowing for a transient inward current responsible for afterdepolarization and triggered activity[4]. Adenosine, which inhibits the formation of c-AMP through inhibition of adenylate cyclase, prevents intracellular calcium overload, afterdepolarizations and triggered activity, and thereby terminates VT. Although controversies exist, this effect was suggested to be specific to VT but caused by c-AMP-mediated, triggered activity[5, 6].

In adult patients the efficacy of adenosine in terminating idiopathic VT originating from the right ventricle has been well defined, however there is limited information concerning pediatric patients[7, 8]. Our series is the largest to date on the use of adenosine in children with idiopathic right ventricular tachycardia. In our cases, VT attacks were suppressed in all patients by intravenous adenosine administration, suggesting that c-AMP-mediated, triggered activity is the probable cause of idiopathic right ventricular tachycardia.

Some studies on this subject have indicated that various antiarrhythmic agents, including beta blockers and verapamil, could be effective in adenosine-sensitive VT. The latter, by blocking the slow-inward calcium current, prevents intracellular calcium overload and hence can terminate triggered activity without producing direct effect on intracellular c-AMP[2, 9]. In our patients verapamil was found to be extremely effective in long-term suppression of VT and related symptoms without any significant side effects.

Cardiac catheterization, angiography and electrophysiologic studies were not performed in our patients, which may be regarded as limitations of the study. Nonetheless, examination of the electrophysiologic effects of adenosine on right ventricular tachycardia, which have been well documented in various studies, was not the aim of the study. Furthermore, the favorable clinical results obtained with drug therapy prevented us from considering invasive electrophysiologic studies in these patients.

In some cases long-term success in preventing recurrences of VT attacks may be achieved by catheter ablation[10, 11]. Because of the relative risks associated with this technique, this method of treatment was not suggested as the first-line therapy[12]. However, for those symptomatic patients whose arrhythmias cannot be controlled with antiarrhythmic drugs, catheter ablation is a reasonable alternative choice.

In conclusion, because of the antiadrenergic effects of adenosine on the ventricular myocardium and Purkinje fibers, termination of VT with adenosine may prove to be a sensitive and specific method for identifying VT caused by c-AMP-mediated, triggered activity in childhood and adolescence. In these patients verapamil is safe, highly effective and may be considered as the drug of choice for long-term therapy.

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GASTRIC EMPTYING TIME IN CHILDREN WITH PROGRESSIVE MUSCULAR DYSTROPHY*

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SUMMARY: Okan M, Alper E, Çil E, Eralp Ö, Ağır H. (Departments of Pediatrics and Nuclear Medicine, Uludağ University Faculty of Medicine, Bursa, Turkey). Gastric emptying time in children with progressive muscular dystrophy. Turk J Pediatr 1997; 39: 69-74.

Gastric emptying was evaluated in 11 male children (mean age 8.2 ± 3.2 years) with progressive muscular dystrophy to detect gastrointestinal smooth muscle involvement. No patient had gastrointestinal symptoms. Gastric emptying studies were performed by using 500 μCi of technetium 99m sulfur colloid bound to a scrambled egg, and scintigraphic measurements were taken continuously for 60 to 90 minutes. The gastric emptying studies were compared with those of eight male children (mean age 8.2 ± 2.8 years) without gastrointestinal or muscular disorders. The mean percentage of retention of gastric isotope was significantly greater in the study group than in the control group. These data suggest that dysfunction of the smooth muscle of the upper gastrointestinal tract is detectable in children with progressive muscular dystrophy, even when gastrointestinal symptoms are absent. *Key words: progressive muscular dystrophy, smooth muscle, gastric emptying.*

The X-linked recessive or progressive type of muscular dystrophy is one of the most common forms of the muscular dystrophies. The disorder is caharacterized by: a) onset in early childhood; b) symmetrical involvement of the pelvic girdle musculature first and of the shoulder girdles later; c) enlargement of the calves (pseudohypertrophy); and d) rapid progression that usually leads to the inability to walk before age 12 or 16, and to death in the second or third decade of life. Patients with Duchenne muscular dystrophy have a dystrophin deficiency, whereas patients with Becker muscular dystrophy have abnormal dystrophin[1]. Immunologic evidence of dystrophin has also been reported in smooth muscle, heart and brain[2,3]. Several autopsy reports in muscular dystrophy patients comment on the presence of typical dystrophic changes in visceral muscle[4-7]. Visceral smooth muscle involvement of the gastrointestinal tract may be prominent in the muscular dystrophies and may give rise to clinical manifestations or may be asymptomatic for some time[7]. We believe that smooth as well as skeletal muscle is affected in progressive muscular dystrophy. Therefore, the purpose of this study was to demonstrate whether the smooth muscle of the stomach is functionally impaired in progressive muscular dystrophy with radionuclide gastric-emptying studies.

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Material and Methods

The study population consisted of 11 male children with progressive muscular dystrophy. No patient had joint contractures or clinical evidence of muscle wasting from birth. The mean age of the patients was 8.2 ± 3.2 years (range 5-13 years). The control group consisted of eight boys without gastrointestinal or muscle disorders. The mean age was 8.2 ± 2.8 years (range 6-12 years). The clinical characteristics of the study group are described in Table I.

Table I: Clinical Characteristics of Patients with Progressive Muscular Dystrophy

Patient no.	Age (months)	Clinical stage	Serum CK (N 27-221 U/L)	Muscle ultrasound	Muscle biopsy	Electromyography
1	56	Mild	13.800	PMD	PMD	Myopathic
2	108	Severe	5.860	PMD	PMD	Myopathic
3	146	Severe	6.024	–	PMD	Myopathic
4	156	Severe	5.218	–	PMD	Myopathic
5	63	Mild	16.500	PMD	PMD	Myopathic
6	66	Moderate	18.000	–	PMD	Myopathic
7	60	Moderate	6.480	PMD	PMD	Myopathic
8	72	Mild	8.600	PMD	PMD	Myopathic
9	87	Moderate	40.000	PMD	PMD	Myopathic
10	132	Severe	9.140	–	PMD	Myopathic
11	13	Severe	4.410	PMD	PMD	Myopathic

CK : Creatine kinase.
PMD : Progressive muscular dystrophy.
Mild : walks and clims stairs without assistance.
Moderate : walks unassisted but cannot rise from chair or climb stairs.
Severe : walks in long leg braces but requires assistance for balance.

The diagnoses in this study were established on the basis of the clinical examination, family history and laboratory investigations. All children were examined by a pediatric cardiologist, and telecardiographic and electrocardiographic studies were done. In all 11 patients, needle electromyography was performed according to the standard procedure. Muscle biopsies were performed under local or general anesthesia. For the histologic studies, the biopsy specimens were stained with hematoxylin-eosin.

None of the patients in the study group had gastrointestinal symptoms. The control subjects were ultimately found to have no gastrointestinal motility or muscle disorders. In all cases, informed written consent for participation in this study was obtained from the parents.

Gastric emptying studies were performed with a modification of methods reported elsewhere[6, 8]. A test meal consisting of an omelet sandwich (one egg, two slices of bread) labeled with 500 μCi of technetium 99m (^{99m}Tc) sulfur colloid with 100 ml of water was ingested after a fast of at least four hours. Continuous scintigraphic measurements were then taken for 60 to 90 minutes with a gamma camera (General

Electric Starcom 3200) positioned over the supine subject's abdomen. Time zero was defined as the time of meal completion.

After correction for decay of ^{99m}Tc and patient movement, gastric emptying was quantitatively expressed as a percentage $CT_t/CT_0 \times 100$ where C_t was the count rate of ^{99m}Tc at any time in the stomach and CT_0 was the initial count rate of ^{99m}Tc in the stomach).

Statistical methods: Data were reported as mean ± SD. Mean values across patient groups were compared using the Mann-Whitney H test. A p value of less than 0.05 was required for statistical significance.

Results

The clinical characteristics in patients with progressive muscular dystrophy are reported in Table I. No serious problems were uncovered by cardiologic examination. The clinical stage of disease was defined according to Rose and Walton[9].

The percentage of retention of solids at 60 minutes was significantly greater ($p < 0.05$) in patients with progressive muscular dystrophy (81 ± 7%; range 70-91%) than in control subjects (58 ± 7%; range 47 69%). The minimal degree of gastric retention at 60 minutes was 70 percent in the study group. However, the maximal degree of gastric retention at 60 minutes was 69 percent in the control group. No patient in the study group had gastric retention results at 60 minutes in the control range. The percentage of solids at 90 minutes in patients with progressive muscular dystrophy and control subjects was also significantly different ($p < 0.05$). The gastric retention rate of the study group was 61 ± 11 percent (range 46-76%), and in the control group was 36 ± 10 percent (range 20-46%, Table II, Fig. 1).

Table II: Gastric Retention Rate in the Study and Control Groups

	Study group		Control group	
Patient no.	60 min %	90 min %	60 min %	90 min %
1	80	57	47	20
2	73	57	59	42
3	82	52	69	43
4	70	53	57	41
5	91	77	56	23
6	88	75	49	21
7	75	55	62	46
8	89	76	61	38
9	79	64	–	–
10	81	46	–	–
11	81	57	–	–
Mean:	80.8 ± 6.6*	61.2 ± 11.2*	57.5 ± 7.0*	36.2 ± 10.0*

* $p < 0.05$.

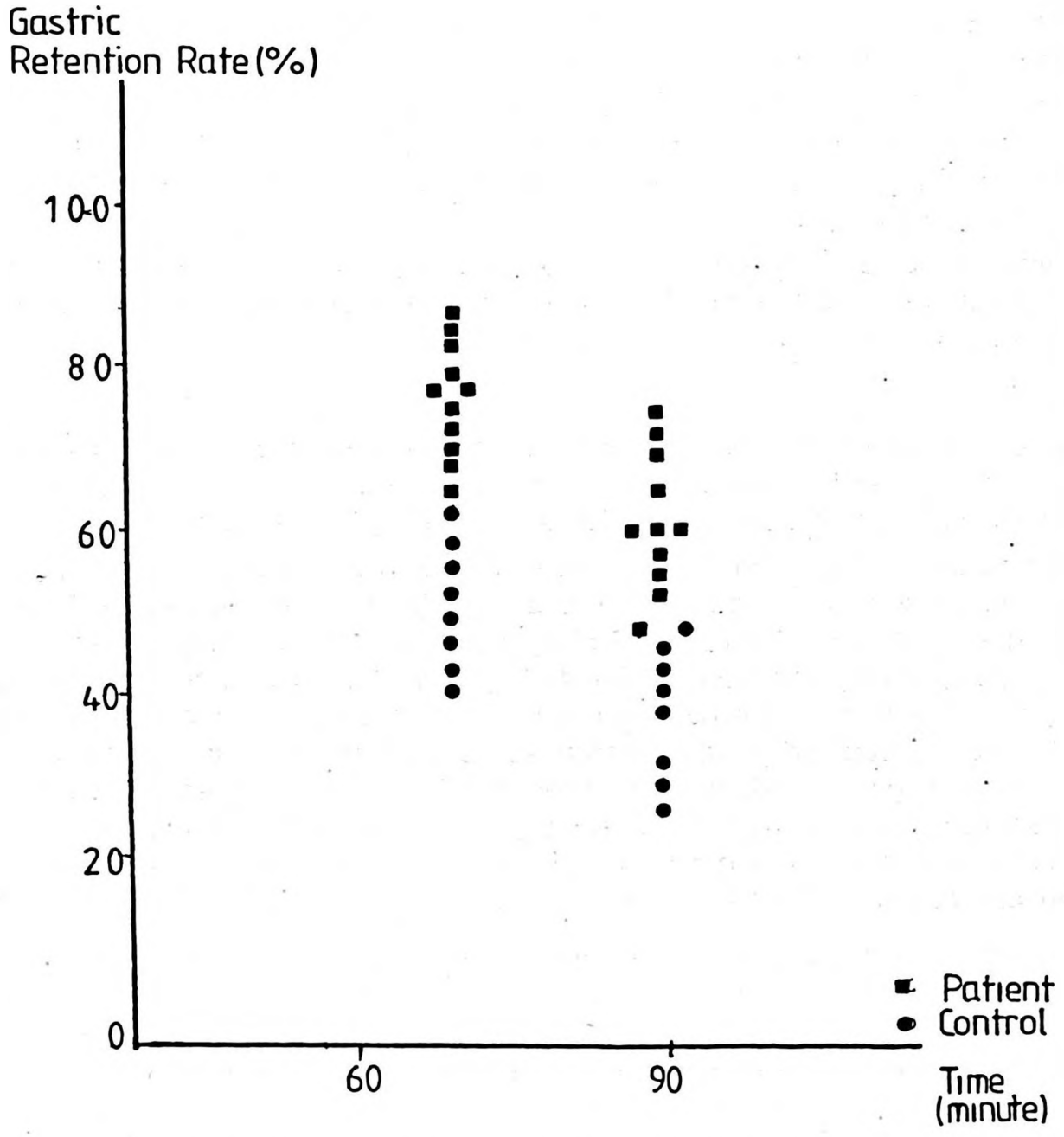

Fig. 1: Gastric Retention in the Study and Control Groups.

Discussion

In the published studies on progressive muscular dystrophy, the pathological and clinical involvement of smooth muscle in the gastrointestinal tract has received little attention[8]. The earliest report of smooth-muscle loss and of its replacement by adipose and connective tissue in the stomach is attributed to Bunting[10]. Later, autopsy descriptions of Duchenne's dystrophy by Bevans[4], Huvos and Pruzunski[5] noted fatty infiltration and smooth-muscle degeneration in the muscular layers of the stomach and intestine. Nevertheless, the prevalence of pathologic

gastrointestinal involvement remains unknown, and a clinical correlation with gastrointestinal symptoms has been infrequently documented[11-13].

The results of this study indicate that many children with progressive muscular dystrophy have gastric motor dysfunction. All of the patients in the present study had delayed gastric emptying. These findings confirm previous observations in adults with various muscular dystrophies[7].

Our subjects had motor dysfunction of the stomach, in which only smooth muscle is present. The delayed gastric emptying is most likely caused by weakness of diseased smooth muscle. The smooth muscle abnormalities were similar to those found in dystrophic skeletal muscle in patients with progressive muscular dystrophy[2, 3, 8, 12].

Progressive muscular dystrophy is a disorder characterized by severe, progressive muscle wasting. Mapping of the gene responsible for these disorders to a specific region of the x-chromosome marked the first step in a series of discoveries leading to the cloning of the gene and identification of its protein product, dystrophin. This protein is localized in the surface membrane of normal muscle fibers. Dystrophin was clearly localized in the smooth muscle layers in the lungs, stomach, digestive organs and ureter but was absent or reduced in the smooth muscles of patients with progressive muscular dystrophy[2, 3, 13]. These results suggested a possible systemic dysfunction of smooth muscle layers due to deficiency of dystrophin in progressive muscular dystrophy[3].

Gastrointestinal involvement in patients with progressive muscular dystrophy may cause a feeling of fullness or bloating, or may even prove to be fatal as a result of pseudo-obstruction syndrome[14, 15]. Gastrointestinal symptoms may dominate the clinical picture, but in most cases motility disorders in patients with progressive muscular dystrophy cause no serious problems[7]. Our findings suggest that gastrointestinal motor abnormalities in our patients were not related to the age of the subjects or the clinical stage of the disease.

We believe that smooth muscle disorders in progressive muscular dystrophy may be more common than is generally appreciated. Early demonstration of gastrointestinal motor dysfunction may lead to earlier treatment (e.g., with prokinetic drugs).

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DELTA INFECTION IN CHILDREN WITH CHRONIC VIRAL HEPATITIS B*

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SUMMARY: Makmudov OS, Inoyatova FI, Kadirov BA, Abdumadjidova SU. (Scientific Research Institute of Pediatrics of the Republic of Uzbekistan, Tashkent, Uzbekistan). Delta infection in children with chronic viral hepatitis B. Turk J Pediatr 1997; 39: 75-80.

The incidence and clinical features of chronic viral hepatitis B associated with the delta infection were studied in 300 children between one and 14 years in age. Anti-delta was found in 42 (14%) of 300 children with chronic viral hepatitis B, predominantly in patients with chronic active hepatitis who had anti-HBe; exacerbations were found in 11 of 12 children with anti-delta, but in only four of 12 children without these antibodies. These findings confirm the assumption that the process of exacerbation in patients with chronic active hepatitis and anti-HBe may be related to super-infection induced by the delta virus. *Key words: chronic viral hepatitis, delta virus infection, HBsAg carriers, children.*

A number of investigators consider the delta virus to be an important etiological factor in the chronicity of viral hepatitis[1, 2]. However, the causes of chronicity of the disease in delta virus infection remain unknown. It is evident, at least, that the association of the delta virus and the HBsAg carrier state, or chronic viral hepatitis B, often leads to the development of chronic active hepatitis delta[3, 4]. As a matter of fact, chronic hepatitis delta is as a rule, a chronic viral process of mixed etiology (HB- and HC- viral), with leading activity of the delta virus. The determination of antibodies to the delta-antigen in the blood of patients with chronic hepatitis D is laboratory confirmation of the presence of delta infection, and a high titer of antibodies to the IgM-type delta-antigen suggests a chronic process[5].

The delta infection is a widely-distributed disease, particularly in regions with a large number of HBsAg-carriers, such as Moldavia in Central Asia[6]. So-called chronic hepatitis B, especially chronic active hepatitis B, appears to be chronic hepatitis D in at least 60 percent of cases[7]. A higher incidence of the delta infection has been documented in patients with chronic active hepatitis and liver cirrhosis[8, 9]. There have been few reports devoted to the delta infection in children[10]. The aim of this work was to identify the peculiarities of delta infection development in children with chronic viral hepatitis B.

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Material and Methods

In the present investigation, the incidence and clinical features of chronic viral hepatitis B associated with the delta infection were studied in 300 children between one and 14 years in age.

The diagnosis of chronic persistent hepatitis and chronic active hepatitis was made on the basis of the serological markers of hepatitis B virus (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc) and anti-delta using radioimmunoassay and enzyme multiple immunoassay (Abbott, USA). Diagnosis was based on clinico-biochemical and immunologic investigations, ultrasound examination, scanning and liver biopsy. Histological investigation of liver biopsy specimens was performed in children with chronic viral hepatitis B; in 98 percent of cases, morphological changes were found in the liver, which is characteristic of chronic active hepatitis and chronic persistent hepatitis.

Statistical analyses were performed using student's t-test.

Results

Anti-delta was found in 95 (31.7%) of 300 children with chronic viral hepatitis B, predominantly in patients with chronic active hepatitis. The antibodies were present in 73 of 159 children with chronic active hepatitis and in 22 of 141 patients with chronic persistent hepatitis. In chronic active hepatitis, anti-delta was found more frequently ($p < 0.01$) in patients with constant activity than in those with alternating periods of exacerbation and remission. Among the patients with chronic viral hepatitis B in association with the delta infection, serum samples revealed high titers of anti-delta in chronic active hepatitis and low titers in chronic persistent hepatitis.

Analysis of patients' health histories revealed that there were no differences in the frequency of intravenous injections or dental extractions in children with and without anti-delta. A history of blood transfusion was noted more frequently in children whose serum samples were positive for anti-delta than in without anti-delta. Jaundice was also more common in patients with anti-delta ($p < 0.01$). This reconfirms the fact that super-infection induced by the delta virus is one of the causes of exacerbation in chronic carriers of hepatitis B virus.

It should be noted that most (80.9%) of the children with chronic viral hepatitis B in association with the delta-infection had acute viral hepatitis B in the past. The course of disease was undulating and had some peculiarities. The initial diagnosis was typically a mild form of viral hepatitis B with HBs-antigenemia. The first "peak" of disease was followed by remission lasting for four weeks to two months, during which period the patient's health was good, jaundice was absent and only moderate hepatomegaly was present; however, HBsAg continued to be noted in all of the children's serum. After remission, patients' conditions

worsened and jaundice reappeared. The "second wave" of hepatitis was severe with more marked intoxication and jaundice. The remaining patients with chronic viral hepatitis B had no previous manifested form of disease but were diagnosed after clinico-laboratory investigations.

The prospective study on the time of diagnosis of chronic disease after acute viral hepatitis revealed that of the 73 children from the group with chronic active hepatitis D, diagnosis was established within one year in 56.2 percent of cases, after two to three years 28.8 percent, and later in 15.0 percent of children. These figures may suggest that delta infection may lead to a chronic process in earlier phases of the disease.

The incidence of anti-delta increased with the age of patients; i.e., these antibodies were found more frequently in children older than seven years than in children one to three years in age. This evidence, obviously, may be explained by the correlation between the age of patients and the duration of disease, because many patients had been contaminated by the hepatitis B virus in early childhood.

The examination of children for identification of hepatitis B virus markers revealed a high rate of HBsAg positivity in all forms of disease (Table I). Anti HBs was found

Table I: Rate of Determination of Hepatitis B Serologic Markers and Delta Infection in children with Different Forms of Chronic Liver Disorders

	Nosologic forms and disease activity						
	Chronic active hepatitis				Chronic persistent hepatitis		
Virus markers (abs./%)	Total (n: 89)	High degree (n: 31)	Moderate degree (n: 27)	Mild degree (n: 31)	Total (n: 35)	Active phase (n: 27)	Passive phase (n: 8)
HBsAg	79/88.8	28/90.3	24/88.8	27/87.1	34/97.1	26/96.3	8/100.0
Anti-HBs	9/10.3	3/9.7	2/7.4	4/12.9	2/5.7	2/74	0/0.0
HBeAg	15/16.9	4/12.9	5/18.5	6/19.3	3/8.6	3/11.1	0/0.0
Anti-HBe	33/37.1	6/19.4	11/40.7	16/51.6	13/37.1	11/40.7	2/5
Anti-delta	73/82.0	29/93.5	24/88.8	20/64.5	22/62.9	22/81.5	0/0.0
Anti-HBc	61/68.5	15/48.4	22/81.5	24/77.4	18/51.4	17/63.0	1/12.5

three times more often in the group of children with chronic active hepatitis than in patients with chronic persistent hepatitis ($p < 0.05$). Infectivity and virulence markers (HBeAg) were found 1.7 times more frequently in cases of chronic active hepatitis than in chronic persistent hepatitis. This may indicate that continuous viral replication is more marked in chronic active hepatitis. There was a considerable frequency of anti-HBe, anti-HBc, and anti-D determination in both forms of the disease. Anti-D was noted in 82.0 percent of chronic active hepatitis cases, which may be an indirect

indication of the severity of the pathological process in children from this group. The rate of anti-D determination during chronic persistent hepatitis was high, which may be related to the predominance of children in the active phase of the disease in this group. During the development of disease activity, an increase in the frequency of anti-D determination was found in the group of children with chronic active hepatitis.

Discussion

Some authors explain the clinico-laboratory exacerbation in patients with chronic viral hepatitis B and the presence of anti-HBe by the accompanying delta infection[11, 12]. Taking into consideration the possible specific effect of virus D on hepatitis B virus replication, we evaluated the rate of determination of the system HBV antigen-antibody in relation to the presence of anti-D (Table II). The less frequent finding of anti-HBs in patients with anti-D and chronic active hepatitis ($p > 0.05$) may be explained by the fact that virus D used the hepatitis B virus surface antigen for its replication and reduced the synthesis of the proper antibodies. Besides, anti-HBs might be connected to circulating immune complexes in blood serum. At the same time anti-HBe and anti-HBc were found more frequently in D-positive forms with the presence of anti-D.

Table II: Rate of Determination of Hepatitis B Virus Markers in Children with Different Forms of Chronic Liver Disorders in Relation to Anti - D Presence

	Nosologic forms with (+) or without (-) anti - D					
	Chronic active hepatitis		Chronic persistent hepatitis		Total	
Hepatitis B virus markers (abs./%)	+ (n: 73)	- (n: 16)	+ (n: 22)	- (n: 13)	+ (n: 95)	- (n: 29)
HBsAg	65/89.0	13/81.3	21/95.5	11/84.7	86/90.5	24/82.8
Anti-HBs	7/9.6	3/18.8	2/9.1	1/7.7	9/9.4	4/13.8
HBeAg	13/17.8	4/25	3/13.6	2/15.4	16/16.8	6/20.7
Anti-HBe	29/39.7	6/37.5	12/54.5	3/23.1	41/43.2	9/31.0
Anti-HBc	54/74.0	6/37.5	16/72.7	4/30.8	70/73.7	10/34.5

Clinical exacerbations in children with chronic active hepatitis associated with delta infection include the development of jaundice ($p < 0.001$); marked extrahepatic features such as large vascular "asters" on the face, back, and shoulders; erythema; increased subcutaneous venous pattern on the breast and abdominal wall; and considerable enlargement of the liver. Marked liver induration is a specific sign of chronic active hepatitis D. Enlarged spleen, sometimes exceeding the liver in size, was found in all children. In chronic active hepatitis

without anti-delta, these features were observed less frequently; exacerbations were diagnosed predominantly with deteriorating biochemical findings. The obtained results were confirmed by physical findings: intoxication, extrahepatic features, jaundice, and hemorrhagic manifestations such as nasal hemorrhage (observed 1.4-1.6 times more often in chronic active hepatitis associated with delta-infection). During decompensation of the process in chronic active hepatitis D, we observed ascites and signs of subacute liver dystrophy (three patients). These findings were absent in cases of chronic active hepatitis B.

The course of disease tended to fluctuate. The above-mentioned clinical signs were most notable during the exacerbation of disease and were diminished in the period of remission. This alternation of exacerbation and remission is characteristic of chronic active hepatitis D. The histological picture of the liver in chronic active hepatitis D was characterized by a more severe pathological process in both the parenchyma and the portal tract, while chronic active hepatitis B was expressed by more marked intralobular infiltration, fibrosis of the portal tracts, and an increase in parenchymal lymphocytes and macrophages.

In chronic persistent hepatitis, the clinical features of intoxication, jaundice and hemorrhagic syndrome were less marked. The exposed changes were more characteristic for anti-delta, chronic persistent hepatitis[13, 14]. An increase in liver size more than three cm below the costal margin was found two times more often, and the presence of an enlarged spleen 2.5 times more often in children with anti-delta chronic persistent hepatitis. The reliable differences were identified in liver function tests in chronic active hepatitis with and without anti-delta. Chronic active hepatitis in children with anti-delta is associated with more profound features of hepato-cellular failure, characterized by the following main syndromes: mesenchymal inflammation, cytolysis and disturbance of protein synthesis function[14, 15]. Functional liver biopsy mainly identified findings of mesenchymal inflammatory syndrome, showing a two-fold increase in the gammaglobulin level. Prolonged cholestasis was noted in these children, accompanied by a high level of bilirubin due to both conjugated and unconjugated bilirubin. Different levels of cytoplasmic enzymes (ALT, AST; $p < 0.001$) were determined in chronic persistent hepatitis with and without anti-delta; their activity in chronic persistent hepatitis with anti-delta was 2.3 and 2.1 times higher, respectively, than without anti-delta.

The results of the investigation show a high incidence of delta-infection among children with chronic active hepatitis. A correlation was found between the frequency of anti-delta occurrence, the duration of the illness, and the presence of exacerbations in the dynamics of disease.

Delta-infection is characterized by a more rapid formation of a chronic process after acute viral hepatitis. The clinical course of D-infection includes frequent and striking exacerbations. It is necessary to take into consideration all these patterns in order to clarify the prognosis of the disease and to individualize treatment.

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CLINICAL RISK FACTORS OF HIRSCHSPRUNG – ASSOCIATED ENTEROCOLITIS I: PREOPERATIVE ENTEROCOLITIS*

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SUMMARY: Sarıoğlu A, Tanyel FC, Büyükpamukçu N, Hiçsönmez A. (Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Clinical risk factors of Hirschsprung-associated enterocolitis. I: Preoperative enterocolitis. Turk J Pediatr 1997; 39: 81-89.

Enterocolitis is still the main source of mortality and morbidity in Hirschsprung's disease (HD). Between 1976 and 1993, 79 (26%) of 302 Hirschsprung patients proved to have Hirschsprung-associated enterocolitis (HAEC). Mortality was 7.6 percent (6 patients). HAEC patients, those who died of HAEC and those without HAEC were analyzed for differences in 34 parameters. The length of the aganglionic segment was found not to be a risk factor for HAEC, but early diagnosis and prompt treatment were found to decrease the occurrence of preoperative HAEC. Although we defined HAEC as foul-smelling, explosive diarrhea, some other symptoms and signs, such as abdominal distention on physical examination, vomiting, dehydration, and a history of nonspecific diarrhea were encountered with significant frequency. None of the patients had Down's syndrome. Sepsis was detected in all of the patients who died of HAEC. The severity of HAEC did not increase with the number of attacks of HAEC, and mortality was greater in the first three attacks. Differences in results between some series seemed to be related to differing definitions of HAEC. *Key words: Hirschsprung's disease, preoperative enterocolitis.*

Enterocolitis related to Hirschsprung's disease (HD) was first recognized by Ehrenpreis in 1946, and other reports followed soon thereafter[1,2]. According to some authors, Hirschsprung-associated enterocolitis (HAEC) has a wide spectrum of symptoms ranging from mild diarrhea without any systemic symptom to abdominal distention, diarrhea and hypovolemic shock, ending in mortality[2,3]. Some others do not accept diarrhea alone to be HAEC[4]. Enterocolitis has been subdivided into inflammatory and ischemic (necrotizing) enterocolitis[5]. Pseudomembranous enterocolitis has also been reported in HAEC[6-8]. The incidence of HAEC was reported to be as high as 58 percent and its mortality rose to 30 percent in some series[9-10]. Suggested etiologies of the disease include: spasm of the aganglionic internal sphincter; infections, especially rota virus and Clostridium difficile; alterations in intestinal mucin and mucosal immune defense mechanisms; increased prostaglandin E_1 activity; and Schwatzman-type allergic reaction[17-26]. The clinical risk factors of the disease have also been studied[9,16,27].

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Trisomy 21 and a delay in diagnosis are the main risk factors reported in different series[9, 16]. Some authors have reported that long-segment aganglionosis is a predisposing factor, while others have found no association between the length of aganglionosis and HAEC[11, 12, 27, 16]. Thus a retrospective study was conducted in order to evaluate the clinical risk factors of preoperative HAEC.

Material and Methods

Over a period of 17 years between 1976 and 1993, 302 Hirschsprung patients were evaluated retrospectively for the presence of preoperative HAEC. The patients with preoperative HAEC were compared with Hirschsprung patients without preoperative HAEC, and patients who died due to HAEC were compared with the overall HAEC group in search of clinical factors influencing the occurrence and mortality. The diagnosis of HAEC was based on the existence of foul-smelling, explosive diarrhea.

The following information was obtained in all cases: A, history, physical examination and symptoms on admission: 1. sex, 2. age of diagnosis, 3. birthweight, 4. gestational age, 5. family history, 6. history of death of a sibling, 7. consanguinity, 8. associated anomaly, 9. delay in the passage of meconium, 10. abdominal distention in history, 11. abdominal distention on physical examination, 12. history of diarrhea, 13. fever, 14. vomiting, 15. dehydration, 16. bloody stool, 17. defecation frequency, 18. presence of stool on rectal examination, 19. intestinal obstruction, 20. intestinal perforation, and 21. length of aganglionic segment; B. clinical picture due to HAEC: 1. pericolic abscess, 2. sepsis, 3. total number of HAEC bouts, 4. number of HAEC bouts during hospitalization, 5. hospitalization period for HAEC, 6. type of microorganism in the stool, 7. duration of antibiotic usage, and 8. type of antibiotic used; C. relative to definitive operations: 1. choice of definitive operation, 2. duration between colostomy and definitive operation, and 3. death after definitive operation, D.relative to diarrhea after colostomy and enterocolitis after definitive operation: 1. diarrhea after colostomy, and 2. enterocolitis after definitive operation.

Short-segment aganglionosis (SS) is accepted to refer to aganglionosis extending from the rectum to the sigmoid colon, long-segment disease (LS) above the sigmoid to the ascending colon, and extensive aganglionosis (EA) as total colonic aganglionosis and beyond. For statistical comparisons, chi-square and Fisher's exact chi-square tests were used, and p values of less than 0.05 were considered to be significant.

Results

Between 1976 and 1993, 79 (26.2%) of 302 Hirschsprung patients were found to have preoperative HAEC, and six (7.6%) of these died due to HAEC. Among 79 patients with preoperative HAEC, 15 (19.0%) were female and 64 (81%) were

male. The female: male ratio was 1:43. Among patients without HAEC, 43 (19.3%) were female and 180 (80.7%) were male ($p > 0.05$). One female patient and five male patients died of HAEC. There was no difference between patients who died of HAEC and those who survived with HAEC in terms the of female: male ratio ($p > 0.05$).

Sixteen (24.1%) patients with preoperative HAEC were newborns, 30 (38.0%) were one to 12 months in age, 25 (31.7%) were 12 months to six years, and five (6.3%) were greater than six years old at the time of diagnosis. A significant difference was detected in terms of age of diagnosis ($p < 0.05$) in the one- to 12-month-old and the newborn groups. Among 114 newborns who were admitted with HD, 79 were diagnosed in one to five days, 13 in six to ten days, five in 11 to 15 days, and 17 in 16 to 30 days. All six patients who died of enterocolitis were less than 12 months of age. A significant difference was found between the patients who died of HAEC and those who survived with HAEC in terms of age of diagnosis ($p < 0.05$).

The birthweights in the HAEC group were 1500 to 2500 g in four (11.4%) paitents, 2500 to 3500 g in 23 (65.7%) patients, and greater than 3500 g in eight (22.9%) patients. In the group without HAEC, patients 2500 to 3500 g in weight constituted 62.8 percent of the total ($p > 0.05$). There were 47 (94.0%) term patients, one (2.0%) preterm patient and two (4.0%) postterm patients in the HAEC group. Of the patients without HAEC, 123 (94.6%) were found to be term infants ($p > 0.05$).

One sister and one brother of the patients in the HAEC group and one sister and three brothers of the Hirschsprung patients without HAEC had the diagnosis of Hirschsprung's disease. Eighteen patients (6.6%) in the HAEC group and 29 (10.6%) in the group without HAEC had a history of death of one of their siblings; six (two with HAEC) had died of verified HD, while 12 (five with HAEC) had a history suggesting HD but no verification. The families of 10 patients (12.7%) with HAEC and 26 patients (13.3%) without HAEC were found to have consanguinity ($p > 0.05$). In 13 patients (16.5%) with HAEC and 36 patients (16.1%) without HAEC, a congenital anomaly was detected ($p > 0.05$). None of the patients with HAEC had Down's syndrome.

Seven patients (12.5%) in the HAEC group passed meconium in the first 24 hours of life, 13 patients (23.2%) between 24 to 48 hours, and 36 patients (64.3%) after 48 hours. These figures were 14 (8.9%), 44 (27.9%) and 100 (63.3%), respectively, among patients without HAEC ($p > 0.05$). A history of distention was present in 77 patients (97.5%) in the HAEC group ($p > 0.05$).On the other hand, distention was found on physical examination statistically more frequently in the HAEC group ($p < 0.05$). The two groups were also searched for the presence of nonspecific diarrhea other than foul-smelling, explosive diarrhea. Seventy-one patients (89.3%) with HAEC had a history of nonspecific diarrhea, whereas only six patients (2.7%)

without HAEC had a history of this sort of diarrhea, with a statistically significant difference between the two groups ($p < 0.05$). Sixteen patients (20.3%) were found to have body temperatures greater than 38 °C ($p > 0.05$). Vomiting was detected in 61 patients (77.2%) in the HAEC group, and this result was statistically higher than in the group without HAEC ($p < 0.05$). Both mild and severe dehydration were significantly more common in the HAEC group (29 and 9 patients, respectively, $p < 0.05$). Bloody stools were detected in two patients (2.5%) in the HAEC group and three patients (1.4%) in the group without HAEC ($p > 0.05$). In the HAEC group 25 patients (35.2%) passed stool every one to three days, 14 (19.7%) every four to six days, seven (9.9%) every seven to 10 days, four (5.6%) at intervals greater than 11 days, 10 (15.5%) more than once a day and 11 (15.5%) only with an enema ($p > 0.05$). In 41 patients (52.6%) with HAEC and in 35 patients (16.3%) without HAEC there was passage of stool after rectal examination ($p > 0.05$). Thirty-four patients (43.1%) with HAEC and 104 patients (46.6%) without HAEC had an intestinal obstruction on x-ray ($p > 0.05$). Intestinal perforation was present in three (3.8%) patients with HAEC and eight (3.6%) without HAEC ($p > 0.05$).

Sixty-three patients with HAEC (82.9%) had SS, 11 (14.5%) had LS disease, and two (2.6%) had EA; among those without HAEC, 155 (78.3%) had SS, 34 (17.2%) had LS disease, and nine (4.6%) had EA ($p > 0.05$). Information on the length of the aganglionic segment was able to be obtained from 274 files. Four patients who died of HAEC (80.0%) and 59 who survived with HAEC (83.1%) had SS disease ($p > 0.05$).

None of the patients with preoperative HAEC had a pericolic abscess. Sepsis was present in all the patients who died of HAEC and nine (12.3%) of those who survived with it ($p < 0.05$). All six patients who died of HAEC died in one of the first three attacks of HAEC. Thirty-six of the patients who survived with HAEC (54.3%) had one to three attacks, and 32 (45.7%) had four or more ($p < 0.05$, Fisher's exact chi-square test). Five patients died of HAEC in the first hospitalization, and one in the second, In the group that survived with HAEC, 37 patients (50.7%) were hospitalized at least once, and 36 (49.3%) were never hospitalized ($p < 0.05$). Two (33.3%) of the six patients who died of HAEC were hospitalized less than three days, one (16.7%) four to seven days, and three (50.0%) for eight to 15 days.

The microorganisms detected in the two groups were as follows:

Died due to HAEC: E coli (1 patient), E.coli + Klebsiella (1 patient), Proteus + E.coli + Pseudomonas (1 patient).

Survived after HAEC: E.coli (5 patients), E.coli + Klebsiella (5 patients), Klebsiella (9 patients), Proteus + Klebsiella (3 patients), Proteus + Enterobacter aerogenes (2 patients), Proteus + Enterobacter aerogenes + E.coli (1 patient), Proteus + E.coli (1 patient), Pseudomonas (1 patient), E.coli + candida albicans (1 patient).

There was no significant difference in the period of antibiotic usage between patients who died due to HAEC and those who survived after HAEC. Antibiotics chosen were mainly penicillin + gentamicin (or tobramycine) + metronidazole in severe cases, and trimethoprim-sulfamethoxazole in mild cases without systemic symptoms.

In the HAEC group, 36 (65.5%) patients had undergone a Swenson operation, 17 (30.9%) a Duhamel operation, one (1.8%) a Boley operation, and one (1.8%) patient a myectomy procedure. One (1.8%) patient in the HAEC group and four patients (2.6%) without HAEC died after definitive operation ($p > 0.05$).

In the HAEC group, the period between the colostomy procedure and definitive operation was between one and three months in one patint (1.9%), three to six months in five patients (9.4%), six to nine months in 10 patients (18.9%) nine to 12 months in six patients (11.3%), 12 to 15 months in four patients (7.6%), 15 to 24 months in 10 patients (18.9%), 24 months to three years in seven patients (13.2%), and greater than three years in 10 patients (18.9%) ($p > 0.05$).

Diarrhea after colostomy was detected in seven patients (10.1%) with HAEC and 20 patients (10.8%) without HAEC ($p > 0.05$). Nine patients (20.5%) with and 25 patients (24.3%) without preoperative HAEC developed HAEC after definitive operation ($p > 0.05$).

Discussion

Although HAEC is still the major source of mortality and morbidity in Hirschsprung's disease, the number of research and retrospective studies on HAEC is limited[9, 16, 27].

In our series the incidence of preoperative HAEC was 26.2 percent and its mortality was 7.6 percent. Although in different series the incidence of HAEC has been as high as 58 percent and the mortality as high as 30 percent, lower mortality rates have been reported in recent publications[16-27].

Tietelbaum et al.[16] found a male predominance (75%) but Carnerio et al.[10] a female predominance. In the present study a male predominance (81.0%) was detected in patients with and without HAEC. The female: male ratios were 1:4.3 for the whole series and 1:4.2 in the HAEC group. The F:M ratio was 1:5 and 1:4.2 for patients who died of HAEC and who survived with HAEC, respectively.

The diagnosis was made most frequently in patients between the ages of one and 12 months. In our series HAEC was less common below one month of age. Early diagnosis of the disease and prompt treatment decrease the occurence of preoperative HAEC. Tietelbaum et al.[16] found that the mean age of diagnosis of HAEC was 16.6 ± 11.3 years and that it was significantly higher than in patients without HAEC. In our series 37.8 percent (114) of patients were diagnosed with HD in the neonatal period. Among the patients with HAEC who were diagnosed

in the neonatal period (19 patients), 47.4 percent were diagnosed in the first five days of life, suggesting that the symptoms can be more severe in the early neonatal period and force the family to bring the baby to the hospital earlier. In fact, all the patients who died of HAEC were less than 12 months of age, and 66.1 percent of them were neonates. Tietelbaum et al.[16] reported a mortality rate of five percent among infants.

Birthweight did not affect the occurrence of HAEC in our series. Tietelbaum et al.[16] reported a family history in their three (4.7%) patients. We detected six (2.0%) patients with a family history among the Hirschsprung patients and two patients (2.5%) in the preoperative HAEC group. Death due to HD was detected in five siblings with HAEC. Consanguinity, although high in both groups, was still below the overall percentages for Turkey[28].

Down's syndrome is being reported with increasing frequency with HD, and in recent years it has also been considered among the clinical risk factors for HAEC. In the series of Surana et al.[9] the incidence of Down's syndrome was reported to be 47 percent. In our series none of the patients with HAEC had Down's syndrome, and only five (1.7%) Down patients were detected in the whole series of 302 Hirschsprung patients. There was no difference in other anomalies between the two groups.

In our series there was no difference between the time of passage of meconium among patients with and without HAEC. Tietelbaum et al.[16] reported the contray, suggesting that patients with HAEC passed meconium later. A history of abdominal distention appeared in equal percentages in both groups. On the other hand, distention on admission proved to be a significant clinical factor in HAEC. We detected abdominal distention in 98.1 percent of our patients with HAEC. Elhalaby et al.[27] reported an 83 percent incidence of abdominal distention. Nonspecific diarrhea was detected in only 2.7 percent of patients without HAEC. Temperatures greater than 38 °C appeared in only 20.3 percent of HAEC patients while vomiting appeared in 77.2 percent of patients. Surana et al.[9] reported that 75.6 percent, and Elhalaby[27] 51 percent, of their patients had the complaint of vomiting. The latter group suggested that mild diarrhea without any other symptoms should be regarded as enterocolitis. In our series mild and severe dehydration was present in 46.8 percent of HAEC patients. These patients should be quickly managed owing to the fact that enterocolitis can result in hypovolemic shock and death. Tietelbaum[16], Surana[9] and Vinton[29] reported 25 five and 10-30 percent incidences of bloody stool in HAEC, respectively. In our series bloody stool was present in only 2.5 percent of HAEC patients. There was no difference in the defecation patterns of the two groups.

In HAEC patients, the rectal examination was found to be more specific, with the presence of stool on rectal examination in 52.6 percent of cases. Elhalaby et al.[27] stated that "gaseous intestinal distention with abrupt cutoff sign at the

level of the pelvic brim was both sensitive (74%) and specific (86%) for HAEC". In our series, intestinal obstruction and intestinal perforation were detected in both groups with no significant difference.

Kleinhaus et al.[11] and Ikeda et al.[12] reported an increased incidence of HAEC with long-segment HD. We found 82.9 percent SS, 14.5 percent LS, and 2.6 percent EA, which resembled the results of Tietelbaum et al.[16] Furthermore, we detected that four of our patients who died of enterocolitis had SS disease, and one had EA.

Sepsis was detected in 14 patients with HAEC and in all six patients who died of HAEC. No pericolic abscess was detected. In our series the first attacks were associated with higher mortality, and the severity did not increase with the number of attacks. This might again be related to the increasing age of the patient. Thirty-seven patients (50.7%) among those who survived with HAEC and all six who died of HAEC had been hospitalized at least once. The duration of hospitalization was less than seven days in 50 percent of the patients who died of HAEC, suggesting a fulminant course. Tietelbaum et al.[16] reported that be hospitalization periods of patients with HAEC were twice as long as those of other Hirschsprung patients. The most frequently isolated organisms were E.coli, Klebsiella and Proteus. We preferred a combination of penicillin + gentamicin (or tobramycin) + metronidazole in severe cases, and trimethoprim-sulfamethoxazole (TMS) + metronidazole (or ornidazole) or metronidazole alone in mild cases.

Patients with preoperative HAEC were treated in the same way as those without HAEC, after the colostomy procedure. The period between the colostomy procedure and definitive operation was not statistically different between the two groups. HAEC did not affect the death rate after definitive operations.

We detected diarrhea in 27 patients after colostomy opening. As the symptoms did not meet the criteria for HAEC diarrhea, this condition was regarded as diarrhea after colostomy. No correlation between preoperative HAEC and diarrhea after colostomy opening was present. The fact that the patient had preoperative attack(s) of HAEC did not imply that they would have HAEC attack(s) after definitive operation, and vice versa.

Since enterocolitis most frequently affects patients with HD between the ages of one and 12 months and it is potentially a lethal complication in this period of life, patients should be carefully evaluated and diagnosed before this period.

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CLINICAL RISK FACTORS OF HIRSCHSPRUNG – ASSOCIATED ENTEROCOLITIS II: POSTOPERATIVE ENTEROCOLITIS*

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SUMMARY: Sarıoğlu A, Tanyel FC, Büyükpamukçu N, Hiçsönmez A. (Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Clinical risk factors of Hirschsprung-associated enterocolitis. II: Postoperative enterocolitis. Turk J Pediatr 1997; 39: 91-98.

Among 302 Hirschsprung patients diagnosed between 1976 and 1993, 213 patients who had undergone definitive operations for Hirschsprung's disease (HD) were reviewed for the occurrence of postoperative Hirschsprung-associated enterocolitis (HAEC). The role of 42 parameters were analyzed. We detected 34 patients (14.0%) with postoperative HAEC with no mortality. In nine patients (26.5%) HAEC persisted postoperatively but no effect of preoperative HAEC on postoperative HAEC was detected. The length of the aganglionic segment did not have any effect on HAEC. Down's syndrome was not present in any of our patients with HAEC. Enterocolitis appeared after Swenson, Duhamel and Boley operations in 23, 10 and one patient, respectively. The incidence of HAEC was inversely proportional to age and weight at the time of definitive operation. The presence of colostomy before or during definitive operation had no effect on postoperative HAEC. Complications of definitive operations, including stricture, did not have any effect on HAEC. *Key words: Hirschsprung's disease, postoperative enterocolitis.*

The surgical principles of Hirschsprung's disease (HD) were put forward by Swenson and Bill in 1948[1]. Later, Duhamel[2], Soave[3], State[4], Martin[5], Boley[6] and others proposed different types of pull-through operations and modifications of these[7]. These operations carry the risk of complications related to both the type of the procedure and the nature of the disease itself[8]. Among these, Hirschsprung-associated enterocolitis (HAEC) is accepted to have the highest incidence and mortality rate[9-11]. However, it is still a matter of debate whether postoperative HAEC is a result of the natural course of the disease, a complication of definitive operations, or both. Some authors have stated that the spasm of the aganglionic sphincter might be the cause of HAEC[9, 12, 13]. Anastomotic stricture and insufficient operation are the other causes that have been attributed to the operation[14]. Although some surgeons still prefer to perform the colostomy procedure before definitive operation, nowadays there is a tendency towards operating on Hirschsprung patients in the newborn period and avoiding a colostomy[15-17]. The incidence of HAEC reported after this sort of operation is very low. A retrospective

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study was planned to evaluate the clinical risk factors of postoperative HAEC, its natural course and whether any relation exists between preoperative and postoperative HAEC.

Material and Methods

Among 302 Hirschsprung patients admitted to Hacettepe University Children's Hospital between 1976 and 1993, 213 patients who had undergone definitive operations for HD in the same period of time were analyzed for the presence of postoperative Hirschsprung associated enterocolitis (HAEC). The patients were compared with others who did not have postoperative HAEC in order to determine clinical risk factors related postoperative HAEC. The diagnosis of HAEC was based on foul-smelling, explosive diarrhea.

The patients were evaluated according the following data: a) history and symptoms on admission: 1. sex, 2. age of diagnosis, 3. birthweight, 4. gestational age, 5. family history, 6. history of death of a sibling, 7. consanguinity, 8. associated anomaly, 9. delay in the passage of meconium, 10. abdominal distention on physical examination, 11. defecation pattern, 12. intestinal obstruction, and 13. intestinal perforation; b) the relation to preoperative HAEC: 1. the presence of preoperative HAEC, and 2. the number of attacks of preoperative HAEC; c) length of aganglionic segment and factors related with definitive operation: 1. length of aganglionic segment, 2. the presence of colostomy before definitive operation, 3. diarrhea after colostomy, 4. type of definitive operation, 5. period between definitive operation and colostomy closure, 6. age at the time of definitive operation, 7. weight at the time of definitive operation, 8. colostomy closure during definitive operation, 9. type of suture used in definitive operation, 10. leakage of anastomosis, 11. mucosal disruption of anastomosis, 12. adhesive intestinal obstruction, 13. postoperative sepsis, 14. postoperative pelvic abscess, 15. stricture of anastomosis, 16. period between definitive operation and colostomy closure, and 17. date of definitive operation; d) clinical course of postoperative HAEC: 1. time of first attack after colostomy, 2. paracolic abscess, 3. perforation, 4. sepsis, 5. number of attacks, 6. number of hospitalizations, 7. period of hospitalization, 8. microorganism, 9. type of antibiotic, 10. period of antibiotic usage.

Short-segment aganglionosis (SS) was accepted as aganglionosis extending from the rectum up to the sigmoid colon, long-segment disease (LS) above the sigmoid up to the ascending colon, and extensive aganglionosis (EA) as total colonic aganglionosis and beyond. For statistical comparisons, chi-square and Fisher's exact chi-square tests were used, and p values less than 0.05 were considered to be significant.

Results

Among 302 Hirschsprung patients diagnosed between 1976 and 1993 at Hacettepe University Children's Hospital, 213 patients underwent definitive operations for HD. In 34 (16.0%) of these patients, postoperative HAEC without mortality was detected. Reliable data about the details of postoperative HAEC could not be obtained from all the files so these data were excluded.

Five (14.7%) female and 29 (85.3%) male patients comprised the postoperative HAEC group ($p > 0.05$). The age of diagnosis was similar in both groups as well ($p > 0.05$). In patients with postoperative HAEC, the age at diagnosis was the neonatal period in 16 cases (47.1%) one to 12 months in eight cases (23.5%) one to six years in nine cases (26.5%), and greater than seven years in one case (2.9%).

The majority of patients in both groups had birth weights of 2500 to 3500 g (60.0% in the HAEC group and 66.7% in the group without HAEC). Similarly, the majority were term babies (95.8% and 93.9% in the groups with and without HAEC, respectively). No statistical test was applied for these two criteria.

HD was detected in only one of the brothers of the postoperative HAEC patients who died after definitive operation for HD outside our hospital. Four other siblings of patients with postoperative HAEC had a history of a disease resembling HD but no diagnostic verification. Consanguinity was detected in only one patient (2.9%) with postoperative HAEC. Consanguinity was present in 16.1 percent of the group without HAEC, and the difference was statistically significant ($p < 0.05$). In seven (20.6%) patients with HAEC and 20 patients (17.7%) without HAEC, an associated congenital anomaly was detected ($p > 0.05$). None of the patients with HAEC had Down's syndrome.

Three patients (11.1%) with postoperative HAEC reportedly passed meconium in the first 24 hours of life, six (22.2%) of them between 24 and 48 hours, and 18 (66.7%) after 48 hours ($p > 0.05$).

Abdominal distention on first admission was present in 94.1% of HAEC patients and 93.8% of patients without HAEC ($p > 0.05$). Defecation patterns before definitive operation were similar in the two groups. Intestinal obstruction on first admission was detected in 50.0 percent of patients with HAEC and 38.1 percent of patients without HAEC.

Among postoperative HAEC patients, only nine (26.5%) had HAEC preoperatively. There was no statistical difference between the groups with and without HAEC in terms of having preoperative HAEC. Six (66.7%) of the nine patients had more than four attacks of preoperative HAEC and 18 (52.9%) patients without postoperative HAEC also had more than four attacks of preoperative HAEC ($p > 0.05$).

The length of the aganglionic segment was not an important factor in the development of postoperative HAEC. Twenty-five (73.5%) patients with HAEC had SS disease, as did 97 (85.8%) of those without HAEC ($p > 0.05$).

In all the patients with postoperative HAEC the definitive operation was preceded by a colostomy procedure.Among patients without postoperative HAEC, 105 (92.9%) had a colostomy before definitive operation ($p > 0.05$). Diarrhea after colostomy was present in 11.8 and 8.7 percent of the patients with HAEC and without HAEC, respectively ($p > 0.05$).

Postoperative HAEC appeared after Swenson operation in 23 patients (67.7%), after Duhamel operation in 10 patients (29.4%), and after Boley operation in one patient (2.9%). Only Swenson and Duhamel operations were taken into consideration for statistical comparison ($p > 0.05$).

The period between colostomy opening and definitive operation was less than six months in nine (26.5%) patients, six to 12 months in 10 (29.4%) patients, 12 to 24 months in seven (20.6%) patients, and more than 24 months in eight (23.5%) patients ($p > 0.05$).

The ages of patients at the time of definitive operation varied significantly ($p < 0.05$). In the HAEC group eight patients (23.5%) were operated on before the age of 15 months, 21 patients (61.8%) at 15 months to three years, and five patients (14.7%) at three years or greater. These percentages were 8.0, 62.0 and 30.1 percent respectively, for the group without HAEC. The weights of patients varied as well. Eight patients (24.2%) were less than 9 kg, 24 (72.7%) were 10-20 kg and one (3.0%) was greater than 21 kg in the HAEC group; these percentages were 10.7 75.0 and 14.3 percent, respectively, in the group without HAEC.

At the end of definitive operation no colostomy was present in seven patients with HAEC and 27 patients without HAEC ($p > 0.05$). Silk was used in 72.0 percent of patients with HAEC for the anastomosis of the pull-through operation, and 52.5 percent of those without it. Silk and stapler was used in 16.0 percent of the HAEC group and 17.5 percent of the group without HAEC. Vicryl and stapler was used in 6.3 percent of patients with HAEC but none without it. Other suture material and a crushing clamp were also used in some patients.

Leakage of the anastomosis was detected in one patient with postoperative HAEC and two patients without it ($p > 0.05$). Mucosal disruption of the anastomosis was present in two patients with HAEC and two patients without it ($p > 0.05$), and adhesive intestinal obstruction after definitive operation in five and seven patients, respectively ($p > 0.05$). Sepsis after definitive operation was found in one of the patients with HAEC and one without it ($p > 0.05$). Of six patients who had pelvic abscess after definitive operation, two developed HAEC ($p > 0.05$). Anastomotic stricture was present in 25 patients, eight of whom developed HAEC ($p > 0.05$).

The period between definitive operation and colostomy closure was three to six weeks in seven patients (25.9%), seven to 12 weeks in five (18.5%) and more than 13 weeks in 15 (55.6%) patients ($p > 0.05$). The patients' definitive operations were performed between 1976 and 1980, 10 between 1981 and 1985, eight between 1986 and 1990, and five between 1991 and 1993 ($p > 0.05$).

Neither pericolic abscess nor perforation developed in postoperative HAEC. The first attack of HAEC started one month after the colostomy closure in 13 patients (38.2%), two months after in six (17.7%), three months after in eight (23.5%), and after one year in seven (20.6%). Twenty-two patients (64.7%) had one to three attacks, seven (20.6%) had four to six attacks, and three patients (8.8%) had more than seven attacks of HAEC. The number of hospitalization due to HAEC was as follows: 15 patients (44.1%) once, six patients (17.7%) two times, five patients (14.7%) three times, and four patients (11.8%) four or more times. Four of these patients (11.8%) were hospitalized for four to seven days, six patients (17.7%) eight to 15 days, and 20 patients (58.8%) more than 16 days.

Microorganisms detected were as follows: E.coli (12 patients), E.coli + Klebsiella (5 patients), Klebsiella (1 patient), Klebsiella + Citrobacter (1 patient), Proteus + E.coli (1 patient), Proteus + E.coli + Klebsiella + Candida albicans (1 patient), Proteus + Enterobacter aerogenes (1 patient), Proteus + Enterobacter aerogenes + E.coli (1 patient), and Pseudomonas (1 patient).

Different combinations of antibiotics were used in patients with HAEC, mainly penicillin + tobramycin (gentamicin) + metronidazole (ornidazole), or trimethoprim-sulphamethoxazole (TMS) + metronidazole. In 11 patients antibiotics were used for five to seven days, in three patients eight to 12 days, and in 17 more than 12 days.

The treatment of postoperative HAEC was as follows: twelve patients underwent several dilatations, two patients sphincterotomy, five patients dilatations + sphincterotomy, four patients dilatations + colostomy opening, one patient dilatations + redo operation, two patients dilatations + ileorectal fistula repair, and two patients dilatations + bridectomy.

Discussion

Postoperative HAEC was detected in 34 (16.0%) patients. Different centers have reported different incidences of postoperative HAEC, some of which were consistent with our results[18-25]. Female patients constituted 14.7 percent of the HAEC patients (female: male ratio 1:5.8). Other parameters such as age on admission, birthweight, gestational age, family history and associated congenital anomalies either were not significantly different or were not suitable for statistical analysis. We encountered consanguinity less frequently in the HAEC group. Although this might suggest that postoperative HAEC did not have a congenital origin, some other parameters such as family history and associated congenital anomaly did not necessarily support this.

The time of passage of meconium, defacation patterns, and the presence of abdominal distention on physical examination on first admission, intestinal obstruction and intestinal perforation before definitive operation was almost the same in the two groups.

The presence of preoperative HAEC and the number of attacks did not create a risk factor for postoperative HAEC. Similar results were present in the series of Tietelbaum et al.[14] In the presented series, 6.1 percent of patients with postoperative HAEC also had preoperative HAEC. Elhalaby et al.[26] reported a 4.8 percent occurrence of postoperative HAEC after preoperative HAEC.

In the present series we report a high incidence of SS disease (73.5%) with postoperative HAEC, with no statistical difference from the group without HAEC.

In all of the patients with postoperative HAEC, definitive operation was performed after colostomy procedure. No difference was found between the patients with and without HAEC in terms of the presence of colostomy before definitive operation. In older children and in cases with considerable colonic dilatation, the colostomy procedure is necessary to facilitate the definitive operation. Surgeons who prefer performing definitive operation in the newborn period without colostomy report a very low incidence of postoperative HAEC.

No relation was found between the diarrhea after colostomy and postoperative HAEC. Similarly, we did not detect a relation between preoperative HAEC and diarrhea after colostomy in the first part of our study. In our study colostomy closure during definitive operation or soon after definitive operation did not have any effect on the occurrence of postoperative HAEC.

We detected postoperative HAEC in 22 patients (63.6%) after Swenson operation, 11 (33.3%) after Duhamel operation, and one (3.0%) after Boley operation. Previous series have reported different percentages for postoperative HAEC in different types of operations for HD[10, 19, 20, 23]. In the present series no difference was detected between the two groups in terms of type of operation (Swenson and Duhamel operations were compared).

Both the age and weight of the patient were risk factors for postoperative HAEC. It seems that if the symptoms of the disease are mild enough to enable the patient to survive with the disease with little or no complaints until the age of 15 months or a weight of greater than 10 kg, the risk of postoperative HAEC decreases.

Complications due to definitive operation, including anastomotic stricture, had no effect on the development of HAEC. Tietelbaum et al.[14] reported that among their four patients with postoperative HAEC, three had anastomotic stricture.

HAEC attacks could start as early as within the first postoperative month and as late as one year later. In 64.7 percent of patients, only one to three HAEC

attacks were detected, and the number of HAEC attacks decreased with time. Similar results were reported by Elhalaby et al.[26] The number of hospitalizations decreased in accordance with the number of attacks, but the period of hospitalization was still high (more than 16 days in 58.8% of patients). In most of the patients the microorganism detected was E.coli. Klebsiella and Proteus were the other two common microorganisms. We preferred penicillin + tobramycin (gentamicin) + metronidazole in severe cases, and TMS + metronidazole or metronidazole alone in mild cases. In the surgical treatment of postoperative HAEC we started with dilatations; other modes of treatment included sphincterotomy, colostomy opening, ileorectal fistula repair, bridectomy and redo operation with success. The colostomies of the four patients were closed later when the barium enema of the distal colon returned to normal. In two patients the signs and symptoms of HAEC obscured those of ileorectal fistula, causing a delay in diagnosis and treatment. Two patients returned to normal after dilatations and bridectomy. In one patient Duhamel operation was performed after Boley operation to treat intractable enterocolitis. None of these patients had the complaint of diarrhea at that moment.

Since postoperative HAEC is frequently encountered following definitive operation among patients weighing less than 10 kg or younger than 15 months of age, delaying the definitive operation beyond these criteria might be preferable.

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A TURKISH FAMILY WITH 6.7 Kb DELETION ASSOCIATED WITH ISOLATED GROWTH HORMONE DEFICIENCY TYPE 1A*

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SUMMARY: Korkmaz KS, Sercan OH, Yazıcıoğlu MV, Sakızlı M, Darcan Ş, Büyükgebiz A. (Endocrinology Unit, Department of Pediatrics, and the Department of Medical Biology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). A Turkish family with 6.7 kb deletion associated with isolated growth hormone deficiency type 1A. Turk J Pediatr 1997; 39: 99-104.

Familial growth hormone deficiency type 1A is an autosomal recessive disease caused by homogenous deletions of both alleles of growth hormone gene 1 (hGH1) in various patterns. The hGH1 gene deletion is an event that probably occurs between the 5' and 3' flanking regions by unequal recombination, and results in deletion of the hGH1 gene in different patterns. Deletions are mostly 6.7 kb and rarely 7.0 kb, 7.6 kb and 45 kb in size. A four-year-old girl diagnosed with growth hormone deficiency syndrome was send to us for further evaluation. DNA samples of the patient, her parents and controls were amplified by polymerase chain reaction (PCR); furthermore, restriction endonuclease analysis was done with Sma I enzyme and the patterns were evaluated. Our gel electrophoresis results show that the gene deletion pattern of the patient represents a homogenous 6.7 kb deletion, while her parents had a heterogeneous 6.7 kb deletion pattern. *Key words: growth hormone deficiency, 6.7 kb deletion, Turkish family.*

The human growth hormone (hGH) gene cluster has five very similar genes: GH1, CSHP1, CSH1, GH2 and CSH2[1-3]. The hGH1 gene and flanking sequences normally give three fragments when cut by EcoRI restriction enzyme[5]. Type 1A isolated growth hormone deficiency (IGHD), which was first described by Illig et al.[4], has an autosomal recessive mode of inheritance and presents a homozygous deletion of DNA containing the hGH1 structural gene[2,5]. IGHD type 1A patients are occasionally characterized by short stature at birth, hypoglycemia and severe growth retardation by the age of six months. The molecular basis of this autosomal recessive disorder depends on the type of deficiency, which is defined by different size deletions from 6.7 kb to 45 kb[1,2,5]. By using standard Southern-Blot and polymerase chain reaction (PCR) methods, 6.7, 7.0, 7.6 and recently a 45 kb gene deletion have been reported by different research groups[1,2,6,7]. We studied a Turkish family with phenotypically normal parents and one affected child.

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Material and Methods

The patient was admitted to the hospital at age four with the complaint of short stature. The delivery, peri and postnatal course were considered to be normal, and the parents were not related. The patient's birth height was 50 cm and weight was 3200 g. Her annual height increments were six cm between one and two years of age and 1.3 cm between two and three years of age. Her bone age was three years according to the Greulich and Pyle method, with a height of 76 cm (height SDS = 5.58), and a weight of 8.2 kg. The upper/lower ratio was 37.7/38.3 cm. Thyroid hormone values were normal. L-Dopa and insulin-induced hypoglycemia (ITT) tests revealed max 1.7 ng/ml GH response.

Preparation of Genomic DNA: Human lymphocyte DNA was isolated by using the CTAB (Cetyl trimethyl ammonium bromide)-DNA isolation method[8]. 150 µl whole blood was first treated with solution A (8% CTAB, 100 mM Tris-Cl pH 8.5, 50 mM EDTA pH 8.0, 1.5 M NaCl) and incubated at 68 °C for five minutes. Chloroform treatment was performed on the lystae, followed by centrifugation at 13.000 rpm in an Eppendorf centrifuge. The supernatant was transferred to a separate tube, and DNA was collected by adding five percent CTAB followed by a precipitation step using absolute ethanol. A second centrifugation at 13.000 rpm was performed. The pelleted DNA was washed with 1.2 M NaCl and a final precipitation using absolute ethanol was performed to recover the DNA for further analysis.

PCR and Restriction Fragment Analysis: PCR amplification of 100 ng template DNA was done using 1µM of each 5',GGATCCAGCCTCAAAGAGCTTAC and 3',GAATTCCCAGAGCCTTGA GCAATGGA hGH1 gene flanking sequence primers (Synthesized by GenoSys Biotech. Inc., Cambridge). A thermal profile (1 min at 94 °C for denaturation, 1 min at 65 °C for annealing, and 2 min at 72 °C for extension) of 30 cycles with an eight-minute initial denaturation at 94 °C and 10 min. at 72 °C for final extension periods was used, Each reaction mixture contained 10X reaction buffer (50 mM KCl, 100 mM TrisCl pH 8.3, 1.5 mM $MgCl_2$, % 0.001 [w/v] Gelatin), 200µM of each dNTP, and 2.5 Units Taq polymerase (Boehringer MN) Volume of in a 100 µl[9]. The DNA of the subject's and control DNA were amplifed and electrophoresed on two percent agarose gel to test the amplifications. The remaining PCR products were digested with Sma I restriction enzyme by adding 10 units of enzyme and 10X enzyme buffer to the amplified products, followed by an incubation period of two hours at 25 °C. Restriction fragments were run on a two-percent agarose gel electrophoresis (5 V/cm).

Results

When genomic DNA is digested by the Eco RI restriction enzyme, the hGH1 gene and its flanking sequences give three fragments. These three fragments are 4.7 kb, 2.6 kb and 4.9 kb in length, and are called R1, R2 and R3 respectively (5' → 3')[5]. The R1 and R3 regions contain a 2.24 kb fragment with 96 percent

homology. Due to this high homology, the same set of primers are used in the PCR amplification of these two regions. The amplified regions having different restriction sites are digested by different restriction enzymes. This knowledges help us to determine whether the tested material belongs to homozygous patients, heterozygous carriers or normal individuals. When the same set of primers are used, we get a 1900 bp amplification product from the R1 region and a 1921 bp amplification product from the R3 region. The 1900 bp R1 amplification product has restriction sites for Bg1 I and Hae II restriction enzymes, while the 1921 bp R3 amplification product contains two SmA I restriction sites[1]. In the 6.7 kb gene deletion, the sequences between the breaking points include the hGH1 gene within it. As a result of unequal recombination, when we use the same primers for the hR1 and R3 regions, we end up with a recombinant product resulting from fusion of the amplified sequences. This recombinant new sequence gives a 1918 bp amplification product, which contains the Bgl restriction site of the 1900 bp sequence and the Sma I restriction site of the 1921 bp sequence. Agarose gel electrophoresis of the PCR amplification products gives one band representing either the 1921 and 1900 bp fragments of the control or a 1918 bp band of a homogeneous patient. It is not possible to detect three bands so close on a two percent agarose gel. Thus, all three bands are detected at the same location (Fig. 1). The agarose gel electrophoresis of the Sma I digestion products showed that the controls gave four bands, size 1900, 761, 712 and 448 bp. Only the 1470 and 448 bp bands were seen in the patient (Fig. 2 lane 1). In the restriction fragment analysis, the parents were found to have an additional 1470 bp fragment in the control pattern. The parents were evaluated as heterozygous carries of this gene deletion (lanes 2 and 3, Fig. 2).

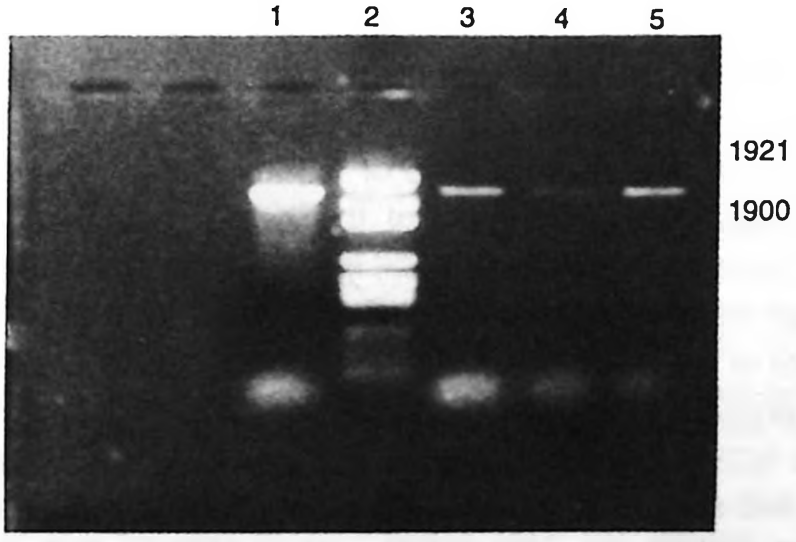

Fig. 1: Ethidium bromide-stained agarose gel electrophoresis patterns of amplified PCR products; lane 1 patient, lane 3 and 4 heterozygous parents, lane 5 control and lane 2 DNA marker (pGEM DNA marker-PROMEGA).

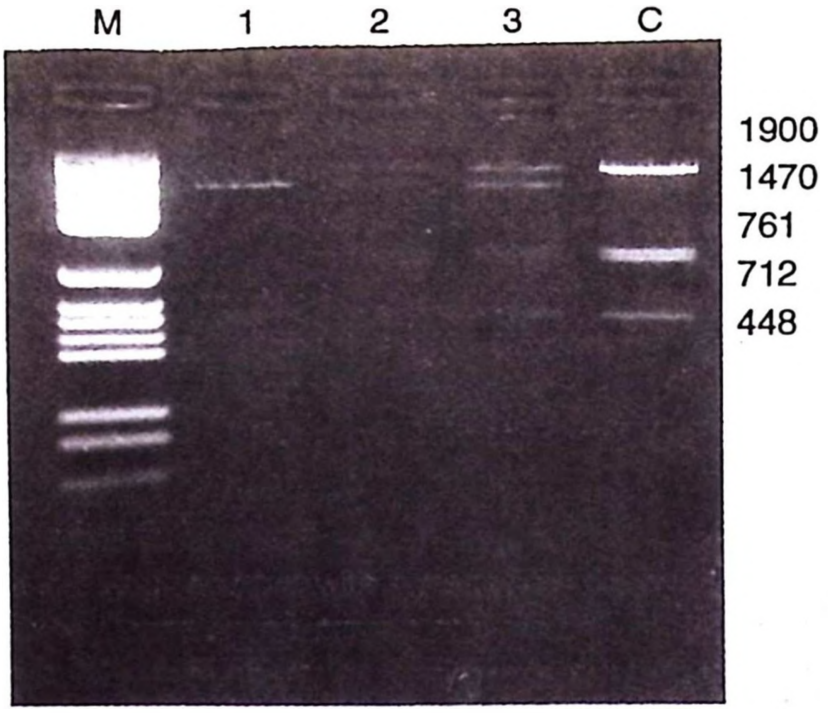

Fig. 2: The patterns of SmaI digested PCR amplification products in 2% agarose gel; lane M: pGEM 2Z DNA marker (PROMEGA). Lane 1 patient with 1470 and 448 bp fragments. Lane 2 and 3 parents with 1900, 1470, 761, 712 and 448 bp fragments. Lane 5 control DNA with fragments 1900, 761, 712, 448 bp in length.

Discussion

The clinical features of patients with IGHD type 1A have been described by Illig et al.[4] as short stature, early growth retardation, typical facial appearance and good response to an initial course of hGH treatment. PCR and restriction endonuclease analysis done from whole blood obtained from families with IGHD type 1A have shown that the affected patients have a deletion of DNA encompassing the hGH-1 gene that encodes hGH endogenously. Deletions are mostly 6.7 kb and in rare cases 7.0 kb or 7.6 kb in size[1]. Different families with the same size gene deletions present the same restriction fragment length polymorphism patterns within their hGH gene locus. This suggests that most deletions result from independent unequal recombination events[9, 10]. The molecular nature of the hGH[1] gene deletions of our patient and her parents were determined by analysis of the amplified PCR products including 5' and 3' flanking regions of the hGH1 gene. Philips et al.[5] reported that the amplified DNA fragments of 1900 and 1921 bp are in the EcoRI segments of the hgH1 gene, referred to as R1 and R3, respectively. The R1 and R3 sequences have extensive homology which includes a 1.38 kb segment which is found to be 96 percent homologous, Alu sequences 0.3 kb in length that are 86 percent homologous,

and 0.56 kb segments that are 88 percent homologous in 5' to 3' order[9, 11, 12]. The recombinational events resulting from these homologies might be the cause of the deletions of the hGH1 gene region of our subjects.

Unequal recombination of these homologous flanking regions yields fusion fragments or deletions as seen in the 6.7 kb hGH1 gene deletion. PCR amplification of the hGH flanking regions in our patient yielded a 1918 bp fragment having one Sma I site and gave a distinct Sma I restriction pattern of two fragments 1470, 448 (Fig. 2 lane 1), while controls gave 1900, 761, 712, and 448 bp fragments. The parents gave an extra 1470 bp band to the control pattern. This was evaluated as the parents being heterozygous for this gene deletion with one normal allele and one deleted allele.

We introduced a homozygous 6.7 kb hGH 1 gene deletion in a Turkish family in which both parents were heterozygous carriers. The method to detect the hGH gene deletions can mainly be divided into three steps: DNA isolation, restriction digestion of amplified products, and finally evaluation of RFLP patterns by agarose gel electrophoresis. These are rare cases and will provide further advances in our understanding of the nature of hGH gene deletions.

Acknowledgement

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YELLOW NAIL SYNDROME IN A 10-YEAR-OLD GIRL*

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SUMMARY: Göçmen A, Küçükosmanoğlu O, Kiper N, Karaduman A, Özçelik U. Chest Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Yellow nail syndrome in a 10-year-old girl. Turk J Pediatr 1997; 39: 105-109.

A 10-year-old girl with yellow dystrophic nails, bronchiectasis, chronic sinusitis and lower-limb lymphedema is presented. The underlying mechanism remains unkown although it has been postulated to be associated with lymphatic abnormalities. To date no causative treatment exists. Our patient was treated with conservative management, including a low-fat diet supplemented with medium-chain triglycerides. Moderate improvement in the lymphedema of the lower extremities was observed. To our knowledge this is the first case of yellow nail syndrome to be treated with diet.

Key words: bronchiectasis, chronic sinusitis, dystrophic nails, yellow nails, lymphedema, special diet.

Yellow nail syndrome is characterized by yellow dystrophic nails in association with lymphedema and respiratory findings, including pleural effusion, bronchiectasis and chronic sinusitis[1-5]. The etiology of this syndrome still remains obscure[6]. Hiller[7] and Beer[8] postulated that the cause of the pulmonary manifestations and lymphedema was hypoplastic or deficient lymphatic vessels. Most published cases have been adults[1-4,7,8]; children with yellow nail syndrome have rarely been reported[5,6]. We present a 10-year-old girl with yellow dystrophic nails, lymphedema, bronchiectasis and chronic sinusitis.

Case Report

A six-year-old girl presented with recurrent respiratory symptoms. Physical examination demonstrated nail changes comprising yellowish discoloration of the nail plate, thickening and exaggeration of the lateral curvature. The remainder of the physical examination was unremarkable. Laboratory investigation revealed a normal hemogram, alpha-1 antitrypsin level, quantitative immunoglobulins and sweat chloride test. Chest radiograph and computed tomography of the thorax showed mild bronchiectasis of the lower left lobe (Fig. 1, 2). Sinus roentgenograms showed a bilateral maxillary sinusitis.

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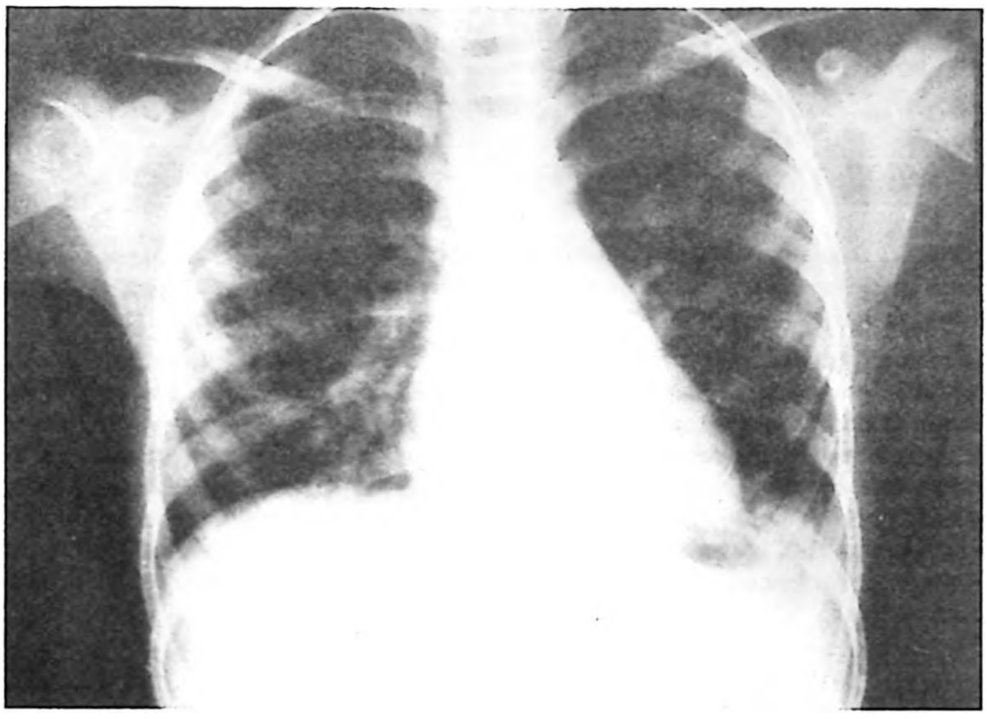

Fig. 1: Chest roentgenogram showing bronchiectasis in the lower left lobe.

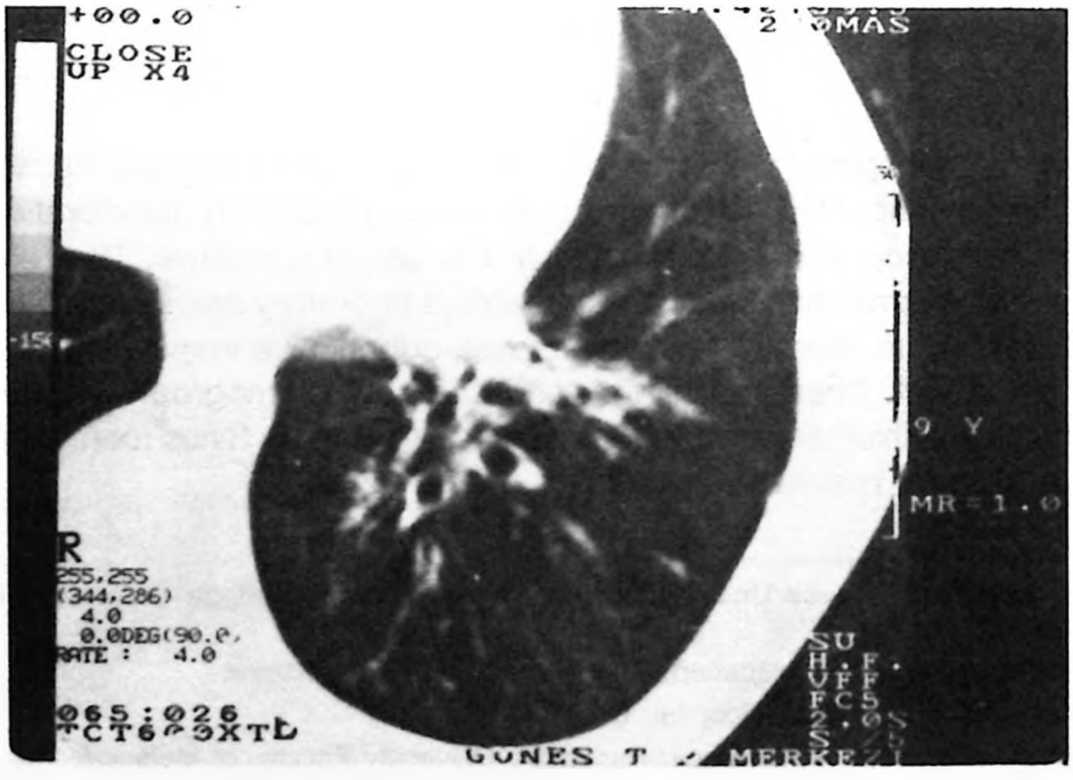

Fig. 2: Computed tomography of the thorax showing bronchiectasis in the lower left lobe.

The nail changes were diagnosed as tinea unguinum. While receiving symptomatic therapy for mild bronchiectasis and sinusitis, the yellow, dystrophic nails were remarkable (Fig. 3). All fingernails and toenails had a yellowish, thickened appearance with increased lateral curvature and loss of the culticles. Repeated nail cultures and smears for bacteria and fungus were negative; thus the diagnosis of tinea unguinum was ruled out.

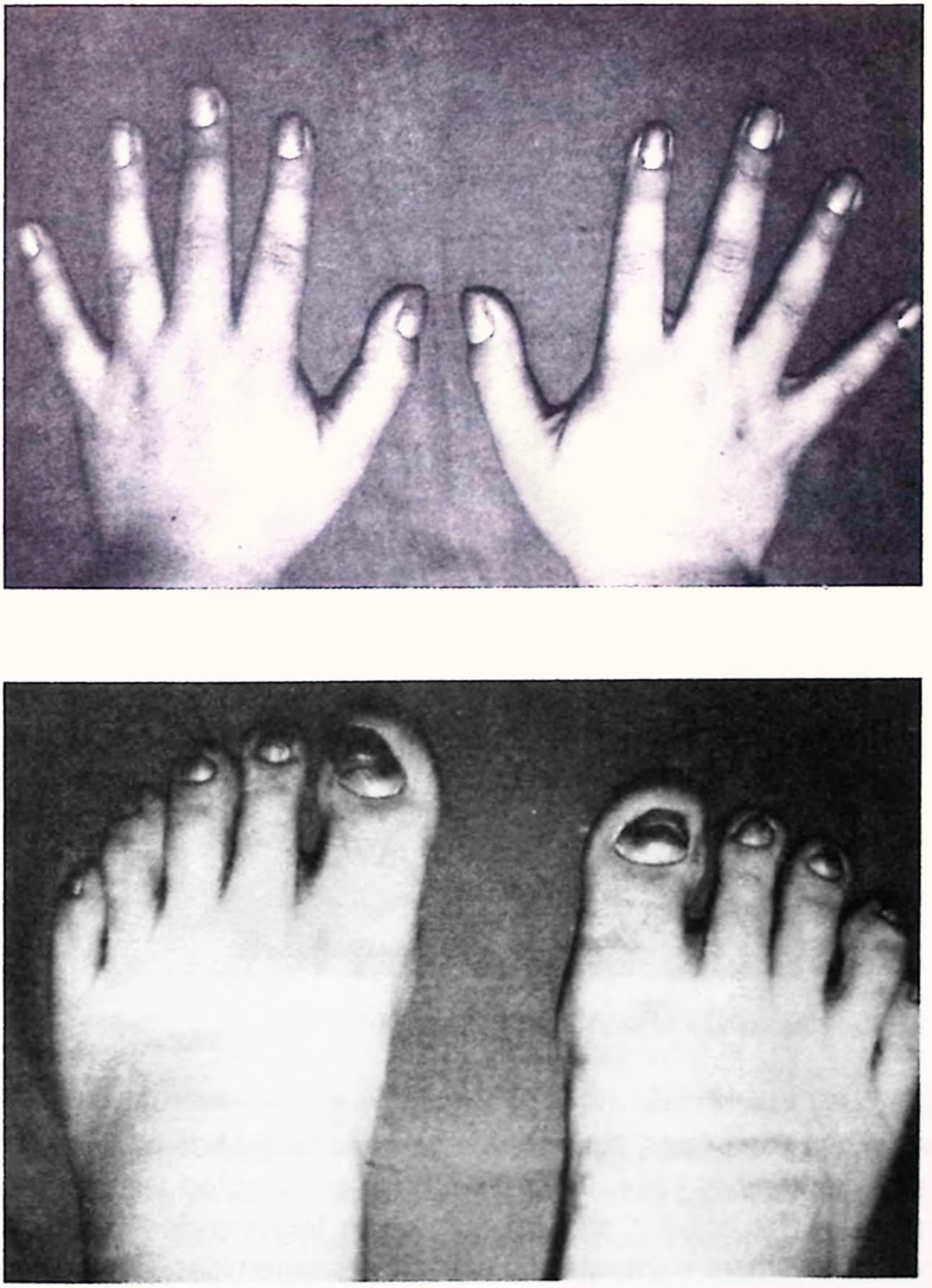

Fig. 3: Fingernails and toenails are yellowish, thickened and opaque, with increased lateral curvature and no visible lunulae.

Three years later, the patient complained of swelling of the lower extremities, and lymphedema was diagnosed (Fig. 4). Doppler ultrasonographic examination revealed normal venous and arterial systems. Lymphangiograms of the lower extremities were abnormal with hypoplastic lymphatic vessels; together with the characteristic nail changes, bronchiectasis and sinusitis, the diagnosis of yellow nail syndrome was established.

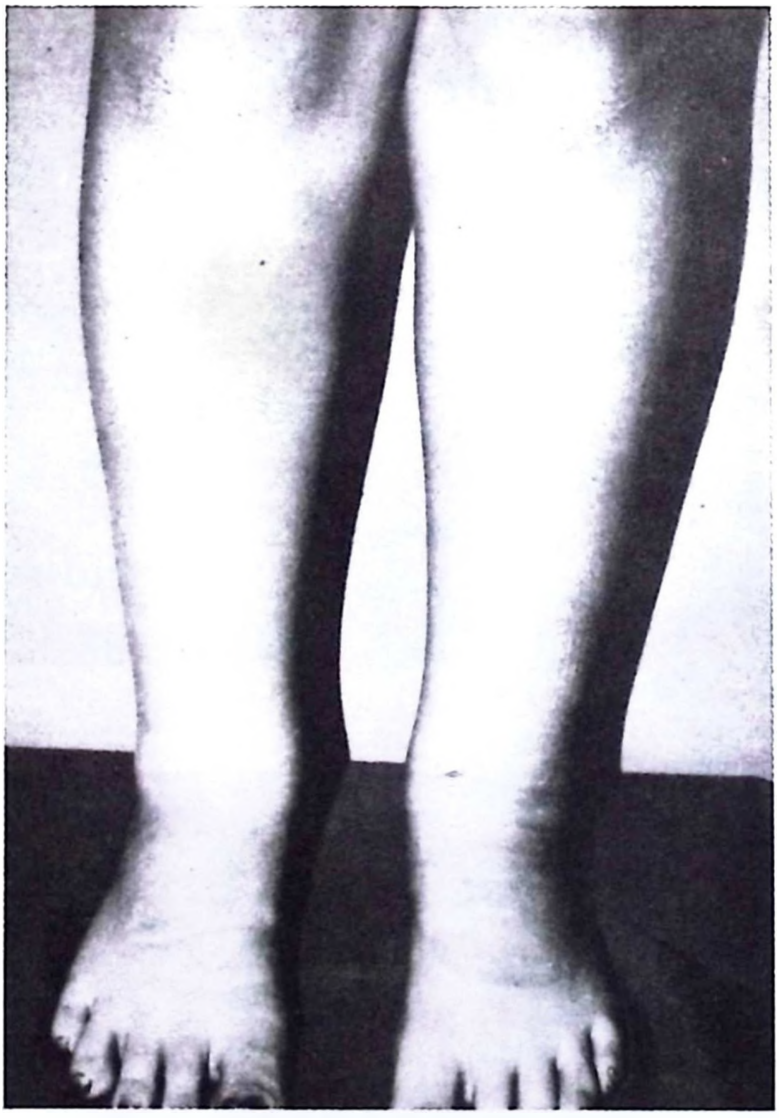

Fig. 4: Lymphedema of the legs.

At follow-up two years later, the nail changes and lymphedema were worse than ever. Since September 1994, the patient has been treated with a specific diet, including a low fat content and medium-chain triglycerides. There has been moderate improvement in the swelling of the lower extremities, but the nail findings have remained unchanged. Because of the improvement in the lymphedema, the diet is being continued.

Discussion

Although yellow nail syndrome was first described in 1964 by Samman and White[1], children with uncommon findings including dystrophic nails and lymphedema had been reported in 1960[5-6]. The classical triad of yellow nail syndrome are slow-growing yellow nails, lymphedema and respiratory manifestations, including pleural effusions, bronchiectasis and bilateral chronic maxillary sinusitis. The main cause of the disease is unknown. The age at onset of symptoms is variable, ranging from birth to the eight decade[2, 3]. Lymphedema is usually the first clinical manifestation, but in some cases nail findings appear first. Eastwood et al.[3] reported a patient with lymphedema beginning in childhood who developed classic nail changes in the eighth decade and pleural effusion in the nineth decade. When any one manifestation of the triad is present, the others should be sought, and the patient should be followed for further developments. The pathogenesis of the pulmonary manifestations is unknown. Airways are richly supplied with lymphatic vessels. It is possible that the hypoplastic lymphatics play a great role in the pathogenesis of bronchial and paranasal sinus infections[7-8]. In some patients bronchiectasis is the only manifestation of pulmonary involvement[7]. No specific treatment is available at the present time.

Conservative management, including a low fat intake supplemented with medium chain triglyceride, which are absorbed directly into the portal venous system, has been suggested in children with cylothorax. We initiated the same diet, including a low fat intake supplemented with medium-chain triglycerides, considering the hypoplastic lymphatic vessels to be the possible etiopathogenesis of yellow nail syndrome. To our knowledge there has been no report regarding therapy for this uncommon disease. This is the first case of yellow nail syndrome that has been treated with a special diet.

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CHLOROQUINE IN IDIOPATHIC PULMONARY HEMOSIDEROSIS*

A Case Report

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SUMMARY: Meral A, Günay Ü, Küçükerdoğan A, Canıtez Y, Özuysal S. (Departments of Pediatric Hematology and Pathology, Uludağ University Faculty of Medicine, Bursa, Turkey). Chloroquine in idiopathic pulmonary hemosiderosis: a case report. Turk J Pediatr 1997; 39: 111-115.

This report describes an 11-year-old boy with idiopathic pulmonary hemosiderosis. His only presenting symptom was severe anemia due to iron deficiency. Idiopathic pulmonary hemosiderosis was diagnosed nine years after the onset of symptoms. During this period many invasive and non-contributory investigations were performed. This report describes the patient's diagnostic problems, clinical features and dramatic improvement with chloroquine (250 mg/day) after failing to respond to megadose methylprednisolone (30 mg/kg). One year later, chloroquine was discontinued. The patient has remained in remission since March 1994. Chloroquine should be used for this life-threatening conditon since it is less toxic than other immunosuppressive drugs.
Key words: iron-deficiency anemia, idiopathic pulmonary hemosiderosis, chloroquine.

Iron-deficiency anemia is common in childhood and usually dietary in origin[1]. If a deficient diet is not the cause, diagnostic attention focuses on the gastrointestinal tract. Respiratory causes are rare, and occult pulmonary hemorrhage is often not considered. We describe a case with idiopathic pulmonary hemosiderosis leading to iron-deficiency anemia in order to draw attention to both the difficulties in making this diagnosis and the response to chloroquine.

Case Report

An 11-year-old boy was hospitalized in February 1993 with fatigue and pallor. He had these complaints since he was three years old and frequently received iron treatment for iron-deficiency anemia. He had also been transfused three times in the previous five years for severe anemia. Despite being transfused, his anemia had recurred, and further investigations including fecal occult blood, barium meal and follow-through, esophagoscopy and colonoscopy were found to be negative. His family history was not notable.

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On admission to the hospital, his body weight was 31 kg (10^{th}-25^{th} percentile), height was 135 cm (10^{th} percentile), temperature was 36.5 °C, pulse was 80 beats/min, respiratory rate was 24 breaths/min and his blood pressure was 100/80 mm Hg. Physical examination revealed 2 cm hepatomegaly, a soft systolic ejection murmur and rales over both lung field. The other systems were found to be normal.

Complete blood count was as follows: white blood cell count 6200/mm^3 (78% polymorphonuclear cells, 2% eosinophils, 20% lymphocytes), hemoglobin 5.1 g/dl, mean corpuscular volume 59.9 fl, mean corpuscular hemoglobin 26.3 pg, mean corpuscular hemoglobin concentration 24 percent, platelets 202,000/mm^3 and reticulocyte count 2.8 percent. The peripheral blood smear showed hypochromic microcytic erythrocytes. The low level of serum iron (3 µg/dL) and increased iron-binding capacity (838 µg/dl) suggested iron-deficiency anemia. Bone marrow aspiration was normocellular with erythroid activation and no stainable iron. Chest x-ray and high-resolution thorax computerized tomography showed bilateral, widespread reticulogranular infiltrates, suggesting hemosiderin deposition in the alveolar space (Figs. 1 and 2).

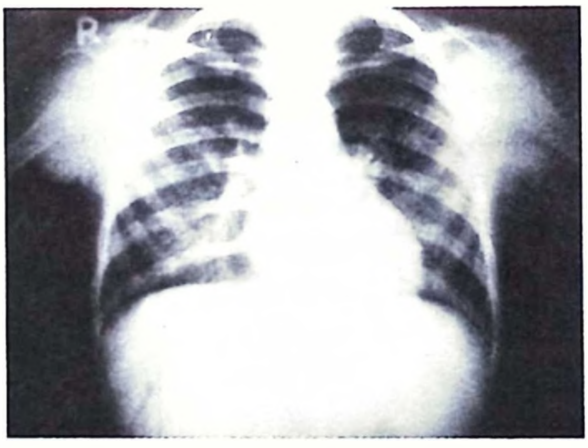

Fig. 1: Plain chest radiogram on admission.

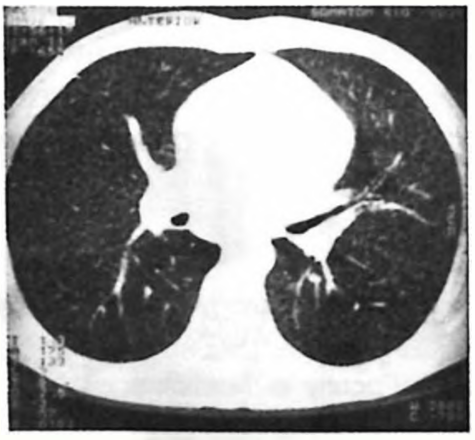

Fig. 2: High resolution computerized thorax tomography demonstrating bilateral reticulogranular infiltrates which indicate hemosiderin deposition in alveolar space.

Autoantibodies were negative. Immunoglobulins A, G, M and E were within normal limits. Our presumptive diagnosis was idiopathic pulmonary hemosiderosis (IPH). To confirm this diagnosis, fiberoptic bronchoscopy was performed. Both the transbronchial biopsy specimen and bronchoalveolar lavage iron-stainable, hemosiderin-laden macrophages (Fig. 3).

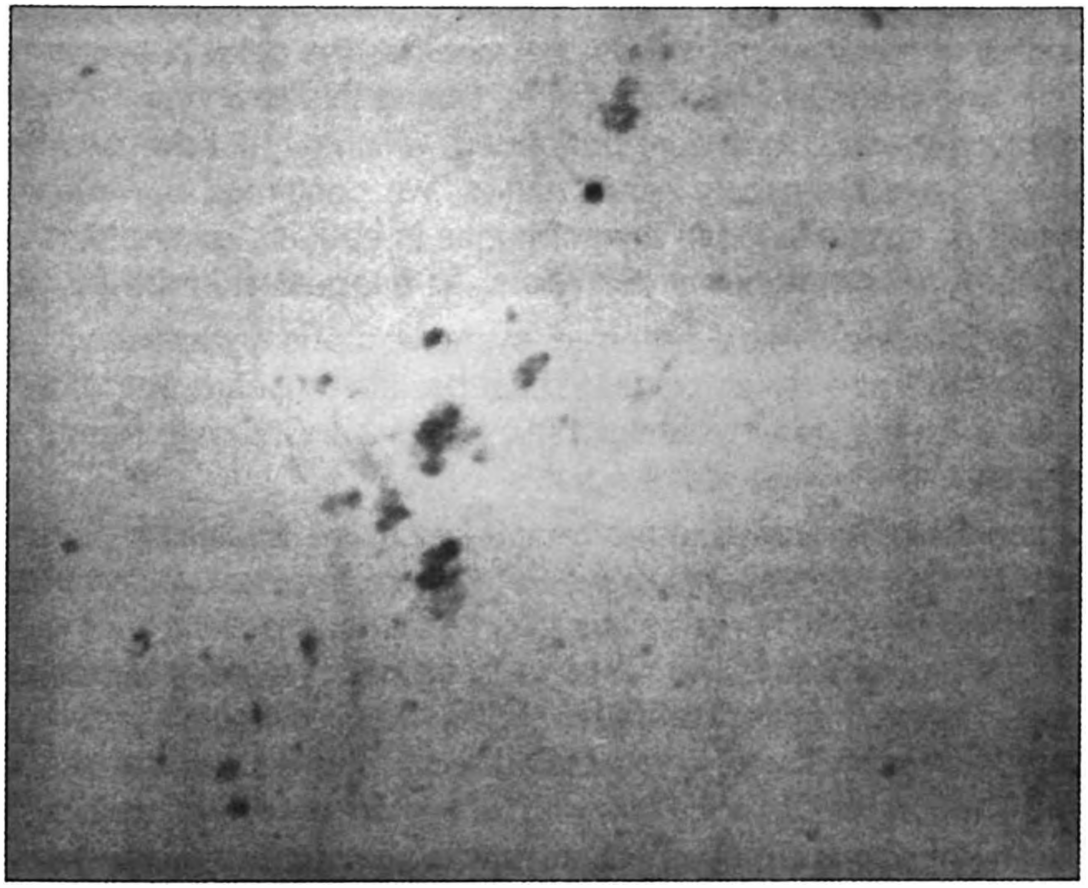

Fig. 3: Bronchoalveolar lavage showing iron stainable hemosiderin-laden macrophages.

The differential diagnosis of Good-Pasture Syndrome, collagen vascular diseases and celiac syndrome was made by normal urinary hemosiderin, sediment, renal function tests, complement, immunoglobulin levels and negative antiglomerular basement membrane antibody, autoantibodies and antigliadin antibodies. The patient was first treated with megadose methylprednisolone (MDMP: 30 mg/kg) tapered off within one month. There was no improvement in the chest films or hematological findings.

Chloroquine sulfate 250 mg PO daily was then initiated. In one month the patient's hemoglobin level increased to nine g/dl and the reticulocyte count decreased. The clinical and laboratory findings returned to normal in the second month of treatment. The final blood count was as follows: Hb 14 g/dl, Hct 38.4%, MCV 84 fl, MCH 34 pg, MCHC 32%, Plt: 254,000/mm^3 and reticulocyte count 1%.

One year later the chloroquine was discontinued. The patient has been in remission since March 1994.

Discussion

The term pulmonary hemosiderosis indicates an abnormal accumulation of iron as hemosiderin in the lungs. Half of affected children have no pulmonary symptoms[2, 3]. Our patient did not have obvious clinical respiratory symptoms; his only presenting symptom was iron-deficiency anemia. The delay between the onset of symptoms and diagnosis was nine years. During this time many invasive and non-contributory investigations were performed, which might have been avoided if the diagnosis had been considered earlier. We confirmed our diagnosis by demonstrating hemosiderin-laden macrophages in sputum, gastric washing and more specifically in the bronchial epithelium, as suggested in the literature[3].

Glomerulonephritis, vasculitis syndromes, systemic lupus erythematosis, juvenile rheumatoid arthritis and celiac disease must be differentiated from IPH[4]. In our case, the complement and immunoglobulin levels were normal. Autoantibodies and gliadin antibodies were also negative.

There are various approaches to the treatment of IPH. Exclusion of cow's milk from the diet in infancy has been suggested[5]. Corticosteroids, cyclophosphamide, azothioprine and plasmapheresis have been tried for the control of pulmonary bleeding[3, 6]. Our patient failed to respond to MDMP. We selected chloroquine for the second-line therapy because of its lack of toxicity compared to immunosuppressive regimens and isolated reports of a dramatic response in childhood[7]. The use of chloroquine may be limited by retinal toxicity; regular ophthalmic examinations are essential and were normal in our case. The possible action of the drug is suppression of lymphocyte proliferation, inhibition of antigen presentation by alveolar macrophages and the effect of immune complex formation[8]. Our patient responded to the drug after two weeks of oral intake and is now in complete remission without any serious complications after having discontinued the treatment.

These findings suggest that a therapeutic trial of chloroquine could be considered in children with IPH who do not respond to MDMP because of its lack of toxicity compared to other regimens.

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The Turkish Journal of Pediatrics 1997; 39: 117-122

INTESTINAL INVOLVEMENT AND VASCULOPATHY IN VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS*

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SUMMARY: Göğüş S, Sarıkayalar F, Akçören Z, Yalnızoğlu D, Hiçsönmez A. (Pathology Unit, Department of Pediatrics, and the Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Intestinal involvement and vasculopathy in von Recklinghausen's neurofibromatosis. Turk J Pediatr 1997; 39: 117-122.

Involvement of the gastrointestinal system and vascular lesions are well-known features of von Recklinghausen's disease, but they are rarely detected in childhood. We report a case of von Recklinghausen's disease with intestinal involvement. The excised right hemicolectomy material of a 16-year-old girl was examined, and diffuse neurofibromatous proliferation with ganglioneuromatous features were observed. Vasculopathy was also seen in some arteries throughout the intestinal segment.
Key words: von Recklinghausen's disease, type I neurofibromatosis, intestinal neurofibromatosis, intestinal ganglioneuromatosis, vasculopathy.

Gastrointestinal (GI) involvement in von Recklinghausen's disease (VRD) or type 1 neurofibromatosis (NF 1) is common[1-4], but diffuse neurofibromatous proliferation involving all layers of the intestinal wall with ganglioneuromatous features has been detected only in occasional cases[1,3-6]. It is also rare in childhood[5,6]. Although vasculopathy is a common finding in neurofibromatosis (NF)[7-11], it has been reported in the GI tract of only a few cases[8-10]. We present a 16-year-old girl who had VRD with diffuse intestinal (ileum, cecum, colon, appendix and mesentery) involvement and arterial lesions in the intestinal wall and mesentery.

Case Report

A 16-year-old girl was admitted to the hospital due to intermittent episodes of abdominal pain and diarrhea since one year of age. There were numerous café-au-lait spots on her body, of which the largest was 3 x 2 cm. Her family history revealed that her father, grandmother and aunt also had multiple café-au-lait spots. She had axillary and inguinal freckling and a cutaneous nodule 0.5 cm

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in diameter on her back. An abdominal mass 4 cm in diameter was palpated in the right lower quadrant. Her arterial blood pressure was within normal limits, and other physical findings were unremarkable.

Ultrasonography revealed thickening of the intestinal wall in the right lower quadrant. Barium studies demonstrated extrinsic pressure on the small bowel and obliteration of the lumen in a 15-cm-long segment of the terminal ileum. A diagnosis of VRD with intestinal involvement was established, and a right hemicolectomy was performed.

The surgical material was composed of a cecum of 8 x 7 x 5 cm, distal ileum of 16 x 16 cm and proximal colon of 15 x 15 cm. A coiled mega-appendix 24 x 2.5 cm in size was found (Fig. 1). The intestinal wall was thickened, especially in the ileum and appendix. Small, greyish-white, fine nodular structures were found in the serosa and mesentery of the colon and appendix. The ileal mucosa had a cobblestone-like appearance with some pseudopolypoid structures, and the colonic mucosa was hypertrophic. The specimen was fixed in 10 percent buffered formalin and was paraffin-embedded. Four micron sections were stained with hematoxylin-eosin, Masson's trichrome and Verhoeff's elastica von Gieson. Immunohistochemistry was performed on the formalin-fixed material with antibodies against neuron-specific enolase, S100 protein and smooth muscle-specific actin.

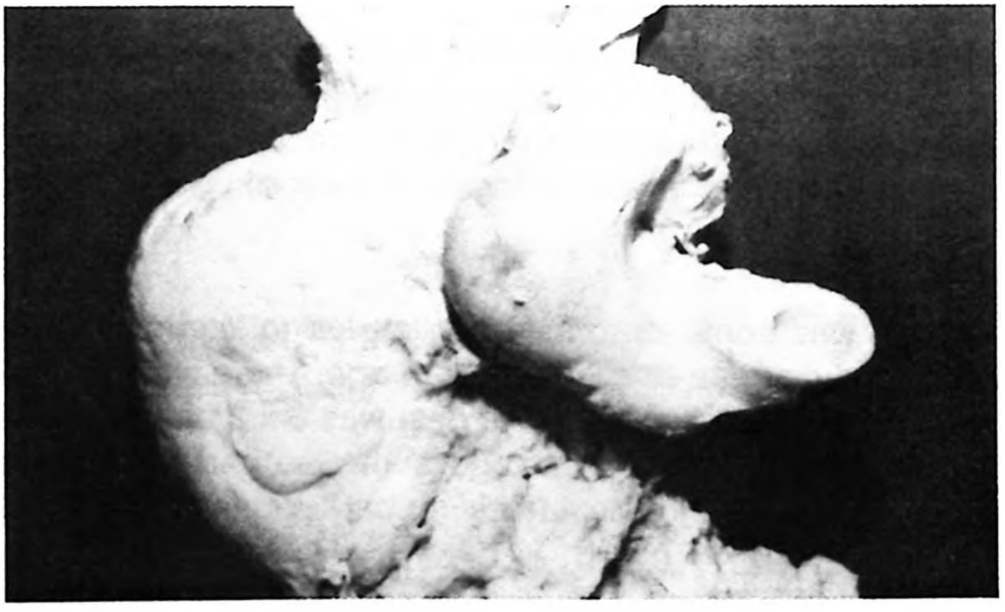

Fig. 1: The surgical material revealed a mega-appendix 24 x 2.5 cm in size. The blind end was cut to show the thickness of the wall

Microscopically varying degrees of hyperplasia and hypertrophy of the nerve plexuses were detected in the wall of the whole intestine, being more apparent in the appendix and colon. There was diffuse mucosal ganglioneuromatosis (GN) throughout the intestine, producing some polypoid structures in the ileum.

Varying degrees of conspicuous proliferation of neural fibers with ganglion cells scattered among them and more pronounced in the lower part were present in the lamina propria (Fig. 2). There was hyperplasia of nerve fibers and ganglion cells with formation of giant ganglia and plexiform lesions in the submucosa. Generally, hyperplasia of the myenteric plexus was less severe than that of the submucosal plexuses in the whole intestine. Ganglion cells were mainly of normal size, however smaller or larger and pale-staining ganglion cells were also detected in the mucosa and other plexuses. Increased fibrous tissue in the muscular layer was found in some sections of the intestine, especially the appendix. Many plexiform lesions were present in the subserosa and mesenteric adipose tissue of the colon and appendix. A few of them had rare ganglion cells. In some of the sections of the intestine, a mainly intimal type of vasculopathy was observed in some small-to large-sized arteries of the submucosa, subserosa and mesenteric adipose tissue (Fig. 3). There were various degrees of concentric or eccentric intimal spindle-cell proliferation and fibrosis. Total hyalinization of the arterial wall and medial thickening were also detected. Increased neural tissue was observed around some of the vessels.

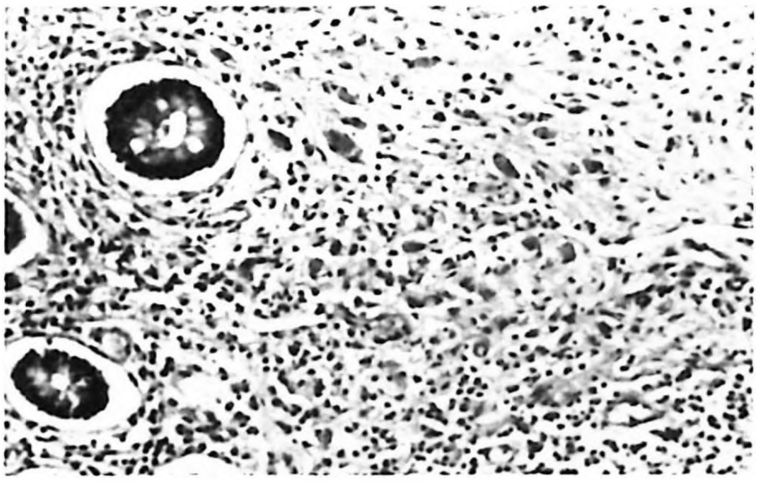

Fig. 2: Ganglion cells and neural fibers in the lamina propria of the ileum.

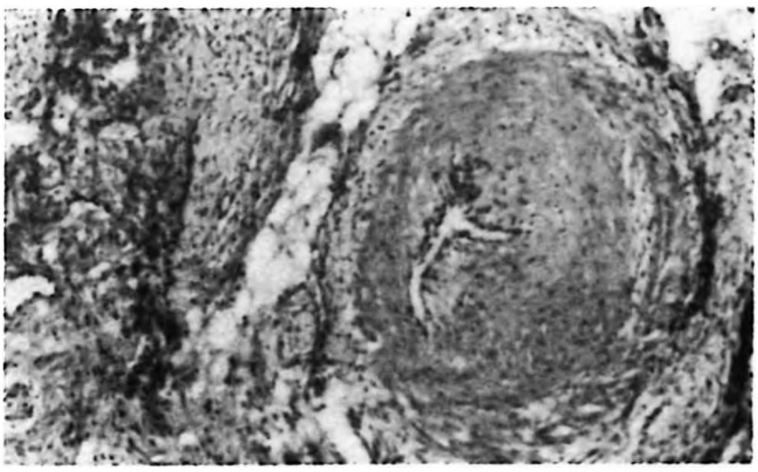

Fig. 3: Arterial lesions showing intimal spindle-cell proliferation in the submucosa of the appendix.

Immunohistochemical studies using smooth muscle-specific actin demonstrated weak to moderate staining of the proliferating spindle cells within the intima of some arteries. S100 protein gave positive results in neural tissue, and similar but weaker staining was obtained with neuron-specific enolase. Most of the ganglion cells were strongly positive for neuron-specific enolase.

Discussion

Von Recklinghausen's disease, also named peripheral neurofibromatosis or type 1 neurofibromatosis, is a relatively common disease characterized by autosomal dominant inheritance, café-au-lait spots and neurogenic tumors of the skin and internal organs[1-4, 6]. Previous studies in the literature have indicated that the GI tract may be involved in 10 to 25 percent of cases with VRD[1, 2, 6]. However, the majority of the GI tumors reported in those cases appear to be mainly localized or multiple neurofibroma and leiomyoma[1, 2, 4-6]. Diffuse GI involvement of NF is rare[1, 3-6]. Neurofibromas usually arise in the submucosa, intramuscularis or subserosa of the intestinal wall, and are composed of Schwann cells, perineural cells and fibroblasts. Tumors may be found anywhere in the GI tract, the ileum being the most frequent site of involvement[12].

Neurofibromatosis of the GI tract may present with a palpable mass, intestinal bleeding, perforation, obstruction, abdominal pain, diarrhea, malabsorption and chronic anemia[2-4, 12, 13]. Cases of diffuse plexiform NF simulating Hirschsprung's disease have also been reported[14, 15]. Our case had abdominal pain and diarrhea since one year of age. Gastrointestinal neurofibroma occurs at all ages but most commonly in the fourth to sixth decade[2-4, 12]. This is probably due to its general tendency to develop after puberty or remain clinically silent. The age of demonstration of GI pathology was eight and 10 years in two patients in a review of 38 cases with VRD and GI involvement[2]. The ages of the other patients ranged from 23 to 68 years.

The term intestinal GN is used for a massive proliferation of nerve fibers, ganglion cells and supporting cells of the intestinal nervous system. Both mucosal and transmural type, focal or diffuse pattern, polypoid ganglioneuroma and ganglioneuromatous polyposis have been described[5, 6]. Ganglioneuromatosis can be seen with multiple endocrine neoplasia (MEN) IIb syndrome, but occasional cases have been reported with VRD[1, 4-6]. Nerve plexus alterations resembling NF or GN can be seen in intestinal neural dysplasia, which is a developmental disorder[5, 6]. Some cases of intestinal GN have probably been referred to in the literature as intestinal neural dysplasia[5, 6]. It is suggested that mucosal GN might be a distinct entity with a lower morbidity rate than the transmural type[5]. In a large series of 43 cases of GI GN, the lesions were located in the colon and rectum, unlike neurofibroma and NF[6]. In our case, mucosal GN was especially

diffuse and prominent, and was detected throughout the intestine. Because of the resemblance to intestinal neuronal dysplasia in some sections, we believe that proper examination of the child and a detailed family history are warranted if limited surgical material is to be investigated.

Gastrointestinal lesions of VRD vary greatly from case to case. Gastrointestinal involvement in VRD occurs in three main forms: 1. hyperplasia of the submucosal and myenteric nerve plexuses and mucosal ganglioneuromatosis, 2. gastrointestinal stromal tumors, and 3. endocrine cell tumors of the duodenum and periampullary region[1]. Our case had form 1 lesions, but there were also plexiform lesions in the subserosa and mesentery. Because of the presence of neural hyperplasia, especially mucosal GN in the surgical margins, we considered the intestinal involvement to be more diffuse than we could detect.

The pathogenesis of GI neuronal and neural hyperplastic lesions in VRD and GN remains unknown. Genetic factors and the presence of some evidence of increased activity of nerve growth factor in the serum of patients with VRD might be responsible[1, 16]. D'Amore et al.[5] indicated that the physiopathology of GN is related to complex hyperplasia of several peptidergic, cholinergic and probably adrenergic nerve fibers instead of selective overgrowth of one type of nerve fiber. A case of vasoactive intestinal polypeptide-secreting GN affecting the entire colon and rectum in a seven-year-old boy who presented with watery diarrhea has been reported[17]. Unfortunately we were not able to investigate our patient for these features.

Vasculopathy, especially arterial lesions, has been well documented in VRD[7-11]. Vascular changes may develop in the entire arterial tree from the proximal aorta to the small arteries, but these changes are most common in the renal arteries, aorta, mesenteric and cerebral arteries[8]. The incidence of vascular lesions is unknown and seems to be underestimated[8]. These lesions are frequently unrecognized clinically, but it has been suggested that, if carefully searched for, they could be found in all patients with NF[8, 10]. Vascular changes have been called either vascular NF or arterial dysplasia in the literature[9, 11]. Six different types of vasculopathy are now known[9, 10]. In our case, the arteriopathy was mainly of the intimal type.

The pathogenesis of the vascular lesions has been subject to controversy. It may be the result of restricted blood flow caused by NF[9]. Salyer and Salyer[10] suggested that Schwann cell proliferation and secondary degenerative fibrosis could cause these changes in both large and small vessels. A myoblast-myofibroblast origin or smooth muscle proliferation has been considered in some cases[7, 8, 11]. We also detected smooth muscle-specific actin positivity in the intima in some vascular lesions. Although involvement of the mesenteric arteries has been described in the literature, there have been few reports describing vascular lesions of the intestinal wall in VRD, and they are rare in children[8-10]. Recently,

severe systemic vasculopathy with hypertension was reported in a four-year-old child with VRD who was diagnosed after examination of the colonic surgical specimen[8]. Our patient has been followed up with this possibility in mind. She is doing well and is symptom-free one year postoperatively.

In conclusion, GI tumors should be considered in every patient with VRD who has symptoms of GI dysfunction.

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TUBERCULOUS OTITIS MEDIA IN A FOUR – MONTH – OLD INFANT*

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SUMMARY: Barlas Ç, Özçelik U, Göçmen A, Söylemezoğlu F, Önerci M, Kiper N. (Chest Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Tuberculous otitis media in a four-month-old infant. Turk J Pediatr 1997; 39: 123-125.

Tuberculosis of the middle ear is currently a rare disease but still occurs and may cause permanent hearing loss. A four-month-old infant with chronic left-ear drainage was diagnosed with tuberculous otitis media by biopsy examination and PPD positivity without BCG. He was treated successfully with antituberculous therapy. Tuberculosis should be considered in the differential diagnosis of chronic ear infection, especially in young infants. *Key words: tuberculosis, otitis media, mastoidits.*

Although tuberculous otitis media and mastoiditis are rare diseases today, they cause significant morbidity when they occur. Because of the low incidence of these diseases, diagnosis may be delayed due to clinicians' unawareness of the characteristic signs and symptoms. This delay in diagnosis, however, may result in deafness, ataxia and cranial nerve palsy for the patient[1,2]. The following case report is offered in hopes of alerting physicians to the rare occurrence of these disease.

Case Report

A four-month-old boy was admitted with a history of neck masses and fever that had persisted for more than twenty days despite parenteral antibiotic treatment. His left ear had been draining for three days. Physical examination showed that his left ear drum was draining. In the postauricular and preauricular regions, masses measuring 1.5 cm in diameter were palpable. The patient had no BCG vaccine scar. Routine laboratory findings, chest x-ray and immunologic investigations were within normal limits. All bacterial and tuberculous cultures of the left ear drainage were negative. As bacterial mastoiditis could not be ruled out, sulbactam-ampicillin and netilmicin administration was initiated.

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After one month of therapy there was no difference in the size of the masses, and the left otorrhea was continuing polypoid mass was then removed from the left ear and found to be "inflammatory granulation tissue" on histopathologic examination. The mass on the left mastoid had slightly softened, and purulent and necrotic material was aspirated via a small incision. The PPD (purified protein derivative) test resulted in 15 mm induration. Bacteriologic and tuberculous cultures of both this material and the granulation tissue were negative. When the left otorrhea stopped and the masses became smaller, the patient was discharged from the hospital.

One month later he was admitted again because the mass on the left mastoid had increased in size (3 x 2 cm) and the left otorrhea had resumed simple mastoidectomy and lymphadenopathy excision was done. The mastoid cavity was filled with gray-colored, loose tissue which extended to the neck. The biopsy report revealed caseous granulomatous tissue (Fig. 1). Examination for acid fast bacilli was negative. The family screening and the mother's genitourinary examinations for tuberculosis were negative. The patient was started on a regimen of isoniazid (10 mg/kg/day) and rifampicin (10 mg/kg/day) daily for fifteen days, then continued at two days per week for nine months. At the follow-up examination the otorrhea had stopped, the size of the mass was reduced, and the patient had gained weight and exhibited good systemic recovery. There has been no recurrence since the end of the therapy.

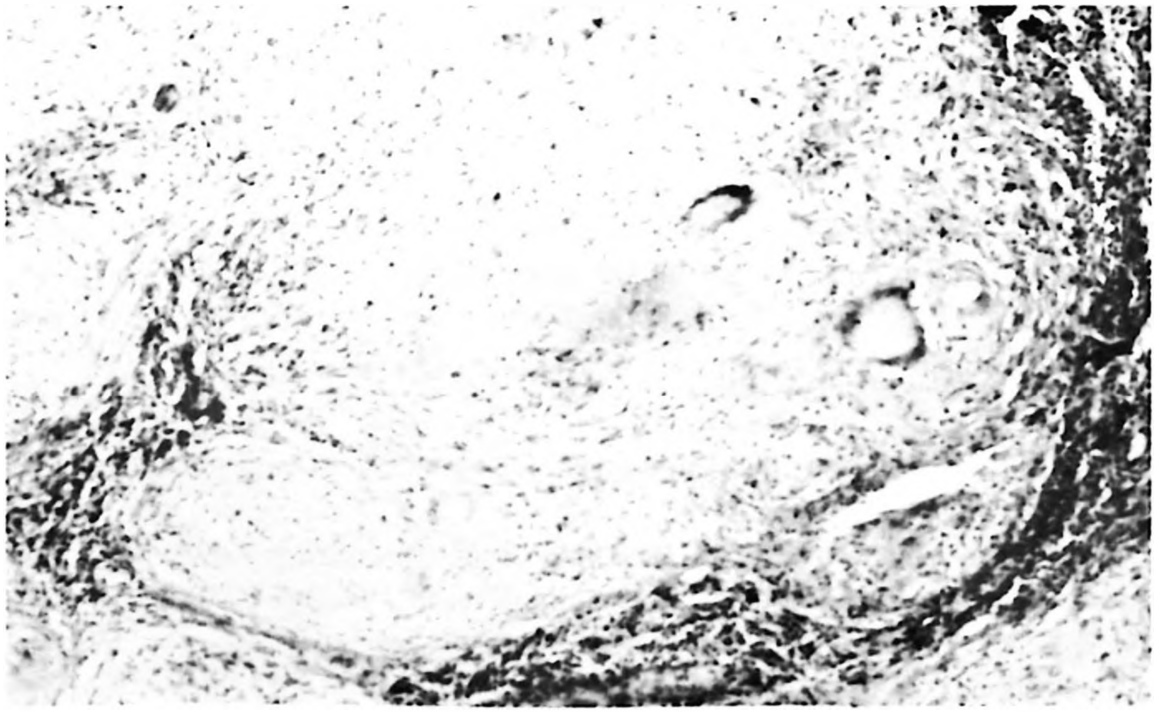

Fig. 1: Histological section of the biopsy showing caseous granulamatous tissue with Langhans giant cells (H + E, x 100).

Discussion

Here in we report an infant with chronic otitis media whose biopsy examination revealed caseous granulamatous tissue. This histopathologic finding can be seen in M.tuberculosis and in atypical mycobacteria infections. Although there was no microbiological proof, the clue to tuberculous infection was the lack of improvement with non-specific antimicrobial therapy, the good response to systemic antituberculous therapy and PPD positivity without BCG vaccination. Wegener's granulomatosis, which can present with granulamatous and chronic otitis media, was excluded by the lack of specific clinical and histopathologic findings[3]. Fungal agents were not found on histopathologic examination.

Before the advent of antituberculous chemotherapy, the occurrence of tuberculous otitis and mastoiditis was frequent and widely recognized. The contribution of M.tuberculosis to the etiology of otitis media in infants has decreased dramatically from an incidence of 25 to 50 percent in 1915[2, 4-7] to the rare case reports of today. Otitis tuberculosis is considered to be either secondary or primary. In a secondary infection, the spread of the organism to the middle ear is hematogenous or via the eustachian tube from the primary focus in adjacent organs[1, 4, 5]. In primary otitis tuberculosis, the spread of the organism to the middle ear is via the eustachian tube. It has mainly been reported in bottle-fed infants in whom milk infected with Bovis strains of M.tuberculosis reached the middle ear[1, 4-6]. In our case, we could not find any primary focus for tuberculosis. The family screening and the mother's genitourinary examinations for tuberculosis were also negative. There was no proof as to the type of mycobacterium because the cultures were negative for tuberculosis. Tuberculous otitis media and mastoiditis have become rare but not nonexistent diseases. They should always be considered in the differential diagnosis of chronic middle ear discharge and mastoiditis that does not respond to convetional antibiotic treatment.

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The Turkish Journal of Pediatrics 1997; 39: 127-135

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY*

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*Gülhis Batmaz MD*****, *Tayyar Sarıoğlu MD******, *Aydın Aytaç MD*******

SUMMARY: Sarıoğlu A, Saltık İL, Sağın-Saylam G, Batmaz G, Sarıoğlu T, Aytaç A. (Pediatric Cardiology Unit, İstanbul University Institute of Cardiology, İstanbul, Turkey). Anomalous origin of the left coronary artery from the pulmonary artery. Turk J Pediatr 1997; 39: 127-135.

Anomalous origin of the left coronary artery from the pulmonary artery (ALCA-PA) is a rare form of congenital heart disease. In this report, three cases with this anomaly are described; two patients presented in infancy with heart failure from myocardial ischemia and infarction, while the third was asymptomatic and ALCA-PA was diagnosed during evaluation of a residual murmur after surgery for associated cardiac defects (ventricular septal defect and patent arterial duct). All three cases underwent aorto-pulmonary tunnel repair (Takeuchi procedure), and to our knowledge two of them are the first infantile cases reported in Turkey. *Key words: coronary artery anomalies, pulmonary artery.*

Anomalous origin of the left coronary artery from the pulmonary artery (ALCA-PA) is a rare congenital anomaly that constitutes 0.24 percent of all congenital cardiac defects, with a reported incidence of 1/300,000[1]. As the mortality rate of untreated patients in the first year of life has been reported to be as high as 93 percent, it is an important form of congenital heart disease with a wide spectrum of clinical presentation[2]. In this report, three cases of ALCA-PA presenting with different clinical features are described.

Case Reports

Case 1

A two-year-old boy known to have congenital heart disease since birth was referred to our clinic for evaluation of his heart conditon. Physical examination, echocardiography, cardiac catheterization and angiography revealed a large perimembranous ventricular septal defect (VSD) and a patent arterial duct (PDA). At the age of three years, patch closure of a 2 x 2 cm VSD and double ligation of the PDA were performed. On postoperative follow-up one year later, a continuous murmur at the 3rd left intercostal space was noticed. Two-dimensional

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echocardiography showed that the left atrium, left ventricle and pulmonary artery were enlarged and the right coronary artery (RCA) was dilated (5 mm). HPRF and color Doppler examination revealed turbulence and continuous flow at the right ventricular apex and the mid-muscular septum (Fig. 1). Repeat cardiac catheterization showed mild pulmonary hypertension (42/26 mmHg) and a step-up in oxygen saturation in the pulmonary artery (Table I). Angiography showed that the RCA was dilated, and the left coronary artery (LCA) was originating from the main pulmonary artery and filled in retrograde fashion from the RCA through collaterals (Fig. 2). The patient underwent "tunnel repair" at the age of five years. The postoperative course was uneventful, and subsequent angiographic study revealed a patent LCA filling from the aorta (Fig. 3).

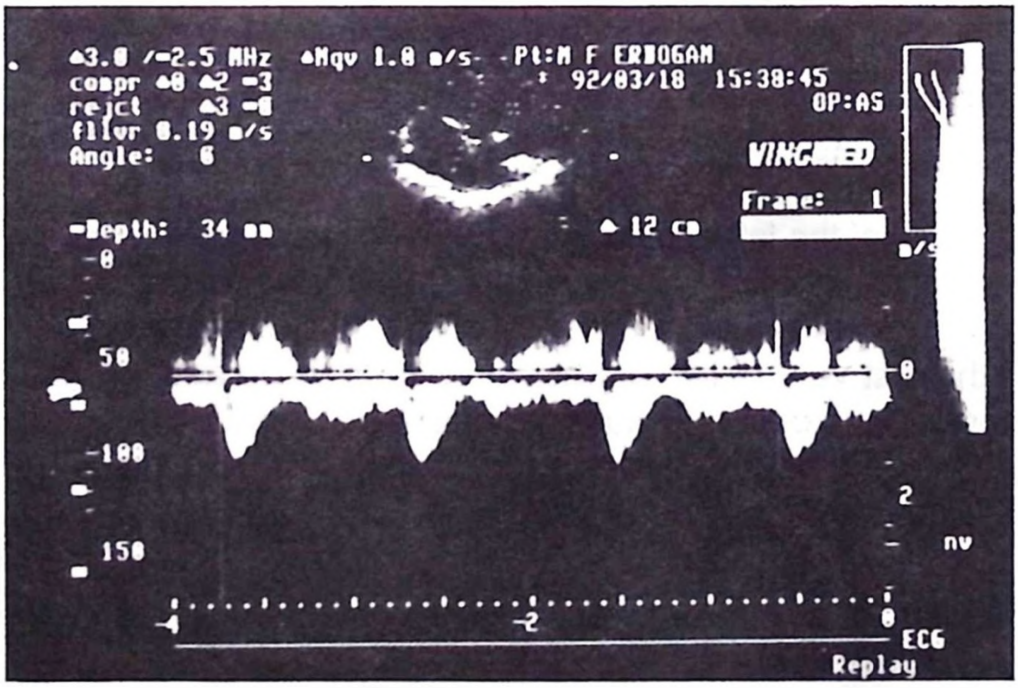


Fig. 1: Sampling by HPRF Doppler in the midmuscular septum showing the presence of continuous flow (Case 1).

Table I: Hemodynamic Findings in Three Cases with ALCA-PA

	Case 1		Case 2		Case 3*
	Pressure** (mmHg)	Oxygen saturation (%)	Pressure (mmHg)	Oxygen saturation (%)	Pressure (mmHg)
Right atrium	15/10 (13)	74.9%	11/6 (8)	27.0%	–
Right ventricle	44/6-12	73%	42/5-10	26%	–
Main pulmonary artery	42/26 (32)	82.7%	35/15 (25)	27%	–
Left ventricle	110/0-10	97.3%	90/2-15	–	75/0-20
Aorta	110/78 (94)	97.3%	90/55 (60)	–	75/38 (50)

* Right heart catheterization was not performed.
** Values in parentheses indicate mean pressures.

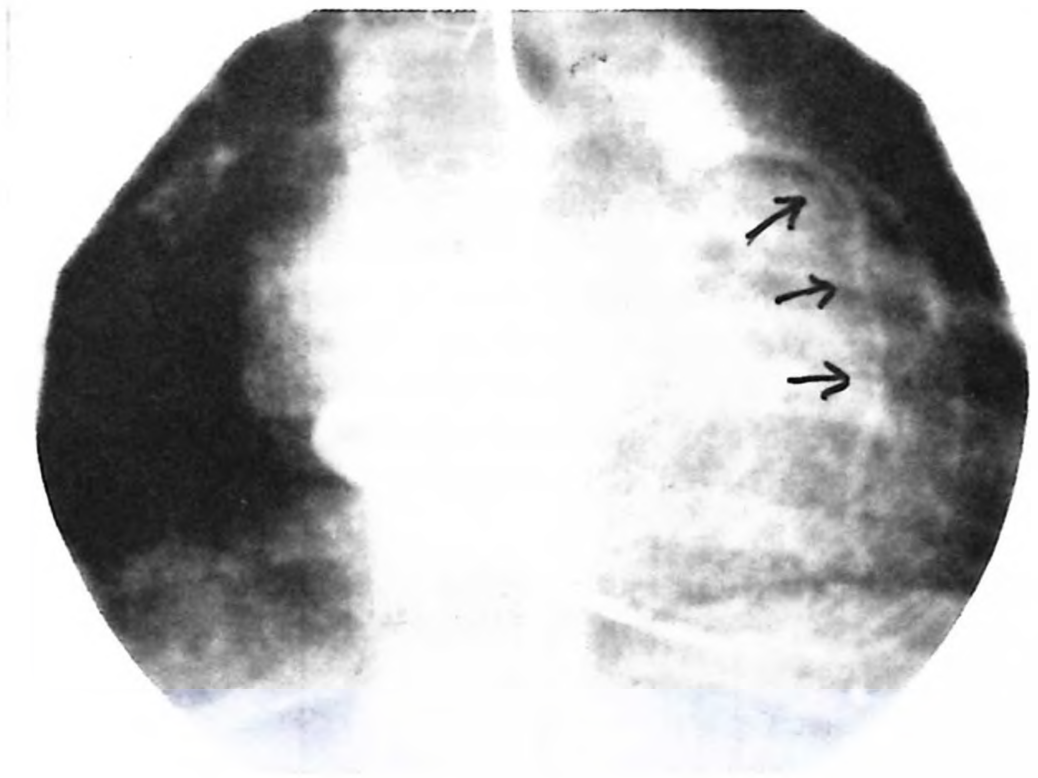
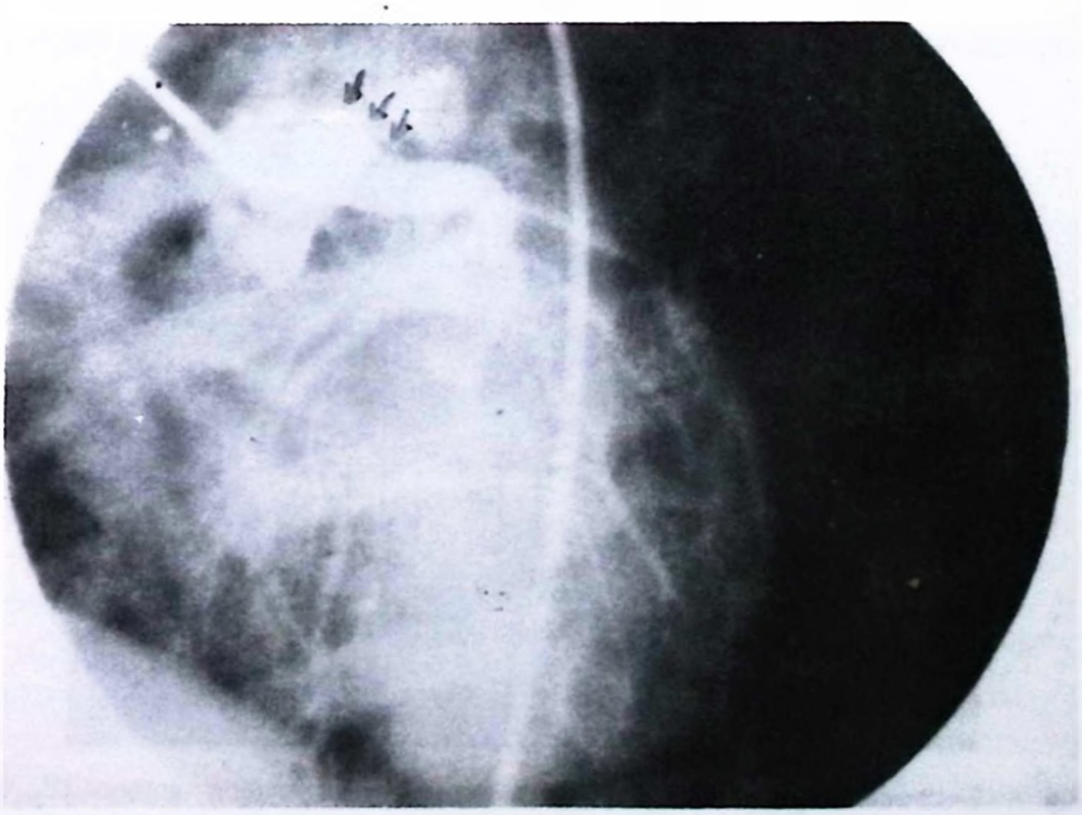


Fig. 2: Preoperative selective right coronary arteriogram in the 45° right arterior oblique view (Case 1) showing dilated RCA and LCA (arrows) filling via collaterals.



Figrue 3: Postoperative left coronary arteriogram in the 45° left anterior oblique view (Case 1) showing the aorta-pulmonary tunnel (arrows) and normal filling of the LCA.

Case 2

A three-month-old girl presented with tachypnea and failure to thrive. She was the 3300 g product of an uneventful pregnancy and delivery. She was noted to have poor feeding and respiratory difficulty since birth and was referred to our clinic for evaluation of a heart murmur. On physical examination, she had tachypnea, dyspnea and tachycardia. The femoral pulses were equal and symmetrical, a grade 2/6 short systolic murmur was audible at the 4^{th}-5^{th} left intercostal space, and the liver edge was palpable 4 cm below the right costal margin. The electrocardiogram showed left-axis deviation, left ventricular hypertrophy and an anterolateral myocardial infarction pattern (Fig. 4). Chest x-ray revealed cardiomegaly (CTR = 0.62) with pulmonary venous congestion.

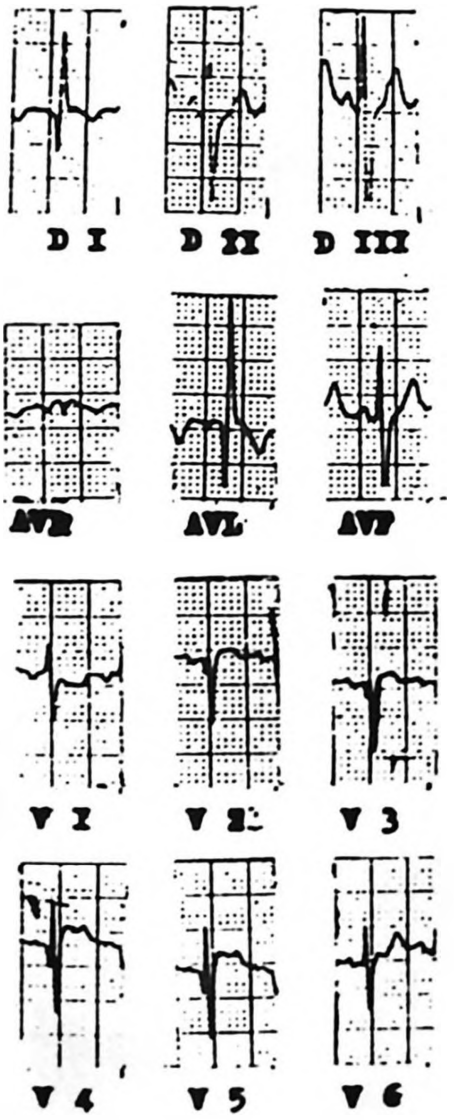


Fig. 4: Electrocardiography of Case 2 showing left-axis deviation, anterior (V_{2-5}) and lateral (lead I, AVL) myocardial infarction pattern, ST segment elevation in V_{2-5} and negative T waves in lead I, AVL.

Two-dimensional color Doppler echocardiography demonstrated an enlarged left atrium, a dilated and poorly contracting left ventricle (fractional shortening = 26%), moderate mitral regurgitation and turbulent flow in the interventricular septum. The aortic origin of the LCA could not be visualized, whereas that of the RCA was well demonstrated. Cardiac catheterization showed a step-up in oxygen saturation in the pulmonary artery (Table I), and the left ventriculogram revealed a dilated chamber with poor contractions. Aortic root injections revealed a dilated RCA, the LCA was visualized after the RCA, filling in retrograde fashion via collaterals, and the main pulmonary artery was opacified through the LCA. Tunnel repair was performed when the patient was seven months old; a zone of anterolateral myocardial infarction was noticed during surgery. The patient died of purulent meningitis and sepsis five days postoperatively.

Case 3

A one-month-old girl who presented with grunting since birth was referred from another hospital because of cardiomegaly. On physical examination, she had tachypnea, dyspnea, and tachycardia. The femoral pulses were equal and symmetrical, and a grade 2/6 short systolic murmur was audible at the 5th intercostal space. The liver edge was palpable two centimeters below the right costal margin. The electrocardiogram revealed left ventricular hypertrophy and a lateral myocardial infarction pattern. Chest x-ray showed cardiomegaly (CTR = 0.66). Two-dimensional echocardiography revealed a grossly dilated, spherical, poorly contracting left ventricle (fractional shortening = 10%), a dilated RCA (3 mm) and LCA originating from the main pulmonary artery (Fig. 5). Color Doppler examination demonstrated

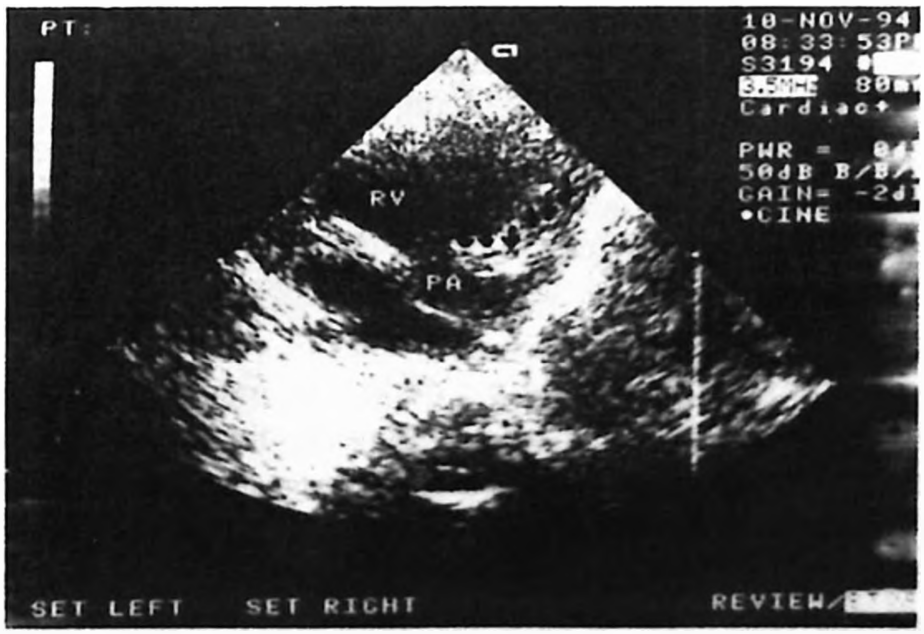


Fig. 5: Two-dimensional echocardiogram in the parasternal short-axis view (Case 3) showing the LCA (arrows) originating from the pulmonary artery.

that the direction of flow in the LCA was towards the main pulmonary artery. Aortography showed a dilated RCA, no origin of the LCA from the aortic root (Fig. 6) with late visualization of the LCA and opacification of the main pulmonary artery through the LCA. The patient underwent tunnel repair at 2.5 months of age. The postoperative course was uneventful. On follow-up nine months later, echocardiography showed that the heart chambers were of normal dimensions and left ventricular contractility was normal (fractional shortening = 38%).

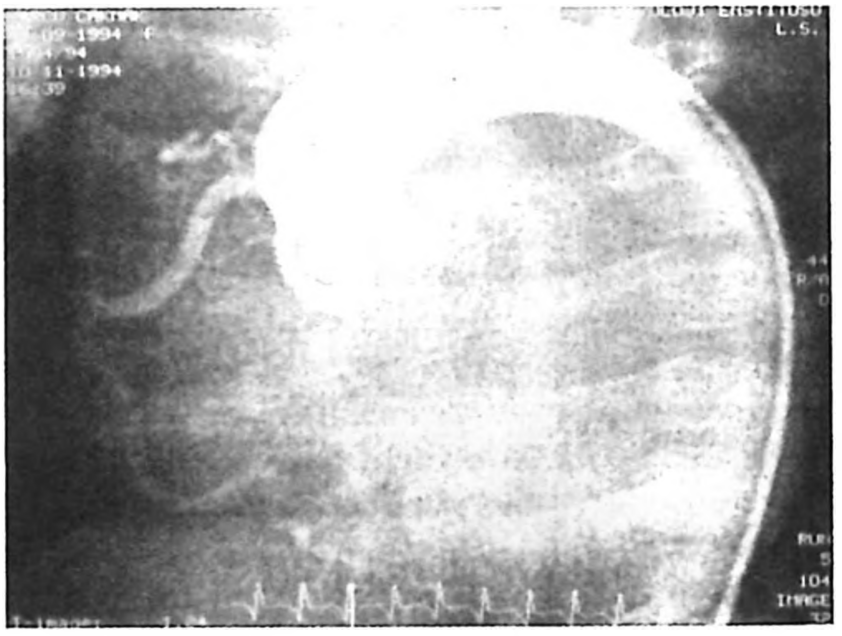


Fig. 6: Preoperative aortogram in 45° left anterior oblique view in Case 3 showing a dilated RCA filling from the aorta with no filling of the LCA.

Discussion

ALCA-PA, also known as Bland-White-Garland syndrome[3], is the most important coronoray anomaly managed by pediatricians and pediatric cardiologists. The clinical spectrum in ALCA-PA may range from the "infantile" form, presenting with signs and symptoms of myocardial infarction and congestive heart failure in infancy, to the "adult" form, which may be asymptomatic and detected in adulthood or on autopsy[4].

In intrauterine life and the early newborn period, pulmonary artery pressure and pulmonary vascular resistance are high; therefore flow in the anomalous LCA originating from the pulmonary artery is antegrade from the pulmonary artery, maintaining adequate myocardial perfusion. As pulmonary artery pressure and pulmonary vascular resistance decrease, antegrade flow from the pulmonary artery through the LCA decreases and myocardial perfusion depends on the presence of collateral circulation between the right and left coronary arteries. If collateral circulation is inadequate, myocardial infarction is likely to occur.

The clinical presentation of such patients includes dyspnea, tachypnea and signs of congestive heart failure, as in Cases 2 and 3. The majority of patients with ALCA-PA present in infancy with heart failure. Wesselhoeft et al.[2], in a review of the literature, found that 116 of 140 patients were diagnosed in infancy. Thirteen out of 15 cases reported by Askenazi and Nadas[5], and 10 out of 11 cases reported by Perry and Scott[6] were of the infantile type. On the other hand, if there is well-developed collateral circulation, as in our Case 1, the patient may be asymptomatic, the only physical sign being a continuous murmur on auscultation. This rare form constitutes only 9 of 140 patients reported in the literature review by Wesselhoeft et al[2]. The only two cases reported in Turkey[7,8] were of the adult type.

ALCA-PA is usually an isolated anomaly, although cases associated with VSD, PDA, pulmonary stenosis and Fallot's tetralogy have been reported[9-11]. In such cases the clinical picture may be dominated by the findings of the associated cardiac defect, and the diagnosis of ALCA-PA may be overlooked. All five cases reported in three articles[9-11] underwent surgery for the associated defect, but ALCA-PA was diagnosed perioperatively in one case, one year following the operation in one, and on autopsy in three. In our Case 1, ALCA-PA was detected one year after open heart surgery for VSD and PDA. The presence of VSD and PDA in this patient may have resulted in an increase in pulmonary artery pressure, thereby permitting the development of adequate collateral circulation.

The electrocardiogram is an important diagnostic tool in infants with ALCA-PA, often demonstrating anterior, anteroseptal or anterolateral myocardial ischemia and infarction patterns[12]. Our Case 2 displayed anterior myocardial infarction characterized by "Q" waves in leads I, AVL, V_{4-5}, and typical ST changes, while Case 3 had a lateral myocardial infarction pattern.

Echocardiography has proved to be useful in the definitive noninvasive diagnosis of ALCA-PA. Two-dimensional echocardiographic findings o ALCA-PA include failure to visualize the aortic origins of two separate coronary arteries, demonstration of a dilated RCA, and direct visualization of the LCA originating from the main pulmonary artery[13-15]. Retrograde flow through the anomalous LCA towards the pulmonary artery can be demonstrated by pulsed wave and color flow Doppler in the parasternal short-axis view[16-18]. Another finding that should alert the echocardiographer to the diagnosis of ALCA-PA is detection of turbulent and continous flow by pulsed wave and color flow Doppler in the interventricular septum. This finding was present in two of our patients (Case 1 and 2) in addition to the presence of a dilated RCA and failure to visualize the aortic origin of the LCA. The importance of this finding has recently been emphasized by others[19]. In Case 3, turbulent flow was not detected in the interventricular septum, but flow in the LCA towards the pulmonary artery was clearly visualized.

The ideal treatment of ALCA-PA is early surgical intervention before myocardial infarction occurs, but unfortunately all cases in infancy come to medical attention only after myocardial ischemia or infarction have occurred. Numerous operative techniques described for the treatment of patients with ALCA-PA include ligation of the LCA, subclavian-to-LCA anastomosis, reimplantation of the ostium of the LCA onto the aorta, saphenous vein by-pass grafting and creation of an aortopulmonary tunnel (Takeuchi procedure)[20-25]. All three cases in this report underwent the Takeuchi procedure.

In conclusion, we would like to emphasize that in the differential diagnosis of unexplained heart failure or cardiomyopathy in infancy and in asymptomatic children under investigation for the presence of precordial continuous murmurs, ALCA-PA should be considered and the coronary arterial anatomy should be carefully delineated by echocardiography. Failure to visualize the aortic origin of the LCA, together with demonstration of a dilated RCA turbulent and continuous flow in the interventricular septum with pulsed wave and color flow Doppler, are invaluable echocardiographic fingins for the diagnosis of ALCA-PA.

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NON – INVASIVE DIAGNOSIS AND MANAGEMENT OF CORONARY ARTERIOVENOUS FISTULA*

A Case Report

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SUMMARY: Akçoral A, Tavlı V, Kozan M, Ergene O, Tavlı T, Ünal N. (Departments of Pediatric Cardiology and Cardiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Noninvasive diagnosis and management of coronary arteriovenous fistula. A case report. Turk J Pediatr 1997; 39: 137-141.

Coronary arteriovenous fistulas are rare anomalies resulting in abnormal communication between the coronary artery and any chamber of the heart. An asymptomatic patient was referred for evaluation of her murmur. Two-dimensional and color Doppler echocardiographic evaluation revealed an enlarged left main coronary artery. A retrograde, eccentric small jet was found within the right ventricular outflow tract at the pulmonary artery valvular level allowing us to detect the entrance site of the fistula. The diagnosis was confirmed by cardiac catheterization and angiocardiography. Although our case was asymptomatic, the decision to perform cardiac surgery was made because of the aneurysmatic appearance of the left coronary artery. In our opinion, visualization of coronary arteries by two-dimensional echocardiography, together with additional information obtained from the Doppler examination, provides an excellent technique for the noninvasive diagnosis of coronary artery fistula. *Key words: coronary arteriovenous fistula, echocardiography.*

Coronary artery anomalies may be classified into three major groups, including anomalies with a shunt, anomalies without a shunt and congenital aneurysms and ectasia. Coronary artery fistulas are abnormal coronary artery communications that may involve any chamber and either or all coronary arteries[1]. In large series, the incidence has been reported to be less than 0.2 percent[2]. More than 90 percent of the communications are to the right side of the heart. Occasionally, both coronary arteries may participate in the fistula. Large shunts are particularly prevalent when the fistula terminates in the atrial chamber[3].

Case Report

An eight-year-old, asymptomatic girl was referred to our outpatient clinic for a murmur. Her growth parameters were at the 50th percentile. Her blood pressure and heart rate were normal, but a continuous murmur was heard at the 3rd left

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intercostal space. Her EKG and telecardiography were normal. Segmental echocardiographic examination was obtained with Acuson-128 and 5 and 7 MHz transducers. The coronary artery anatomy was examined mainly in the parasternal short-axis view with the use of high-frequency transducers. In the parasternal short-axis plane, the aortic valve was seen to be flanked by the tricuspid valve on the left, and by the right ventricular outflow tract and pulmonary artery on the right (Fig. 1). Two-dimensional and Doppler echocardiographic evaluation revealed an enlarged left main coronary artery and a small color jet streaming retrograde mainly in diastole at the pravalvular level within the right ventricular outflow tract. The latter finding was considered as the site of the fistulous connection as seen in Figure 1. Right and left heart catheterization was performed to evaluate the magnitude of shunting and to demonstrate the coronary arteries selectively. Oxygen saturation did not show a significant step-up in the right ventricular outflow tract or the main pulmonary artery. Left- and right-sided pressures were normal. Cineangiographic films were obtained using Toshiba DF-P50 at 50 frames/sec with the DVM mode at 256 x 516 pixel density. Aortic root and selective left and right coronary artery injections showed a tortuous, ectasic main left coronary artery fistulating into the right ventricular outflow tract at the paravalvular level opacifying the main pulmonary artery (Fig. 2). The right coronary artery was normal.

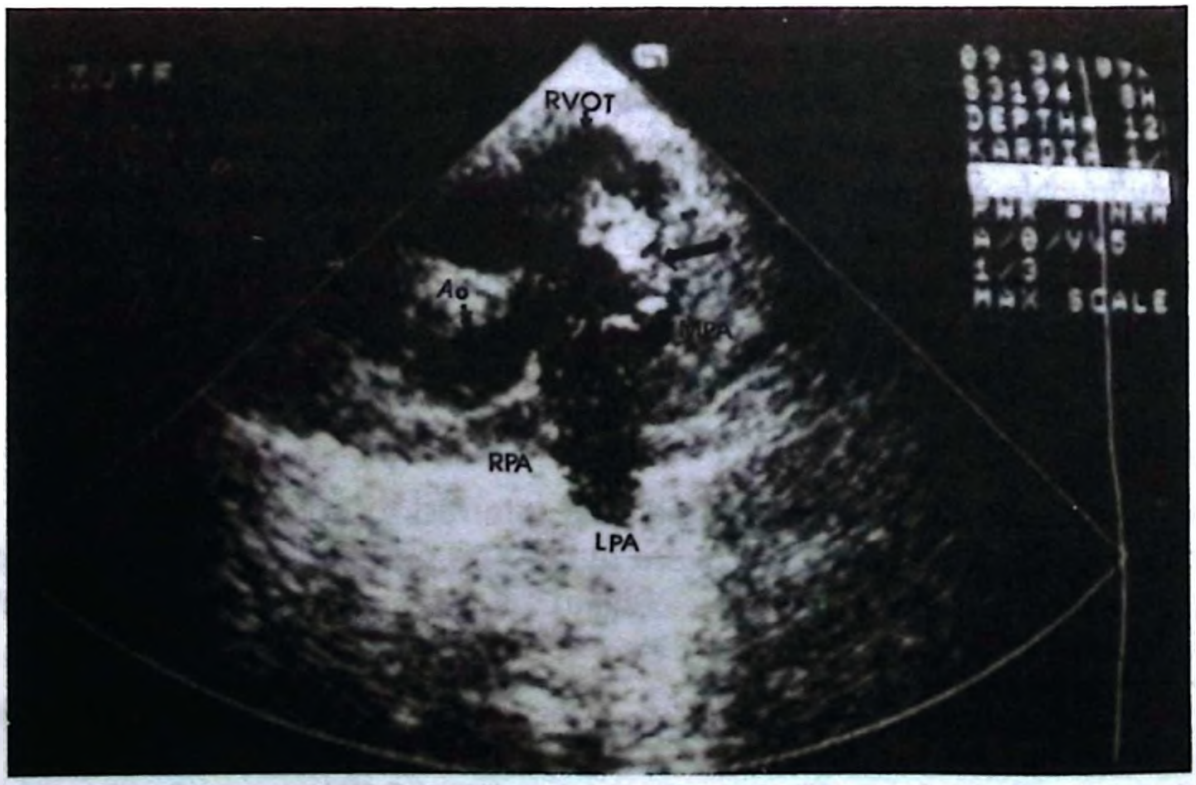

Fig. 1: Doppler color flow imaging of the left coronary artery fistulating into the right ventricular outflow tract in the parasternal short-axis view. The large arrow indicates the site of entrance of the fistula, producing a yellow aliasing jet area. Ao: aorta, MPA: main pulmonary artery. LPA: left pulmonary artery, RPA: right pulmonary artery, RVOT: right ventricular outflow tract.

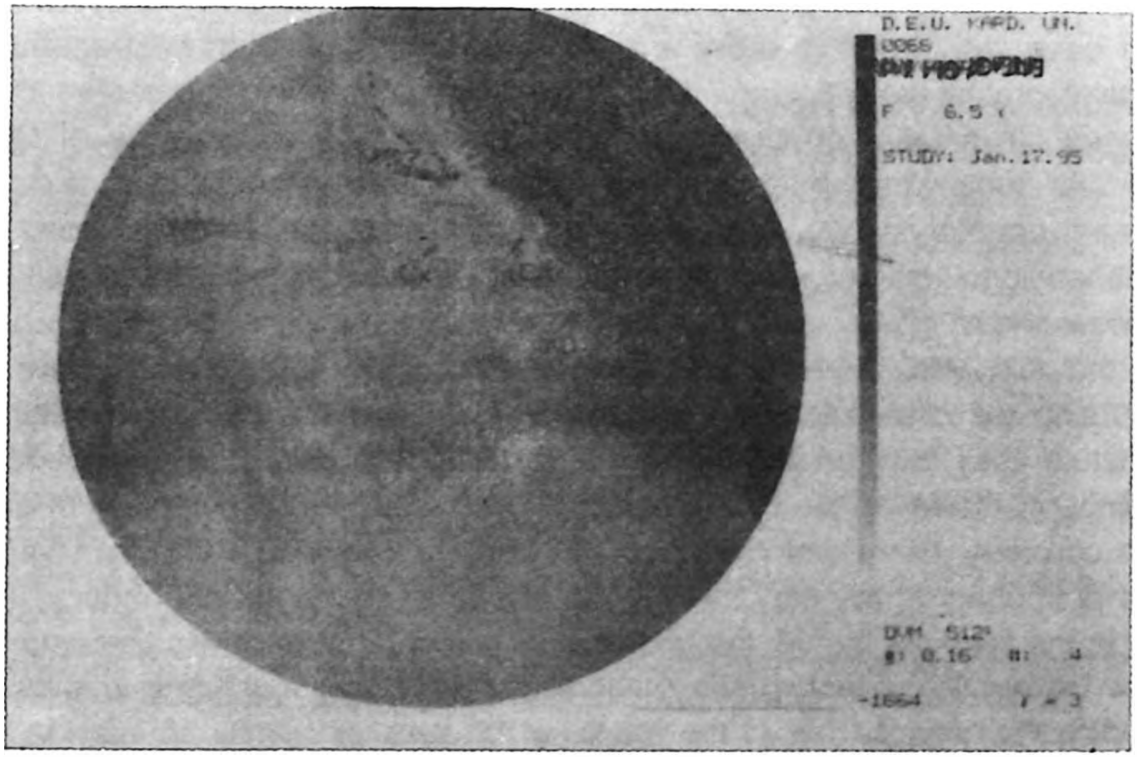

Fig. 2: Selective left coronary artery injection in the 45-degree, right anterior oblique projection shows an ectasic left main coronary artery giving rise to a thin segment which opacifies the pulmonary artery. The large arrow indicates the entrance site of the fistula into the right ventricular outflow tract at the pravalvular level. The fistulous jet is outlined with black dots. Cx: circumflex branch of the left coronary artery (LCA), LAD: left anterior descending branch of the LCA, MPA: main pulmonary artery. The large arrow indicates the entrance site.

Discussion

Coronary artery fistulas are rare anomalies. The incidence in our department was 1/4000 between July 1991 and January 1995. The incidence in large adult series has been reported at 0.2 percent[2].

The differential diagnosis in an acyanotic patient with a continuous murmur includes patent ductus arteriosus (PDA), aorto-pulmonary window, ventricular septal defect with aortic insufficiency, arterio-venous malformation of the chest wall or lung, and coronary artery fistula. The location of the maximum intensity of the continuous murmur gives a clue as to the appropriate clinical diagnosis[3]. In our case, the murmur was best heard at the left 3rd intercostal space, excluding the possibility of a PDA. Echocardiography and angiocardiography clearly differentiate such diagnoses.

The coronary artery anatomy may be especially important in certain forms of complex congenital heart disease, such as tetralogy of Fallot and transposition of the great arteries. Coronary artery anomalies have been reported to be detected by echocardiography[4,5]. Trans-esophageal echocardiography may be necessary

in older and overweight people in order to obtain efficient coronary artery imaging. In our case, the coronary artery anatomy was best deliniated by transthoracic echocardiography using 5 and 7 MHz transducers mainly in the parasternal short-axis view. In smaller children, the subcostal four-chamber view of the left ventricular outflow tract may be an adjunctive plane for visualization of portions of the left coronary artery. A coronary artery fistula should be suspected when two-dimensional imaging of the main coronary arteries in the parasternal short-axis view shows one coronary artery dilated while the other coronary artery is of normal size. Multiple two-dimensional echocardiographic planes were used in coursing the dilated left coronary artery in the parasternal short-axis plane. The fistula itself may be difficult to image despite a very carefully performed examination. However, the two-dimensional echocardiographic image of dilation of the coronary artery and detection of turbulent flow within the right ventricle or the pulmonary artery may identify the site of the fistulous connection. If flow through the fistula is heavy, the chamber or vessel that receives the fistula can be seen to be dilated. In our case, meticulous color Doppler imaging was essential for finding the entrance site of the fistula, which was very small as seen in Figure 1. The diagnosis was confirmed by angiocardiography, which showed prompt opacification of the right ventricular outflow tract during aortic root and selective coronary arteriography. The echocardiographer must remember that in order to position the Doppler beam in a parallel orientation to flow, an unusual position and angle may become necessary.

Coronary artery fistulas are generally reported as isolated lesions. Coronary artery-pulmonary artery communication may develop later in life in response to infection or profound cyanosis[6]. In the case presented, the left coronary artery was involved, which is relatively rare compared to right coronary artery fistulas[7]. Although the fistula in this case was thought to be congenital, the aneurysmatic appearance of the main coronary artery may suggest a previous Kawasaki disease episode that may have been misinterpreted as an allergic reaction, as learned from the patient's history.

Coronary arteriovenous fistulas have been reported to close spontaneously[8] Complications include infective endocarditis, myocardial ischemia, dysrhythmia and rupture[9-12]. Large fistulas may create hemodynamic overloading, resulting in heart failure. Aneurysmatic fistulas may gradually enlarge over time, compressing relatively softer cardiac structures or obstructing systemic or pulmonary venous return. Thrombosis and embolizations may occur. Myocardial ischemia may ensue due to the steal syndrome. Surgical treatment is recommended before any complications occur[13]. Clamping and ligating of the fistula is generally sufficient although, bypass operation may occasionally be necessary. Mortality is reported as zero to four percent[11, 13]. Microcoil embolization

and balloon occlusion of the fistula have recently been used successfully[14-16]. Our patient remains asymptomatic six months post-operatively.

In conclusion, although more than 50 percent of patients remain asymptomatic, coronary-arteriovenous fistulas require special attention in terms of possible complications if left untreated. Besides angiocardiography, which is the gold standard, echocardiography is considered to be a valuable diagnostic tool in the diagnosis of coronary artery anomalies in pediatric patients.

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PERIPHERAL ARTERIAL THROMBOSIS IN SYSTEMIC LUPUS ERYTHEMATOSIS AND NEPHROTIC SYNDROME: POSSIBLE ASSOCIATION WITH PROTEIN S DEFICIENCY*

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SUMMARY: Beşbaş N, Doğru D, Bakkaloğlu A, Özen S, Balkancı F, Saatçi Ü. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Peripheral arterial thrombosis in systemic lupus erythematosus and nephrotic syndrome: possible association with protein S deficiency. Turk J Pediatr 1997; 39: 143-147.

Arterial thrombosis in systemic lupus erythematosus (SLE) and nephrotic syndrome have been infrequently reported. A 16-year-old boy with SLE and longstanding nephrotic syndrome presented with peripheral arterial thrombosis when his lupus was at an inactive stage. He did not have antiphospholipid antibodies but had low serum antithrombin III and protein S levels. We suggest that the thrombotic event is not related to antiphospholipid antibodies but to nephrotic syndrome and possibly to acquired protein S deficiency. *Key words: arterial thrombosis, systemic lupus erythematosus, nephrotic syndrome, protein S deficiency.*

Thrombotic episodes have been reported as one of the manifestations of systemic lupus erythematosis (SLE), although arterial thromboses are less common[1]. Although vasculitis may play a role, there is increasing evidence that antibodies against phospholipids, namely anticardiolipin antibodies or lupus anticoagulant, may initiate clotting. On the other hand, thrombotic complications are also observed in nephrotic syndrome and are believed to be secondary to alterations in the coagulation and thrombolytic pathways[2]. Arterial thrombosis is much less common than venous thrombosis in this situation as well[3].

We report a patient with SLE and longstanding nephrotic syndrome presenting with peripheral arterial thrombosis who did not have antiphospholipid antibodies but had low serum levels of antithrombin-III (AT-III) and protein S.

Case Report

This 16-year-old boy was diagnosed with SLE four years previously with the following features: malar rash, erythematous macules on the extremities and trunk, fever, hepatosplenomegaly, proteinuria, cellular casts in the urine, anemia

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(Hb: 6.6 g/dl), low levels of C3 (37 mg/dl N: 60-120) and C4 (7 mg/dl, N: 20-40), positive antinuclear antibody and high anti-DNA titer (150 U/ml, N: 0-25). He was treated with methylprednisolone, cyclophosphamide and furosemide. While he was on maintenance therapy with low-dose prednisone, captopril and azathioprine, he was admitted to the hospital with a one-week history of dyspnea, edema of the face, abdomen and legs, and pain in the left hand.

Physical examination on admission revealed a dyspneic boy with a pulse of 128/min and respiratory rate of 32/min. His blood pressure was 180/140 mmHg. He had edema of the face, prominent on the eyelids, and of the scrotal region. His left arm and hand were cold and cyanotic, and the radial pulse of the same extremity was not palpable. He was unable to extend his left arm fully because of severe pain.

Laboratory examination revealed a white cell count of 9,600/mm^3 and platelet count 275,000/mm^3. His hemoglobin was 11.3 g/dl and hematocrit was 35 percent. Heavy proteinuria, leukocytes, red blood cells and granular casts were noted in the urine examination. Protein loss in the urine was calculated as 5 g/m^2/day. His total serum protein and albumin were 3.6 and 1.5 g/dl, respectively. The chest x-ray revealed pulmonary edema. The serum C3 level was 51 mg/dl (N: 60-120) and the C4 level was 19 mg/dl (N: 20-40). The antinuclear antibody test was negative. Anti-DNA was 6.7 IU/ml (N: 0-7). Prothrombin time (PT) (13 sec), partial thromboplastin time (PTT) (35 sec) and the test for fibrin degradation products were within normal limits. Anticardiolipin antibodies were measured by a sandwich ELISA kit (Biolab Malakit Cardiolipin isotyping kit). Results of the IgM and IgG fractions of anticardiolipin were expressed as MPL and GPL units, respectively. In our patient IgM and IgG fractions were less than 1 MPL U/ml (N: < 5) and less than 1 GPL U/ml (N: < 9). The patient had a normal protein C level of 105 mg/dl (N: 60-120) but a low protein S level of 27 (N: 73-210) as well as a low AT-III level of 13 mg/dl (N: 18-28).

Doppler ultrasonography revealed the absence of flow in the left brachial, radial and ulnar arteries. An aortogram and selective arteriogram via the right femoral route demonstrated an obstruction at the juncture of the left axillary left subclavian arteries (Fig. 1). An echocardiogram revealed normal heart valves without vegetations or intracardiac thrombus.

As the patient's renal function gradually deteriorated, hemodialysis was applied every other day via a subclavian catheter for two weeks. He was treated with rheomacrodex, vasodilators, furosemide, cyclophosphamide, prednisone and antiaggregants, and his complaints gradually subsided. After the 15^{th} day of treatment, the peripheral pulses of the left arm became palpable and the clinical findings in the same arm improved.

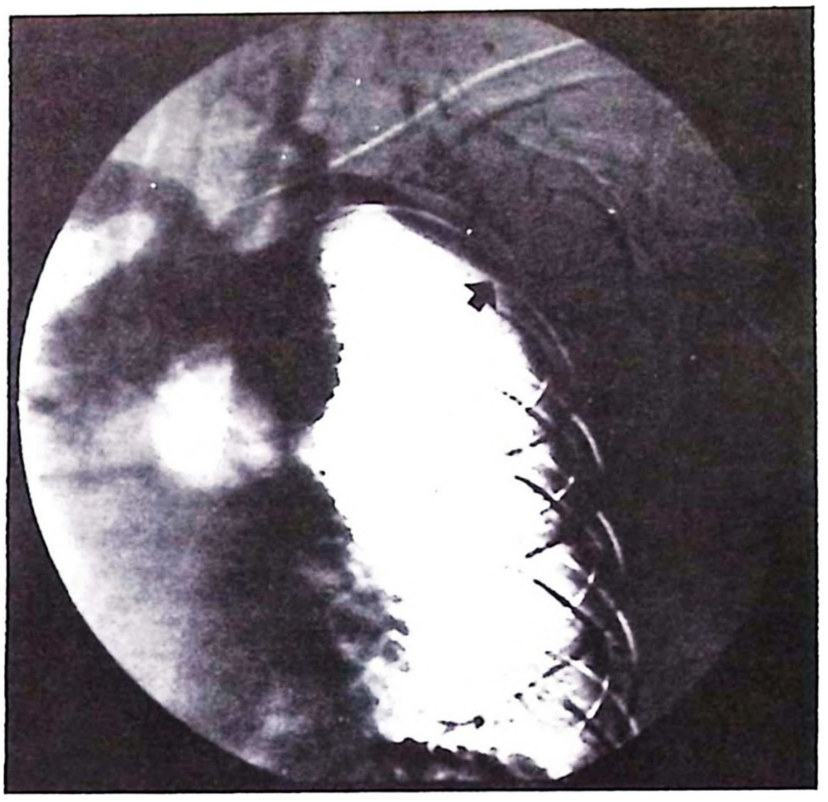

Fig. 1: Complete occlusion of the proximal portion of the left axillary artery and constriction at he origin of the brachial artery.

Discussion

The reported patient was diagnosed with SLE according to the American Rheumatism Association (ARA) criteria. Four years after the initial diagnosis he presented with arterial thrombosis when his lupus was at an inactive stage; however, he had longstanding nephrotic syndrome.

We evaluated 56 children with SLE who were seen at our center between 1978 and 1990. All eligible patients met at least four of the ARA's revised criteria for SLE. At the time of diagnosis, renal involvement was found in 69 percent of cases. None of the patients had a thrombotic event except a girl with SLE who had chorea as the initial manifestation and subsequently developed thrombotic events associated with the presence of antiphospholipid antibodies[4].

Thromboses may complicate the course of lupus. Asherson et al.[5] reported that in SLE patients with anti-phospholipid antibody (aPL), disease activity was an important predictor for the development of thrombotic events. Apart from aPL, there are other risk factors present in lupus, including depressed release of plasminogen activator and possibly antagonists of plasmin, decreased plasma concentration of free protein S and increased levels of von Willebrand factor as well as increased monocyte-derived procoagulant activity. Furthermore, when a child with lupus develops nephrotic syndrome, the thrombogenic potential of the

alterations in platelet function and plasma coagulation factors seen in nephrotics are added to the thrombogenic stimuli of lupus[6]. Our patient did not have active SLE at the time of the thrombotic event. Furthermore, he lacked aPL, which is one of the most important determinants of thrombotic events in SLE.

Thrombotic events have been previously reported in nephrotic patients and have been associated with acquired protein S deficiency[7]. Low AT-III levels together with other factors are a well-recognized feature of nephrotic syndrome and are believed to be due to excess urinary loss of AT-III[8]. In one study, AT-III levels were found to be normal and decreased in both primary nephrotic syndrome and primary amyloidosis, and it was concluded that AT-III levels were not only altered by urinary loss, but were also affected by the synthesis, degradation and distribution rate[9]. We suggest that our patient's arterial thrombotic event took place in the course of nephrotic syndrome with low protein S and AT-III levels. On the other hand, reduced free protein S concentrations have been suggested to be an important factor in the pathogenesis of venous thromboembolism associated with lupus anticoagulant as well[10]. Other factors for thrombosis in our patient may have been dehydration caused by diuretics plus corticosteroid therapy and hypoalbuminemia, which lead to a further decrease in intravascular volume.

We conclude that in SLE patients with longstanding nephrotic syndrome, especially those on diuretic and corticosteroid therapy, additional care must be taken to prevent a thrombotic event-even in those without antiphospholipid antibodies. In such cases, early diagnosis and medical treatment may avoid the need for surgical intervention.

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