THE TURKISH JOURNAL OF PEDIATRICS

VOLUME: 38 NUMBER: 2 APRIL - JUNE 1996

A joint publication of the
Turkish National Pediatric Society
and the Hacettepe University
Institute of Child Health

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This Journal is listed in Current Contents, Index Medicus, Abstracts on Hygiene and Communicable Diseases, Tropical Diseases Bulletin, the CAB Abstracts database and the Excerpta Medica database EMBASE.

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GENE KLINGBERG

İhsan Doğramacı MD, DSc, LLD, FVCP (Lond)[*]

In 1946, when I was working in the United States as a pediatric fellow at the St. Louis Children's Hospital of Washington University, I had the good fortune of meeting Dr. Gene Klingberg, a young and dynamic member of the teaching staff. Our supervisor, Professor Alexis F. Hartmann, very frequently called on Dr. Klingberg for his opinion. At the time, Klingberg was one of the youngest people on the staff. Professor Hartmann, in addition to being known the world over, was a man of marked human feelings. He was well in advance of his times. In the America of the 1940s, especially in the southern states, racism was at a peak. Afro-Americans were hospitalized on separate wards, or were forced to be examined and hospitalized in separate institutions. Even public toilets were segregated for use by white and colored people. In busses blacks sat in the back rows of seats while the front rows were reserved for whites. Even if there were empty seats in the section reserved for whites, black people had to stand at the rear. In this climate there was an outbreak of polio in St. Louis. Although there were empty beds in the white children's ward, sick colored youngsters were not being admitted. Seeing this, one day Dr. Hartmann called Klingberg and told him, "This segregation must be brought to an end. We are going to open these wards to all children, no matter what their color".

Conservative members of the teaching staff were in opposition. In fact, Washington University, as a private institution, was in danger of losing its funding. But with Klingberg's support this change was brought about. These events increased my already great respect and admiration for Dr. Klingberg. It was only many years later that de-segregation began in the United States as a whole.

When in the 1950s I was in the process of establishing a children's clinic, institute and hospital, even more important than obtaining buildings and equipment was the question of finding the proper instructors to train the students and residents. With this in mind, while selecting outstanding medical graduates from the İstanbul and Ankara Medical Schools, I was busy trying to arrange for them to have good modern pediatric training. Part of this plan was to send some of them abroad for training and to bring teachers to Turkey from other countries. This was to

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occur in two stages. At that time, most doctors who were doing specialization in the Turkish university hospitals were not paid, so apart from a few hours doing rounds each day, they spend the rest of their time working in schools or on construction sites or as salesman for pharmaceutical firms. And at the end of the prescribed time period they were certified as specialists. With the establishment of Hacettepe, it was our intention to start a residency program as practiced in the United States. I invited Dr. Joe Wray, whom I had met in the United States, to help set up the program and serve as chief resident. He remained for four and a half years. By that time I had been back from the United States for six or seven years. During that time I had been so involved with setting up an institution that I had not had the time to do any research. For this reason, I at once thought of inviting Dr. Gene Klingberg to come and help train the residents. At first he hesitated and said, "Aren't you the best person for this task?" I replied that if I had thought so, I would not have asked him to come. So he agreed to come for six months. When he got to Ankara and sensed our excitement in establishing Hacettepe, he became equally enthused and stayed for a year and a half. He put his stamp on every area of pediatrics, in particular pediatric hematology. And he said at the inauguration of the hospital, "This institution will be on a level with the best in the United States".

Gene Klingberg has passed away, but his memory will live on in our hearts as one of the founders of Hacettepe.

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GENE KLINGBERG*

A Dedicated Teacher and An Excellent Physician

*Şinasi Özsoylu MD***

Dr. Klingberg arrived in Ankara on April 1, 1957, when İhsan Doğramacı (originally Hacettepe) Children's Hospital was under construction. Dr. Klingberg and Dr. Joe Wray (who was our first chief resident) took us (Dr. Ahmet Ajun, Dr. Sevinç Oral and me) to Telsizler Health Center (a slum area in those days) six days a week to teach us modern pediatric techniques in an outpatient setting. Although this was a new way of teaching for our mentors, Dr. Klingberg easily adapted himself and us to an uneasy situation. Although we complained sometimes about the conditions, Dr. Klingberg always did his best without showing any sign of disappointment. In addition to patient care and environmental studies we had our first Journal Club experiences in that health center. Because laboratory facilities were not available, we were taught to use simple methods including the growth chart for evaluation of child nutrition. Ear, nose, throat and eye ground examinations became a routine part of the physical examination in pediatrics with Dr. Klingberg's astonishing patience and firm insistence.

Although we were very fond of inpatient teaching, in a relatively short time we began to understand the importance of outpatient care. When I look back I can see that the hospital was not ready for inpatient care. We were very fortunate to have had mentors like Dr. Klingberg and Dr. Wray, who knew the best patient care in rural settings. In a short time we became aware that Dr. Klingberg's questions were the best stimulation for us. The first exchange transfusion was also performed in Turkey by Dr. Klingberg and Dr. Wray in an obstetric theater at Ankara Medical Faculty in May 1957.

In June 1957, Dr. Klingberg and Dr. Wray took us to the mother and child center at Yenimahalle where they demonstrated how to practice pediatrics in an urban setting. The importance of routine immunizations was shown to us by analyzing cases with polio sequelae and/or diphtheria, which were prevalent in Turkey at that time.

When the outpatient clinic was completed, Dr. Klingberg began teaching us with "snap diagnosis". He taught us with simple laboratory tests, including radioscopic

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examination. Hand-washing became routine after the examination of each patient. With his patience, every resident began to operate the Beckman spectrophotometer, and the Van Slyke for gas analysis. Determination of bilirubin, glucose, calcium, etc., became a routine part of the pediatric residency program in this new hospital. Some patients were visited at home since inpatient care was not yet available. These visits were helpful for detection of the source of some infections and for evaluation of our patients' living conditions.

Through Journal Club discussions we learned to criticize our so-called classical knowledge. Although Dr. Klingberg did not know Turkish, under his guidance and questioning, history-taking became the most important part of patient evaluation.

On Sunday, July 8, 1957, I had a call about the admission of a premature baby (Levent) with hyperbilirubinemia. On my arrival at the hospital I found Dr. Klingberg busy opening boxes to take out an incubator. With the improvement of this very first premature baby, several premature infants were brought to the hospital. For that reason our hospital began to operate by opening a premature nursery. In a short period of time the "Observation Ward" had to be opened because of some referrals from other hospitals. Dr. Klingberg used to change diapers during rounds because of the shortage of nurses, which was a good example to all of us.

Since Dr. Doğramacı was extremely busy with administrative work, including funding of the hospital, teaching was basically dependent on Dr. Klingberg's effort. He also established biochemistry and hematology laboratories as well as the first blood bank in a hospital in Turkey. Dr. Klingberg and Dr. Wray were available to the residents virtually 24 hours a day, seven days a week, except for 7:30 to 9:30 P.M. every Thursday when Dr. Klingberg went to church.

Dr. Klingberg's ward rounds were an exceptional experience for all residents. Following inpatient admissions, mortality conferences, patient discussions and X-ray meetings were started under his guidance. He was a one-man army for the success of a new hospital.

Dr. Klingberg came to Turkey for six months, but fortunately stayed in this hospital 17 months until September 1, 1958. Four years after his return to St-Louis Children's Hospital he was appointed as Professor and Head of the Department of Pediatrics at the West Virginia School of Medicine at Morgantown. He dedicated himself to his children and wife (Mrs. Gene Klingberg) because of her chronic disabling disease. He served as Professor Emeritus following his retirement in 1986 from Morgantown.

After marrying his second wife Rita, he moved to Tulsa, Oklahoma, where he helped with the education of medical students until his death on May 20, 1995.

Dr. Klingberg kept his interest in İhsan Doğramacı Children's hospital and in his former residents. He visited İhsan Doğramacı Children's Hospital in 1974, 1983 and 1989 and followed his former residents in Turkey as well as abroad.

As his former residents at İhsan Doğramacı Children's Hospital, we all owe him a lot, not only with regard to patient care, stimulation, teaching and being so thoughtful and kind to us, but also in terms of helping this hospital function smoothly and establishing the laboratories. We learned a great deal from Dr. Klingberg in every respect. He was a great man and excellent physician and teacher. He showed interested in his residents in every respect. With his death we lost a great friend, and the medical world lost one excellent example of a physician and teacher.

The Turkish Journal of Pediatrics 1996; 38: 149-153

THE PREVALENCE OF ASTHMA AND OTHER ALLERGIC DISEASES IN A PROVINCE OF TURKEY*

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SUMMARY: Küçüködük Ş, Aydın M, Çetinkaya F, Dinç H, Gürses N, Saraçlar Y. (Department of Pediatrics, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey). The prevalence of asthma and other allergic diseases in a province of Turkey. Turk J Pediatr 1996; 38: 149-153.

To document the prevalence of asthma and other allergic disorders among children, a questionnaire study involving 3,118 children aged six to 14 years was done. The overall prevalence of allergic diseases was 27.4 percent and the prevalence of each disorder was as follows: rhinitis 11 percent, asthma 10.2 percent, conjunctivitis 7.1 percent, and skin diseases 6.3 percent. Atopic diseases were reported most commonly among the families of children with allergic rhinitis. When compared with internal regions of Turkey, the prevalence of allergic diseases was found to be very high. It was concluded that allergic diseases are an important health problem among children in our region. *Key words: allergic diseases, asthma, childhood, prevalence.*

Asthma and other allergic disorders are a leading cause of morbidity in children all over the world[1-3]. The prevalence of asthma and other allergic diseases is increasing in industrialized countries[4-6], but the situation in developing countries is not known.

In this report the prevalence of asthma and other allergic diseases in Samsun, a province of Turkey in the Black Sea region, was investigated with an internationally standardized questionnaire.

Material and Methods

A total of 3,500 children aged six to 14 years were chosen for the survey. The study was done in seven elementary schools located in districts with different socioeconomic levels. A standard questionnaire, which was modified from three worldwide known questionnaires[7-9], was distributed to the students for completion by their parents. The questionnaire included questions related to demographic data, symptoms of bronchial hyperreactivity and asthma, allergic rhinitis, allergic conjunctivitis, skin allergies and any atopic disease in a first-degree relative. In

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.the questionnaire, hay fever or seasonal allergic rhinitis was defined as itchy, runny nose associated with paroxysms of sneezing, and itchy, allergic conjunctivitis as runny eyes in the spring and summer. Skin allergies were likened to any itchy, red rash in the crease of elbows and knees and on the cheeks. The presence of asthma was indicated by an affirmative response to the following questions: 1. Has your child been diagnosed with asthma by a doctor? 2. Do any of the following make your child start to wheeze or cough: flowers or trees, animals, exercise, smoke, cold or foggy air? 3. Does your child cough frequently during the night? 4. Does your child use any anti-asthmatic drug? 5. Does your child produce sputum in the morning? Associations between the reported symptoms and the putative risk factors-age, sex, atopy, parental allergic symptoms, skin allergies and asthma were assessed using chi-square test with SPSS (The Statistical Package for the Social Sciences) statistical program. A p level < 0.05 was considered to be statistically significant.

Results

A total of 3,118 replies from 1,514 females and 1,604 males were received from the 3,500 questionnaires sent, representing an overall response rate of 89 percent. The mean age of the subjects was 9.3 ± 1.5 years (range 6-14 years). The age and sex distribution of the subjects are shown in Table I. The overall prevalence of allergic diseases was 27.4 percent, and the prevalence of each diseases was as follow: rhinitis 11 percent, asthma 10.2 percent, conjunctivitis 7.1 percent and skin allergies 6.3 percent (Table II). In one-third of children with rhinitis, other disease were present as well. The disease associations were as follows: skin allergies plus rhinitis was diagnosed in 138 subjects (4.4%). rhinitis plus conjunctivitis in 135 subjects (4.3%), rhinitis plus asthma in 110 subjects (3.5%), skin allergies plus asthma in 79 subjects (2.5%) and skin allergies plus conjunctivitis in 115 subjects (3.7%). No significant difference in age or gender was found among either asthmatic or healthy subjects (X^2 test, $p > 0.05$). The children with rhinitis had the highest rate of parental histories of allergic symptoms percent (Table III). A positive family history of the same atopic disease was reported in 40.6 percent of asthmatic children, in 38 percent of children with rhinitis, in 41.6 percent of children with skin allergies and in 35.6 percent of children with conjunctivitis (Table III).

Table I: Age and Sex Distribution of the Subjects

Age Group	Girls (%)	Boys (%)	Total (%)
6-7 years	219 (14.6)	274 (17.0)	493 (15.8)
8-9 years	545 (36.2)	566 (35.0)	1,111 (35.6)
10-11 years	651 (43.3)	659 (40.8)	1,310 (42.2)
12-14 years	88 (5.9)	116 (7.2)	204 (6.5)
Total	1,503 (100)	1,615 (100)	3,118 (100)

Table II: Distribution of Disorders According to Age and Sex

Diagnosis	Girls (%)	Boys (%)	Total (%)
Asthma	118 (45.9)	138 (54.1)	256 (8.2)
Rhinitis	197 (46.5)	227 (53.5)	424 (13.6)
Conjunctivitis	154 (49.2)	158 (50.8)	312 (10.0)
Skin allergies	198 (49.5)	201 (50.5)	399 (12.8)

Table III: Parental Allergic Symptoms and Reported Allergic Diseases in Subjects

	Parental Allergic Symptoms		
Clinical Diagnosis in Subjects	Asthma	Rhinitis	Skin Allergies
Rhinitis (n: 427)	162 (38%)	159 (37.2%)	95 (22.2%)
Skin allergies (n: 399)	166 (41.6%)	130 (32.6%)	107 (26.8%)
Conjunctivitis (n: 312)	111 (35.6%)	131 (42%)	72 (23%)
Asthma (n: 256)	104 (40.6%)	86 (33.6%)	54 (21.1%)

Discussion

The lack of a gold standard for the diagnosis of asthma and other allergic diseases makes accurate assessment and comparison of prevalence rates between populations difficult[10, 11]. Some studies have used similar survey methods in different areas and found evidence that developed countries and communities seem to have more asthma than those that are underdeveloped[12, 13].

Studies have recently been done in an attempt to document the prevalence of asthma and other allergic diseases in Turkey[14, 15].

A study with the same questionnaire done by Saraçlar et al.[14] in Ankara including 3,024 primary school children revealed the prevalence of asthma as 6.9 percent, allergic rhinitis as 11.7 percent, allergic conjunctivitis as 4.6 percent and allergic skin diseases as 2.6 percent. Another study with a different questionnaire by Kalyoncu et al.[15] reported higher prevalence. In the present study the overall prevalence of allergic diseases was 27.4%; allergic rhinitis was the most common clinical diagnosis and was usually associated with other allergic diseases. However, it is possible that none of these studies reflects the current prevalence of allergic diseases in our country, due to the geographic and socioeconomic differences in various regions of Turkey. It has been reported that the prevalence of asthma varies in different geographic locations[16, 17], but evidence is sparse owing to the lack of multicenter surveys using common protocols. Burr et al[16]. conducted a survey with the same questionnaire in 4,353 children living in defined areas of New Zealand, Wales, South Africa and Sweden and found the prevalence

of asthma as follows: 16.8 percent of children in New Zealand, 12.0 percent in Wales, 11.5 percent in South Africa and 4.0 percent in Sweden. These authors concluded that the prevalence of asthma in children showed geographical variation which is parallel to that of asthma mortality. Samsun is located in northern Turkey and the weather is rainier than in internal regions of Turkey. The discrepancy between data from Ankara and Samsun may result from climatic differences. Moreover, while it has been reported that asthma was more common in boys than in girls[18, 19], we found no significant difference between the genders ($p > 0.05$).

Studies of familial aggregation of asthma have shown an increased prevalence of asthma among first-degree relatives of an index subject[20, 21]. Sibbald et al.[20] reported an increased prevalence of asthma among first-degree relatives of asthmatic children compared with relatives of nonasthmatic children evaluated in a general practice. Foucard and Sjoberg[21] found that infants and children with wheezy bronchitis and a family history of asthma or allergy had twice the risk of developing persistent asthma of those without such a family history. In our study the least atopic diseases were seen in the families of children with asthma, and the most in the families of children with allergic rhinitis.

Increasing prevalence and mortality of asthma have been reported in several studies[22-24]. An increase of 28 percent in current asthma has been found among children six to 16 years of age in a survey in the United States[22]. A more significant increase (90%) has been reported between 1969 and 1982 in New Zealand[23]. Mortality from asthma reportedly increased 4.7 percent every year in the five to 34-year age group between 1974 and 1984 in England[24]. The increase in neither the prevalence nor the mortality can be explained precisely.

The evidence from this study suggests that asthma and other allergic diseases are important childhood health problems in Samsun, similar to some other places in the world, and we need more comprehensive and longitudinal studies to document the current prevalence of asthma and allergic dieases in Turkey.

REFERENCES

1. Evans R. Epidemiology and natural history of asthma, allergic rhinitis, and atopic dermatitis. In: Middleton E, Reed C (eds). Allergy: Principles and Practice (4th ed.) Vol. 2. St. Louis: Mosby-Year Book Inc, 1993: 1109-1136.
2. Leung R, Jenkins M. Asthma, allergy and atopy in southern Chinese school students. Clin Exp Allergy 1994; 24: 353-358.
3. Mutius EV, Fritzsch C, Weiland SK, et al. Prevalence of asthma and allergic disorders among children in United Germany: a descriptive comparison. Br Med J 1992; 305: 1395-1399.
4. Halfon N, Newacheck PW. Trends in the hospitalization for acute childhood asthma, 1970-1984. Am J Public Health 1986; 76: 1308-1311.
5. Kjellman B, Petterson R, Hensji B. Allergy among school children in a Swedish country. Allergy 1982; 37 (suppl 2): 5-6.

6. Lee DA. Winslow NR, Speight AN, Hey EN. Prevalence and spectrum of asthma in childhood. Br Med J 1983; 286: 1256-1258.
7. Epidemiology standardization project. Am Rev Respir Dis 1978; 118: 1-120.
8. Samet JM. A historical and epidemiological perspective on respiratory symptoms questionnaires. Am J Epidemiol 1978; 108: 435-446.
9. Helsing KJ, Comstock W, Speizer FE, et al. Comparison of three standardized questionnaries on respiratory symptoms. Am Rev Respir Dis 1979; 120: 1221-1231.
10. Robertson CF, Bishop J, Sennhauser FH, Mallol J. International comparison of asthma prevalence in children: Australia, Switzerland, Chile. Pediatr Pulmonol 1993; 16: 219-226.
11. Pearce N, Weiland S, Keil U, et al. Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: an international comparison using the ISAAC protocol. Eur Respir J 1993; 6: 1455-1461.
12. Waite DA, Eyles EF, Tonkins SL, O'Donnell TV. Asthma prevalence in Tokelauan children in two environments. Clin Allergy 1980; 10: 71-75.
13. Keeley DJ, Neill P, Gallivan S. Comparison of the prevalence of reversible airways obstruction in rural and urban Zimbabwean children. Thorax 1991; 46: 549-553.
14. Saraçlar Y, Yiğit Ş. Adalıoğlu G, Tuncer A, Tunçbilek E. Prevalence of allergic diseases in school children in Ankara (Turkish). Çocuk Sağlığı ve Hastalıkları Dergisi 1994; 37: 215-226.
15. Kalyoncu AF, Selçuk ZT, Karakoca Y, et al. Prevalence of childhood asthma and allergic diseases in Ankara, Turkey. Allergy 1994; 49: 485-488.
16. Burr ML, Limb ES, Andrae S, et al. Childhood asthma in four countries: A comparative survey. Int J Epidemiol 1994; 23: 341-347.
17. Andrae S. Axelson O. Björksten B, Fredriksson M, Kjellman NI. Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. Arch Dis Child 1988; 63: 473-478.
18. Mak H, Johnston P, Abbey H, Talamo RC. Prevalence of asthma and health service utilization of asthmatic children in an inner city. J Allergy Clin Immunol 1982; 70: 367-372.
19. Sears MR, Jones DT, Silva PA, et al. Asthma in seven year old children: a report from the Dunedin Multidisciplinary Child Development Study. NZ Med J 1982; 95: 533-536.
20. Sibbald B, Horn ME, Greeg I. A family study of the genetic basis of asthma and wheezy bronchitis. Arch Dis Child 1980; 55: 354-357.
21. Foucard T, Sjoberg O. A prospective 12-year follow-up study of children with wheezy bronchitis. Acta Paediatr Scand 1984; 73: 577-583.
22. Halfon N, Newacheck PW. Trends in the hospitalization for acute childhood asthma, 1970-1984. Am J Public Health 1986; 76: 1308-1311.
23. Mitchell EA. Increasing prevalence of asthma in children. NZ Med J 1983; 96: 463-464.
24. Burney PG. Asthma mortality in England and Wales: evidence for a further increase, 1974-1984. Lancet 1986; 2: 323-326.

The Turkish Journal of Pediatrics 1996; 38: 155-159

EFFICACY OF OXYBUTYNIN, PSEUDOEPHEDRINE AND INDOMETHACIN IN THE TREATMENT OF PRIMARY NOCTURNAL ENURESIS*

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*Ayşın Bakkaloğlu MD***, Nesrin Beşbaş MD****

SUMMARY: Varan B, Saatçi Ü, Özen S, Bakkaloğlu A, Beşbaş N. (Nephrology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Efficacy of oxybutynin, pseudoephedrine and indomethacin in the treatment of primary nocturnal enuresis. Turk J Pediatr 1996; 38: 155-159.

The efficacy of oxybutynin, pseudoephedrine and indomethacin treatment was investigated in 29 patients with primary nocturnal enuresis. Patients were randomly assigned to either oxybutynin (1st group, n = 9), pseudoephedrine (2nd group, n = 11) or indomethacin (3rd group, n = 9) treatments.

Oxybutynin and indomethacin did not cause a statistically significant difference in the number of dry nights ($p > 0.05$), but patients treated with pseudoephedrine had a significant increase in the number of dry nights ($p < 0.05$). Five patients in the oxybutynin and one patient in the indomethacin group experienced side effects. None of the patients in the pseudoephedrine group had any complaints with the drug. We therefore conclude that pseudoephedrine can be an alternative in the treatment of primary nocturnal enuresis.
Key words: enuresis, oxybutynin, pseudoephedrine, indomethacin.

Enuresis is a troublesome condition in childhood, affecting as many as 15-20 percent, five percent and one percent of five-year-olds, 10-year-olds and 15-year-olds, respectively[1]. The benign nature and high spontaneous cure rate of 15 percent annually necessitates a careful assessment of the risk-benefit ratio of therapy[2]. Tricyclic antidepressants and desmopressin are the most widely used and investigated drugs. The dangerous side effects of imipramine and the high cost and relapse rate of desmopressin led us to investigate alternative drugs. There are limited reports and controversial results regarding the drugs acting on the function of the urinary bladder. Thus, in this study the efficacies of oxybutynin, pseudoephedrine and indomethacin in children with primary nocturnal enuresis were evaluated.

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Material and Methods

Children admitted to Hacettepe University İhsan Doğramacı Children's Hospital, Department of Pediatric Nephrology with the complaint of bedwetting were the subject of this study. The inclusion criteria were: 1. age equal to or greater than six years; 2. absence of a six-month or longer period of dry nights; 3. absence of neurologic or renal disease, or recurrent urinary tract infections; 4. presence of at least three wet nights in a week in the last two-week period.

The age and sex of the patients, the socioeconomic condition of the family and the family history for enuresis were recorded. Urinalysis, urine culture and simultaneous urine and blood osmolality after 12 hours of water deprivation of the patients were obtained. All patients were asked to keep a calendar for dry and wet nights for two weeks. At the end of the two weeks they were randomly put on either oxybutynin (0.5 mg/kg), pseudoephedrine (2 mg/kg) or indomethacin (2 mg/kg) therapy in two or three doses for four weeks. There were nine children in the oxybutynin group (1st group), 11 in the pseudoephedrine group (2nd group) and nine in the indomethacin group (3rd group). Their ages ranged from six to 15 years. Their complaints about the medications and blood pressures were recorded during the treatment period. Treatment results were evaluated by testing the significance of the differences between the average number of dry nights in the two weeks before and after treatment, by use of the Wilcoxon Matched-Pairs Signed-Ranks test. Differences between parameters were assessed by Kruskal-Wallis analysis of variance.

Results

There were no differences between the three groups in regard to the average age of the patients, the specific gravity and osmolality of the urine, and the average number of dry nights before treatment ($p > 0.05$) (Table I).

Table I Initial Parameters of The Patients

	1. Group (n = 9)	2. Group (n = 11)	3. Group (n = 9)
Average age (years)	10.8 ± 2.8	8.6 ± 2.2	9.0 ± 2.6
Specific gravity of the urine	1021.6 ± 5.6	1023.2 ± 5.6	1019.4 ± 5.8
Osmolality of the urine (mosmol/L)	781.5 ± 171.4	808.5 ± 192.3	881.6 ± 192.0
Number of dry nights in the two weeks before treatment	2.4 ± 2.2	2.5 ± 2.2	2.0 ± 2.3

The presence of a family history of enuresis and the socioeconomic condition of the families in the three groups were also similar.

Treatment Results: The significance of the difference between the average number of dry nights before and after treatment was tested. The number of dry nights in the two-week period were found to increase from 2.4 ± 2.2 to 4.7 ± 3.9 with oxybutynin, and from 2.0 ± 2.3 to 4.3 ± 4.0 with indomethacin; however, the differences were not statistically significant ($p > 0.05$). In the pseudoephedrine group the number of dry nights increased from 2.5 ± 2.2 to 6.2 ± 3.8 and the difference was statistically significant ($p < 0.05$) (Fig. 1).

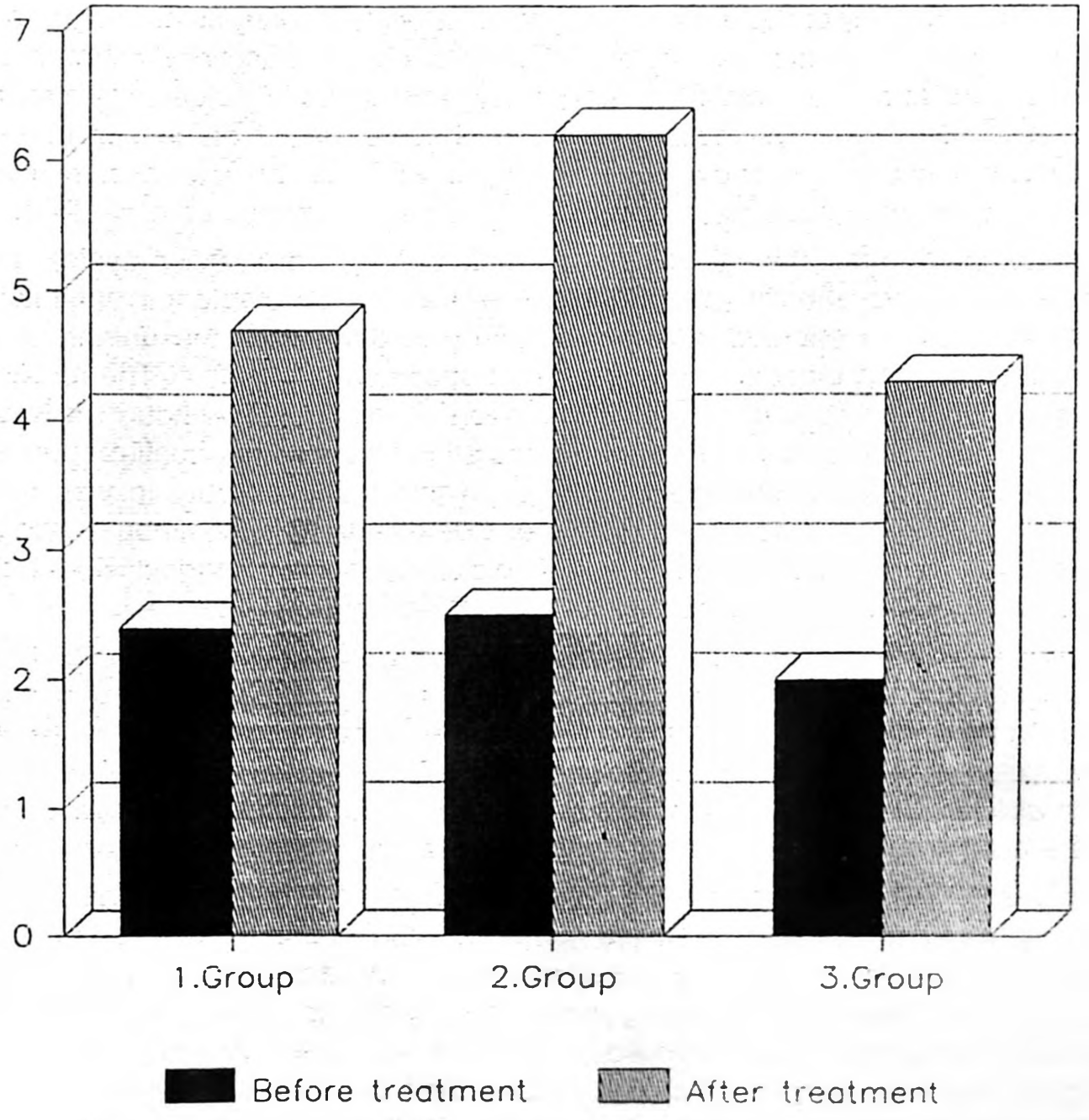

Fig. 1: Number of dry nights before and after treatment.

Side Effects: Three patients in the oxybutynin group had epistaxis that could not be explained by other causes. Epistaxis recurred in two of these patients and ceased only after the dose of oxybutynin was reduced. Another patient on oxybutynin therapy complained of flushing, vertigo and dryness of the hands and also required reduction of the dose. One patient had urinary hesitancy and incomplete evacuation of the bladder.

Indomethacin caused gastrointestinal irritation in one patient. There were no side effects in the pseudoephedrine group.

Discussion

The pathophysiology of nocturnal enuresis remains unclear. Many studies highlight the importance of urodynamic factors (bladder-urethra dysfunction)[3-6]. Enuretic children are known to void more frequently, and to have functionally small bladders[5]. Detrussor dysfunction has been observed in 82 percent of these patients with cystometric and micturition studies, whereas sphincter dysfunction has been detected in 20 percent with sphincter electromyographic studies[7].

We attempted to test the efficacies of an anticholinergic drug (oxybutynin), an alpha-adrenergic agonist (pseudoephedrine) and a prostaglandin inhibitor (indomethacin) in enuretic children. Oxybutynin decreases the uninhibited contractions of the bladder and has a direct spasmolytic effect[8-10]. The results of oxybutynin in enuretic children have been controversial. Although it was reported to be effective in 31 out of 39 enuretics, this was not confirmed in a double-blind, placebo-controlled trial[11, 12]. In this study oxybutynin was not effective in primary enuretics. Furthermore, side effects were common. Among these side effects this is the first report of epistaxis, which we suggest is related to drying of the nasal mucosa due to the anticholinergic effect.

Prostaglandin inhibitors decrease the tonus of the detrussor muscle[13]. Prostaglandins are known to inhibit secretion of antidiuretic hormone[14]. Prostaglandin inhibitors are used in partial diabetes insipidus and nephrogenic diabetes insipidus because of their potentiating effect on antidiuretic hormone[15]. On the limited number of studies with diclofenac sodium and indomethacin in patients with nocturnal enuresis, both were found to be effective[16-18]. In this study, however, indomethacin was not effective.

Alpha-adrenergic agonists relax the detrussor muscle while contracting the trigon and sphincter muscles[19]. The limited number of studies with these agents have disclosed different results[20, 21]. We used pseudoephedrine as an alpha-adrenergic agonist and obtained encouraging results in our enuretic patients with no side effects. These children experienced a significant increase in the number of dry nights. We thus suggest that pseudoephedrine can be used safely as an alternative drug in nocturnal enuretic patients. Further cystometric studies may reveal the exact mechanism of its effect.

REFERENCES

1. Oppel WC, Harper PA, Rider RV. The age of attaining bladder control. Pediatrics 1968; 42: 614-626.
2. Forsythe WI, Redmond A. Enuresis and spontaneous cure rate. Arch Dis Child 1974; 49: 259-263.
3. Scharf MB, Pravda MF, Jenings SW, et al. Childhood enuresis: a comprehensive treatment programme. Psychiatr Clin North Am 1987; 10: 655-666.
4. McLorie GA, Husmann DA. Incontinence and enuresis. Pediatr Clin North Am 1987; 34: 1159-1174.
5. Zaleski A, Gerrad JW, Shokeir MHK. Nocturnal enuresis: the importance of a small bladder capacity. In: Kolvin I, Mac Keith RC, Meadow SR (eds). Bladder Control and Enuresis. London: Heinemann Medical Books; 1973: 95-101.
6. Hallman N. On the ability of enuretic children to hold urine. Acta Paediatr 1950; 39: 87-93.
7. Webster GD, Koefoot RB Jr, Sihelnik S. Urodynamic abnormalities in neurologically normal children with micturition dysfunction. J Urol 1984; 132: 74-77.
8. Rushton HG, Nocturnal enuresis: epidemiology, evaluation, and currently available treatment options. J Pediatr 1989; 114: 691-696.
9. Schmitt BD. Nocturnal enuresis: an update on treatment. Pediatr Clin North Am 1982; 29: 21-36.
10. Brown JH. Atropine. Scopolamine and related antimuscarinic drugs. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York: Pergamon Press; 1990: 160.
11. Buttarazi PJ. Oxybutynin chloride (Ditropan) in enuresis. J Urol 1977; 118: 46.
12. Lovering JS, Tallett SE, McKendry JB. Oxybutynin efficacy in the treatment of primary enuresis. Pediatrics 1988; 82: 104-106.
13. Husted S. Sjögren C, Anderson KE. Role of prostaglandins in the responses of rabbit detrusor to non-cholinergic, non-adrenergic nerve stimulation and to ATP. Arch Int Pharmacodyn Ther 1980; 246: 84-97.
14. Anderson RJ, Berl T, McDonald KM, Schrier RW. Evidence for an in vivo antagonism between vasopressin and prostaglandin in the mammalian kidney. J Clin Invest 1975; 56: 420-426.
15. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1984; 310: 563-572.
16. AL-Waili NS. Diclofenac sodium in the treatment of primary nocturnal enuresis: double-blind crossover study. Clin Exp Pharmacol Physiol 1986; 13: 139-142.
17. Metin A, Aykol N. Diclofenac sodium suppository in the treatment of primary nocturnal enuresis. Int Urol Nephrol 1992; 24: 113-117.
18. AL-Waili NS. Indomethacin suppository to treat primary nocturnal enuresis: double blind study. J Urol 1989; 142: 1290-1292.
19. Hoffman BB, Lefkowitz RJ. Catecholamines and sympathomimetic drugs. In: Gilman AG, Rall TW, Nies AS, Taylor P. (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York: Pergamon Press; 1990: 196.
20. Ress DL, Ransley PG. Eskornade in the treatment of diurnal incontinence in children. Br J Urol 1980; 52: 476-479.
21. Barton JL, Felker JR. Daytime enuresis. Br J Psychiatry 1982; 140: 325.

The Turkish Journal of Pediatrics 1996; 38: 161-168

THE FREQUENCY OF IgG SUBCLASS DEFICIENCY IN CHILDREN WITH RECURRENT RESPIRATORY INFECTIONS*

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SUMMARY: Güneşer S, Antmen B, Altıntaş D, Yılmaz M. (Allergy and Immunology Unit, Department of Pediatrics, Çukurova University Faculty of Medicine, Adana, Turkey). The frequency of IgG subclass deficiency in children with recurrent respiratory infections. Turk J Pediatr 1996; 38: 161-168.

We studied the frequency of IgG subclass deficiency in 61 children (ages 1-7 years, mean 3.8 years) with recurrent respiratory tract infections by using the radial immunodiffusion method. The overall frequency of IgG subclass deficiency was found to be 39.3 percent (24 patients). Among 26 children who had major immunoglobulin abnormalities, we found IgG subclass deficiency in 11 patients (42.3%). In children with normal immunoglobulin levels, the frequency of IgG subclass deficiency was 37.1 percent (13 patients). *Key words: IgG subclass deficiency, recurrent infections.*

Recurrent infections have been associated with agammaglobulinemia, hypogammaglobulinemia and IgG-subclass deficiencies[1]. IgG-subclass deficiencies have been described in patients with common variable hypogammaglobulinemia, ataxia telangiectasia[4], the Wiscott-Aldrich syndrome[3] and IgA deficiency[2]. More recently IgG-subclass deficiencies have also been reported in patients with hypergammaglobulinemia[5], recurrent bronchitis[6], acute myeloid leukemia[7], corticosteroid-dependent reversible airway obstruction[8], and obtructive lung disease[9]. In addition, impairment of the antibody response to specific microbial antigens predisposes patients with selective IgG-subclass deficiencies to recurrent infections[10].

The incidence of IgG-subclass deficiency has been reported in few studies among pediatric patients. In this study, we determined the frequency of IgG-subclass deficiency in pediatric patients with recurrent respiratory infections.

Material and Methods

Patients: This study included 61 children with recurrent respiratory tract infections. The mean age of the patients was mean 3.8 ± 2.0 (1-7) years. Of the 61 patients, 43 (70.4%) were male and 18 (29.5%) were female.

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All of the patients had been referred to the Pediatric Allergy and Immunology Department because of recurrent respiratory tract infections. Fourteen patients had had at least four episodes of otitis media, and 25 patients had experienced three episodes of upper respiratory infections including sinusitis. Seven patients had had at least four episodes of otitis media together with pneumonia. Twelve patients had suffered from at least three episodes of recurrent pneumonia. Recurrent sinopulmonary infections were associated with bronchiectasia in three patients. Thirty-two patients (52.4%) were found to be atopic (Table I). All patients had been seen by their pediatricians, and many had also been examined by an otolaryngologist before being referred to our department. Fifteen patients had undergone at least one surgical procedure, including placement of a middle ear tube, sinus surgery, tonsillectomy or adenoidectomy.

Table I: Clinical Characteristics of Patients with Recurrent Infections (n = 61)

Mean age ± SD (yr)	3.8 ± 2.0	
Range (yr)	1-7	
Sex		
Male	43 (70.4%)	
Female	18 (29.5%)	
Infections	Patients (n)	(%)
– Recurrent otitis*	14	22.9
– Recurrent upper respiratory infections**	25	40.9
– Recurrent pneumonia**	12	19.6
– Recurrent otitis with pneumonia*	7	11.4
– Bronchiectasia with sinopulmonary infection	3	4.9
Patients;		
– Non-atopic	29 (47.5%)	
– Atopic	32 (52.4%)	

* at least four episodes in a year.
** at least three episodes in a year.

Immunologic Studies: Serum total IgG, IgA and IgM levels were measured using an auto-analyzer fluoronephelometer (Technicon Instruments Corp., Tarrytown, N.Y.). Serum total IgE levels were measured using Phadebas IgE Prist kit (Pharmacia Diagnostics, Uppsala, Sweden). Serm IgG-subclass levels were determined by radial immunodiffusion technique (The Binding Site Limited^{R}-UK). If the serum IgG-subclass levels were greater than two standard deviations below the mean value of normal, healthy, age-matched controls (Table II), it was considered IgG-subclass deficiency. None of our patients had total absence of any immunoglobulin (Table III).

Table II: Serum IgG Subclass Levels (mg/dL) in Normal Healthy Children (Mean and Ranges)

Age (Year)	n	IgG1	IgG2	IgG3	IgG4
1-2	12	510 (280-890)	140 (30-330)	45 (18-80)	22 (1-65)
3-4	13	605 (385-890)	190 (70-445)	58 (17-95)	7 (0-20)
5-6	25	695 (390-840)	210 (80-515)	64 (8-110)	5 (0-12)
7-8	23	710 (400-895)	275 (110-485)	80 (15-135)	4 (0-7)

Table IIIa: Serum Immunoglobulin and IgG Subclass Levels in Children with Recurrent Respiratory Infections

			Serum Immunoglobulin Levels (mg/dL)							
Patients	Age (Year)	Sex	IgG	IgA	IgM	IgE (iu/mL)	IgG1	IgG2	IgG3	IgG4
1-O.G.	4	F	1130	42	243[a]	15	530	UD	305	47
2-S.C.	2	M	990	45	79	9	750	UD	485	> 1[b]
3-E.Y.	2.5	M	963	48	87	8	670	90	62	> 1[b]
4-E.Y.	2	F	3170[a]	444[a]	275[a]	104	1100	UD	115	33
5-H.T.	7	F	900	41	89	12	660	120	242	UD
6-I.K.	7	M	1615[a]	51	90	23	600	190	40	UD
7-E.B.	7	M	1062	165	96	42	1230	UD	1700	> 1[b]
8-C.A.	2	M	1070	48	243[a]	13	1230	UD	1820	> 1[b]
9-M.G.	7	M	1740[a]	135	147	300[a]	530	300	85	45
10-E.K.	3	M	1250	126	243[a]	76	8360	UD	789	50
11-A.C.Y.	1.5	M	892	86	126	51	5130	90	28	> 1[b]
12-E.D.	7	M	1051	134	204	155	440	250	45	30
13-U.S.	6	M	713	61	143	200	320	UD	24	35
14-Y.K.	7	M	1970[a]	163	192	300[a]	431	UD	23	40
15-M.A.A.	1	M	822	5[b]	121	42	300	100	30	UD
16-E.B.	1	M	570	4[b]	149	5	325	90	22	UD
17-A.K.	1	M	707	4[b]	163	77	1670	90	886	30
18-O.B.	1	M	680	105	20[b]	29	800	450	100	25
19-G.A.	7	M	878	59	51	324[a]	520	900	30	4
20-O.U.	5	F	912	112	125	17	325	200	28	40
21-G.N.	7	F	1234	105	176	56	430	UD	25	20
22-S.K.	2.5	F	1140	UD	220	10	640	250	40	50
23-Z.S.	5	F	2370[a]	135	120	54	648	300	85	45
24-Y.K.	3	M	2974[a]	61	178	78	1100	230	242	41
25-A.A.	3	M	1175	75	105	67	500	200	90	> 1[b]
26-E.C.G.	4	F	1194	153	152	533[a]	600	200	29	22
27-B.A.	5	M	978	80	115	69	450	250	40	30
28-F.S.	7	M	785	97	98	77	600	180	35	18
29-I.G.	3	M	1100	85	89	89	450	200	25	35
30-Y.D.	6	F	980	124	90	15	325	290	45	35
31-B.B.	5	M	890	125	77	78	449	700	30	7
32-N.G.	7	F	1450	76	123	82	740	700	35	21

Table IIIb: Serum Immunoglobulin and IgG Subclass Levels in Children with Recurrent Respiratory Infections

Patients	Age (Year)	Sex	Serum Immunoglobulin Levels (mg/dL)							
			IgG	IgA	IgM	IgE (iu/mL)	IgG1	IgG2	IgG3	IgG4
33-G.N.	5	F	1256	90	99	91	630	650	25	45
34-S.U.	7	M	975	210	129	76	450	550	28	37
35-H.G.K.	7	M	750	86	187	56	538	510	39	18
36-H.Y.	4	M	880	95	145	34	500	UD	38	26
37-O.G.	5	M	1245	167	134	45	460	130	26	8
38-B.S.	1	F	690	179	185	34	890	95	24	12
39-S.N.S.	4	F	895	87	132	21	412	75	21	17
40-B.S.	1	M	1259	162	103	132	825	UD	770	13
41-E.K.	4	F	1338	167	215	171	1060	126	101	11
42-K.A.	2.5	M	1139	99	114	305[a]	1400	241	166	57
43-O.C.	4	F	1376	119	170	131	1100	116	79	43
44-A.S.	4	M	2582[a]	120	128	112	797	129	20	39
45-G.G.	4	M	1497	1497[a]	390[a]	317[a]	1030	204	79	20
46-B.S.	5	M	1024	74	87	42	715	9	48	19
47-S.K.	3.5	M	1704[a]	132	188	284	812	116	37	7
48-H.O.	1.5	M	965	68	127	143	763	116	166	3
49-S.O.	2	F	2340[a]	300[a]	128	1005[a]	1450	241	114	33
50-G.K.	1	F	1138	50	65	2160[a]	513	67	79	3
51-A.E.V.	2	M	605	10	116	68	4210	UD	204	58
52-Y.E.S.	4	M	1336	199[a]	169	494[a]	1100	676	79	72
53-Y.S.E.	3.5	M	2974[a]	67	162	85	1100	UD	242	UD
54-E.I.	3	M	590	50	68	17	513	67	63	1
55-B.A.	1	M	924	63	98	40	450	250	40	30
56-T.K.	2	F	972	152	95	258[a]	1050	576	70	51
57-K.G.	3.5	M	1028	143	204	111	715	150	60	42
58-K.G.K.	4.5	M	986	64	97	35	512	UD	48	61
59-M.K.A.	4	M	1135	145	192	70	875	UD	85	35
60-Y.K.	2.5	M	455	24	110	90	812	144	77	42
61-S.S.K.	3.5	M	1779[a]	95	123	38	585	UD	62	60

a: Ig levels were more than 2 SD above the mean value of the age-matched controls.
b: Ig levels were more than 2 SD below the mean value of the age-matched controls.
UD: Undetectable.

Results

IgA deficiency was determined in four patients (6.5%), and the total IgG level was found low in one patient (1.6%) who had recurrent pneumonia and bronchiectasia. The overall frequency of IgG-subclass deficiency was found to be 39.3 percent (24 patients).

IgG, IgA, IgM and IgE levels were normal in 35 patients. In this group, the frequency of IgG-subclass deficiency was 37.1 percent (13 patients). Selective IgG2 deficiency was detected in seven patients, selective IgG4 deficiency in four patients, and combined IgG2-IgG4 deficiency in two patients (Table IV). In patients who had selective IgA deficiency, we found selective IgG2 deficiency in one patient and selective IgG4 deficiency in one patient.

Table IV: The Frequency of IgG Subclass Deficiency in Patients with Normal and Abnormal Immunoglobulin Levels

	Patients (n = 39)		
	with Normal Ig Levels* (n = 35)	with Normal Ig Levels** (n = 26)	Total (n = 61)
IgG2 deficiency	7	5	12
IgG4 deficiency	4	4	8
IgG2-IgG4 deficiency	2	2	4
Total	9	8	24
(%)	(37.1%)	(42.3%)	(39.3%)

* Ig levels were normal the mean values of the age matched controls.
** Ig levels were more than 2 SD below or above the mean values of the age-matched controls.

An increased serum IgM level was found in three patients, including one patient with IgG2 deficiency and one with combined IgG2-IgG4 deficiency. An increased serum IgG level was found in six patients, including two patients with IgG4 deficiency, one with IgG2 deficiency and one with combined IgG2-IgG4 deficiency. An increased IgE level was found in five patients, including one patient who had selective IgG4 deficiency. The other major immunoglobulin abnormalities are shown in Table V. In addition, the frequency of IgG-subclass deficiency was found to be 31.2 percent (10 of 32 patients) among atopic patients with recurrent infections.

Table V: Distributions of Patients Who Had Abnormal Ig Levels Associated with IgG-Subclass Deficiency

Major Ig Abnormalities*	n	IgG2 Deficiency	IgG4 Deficiency	IgG2-IgG4 Deficiency
Increased IgM	3	1	–	1
Increased IgG	6	1	2	1
Increased IgE	5	–	1	–
Increased IgG, IgE	3	–	–	–
Increased IgA, IgE	1	–	–	–
Increased IgA, IgG, IgE	1	–	–	–
Increased IgA, IgG, IgM	1	–	–	–
Increased IgA, IgM, IgG	1	1	–	–
IgA Deficiency	1	1	–	–
Low IgA Level**	3	–	1	–
Low IgM level	1	–	–	–

* Ig levels were more than 2 SD below or above the mean values of the age-matched controls.
** Partial IgA deficiency.

Discussion

Human IgG immunoglobulins are divided into four subclasses: IgG1, IgG2, IgG3 and IgG4. Recent improvements in measuring IgG subclasses have led to numerous reports of patients with recurrent infections[10, 14-16]. The association between IgG subclass deficiency and recurrent pyogenic infections was first reported by Schur et al.[10] in 1970. The actual incidence of IgG-subclass deficiency is unknown, especially in pediatric patients. Shackelford et al.[11] reported low IgG2 concentrations in seven of 30 children with recurrent infections. In their patient group, immunologic abnormalities were heterogenous, as in our patients. They reported isolated IgG2 deficiency in two patients, combined IgG2-IgG4 deficiency in two patients, IgG2-IgG4-IgA deficiency in one, IgG2-IgGA deficiency in one and severe IgG1-IgG2 deficiency in one patient. Gross et al.[12] reported the incidence of IgG-subclass or major immunoglobulin isotype deficiency as 58 percent in a highly selected population. Twenty-six of 267 patients with recurrent infection had partial IgG-subclass deficiency. Moss et al.[13] reported that isolated IgG4 deficiency had a significantly higher prevalence among patients with recurrent infections (17%). However, they found the prevalence of isolated IgG4 deficiency to be only seven percent among atopic patients. In our study, we found isolated IgG4 deficiency in four of 35 patients (11.4%) with recurrent infections. In addition, we found both IgG4 deficiency and major immunoglobulin abnormalities in four of 26 patients (15.3%). Nevertheless, IgG4 levels could not be detected in 20 percent of normal healthy children by RIA method[19]. Berkel et al.[20] also reported that IgG4 levels had a non-homogenous distribution in Turkish children. Tezcan et al.[17, 18] found IgG-subclass deficiency in five of 11 symptomatic IgA-deficient patients and in two of 12 patients (16.6%) with recurrent infections.

DeBaets et al.[6] studied the incidence of IgG subclass deficiency in 53 children with recurrent bronchitis. They reported the incidence of IgG-subclass deficiency to be 57 percent. In their study, nine patients (17%) were deficient for IgG2, nine (17%) for IgG3, and 20 (38%) for IgG4. None of their patients had IgG1 deficiency, as in our study. We found 12 patients (19.6%) were deficient for IgG2, eight (13.1%) for IgG4 and four (6.5%) for combined IgG2-IgG4. In the children with IgG2 deficiency, Umetsu et al.[15] reported that serum antibody concentrations to the capsular polysaccharide of Haemophilus influenzae type B (Hib) were significantly lower than those in age-matched controls, both before and after immunization with the Hib capsular polysaccharide antigen. Also, IgG2 may be present in normal amounts but non-functional. Thus, serum antibody titers to the tetanus and diphtheria toxoid proteins and Hib capsular polysaccharide antigens should be evaluated in children with recurrent infections[1, 12, 21].

On the basis of these observations, we recommend the evaluation of IgG-subclasses in patients with recurrent infections, whether or not major immunoglobulin abnormalities are present. On the other hand, we suggest that IgG-subclass deficiencies also be evaluated, especially in atopic patients with recurrent infections.

REFERENCES

1. Ambrosino DM, Umetsu DT, Siber GR, et al. Selective defect in the antibody response to Haemophilus influenzae type b in children with recurrent infections and normal serum IgG subclass levels. J Allergy Clin Immunol 1988; 81: 1175-1179.
2. Oxelius VA, Laurell AB, Lindquist B, et al. IgG subclasses in selective IgA deficiency: importance of IgG2-IgA deficiency. N Engl J Med 1981; 304: 1476-1477.
3. Ochs HD, Wedgwood RJ. Disorders of the B cell system. In: Stiehm ER (ed). Immunologic Disorders in Infants and Children (3rd ed). Philadelphia: WB Saunders Company; 1989: 226-256.
4. Oxelius VA, Berkel AT, Hanson LA. IgG2 deficiency in ataxia telangiectasia. N Engl J Med 1982; 306: 515-517.
5. Jeandel C, Gueant JL, Petipain N, et al. Hypergammaglobulinaemia and IgG subclass deficiency (letter). Lancet 1992; 340: 1225-1226.
6. DeBaets F, Kint J, Pauwels R, Leroy J. IgG subclass deficiency in children with recurrent bronchitis. Eur J Pediatr 1992; 151: 274-278.
7. Preud'homme JL, Lacombe C, Cordonnier C, et al. IgG subclass deficiency in acute myeloid leukemia. Nouv Rev Fr Hematol 1989; 31: 349-351.
8. Klaustermeyer WB, Wong SC, Schoettler JJ, et al. Quantitative immunoglobulins and IgG subclasses in patients with cortico-steroid-dependent reversible airway obstruction. Ann Allergy 1989; 63: 327-330.
9. Klaustermeyer WB, Gianos ME, Kurohara ML, et al. IgG subclass deficiency associated with corticosteroids in obstructive lung disease. Chest 1992; 102: 1137-1142.
10. Schur PH, Bovel H, Gelfand EN, et al. Selective gamma-G globulin deficiencies in patients with reurrent pyogenic infections. N Engl J Med 1970; 283: 631-634.
11. Shackelford PG, Polmar SH, Mayus JL, et al. Spectrum of IgG2 subclass deficiency in children with recurrent infections: prospective study. J Pediatr 1986; 108: 647-653.
12. Gross S, Blaiss MS, Herrod HG. Role of immunoglobulin subclasses and specific antibody determinations in the evaluation of recurrent infection in children. J Pediatr 1992; 121: 516-522.
13. Moss RB, Carmack MA, Esrig S. Deficiency of IgG4 in children: association of isolated IgG4 deficiency with recurrent respiratory tract infection. J Pediatr 1992; 120: 16-21.
14. Oxelius VA. Immunoglobulin G (IgG) subclasses and human disease. Am J Med 1984; 76: 7-18.
15. Umetsu DT, Ambrosino DM, Quinti I, et al. Recurrent sinopulmonary infection and impairment antibody response to bacterial capsular polysaccharide antigen in children with selective IgG-subclass deficiency. N Engl J Med 1985; 313: 1247-1251.
16. Hanson LA, Soderstrom R, Avanzini A, et al. Immunoglobulin subclass deficiency. Pediatr Infect Dis J 1988; 7 (5 Suppl); S17-21.
17. Tezcan I, Ersoy F, Sanal O, Göçmen A, Yeniay I. IgG subclass deficiency in children with recurrent infections. Turk J Pediatr 1991; 33: 163-166.
18. Tezcan I, Ersoy F, Sanal O. IgG subclasses in symptomatic IgA deficiency. Turk J Pediatr 1992; 34: 1-4.

19. Lau YL, Jones BM, Ng KW, Yeung CY. Percentile ranges for serum IgG subclass concentrations in healthy Chinese children. Clin Exp Immunol 1993; 91: 337-341.

20. Berkel AI, Tezcan I, Ersoy F, Sanal O. Serum immunoglobulin G subclass values in healthy Turkish children and adults. Turk J Pediatr 1994; 36: 197-204.

21. Sanal O, Metin A, Ersoy F, et al. Tekrarlayan enfeksiyonları olan çocuklarda IgG alt-sınıflarının ve spesifik antikor cevabının yeri. Çocuk Sağlığı ve Hastalıkları Dergisi 1993; 36: 333-339.

The Turkish Journal of Pediatrics 1996; 38: 169-175

INHALATION THERAPY WITH MAGNESIUM SULFATE AND SALBUTAMOL SULFATE IN BRONCHIAL ASTHMA*

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SUMMARY: Meral A, Çoker M, Tanaç R. (Allergy and Chest Disease Unit, Department of Pediatrics, Ege University Faculty of Medicine, İzmir, Turkey). Inhalation therapy with magnesium sulfate and salbutamol sulfate in bronchial asthma. Turk J Pediatr 1996; 38: 169-175.

Inhalation therapy with magnesium sulfate and salbutamol sulfate was applied to two groups, each consisting of 20 patients with acute asthma. The effects of inhaled magnesium sulfate and salbutamol sulfate were compared. The evaluation of patients was done using respiratory score, peak expiratory flow rate with a Wright peak flow meter, respiration rate, heart rate and blood pressure. Although magnesium sulfate's bronchodilating effect continued for approximately one hour, treatment of acute asthma using salbutamol sulfate inhalation was found to be more successful and its effect continued for six hours. *Key words: childhood asthma, magnesium sulfate, inhalation therapy.*

Asthma is one of the most common chronic diseases of childhood. new treatment protocols have been developed due to improvement of our knowledge of asthma pathogenesis. Recent studies have proved that the magnesium (Mg^{+2}) ion inhibitis contraction of smooth muscle, acetylcholine release from cholinergic nerve terminals and histamine release from mast cells[1-4]. Thus, magnesium sulfate ($MgSO_4$) administration has become one of the treatment modalities for symptomatic asthmatic patients.

This study was designed to evaluate the effect of $MgSO_4$ inhalation on bronchoconstriction in bronchial asthma and compare its possible usefulness as a bronchodilating agent with salbutamol sulfate inhalation.

Material and Methods

Forty patients who had previously been diagnosed according to the American Thoracic Society's definitions[5] of asthma at the Department of Pediatric Allergy of Ege University Hospital, İzmir, Turkey were randomly selected for the study. All patients gave voluntary consent. Patients were divided into two groups; the first group received $MgSO_4$ inhalation and the second received salbutamol sulfate during asthma attacks. All patients had received maintenance therapy consisting

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of beta-2 adrenoreceptor stimulants and/or theophylline derivatives, but none of them had taken medication within 12 hours before the attack. They had neither cardiac nor renal dysfunctions.

The mean age was 10 years (10.55 ± 2.37) for the first group receiving $MgSO_4$ inhalation, and 11 years (10.95 ± 2.45) for the second group receiving salbutamol sulfate inhalation. They were all evaluated and found to be in the normal range according to Neyzi et al's[6] Growth and Development Chart for Turkish Children.

In each subject, a respiratory distress score according to Davis-Leffert-Dabbous' scoring system[7-9] (Table I), heart rate, respiratory rate, blood pressure and peak expiratory flow rate (PEFR) were measured before $MgSO_4$ or salbutamol sulfate inhalations. PEFRs were measured by using the Wright peak flow meter[10], and the increase observed in PEFR values was compared with the height-adjusted predicted PEFR values of normal children as determined by Süren et al.[11] The patients whose PEFR values had decreased 25 percent or more were considered to have acute asthma. Salbutamol sulfate solution (commercially available as Ventolin Nebules 2.5 mg in 2.5 ml) or $MgSO_4$ solution 2 ml (280 mmol/L, 258 mOsm, pH: 6.7) was inhaled by an ultrasonic inhaler in 10 to 15 minutes. The same parameters were again determined after 5, 15, 30, 60, 180, 240, and 360 minutes of $MgSO_4$ or salbutamol sulfate inhalations. The subjects were also evaluated for possible adverse effects of the drugs.

Table I: Respiratory Score Standardization was Accomplished by Taking 5 Points or More Into Consideration

Nasal flaring	0	Absent
	1	Present
Cyanosis	0	Absent
	1	Present
Retractions	0	Absent
	1	Mild (Subcostal + inferior costal)
	2	Moderate (1 + supraciavicular)
	3	Severe (2 + superior intercostal)
Wheezing	0	Absent
	1	Sibilation with stethoscope
	2	1 + mild wheezing
	3	2 + severe wheezing
	4	3 + prolongation of expirium
	5	Decreased or absent breath sounds

The paired t test, student's t test and correlation analysis were used to analyze differences between the two groups. Statistical significance was considered to be at $p < 0.05$.

Results

The parameters measured in each group before the treatment had no statistical differences (Table II). PEFR began to increase five minutes after $MgSO_4$ inhalation,

Table II: Physical Examination Signs at the Beginning of the Therapy

	MgSO4	Salbutamol Sulfate
Respiratory score	5.50 ± 0.60	6.40 ± 0.90
Decrease in PEFR	40.23 ± 13.27	45.94 ± 12.95
Respiration rate	29.40 ± 5.62	33.40 ± 8.80
Heart rate	107.60 ± 20.60	11.80 ± 17.95
Systolic blood pressure	105.00 ± 10.50	103.20 ± 9.65
Diestolic blood pressure	66.00 ± 8.20	68.75 ± 10.49

reaching its maximum value at the end of one hour. By six hours, it decreased to a value which was not statistically different from the PEFR measured before $MgSO_4$ inhalation. In the second group receiving salbutamol sulfate inhalation, PEFR values were found to be significantly higher at five minutes, at the time of maximal response, and at six hours than the values of the $MgSO_4$-inhaling group (Table III, Fig. 1).

Table III: PEFR Values with $MgSO_4$ and Salbutamol Sulfate Inhalation Ratio of Increase in PEFR (%)

	$MgSO_4$ Increase (I)	Salbutamol Sulfate Increase (II)	Statistical Analysis
5^{th} min. (a)	16.31 ± 6.43	42.19 ± 23.18	I-II: $p < 0.01$
Maximum response (1^{st} hour) (b)	42.63 ± 20.21	79.40 ± 52.09	I-II: $p < 0.05$
6^{th} hour (c)	14.54 ± 23.42	75.10 ± 56.72	I-II: $p < 0.01$
Statistical analysis	a-b: $p < 0.01$	a-b $p < 0.01$	
	a-c: $p > 0.05$	a-c: $p < 0.05$	
	b-c: $p < 0.01$	b-c: $p < 0.01$	

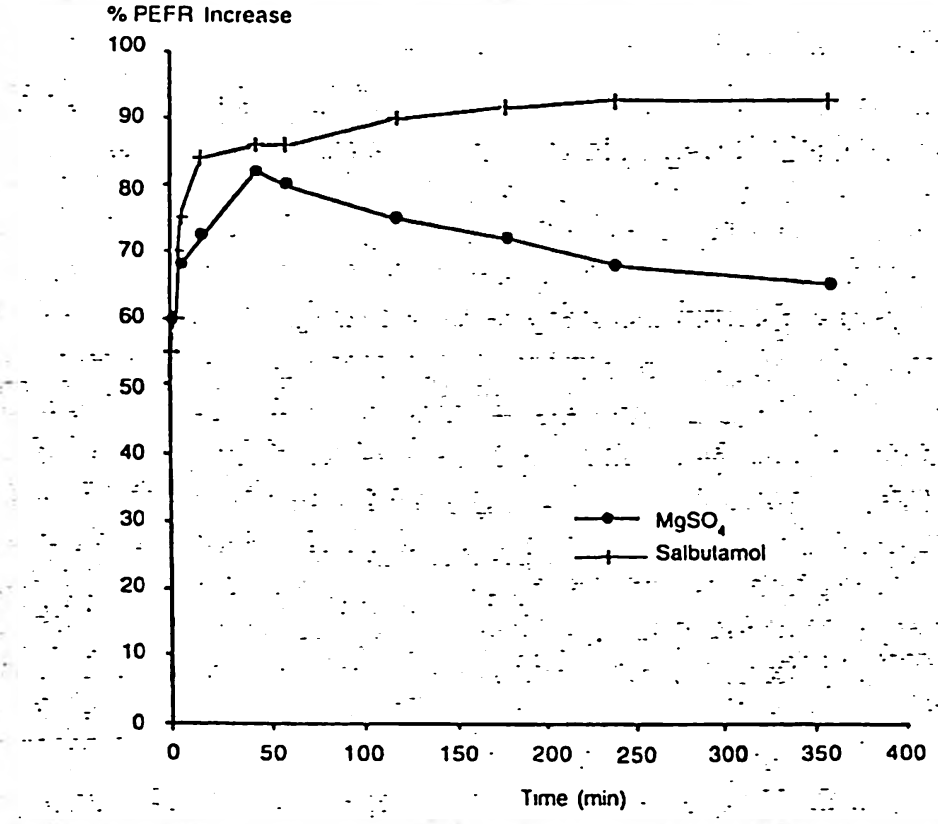

Fig. 1: Ratio of increase in PEFR (%)

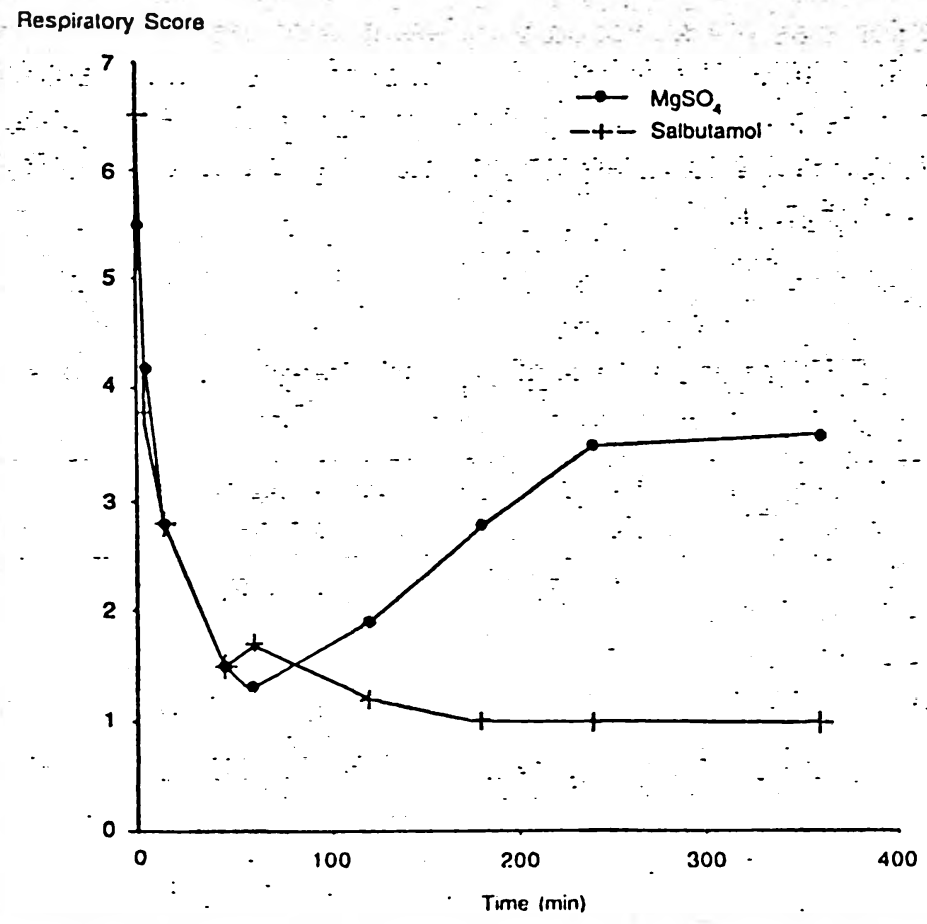

Fig. 2: Ratio of decrease in respiratory score (%)

Although the respiratory distress score improved in both groups, the most significant decrease in the fifth minute and the sixth hour were found in the second group ($p < 0.01$). There was no statistically significant difference in the decrease in respiratory distress scores between the two groups. The respiratory distress score was increased at six hours in the first group parallel to the decrease of PEFR values in the same group ($r = 0.5$, $p < 0.05$). The respiratory distress score decreased and was maintained until the end of the sixth hour only in the salbutamol sulfate inhaling group (Table IV, Fig. 2).

Table IV: The Improvement of Respiratory Scores with $MgSO_4$ and Salbutamol Sulfate Inhalation

	Ratio of Decrease in Respiratory Score (%)		
	$MgSO_4$ Inhalation (I)	Salbutamol Sulfate Inhalation (II)	Statistical Analysis
5th min. (a)	23.33 ± 17.70	43.14 ± 22.12	I-II: $p < 0.01$
Maximum response (1st hour) (b)	79.97 ± 19.18	83.17 ± 26.73	I-II: $p > 0.05$
6th hour (c)	30.80 ± 34.79	80.41 ± 30.32	I-II: $p < 0.01$
Statistical analysis	a-b: $p < 0.01$ a-c: $p > 0.05$ b-c: $p < 0.01$	a-b $p < 0.01$ a-c: $p < 0.01$ b-c: $p > 0.05$	

Respiratory rate, heart rate and blood pressures were in the normal range in both groups, and no statistical differences in the parameters were found between the two groups ($p > 0.05$).

Discussion

There have been new approaches related to the pathogenesis of asthma in recent years. Mg^{+2} itself as a physiologic antagonist of calcium (Ca^{+2}) induces an inhibitory action on smooth muscle contraction by blocking the intracellular influx of Ca^{+2} [12-15].

In this study, we investigated the bronchodilating effect of Mg^{+2} in acute asthma crisis and compared it with a beta-2 adrenoreceptor agonist, salbutamol sulfate. In both groups, PEFR increased at five minutes. However, the increase in the salbutamol sulfate-inhaling group was more significant ($p < 0.01$). The maximum effect of $MgSO_4$ was reached by one hour. However, its effect was short-term compared to that with salbutamol sulfate inhalation, since the PEFR values were still high by six hours in the salbutamol sulfate-inhaling group and was decreased

to the beginning values by six hours in the $MgSO_4$-inhaling group. Similar results were obtained in the respiratory distress scores.

There was no adverse reaction in either group, as the blood pressure and heart rate did not change ($p > 0.01$). Hypotension and tachycardia noted in the literature during intravenous $MgSO_4$ administration were also not observed in our study[16, 18].

Hiroshi et al.[19] showed that intravenous $MgSO_4$ had a fast but short-term bronchodilating effect; its effect started in two minutes but declined after 10 minutes of administration. In several studies, it has been suggested that $MgSO_4$ can be used in mild or severe acute asthma attacks either with a beta-2 adrenoreceptor agonist or alone in non-responders to beta-2 agonists[3, 16, 18].

In our study, we found that the inhalable form of $MgSO_4$ takes effect as quickly as the intravenous forms but lasts longer. Its effect continued for one hour and then started to decline in our study. Salbutamol sulfate inhalation was found to be more effective, and its effect continued for six hours.

In conclusion, the results indicate that $MgSO_4$ inhalation produces statistically significant but shot-term bronchodilatation in asthmatics. Therefore, it should not be the first agent used in acute asthmatic attacks but may be used as an adjuvant agent with a beta-2 agonist. Further investigations are needed to provide more data on this subject.

REFERENCES

1. Brunner EH, Delabroise AM, Haddad ZH. Effect of parenteral magnesium on pulmonary function, plasma cAMP, and histamine in bronchial asthma. J Asthma 1985; 22: 3-11.
2. Mathew R, Altura BM. Magnesium and the lungs. Magnesium 1988; 7: 173-187.
3. McNamara RM, Spivey WH, Skobeloff E, Jacubowitz S. Intravenous magnesium sulfate in the management of acute respiratory failure complicating asthma. Ann Emerg Med 1989; 18: 197-199.
4. Rolla G, Bucca C, Arossa W, Bugiani M. Magnesium attenuates methacholine-induced bronchoconstriction in asthmatics. Magnesium 1987; 6: 201-204.
5. American Thoracic Society. Chronic bronchitis, asthma and pulmonary emphysema: a statement by the committee on diagnostic standards for non-tuberculous respiratory diseases. Am Rev Respir Dis 1962; 85: 762-768.
6. Neyzi O, Günöz H. Büyüme ve Gelişme Bozuklukları. In: Neyzi O, Ertuğrul T (eds). Pediatri (1st ed) Vol. 1. İstanbul: Nobel Tıp Kitabevi; 1989: 89-116.
7. Davis WJ. Terbutaline in the treatment of acute asthma in childhood. Chest 1977; 72: 614-617.
8. Leffert F. The management of acute severe asthma. J Pediatr 1980; 96: 1-2.
9. Shapiro GG, Simons E, Pierson WE, Bierman CW. The management of status asthmaticus in children, the critically ill child. In: Smith CA (ed). The Critically Ill Child (2nd ed.) Philadelphia: WB Saunders Co; 1977: 178-195.
10. Wright BM, McKarrow CB. Maximum forced expiratory flow as a measure of ventilatory capacity. Br Med J 1959; 2: 1041-1047.
11. Süren T, Tanaç R, Kurugöl Z. 0-13 yaş grubundaki çocuklarda ekspirasyon tepe akım hızı değerleri. XX. Türk Pediatri Kurumu Kongresi, 22-27 Haziran, İstanbul Bildiri Kitabı, Pediatrik Pnömotoloji, 1981, s. 281.

12. Altura BM, Altura BT. New perspectives on the role of magnesium in the pathophysiology of the cardiovascular system. I. Clinical aspects. Magnesium 1985; 4: 226-224.

13. Altura BM, Altura BT. New perspectives on the role of magnesium in the pathophysiology of the cardiovascular system. II. Experimental aspect. Magnesium 1985; 4: 245-271.

14. Altura BM, Altura BT. Influence of magnesium on drug induced contractions and ion content in rabbit aorta. Am J Physiol 1987; 220: 938-943.

15. Triggle DJ. Calcium, the control of smooth muscle function and bronchial hyperacitivity. Allergy 1986; 38: 1-9.

16. Noppen M, Vanmaele L, Impens N, Schandevyl W. Bronchodilating effect of intravenous magnesium sulfate in acute severe bronchial asthma. Chest 1990; 97: 373-376.

17. Rolla G, Bucca C. Acute effect of intravenous magnesium sulfate on airway obstruction of asthmatic patients. Ann Allergy 1988; 61: 388-391.

18. Skobeloff EM, Spivey WH, McNamara RM, Grenspon L. Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. JAMA 1989; 262: 1210-1213.

19. Hiroshi O, Takashi A, Michiko O, et al. Bronchodilating effect of intravenous magnesium sulfate in bronchial asthma. Preliminary communication. JAMA 1987; 257: 1076-1082.

The Turkish Journal of Pediatrics 1996; 38: 177-182

"ACQUIRED" SUBVALVULAR AORTIC STENOSIS AFTER REPAIR OF SEVERAL CONGENITAL CARDIAC DEFECTS*

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SUMMARY: Tokel K, Özme Ş, Çil E, Özkutlu S, Çeliker A, Saraçlar M, Bilgiç A, Özer S. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). "Acquired" subvalvular aortic stenosis after repair of several congenital cardiac defects. Turk J Pediatr 1996; 38: 177-182.

Discrete subvalvular aortic stenosis is a progressive lesion. In this report we presented nine patients who had no significant left ventricular-aortic obstruction at initial cardiac catheterization or echocardiographic examination, but later developed significant sbvalvular aortic stenosis. Associated lesions included ventricular septal defect in three, patent ductus arteriosus in two, aorticopulmonary window in one, tetralogy of Fallot in one, supramitral membrane in one, and ventricular septal defect and patent ductus arteriosus in one case.

Nine patients were diagnosed with subvalvular aortic stenosis 18 months to eight years after surgical correction. Eight of the patients required surgery for subvalvular obstruction.

In conclusion, discrete subaortic stenosis is a rare, late complication of the surgical repair of several congenital heart defects. It is a progressive lesion after surgery; therefore these patients require careful follow-up. *Key words: subaortic stenosis, surgery, follow-up.*

Discrete subaortic stenosis accounts for approximately 10 percent all cases of congenital aortic stenosis[1]. It is frequently associated with congenital heart defects, including ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot and coarctation of the aorta[2-4]. Although the development of "acquired" subaortic stenosis (SAS) after surgical repair of ventricular septal defect, tetralogy of Fallot, double outlet right ventricle and common atrioventricular canal defects has been described previously, there is little data about the relative incidence of post-surgical subaortic stenosis.

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The purpose of this report was to present the development of subaortic stenosis after surgical treatment in patients who had no subaortic obstruction at initial echocardiography or cardiac catheterization.

Material and Methods

Nine patients who had undergone cardiovascular surgery for congenital heart defects between 1982 and 1989, and who later developed subaortic stenosis as shown by two-dimensional echocardiography during follow-up, were reviewed retrospectively. Patients who had subaortic stenosis preoperatively were excluded.

Two-dimensional and Doppler echocardiographic examination was performed with Toshiba SSH 60 equipment with 2.5, 3.75 and 5.0 MHz transducers pre- and postoperatively. The standard subcostal, parasternal, apical and supra-sternal views were used.

Seven patients underwent left cardiac catheterization. Left ventricular angiography was performed by using long-axis (60° left anterior oblique with 30° cranial angulation) and four-chamber (45° left anterior oblique with 30° cranial angulation) wiews. The diagnosis of acquired subaortic stenosis was made in all patients by two-dimensional and Doppler echocardiography. The last two patients underwent surgery without cardiac catheterization.

The indications for surgery included a subaortic gradient > 25 mmHg or a subaortic gradient < 25 mmHg with aortic regurgitation on echocardiography or cardiac catheterization.

Results

We studied nine patients (six boys and three girls). The median age on admission was 10 months (range six months to five years). The mean age at first operation was 3.6 ± 1.4 years (range 2-6.5 years). The mean age at diagnosis of subvalvular aortic stenosis was 7.8 ± 1.8 years (range 4.9-11 years). The diagnosis of SAS was made at a mean interval of 4.26 ± 1.7 years (range 1.5-8 years) after the operation.

Table I shows the age at operation, type of surgical repair and follow-up of the nine patients. Before surgery we did not demonstrate a subaortic membrane in any patient on echocardiographic examination. In three patients there was no pressure gradient between the left ventricle and the aorta. We diagnosed a ventricular septal defect in three patients, patent ductus arteriosus in two patients, aorticopulmonary window, supramitral membrane, tetralogy of Fallot, ventricular septal defect and patent ductus arteriosus in one patient each.

Two patients underwent surgery for subaortic stenosis after echocardiographic examination only. Table II shows the results of the cardiac catheterization in seven patients together with Doppler gradients. The subaortic gradient on Doppler

examination was 3.5 ± 9.5 mmHg. The mean gradient between the left ventricle and the aorta was much higher (mean 58.8 ± 32 mmHg, range 0-90 mmHg). The difference between data related to gradients gathered by Doppler versus cardiac catheterization was statistically significant. This difference may be related to the time between Doppler examination and catheterization. (i.e., in one patient admitted with the complaint of chest pain four years after Doppler examination, an 82 mmHg left ventricle to aortic gradient was detected on cardiac catheterization).

The subaortic membrane was resected in five patients. Three patients were awaiting surgery as of this writing.

Table I: Age at Operation, Type of Surgical Repair and Follow-up in 9 Patients

Age on Admission	Age at Operation and Type of Surgical Repair	Procedure Before Operation	Period Before Subaortic Stenosis Occurence	Follow-up
7 moths	2 Y PDA ligation 3 Y VSD closure	E + C	8 years	Operation
5 years	5 Y BT Shunt 6.5 Y Total correction	E	1.5 years	Membrane resection
2.5 years	3 Y APW closure	C + E	3 years	Clinical follow-up
7 months	10 months Pulmonary banding 22 months Depanding + VSD closure + patch for RVOT	E	4 years	Operation
7 months	3 Y Supramitral memb. resection	E + C	3.5 years	Operation
6 months	4 Y VSD closure	E + C	4.5 years	Membrane resection
5 years	5 Y PDA ligation	E	5 years	Membrane resection
16 months	2 Y PDA ligation	E + C	4 years	Membrane resection
10 months	4 Y VSD closure	E + C	4 years + 9 month	

Y : Years.
E : Echocardiography.
C : Catheterization.
PDA : Patent ductus arteriosus.
VSD : Ventricular septal defect.
APW : Aorticopulmonary window.
BT : Blalock-Taussing.
RVOT : Right ventricular outflow tract.

Table II: Catheterization Results and Doppler Echocardiography Gradients

Number	Echo Gradient*	LV Pressure*	Subaortic Pressure*	Aortic Pressure*	Subaortic Gradient*
1	28	177	95	95/71 Mean: 81	82
2	24	195	115	100/62 Mean: 79	80
3	20	120	120	120/66 Mean: 90	0
4	31	Underwent Operation with Echocardiography			
5	40	165	120	115/78 Mean: 98	45
6	40	180	140	120/80 Mean: 100	40
7	45	200	110	95/60 Mean: 71	90
8	40	Underwent Operation with Echocardiography			
9	47	200	125	125/75 Mean: 92	75
Mean	35 + 9.5**				58.8 + 32

* mmHg.
** Mean Doppler gradient in patients who have a catheterization subaortic gradient.
LV: Left ventricle.

Discussion

The development and incidence of subaortic stenosis after surgical repair of several congenital heart defects have been documented previously[4-7]. Although the number of patients in the series was small, Ciccini et al.[8] reported that the incidences of subaortic stenosis in ventricular septal defect, tetralogy of Fallot and double outlet right ventricle were 3.2, 2.1 and 21.4 percent, respectively. In the presence of a ventricular septal defect, hemodynamic diagnosis of a subaortic obstruction may be difficult to make using Doppler echocardiography or peak-to-peak catheterization gradient. A ventricular septal defect decompresses the left ventricle and minimizes the left ventricular outflow tract pressure gradient until it is closed. The other factor masking the presence of the membrane is shunting of the contrast material through the ventricular septal defect at angiocardiography[8-9]. Therefore, the diagnosis of subaortic obstruction is usually made on the basis of morphologic data obtained by two-dimensional echocardiography rather than on the basis of the hemodynamic gradient[8]. In our cases, there was no evidence of obstruction on angiocardiographic (in seven patients) and two-dimensional echocardiographic (in nine patients) examination obtained before surgical correction of the cardiac defects.

The occurrence of a subaortic membrane post-operatively has been reported in cases of tetralogy of Fallot, ventricular septal defect, common atrioventricular canal, double outlet right ventricle and patent ductus arteriosus. The etiology and pathogenesis of subaortic stenosis are still not completely understood.

Possible mechanisms have been proposed. Pathogenesis as suggested by Keith[10] may be caused by malamalgamation of the subaortic conus with the ventricular septum, followed by incomplete absorption of the aortic infundibulum. Van Praagh et al.[11] suggested that maldevelopment of the atrioventricular canal and subsequent constriction of the left ventricular outflow tract by abnormal migration of the endocardial cushion tissue into the subaortic region could be responsible. Pyle et al.[12] hypothesized that the fibrocartilagenous ring of subaortic stenosis is derived from persistent embryonal endocardial cushion tissue that retains its proliferative capacity. They also suggested that subaortic stenosis was not a true congenital defect but developed postnatally. Recently Gewillig et al.[13] suggested that the turbulent blood flow that may be created by the patch sewn on the right ventricular side of the interventricular septum may damage the endothelium and thereby initiate the formation of a subaortic ridge. Sommerville[14] postulated the idea of turbulence which stimulates the formation of discrete subaortic stenosis.

In one of our cases, the cause of the discrete subaortic membrane may have been a malalignment-type ventricular septal defect. Zielinsky et al.[15] demonstrated that a malalignment-type ventricular septal defect is a constant feature in patients who develop preoperative or postoperative discrete subaortic stenosis with ventricular septal defect[14]. In the other cases with ventricular septal defect, turbulence originating from an abnormally contracting myocardium and patch may have been the reason for a discrete subaortic membrane.

In two patients with patent ductus arteriosus and one patient with an aorticopulmonary window, it is impossible to explain the mechanism of formation of the subaortic membrane after surgery. However, there are reports in the literature about the formation of a membrane after patent ductus arteriosus ligation. Leichter et al.[6] reported 12 cases with patent ductus arteriosus either alone or in combination with other cardiac defects, such as ventricular septal defect, aorticopulmonary window, atrioventricular canal defect and pulmonary stenosis. Two of our cases underwent surgery after only echocardiographic examination. In one patient with aorticopulmonary window we did not find any gradient between the left ventricle and the aorta in the pullback of the left ventricle to aorta before surgery. However, three years after the operation we demonstrated a subaortic membrane with 31 mmHg instantaneous peak gradient by two-dimensional and Doppler echocardiographic examination.

In previous reports the time lapse between surgery and development of the subaortic membrane was reported as three months to 18 years, with a mean of two years and nine months[5, 6, 8]. In our study this period averaged 4.2 ± 1.7 years (range 18 months to eight years). Five patients were operated on for resection of membranes. Three patients were awaiting surgery as of this writing.

In conclusion we believe that discrete subaortic stenosis is a rare, late complication of several congenital heart defects and that it is an acquired condition. Because of its progressive nature after surgery, these patients must be followed carefully. If the patient has a significant heart murmur or electrocardiographic findings, two-dimensional echocardiography and catheterization must be performed. Because two-dimensional echocardiography is useful in demonstrating the subaortic membrane, we recommend echocardiography for patients with subaortic stenosis to assure accurate diagnosis and proper management.

REFERENCES

1. Newfeld EA, Muster AJ, Paul MH, Idriss FS, Riker WL. Discrete subaortic stenosis in childhood. Am J Cardiol 1976; 38: 53-61.
2. Vogel M, Freedom RM, Brand A, Trusler GA, Williams WG, Rowe RD. Ventricular septal defects and subaortic stenosis: an analysis of 41 patients. Am J Cardiol 1983; 52: 1258-1263.
3. Sander JH Jr, Van Praagh R, Sade RM. Tetralogy of Fallot with discrete subaortic stenosis Chest 1976; 69: 534-544.
4. Moene RJ, Gilttenberger-de Groot AC, Oppenheimer-Dekker A, Bartelings MM. Anatomic characteristics of ventricular septal defect associated with coarctation of the aorta. Am J Cardiol 1987; 59: 952-955.
5. Christy C, Noonan J, O'Connor W. Discrete subvalvar aortic stenosis after tetralogy of Fallot repair. Br Heart J 1983; 49: 510-512.
6. Leichter DA, Sullivan I, Gersony WM. "Acquired" discrete subvalvular aortic stenosis: natural history and hemodynamics. J Am Coll Cardiol 1989; 14: 1539-1544.
7. Ben-Shacher G, Moller JH, Castaneda-Zuriga W, Edwards JE. Signs of membranous subaortic stenosis appearing after correction of persistent common atrioventricular canal. Am J Cardiol 1981; 48: 340-344.
8. Cicini MP, Giannico S, Marino B, Iorio FS, Corno A, Marceletti C. "Acquired" subvalvular aortic stenosis after repair of a ventricular septal defect. Chest 1992; 101: 115-118.
9. Freedom RM, Culham J, Rowe RD. Angiocardiography of subaortic obstruction in infancy. AJR 1977; 129: 813.
10. Keith JD, Rowe RD, Vlad P. Heart Disease in Infancy and Childhood (3rd ed). New York: MacMillan Co; 1987: 736.
11. Van Praagh R, Corwin RD, Dahiquist EH, Freedom RM, Mattioli L, Nebesar RH. Tetralogy of Fallot with severe left ventricular outflow tract obstruction due to anomalous attachment of the ventricular septum. Am J Cardiol 1970; 26: 93-101.
12. Pyle RL, Patterson DF, Chacko S. The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog. Am Heart J 1976; 92: 324-334.
13. Gewillig M, Daenen W, Dumoulin M, Van der Hauwaert L. Rheologic genesis of discrete subvalvular aortic stenosis: a Doopler echocardiographic study. J Am Coll Cardiol 1992; 19: 818-824.
14. Sommerville J. Congenital heart disease-changes in form and function. Br Heart J 1979; 41: 1-22.
15. Zielinsky P, Rossi M, Haertel JC, Vitola D, Lucchese FA, Rodrigues R. Subaortic fibrous ridge and ventricular septal defect: role of septal malalignment. Circulation 1987; 75: 1124-1129.

The Turkish Journal of Pediatrics 1996; 38: 183-188

CONVULSIONS IN CHILDHOOD SHIGELLOSIS AND ANTIMICROBIAL RESISTANCE PATTERNS OF SHIGELLA ISOLATES*

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SUMMARY: Öztürk MK, Çaksen H, Sümerkan B. (Departments of Pediatrics and Microbiology, Erciyes University Faculty of Medicine, Kayseri, Turkey). Convulsions in childhood shigellosis and antimicrobial resistance patterns of shigella isolates. Turk J Pediatr 1996; 38: 183-188.

Drug resistance patterns of 68 shigella strains were investigated prospectively in Kayseri during a period of approximately two years. The resistance was highest with ampicillin (58.8%) followed by co-trimoxazole (50%) and ampicillin-sulbactam (13%). Only 2.8 percent of cases were resistant to gentamicin, and all serogroups were sensitive to ceftriaxone. We conclude that in children with severe shigellosis, treatment with ceftriaxone is effective and better than ampicillin and co-trimoxazole for obtaining a clinical cure.

We followed 18 children who experienced convulsions associated with shigellosis. Only one child had a history of febrile convulsions, and two children had histories of convulsive disorders. The majority of the children had generalized, self-limited convulsions which lasted less than ten minutes. Due to the benign and self-limited nature of most of the convulsions, neither diagnostic procedures nor drug therapy are usually necessary. These measures should, however, be considered in complicated cases characterized by focal or prolonged seizures. *Key words: childhood shigellosis, convulsions, antibiotic resistance.*

The shigella species remains a major cause of enteral diarrhea in developing countries. Shigellosis is an acute inflammatory disease of the colon characterized by fever, general toxicity, crampy abdominal pain, and frequent loose stools which contain pus, mucus, and blood. Convulsions occur in 12 to 45 percent of children with shigellosis and are more frequent than in other common febrile infections. Other neurologic findings include headache, lethargy, confusion, nuchal rigidity and hallucination. All of these findings may be present before or after the onset of diarrhea. Although these symptoms have been attributed to the neurotoxicity of shigatoxin in the past, the cause of these neurologic findings has not yet been identified[1,2].

In this study, drug resistance patterns of shigella strains were investigated prospectively in Kayseri between January 1992 and December 1993. Here we reviewed the clinical features of children with shigellosis-associated convulsions and offered guidelines for diagnosis and treatment.

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Material and Methods

We examined the medical records of 68 children who had been admitted to the Department of Pediatrics of the University Hospital in Kayseri with culture-proven shigellosis between January 1992 and December 1993. Each patient's medical and family history as well as clinical and laboratory data were analyzed. All of the 68 isolated serogroups were tested for their susceptibility to ampicillin, ampicillin-sulbactam, co-trimoxazole, gentamicin and ceftriaxone by the agar dilution method[3].

Encephalopathy was defined as a complex of at least two of the following symptoms on admission: severe headache, jitteriness, lethargy, hallucination, confusion, stupor or coma. Convulsions were diagnosed either on the basis of the history taken on admission or if observed during the hospital course. Laboratory investigations included routine hematologic and biochemical examinations, stool cultures, cerebrospinal fluid (CSF) and electroencephalographic (EEG) examination in most of the patients with neurological involvement, and antibiotic treatment was applied according to the antibiogram.

Results

Shigella gastroenteritis was diagnosed by bacteriologic studies in all 68 children. Of the 24 children (35%) who had neurologic symptoms, six (9%) had encephalopathy alone, two (3%) had convulsions and encephalopathy, and 16 (23%) had convulsions alone. EEG tracings were epileptic in three children who did not have a history of convlsive disorders, and lumbar punctures were performed in 14 children. In all of them the CSF chemistry was normal and cultures were negative. Mild lymphocytic pleocytosis, up to 12 cells/mm^3, was noted in only one child.

The mean age was 5.27 years and ranged from one month to 15 years; only two patients were younger than six moths of age, those being one and three months old. Thirty-eight (55.8%) children were between one and five years of age, while 22 (32.3%) children were six to 15 years of age. Forty-seven (69%) of the cases presented during summer and fall. The male to female ratio was 1.22 (41/27).

During clinical follow-up, convulsions were seen in 18 (26.4%) patients and electrolyte imbalances were noted in 14 (20.5%) patients. The distribution of patients according to clinical presentation is summarized in Table I. Mortality was not recorded. The mean hospitalization period was 4.75 days (2-14 days) in 26 children, while the remaining 42 children out of 68 were outpatients.

Table I: Patient Population According to Clinical and Laboratory Presentation

	Patients Without Neurologic Symptoms		Patients with Convulsions Alone		Encephalopathy Alone		Convulsions and Encephalopathy		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total no. of patients	44	66	16	23	6	9	2	3	68	100
History of febrile convulsions	0	0	1	6	1	17	0	0	2	3
History of convulsive disorders	0	0	2	13	0	0	0	0	2	3
Sex										
Male	25	57	13	81	3	50	1	50	42	62
Female	19	43	3	19	3	50	1	50	26	38
Age										
1-11 months	6	14	2	13	0	0	0	0	8	12
1-5 years	26	59	8	50	3	50	1	50	38	56
6-15	12	27	6	37	3	50	1	50	22	32
Fever										
Lower than 38 °C	28	64	4	25	1	17	1	50	34	50
Higher than 38 °C	16	36	12	75	5	83	1	50	34	50
Vomiting	23	52	6	38	4	67	1	50	34	50
Blood/mucus in stool	23	52	10	63	5	83	2	100	40	59
Leukocytosis	9	20	5	31	3	50	1	50	18	26
Leukopenia	4	9	3	19	0	0	0	0	7	10
Shift to the left	8	18	10	63	2	33	1	50	21	31
Hyponatremia	3	7	4	25	2	33	1	50	10	15
Hypernatremia	1	2	0	0	0	0	0	0	1	1.5
Hypokalemia	0	0	2	13	0	0	0	0	2	3
Hyperkalemia	0	0	1	6	0	0	0	0	1	1.5

It was observed that S.sonnei was the most common cause of bacillary dysentery (50%). S.flexneri was second in frequency (44%), three patients had S.boydii (4%) and one patient had S.dysenteriae (1%). Table II summarizes the bacterial serogroups of shigella by neurological status.

Co-trimoxazole resistance ranged from 63.3 percent among isolates of S.flexneri to 44.1 percent among S.sonnei strains. Ampicillin-Sulbactam resistances ranged from 26.6-83.3 percent among S.flexneri and 2.9-42.3 percent among isolates

of S.sonnei strains. Gentamicin resistance was found in 5.8 percent of cases with S.sonnei, and no resistance was observed among S.flexneri. All shigella organisms isolated were susceptable to ceftriaxone. Antimicrobial resistance among shigella isolates is summarized in Table III.

Table II: Bacterial Serogroup of Shigella By neurological Status

	Patients Without Neurologic Symptoms		Patients With Convulsions Alone		Patients With Encephalopathy Alone		Patients With Convulsions and Encephalopathy		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total patients	44	65	16	23	6	9	2	3	68	100
Shigella sonnei	25	57	7	44	2	33	0	0	34	50
Shigella flexneri	17	39	8	50	3	50	2	10	30	44
Shigella boydii	1	2	1	6	1	17	0	0	3	4.5
Shigella dysenteriae	1	2	0	0	0	0	0	0	1	1.5

Table III: Antimicrobial Resistance Among Shigella Isolates

Antimicrobial Agent	No. and (%) of Resistant Isolates S.sonnei (n: 34)	S.flexneri (n: 30)	S.boydii (n: 3)	S.dysenteriae (n: 1)	Total (n: 68)
Ampicillin	14 (41)	25 (83.3)	1 (33.3)	None	40 (58.8)
Ampicillin/Sulbactam	1 (2.9)	8 (26.6)	None	None	9 (13)
Co-trimoxazole	15 (44)	19 (63.3)	None	None	34 (50)
Gentamicin	2 (5.8)	None	None	None	2 (2.9)
Ceftriaxone	None	None	None	None	None

Discussion

Convulsions-associated shigellosis has been widely reported in the literature; however, the incidence ranges in different reviews between 12 and 45 percent[4-6]. The overall frequency of convulsions in our study was 26.4 percent, but the frequency of convulsions in hospitalized children was 56.7 percent, not similar to other series. The true incidence of convulsions in shigellosis is probably lower, if children with mild cases who are not hospitalized are included. Among patients with convulsions and encephalopathy only one child was noted to have mild lymphocytic pleocytosis. In all of them CSF chemistry and cultures were found to be normal.

The majority of convulsions were generalized, tonic-clonic and self-limited. The convulsions lasted less than ten minutes, and none of the patients required anticonvulsive therapy.

Shigella sonnei and S.flexneri currently account for most cases of shigella-associated seizures[6], although these species do not usually produce Shiga toxin as demonstrated by toxin neutralization[7]. In fact, in vivo production of shiga toxin in patients with shigella-associated neurologic manifestations or the presence of toxin in their CSF has not been reported, nor has shiga toxin production in vitro by shigella strains been isolated from these patients. In 26 percent of our patients, convulsions were noted. Convulsions have been described in 12-45 percent of hospitalized patients with culture-proven shigellosis, an incidence four times higher than that in other causes of acute gastroenteritis[8]; thus, neurological symptoms are among the most frequent extraintestinal manifestation of shigellosis. However, children may develop seizures during shigellosis even if they do not experience seizures during other febrile infections[9], and shigella-associated convulsions occur in children older than the usual age for febrile seizures[9-10].

The mechanism for the increased frequency of convulsions in shigellosis is unclear. The cell-free neurotoxin secreted by the bacteria Shiga-toxin is not related[7, 11]. Disturbances of electrolyte and glucose blood levels are not usually mentioned as a possible contributing factor in the development of seizures in shigellosis. High fever, hypocalcemia and hypoglycemia, most likely in combination with other factors, may contribute to the occurrence of seizures. Because the convulsions in sihgellosis are usually benign and self-limited, we do not recommend the routine use of diagnostic procedures such as EEG, roentgenography of the skull or computed tomography. In complicated cases, both diagnostic procedures and drug therapy should be considered.

The traditionally used therapeutic agents, ampicillin and co-trimoxazole, have lost much of their effectiveness over the last decade because of increasing multiple antibiotic resistance of shigella due to conjugative resistance to plasmids[12]. These agents are safe for use in children; however, in our study 58.8 percent of shigella organisms were resistant to ampicillin.

Resistance to co-trimoxazole was found in 63.3 percent and 44 percent of S.flexneri and S.sonnei isolates, respectively. A high resistance to streptomycin (80%), co-trimoxazole (53%) and ampicillin (43%) has previously been demonstrated among shigella isolates in Turkey[13]. Resistance to newer quinolones is rare among Shigella species, but their use is not approved in children[10].

All strains isolated from our patients were susceptible to ceftriaxone. Varsano et al.[14] also reported that all shigella organisms isolated were susceptible to ceftriaxone. Shigella remain was almost uniformly susceptible to gentamicin. It is possible that parenterally administered gentamicin might be useful, but it would be appropriate only for seriously ill patients[10].

It is generally accepted that effective antimicrobial therapy for shigellosis shortens the duration of illness. This is particularly important in pediatric populations from less developed countries in its potentially significant positive impact on the growth and nutritional status of the affected children[14]. Ceftriaxone has been shown to be highly active against shigella strains. An important advantage of this cephalosporin is its long serum half-life of 41/2 to 9 hours, which allows once-daily administration[15].

REFERENCES

1. Cleary TG. Shigellosis. In: Behrman RE, Kliegman RM, Nelson WE, Vaughan VC III (eds). Nelson Textbook of Pediatrics (14th ed). Philadelphia: WB Saunders; 1992; 734-736.
2. Cleary TG, Pickering LK. Acute gastroenteritis. In: Krugman S, Katz SL, Gershon AA, Wilfert CM (eds). Infectious Diseases of Children (9th ed). St. Louis: Mosby; 1992: 105-126.
3. Barry AL, Thornsberry C. Susceptibility tests: diffusion test procedures. In: Lennette EH, Balows A, Hausler WJ Jr, (eds). Shadomy HJ. Manual of Clinical Microbiology (4th ed). Washington DC: American Society for Microbiology; 1985: 978-987.
4. Ashkenazi S, Dinari G, Weitz R, Nitzan M. Convulsions in shigellosis. Am J Dis Child 1983; 137: 985-987.
5. Avital A, Maayan C, Goitein KJ. Incidence of convulsions and encephalopathy in childhood shigella infections. Clin Pediatr 1982; 21: 645-648.
6. Ashkenazi S, Dinari G, Zevulunov A, Nitzan M. Convulsions in childhood shigellosis. Am J Dis Child 1987; 208-210.
7. Prado D, Cleary TG, Pickering LK, et al. The relation between production of cytotoxin and clinical features in shigellosis. J Infect Dis 1986; 154: 149-155.
8. Donald WD, Winkler CH Jr, Bargeron LM Jr. The occurrence of convulsions in children with shigella gastroenteritis. J Pediatr 1956; 48: 323-327.
9. Kowlessar M, Forbes GB. The febrile convulsion in shigellosis. N Engl J Med 1958; 258: 520-526.
10. Salam MA, Bennish ML. Antimicrobial therapy for shigellosis. Rev Infect Dis 1991; 13 (Suppl 4): 332-341.
11. Ashkenazi S, Cleary KR, Pickering LK, Murray BE, Cleary TG. The association of shiga toxin and other cytotoxins with the neurologic manifestations of shigellosis. J Infect Dis 1990; 161: 961-965.
12. Barg NL, Hutson FS, Wheeler LA. Novel dihydrofolate reductases isolated from epidemic strains of trimethoprim/sulfamethoxasole-resistant Shigella sonnei. J Infect Dis 1990; 162: 466-473.
13. Korten V, Mert A, Övinç K, Ceyhan M, Acar S, Ulaş T. Etimesgut bölgesinde 1987 yılında izole edilen shigella serotipleri ve antibiyotik dirençleri. Mikrobiyoloji Bülteni 1988; 22: 89-94.
14. Varsano I, Eiditz -Marcus T, Nussinovitch M, Elian I. Comparative efficacy of ceftriaxone and ampicillin for treatment of severe shigellosis in children. J Pediatr 1991; 118: 627-632.
15. Richards DM, Hell RC, Brogden RN, Speight TM, Avery GS. Ceftriaxone: a review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs 1984; 27: 469-527.

The Turkish Journal of Pediatrics 1996; 38: 189-194

JUVENILE RHEUMATOID ARTHRITIS: CERVICAL SPINE INVOLVEMENT AND MRI IN EARLY DIAGNOSIS*

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SUMMARY: Ören B, Ören H, Osma E, Çevik N. (Departments of Pediatrics and Radiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Juvenile rheumatoid arthritis: cervical spine involvement and MRI in early diagnosis. Turk J Pediatr 1996; 38: 189-194.

Magnetic resonance imaging (MRI) of the cervical spine was performed on 20 patients (mean age 10 years) with a preliminary diagnosis of juvenile rheumatoid arthritis (JRA). In all patients conventional x-rays of the cervical spine were obtained, and the relationship between clinical status and MRI findings were evaluated. Two patients with clinical manifestations, including neck pain and diminished range of motion, exhibited significant pathologic features on radiogram and MRI, the latter providing more detailed information. Among 18 patients who had no complaints about their cervical spines, 3 patients (65%) had either soft tissue involvement, pannus formation or erosions on the surface of atlantoaxial joints; only four patients (20%) had erosions on plain x-ray views. Since the early diagnostic ability of MRI in JRA allows early therapeutic intervention, every patient with a probable diagnosis of JRA would benefit from MRI. *Key words: cervical spine, juvenile rheumatoid arthritis, magnetic resonance imaging.*

Juvenile rheumatoid arthritis (JRA) is a chronic synovitis of childhood associated with a number of extra-articular manifestations. The cervical spine is frequently affected in patients with JRA, a finding that can be of diagnostic value if its involvement can be exhibited properly[1-4]. Chronic synovitis and synovial proliferation, consequent erosion of articular cartilage and pannus formation can best be demonstrated by magnetic resonance imaging (MRI), even in cases without apparent clinical manifestations[3-7].

Although there are several articles in the literature presenting MRI findings of cervical spine involvement in rheumatoid arthritis, they mostly concern adults[3, 5, 7]. In this study we presented the MRI findings of the cervical spine in a series of 20 young patients with JRA and compared the results with plain x-ray views and clinical features.

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Material and Methods

The cervical spines of 20 patients with different types of JRA were examined by MRI over a period of 32 months, beginning in 1991. The patients consisted of seven females and 13 males between the ages of three and 16 years (mean age 10 years). We reviewed the medical records of all patients and noted the presence or absence of neck pain, reduced range of motion, neurological symptoms and signs attributable to neck involvement. Anteroposterior and lateral x-ray views of the neck were obtained in all cases, including flexion-extension views.

All patients were examined with a Siemens 1.0-T Magnetom MR imager. T1-weighted spin-echo 500/15 msec (TR/TE) pulse sequences were performed, as were T2-weighted 2500/22.9 msec sequences with the multiplanar guide imaging technique. A head coil was used for evaluation of the craniocervical junction, and a neck coil was used for the middle and distal parts of the cervical spine. The slice thickness was 4 mm with an interval of 0.4 mm. Sagittal, coronal and axial images were obtained with the head in the neutral position. Anterior atlantoaxial subluxation was considered to be present if the distance from the posterior margin of the corpus of C1 to the anterior margin of the odontoid process was greater than 2.5 mm[8]. In reviewing the MR images, abnormalities of the spinal cord, bones, disc-vertebral joints and soft tissue were noted.

Results

Table I lists the data for the 20 patients studied. Two patients were seropositive for the rheumatoid factor and the others were seronegative. The average duration of disease was 21 months, with a range of one month to eight years. Two patients (10%) had neck pain and diminished range of motion, and none had neurologic deficits attributable to cervical involvement. They had erosions and atlantoaxial subluxation both on plain films and MRI (Fig. 1). Eighteen patients (90%) were free of complaints related to their cervical spines, and no positive physical findings could be detected. Even though they had no complaints, 13 patients (65%) had soft tissue involvement and pannus formation on the MR images; six of them (30%) also demonstrated erosions (Figs. 2-4). On the plain radiographs only four patients (20%) showed erosion of the atlantoaxial joint.

There was no correlation between age and duration of disease in our cases; however, the cases with systemic and polyarticular types of JRA revealed more advanced erosions and soft tissue involvement on cervical MR images than did patients with oligoarticular JRA. Comparisons between groups could not be analyzed statistically because of the small number of cases.

Table I: Patient Data

Patient No.	Age (yrs) / Sex	Type of JRA	Duration of Disease	Radiologic x-ray	Key MRI Findings
1	11/F	Oligoarthritis	< 1 year	–	–
2	14/F	Oligoarthritis	> 1 year	–	+ (Pannus)
3	11/F	Polyarthritis	> 1 year	–	+ (Pannus)
4	5/M	Systemic	> 1 year	–	+ (Soft tissue)
5	12/M	Polyarthritis	< 1 year	+	+ (Subluxation)
6	15/F	Polyarthritis	> 1 year	–	+ (Erosion)
7	5/M	Polyarthritis	> 1 year	+	+ (Erosion)
8	8/M	Polyarthritis	< 1 year	+	+ (Erosion)
9	13/M	Oligoarthritis	> 1 year	–	+ (Erosion)
10	12/M	Polyarthritis	< 1 year	–	+ (Erosion)
11	16/M	Systemic	> 1 year	+	+ (Subluxation)
12	8/M	Polyarthritis	< 1 year	–	–
13	10/F	Systemic	> 1 year	+	+ (Erosion)
14	10/M	Oligoarthritis	< 1 year	–	+ (Soft tissue)
15	3/M	Oligoarthritis	< 1 year	+	+ (Erosion)
16	6/M	Systemic	< 1 year	–	–
17	12/M	Polyarthritis	< 1 year	–	–
18	4/M	Polyarthritis	> 1 year	–	+ (Pannus)
19	14/F	Polyarthritis	> 1 year	–	+ (Soft tissue)
20	12/F	Oligoarthritis	< 1 year	–	–

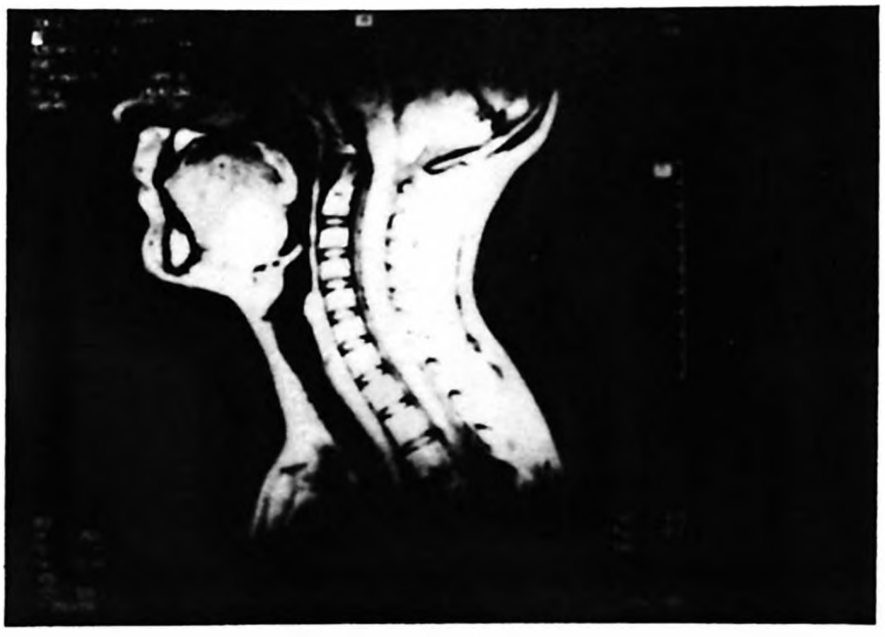

Fig. 1: T.1-weighted MRI of a 16-year-old patient with an 8-year history of JRA. Atlantoaxial subluxation, and destruction and irregularity at the odontoid process.

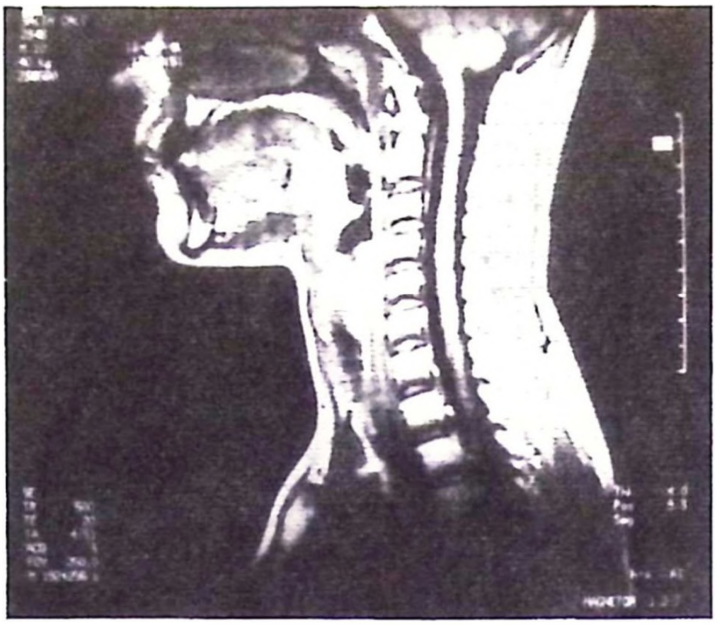

Fig. 2: MRI of a 13-year-old patient with a 12-month history of JRA. Odontoid process surrounded by pannus.

Fig. 3: Constriction at the odontoid process of C-2 and diminished signal intensity of a 3-year-old patient with JRA.

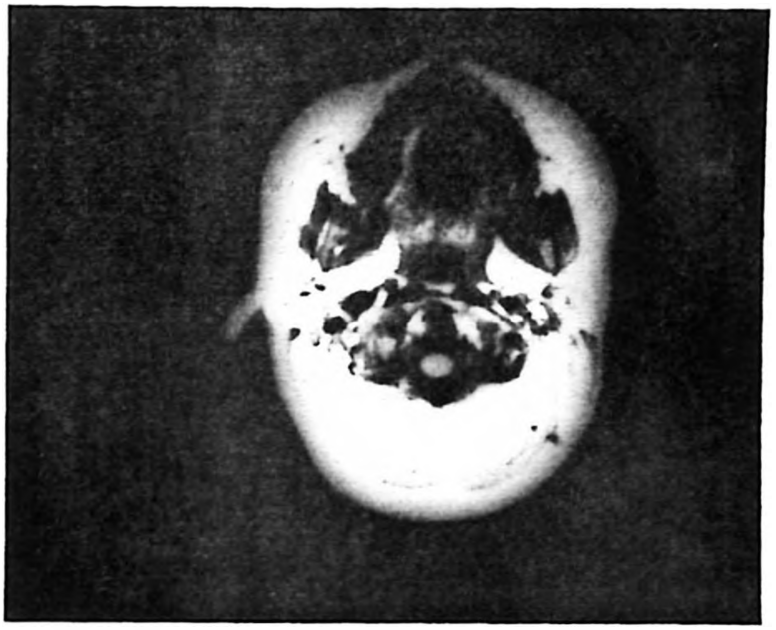

Fig. 4: MRI of a 10-year-old girl with an 8-year history of systemic JRA. Periodontal pannus formation and erosion of odontoid process.

Discussion

Cervical spine involvement in patients with JRA is common, and the evaluation of radiographic findings plays an important role in diagnosis[2, 4, 9]. In cases with JRA, plain films of the neck are not usually satisfactory. Conventional tomography is often helpful but allows demonstration only of bony structures; it is not ideally suited for demonstrating the relationship of the cord to the spinal canal, and contrast agent is generally required[4]. On the other hand, MRI has the capacity to image soft tissues such as the pannus formation, spinal cord and brain stem with great anatomic detail in any plane and generally without the need for contrast material[3, 7].

Our findings demonstrate that MRI can provide useful information, especially in the early diagnosis of JRA. In two patients with clinical manifestations, atlantoaxial subluxation was present, and the degree of subluxation and its projection on the cervical portion of the spinal cord was directly imaged by MRI, whereas it could not be clearly seen on plain films. JRA may involve the cervical spine without apparent clinical manifestations, and this can be demonstrated by different radiological methods[9]. In our study, among 18 patients without any clinical manifestations of cervical involvement, 13 (65%) had soft tissue involvement, pannus formation and erosions on MRI. On plain x-ray views, only erosion could be seen in four patients (20%).

As an interesting finding, the MRI revealed no correlation between the patients' ages and the duration of disease in our cases; however, the type of JRA was important. In systemic and polyarticular types of JRA, mostly erosions and soft

tissue involvement were present. Relying on these findings, cervical spine involvement in cases of systemic and polyarticular-type JRA should always be taken into consideration, especially for early diagnosis of the disease.

The early diagnostic ability of MRI in JRA is very valuable in preventing severe deformities and neuroloogical sequelae and in facilitating early therapeutic intervention. In conclusion, MRI has much to offer in the evaluation of the rheumatoid cervical spine. Every patient with a probable diagnosis of JRA will certainly benefit from MRI in given its ability to confirm the diagnosis and allow for early intervention. However, further cases must be evaluated through MRI in order to make definite conclusions in this regard.

REFERENCES

1. Conlon PW, Isdale IC, Rose BS. Rheumatoid arthritis of the cervical spine. Ann Rheum Dis 1966; 25: 120-26.
2. Bland JH. Rheumatoid arthritis of the cervical spine. J Rheumatol 1974; 1: 319-342.
3. Aisen AM, Martel W, Ellis JH, McCune WJ. Cervical spine involvement in rheumatoid arthritis MR imaging. Radiol 1987; 165: 159-163.
4. Reynolds H, Carter SW, Murtagh FR, Rechtine GR. Cervical rheumatoid arthritis: value of flexion and extension views in imaging. Radiol 1987; 164: 215-218.
5. Larson EM, Holtoas S, Zygmunt S. Pre-and postoperative MR imaging of the craniocervical junction in rheumatoid arthritis. AJR 1989; 152: 561-566.
6. Breedveld FC, Algra PR, Vielvoye CJ, Cats A. Magnetic resonance imaging in the evaluation of patients with rheumatoid arthritis and subluxations of the cervical spine. Arthritis Rheum 1987; 30: 624-629.
7. Pettersson H, Larsson EM, Holtoas S, Cronqvist S, Egund N, Zygmunt S. MR imaging of the cervical spine in rheumatoid arthritis. AJNR 1988; 9: 573-577.
8. Jackson H. The diagnosis of minimal atlantoaxial subluxation. Br J Radiol 1950; 23: 672-674.
9. Wolfe BK, O'Keefe D, Mitchell DM, Tchang SP. Rheumatoid arthritis of the cervical spine: early and progressive radiographic features. Radiology 1987; 165: 145-148.

The Turkish Journal of Pediatrics 1996; 38: 195-197

PLASMA PLASMINOGEN LEVELS IN EARLY RESPIRATORY DISTRESS SYNDROME*

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SUMMARY: Yurdakök M, Yiğit Ş, Gürakan B, Dündar S, Kirazlı Ş, (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Plasma plasminogen levels in early respiratory distress syndrome. Turk J Pediatr 1996; 38: 195-197.

The serum plasminogen status in 35 preterm infants with or without respiratory distress syndrome (RDS) was determined in the first few hours of life. Blood smaples for plasminogen testing (Synthetic chromogenic substrate method; Stachorm PLG. Diagnostica Stago) were obtained from a peripheral vein within six hours after birth. Among 35 infants, 20 infants who were in stable clinical condition served as the control group. Fifteen developed RDS with clinical, laboratory and radiological findings. The mean plasma plasminogen levels were found to be similar in the two groups ($p > 0.05$ by Mann-Whitney U test). These findings are discussed along with our previous findings showing normal tissue plasminogen activator (tPA) but lower D-dimer and higher plasminogen activator inhibitor (PAI) levels within the first few hours of life in preterm infants who later developed RDS compared to the control group. *Key words: newborn infant, plasma, plasminogen, respiratory distress syndrome.*

Disseminated intravascular coagulation (DIC) is frequently encountered in preterm neonates with advanced respiratory distress syndrome (RDS)[1]. However, we previously reported normal plasma fibrinogen, antithrombin III (AT-III), protein C and tissue plasminogen activator (tPA), but lower D-dimer and higher plasminogen activator inhibitor (PAI) levels within the first few hours of life in preterm infants who later developed RDS compared to the control group[2].

The assays commonly used in the diagnosis of DIC, i.e., prothrombin time, activated partial thromboplastin time, fibrinogen or fibrin degradation products (FDP), are insensitive and nonspecific. Evaluation of the plasminogen level is also important in the biological interpretation of the serum level of FDP including D-dimers in cases of DIC. If the concentration of plasminogen is very low in these patients, the degradation of fibrin will be deficient; thus a low level of FDP cannot rule out DIC[3].

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Therefore, we studied the serum plasminogen status in 35 preterm infants with or without RDS in the first few hours of life in an effort to determine the etiology of reduced D-dimer levels.

Material and Methods

All neonates received vitamin K1 1 mg intramuscularly upon delivery. Blood samples for plasminogen testing (Synthetic chromogenic substrate method; Stachorm PLG, Diagnostica Stago, Asnieres-Sur-Seine, France)[4] were obtained from a peripheral vein within six hours after birth, and were mixed with 3.8 percent trisodium citrate in an amount selected according to the hematocrit levels. The tubes were centrifuged at 3.000 rpm for 10 minutes within 30 minutes of collection. The plasma was stored at -20 °C for less than one month before the procedure.

Results

Among 35 infants, 20 infants who were in stable clinical condition served as the control group. Fifteen developed RDS, which was considered to be present if all of the following diagnostic criteria were fullfilled: symptoms of respiratory distress within one hour after birth and present for at least 24 hours, respiratory support including mechanical ventilation, and typical findings on lung x-ray and arterial blood gas analysis. None of the infants with RDS had any other disease.

The mean plasma plasminogen levels were found to be similar in the two groups ($p > 0.05$ by Mann-Whitney U test; Tabel I).

Table I: Plasma Plasminogen Levels in Preterm Infants with or without RDS (mean ± SD).

	Controls (n: 20)	Infants with RDS (n: 15)
Gestational age (weeks)	32.1 ± 2.1	32.4 ± 1.7
Birth weight (g)	1614 ± 439	1851 ± 602
Plasminogen (%)	55.28 ± 33.12	41.43 ± 19.24

Plasminogen levels are expressed as a percentage of control.
In all comparisons, $p > 0.05$ by Mann-Whitney U test.

Discussion

D-dimers are the end-products of fibrinolysis which results from the conversion of an inert plasma proenzyme (plasminogen) into a proteolytic enzyme (plasmin)[5]. Reduced D-dimer levels found in the previous study[2] within six hours after delivery in preterm infants who developed RDS could not be explained by the normal plasminogen levels found in this study. However, reduced D-dimer levels may be due to an increase in the clearance of FDP or over-consumption in DIC. FDPs,

even large FDPs containing the D domain, are removed from the circulation by clearance mechanisms in the liver, kidney, and reticuloendothelial system. In addition, FDP products and their complexes profoundly impair the hemostatic process and are presumably a major cause of hemorrhage in DIC and fibrinolysis by inhibiton of coagulation and impairment of platelet functions[5].

Normal plasminogen levels in the early stages of RDS could be explained by normal levels tPA, of which converts plasminogen into plasmin[2]. However, the presence of increased PAI levels without any increase in tPA levels remains to be elucidated. Both tPA and PAI are isolated from many cells, including the endothelium[5]. The increased levels of PAI in the previous study may be related to endothelial damage during RDS, because increased von Willebrand antigen levels, which is a reliable marker for systemic and/or lung endothelial damage, were found in the early stages of RDS[6].

These abnormalities seen in the early stages of RDS are presumably different from those found in the later stages of the disease. Further studies are needed to clarify the changes in the hemostatic system in earlier and later stages of RDS.

REFERENCES

1. Stark CR, Abramson D, Erkan V. Intravascular coagulation and hyaline-membran disease of the newborn. Lancet 1968; 1: 1180-1181.
2. Yurdakök M, Oran O, Dündar S, Tekinalp G, Kirazlı Ş. Reduced fibrinolytic state in early respiratory distress syndrome. Am J Hematol 1993; 42: 233-234.
3. Feinstein DI. Diagnosis and management of disseminated intravascular coagulation: the role of heparin therapy (Review). Blood 1982; 60: 284-287.
4. Silverstein RM. The determination of human plasminogen using N^{α}-CBZ-L-Lysine p-nitrophenyl ester as subtrate. Anal Biochem 1975; 65: 500-506.
5. Bithell TC. Blood coagulation. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds) Wintrobe's Clinical Hematology, (9^{th} ed) Vol 1. Philadelphia: Lea and Febiger; 1993: 566-615.
6. Yurdakök M, Gürakan B, Ergin H, Kirazlı Ş. Increased von Willebrand factor antigen in early respiratory distress syndrome. Am J Hematol 1995; 49: 95-96.

The Turkish Journal of Pediatrics 1996; 38: 199-204

THE RISK OF BILIRUBIN ENCEPHALOPATHY IN NEONATAL HYPERBILIRUBINEMIA*

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SUMMARY: Oktay R, Satar M, Atıcı A. (Neonatology Unit, Department of Pediatrics, Çukurova University Faculty of Medicine, Adana, Turkey). The risk of bilirubin encephalopathy in neonatal hyperbilirubinemia. Turk J Pediatr 1996; 38: 199-204.

Jaundice is the most common and one of the most annoying problems that can occur in the newborn. Although most jaundiced infants recover without any serious problem, there is always a risk of bilirubin encephalopathy during the period of hyperbilirubinemia.

The relationship between encephalopathy and serum free bilirubin levels was investigated in 83 newborn infants (40 premature, 43 mature) with unconjugated hyperbilirubinemia. A complete physical examination was done in all patients, and signs of bilirubin encephalopathy were noted if present. The serum free bilirubin level exceeded 0.1 mg/dl in 13 infants, and 12 of them showed signs of encephalopathy. On the other hand, none of the infants whose serum free bilirubin levels were below 0.1 mg/dl showed signs of encephalopathy.

Although there is a significant positive correlation between serum total and free bilirubin levels, it is not clear at what total bilirubin level free bilirubin will appear. Serial determinations of free bilirubin appear to be more helpful in the management of hyperbilirubinemia in infants with an increased risk of bilirubin toxicity. *Key words: encephalopathy, free bilirubin, jaundice, neonatal hyperbilirubinemia.*

Hyperbilirubinemia is one of the most common problems during the neonatal period, and the risk of bilirubin encephalopathy was first recognized many years ago. Bilirubin encephalopathy is a neurologic syndrome resulting from the deposition of bilirubin in brain cells. The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable[1-4].

Several studies have suggested that there is a relationship between bilirubin encephalopathy and serum free bilirubin levels, but it has also been reported that albumin-bound bilirubin may cause bilirubin encephalopathy in cases of acute blood-brain barrier damage. Many of the biochemical and physiological factors involved in the pathogenesis of bilirubin encephalopathy have been identified during recent years, but their relative importance remains unclear[4-6].

The aim of this prospective study was to investigate the relationship between bilirubin encephalopathy and serum free bilirubin levels in neonatal hyperbilirubinemia.

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Material and Methods

Çukurova University Medical Faculty Research Hospital is one of the main referral centers in south and southeast Turkey for the management of neonatal hyperbilirubinemia. A total of 83 newborns who were referred to us with unconjugated hyperbilirubinemia formed the study group.

A detailed history was obtained in all cases, and a complete physical examination was done by an experienced pediatrician working in the field of neonatology. Signs of bilirubin encephalopathy, such as lethargy, irritability, poor sucking, hypertonia and high-pitched cry were noted if present[4,6]. Other possible reasons for these symptoms (hypoglycemia, systemic infection, intracranial hemorrhage, etc.) were carefully evaluated.

The gestational age of each patient was calculated from the mother's last normal menstrual period or by using the Dubowitz method[7]. Forty of the 83 infants were premature, and the remainder were term, with a mean gestational age of 34.9 ± 2.0 and 39.3 ± 1.2 weeks, respectively.

Total and direct bilirubin concentrations and serum albumin levels were determined by using Technicon RA-XT (England). Sephadex G-25 gel filtration method, which was modified by Blondheim et al.[8], was used to determine the patients' serum free bilirubin levels.

The collected data was evaluated using the SPSS-X (Rel. 4.1) package program. The statistical analyses were done with Student t, Mann Whitney U and correlation coefficient tests.

Results

The characteristics of the mature and premature infants are shown in Table I. The mean albumin and total, direct and free bilirubin levels were not different in the premature and mature groups ($p > 0.05$) (Table II).

Table I: Selected characteristics of the Infants

		Premature	Mature
Sex	Female	13	21
	Male	27	22
	Total	40	43
Gestational age (weeks) (Mean ± SD)		30-37 (34.9 ± 2.0)	38-42 (39.3 ± 1.2)
Birth weight (grams) (Mean ± SD)		1330-4000 (2515 ± 579)	2455-4850 (3292 ± 459)
Postnatal age (days) (Mean ± SD)		1-20 (6.5 ± 4.5)	1-11 (5.5 ± 2.3)

Table II: Mean Albumin; Total, Direct and Free Bilirubin Levels in Premature and Mature Infants

	Premature	Mature	p
Number of infants	40	43	
Total bilirubin (mg/dl) (Mean ± SD)	7.2-33.6 (20.2 ± 5.4)	3.4-40.4 (20.7 ± 7.8)	> 0.05
Direct bilirubin (mg/dl) (Mean ± SD)	0.4-2.0 (1.06 ± 0.39)	0.4-2.0 (0.95 ± 0.35)	> 0.05
Albumin (g/dl) (Mean ± SD)	1.9-5.3 (3.7 ± 0.7)	2.9-5.0 (3.9 ± 0.5)	> 0.05
Free bilirubin (mg/dl) (Mean ± SD)	0.000-0.270 (0.043) ± 0.044)	0.000-0.660 (0.045 ± 0.122)	> 0.05

Free bilirubin was found in the sera of 27 premature (67.5%) and 15 mature (34.8%) infants. However, only six infants in the premature (15%) and six infants in the mature (13.9%) groups showed signs of encephalopathy on admission, and none of them subsequently developed encephalopathy. A significant positive correlation was found between serum total and free bilirubin levels ($r = 0.70$, $p < 0.01$). The mean total and free bilirubin levels were not different in premature and mature infants who showed signs of encephalopathy (Table III).

Table III: Mean Total and Free Bilirubin Levels in Infants with Encephalopathy

	Premature	Mature	p
Number of infants	6	6	
Total bilirubin (mg/dl) (Mean ± SD)	19.9-33.6 (27.1 ± 5.7)	18.5-40.4 (32.7 ± 8.4)	> 0.05
Free bilirubin (mg/dl) (Mean ± SD)	0.104-0.270 (0.173 ± 0.062)	0.108-0.660 (0.278 ± 0.220)	> 0.05

Serum free bilirubin was greater than 0.1 mg/dl in all of the infants who showed signs of encephalopathy, while only one of the normal infants had serum free bilirubin greater than this level. The serum total and free bilirubin levels of the patients are shown in Table IV, and these levels were significantly higher among patients with signs of encephalopathy.

Table IV: Serum Total and Free Bilirubin Levels in Patients with and without Encephalopathy

	Encephalopathy (+)	Encephalopathy (-)	p
Number of infants	12	71	
Free bilirubin (mg/dl) (Mean ± SD)	0.104-0.660 (0.225 ± 0.164)	0.000-0.112 (0.013 ± 0.022)	< 0.001
Total bilirubin (mg/dl) (Mean ± SD)	18.5-40.4 (29.9 ± 7.4)	3.4-29.9 (18.9 ± 5.1)	< 0.001

Discussion

The present study reviews our experience with neonatal hyperbilirubinemia and bilirubin encephalopathy. It is a well-known fact that free bilirubin has toxic effects on the brain, and that the amount of bilirubin entering the brain increases dramatically when total serum bilirubin levels exceed 20 mg/dl[1, 9-11]. The management of hyperbilirubinemia is usually based on serum total bilirubin levels in many centers. Although a significant positive correlation was found between serum total and free bilirubin levels, it is almost impossible to predict when free bilirubin which is directly toxic to the brain, will appear in the serum[8, 12, 13].

In general, prematurely born infants appear to be more susceptible than mature neonates to the development of bilirubin encephalopathy[14]. In the present study, premature infants seemed to have free bilirubin in their sera more frequently than term infants, although there were no differences between their serum total bilirubin and albumin levels. The lower binding capacity of albumin in premature infants may play a role in the increase in free bilirubin levels[15]. However, unexpectedly, the number of infants with signs of kernicterus was the same in the premature and mature groups.

It is well known that free bilirubin is not the only factor in the pathogenesis of bilirubin encephalopathy. Many of the biochemical, physiological, environmental and genetic factors that may play a role in the pathogenesis of bilirubin encephalopathy have been defined recently[4]. These include the binding of bilirubin to albumin, which increases with postnatal age, the transport and passage of bilirubin across the blood-brain barrier, and the susceptibility of the target neurons[4, 6]. The role of free fatty acids in altered bilirubin binding is still controversial[16]. Although the development of hyperbilirubinemia is reported to be more probable in neonates with high alpha-fetoprotein levels in the umbilical cord[17], the relationship between alpha-fetoprotein, the transferrin/alpha-fetoprotein ratio and hyperbilirubinemia is still under investigation[18, 19]. The duration of exposure to high concentrations of free bilirubin may also play a role in bilirubin encephalopathy, but it was impossible to predict this duration in the present study.

Makamura et al.[12] and Zamet et al.[13] reported that all the kernicteric infants in their study groups had serum free bilirubin levels greater than 0.1 mg/dl. Similarly, in the present study, we found 13 infants with serum free bilirubin levels exceeding 0.1 mg/dl, and 12 of them subsequently showed signs of encephalopathy. On the other hand, none of the infants whose serum free bilirubin levels were below 0.1 mg/dl showed signs of encephalopathy. A serum free bilirubin level exceeding 0.1 mg/dl seems to be a good indicator of a high risk for bilirubin encephalopathy.

Thus, we believe that serial free bilirubin measurements, in addition to assessment of the other risk factors mentioned above, would be helpful in the management of jaundiced infants at risk for bilirubin encephalopathy.

REFERENCES

1. Brodersen R. Binding of bilirubin to albumin. Crit Rev Clin Lab Sci 1980; 11: 305-309.
2. Brodersen R, Stern L. Deposition of bilirubin acid in the central nervous system a hypothesis for the development of kernicterus. Acta Paediatr Scand 1990; 79: 12-19.
3. Deziel MR, Girotti AW. Photodynamic action of bilirubin on liposomes and erythrocyte membranes. J Biol Chem 1980; 255: 8192-8198.
4. Wennberg RP. Bilirubin physiology. In: Roberton NRC (ed). Textbook of Neonatology (2nd ed). London: Churchill Livingstone; 1992: 605-617.
5. Bratlid D. How bilirubin gets into the brain. Clin Perinatol 1990; 17: 449-465.
6. Gartner LM, Lee KS. Unconjugated hyperbilirubinemia. In: Fanaroff AA,Martin RJ (eds). Neonatal-Perinatal Medicine (5th ed). Missouri: Mosby-Year Book; 1992: 1075-1104.
7. Dubowitz L, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediatr 1970; 77: 1-10.
8. Blondheim SH, Kapitulnik J, Valaes T. Use of a sephadex column to evaluate the bilirubin-binding capacity of the serum of infants with neonatal jaundice. Israel J Med Sci 1972; 8: 22-28.
9. Brodersen R. Bilirubin transport in the newborn infant, reviewed with relation to kernicterus. Pediatrics 1980; 96: 349-356.
10. Maisels MJ. Jaundice. In: Avery GB, Fletcher AM, McDonald MG (eds). Neonatology (4th ed). Philadelphia: JB Lippincott; 1994: 630-725.
11. Robinson PJ, Rapoport SI. Binding effect of albumin on uptake of bilirubin by brain. Pediatrics 1987; 79: 553-558.
12. Nakamura H. Lardinois R. Unbound bilirubin in icteric newborns. Biol Neonate 1972; 21: 400-417.
13. Zamet P, Chunga F. Separation by gel filtration and microdetermination of unbound bilirubin. II. Study of sera in icteric newborn infants. Acta Pediatr Scand 1971; 60: 33-38.
14. Gartner LM, Snyder RN, Chabon RS. Kernicterus: high incidence in premature infants with low serum bilirubin concentrations. Pediatrics 1970; 45: 906-917.
15. Hansen TW, Bratlid D. Bilirubin and brain toxicity. Acta Paediatr Scand 1986; 75: 513-522.
16. Ostrea EM Jr, Bassel M, Fleury CA, et al. Influence of free fatty acids and glucose infusion on serum bilirubin and bilirubin binding to albumin: clinical implications. J Pediatr 1983; 102: 426-432.

17. Hodr R, Stroufova A, Kepertova M, Ondrackova Z, Skutilova J. Alpha-fetoprotein in umbilical cord blood and hyperbilirubinemia in normal neonates. Cesk Pediatr 1990; 45: 390-393 (Eng. Abstr.).

18. Montagna O, Mautone A, Altomare M, et al. Transferrin/alpha-fetoprotein ratio as a predictive index in hyperbilirubinemia. Minerva Pediatr 1987; 39: 361-363 (Eng. Abst.).

19. Laszlo V, Kurcz M, Nagy I, Felszegi K. Serum alpha-fetoprotein patterns in the newborn with indirect hyperbilirubinemia. Orv Hetil 1985; 126: 507-508, 511-514 (Eng. Abstr.).

The Turkish Journal of Pediatrics 1996; 38: 205-216

PUBLICATION POTENTIAL IN PEDIATRICS IN TURKEY*+

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SUMMARY: Tınaztepe K. (Nephropathology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Publication potential in pediatrics in Turkey. Turk J Pediatr 1996; 38: 205-216.

In this article, the publication potential in pediatrics in Turkey was investigated. In this context, native pediatric journals, publication activities of medical faculties as the main source of scientific publication and certain data obtained from some of the international indexes' sources were analyzed. The Turkish Journal of Pediatrics (Turk J Pediatr) and Çocuk Sağlığı ve Hastalıkları Dergisi are two native pediatric journals which have been published without interruption for 36 and 37 years, respectively. Both are indexed in BIOSIS (Bioscience Information Service) and Excerpta Medica. In addition, Turk J Pediatr is indexed in Index Medicus and Current Contents, and is the only Turkish medical journal indexed in Index Medicus at present. Eighty percent of papers submitted to both journals are from medical faculties all over the country (60% of these from Hacettepe Faculty of Medicine), while 15% are from the teaching hospitals of the Ministry of Health and 5% from outside the country. In 1994, Hacettepe University School of Medicine was the leader with 244 (21%) of the 1165 articles published in the health sciences from 22 medical faculties in Turkey. In the same year, 32 percent of all international medical publications by Hacettepe Faculty of Medicine were in the field of pediatrics. In addition, of 353 papers by Turkish authors appearing in Current Contents during the three-month period July-September 1993, 70 (20%) were pediatric articles. All of these findings may indicate that publications in the field of pediatrics have increasing potential and an important impact on the scientific medical publication's platform in our country. *Key words: scientific publication potentials, pediatrics, Turkish Journal of Pediatrics, Çocuk Sağlığı ve Hastalıkları Dergisi, Turkey.*

The universities are the main source of the scientific publication potential in a given country. In the case of Turkey, medical faculties will be of great importance in assessing this potential in the field of pediatrics. In this respect, governmental teaching hospitals with a small impact on the publication potential will also be considered worthy of evaluation. During the last ten years, scientific publications in Turkey have steadily increased and reached a peak in 1994[1,2]. The increment rate in this period was one-fold per year until 1993, but threefold in the last year,

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+ *This study was partly presented as a conference in "Scientific writing, editing and auditing in medicine" held by TUBITAK, November 18, 1994, Ankara.*

\# *Editor:*
The Turkish Journal of Pediatrics
Çocuk Sağlığı ve Hastalıkları Dergisi
1981-1993

indicating rapid progress as compared with the uniform, slow rate per year in the previous seven years[2]. This improvement has certainly been affected by the developments in medical faculties that have existed for more than 30 years and by the additional publication activities of newly established medical faculties. It is possible to evaluate the publication potential in pediatrics to a certain degree by noting pediatric papers published in international journals and also by reviewing the native journals in which all or the majority of the articles are in the field of pediatrics. In this article, I will introduce two native pediatric journals entitled, "The Turkish Journal of Pediatrics" and "Çocuk Sağlığı ve Hastalıkları Dergisi" for which I acted as a scientific and managing editor during the 12 year period from 1981 through 1993. I will also mention the experience of the managing team of these journals in terms of the publication potential in pediatrics. Finally, the summary of available data obtained from national and international documentation sources about this subject will be given[1-3].

As noted in Table I, under the list of "Current Pediatric Journals" there are approximately 10 native pediatric journals registered in Turkey's National Library[1]. The native pediatrics periodicals occupying the first two ranks in the list and entitled The Turkish Journal of Pediatrics (Turk J Pediatr) and Çocuk Sağlığı ve Hastalıkları Dergisi (ÇSHD) were founded by Professor İhsan Doğramacı and have been published for 36 and 37 years, respectively. These two periodicals have been supported both scientifically and financially by him since their first appearance.

Table I: Current Pediatric Journals in Turkey*

		Language	
Title	Volume (yrs)	English	Turkish
Turkish Journal of Pediatrics	36	Full-text	–
Çocuk Sağlığı ve Hastalıkları Dergisi	37	Abstr.	Full-text
İstanbul Çocuk Kliniği Dergisi	29	Abstr.	Full-text
Yeni Tıp Dergisi	11	Abstr.	Full-text
Pediatrik Cerrahi Dergisi	7	Full-text mixed	
Türkiye Klinikleri Pediatri	3	Abstr.	Full-text
Jinekoloji Obstetrik Pediatri	1	Abstr.	Full-text
Journal of Neonatology	1	Full-text	–
Pediatride Yönelişler	1	Abstr.	Full-text
Katkı Pediatri Dergisi (Review in Ped.)	15	–	Full-text
Others			

* Registered periodicals in National Library, 1994.
All have editorial board.

The Turkish Journal of Pediatrics (Turk J Pediatr): Turk J Pediatr is an English-language quarterly journal which has been published since 1958 without interruption[4,5]. Some specifications of this journal given in Ulrich's International Periodicals Directory[4] are seen in Table IIa. This periodical was published by the Turkish National Pediatric Society and the Turkish and International Children's Center (TICC) between 1981 and 1993. After September 1993, Hacettepe University Institute of Child Health replaced TICC. Turk J Pediatr has been indexed in Index Medicus since 1962 (32 years without interruption). It has also been indexed in Excerpta Medica and has been appearing in Current Contents since 1990[4]. Therefore, this journal with its English abstracts is readily seen in a Medline-DATABASE search. The medical journals indexed in Index Medicus in our country are shown in Table III. As seen here, Turk J Pediatr was the only medical journal listed in Index Medicus as of 1994[6]. As seen in Tables IV and V, Turk J Pediatr received several citations in the periodicals listed in the Science Citation Index (SCI) shortly after it was published in 1958. I should mention right here that these figures represent random and individual sampling. Similarly, Turk J Pediatr has also appeared as a cited reference in some international textbooks (Table VI). In summary, Turk J Pediatr is a continuously cited journal, even though the number of citations is limited. In this context, Figure 1 indicates the rising "impact factor" of The Turkish Journal of Pediatrics during the last four years of my editorship[7].

Table IIa: Some Specifications of Turk Journal Pediatr Reported in Ulrich's International Periodicals Directory

Reference: Ulrich's International Periodicals Directory 1994-1995, 33rd ed, Vol: 3, 618.92 TU ISSN 0041-4301

Turkish Journal of Pediatrics
(Text in English)
1958.q. Turkish and International
Children's Center, P.O. Box 66,
Samanpazarı, 06240 Ankara - Turkey.
(Co-sponsor: Turkish National
Pediatric Society).bk. rev.; abstr.;
bibl.; charts; illus.; index: circ. 1500.
Indexed: Biol. Abstr., Curr. Adv. Ecol. Sci.
Dent. Ind., Nutr. Abstr. (CAB), Abstr. Hygiene
Commun. Dis. Tropical Dis. Bull.,
Excerpta Medica,
Index Medicus, Current Contents.

Table III: Turkish Journals Included in Index Medicus*

Names of Journals	Years of Indexed	Duration
Türk Tıp Cemiyeti Bülteni	1960	1 yr
Türk Tıp Encümeni Arşivi	1963	1 yr
Tıp Fakültesi Mecmuası (İst.)	1962-1984	22 yrs
Türk Hijyen Tecrübi Biyoloji Der.	1974	1 yr
Mikrobiyoloji Bülteni	1976-1993	17 yrs
Turkish Journal of Pediatrics**	1962-1995	33 yrs
		Continuing

* Data were renewed in 1995[4].
** Only Medical Journal present in Index Medicus List in 1995 from Turkey.

Table IV: Some Journals Citing Turkish Journal of Pediatrics (Random and Individual Sampling) (Part I)

Turk J Pediatr 1958; 1: 173.
Cited in: British Journal of Urology 1960; 32: 269-272.

Turk J Pediatr 1959; 2: 60.
Cited in: Lancet 1961; i: 20-22., Arch Dis Child 1961; 36: 137.

Turk J Pediatr 1966; 8: 206-215.
Cited in: Ann NY Acad 1970; 174: 592, and multiple journals.

Turk J Pediatr 1973; 15: 82.
Cited in: Cancer 1977; 40: 1519.

Turk J Pediatr 1976; 18: 53.
Cited in: Am J Dis Child 1979; 133: 1160.

Turk J Pediatr 1966; 8: 216.
Cited in: Laryngoscope 1980; 90: 635.

Turk J Pediatr 1973; 15: 129.
Cited in: Int J Cancer 1981; 15: 129., Br J Cancer 1984; 49: 503.

Turk J Pediatr 1969; 11: 146.
Cited in: J Neurosurgery 1984; 61: 167.

Turk J Pediatr 1982; 24: 211.
Cited in: The Pediatric Clinics of North America 1987; 34: 626.

Table V: Some Journals Citing Turkish Journal of Pediatrics (Random and Individual Sampling) (Part II)

Turk J Pediatr 1983; 25: 91. Cited in: Ultrasound MR 1987; 9: 13.
Turk J Pediatr 1978; 20: 133. Cited in: J Pediatr 1988; 133: 30.
Turk J Pediatr 1981; 23: 269. Cited in: Arch Neurology 1989; 46: 510.
Turk J Pediatr 1981; 23: 37. Cited in: N Engl J Med 1990; 323: 315.
Turk J Pediatr 1986; 28: 165. Cited in: Am J Trop Pediatr 1991; 37: 240.
Turk J Pediatr 1987; 29: 187. Cited in: Int J Cardiology 1992; 37: 329.
Turk J Pediatr 1981; 23: 269. Cited in: J Neurosurgery 1992; 76: 696.
Turk J Pediatr 1987; 29: 171. Cited in: Acta Paediatr 1993; 82: 327.
Turk J Pediatr 1986; 28: 219. Cited in: Ped Hematol Oncol 1994; 11: 223.

Table VI: Some of the International Textbooks Citing Turkish Journal of Pediatrics (Random Sampling)

Recognizable Patterns of Human Malformation Smith DW (ed). Philadelphia: W.B. Saunders Co; 1976.
Otolaryngology Paparella and Shumrick (eds). W.B. Saunders Co; 1980.
Current Pediatric Diagnosis and Treatment Hathaway WE, Groothuis JR, Hay WW, Paisley JW (eds). New Jersey: Appleton and Lange; 1991.
Effective Care of The Newborn Infant Sinclair JC and Bracken MB (eds). Oxford University Press; 1992.

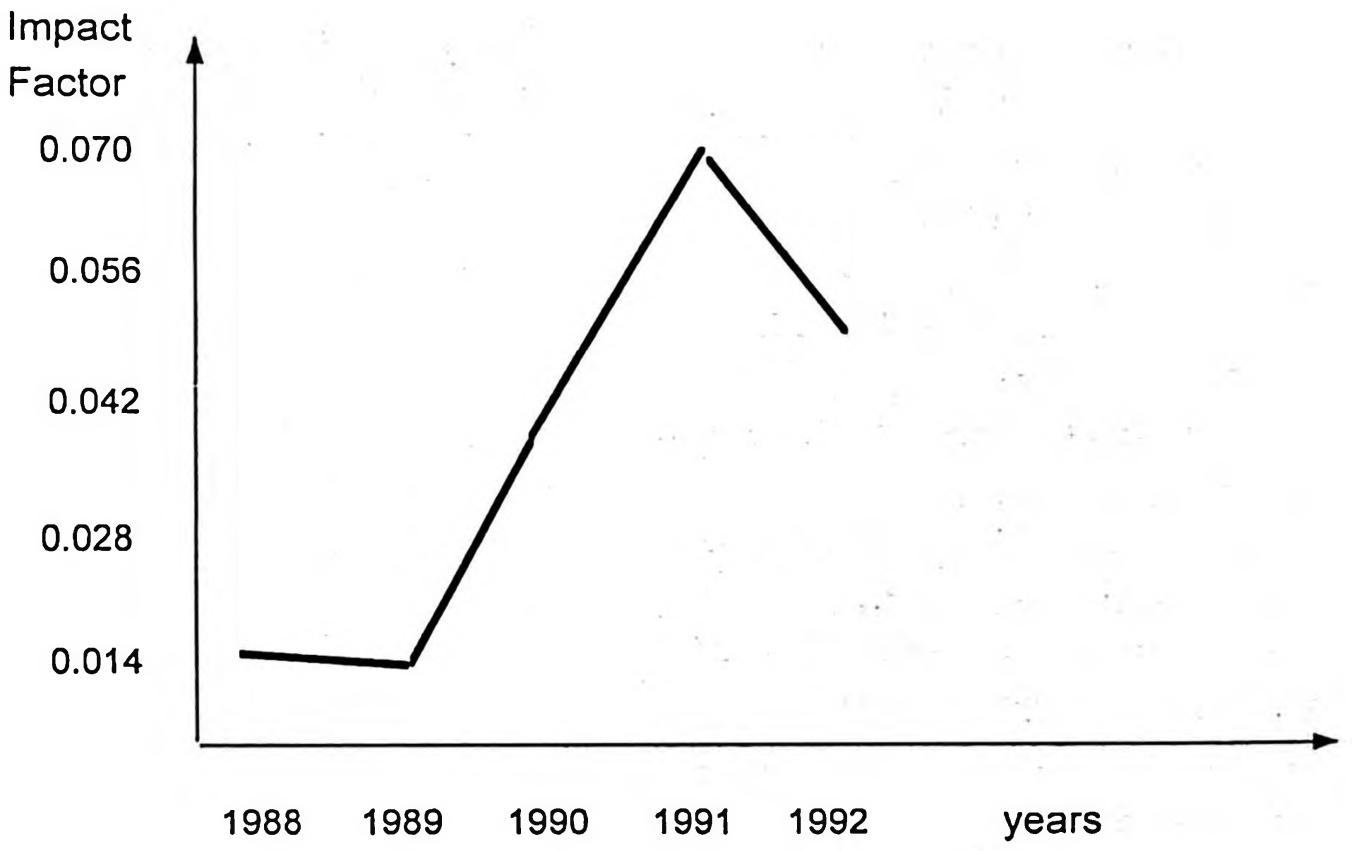

Fig. 1: The impact factor of Turkish Journal of Pediatrics between 1988-1992.

Çocuk Sağlığı ve Hastalıkları Dergisi (ÇSHD): Çocuk Sağlığı ve hastalıkları Dergisi ranks second in our current pediatric journals' list. Çocuk Sağlığı ve Hastalıkları Dergisi* (text in Turkish with English abstracts) is a quarterly journal and has been published since 1957 without interruption[4] (Table IIb). It was published by the Turkish National Pediatric Society and the Turkish and International Children's Center (TICC) between 1981 and 1993. After September 1993, Hacettepe University Institute of Child Health replaced TICC. In addition to BIOSIS (Bioscience Information Service), it has been covered in Excerpta Medica since 1992. Because it contains English abstracts, it is cited, though rarely, in the journals listed in SCI and in international conferences' proceedings, as seen in Table VII.

Back to Table I: Excluding Katkı Pediatri Dergisi** which fully consists of reviews in pediatrics, the majority of the journals published in our country are recent publications, and they have not yet been included in any of the international indexes. Although they have editorial boards, they need to improve by publishing peer-reviewed articles with representative abstracts in English[8]. When I reviewed some of their articles I noticed that they include certain phrases such as "discussed in the view of literature" which is not an accepted way of writing in scientific publications.

* Turkish title is translated as "Bulletin of Child Health and Diseases"

** Bimonthly Turkish-language journal, a joint publication of Hacettepe University Faculty of Medicine, Department of Pediatrics and Hacettepe University Institute of Child Health.

Table IIb: Some Specifications of Çocuk Sağlığı ve Hastalıkları Dergisi Reported in Ulrich's International Periodicals Directory

Reference: Ulrich's International Periodicals Directory 1994-1995, 33rd ed, Vol: 3, 618.92 TU ISSN 0010-0161 Coden: CHSDAO
Çocuk Sağlığı ve Hastalıkları Dergisi (Text in Turkish; summaries in English) 1958.q. Turkish and International Children's Center-Türkiye ve Uluslararası Çocuk Sağlığı Merkezi, P.O. Box 66, Samanpazarı, 06240 Ankara - Turkey. (Co-sponsor: Turkish National Pediatric Society).bk. rev.; abstr.; bibl.; charts; illus.; index: circ. 1500. Indexed: Biological Abstracts, Excerpta Medica (1992-).

Table VII: Some of the Journals, International Registry Books and International Conferences' Proceedings Citing Çocuk Sağlığı ve Hastalıkları Dergisi* (Random Sampling)

Çocuk Sağlığı ve Hastalıkları Dergisi 1979; 22: 52. Cited in: Acta Haematol 1984; 71: 69.
Çocuk Sağlığı ve Hastalıkları Dergisi 1982; 25: 365. Cited in: Hemoglobin 1985; 9: 209.
Çocuk Sağlığı ve Hastalıkları Dergisi 1972; 14: 155. Cited in: Human and Experimental Toxicology 1990; 9: 273.
Çocuk Sağlığı ve Hastalıkları Dergisi 1990; 33: 3-13. Cited in: Register of Tetrahydrobiopterin Deficiencies. Dhont JL (Ed), 1991, p. 69.
Çocuk Sağlığı ve Hastalıkları Dergisi Special issue 1991; 34: 247-379. Title: Anne sütü (Breast feeding) Copied and distributed for Proceedings of UNICEF/WHO/IPA International Conference 1992, Ankara.

* Quarterly Journal of Child Health and Diseases: Full-text in Turkish with English abstracts.

In order to establish an opinion about the scientific pediatric publication potential in our country, I will give three informative examples. In the first example, the contents of Turk J Pediatr and ÇSHD are evaluated. The sort and number of the articles submitted to Turk J Pediatr and ÇSHD in the period 1988-1993 are summarized in Tables VIII and IX (Figs. 2-4). In this five-year period, of 588 articles

submitted to both journals, 80 percent were accepted for publication, yielding an average of 95 articles published per year[9]. As shown in Table VIII, 60 percent of the articles were from Hacettepe University Faculty of Medicine, 20 percent from other native medical faculties, 15 percent from teaching hospitals of the Ministry of Health, and five percent from foreign authors. As seen from these figures, the majority of the articles were submitted by Hacettepe Faculty of Medicine. In this context, as an editorial board member I will describe the process of obtaining articles having scientific publication norms for both journals: The first step is evaluation of the submitted articles by at least two board advisors as well as one of the managing board members, who identify all of the necessary corrections in detail regarding the writing style and the scientific content of the articles, and then demanding the authors to make corrections in accordance with their critiques and topic-related references. The majority of the articles needed this type of process, and some of the articles were almost rewritten. This approach is, in fact, our policy of scientific writing education. By this effort, we believe that we promote the scientific publication potential especially in newly established faculties and governmental teaching hospitals. On the other hand, we must solve the new problem that developed in terms of the accumulation of accepted papers waiting for publication. Therefore, we planned to publish more scientific articles per year. In order to achieve this goal, the organization of appropriate secretarial functions, documentation and circulation team work had to be provided. Naturally, adequate financial support is necessary to accomplish this aim; thus, we were provided with more financial support. With the devoted efforts of each member of the managing board, the number of articles published per issue was increased by the year 1990 and the increment rate reached 50 percent per volume by the year 1995.

Table VIII: Types of Submitted/Accepted Papers to Turkish Journal of Pediatrics 1988-1993

Paper	Originals	Case Reports	Others**	Total
Submitted* (n)	187	113	15	315
Published (n)	131	105	12	248
Publication percentage	...70%	.... 93%.....	...80%	80%
Unpublished:	56	8	3	67
				20%
Rejected/Loss of communication	14/42	4/4	3/0	21/46

* Editorial board records. ** Invited topics and seminars.

1. Hacttepe Faculty of Medicine 60%
2. Medical Faculties all over the country..... 20%
3. Governmental teaching hospitals 15%
4. Outside contributions 5%

Table IX: Types of Submitted/Accepted Papers to Çocuk Sağlığı ve Hastalıkları Dergisi 1988-1993

Paper	Originals	Case Reports	Others**	Total
Submitted* (n)	166	75	32	273
Published (n)	126	73	29	228
Publication percentage	...76%	.... 97%.....	...90%	84%
Unpublished:	40	2	3	45%
				16%
Rejected/Loss of communication	10/30	1/1	3/0	14/31

* Editorial board records. ** Invited topics and seminars.

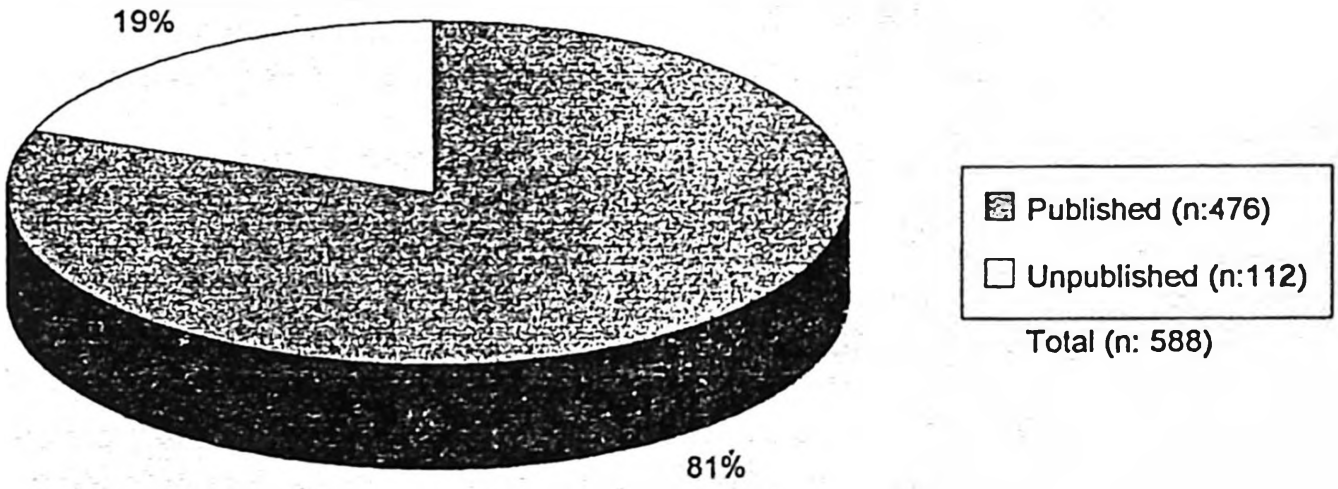

Fig. 2: Publication ratio of papers submitted to Turk J Pediatr and Çocuk Sağlığı ve Hastalıkları Dergisi.

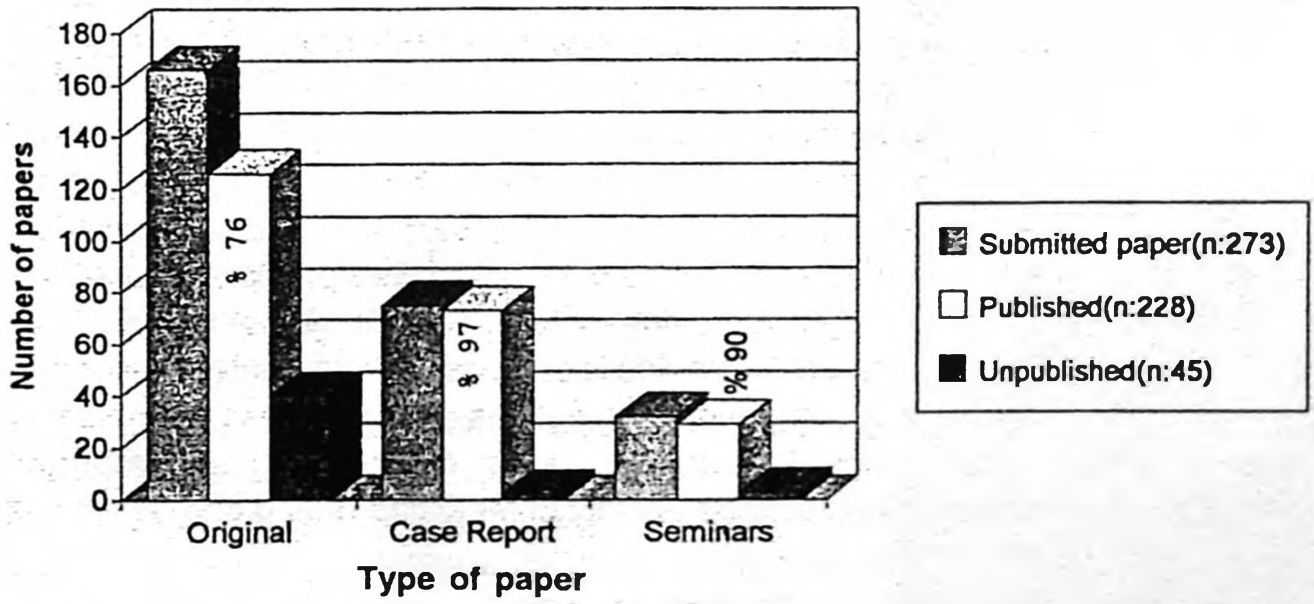

Fig. 3: Type and publication ratio of papers submitted to Çocuk Sağlığı ve Hastalıkları Dergisi.

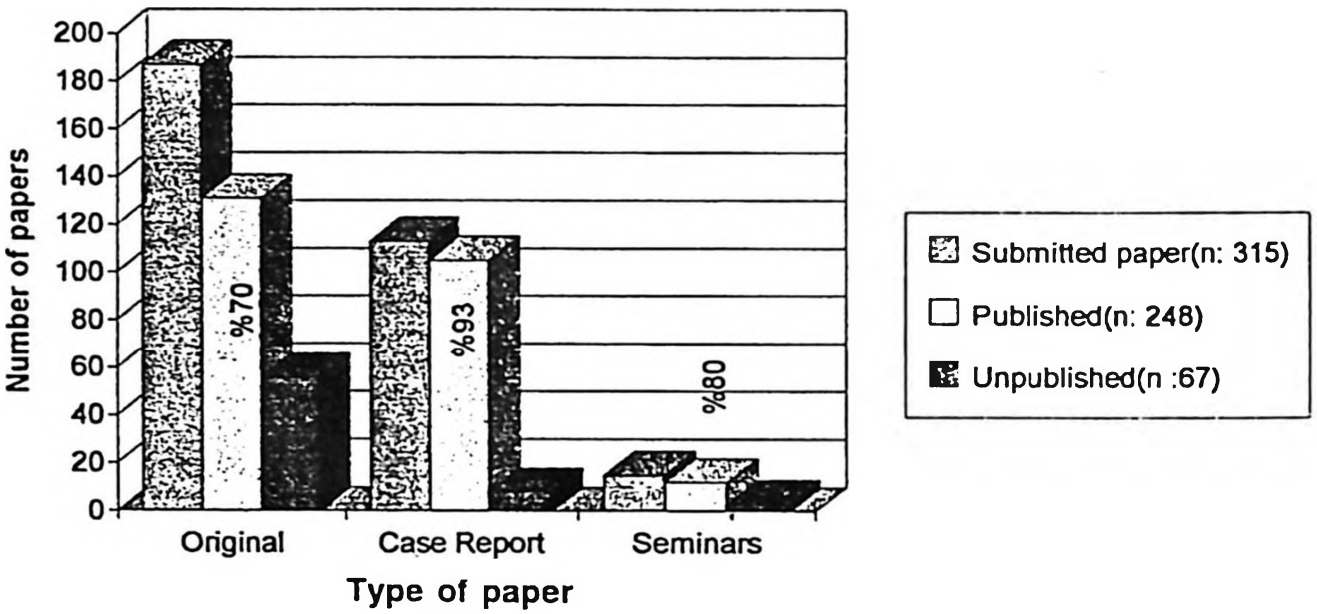

Fig. 4: Type and publication ratio of papers submitted to Turk J Pediatr (1988-1993).

In the second example, the archive documents of national and international scientific publications by Hacettepe School of Medicine were evaluated (Table Xa and Xb)[10]. By the way, I wish to refer to data reported in the article, "Üniversite'de bilimsel performans değerlendirilmesi"*[1]. According to this data, Hacettepe University with 1,100 articles is the leader among 24 universities in terms of the number of publications in the Health Sciences in the period 1980-1992. (It is also in first place with a ratio of 2.24 papers per academic staff member). Beginning with this sampling, the distribution of scientific publications in all medical specialities of Hacettepe Faculty of Medicine in academic year 1993-1994 was examined. It was found that 935 articles were published in this one-year period, 26 percent of which were studies in the field of pediatrics. When the number of publications during the 12-year period 1980-1992 are considered, these figures clearly show a burst in scientific publications from Hacettepe Faculty of Medicine. However, as novel data, in calendar year 1994, 335 papers were published from Hacettepe Faculty of Medicine in the journals covered by international indexes (Table Xb). Of these, 118 (35%) were in the field of pediatrics. These data provide us with further evidence of the increased publication potential in the field of medicine. In recent years, the increment in the number of teaching staff members and improvement in the facilities in academic centers seems to have strengthened this burst in medical publications. This progress will naturally show its effects in pediatrics. In summary, when comparing the number of international publications by Hacettepe Faculty of Medicine during one academic

* English version: "Evaluation of scientific performance of the universities".

year (1993-1994) and one calendar year (1994) with the number of articles by each medical discipline, pediatrics accounts for the largest portion of all medical publications with one-to-four and one-to-three ratios, respectively.

Table Xa: Scientific Publications of Hacettepe Faculty of Medicine in Periodicals (199-1994)*

Specialty Fields	Publications in English**	Publications in Turkish	Total
Pediatrics	134	111	245
	32%	23%	26%
Others	309	381	690
	68%	77%	74%
Total	443	492	935

* Documents of Hacettepe University Faculty of Medicine, October 1994[10].
** Publications in periodicals covered in international indexes.

Table Xb: The Number of International Publications Published from Hacettepe Faculty of Medicine in Calendar Year 1994

Specialty	No. of Publications	Percent
Pediatrics	118	35%
Others	227	65%
Total	335	100%

Table XI: Medical Publications of Turkish Authors Appearing in Current Contents in July, August, September 1993[12]

Specialty Field	Number of Article	Percentage
Pediatrics	70	20%
All medical disciplines excluding Pediatrics	283	80%
Total	353	100%

In the third example of the evaluation of the publication potential in pediatrics, medical publications of Turkish authors appearing in Current Contents were analyzed during the period July-September 1993[11]. Of 353 articles, 70 (20%) were related to pediatrics, indicating that pediatrics also has a great publication potential in our country among all medical disciplines, resembling the Hacettepe sample.

In conclusion, though publications concerning pediatrics seem to be dominating among the articles of all medical disciplines in our country according to our limited data, nationwide extensive studies are needed to obtain more reliable results. However, it is reasonable to accept that studies in the field of pediatrics have been showing an increasing dynamic effect on the medical publication potential in our country.

REFERENCES

1. Pak NK. Üniversitede bilimsel performans değerlendirilmesi. Türkiye Bilimler Akademisi (TÜBA). Dünya'da ve Türkiye'de Bilim, Etik ve Üniversite Bilimsel Toplantısı. 26 Mayıs 1994, TUBITAK, Ankara, Sempozyum kitabı, TUBITAK Matbaası, 1994, 93-111.
2. Science Citation Index/CD-ROM, 1994.
3. T.C. Kültür Bakanlığı Milli Kütüphane Başkanlığı arşiv 1994 kayıtları.
4. Medical Sciences: Pediatrics. In: Salk J (ed). Ulrich's International Periodicals Directory 1994-1995 (33rd ed). New Providence, NJ: Reed Publishing Inc; 1995: 4113, 4122.
5. Sutherland FM, Jenkins SR. Indexes, abstracts, bibliographies and reviews. In: Morton LT, Godbolt S (eds). Information sources in the medical sciences (4th ed). London: Bowker-Saur; 1992: 43-66.
6. Index Medicus/List of journals indexed, National Library of Medicine, 1995.
7. Science Citation Index/Journal Citation Reports. 1988-1992.
8. Kassirer JP, Campion EW: Peer review: crude and understudied, but indispensable. JAMA 1994; 272: 96-97.
9. The Turkish Journal of Pediatrics ve Çocuk Sağlığı ve Hastalıkları Dergisi arşiv dökümanları 1988-1993.
10. Hacettepe Tıp Fakültesi Dekanlığı arşivi:. 1993-1994. Eğitim ve Öğretim yılı Üniteler Bilimsel faaliyet raporları.
11. Uluslararası tıp sahasındaki Türk doktorları. Yeni Tıp Dergisi 1994; 11: 51-63.

The Turkish Journal of Pediatrics 1996; 38: 217-222

TREATMENT OF X-LINKED LYMPHOPROLIFERATIVE DISEASE (DUNCAN DISEASE) WITH HIGH-DOSE METHYLPREDNISOLONE AND ETOPOSIDE (VP-16)*

*Aytemiz Gürgey MD***, Tülin Şaylı MD***, Abdurrahman Kara MD***
*Gülsev Kale MD***, İzzet Berkel MD***

SUMMARY: Gürgey A, Şaylı T, Kara A, Kale G, Berkel İ. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Treatment of X-linked lymphoproliferative disease (Duncan disease) with high-dose methylprednisolone and etoposide (VP-16). Turk J Pediatr 1996; 38: 217-222.

A five-year-old boy in the acute phase of X-linked lymphoproliferative (XLP) syndrome (Duncan disease) with high fever and hepatosplenomegaly was treated successfully with high-dose methylprednisolone and VP-16 for 15 months. He had been alive for four years after diagnosis as of this writing. We recommend high-dose methylprednisolone and VP-16 in patients with XLP who have to wait for a suitable donor before bone marrow transplantation. *Key words: X-linked lymphoproliferative disease, high-dose methylprednisolone, VP-16, treatment.*

Purtilo et al.[1] described a fatal X-linked condition which affected 18 males in four generations in 1975. This condition is known as X-linked lymphoproliferative disease (XLP) or Duncan disease. XLP is a lethal disease associated with a lack of effective immune response to Epstein-Barr virus (EBV). One half of the patients with XLP have developed infectious mononucleosis (IM). Unfortunately most of the cases with infectious mononucleosis died[1-3]. Various therapeutic agents have been tried unsuccessfully in XLP patients experiencing acute EBV infection[4,5]. Here we report a patient with XLP treated with high-dose methylprednisolone and etoposide (VP-16), and we comment on two of his relatives who were also affected by XLP.

Case Reports

Case 1

In 1991, a two-year-old boy was admitted to Hacettepe Children's Hospital with a three-week history of fever. He was the third product of a marriage between first cousins. Six boys in the family, including his brother had died between the ages of 1.5 and four years with similar clinical pictures (Fig. 1).

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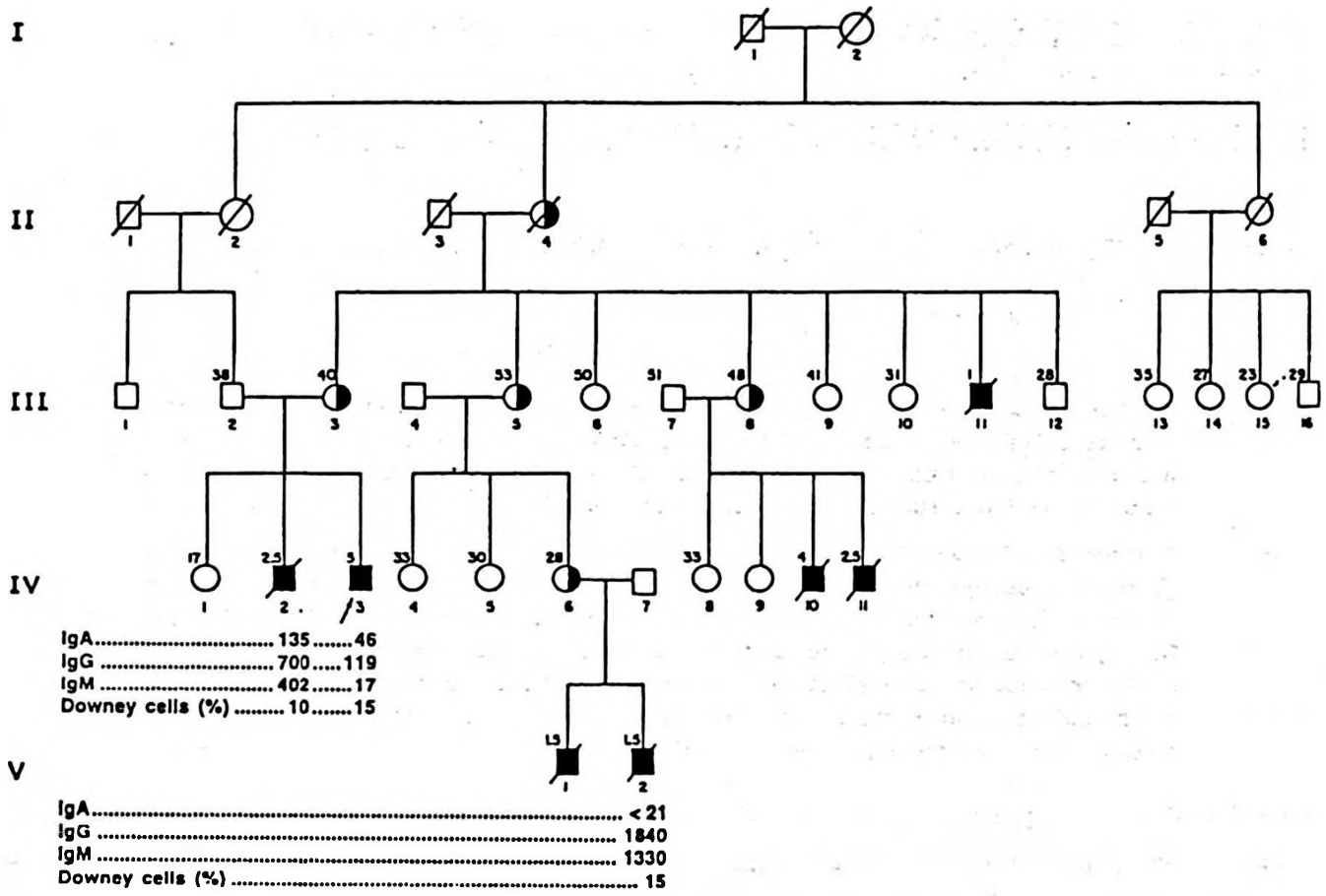

Fig. 1: Pedigree of the family.

On physical examination, he was an ill-looking boy with a body temperature of 39.5 °C He had hepatomegaly of 8 cm and splenomegaly of 10 cm below the respective costal margins.

On laboratory examination, the hemoglobin (Hb) level was 9.4 g/dL, white blood cell count (WBC) 4.600/mm^3 and the thrombocyte count was 220.000/mm^3. In the peripheral blood smear, 70 percent of the white cells were lymphocytes; Downey cells and normochrome normocytic erythrocytes were also noted. Liver function tests, viral and bacterial investigations for hepatitis B, C, cytomegalovirus (CMV), salmonella and brucella were negative. The patient also had hypoglobulinemia (IgG = 119 mg/dl, IgA = 46 mg/dl and IgM = 17 mg/dl).

Bone marrow aspiration was normal, and a splenic fine needle aspiration revealed hemophagocytosis.

The patient had a continuous high-grade fever and massive hepatosplenomegaly, and antibiotic treatment was ineffective. High-dose methylprednisolone (30 mg/kg/day for one week, 20 mg/kg/day for the second week, and 10 mg/kg/day for two weeks) treatment was started orally during the second week after admission, and the patient was without fever within 24 hours. In addition

to methylprednisolone, he was given intravenous (IV) VP-16 (150 mg/m^2) and intrathecal therapy with methotrexate (10 mg) and cytosine arabinoside (20 mg); prednisolone (10 mg) was given once a week for four weeks and intravenous gammaglobulin (400 mg/kg) monthly (Fig. 2). The Hb, hematocrit and WBC counts improved gradually, and the hepatosplenomegaly regressed within two months. Maintenance therapy consisted of progressively less frequent treatments with intravenous VP-16 down to one infusion of 150 mg/m^2 every sixth week, which was discontinued 15 months after the diagnosis. As of this writing, the patient was six years old, clinically healthy and receiving IV immunoglobulin monthly. The patient is considered to have XLP. Serum and DNA samples from family members were shipped to the University of Nebraska Medical Center (Dr. Purtilo) for analysis of XLP. Antibodies to EBV antigens [viral capsid antigen (VCA)-IgM < 10:10., IgG < 1:10., Epstein-Barr nuclear antigen (EBNA) < 1:5]. were lacking, consistent with XLP disease. The family was screened for eight markers on the X-chromosome, close to the XLP gene. The markers DXS-37 and DXS-10 have been identified as informative for detection of carrier females in the family.

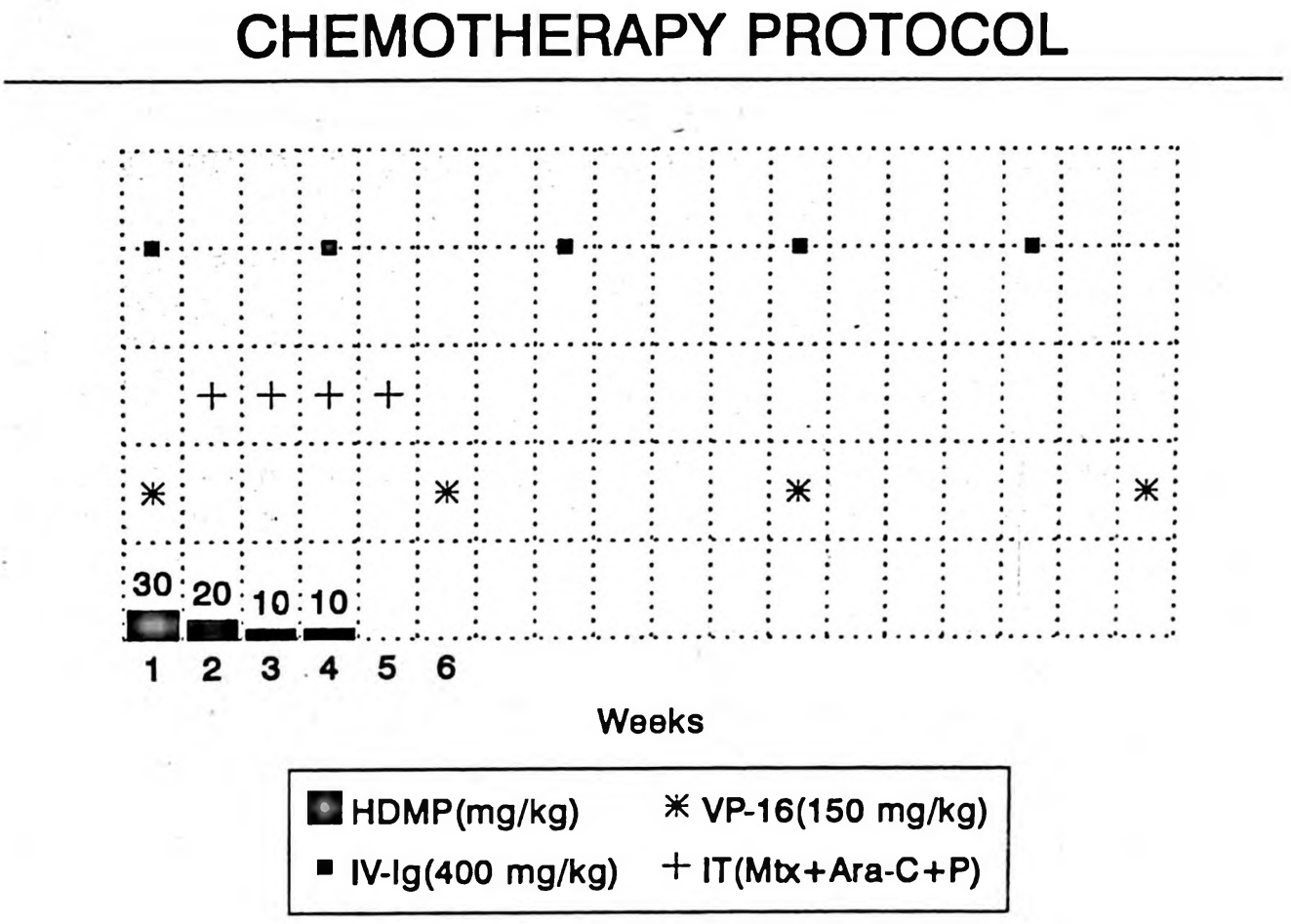

Fig. 2: The Chemotherapy Protocol. VP-16: Etoposide, i.v.: intravenous immunoglobulin, I.T.: Intratechal, Mtx: Methotrexate, ARA C: Cytosine Arabinoside, P: Prednisolone, HDMP: High-dose Methyl Prednisolone.

We also studied two other members of this family, in which seven boys were affected by XLP.

Case 2

In 1986, older brother of Case 1 (Fig. 1, IV-2) had a two-week febrile episode with massive hepatosplenomegaly and skin rashes at the age of 2.5 years. Laboratory data revealed hemoglobin 7.4 g/dL, WBC count 4,700/mm^3 (10% Downey cells), aspartate aminotransferase 305 I.U and alanine aminotransferase 155 I.U. The patient died within three months with profound lymphoid depletion as well as necrosis of the spleen and liver on autopsy.

Case 3

An 18-month-old boy (Fig. 1, V-2) was admitted to our hospital in 1994 with a two-week history of febrile episodes and massive hepatosplenomegaly. His elder brother had died of a similar condition at the age of 1.5 years. Laboratory data revealed Hb 7.3 g/dL, WBC 6,300/mm^3, platelet count 40,000/mm^3, aspartate aminotransferase 1013 IU, alanine transferase 302 IU and total bilirubin of 5.4 mg/dL. Viral and bacterial investigations for hepatitis A, B, C, CMV, toxoplasmosis, salmonella and brucella were negative. Bone marrow aspiration showed a lymphocyte predominance. The patient died of hepatic failure within 24 hours of admission. Postmortem examination revealed extensive necrosis of the liver.

Discussion

The immune defenses of the body normally react against an EBV infection by producing specific antibodies. In normal subjects, following EBV infection, B lymphocytes are transformed into proliferating lymphoblastoid cells. These cells can be killed by other proliferating cells induced by the immune response. EBV-induced lymphoproliferation is fatal in some subjects with both inherited and acquired immunodeficiencies.

Before EBV infection occurs, boys with an XLP mutation have normal cellular and humoral immune responses and respond normally to bacterial and viral infections other than EBV. Following EBV infection, about 75 percent of boys with XLP disease develop fatal IM, with liver destruction being the frequent cause of death[1-3]. In XLP, the inherited immunodeficiency is transmitted at the time of conception from unaffected women, known as carriers, to some of their male children.

Treatment of patients with XLP with antiviral agents such as acyclovir, interferon-gamma and interferon-alpha combined with high-dose immunoglobulins has been disappointing[4, 5].

In the treatment of our patient, high-dose methylprednisolone and VP-16 was used successfully. Similar therapy has also been used successfully in the treatment of some patients with hemophagocytic lymphohistiocytosis and Griscelli syndrome[6,7]. It is probable that glucocorticoid hormones inhibit the production of tumor necrosis factor, which is an inflammatory cytokine in the inflammatory response[6]. Good responses with high-dose methylprednisolone have been reported in hematologic disorders[8]. VP-16 has also been used successfully in the treatment of the acute phase of hemophagocytic lymphohistiocytosis syndromes. A boy with XLP and acute infectious mononucleosis reportedly underwent clinical remission with VP-16 and subsequent allogeneic bone morrow transplantation from a sibling[3]. Recently four boys with XLP received allogeneic bone marrow transplants, but only one of them is alive and well up to 24 months after transplantation[3]. Williams et al.[9] showed that allogeneic bone marrow transplantation can correct the lethal immune deficits in a patient with XLP and non-Hodgkin's lymphoma. Another child is alive and well more than one year after having received a transfusion of umbilical cord blood from his newborn brother[10]. Our patient is doing well four years after the diagnosis.

Note Added in Proof

Our personel communication with Dr. Gross revealed some unpublished long-term survivals according to their retrospective review of XLP registry cases.

Acknowledgements

We would like to express our thanks to Dr. D.T. Purtilo (deceased), H. Girerson and T.G. Gross for their invaluable help in studying this patient. This study was supported in part by a grant from the Institute of Child Health, Hacettepe University.

REFERENCES

1. Purtilo DT, Cassel CK, Yang JP. X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). Lancet: 1975; 1: 935-940.
2. Purtilo DT, Girersonn HL, Davis JR, Okano M. The X-linked lymphoproliferative disease: from autopsy toward cloning the gene. Pediatr Pathol 1991; 11: 685-710.
3. Seemayer TA, Girerson H, Pirruccello SJ, et al. X-linked lymphoproliferative disease. Am J Dis Child 1993; 147: 1242-1245.
4. Okano M, Pirruccello SJ, Girerson HL, Johnson DR, Thiele GM, Purtilo DT. Immunovirological studies of fatal infectious mononucleosis in a patient with X-linked lymphoproliferative syndrome treated with intravenous immunoglobulin and interferon alpha. Clin Immunol Immunopathol 1990; 54: 410-418.
5. Shapiro RS, Chauvenet A, McGuire W, et al. Treatment of B-cell lymphoproliferative disorders with interferon alpha and intravenous gamma globulin. N Engl J Med 1988; 318: 1334.
6. Henter JI, Elinder G. Familial hemophagocytic lymphohistiocytosis. Clinical review based on the findings in seven children. Acta Paediatr Scand 1991; 80: 269-277.

7. Gurgey A, Şaylı T,Gunay M, et al. High-dose methylprednisolone and VP-16 in treatment of Griscelli syndrome with central nervous system involvement. Am J Hematol 1994; 47: 331-332.
8. Özsoylu Ş. High dose intravenous methylprednisolone in hematologic disorders. Hemat Rev 1990; 4: 197-201.
9. Williams LL, Rooney CM, Conley ME, Brenner MK, Krance RA, Heslop HE. Correction of Duncan's syndrome by allogeneic bone marrow transplantation. Lancet 1993; 342: 587-588.
10. Vowels MR, Lam-Po-Tang J, Berdoukas V, et al. Correction of X-linked lymphoproliferative disease by transplantation of cord-blood stem cells. N Engl J Med 1993; 320: 1623-1625.

The Turkish Journal of Pediatrics 1996; 38: 223-225

SEVERE ACUTE THINNER INTOXICATION*

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SUMMARY: Akısü M, Mir S, Genç B, Cura A. (Department of Pediatrics, Ege University Faculty of Medicine, Bornova-İzmir, Turkey). Severe acute thinner intoxication. Turk J Pediatr 1996; 38: 223-225.

Thinner which contains aromatic hydrocarbons such as xylene, toluene and N-hexane is widely used in industrial plants manufacturing dyes, plastic, varnishes and glues. Chronic intoxication due to abuse of solvents, including thinner, by workers who inhale the solvent vapor is frequently encountered. Acute intoxication with ingestion of excessive amounts is relatively rare and usually fatal. It is reported that 45-50 ml of orally ingested thinner is enough to cause severe complications.

The case reported here was forced to drink 200 ml of thinner by an older friend, and presented with severe complications such as rhabdomyolysis, polyneuropathy, chemical pneumonia and coma. To the best of our knowledge this is the first case reported in the literature to survive acute thinner intoxication with such complications.
Key words: aromatic hydrocarbons, toxic polyneuropathy, toluene intoxication.

Thinner which contains aromatic hydrocarbons, such as toluene, xylene and N-hexane, is widely used in the industrial manufacturing of plastics, varnishes, paints and glues. Chronic intoxication due to abuse of solvents, including thinner, and among industrial workers who inhale solvent vapor is frequently observed[1-5]. However, acute intoxication due to ingestion of excessive amounts is unusual and often fatal. This patient, who was forced to drink approximately 200 ml of thinner by his friends, presented with severe complications related to aromatic hydrocarbons. Although the estimated lethal, oral dose of thinner is reported to be 45-50 ml, this patient survived after one month in intensive care[2].

Case Report

A 14-year-old male patient presented with severe muscle weakness, difficulty in walking, edema of the extremities and neck, and accompaning oral ulcerations. The initial examination findings were as follows: heart rate 130 bpm, blood pressure 110/70 mmHg, respiratory distress and rales on auscultation, severe muscle weakness, flaccid quadriplegia, absence of deep tendon reflexes and stupor. Fasciculation and Babinski sign positivity were not observed. Two hours after he was admitted to the hospital, he experienced a cardiopulmonary arrest. He was resuscitated and put on mechanical ventilation, since spontaneous

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respirations were absent. Laboratory investigations were as follows: hemoglobin 10.6 g/dl, reticulocytes 1.8%, leukocytes 17,600/mm^3 and platelets 113,000/mm^3. Urinalysis revealed mild proteinuria and microscopic hematuria. Serum sodium was 132 mmol/L, potassium 7.2 mmol/L, AST 2,484 IU/L, ALT 548 IU/L, lactate dehydrogenase (LDH) 8,096 U/L (150-320 U/L), creatine kinase (CPK) 121, 168 U/L (25-90 U/L), and myocardial CPK (CK-MB) 1,860 U/L (5-35 U/L). BUN, glucose and other electrolytes were within normal limits. Antinuclear antibody was negative. Chest roentgenogram revealed marked cardiomegaly, patchy infiltration, areas of atelectasis and bilateral pleural effusion. Voltages were depressed in all derivations in the ECG, indicating myocardial damage. Electromyographic features revealed a mixed (motor, sensory and otonomous), mainly axonal polyneuropathy. Sural nerve biopsy showed axonal degeneration and segmental demyelination. Biceps muscle biopsy displayed muscle fiber degeneration and an increase in connective tissue. Bone marrow aspirate was normal. The initial diagnosis was fulminant polymyositis according to the clinical and laboratory findings. On the 7th day, in an effort to clarify the etiology of this clinical course, the patient admitted that he had been forced to drink approximately 200 ml of thinner by his friends at the plant where he was working. The thinner consumed at this plant was found to contain 60 percent toluene, 25 percent N-hexane and five percent xylene. These findings completely explained the severity of the clinical course. He was initially put on mechanical ventilation and supported with vitamins B1, B6 and E, and physical therapy and rehabilitation were initiated on day 15. He was extubated on the 7th day of his admission, and by the end of the second month of hospitalization, all the pathological laboratory findings had returned to normal except for severe mixed polyneuropathy (Fig. 1).

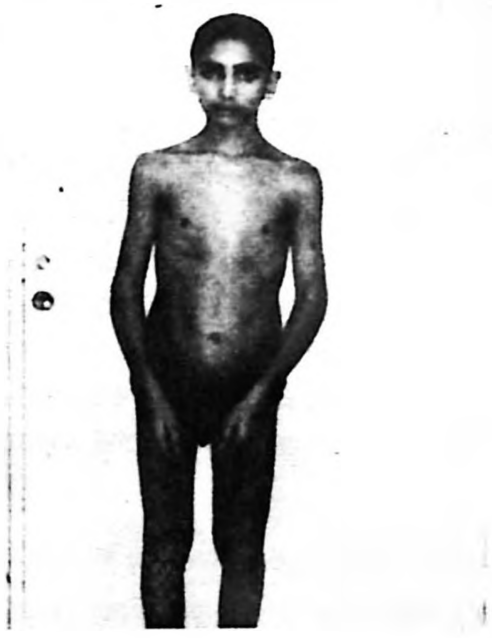

Fig. 1: The appearance of the patient with severe muscular atrophy after treatment.

Discussion

Abuse of thinner containing toluene is very common, and this solvent is the most common agent among the hydrocarbons[2, 4]. Toluene appears to have more severe, acute effects when combined with N-hexane[3]. Toluene and xylene cause generalized central nervous system depression, which may cause ataxia, convulsion, coma and respiratory arrest. Like other hydrocarbons, they may sensitize the myocardium to the arrhythmogenic effects of catecholamines. Ventricular arrhythmias and cardiac arrest may occur. Pulmonary aspiration can cause pulmonary edema and hemorrhagic alveolitis. A high dose of toluene exposure may produce rhabdomyolysis and myocardial involvement with elevated CPK and CK-MB levels[1, 2]. Acute exposure of toluene in this patient led to severe rhabdomyolysis, muscle atrophy and myocardial involvement. Hepatomegaly and centrilobular hepatic necrosis have also been described in the literature in cases of acute exposure[1]. Bone marrow depression has not been described as a result of either chronic or acute exposure to toluene, in contrast with benzene, which produces bone marrow toxicity. N-hexane rather than toluene is suggested to be chiefly responsible for polyneuropathy[3]. The renal abnormalities encountered in toluene sniffers include proteinuria, hematuria and distal renal tubular acidosis[4]. It has been reported that clinical recovery takes up to three years in the most severe cases[3, 5].

We considered this case to be interesting because, to our knowledge, there is no reported surviving case in the literature with such severe complications. We would like to warn physicians to suspect intoxication with aromatic hydrocarbons in patients presenting with rhabdomyolysis, severe polyneuropathy and coma.

REFERENCES

1. Graham DR. Solvent abuse. In: Haddad LM (ed). Poisoning and Drug Overdose. Philadelphia: Saunders Co; 1990: 1256-1260.
2. Twieg M, Olson KR. Toluene and xylene. In: Olson KR (ed). Poisoning and Drug Overdose (1st ed). London: Appleton and Lange; 1990: 281-282.
3. Herskowitz A,Isi N, Schaumburg H. N-hexane neuropathy. N Engl J Med 1970; 285: 82-85.
4. Goto I, Matsumura M, Inoue N, et al. Toxic polyneuropathy due to glue sniffing. J Neurol Neurosurg Psychiatr 1974; 37: 848-853.
5. Cianchetti C, Abbritti G, Perticoni G, et al. Toxic polyneuropathy of shoe-industry workers. J Neurol Neurosurg Psychiatr 1976; 39: 1151-1161.

The Turkish Journal of Pediatrics 1996; 38: 227-229

SPONTANEOUS COMPLETE REMISSION IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA*

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*Namık Özbek MD******

SUMMARY: Yetgin S, Tuncer AM, Güler E, Özbek N. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Spontaneous complete remission in a child with acute lymphoblastic leukemia. Turk J Pediatr 1996; 38: 227-229.

A five-year-old girl was admitted to the hospital with fever and tender lymphadenopathy. She was diagnosed with acute lymphoblastic leukemia (ALL-L_3). Because of infection she was given antibiotics and a blood transfusion. Her bone marrow was in remission after 15 days without chemotherapy. This case emphazes the role of transfusion and/or infection in obtaining complete remission without chemotherapy. *Key words: leukemia, spontaneous complete remission, blood transfusion, infection.*

Spontaneous complete remission (SCR) has been reported in a few cases of acute leukemia[1-3]. The definite cause of this very rare event is nearly always vague because of overlapping factors which are believed to be responsible for SCR. We report a case of acute lymphoblastic leukemia (ALL) who developed SCR probably as a result of blood transfusion and/or infection.

Case Report

A five-year-old girl was admitted to our hospital with a four-month history of asthenia, fever and poor appetite. On physical examination, high fever (38.5 °C) and tender cervical lymphadenopathy as large as 2 x 2 cm were observed. The liver was palpable 2 cm below the costal margin. Laboratory findings were as follows: hemoglobin (Hb) 5.68 g/dL, white blood cell count (WBC) 1 x 10^9/L with 95 percent lymphoblasts and thrombocytopenia (200 x 10^9/L). Bone marrow aspiration revealed mild hypocellularity with 80 percent lymphoblasts. According to the FAB classification, 83 percent of the bone marrow blasts were L_3 and 17 percent were L_2 subtype (Fig. 1). Immunohistochemical and immunophenotyping studies of blasts with sudanblack, periodic-acid Schiff stain and CD_2, CD_{14}, CD_{34},

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CD_{33}, Gp IIb/IIIa were found to be negative. Tdt and CD_{19} were positive. Serum electrolytes, calcium, phosphorus, protein, liver and kidney function tests assayed before chemotherapy were normal. Cultures of blood, urine and the throat were negative. Viral studies for Epstein-Barr and cytomegalovirus were negative. Because of anemia, neutropenia, fever and tender cervical lymph nodes, an infectious etiology was thought to be responsible and the patient was treated with a combination of methicillin and amikacin, and was given three blood transfusion. Although the patient showed some improvement in clinical and laboratory findings (Hb 10 g/dL, WBC 4.5×10^9/L, and on the peripheral smear 66% PNL, 28% lymphocytes and 6% monocytes), mild tenderness of the lymph nodes persisted. Since the peripheral blood was in remission on day 15, bone marrow aspiration was performed and was found to be in remission with normal cellularity. When the decision to start chemotherapy was made, the patient had enlarged lymph nodes, recurrence of fever, and enlarged liver and spleen (4 cm each), massive eruptions on the body. Although microbiological studies revealed no pathogenic microorganism, antistreptolysin-O was 333 Todd U, and C-reactive protein was (+). She was thought to have a deep cervical infection and was put on penicillin ornidazole and sulfamide therapy. On the 27^{th} day of hospitalization, she was healing with no physical signs. Her CBC was as follows: Hb 11.2 g/dL, WBC 6.3×10^9/L with 54% PNL and 46% lymphocytes, and platelet count 80,000/mm^3. She was given remission induction therapy with vincristine, L-asparaginase, duaunorubicin and prednisolone followed by consolidation and maintenance. As of this writing she had been making good progress for three years.

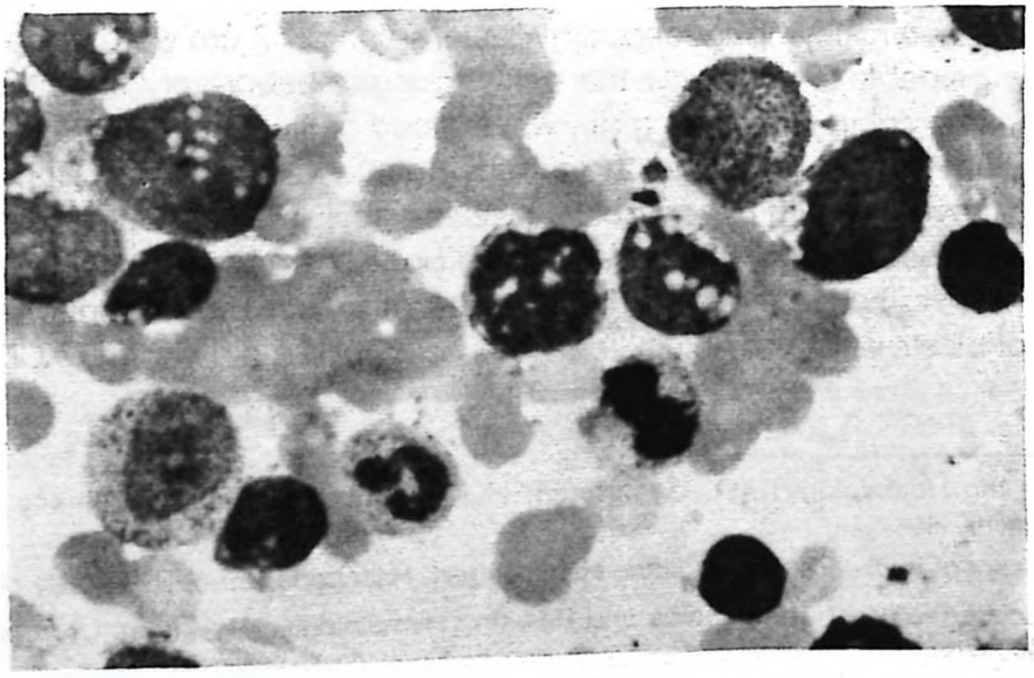

Fig. 1: First bone marrow aspiration of the patient showing L_3-type lymphoblasts.

Discussion

Cases of SCR in patients with acute leukemia have been known since 1878 and many cases had been reported by the year 1955[2]. Advanced chemotherapy and early treatment of patients immediately after diagnosis may gradually decrease the frequency of SCR. Here we reported a case of ALL who had SCR probably due to blood tranasfusions and/or infection. Some studies have suggested that infections and blood transfusion seem to be related to SCR; however, SCR was also reported in a patient with acute myeloblastic leukemia without infection or blood transfusion[3]. These two factors may cause spontaneous release of differentiation factors. In any state, the patient's condition allow for a normal response to stimulating factor. Preconditions such as subclinical graft versus host disease[4,5], white blood cell count, cellularity of bone marrow, type of leukemia and cytogenetic abnormalities may have important antileukemic effects. Our patient had leukopenia and mildly hypocellular bone marrow, the latter of which seems to be an important factor in the development of SCR. The patient's infection on admission led us to the conclusion that blood transfusion was the main cause of SCR. As far as we know, all of the patients with SCR that have been reported in the literature had relapses soon there after. For that reason, we put our patient on chemotherapy to keep her in remission even though SCR had been observed. This case emphasizes the importance of keeping the Hb level within the normal range during remission induction in patients with ALL.

REFERENCES

1. Charak BS, Parikh F, Girl N, Ahuja RP, Advani SH. Spontaneous complete remission in acute lymphoblastic leukemia. Indian J Cancer 1989; 26: 10-13.
2. Ifrah N, James JM, Viguie F, Marie JP, Zittoun R. Spontaneous remission in adult acute leukemia. Cancer 1985; 56: 1187-1190.
3. Spadea A, Latagliata R, Martinelli E, Petti ME. Transient spontaneous remission in a case of adult acute myelogenous leukaemia. Br J Haematol 1990; 76: 154.
4. Kolb HJ, Mittermüller J, Clemm Ch, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. Blood 1990; 76: 2462-2465.
5. Tucker J, Murphy MF, Gregory WM, et al. Apparent removal of graft-versus-leukaemia effect by the use of leucocyte-poor blood components in patients with acute myeloblastic leukaemia. Br J Haematol 1989; 73: 572-574.

The Turkish Journal of Pediatrics 1996; 38: 231-234

SYSTEMIC LUPUS ERYTHEMATOSUS PRESENTING WITH THROMBOCYTOPENIA*

Report of a Child with Positive Anticardiolipin Antibodies

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SUMMARY: Kanra G, Erdem G, Özen S, Anlar FY, Beşbaş N, Ceyhan M. (Infectious Diseases and Nephrology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Systemic lupus erythematosus presenting with thrombocytopenia: report of a child with positive anticardiolipin antibodies. Turk J Pediatr 1996; 38: 231-234.

We report a case of systemic lupus erythematosus initially presenting with thrombocytopenia and diagnosed as immune thrombocytopenic purpura. The patient subsequently developed lymphadenopathy, arthritis and cardiac involvement along with anticardiolipin antibodies. We would like to emphasize the fact that these autoantibodies have a role in the pathogenesis of thrombocyte destruction, and that patients with immune thrombocytopenic purpura should be followed for signs of systemic lupus erythematosus. *Key words: systemic lupus erythematosus, thrombocytopenia, anticardiolipin antibodies.*

Systemic lupus erythematosus (SLE) is a multisystem disease manifesting with a wide range of autoantibodies. Among these, anticardiolipin antibodies are gaining popularity in the pathogenesis of a number of systemic manifestations.

Thrombocytopenia is a well recognized feature of SLE and may be the initial presentation. We report a boy with thrombocytopenia as the initial manifestation of the disease. We also discuss the relevant role of anticardiolipin antibodies.

Case Report

An 11-year-old boy was admitted with a one-week history of left-sided neck swelling and a three-week history of fever and arthritis of the knees and ankles. Seven months previously he had epistaxis and easy bruising. At that time his thrombocyte counts were 100,000-150,000/mm^3, and a diagnosis of immune thrombocytopenic purpura was made after bone marrow examination. The patient was treated with intravenous immunoglobulin, and the thrombocytopenia remitted. His family and personal histories were otherwise unremarkable.

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The physical examination revealed a temperature of 39.3 °C, and there was tender erythematous lymph node enlargement in the left submandibular region. A low-grade systolic murmur was heard in the mitral area, and the liver and spleen were palpable one and two centimeters below the respective costal margins. Pertinent laboratory studies demonstrated a white blood cell count of 2,000/mm^3 and hemoglobin of 7.8 g/dl. Thrombocyte counts and biochemical tests including transaminases, creatinine and blood urea nitrogen were normal. The serum iron level was low, and the direct Coombs test was negative. Other findings included a raised erythrocyte sedimentation rate of 110 mm/hour, decreased early complement components including C3: 26.3 mg/dl (normal: 60-120 mg/dl) and C4: 7 mg/dl (normal: 20-55 mg/dl); increased antinuclear antibodies of 1/160 and anti-dsDNA titers of 1/163. Both immunoglobulin G and immunoglobulin M type anticardiolipin antibodies were increased. Echocardiography revealed a slight pericardial effusion and mitral insufficiency. Lymphadenitis was treated with ampicillin, and subsequently prednisolone 2 mg/kg/day was started. The lymph nodes had diminished dramatically in size and the fever had subsided when the patient was discharged within nine days after the start of steroid therapy.

Discussion

Mild thrombocytopenia such as in our patient has been reported in 25-50 percent of SLE patients. Thrombocytopenia is mainly attributed to the autoantibodies observed in SLE. Other causes are myeloproliferative disorders, ineffective thrombopoiesis, abnormal platelet distribution, dilutional effect and abnormal platelet destruction[1].

There are several reports of an association between thrombocytopenia and lupus anticoagulant in patients with SLE[2]. Anticardiolipin antibodies including immunoglobulins of IgG, IgM and IgA classes correlate with the activity of lupus anticoagulants[3]. Most, but not all, lupus anticoagulants are anticardiolipin antibodies. Lupus anticoagulants and anticardiolipin antibodies may mediate platelet destruction in some SLE patients by binding and interacting with the phospholipid moiety of platelet membranes[3]. The true antigenic epitope for lupus anticoagulant may be an altered lipid structure, such as the hexagonal phase of phosphatidyl ethanolamine. Altered phospholipid structures and subsequent antibody formation to this neoantigen may be responsible for the thromboembolic complications observed in patients with antiphospholipid antibodies[3]. However, there is minimal evidence that lupus anticoagulant and anticardiolipin antibodies (aCL) are able to bind platelet, and their interaction with membrane phospholipids seems impossible because of steric hindrance from glycoprotein and glycolipids and because anionic phospholipids are confined to the cytosolic surface[4]. A serum cofactor was therefore sought and identified as beta-2-glycoprotein I (apolipoprotein H). This cofactor has an affinity for anionic phospholipids and

behaves as a natural anticoagulant[4]. In patients with SLE, the average prevalence of the lupus anticoagulant is 34 percent, and the prevalence of anticardiolipin antibodies is 44 percent[5,6].

Moderate thrombocytopenia is noted in nearly 50 percent of patients with lupus anticoagulants, but in many cases it apparently is the result of an underlying disorder[1]. It may be the result of platelet sensitization by antibodies attached to surface phospholipids[3]. IgM class anticardiolipin antibodies are usually associated with thrombocytopenia and central nervous system manifestations, whereas thromboses are most frequently associated with IgG class antibodies[1,3,7]. Both IgM and IgG type antibodies were increased in our case.

The triad of antiphospholipid antibodies, thrombosis and fetal loss and other manifestations, such as thrombocytopenia, autoimmune hemolytic anemia, non-thrombotic neurological findings and skin findings, left heart valvulopathy and pulmonary hypertension, have all been considered as a part of antiphospholipid (aPL) syndrome[1,3]. Our patient is a secondary aPL syndrome case, since findings such as thrombocytopenia, left heart valvulopathy and pleural effusion occurred in the setting of SLE. Thrombocytopenia may also be found without any associated autoimmune disease as in primary aPL syndrome; thus, patients presenting with thrombocytopenia such as our patient must be screened for aPL antibodies, including anticardiolipin antibodies[1]. There have also been occasional cases with a clinical picture of aPL syndrome followed by the development of clinical and immunological features of SLE[8]. A history of immune thrombocytopenic purpura is usually related to the persistence of IgG class anticardiolipin antibodies. These patients have milder disease activity when compared with the anticardiolipin antibody-positive cases in the acute phase of the disease[6].

This case is yet another example reinforcing the fact that thrombocytopenia may be the initial manifestation of SLE; early symptoms of SLE should be looked for in these cases. Each case with thrombocytopenia of obscure etiology should also be screened for antiphospholipid antibodies. The correlation of anticardiolipin antibodies and thrombocytopenia suggests that these autoantibodies are indeed effective in thrombocyte destruction.

REFERENCES

1. Bithell TC. Acquired coagulation disorders. In: Lee GR, Bithell TC, Foerster JJ, Athens JW, Lukens JN (eds). Wintrobe's Clinical Hematology (9th ed) Vol. 2. Philadelphia: Lea and Febriger; 1993: 1497-1498.

2. Harris EN, Asherson RA, Gharavi AE, Morgan SH, Derue G, Hughes GR. Thrombocytopenia in SLE and related autoimmune disorders: association with anticardiolipin antibody. Br J Haematol 1985; 59: 227-230.

3. Woods VI Jr. Pathogenesis of systemic lupus erythematosus. In: Kelley WN, Harris ED, Ruddy S, Sledge C (eds). Textbook of Rheumatology (4th ed) Vol. 2. Philadelphia: W.B. Saunders Company; 1993: 999-1016.

4. Ravelli A, Martini A, Burgio GR. Antiphospholipid antibodies in paediatrics. Eur J Pediatr 1994; 153: 472-479.
5. May KP, West SG, Moulds J, Kotzin BL. Different manifestations of the antiphospholipid antibody syndrome in a family with systemic lupus erythematosus. Arthrit Rheum 1993; 36: 528-533.
6. Ishii Y, Nagasawa K, Mayumi T, Niho Y. Clinical importance of persistence of anticardiolipin antibodies in systemic lupus erythematosus. Ann Rheum Dis 1990; 49: 387-390.
7. Khamashta M, Hughes GR. Antiphospholipid syndrome: a common cause of thrombosis Br Med J 1993; 307: 883-884.
8. Andrews PA, Frampton G, Cameron JS. Antiphospholipid syndrome and systemic lupus erythematosus. Lancet 1993; 342: 988-989.

The Turkish Journal of Pediatrics 1996; 38: 235-238

CONGENITAL CHLORIDE DIARRHEA IN A TURKISH BOY*

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SUMMARY: Özen H, Tanrıöğer N. (Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Congenital chloride diarrhea in a Turkish boy. Turk J Pediatr 1996; 38: 235-238.

Congenital chloride diarrhea (CCD), first described in 1945, is a rare, autosomal-recessively inherited disease. It is characterized by chronic, watery diarrhea with a high fecal chloride concentration, hyponatremia, hypokalemia, and hypochloremic metabolic alkalosis. In this report, a 7.5-year-old boy with CCD diagnosed by high fecal chloride concentration is presented. Until now CCD had not been reported from Turkey, although consanguineous marriages are common. *Key words: congenital chloride diarrhea, stool chloride.*

Congenital chloride diarrhea (CCD) was first described by Gamble et al.[1] and Darrow[2] in 1945, when each reported a child with "congenital alkalosis with diarrhea". CCD is a rare disease with autosomal recessive inheritance[3], and is characterized by life-long secretory diarrhea with a high fecal chloride (Cl^-) concentration, retarded growth and development and biochemical findings of hyponatremia, hypokalemia, and hypochloremic metabolic alkalosis[4]. Watery diarrhea is present from birth but often goes unnoticed because the fluid in the diaper is thought to be urine. Thus, many patients may go unrecognized.

Diarrhea in CCD is a consequence of the selective malabsorption of Cl^-, probably situated at the Cl^-/HCO_3^- exchange transport system in the epithelium of the ileum and colon[5,6]. The effect of this defect is watery diarrhea with a high Cl^- and a low HCO_3^- concentration as well as a low pH.

Since its first description, fewer than 100 patients have been reported[7]. Although patients have been reported from various countries[4,7,8], to the best of our knowledge this is the first case reported from Turkey.

Case Report

The patient was seven years and five months old when the diagnosis of CCD was made. He was referred to us because of chronic watery diarrhea since birth. His weight (18.5 kg) and height (117 cm) were both below the 5th percentile. At that time, the diagnosis was made by estimating stool electrolytes (volume 1500 ml/day; Na^+: 101 mEq/L; K^+: 15.3 mEq/L; and Cl^-: 166 mEq/L).

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Reducing substances were absent from the stool, and no pathogens were isolated on stool culture. The stool pH was 5. The serum aldosterone concentration was at the upper limit of normal (310 pg/ml; normal 40-310 pg/ml), while the renin concentration was six times higher than the upper limit of normal (34.3 ng/ml/hour; normal 1.5-5.7 ng/ml/hour). He had been taking KCl supplements since the age of six months, and salicylate (25 mg/kg per day) since six years of age.

His history revealed that he was born as a dizygotic twin at 35 weeks of gestation by cesarean section. His parents were cousins. Prenatal ultrasonographic examination had revealed distended loops of intestines. His birth weight was 2000 g, appropriate with his gestational age. His abdomen was large and distended. He developed diarrhea during his first day of life, and intravenous electrolyte therapy was initiated. A plain x-ray of the abdomen showed dilated and distended loops of intestines. He had hyperbilirubinemia, and an exchange transfusion was performed. Serum electrolytes on the fourth day of life were Na^+: 128 mEq/L; K^+: 5.4 mEq/L; Cl^-: 96 mEq/L; and CO_2 content 30 mEq/L. Table I demonstrates the biochemical findings during follow-up until this writing. He was discharged after a two-week hospitalization. Diarrhea was thought to be due to gastroenteritis, and distended intestinal loops possibly due to Hirschsprung's disease.

Table I: Electrolyte Concentrations (mEq/L) of Serum, Feces and Urine

	Serum				Feces*			Urine		
Age	Na	K	Cl	CO_2	Na	K	Cl	Na	K	Cl
4 days	128	5.4	96	30	–	–	–	7.6	0.5	–
7 days	131	2.6	102	–	–	–	–	–	–	–
6 mos.	127	2.3	62	42	18	25	112	–	–	5
8.5 mos.	118	3	56	38	–	–	–	–	–	–
3 yrs-4 mos.	126	2	90	–	–	–	–	–	–	–
6 yrs.	138	3.7	99	–	–	–	–	–	–	–
7 yrs-5 mos.	137	3	98	–	101	15.3	166	–	–	very low

* Normal volume and ionic composition of feces in infancy: volume 5-10 ml/kg/day; Na 22 mEq/L; K 54 mEq/L; Cl 21 mEq/L[12].

He was hospitalized two more times during the first three years of life at six and 8.5 months of age because of episodes including dehydration, hypoelectrolytemia including hypochloremia, and metabolic alkalosis. At six months of age, the diagnosis of Bartter syndrome was made because of high aldosterone (1800 pg/ml, normal 20-200 pg/ml) and renin (> 25 ng/ml/hour, normal 0.4-3.2 ng/ml/hour) concentrations. During this admission, stool electrolytes were studied and revealed a high chloride concentration which exceeded the sum of fecal sodium and potassium. Although it was thought that the patient might have

CCD at that time, stool electrolyte concentrations were disregarded because of unreliable laboratory methods. Potassium supplementation was started. The sweat chloride test was done three times and found to be within normal limits. Electrolytes studies were not done between hospitalizations. At the age of six years, salicylate therapy was initiated at a dose of 25 mg/kg per day as a prostaglandin synthetase inhibitor with the diagnosis of Bartter syndrome.

Discussion

CCD is characterized by watery diarrhea of intrauterine onset, and the clinical features of the disease vary with the age of the child[4, 7]. Diarrhea sometimes cannot be noticed during the neonatal period because the stools in diapers may be mistaken for urine. Prenatal diagnosis by ultrasonography is possible[9]. It shows maternal polyhydramnios and distended loops of ileum filled with fluid. Although polyhydramnios was not mentioned, our patient had dilated intestinal loops.

Almost all patients with CCD are born preterm with normal weights and lengths for gestational age. The prematurity is presumably a consequence of polyhydramnios[7]. The abdomen is usually distended. Loops of ileum and colon are dilated with air and fluid. The distended abdomen may lead to a misdiagnosis of Hirschsprung's disease[4]. Our patient was also premature with appropriate weight for gestational age, and Hirschsprung's disease was the initial diagnosis because of the dilated intestinal loops with air. Hyperbilirubinemia has been reported in 68 to 100 percent of patients with CCD[4, 7]. Our patient also had hyperbilirubinemia, and an exchange transfusion was performed. The cause of hyperbilirubinemia is not known, although the dehydration may partly contribute to it.

The correct diagnosis of CCD can be made when fecal chloride is measured and exceeds 100 mEq/L in stools and the sum of the Na^+ and K^+ concentrations[5, 7]. Bartter syndrome and cystic fibrosis were ruled out due to the presence of chronic watery diarrhea and repeated normal sweat chloride concentrations, respectively. The severity of the electrolyte disturbance depends on salt intake and the effectiveness of the activation of the renin-aldosterone system, which invariably occurs, as in our patient[5, 7].

There is no specific treatment for CCD. Acute attacks should be treated with intravenous fluid therapy. Oral NaCl (8-10 mEq/kg per day) and KCl (2-3 mEq/kg per day) should be prescribed as maintenance therapy[4, 7, 10]. Our patient was administered 10 mEq/kg per day of NaCl and 3 mEq/kg per day of KCl. Prostaglandin synthetase inhibitor therapy has been given with the suggestion that prostaglandins may be involved in stimulating the renin-aldosterone system in CCD, but the results have been unsuccessful[7, 11]. Although a decline in the plasma renin and aldosterone concentrations was obtained, the watery diarrhea persisted, similar to our patient.

The estimated incidences of CCD in Kuwait and Finland are 7.6 and 10 per 100.000 live births, respectively[4,7]. We can suppose that the incidence of CCD in Turkey is at least at this level because of the high frequency of consanguineous marriages. In addition to testing reducing substances in stool, stool electrolytes must be studied in every neonate with watery diarrhea to rule out CCD. Special attention should be given to neonates with distended abdomens and dilated intestinal loops. The morbidity and mortality are highest during the neonatal and infancy periods, in which the patient cannot regulate water and salt intake. After the neonatal period, hypokalemia, hypochloremia and metabolic alkalosis are common but not inevitable. The final diagnostic criterion is the high fecal concentration of Cl^-[4]. Adequate growth and development depends on adequate fluid and Cl^- supplementation.

REFERENCES

1. Gamble JL, Fahey KR, Appleton J, Maclachlan E. Congenital alkalosis with diarrhea. J Pediatr 1945; 26: 509-518.
2. Darrow DC. Congenital alkalosis with diarrhea. J Pediatr 1945; 26: 519-532.
3. Norio R, Perheentupa J, Launiala K, Hallman N. Congenital chloride diarrhea, an autosomal recessive disease. Genetic study of 14 Finnish and 12 other families. Clin Genet 1971; 2: 182-192.
4. Holmberg C, Perheentupa J, Launiala K, Hallman N. Congenital chloride diarrhoea. A clinical analysis of 21 Finnish patients. Arch Dis Child 1977; 52: 255-267.
5. Holmberg C, Perheentupa J, Launiala K. Colonic electrolyte transport in health and in congenital chloride diarrhea. J Clin Invest 1975; 56: 302-310.
6. Bieberdorf FA, Gorden P, Fordtran JS. Pathogenesis of congenital alkalosis with diarrhea. J Clin Invest 1972; 51: 1958-1968.
7. Lubani MM, Doudin KI, Sharda DC, et al. Congenital chloride diarrhoea in Kuwaiti children. Eur J Pediatr 1989; 148: 333-336.
8. Turnberg LA. Abnormalities in intestinal electrolyte transport in congenital chloride diarrhoea. Gut 1971; 12: 544-551.
9. Kerkinen P, Joppila P. Prenatal ultrasonic findings in congenital chloride diarrhoea. Prenat Diagn 1984; 4: 457-461.
10. McReynolds EW, Roy S III, Etteldorf JN. Congenital chloride diarrhea. Am J Dis Child 1974; 127: 566-570.
11. Mayatepek E, Seyberth HW, Nützenadel W. Effects of indomethacin in congenital chloride diarrhea. J Pediatr Gastroenterol Nutr 1992; 14: 319-322.
12. Rhoads JM, Powell DW. Diarrhea. In: Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB (eds). Pediatric Gastrointestinal Disease; Pathophysiology, Diagnosis, Management. Vol. 1. Philadelphia: B.C. Decker Inc; 1991: 62-78.

The Turkish Journal of Pediatrics 1996; 38: 239-243

THE MANAGEMENT OF RENAL CANDIDIASIS IN THE NEWBORN*

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SUMMARY: Üçsel R, Çoban A, Metin F, Yücer G, Ziylan O, Tonguç E, Bilge I, Rouzbeksalah K, Can G. (Department of Pediatrics, İstanbul University Faculty of Medicine, Çapa-İstanbul, Turkey). The management of renal candidiasis in the newborn. Turk J Pediatr 1996; 38: 239-243.

Renal candidiasis in the neonate is encountered infrequently. We report a newborn with ichthyosis, who during the hospital course had five episodes of culture-proven sepsis, probably due to skin lesions. For these infections various antibiotic combinations were used. During the therapy of the last sepsis attack, unilateral hydronephrosis developed secondary to renal candidiasis. Percutaneous nephrostomy with amphotericin B irrigation, coupled with five weeks of intravenous amphotericin B therapy was successful. We believe that with this approach the mortality and morbidity of renal candidiasis could be reduced. *Key words: renal candidiasis, percutaneous nephrostomy, amphotericin B.*

Candidal infection of the urinary tract is a well-known entity in adults, but it has been less well recognized in infants and children. However, with the improved survival of neonates and the widespread use of broad-spectrum antibiotics and intravascular catheters, the incidence of systemic and renal candidiasis has increased[1]. Involvement of the kidney is usually secondary to generalized systemic disease, but on occasion the kidney may be the only organ affected[2]. Herein we report a case of isolated, obstructive, upper urinary tract candidiasis in which percutaneous nephrostomy had a major role in the successful management.

Case Report

A 2700 g infant was born vaginally to a 23-year-old woman (gravida 2, para 2) at 35 weeks of gestation. He was brought to the neonatology unit on day 15 of life with poor sucking. It was reported that the pregnancy and labor had been

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uncomplicated. The baby had been well during the first two weeks of life. On admission, physical examination revealed a hypotonic infant with erythematous scaling skin lesions over the entire body. Given the clinical and laboratory findings, sepsis and ichthyosis were suspected, and antibiotic therapy was initiated. During the hospital course the patient had five episodes of culture-proven sepsis, and various antibiotic combinations were used. The immunological work-up was normal. On day 62 of life, the infant became hypertensive, his systolic blood pressure (BP) ranged between 80 and 120 mmHg, and his mean BP ranged from 70 to 80 mmHg. Leukocytosis, thrombocytopenia, and high C-reactive protein levels were noted. A mass was palpated on the left side of the abdomen. Serum creatinine, urine output and urine sediment were normal. Because of hypertension and the palpable mass, abdominal ultrasound was performed and revealed a hydropyonephrotic left kidney (Fig. 1). A percutaneous nephrostomy tube was inserted. Candida albicans grew in the specimen obtained directly by percutaneous puncture. Blood, urine and cerebrospinal fluid cultures yielded no organisms. The voiding cystoureterogram was unremarkable, but radionuclide scan showed a concentration defect of the left kidney. Administration of intravenous amphotericin B was initiated, and the dose was increased from 0.1 to 1 mg/kg/day over a one-week period. In addition, a solution of amphotericin B (1 mg/dl) was used for daily irrigation of the nephrostomy tube. Cardiac echography and ophthalmological examination were unremarkable. The patient's hypertension resolved on the second day, and control cultures grew no organisms. On the eighth day of therapy, renal ultrasound revealed resolution of the hydronephrosis (Fig. 2), and the nephrostomy tube was removed. A total dose of 35 mg/kg of i.v. amphotericin B was administered. No side effects were observed, and the infant recovered completely.

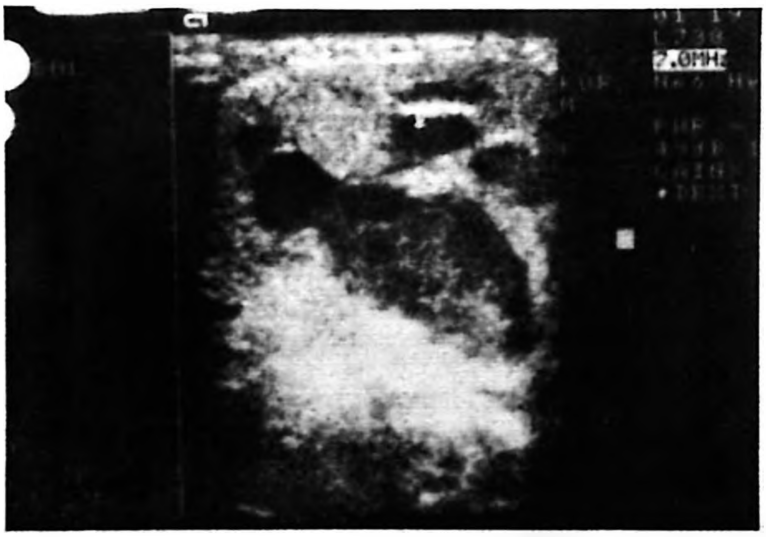

Fig. 1: Renal ultrasound showing grade II-III dilatation of the pelvicalyceal system. Distal to the calyces, fresh urine and hyperechogenic pus were seen.

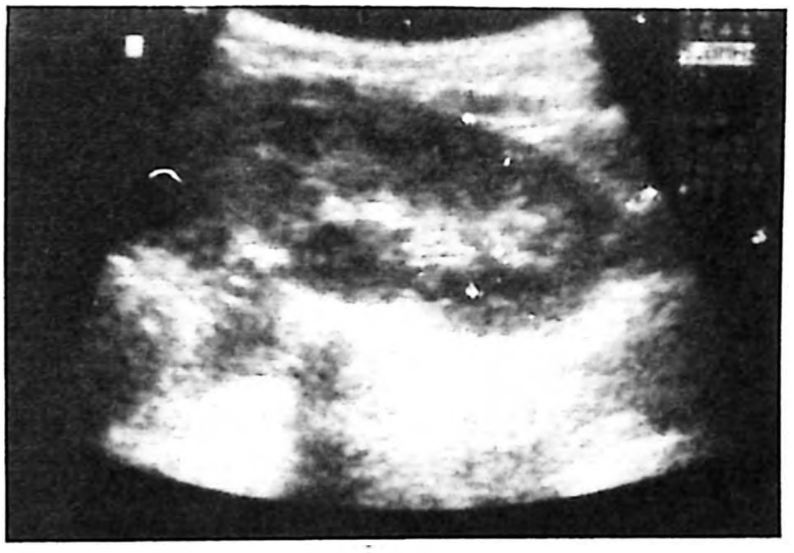

Fig. 2: Ultrasound scan demonstrating normal pelvicalyceal system after therapy.

Discussion

Despite improved survival rates of neonates, sepsis remains an important cause of morbidity and mortality. Although bacterial infections are most common, the incidence of fungal infections has also increased. Predisposing factors include antibiotic therapy (57%), prematurity (29%), intravenous and umbilical artery catheterization (24%), and parenteral alimentation (18%)[3]. Candida albicans is responsible for 75 percent of fungal infections during the neonatal period[4]. Two major forms of candida infections are recognized. Systemic candidiasis runs a course in which there is multiple organ involvement with candidemia. The second form, or primary renal candidiasis, presents with a less serious clinical picture, with renal invasion being the primary feature[5]. Hurley and Winner[6] demonstrated that large doses of candida given intravenously to mice produced systemic candidiasis, whereas smaller doses caused isolated renal disease. That shows that primary renal candidiasis is indeed the end-stage of an initially mild candidemia. Factors related to the kidney are 1. a delay in the renal inflammatory response, and 2. a favored environment for candida in the tubular lumen. The combination of urine acidity and hypertonicity is believed to promote mycelial proliferation[7].

Renal infection may be clinically silent or present as acute renal failure, systemic hypertension or flank masses[2,8,9]. The infection may be limited to the bladder or may include multiple renal abscesses and renal papillary necrosis. Fungal ball formation may occur, usually at the ureteropelvic junction, and may result in obstruction and hydronephrosis.

When there is a clinical suspicion of renal candidiasis, appropriate cultures of blood, urine and catheter tips should be taken and renal ultrasonography should be performed. Candida has been difficult to demonstrate in children's blood

cultures, but candiduria is quite common. Examination of the urinary sediment revealing yeast as well as candida may be an indication for agressive antifungal therapy. Urine cultures with colony counts > 15,000/ml reveal significant candida growth[10]. However, despite the severity of renal involvement, only 37 percent of the infants in one study had positive urine cultures[3]. This emphasizes the importance of direct renal access for culture in suspected cases of candidiasis. The simplest method of obtaining it is by percutaneous puncture. With the widespread availability of real-time ultrasound, renal candidiasis can be diagnosed and managed earlier[11]. Two sonographic patterns may be seen: a dilated collecting system with echogenic masses (snowballs) within the renal pelvis and/or bladder, or enlarged kidneys with homogenous echogenity and loss of architecture[12].

The diagnosis is made from the patient's history, the typical ultrasound appearance, the microscopic finding of mycelium in the urine and appropriate cultures. Therapy consists of antifungal treatment and percutaneous nephrostomy under sonographic guidance[13]. This may not be sufficiently effective in removing the fungal masses, and surgical revision may be necessary to relieve the obstruction[14].

Medical therapy presents a difficult problem. It usually includes i.v. amphotericin B combined with p.o. 5-fluorocytosine, and local irrigation with amphotericin B (1 mg of amphotericin B per deciliter of normal saline) via percutaneous nephrostomy tube[2, 15]. Bartone at al.[16] suggested that prompt irrigation and guide-wire manipulation to disintegrate obstructing mycelia may prevent the need for surgery in some cases. The combination of amphotericin B and 5-fluorocytosine reduces the development of resistence, and the drugs are believed to act synergistically. The duration of treatment is usually approximately six weeks, but no objective data exist regarding the appropriate length of therapy. Another possible therapy in pelviureteric candidal bezoars is placement of a nephrostomy tube, shot-term irrigation with amphotericin B and later oral administration of fluconazole, which is an antifungal agent of triazole class[17].

In our patient, the scaling skin lesions led to recurrent infections, and renal candidiasis probably developed due to long-term antibiotic treatment during these infections. A nine-day course of drainage and irrigation, and five weeks of i.v. amphotericin B therapy were successful. This case emphasizes the fact that in any neonate with a clinical suspicion of renal candidiasis, renal ultrasonography should be performed to facilitate early diagnosis and treatment of renal fungal disease. In the presence of obstructive uropathy due to secondary renal candidiasis, percutaneous nephrostomy drainage should be the initial management of choice. This provides for renal decompression and amphotericin B irrigation. Intravenous and local amphotericin B are sufficient in treating renal candididasis. With this approach, the morbidity and mortality associated with renal candidiasis will be reduced.

REFERENCES

1. Baley JE. Neonatal candidiasis. The current challange. Clin Perinatol 1991; 18: 263-280.
2. Pappu LD, Purochit DM, Bradford BF, Turner WR Jr, Levkoff AH. Primary renal candidiasis in two preterm neonates. Report of cases and review of literature on renal candidiasis in infancy. Am J Dis Child 1984; 138: 923-926.
3. Keller MA, Sellers BB, Melish MF, Kaplan GW, Miller KE, Mendoza SA. Systemic candidiasis in infants. A case presentation and literature review. Am J Dis Child 1977; 131: 1260-1263.
4. Butler KM, Baker CJ. Candida: an increasingly important pathogen in the nursery. Pediatr Clin North Am 1988; 35: 543-563.
5. Noe HN, Tonkin IL. Renal candidiasis in the neonate. J Urol 1982; 127: 517-519.
6. Hurley R, Winner HI. Experimental renal moniliasis in the mouse. J Pathol 1963; 86: 75-82.
7. Wise GJ, Goldberg PK. Genitourinary candidiasis: diagnosis and treatment. J Urol 1976; 116: 778-780.
8. Ekkelkamp S. Anuria in a newborn secondary to bilateral ureteropelvic fungus balls. J Urol 1982; 128: 1331-1335.
9. Greenwalt B, Debaz B, Kumar ML. Bladder fungus ball: a reversible cause of neonatal obstructive uropathy. Pediatrics 1988; 81: 826-829.
10. Kozinn DJ, Taschdjiyan CI, Goldberg PK, Wise GJ, Toni EF, Seelig MS. Advances in the diagnosis of renal candidiasis. J Urol 1978; 119: 184-189.
11. Kintanar C, Cramer BC, Reid WD, Andrews WL. Neonatal renal candidiasis: sonographic diagnosis. AJR 1986; 147: 801-805.
12. Cohen HL, Haller JO. Schechter S, Slovis T, Merola R, Eaton DH. Renal candidiasis of the infant: ultrasound evaluation. Urol Radiol 1986; 8: 17-21.
13. Matsumoto AH, Dejer SW Jr, Barth KH, Gibbons MD. Percutaneous nephrostomy drainage in the management of neonatal anuria secondary to renal candidiasis. J Pediatr Surg 1990; 25: 1295-1297.
14. Laufer J, Reichman B, Graif M, Brish M. Anuria in a premature infant due to ureteropelvic fungal bezoars. Eur J Pediatr 1986; 145: 125-127.
15. Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low-birth-weight infants: therapeutic toxicity. Pediatrics 1984; 73: 153-157.
16. Bartone FF, Hurwitz RS, Rojas EL, Steinberg E, Franceschini R. The role of percutaneous nephrostomy in the management of obstructing candidiasis of the urinary tract in infants. J Urol 1988; 140: 338-341.
17. Bergman KA, Meis JF, Horrevorts AM, Monnens L. Acute renal failure in a neonate due to pelviureteric candidal bezoars successfully treated with long-term systemic fluconazole. Acta Paediatr 1992; 81: 709-711.

The Turkish Journal of Pediatrics 1996; 38: 245-251

TRANSCATHETER EMBOLIZATION OF A RESIDUAL CONGENITAL CORONARY ARTERIOVENOUS FISTULA WITH A DETACHABLE BALLOON; SUPERIORITY OF INTERVENTIONAL CARDIOLOGY?*

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SUMMARY: Aydoğan Ü, Dindar A, Ayhan Yİ, Tanman B, Ertuğrul T, Ömeroğlu R, Cantez T. (Cardiology Unit, Department of Pediatrics, İstanbul University Faculty of Medicine, Çapa, İstanbul, Turkey). Transcatheter embolization of a residual congenital coronary arteriovenous fistula with a detachable balloon; superiority of interventional cardiology? Turk J Pediatr 1996; 38: 245-251.

A ten-year-old girl who presented with a continuous murmur was diagnosed with a right coronary to right ventricular fistula with colored Doppler echocardiography and selective arteriography. She underwent traditional treatment-ligation of the fistula by sternotomy. Afterwards, the systolic component of the murmur persisted and repeat arteriography showed a residual shunt through the fistula, with no change in the diameter of the right coronary artery. We describe the first case in which a residual fistula was treated with a detachable balloon embolization. *Key words: interventional cardiology, arteriovenous fistula, fistula, coronary fistula.*

Congenital arteriovenous fistulas are uncommon coronary arterial anomalies that usually cause no symptoms in young patients but are associated with symptoms and complications in older patients[1,2]. Early elective ligation is therefore indicated because of the high incidence of late symptoms and complications. We report a case in whom a residual fistula between the right coronary artery and the right ventricle was completely occluded with a detachable balloon after an unsuccessful surgical ligation procedure.

Case Report

A ten-year-old girl was initially referred at eight years of age for evaluation of a cardiac murmur. The murmur was continuous and was best heard at the lower left sternal border. Otherwise she was symptom-free, active and thriving. The

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chest x-ray showed mild cardiac enlargement (cardiothoracic index of 55%) with increased pulmonary blood flow. electrocardiography revealed left atrial dilatation with biphasic P waves in right precordial derivations and left ventricular hypertrophy with 56 mm R waves in left precordial derivations. Two-dimensional and colored Doppler examination demonstrated a dilated right coronary artery with a fistulous connection to the right ventricular apex. Cardiac catheterization showed normal intracardiac pressures and a Qp/Qs ratio of 2.0:1.0 calculated by the Fick method. Selective right coronary angiography confirmed the echocardiographic diagnosis (Fig. 1). The traditional method of treatment was performed initially, and the patient underwent surgical ligation of the fistula by sternotomy.

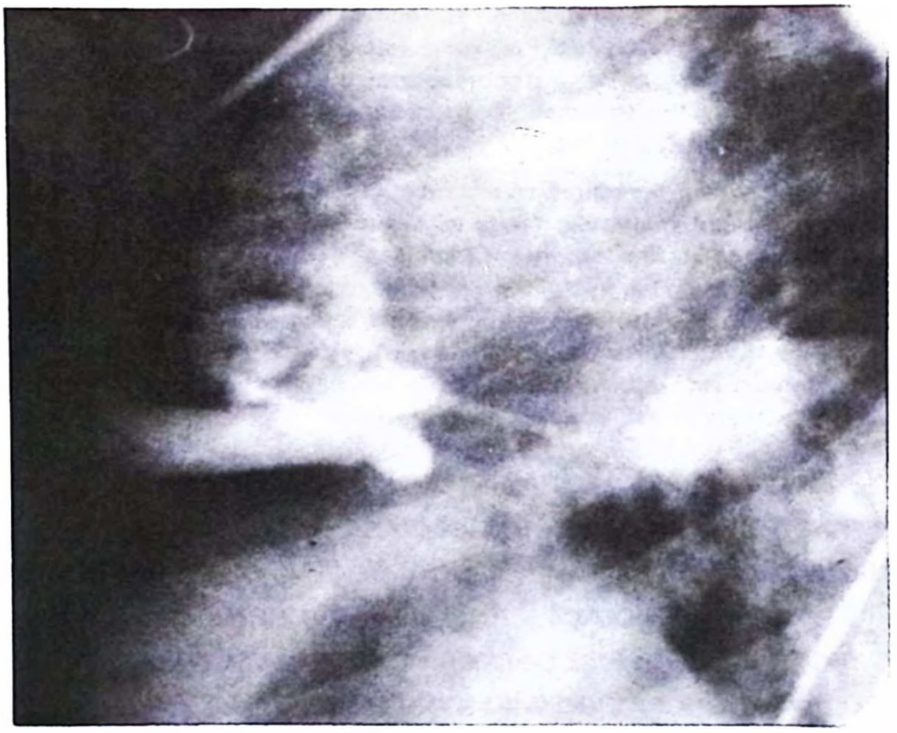

Fig. 1: Right coronary arteriography of the patient demonstrating a residual fistula between the right coronary artery and right ventricle after an unsuccessful surgical ligation procedure.

Postoperative examination of the patient revealed that the systolic component of the murmur was persisting, and repeat laboratory investigations demonstrated that there was no change in echocardiographic and radiologic findings, while electrocardiography was within normal limits. diagnostic selective coronary arteriography demonstrated that there was still an obvious shunt through the fistula. The parents resisted re-operation but preferred transcatheter intervention, and transcatheter embolization was performed two years after the initial operation.

In order to perform the procedure, a 6.5-French vascular introducing sheath was introduced through the right femoral artery with a standard Seldinger vascular puncture. A 6-French right Judkins coronary catheter was replaced with the dilator

of the sheath and the right coronary artery was catheterized. Then a 0.035" exchange guide wire was introduced through the Judkins catheter, and the catheter was removed from the sheath leaving the guide wire in position. The coaxial introducing catheter of the detachable balloon system was advanced over the guide wire up to the mid-portion of the right coronary artery, and the guide wire was then removed. Advancement of the 6.5 French (> 2 mm in diameter) coaxial introducing catheter more distally enabled it to enter the right ventricle through the fistula (Fig. 2).

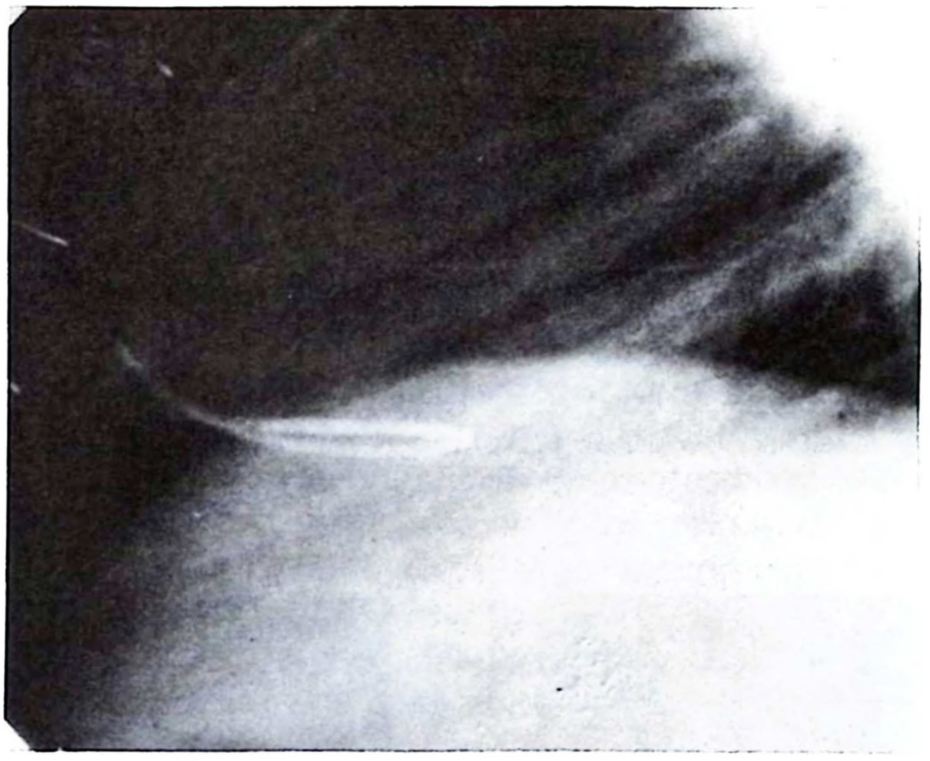

Fig. 2: Right ventriculography of the patient via a 6.5 French (> 2 mm) coaxial catheter which passed from the right coronary artery through the fistula.

The mini-balloon (Haps Emballoon; Haps ICO, William A. Cook, Australia) was mounted on the tip of its delivery catheter after it had been assembled through its coaxial teflon outer sleeve and side arm fitting (Fig. 3). Afterwards, the side arm fitting was locked onto the coaxial introducing catheter, and the delivery catheter, teflon sleeve and mini-balloon were advanced as one unit through the introducing catheter. After the exit of the mini-balloon from the introducing catheter, it was advanced more distally towards the fistula, while inflating and deflating the balloon assisted it into position. Nonionic contrast media was diluted one-to-one with distilled water in order to obtain an isotonic solution for inflation of the balloon. Coronary arteriography was performed through the side-arm fitting of the introducing catheter when it was thought that the balloon was in the target position. It showed that the shunt through the fistula was still persisting, but the

balloon was fluctuating in the right ventricle. Thus the balloon was deflated and repositioned a few milimeters more proximally and inflated again when it was thought to be in the appropriate position in the fistulous communication. It was wedged in the fistula and another arteriography was performed showing that the fistula was completely occluded, but a coronary branch artery was visualized to be originating a few milimeters proximal to the balloon, which was not obvious before the occlusion procedure (Fig. 4). The patient was monitored electrocardiographically (ECG) for 15 minutes, and the balloon was detached with gentle traction after seeing that no voltage changes had occurred. The final selective right coronary arteriogram demonstrated complete closure of the fistula.

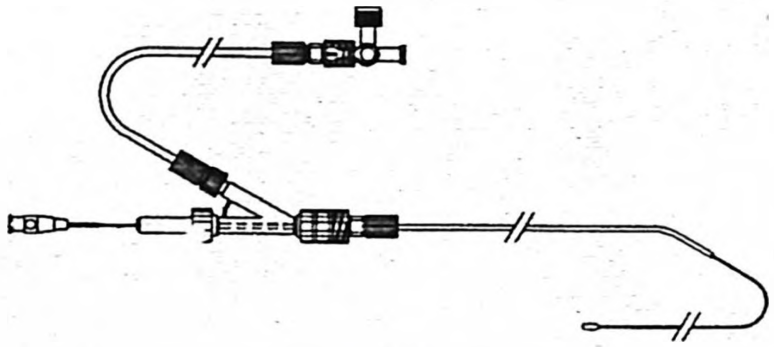

Fig. 3: Detachable vascular occlusive balloon system which was used for the coronary arteriovenous fistula occlusion procedure.

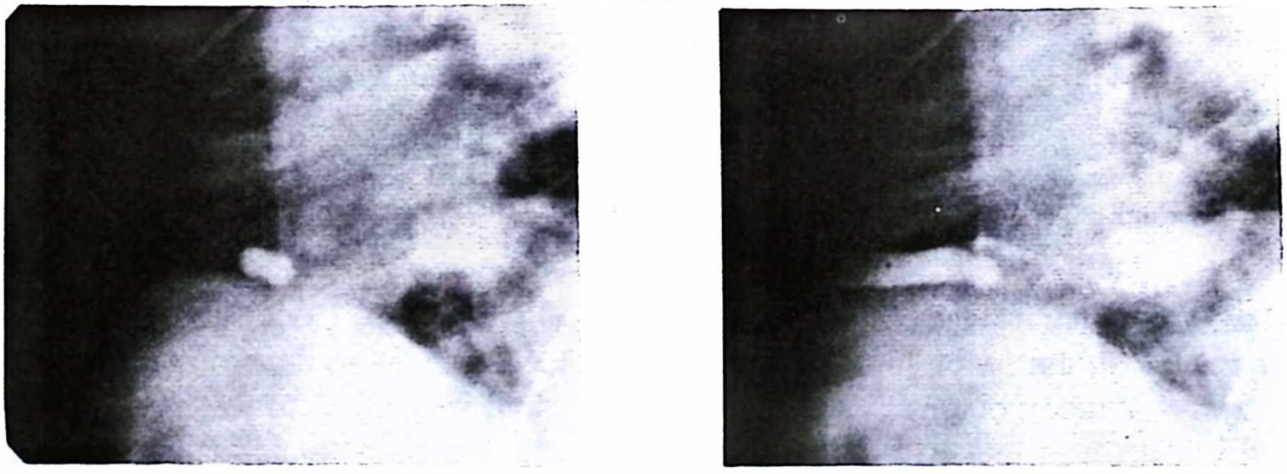

Fig. 4a: Wedging of the detachable balloon in the coronary arteriovenous fistula before detachment. b: Right coronary arteriography showing complete occlusion of the fistula and the well-visualized branch coronary artery which was partially occluded by the balloon.

The child was observed for 48 hours in the intensive care unit. Serial ECGs and a myosine band of creatinine phosphokinase levels (CPK-MB) showed normal values in this period. Colored Doppler examination performed on the third day showed no flow through the fistula, and the patient was discharged. Physical examination and colored Doppler study of the patient demonstrated normal

findings, but the dimension of the right coronary artery was still unchanged (19 mm) three months after the occlusion procedure. On the other hand, direct radioscopy of the heart on the tenth day showed that the balloon was very small compared to its original size.

Discussion

Coronary arteriovenous fistulas are uncommon, and at least initially are often asymptomatic lesions. Because of the potential for the complications[1, 3], surgical obliteration is generally recommended, though spontaneous closure of the fistula has been reported[4, 5]. Although the operative results are good and surgical morbidity and mortality are low, the patient undergoes thoracotomy or sternotomy and, in most cases, cardiopulmonary bypass with its associated morbidity as in the case reported here. On the other hand, even in very experienced centers significant complications may occur in up to 27 percent of patients undergoing surgical closure of an isolated coronary artery fistula[6].

It is known that coronary fistulas can often be anatomically complex[3, 6], and attempts to close a large fistula channel surgically could result in a smaller, but hemodynamically significant, channel being missed[7]. Angiographic visualization of a secondary fistula may only be possible after the deleterious effects of a myocardial "steal" on coronary opacification are reversed by closure of the main channel. On the other hand, recanalization of the main fistula channel is also possible by the ligation procedure. Sapin et al.[3] reported that the incidence of residual shunting was nine percent after ligation of a coronary artery fistula, as in the case reported here. Finally, immediate assessment of interruption of the flow in the target lumen angiographically, symptomatically and physiologically is another advantage of the transcatheter intervention to surgery.

Although various methods for performing transcatheter embolization of arteriovenous fistulas have been developed in recent years, descriptions of coronary arterial fistulas are uncommon[7-16]. The techniques used in embolization of such a fistula include an ivalon particle, steel coil, platinum microcoil and a detachable balloon. When ivalon particles or coils are used, it is essential for the tip of the catheter to be positioned at the point where occlusion is to be effected. This may be difficult using standard catheters, especially when the feeding arteries are tortuous or a very distal occlusion is needed. Coaxial embolization techniques with microcoils allow for a safer and more distal occlusion. When there is a high level of flow in an artery, a collection of coils packed together may be needed to occlude the fistula completely, which would be more expensive.

The major advantage of using a detachable balloon is that it can be positioned in the vessel at the exact point where occlusion is required. A distal fistula can be occluded without advancing the guiding catheter into the fistula, and a

multichannel fistula can be occluded with one balloon since it assumes an elongated shape as it expands. An improperly placed balloon, unlike all other forms of embolization, can be repositioned; test occlusions can be performed before the final release. In fistulous vascular connections and malformations with large vessels and high flow, the risk of distal embolism is avoided. Another advantage of using Haps Emballoon is that it has almost no tail, unlike other detachable balloons, so the predisposition for thrombosis formation in the feeding coronary artery itself can be avoided.

There are also disadvantages to the detachable balloon technique, including the need for a large guiding catheter, the risk of early deflation of the balloon and inadvertent embolization to other sites. Detachable balloons can be inflated with either silicone or contrast medium. When a balloon is inflated with silicone, permanent occlusion results once polymerization has occurred, and this process is irreversible. Inflating the balloon with contrast medium is safer and reversible, but there is always a possibility of early deflation, as was seen by direct radioscopy of our case. Contrast medium must not be used in the coronary fistulas draining into the left side of the heart. Finally, since this is the first reported case of successful embolization of a residual coronary fistula after unsuccessful surgical intervention, this form of therapy must still be regarded as experimental until more cases are collected before saying that it is superior to surgical ligation.

REFERENCES

1. Liberthson RR, Sagar K, Berkoben JP, et al. Congenital coronary arteriovenous fistula. Report of 13 patients, review of the literature and delineation of management. Circulation 1979; 59: 849-854.
2. Lowe JE, Oldham HN Jr, Sabiston DC Jr. Surgical management of congenital coronary artery fistulas. Ann Surg 1981; 194: 373-380.
3. Sapin P, Frantz E, Jain A, et al. Coronary artery fistula: an abnormality affecting all age groups. Medicine 1990; 69: 101-113.
4. Shubrooks SJ, Naggar CZ. Spontaneous near closure of coronary artery fistula. Circulation 1978; 57: 197-199.
5. Mahoney LT, Schieken RM, Lauer RM. Spontaneous closure of a coronary artery fistula in childhood. Pediatr Cardiol 1982; 2: 311-312.
6. Urrutia-S CO, Falaschi G, Ott DA, Cooley DA. Surgical management of 56 patients with congenital coronary artery fistulas. Ann Thorac Surg 1983; 35: 300-307.
7. Reidy JF, Tynan MJ, Qureshi S. Embolisation of a complex coronary arteriovenous fistula in a 6 year old child: the need for specialised embolisation. Br Heart J 1990; 63: 246-248.
8. Bennett JM, Maree E. Successful embolization of a coronary arterial fistula. Int J Cardiol 1989; 23: 405-406.
9. Nguyen K, Myler RK, Hieshima G, et al. Treatment of coronary artery stenosis and coronary arteriovenous fistula by interventional cardiology techniques. Cathet Cardiovasc Diagn 1989; 18: 240-243.

10. Reidy JF, Sowton E, Ross DN. Transcatheter occlusion of coronary to bronchial anastomosis by detachable balloon combined with coronary angioplasty at same procedure. Br Heart J 1983; 49: 284-287.
11. Reidy JF, Jones OD, Tynan MJ, et al. Embolization procedures in congenital heart disease. Br Heart J 1985; 54: 184-192.
12. Hartnell GG, Jordan SC. Balloon embolization of a coronary arterial fistula. Int J Cardiol 1990; 29: 381-383.
13. Issenberg HJ. Transcatheter coil closure of a congenital coronary arterial fistula. Am Heart J 1990; 120: 1441-1443.
14. Doorey AJ, Sullivan KL, Levin DC. Successful percutaneous closure of a complex coronary to pulmonary artery fistula using a detachable balloon: benefits of intra-procedural physiologic and angiographic assessment. Cathet Cardiovasc Diagn 1991; 23: 23-27.
15. Reidy JF, Anjos RT, Qureshi SA, et al. Transcatheter embolization in the treatment of coronary artery fistulas. J Am Coll Cardiol 1991; 18: 187-192.
16. Krabill KA, Hunter DW. Transcatheter closure of congenital coronary arterial fistula with a detachable balloon. Pediatr Cardiol 1993; 14: 176-178.

The Turkish Journal of Pediatrics 1996; 38: 253-256

GYRATE ATROPHY OF THE CHOROID AND RETINA*

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SUMMARY: Hasanoğlu A, Biberoğlu G, Tümer L. (Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey). Gyrate atrophy of the choroid and retina. Turk J Pediatr 1996; 38: 253-256.

Gyrate atrophy of the choroid and retina is characterized by autosomal recessive inheritance, progressive chorioretinal atrophy beginning in late childhood, and hyperornithinemia with ornithinuria caused by deficient ornithine aminotransferase activity. In this paper, four patients with gyrate atrophy are described. All patients had visual impairment, mental retardation, hyperornithinemia, hypolysinemia, ornithinuria and lysinuria. The first case had hypermetropic astigmatism in contrast to other reported gyrate atrophies.

These are the first reported cases from Turkey, but gyrate atrophy may not be rare in Turkey since the frequency of some other metabolic disorders has also been reported to be high. It is suggested that gyrate atrophy must be considered in all patients with chorioretinal atrophy. *Key words: gyrate atrophy, hyperornithinemia.*

Gyrate atrophy of the choroid and retina is a rare, autosomal-recessive inherited form of progressive chorioretinal degeneration beginning in late childhood[1-8]. A relationship between this disease and increased plasma ornithine levels was first reported in 1973, and then it was considered an inborn error of metabolism[7]. The major clinical feature is a slowly progressive loss of vision leading to blindness, usually by the fourth decade of life[1-6]. Myopia and decreased night vision are early symptoms, usually already present in childhood[1-6]. The earliest ophthalmologic finding is small, yellowish 'dots' in the midperiphery of the ocular fundus, which gradually enlarge to circular areas of chorioretinal degeneration. These lesions enlarge and extend toward the posterior pole of the fundus. This is associated with constriction of visual fields, usually in the second decade of life. Virtually all patients develop cataracts in the late second or third decade and need surgery[1-6].

More than 100 biochemically confirmed cases of gyrate atrophy have been reported[1]. Here we report four patients with gyrate atrophy, the first reported cases in our country.

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Case Reports

Case 1 (Y.Y.)

A 16-year-old girl was first referred at the age of 12 because of night blindness and decreased vision. A presumptive diagnosis of astigmatism was made, and she was not seen again until the age of 16. Her parents were consanguineous and her aunt was blind. When she was referred to us, examination revealed hypermetropic astigmatism and midperipheral chorio-retinal atrophy (Fig. 1). She also had mild mental retardation.

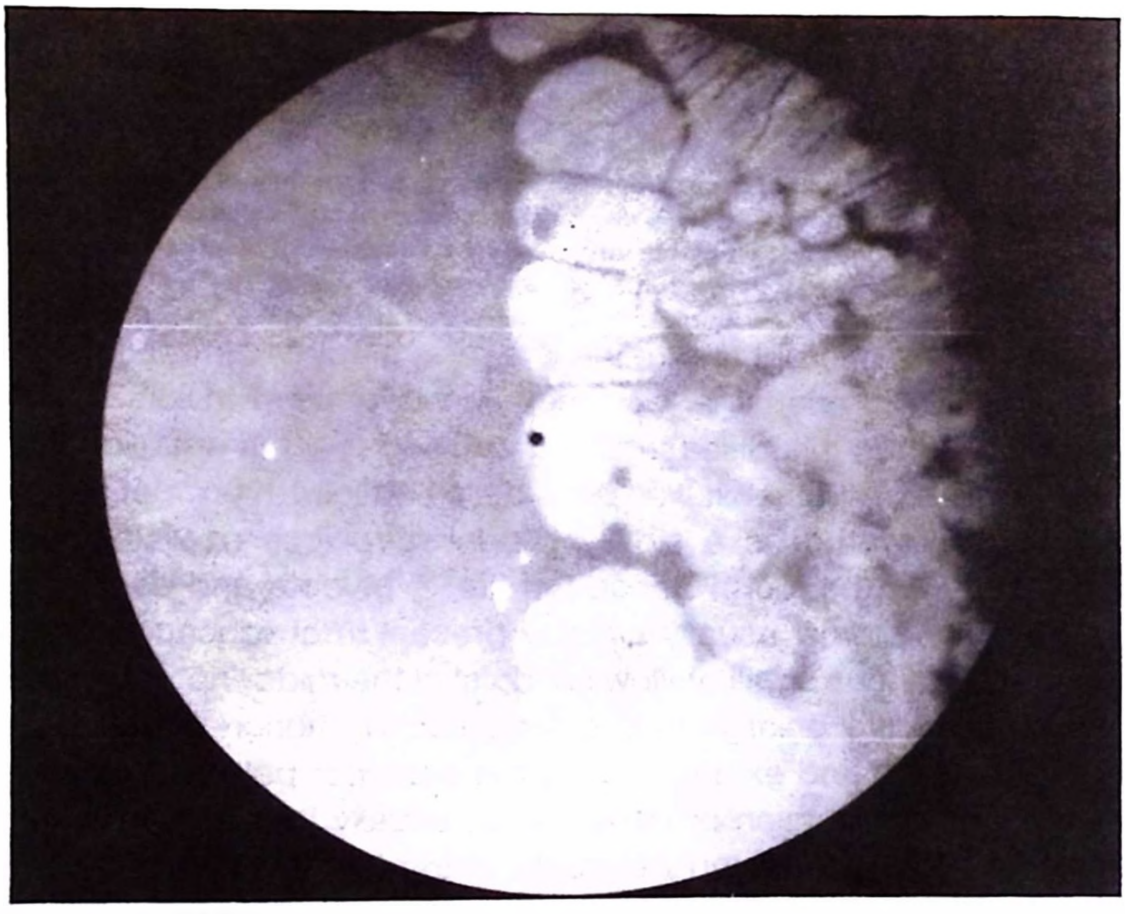

Fig. 1: Ophthalmoscopic examination of the first case.

On laboratory examination, serum ammonium, electroencephalography and electromyography findings were normal. Plasma ornithine levels were increased, and plasma lysine and arginine levels were decreased (Table I). Urine ornithine, lysine and arginine levels were increased (Fig. 2). Her mother's urine ornithine, lysine and arginine levels were also increased. Pyridoxine was administered to the patient at a dose of 500 mg/day.

Cases 2 and 3 (H.D., Y.D.) were siblings. They were 25 and 30 years old, respectively. Diagnosis was made by ophthalmoscopic examination, and hyperornithinemia was demonstrated with laboratory techniques (Table I).

A marked deficiency of ornithine amino transferase activity in cultured fibroblasts was demonstrated in the siblings.

Case 4 (G.H.) was a 21-year-old male whose visual symptoms started at the age of eight. He was also mentally retarded. On examination, bilateral myopy, cataract and peripheral chorioretinal atrophy was revealed. Laboratory evaluation confirmed hyperornithinemia and ornithinuria (Table I).

Table I: Plasma and Urine Ornithine and Lysine Concentrations of the Patients

	Plasma (mmol/dl)		Urine (mmol/dl)	
Patient	Ornithine	Lysine	Ornithine	Lysine
Y.Y.	44.3	7.10	1658.5	694.50
H.D.	32.6	2.40	1277.0	434.90
Y.D.	27.3	2.30	977.2	345.02
G.H.	33.5	4.33	1730.9	389.60
Control	7.5 ± 0.5	20.07 ± 09	18 ± 13	155 ± 114

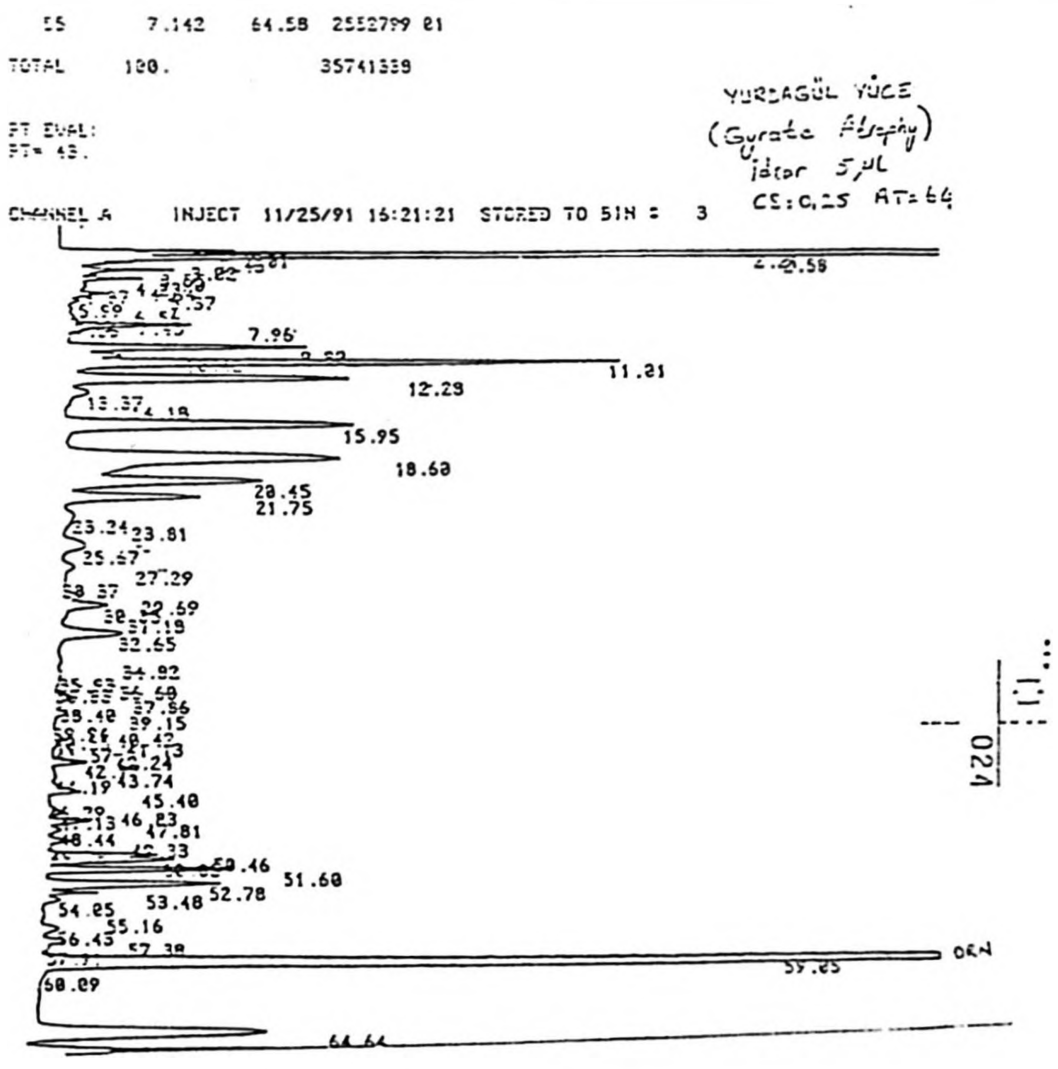

Fig. 2: Urine amino acid chromatography of the first case

Discussion

Gyrate atrophy has been a known entity since 1888, but the relation between this disease and increased plasma ornithine levels was first reported in 1973 by Simell and Tokhi[7]. The 10 to 20-fold increase in the plasma ornithine concentration is caused by deficient ornithine aminotransferase activity, which is the major enzyme that catabolizes ornithine[1,8]. Deficiency of this enzyme has been documented in cultured skin fibroblasts, phytohemagglutinin-stimulated lymphocytes, skeletal muscle cultures, hair roots and liver biopsy material[1]. This enzyme needs pyridoxal phosphate as a co-factor. In gyrate atrophy, along with hyperornithinemia there is hyperornithinuria, hypolysinemia and hyperlysinuria[1,8]. We observed ornithinuria, lysinuria and hypolysinemia in all of our patients.

Before visiual impairment, patients with gyrate atrophy are, for the most part, asymptomatic. The earliest symptoms are myopia and decreased night vision. Our first case had hypermetropic astigmatism in contrast to other published gyrate atrophies.

There are four general approaches for the treatment of patients[1,2]: stimulation of residual ornithine aminotransferase activity with pharmacologic doses of pyridoxine, correction of ornithine accumulation by reducing the intake of its precursor arginine and/or increasing renal ornithine losses, administration of creatinine and administration of proline.

In our first patient, restriction of protein intake and administration of pyridoxine at a dose of 500 mg/day was tried but failed to reduce plasma ornithine. Restriction of protein and administration of pyridoxine was also attempted in the other patients, but they could not be followed after diagnosis.

REFERENCES

1. Valle D, Simell O. The hyperornithinemias. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). The Metabolic Basis of Inherited Disease (6th ed) vol. 1. New York: McGroaw Hill Co; 1989: 599-628.
2. Poll-The BT, Billette de Villemeur T, Abitbol M, et al. Metabolic pigmentary retinopathies: diagnosis and therapeutic attempts. Eur J Pediatr 1992; 151: 2-11.
3. Sulonen KU, Spila I, Vannas A, et al. Gyrate atrophy of the choroid and retina. Ophthalmology 1985; 92: 1719-1727.
4. Stoppoloni G, Prisco F, Tolone SC. Hyperornithinemia and gyrate atrophy of choroid and retina. Helv Paediat Acta 1978; 33: 429-433.
5. Sulonen KV. Progression of gyrate atrophy of the choroid and retina. Acta Ophthal 1987; 66: 101-109.
6. Stell D, Wood CM, Richardson J, McCarthy J. Anterior subcapsular plaque cataract in hyperornithinaemia gyrate atrophy-a case report. Br J Ophthalmol 1992; 76: 762-763.
7. Simell O, Takki K. Raised plasma ornithine and gyrate atrophy of the choroid and retina. Lancet 1973; 1: 1031-1033.
8. Yatziv S, Statter M, Merin S. Metabolic studies in two families with hyperornithinemia and gyrate atrophy of the choroid and retina. J Lab Clin Med 1979; 93: 749-757.

The Turkish Journal of Pediatrics 1996; 38: 257-260

FATAL INTRACRANIAL HEMORRHAGE IN A NEWBORN WITH FACTOR VII DEFICIENCY*

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SUMMARY: Üçsel R, Savaşan S, Çoban A, Metin F, Can G. (Department of Pediatrics, İstanbul University Faculty of Medicine, Çapa-İstanbul, Turkey). Fatal intracranial hemorrhage in a newborn with factor VII deficiency. Turk J Pediatr 1996; 38: 257-260.

Factor VII deficiency is a rare congenital coagulopathy. Prolonged prothrombin time with normal partial thromboplastin time indicates factor VII deficiency. For the definitive diagnosis, the specific factor VII level should be investigated. We report a seven-day-old, male, full-term newborn who was admitted with the diagnosis of sepsis. Hematological tests revealed prolonged prothrombin time and a factor VII level of five percent. After antibiotic therapy and fresh frozen plasma replacement his clinical status improved but the prothrombin time continued to be prolonged. On the 14th day, just before the end of antibiotic therapy, the infant died of sudden intracerebral hemorrhage. In this article, the clinical features and management of factor VII deficiency are discussed. *Key words: factor VII deficiency, newborn, intracerebral hemorrhage.*

Factor VII (F VII) is a vitamin K-dependent glycoprotein, which is essential for coagulation activation by the extrinsic pathway. Its deficiency is expressed in different ways and leads to various clinical pictures[1-3]. F VII deficiency, along with hemophilia, vitamin K deficiency, disseminated intravascular coagulation and protein C deficiency, is one of the rare causes for intracranial hemorrhage during the newborn period[4-6]. Here we report a newborn with F VII deficiency who developed fatal intracranial hemorrhage after therapy for sepsis.

Case Report

A seven-day-old baby boy was brought to the neonatology unit with the complaints of jaundice, bloody stool and bloody vomiting. He was born vaginally to a 24-year-old mother (gravida 1, para 1) at 38 weeks of gestation. The parents were wirst cousins. His birth weight was 3100 g (50^{th} - 90^{th} percentile); Apgar scores were 8 and 10 at 1 and 5 minutes, respectively. The jaundice started on day three of life, but the baby was brought to the hospital after bloody stool and vomiting began. The physical examination revealed hypotonia and jaundice. Laboratory results were as follows: hematocrit 27 percent, white bood cells 8,200/mm^3 (72% neutrophils, 14% band forms, 14% lymphocytes), and

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erythrocyte morphology was normal. Reticulocyte count was four percent; direct Coombs test was negative. There was no blood group incompatibility between the mother and baby. Total bilirubin was measured as 10.5 mg/dl. Hematological test results showed a platelet count of 313,000/mm^3, prothrombin time (PT) 34 sec. (control 13 sec.), partial thromboplastin time (PTT) 31 sec. (control 30-40 sec.), and bleeding time as one minute 25 sec.

The blood culture obtained on admission grew coagulase-negative staphylococci, and the infant was given ampicillin + cephotaxime for a total of 14 days. Cerebrospinal fluid examination was normal. Head ultrasonography was unremarkable.

Fresh frozen plasma (FFP), packed red blood cells and vitamin K were administered to correct the anemia and prolonged PT. Although PTT was within normal limits (32-38.6 sec.), PT remained prolonged (56.5-40.5 sec.) despite the above treatment. Activated PTT was one minute 35, and the fibrinogen level was 320 mg/dl. Factor XIII was positive, and the F VII level was five percent. Based on these findings, a factor VII deficiency was considered[7], and FFP replacement was suggested during symptomatic periods.

Because of the mother's history of mucosal bleeding, consanguinity, and autosomal recessive inheritance of F VII deficiency, the parents' F VII levels were also obtained. The father's and mother's F VII levels were 50 percent and 40 percent, espectively. These results indicated the parents as carriers.

After the antibiotic therapy, FFP and packed red blood cell administration, the clinical status of the infant became stable. However, on the 14^{th} day of the antibiotic therapy (day 21 of life), the patient suddenly deteriorated. Cerebral ultrasonography (Fig. 1) and computerized tomography showed a large intraparenchymal hemorrhage on the right side. The baby was immediately placed on mechanical ventilation, but he did not respond to the therapy and died the next day.

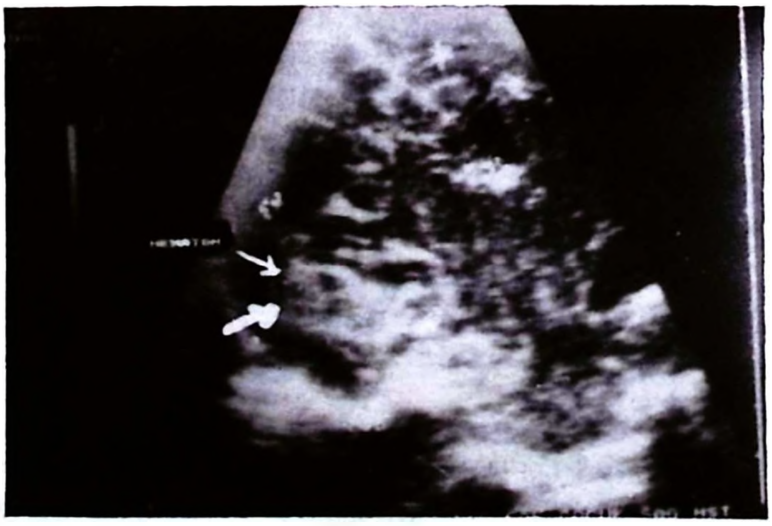

Fig. 1: Cerebral ultrasonography showing intraparenchymal hemorrhage on the right side. There is also a shift towards the left side.

Discussion

F VII deficiency is a rare, autosomal-recessive, hereditary disorder of which different immunological and genetic types have been described[1]. This illness is characterized by normal PTT and prolonged PT. Definitive diagnosis requires a specific F VII assay. In congenital F VII deficiency, bleeding can occur during any period of life. Most commonly, menorrhagia and metrorrhagia occurs in females and hemarthrosis in both sexes[1, 8, 9]. Central nervous system hemorrhages are not uncommon, and may develop during the newborn period or early childhood[5, 6]. The bleeding problem occurs generally in homozygotes. Insignificant non-life-threatening hemorrhages have also been reported in heterozygotes with a wide range of F VII levels[10].

Our patient's mother occasionally, experienced mucosal bleeding, and her F VII level was found to be 40 percent. The father, whose F VII level was 50 percent, was also a possible carrier, but he did not have a bleeding problem.

Currently, in classical hemophilia (F VIII deficiency), prophylactic replacement therapy is being discussed[11]. However, the same prophylactic replacement strategy has not been considered for F VII deficiency. The explanation for this may be that this coagulation disorder is very rare and symptoms are very variable. According to reports in the literature of newborns with hemorrhage problems, replacement therapy should be started during the peripartum period in infants born to a homozygotic mother or to heterozygotic parents[12]. Administration of FFP or F VII concentrates to pregnant women with F VII deficiency should also be considered[13, 14]. In our patient, after the diagnosis of F VII deficiency, FFP replacement was continued until the symptoms of hemorrhage subsided. He also responded well to antibiotic therapy. However, afterwards, during a clinically stable period, intracerebral hemorrhage suddenly developed. We can not relate the hemorrhage in our patient only to the F VII status. The last FFP administration was five days earlier, and the half-life of F VII is five hours. Thus, the F VII level should already have decreased to its previous level, which would have led to hemorrhage earlier. Actually, in patients with a bleeding tendency, the quality of the protein plays a significant role in addition to the F VII level[2]. Sometimes in people with low F VII levels, although coagulation test results may be in the normal range, arterial thrombosis may develop due to the high guality of protein[15]. Since the clinical picture of F VII deficiency is very heterogenous, in newborns with abnormal coagulation tests and/or in the presence of predisposing factors to hemorrhage, e.g. sepsis, replacement therapy should be administered until the risky period is over.

REFERENCES

1. Mariani G, Mazzucconi MG. Factor VII congenital deficiency. Clinical picture and classification of the variants. Hemostasis -1983; 13: 169-177.
2. Fujita I, Takahashi Y, Sakaguchi T, Joh K, Ueda K, Takamiya O. Congenital factor VII abnormality discovered in an infant at a routine checkup. Am J Pediatr Hematol Oncol 1991; 13: 47-48.
3. Shih LY, Hung IJ. Hereditary factor VII deficiency in a Chinese family. Scand J Haematol 1983; 30: 97-102.

4. Yoffe G, Buchanan GR. Intracranial hemorrhage in newborn and young infants with hemophilia. J Pediatr 1988; 113: 333-336.
5. Miano C, Rosati D, Donfrancesco A, Lombardi A, Zama F. Recurrent intracranial hemorrhage in an infant with congenital factor VII deficiency. Haematologica 1987; 72: 188-189.
6. Horng YC, Chou YH, Chen RL, Tsou KI, Lin KH. Congenital factor VII deficiency complicated with hemoperitoneum and intracranial hemorrhage: report of a case. J Formos Med Assoc 1993; 92: 85-87.
7. Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. Blood 1987; 70: 165-172.
8. Papa ML, Schisano G, Franco A, Nina P. Congenital deficiency of factor VII in subarachnoid hemorrhage. Stroke 1994; 25: 508-510.
9. Hassan HJ, Calabore P, De Laurenzi A, Petti N, Sinibaldi L, Orlando M. Hereditary factor VII deficiency: report of a case of intracranial hemorrhage. Haemostasis 1984; 14: 244-248.
10. Bhavnani M, Evans DI. Carriers of factor VII deficiency are not always asymptomatic. Clin Lab Haematol 1984; 6: 363-368.
11. Montgomery RR, Scott JP. Hemostasis: Diseases of the fluid phase. In: Nathan DG, Oski FA. (eds). Hematology of Infancy and Childhood (4th ed) Vol. 2. Philadelphia: WB Saunders Company; 1993: 1605-1650.
12. Chen SC, Chang TK, Chi CS, Shu SG. Factor VII deficiency with intracranial hemorrhage: a case report. Chung Hua I Hsueh Tsa Chih (Taipei) 1993; 52: 190-193.
13. Robertson LE, Wasserstrum N, Banez E, Vasquez M, Sears DA. Hereditary factor VII deficiency in pregnancy: peripartum treatment with factor VII concentrate. Am J Hematol 1992; 40: 38-41.
14. Fadel HE, Krauss JS. Factor VII deficiency and pregnancy. Obstet Gynecol 1989; 73: 453-454.
15. Lefrere JJ,Chaunu MP, Conard J, Horellou MH, Samama M. Congenital factor VII deficiency and cerebrovascular stroke. Lancet 1985, ii: 1006-1007.

The Turkish Journal of Pediatrics 1996; 38: 261-264

ASSOCIATION OF XERODERMA PIGMENTOSUM WITH THROMBASTHENIA*

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SUMMARY: Hasanoğlu A, Gücüyener K, Tümer L, Gürsel T. (Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey). Association of xeroderma pigmentosum with thrombasthenia. Turk J Pediatr 1996; 38: 261-264.

Xeroderma pigmentosum (XP) is an autosomal recessive disorder characterized by severe sun-sensitivity, early skin cancers and abnormal DNA repair. XP has a worldwide distribution with an approximate frequency of 1/250,000. It is classified into nine complementation groups, and distribution of patients among the various groups is related to ethnic origin.

To our knowledge, the association of XP with thrombasthenia has not been reported perviously; here a 12-year-old girl with this combination is reported. She was first noted to have skin erythema on exposure to sunlight at the age of six months and was diagnosed with XP. At the age of one she had the complaints of easy bruising and epistaxis. A diagnosis of thrombasthenia was made based on the absence of platelet aggregation response to ADP, collagen and adrenaline and reduced clot retraction. In clinical management, oral isotretinoin was given in order to supress tumor formation. *Key words: xeroderma pigmentosum, Glanzmann's thrombasthenia.*

Xeroderma pigmentosum (XP) and Glanzmann's thrombasthenia (GT) are two rare, autosomal-recessive hereditary disorders[1-6]. The typical clinical findings of both disorders are reported in a 12-year-old girl as the first example of this association.

Case Report

The patient was the second product of consanguineous parents. The pregnancy and delivery were uneventful, and psychomotor development in the first two years of life was normal. At the age of six months she suffered from hyperpigmented macules of the skin in sun-exposed areas. She also had had frequent ecchymosis, epistaxis and dental bleeding since infancy. A skin biopsy confirmed the diagnosis of XP.

Physical examination revealed hypo/hyperpigmented macules, ecchymosis and petechiae. Her eyelashes had fallen out with bilateral ectropion, and bilateral opacities were observed on the lower part of the cornea (Fig. 1). The rest of the physical examination revealed no pathology.

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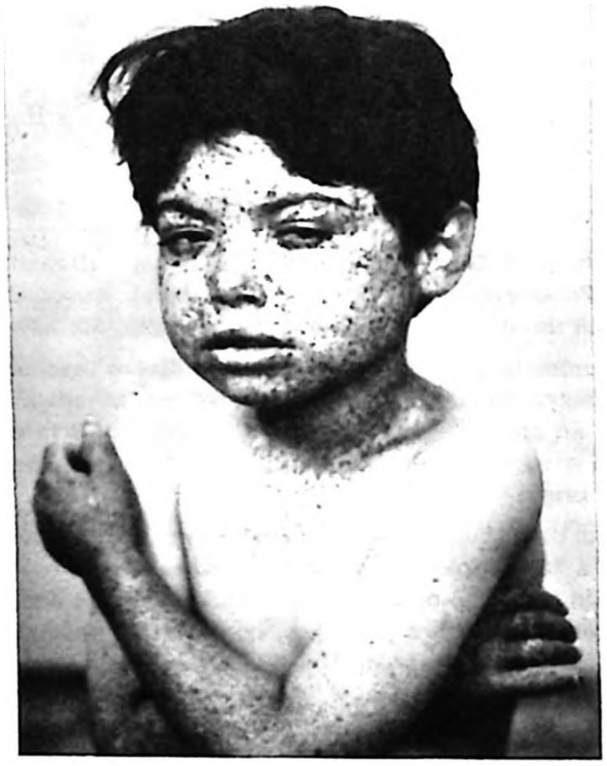

Fig. 1: Patient at 10 years of age.

Laboratory findings: electroencephalography, electromyography, computerized brain tomography and brain auditory evoked potentials were normal, ruling out auditory and neurologic involvement[7-9]. Hematological investigations including hemoglobin, leukocyte count and red blood cell morphology were normal. The platelet count was 239,000/mm^3. Platelets remained discrete, round and isolated in stained blood smears. The prothrombin and partial thromboplastin times were normal, but the bleeding time was greater than 15 minutes. Platelet aggregation response to ADP, collagen and adrenaline was impaired, and to ristosetin was normal (1.5 ng/ml).

A low dose (0.5 mg/kg/day) of oral isotretinoin was initiated since the patient had not developed skin neoplasm and no side effects or malignancy had been observed in two years.

Discussion

Xeroderma pigmentosum is a rare, autosomal-recessive disease characterized by severe photosensitivity and early skin cancers. Patients without neurological symptoms comprise 75 percent of cases and are diagnosed between six and 18 months of age. They reach the tumor stage before the age of 20, but a few run a more benign course as in our case[1, 2, 4-6]. XP has a worldwide distribution

with an approximate frequency of 1/250,000 with equal sex and race preponderence[4-6]. However, the incidences of both XP and thrombasthenia are relatively high in this country because of the high rate of consanguinity[10]. The distribution of XP patients among the various complementation groups is related to ethnic origin[5, 6].

In clinical management, strict, early measures to protect the patient from harmful radiation are necessary[3, 11]. The finding that tumor formation can be rapidly and reversibly supressed by isotretinoin therapy led us to administer low-dose oral isotretinoin to our patient[12].

The lifelong bleeding history, prolonged bleeding time and platelet aggregation pattern in our patient were consistent with GT. This autosomal-recessive disorder of platelet fnuction could be related to quantitative or qualitative abnormalities of platelet membrane glycoprotein IIb/IIIa complex[3]. Platelet dysfunction may also complicate a wide variety of heritable and acquired disorders such as heritable disorders of connective tissue, drug usage, disorders involving the hematopoietic system, uremia, congenital heart disease and liver disease[13]; however, in our case the patient's clinical and laboratory findings were discordant with these disorders.

Although the association of XP with two other diseases of DNA repair defects- Cockayne's syndrome and trichothiodystrophy- has been reported[1, 14], this is the first report of its association with thrombasthenia. Further case reports will shed light on the association of xeroderma pigmentosum and thrombasthenia.

REFERENCES

1. Bohr AV, Evans KV. Heterogeneity of DNA repair: implications for human disease and oncology. Pediatr Hem Oncol 1990; 7: 47-69.
2. English JS, Swerdlow AJ. The risk of malignant melanoma, internal malignancy and mortality in xeroderma pigmentosum patients. Br J Dermatol 1987; 117: 457-461.
3. Stuart MJ, Kelton JG. The platelet: quantitative and qualitative abnormalities. In: Nathan D, Oski F (eds). Hematology of Infancy and Childhood, Volume II. London: Saunders Co; 1987: 1436-1437.
4. Robbins JH. Xeroderma pigmentosum. Defective DNA repair causes skin cancer and neurodegeneration. JAMA 1988; 260: 384-388.
5. Robbins JH, Kraemer KH, Lutaner MA. An inherited disease with sun sensitivity, multiple cutaneous neoplasms and abnomal DNA repair. Ann Intern Med 1974; 80: 221-226.
6. Wood DR, Robins P, Lindhal T. Complementation of the xeroderma pigmentosum DNA repair defect in cell free extracts. Cell 1988; 53: 97-106.
7. Kenyon GS, Booth BJ, Prasher DK, Rudge P. Neuro-otological abnormalities in xeroderma pigmentosum with particular reference to deafness. Brain 1985; 108: 771-784.
8. Mimaki T, Itoh N, Abe J, et al. Neurological manifestations in xeroderma pigmentosum. Ann Neurol 1986; 20: 70-75.
9. Mimaki T, Tagowa T, Tanaka J, Sato K, Yabuuchi H. EEG and CT abnormalities in xeroderma pigmentosum. Acta Neurol Scand 1989; 80: 136-141.
10. Hiçsönmez G. Congenital qualitative platelet disorders in children. Report on 60 patients. Turk J Pediatr 1982; 24: 21-28.

11. Osguthorpe JD, Lang P. Management of xeroderma pigmentosum. Arch Otolaryngol Head Neck Surg 1987; 113: 292- 294.

12. Kraemer KH, DiGiovanna JJ, Moshell AN, Tarone RE, Peck GL. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. N Engl J Med 1988; 318: 1633-1637.

13. Bithell TC. Qualitative disorders of platelet function. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds). Wintrobe's Clinical Hematology, Volume II. London: Lea and Febiger; 1993: 1397-1422.

14. Nuzzo F, Zei G, Stefanini M, et al. Search for consanguinity within and among families of patients with trichothiodystrophy associated with xeroderma pigmentosum. J Med Genet 1990; 27: 21-25.

The Turkish Journal of Pediatrics 1996; 38: 265-270

OSSIFYING FIBROMA*

A Case Report

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*Mustafa Yiğit Saysel DDS PhD*******

SUMMARY: Taşar F, Giray CB, Taşman U, Saysel MY. (Department of Oral Surgery, Hacettepe University Faculty of Dentistry, Ankara, Turkey). Ossifying fibroma: a case report. Turk J Pediatr 1996; 38: 265-270.

Ossifying fibroma is a benign tumor of connective tissue origin which occurs in fibro-osseous lesions. The lesion is seen most commonly in children and young adults. It is asymptomatic and slow-growing, but in some cases may show aggressive behavior. Though it has a slight predilection for the mandible, it may involve both jaws. The lesion is generally asymptomatic until it produces noticeable swelling, and mild deformity and migrations of teeth may be an early clinical feature. Pediatricians and dentists must be aware when asymmetry of the face occurs, and the lesion must be well diagnosed as it has a cancer-like radiographic appearance. In this article a nine-year-old patient with a massive mandibular ossifying fibroma is presented. *Key words: ossifying fibroma, mandible, extensive.*

Fibrous dysplasia, periapical cemental dysplasia, ossifying fibroma, periostitis of Garre, focal sclerosing osteomyelitis and osteitis deformans are a variety of disease processes under the name "benign fibro-osseous lesions"[1]. Distinct differentiation among various fibro-osseous entities is difficult because of overlapping clinical and histopathologic criteria. Even when a clear diagnosis can be made, management of the lesion may depend on the patient's past medical history. According to Eversole et al.[2], ossifying fibromas elaborate bone, cementum and sphenoidal calcifications; when bone predominates, ossifying fibroma is the appellation, while the term "cementifying fibroma" has been assigned when trabeculae or sphenoidal calcifications are encountered. Shafer et al.[3] defined ossifying fibroma as a benign, relatively slow-growing lesion in which osteoblasts proliferate and form bone.

Clinically, ossifying fibroma may occur at any age but is more common in young adults. The mandible is the most commonly affected site among the cranial bones. According to Eversole et al.[2], there is a marked predilection for female patients and arising in the molar-premolar region of the mandible. Even though it is a slow-growing tumor, some cases may show aggressive behavior, reaching massive dimensions with extensive cortical expansion. Most of the lesions occur in children and have promoted the designation "juvenile aggressive" or "active

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ossifying fibroma"[4]. The lesion is generally asymptomatic until the growth produces noticeable swelling and asymmetry. Displacement of the adjacent teeth may be an early clinical feature, and on rare occasions pain and paresthesia may result from pressure on the related nerves[3, 5].

The differential diagnosis usually consists of fibrous dysplasia and cementifying fibroma. Total excision of the tumor is the main treatment choice, and the recurrence rate is very low after adequate surgical resection[2, 3].

This type of central, fibro-osseous lesion should be well-defined and taken into consideration in differential diagnoses, especially in children. They are rare non-odontogenic tumors of the jaws that need to be carefully managed.

Case Report

A nine-year-old male patient was referred to the University of Hacettepe Faculty of Dentistry, Department of Oral Surgery, with the complaint of swelling in his right mandibular molar region. He stated that he first became aware of the lesion five months previously, and a dentist in his home town performed an incisional biopsy with the primary diagnosis of osteomyelitis. The specimen was reported as an ossifying fibroma, and his doctor referred him to our clinic for further examination and surgery.

There was no history of trauma, and his medical and dental histories were unremarkable. He had a mild deformity on the right side of his face. On intra-oral examination, a hard, bony expansion from the alveolar ridge through the basis of the mandible was noted. The mucosa was normal in color and intact. The panoramic radiograph revealed a large multilocular radiolucent area showing casual opacities in the right corpus of the mandible (Fig. 1).

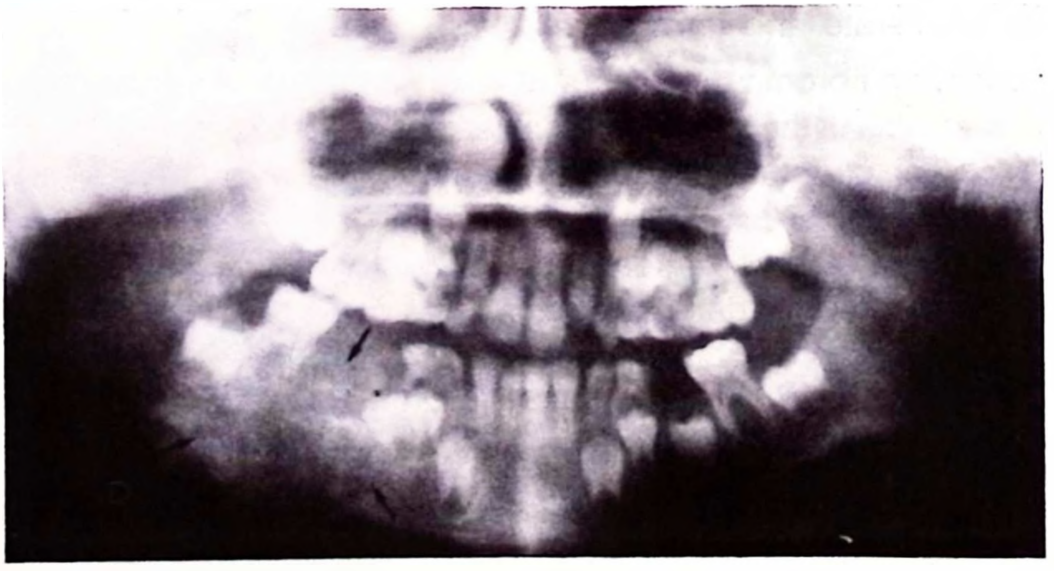

Fig. 1: Panoramic radiographic view of the lesion in the right mandibular corpus (arrows).

Surgery was performed under general anesthesia ten days after his referral. The mucoperiosteal flap between the angulus and the right mandibular canine was elevated, and the bone overlying the lesion was removed with roungers and burs. The first mandibular molar was extracted, and the affected germ of the first and second premolars was enucleated. The inferior alveolar neurovascular bundle was protected and the lingual portion of the mandibular bone was left intact. The flap was closed primarily, and antibiotic therapy (amoxycillin 500 mg p.o. 3 x 1) was given for one week postoperatively.

Histopathological Findings

The specimen was fixed in 10% formaline solution and processed for routine light microscopy. Macroscopically, the curettage material was hard and covered with bony-like structures. There were occasional soft compositions attached to the trabecular bone in the tumor tissue. Microscopic examination of hematoxylin-eosin-stained sections revealed plentiful number of active fibroblast cells, and rare, irregular, bony trabeculae were observed (Fig. 2a). At higher magnifications,

Fig. 2a: Appearance of the islands of ossification (arrows) in a wealthy fibrous stroma (H + E x 115).

massive interlacing collagen fibers and an island of ossification was noticed in the fibrous stroma (Fig. 2b). The histopathologic report declared the lesion as an "ossifying fibroma".

The patient was followed up every three months, and after three years of follow-up there was no sign of recurrence (Fig. 3).

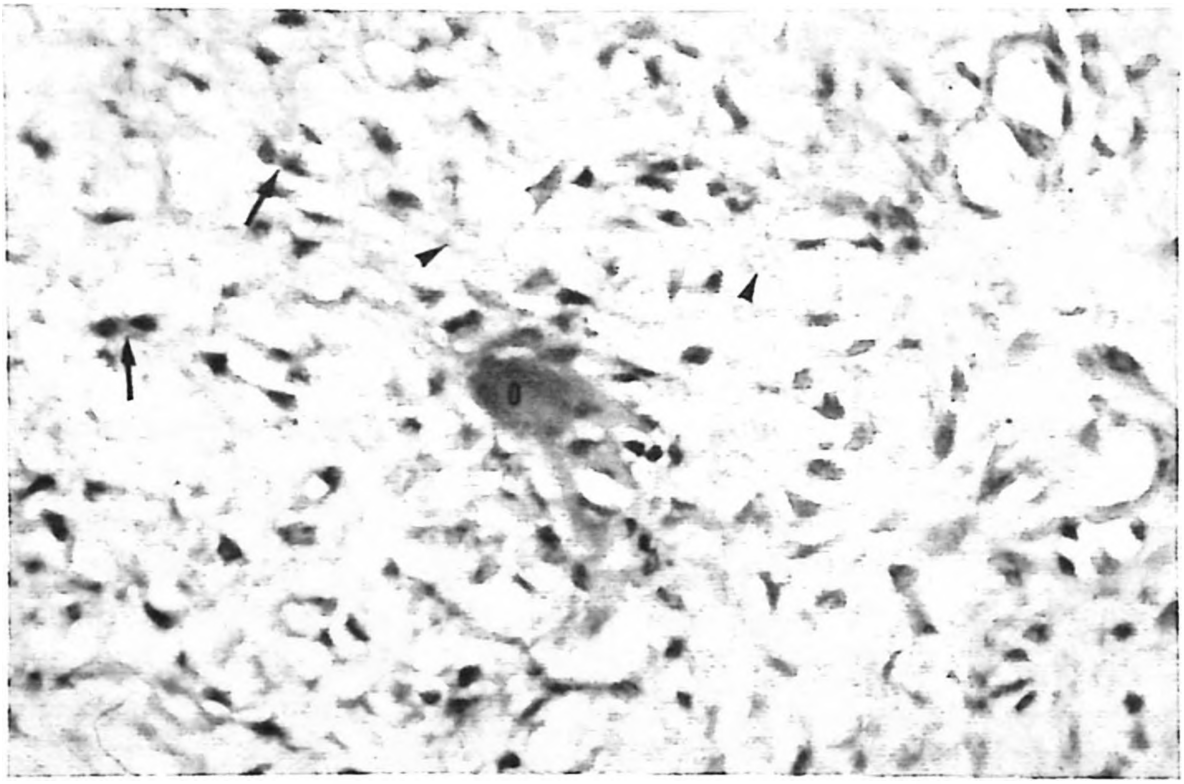

Fig. 2b: Section of the tumor tissue interlacing collagen fibers (arrow head) and proliferating fibroblasts (arrow) and an irregular trabecula of osteoid. (O) (H + E x 460).

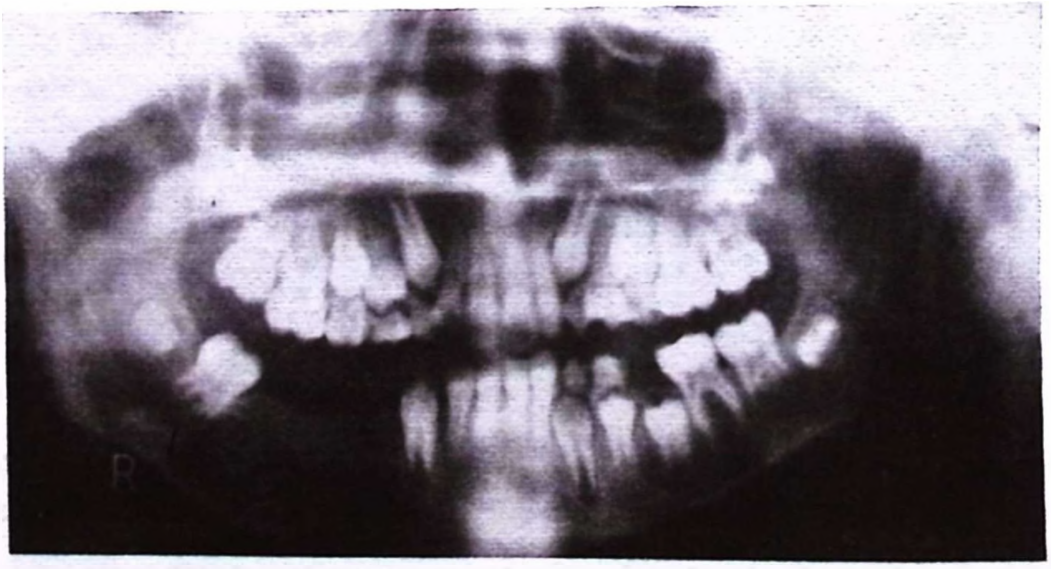

Fig. 3: Radiographic appearance of the mandible three years postoperatively. The basis of the right mandible is healthy and intact (arrow).

Discussion

This case has the characteristics of a typical ossifying fibroma lesion. The main symptom was swelling on the right side of the patient's face. In most cases the lesions are asymptomatic and painless and stop growing after reaching a certain size. However, some lesions are capable of accelerated growth and recur following the curretage. The recurrence rate after curretage is 28 percent[2]. Some other types of fibroosseous lesions, such as cemento-ossifying fibroma, have a higher recurrence and need at least a five-year follow-up period. Curretage is the most proper treatment option for such lesions; if a severe recurrence occurs, block resection may be indicated[3].

Because of the difficulty of differentiating fibro-osseous lesions on a histologic basis and predicting their behavior solely on the basis of those findings, a good history and review of radiographic and surgical findings are always necessary[1, 7]. The neoplasm presents an extremely variable reontgenographic appearance depending on its stage of development. In early stages, the noplasm is generally well demarcated and may be radiolucent, radiolucent with central opacification, or have a multilocular radiolucent appearance. However, in nearly all cases the lesions have well-defined radiographic borders[6].

Prior to biopsy, the differential diagnosis usually includes ameloblastoma, odontogenic fibromas, chondrosarcoma and giant cell granuloma[3, 8]. In our case the patient was referred to us with an earlier histopathological report taken from the city hospital in his home town; thus we did not have reason to suspect other entities and when we compared the clinical findings the lesion displayed the main characteristics of ossifying fibroma. According to Eversole et al.[2], all fibro-osseous jaw lesions arise from the periodontal ligament with the potential for both osseous and cemental differentiation as witnessed by the presence of woven and lamellar osseous trabecular and non-linear cementum.

The ossifying fibroma contains woven bone often rimmed by osteoblasts that lay down layers of lamellar bone. Basically, the lesion is composed of many delicate interlacing collagen fibers, interspersed by large numbers of active proliferating fibroblasts. This connective tissue characteristically presents many small foci of irregular bony trabeculae. When the tumor matures, the islands of ossification increase in number with a probable calcification that accounts for high radio-opacities in the radiograph[3]. This may resemble areas of cementum appearing as psammoma bodies embedded in a benign fibrous stroma[7]. In the present case, our histopathological and radiographic findings correlated with these findings. In fact there are many types of histologic patterns of these lesions, but no difference in behavior between the histologic destinations can be found.

Among fibro-osseous tumors, ossifying fibroma is one of the most common lesions occuring in children. When the tumor is diagnosed and treated properly and meticulously, the recurrence rate is low, even when the tumor is large, as in our case.

REFERENCES

1. Cooke BD. Benign fibro-osseous enlargements of the jaws. Part II. Neoplastic enlargements. Br Dent J 1957; 102: 49-59.
2. Eversole LR, Leider AS, Nelson K. Ossifying fibroma: a clinicopathologic study of sixty-four cases. Oral Surg Oral Med Oral Pathol 1985; 60: 505-511.
3. Shafer GW, Hine KM, Levy MB. A Text Book of Oral Pathology (4th ed). Philadelphia: W.B. Saunders Co; 1983: 141-142.
4. Walter JM, Terry BC, Small EW, Matteson RR, Howell RM, Hill C. Aggressive ossifying fibroma of the maxilla: review of the literature and report of a case. J Oral Surg 1979; 37: 276-286.
5. Chidzonga MM. Ossifying fibroma: management of a case with a 20-year history. J Oral Maxillofac Surg 1987; 45: 1062-1064.
6. Eversole LR, Merrell PW, Strub D. Radiographic characteristics of central ossifying fibroma. Oral Surg Oral Med Oral Pathol 1985; 59: 522-527.
7. Hall EH, Naylor GD, Mohr RW, Warnock GR. Early aggressive cemento-ossifying fibroma: a diagnostic and treatment dilemma. Oral Surg Oral Med Oral Pathol 1987; 63: 132-136.
8. Waldron CA,Giansanli JS. Benign fibro-osseous lesions of the jaws: a clinical, radiologic-histologic review of sixty-five cases. Part II. Benign fibro-osseous lesions of periodontal ligament origin. Oral Surg Oral Med Oral Pathol 1973; 35: 340-350.

The Turkish Journal of Pediatrics 1996; 38: 271-276

ASYMMETRIC CRYING FACIES: AN INDEX OF OTHER MALFORMATIONS*

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SUMMARY: Aslan Y, Mocan H, Erduran E, Aynacı M, Ökten A. (Department of Pediatrics, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Asymmetric crying facies: an index of other malformations. Turk J Pediatr 1996; 38: 271-276.

Congenital hypoplasia or absence of the depressor anguli oris muscle is a minor congenital anomaly causing asymmetrical crying facies (ACF). The interesting aspect of this abnormality lies in the frequently associated abnormalities. Cardiac, urogenital, musculoskeletal, respiratory and cervicofacial defects have been described in cases with ACF. Therefore it is suggested that ACF can be used as an index of other congenital malformations. We report three cases with ACF who had varied congenital anormalies. *Key words: asymmetric crying facies.*

An infant whose face appears symmetrical at rest yet whose face is pulled downward to one side when crying is said to have "asymmetrical crying facies (ACF)"[1]. The cause of the facial asymmetry in this disorder is congenital absence or hypoplasia of the depressor anguli oris muscle (DAOM) at the corner of the mouth[2-5].

A variety of anomalies have been observed in patients with ACF[1]. Therefore it is suggested that ACF can be used as an index of other congenital anomalies[1]. We report here three infants who were referred for evaluation of ACF and were investigated for other congenital anomalies.

Case Reports

Case 1

A 12-month-old female infant was referred to our clinic for evaluation of a striking asymmetry on the left corner of the mouth when crying, as well as intermittent cyanosis. She was the seventh baby of this mother following a full-term uncomplicated gestation, labor and delivery. She weighed 3400 g at birth, and no neonatal complications had been recognized. Her motor and mental development had been normal, and her parents and siblings were healthy.

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On physical examination, the pulse rate was 118/min. The patient had a normal appearance at rest and asymmetric facies when she was crying; the left corner of the mouth drew left and downward while the right moved very little (Fig. 1). There was no sign related to facial paralysis. She had mild perioral cyanosis and clubbing. On auscultation of the heart, a systolic ejection murmur and a third heart sound were heard, and the second sound was single and loud. The rest of the physical and neurological examination findings were normal.

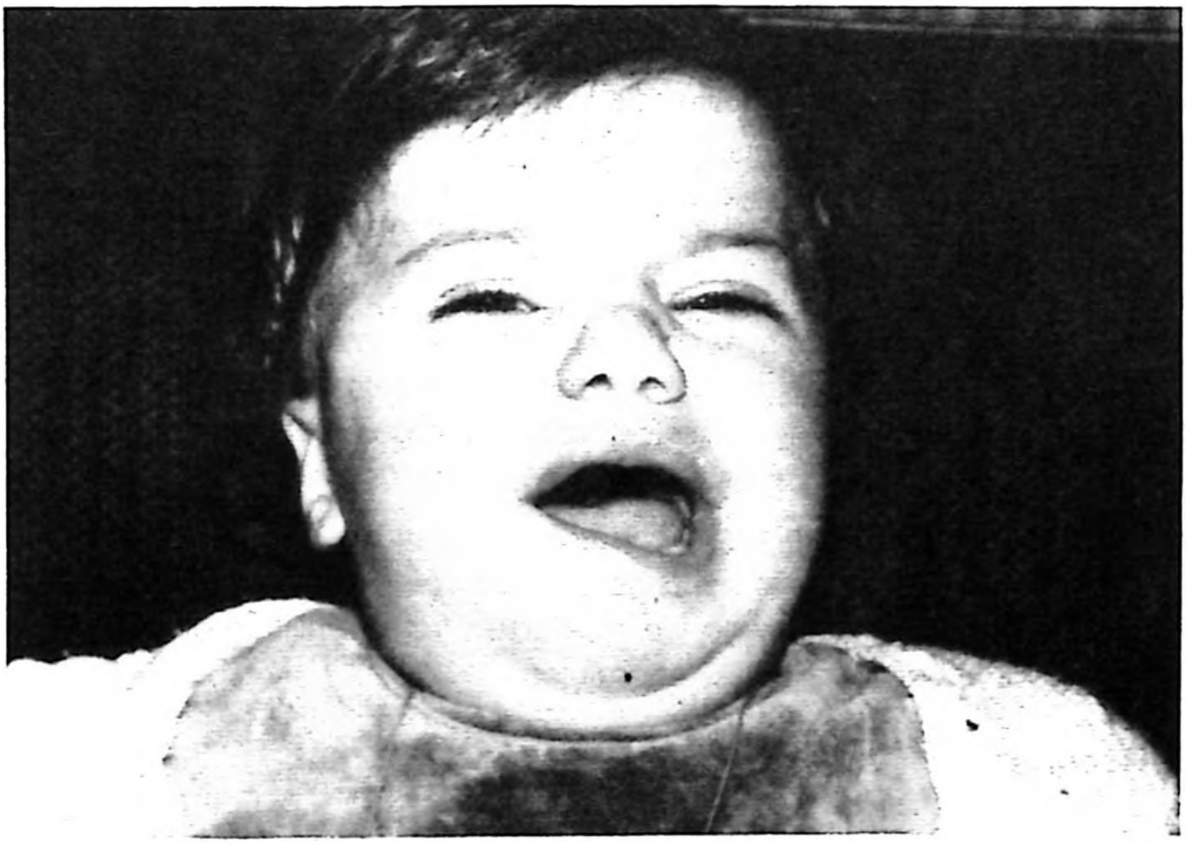

Fig. 1: Facial asymmetry of Case 1 on crying.

Arterial blood gases indicated mild hypoxemia, and the chest x-ray showed cardiomegaly and increased pulmonary vasculature. The electrocardiogram suggested biventricular hypertrophy, and echocardiography (ECHO) showed absence of the ventricular septum and a single ventricle (Fig. 2). On electroneuromyographic (ENMG) examination, the facial nerve excitability was intact and equal on each side; the right DAOM showed diminished motor unit activity (MUA) even while the patient was crying, while the left DAOM showed normal MUA. At rest there were no denervation potentials. The other laboratory investigations were normal. The diagnosis of hypoplastic right DAOM and single ventricle was made.

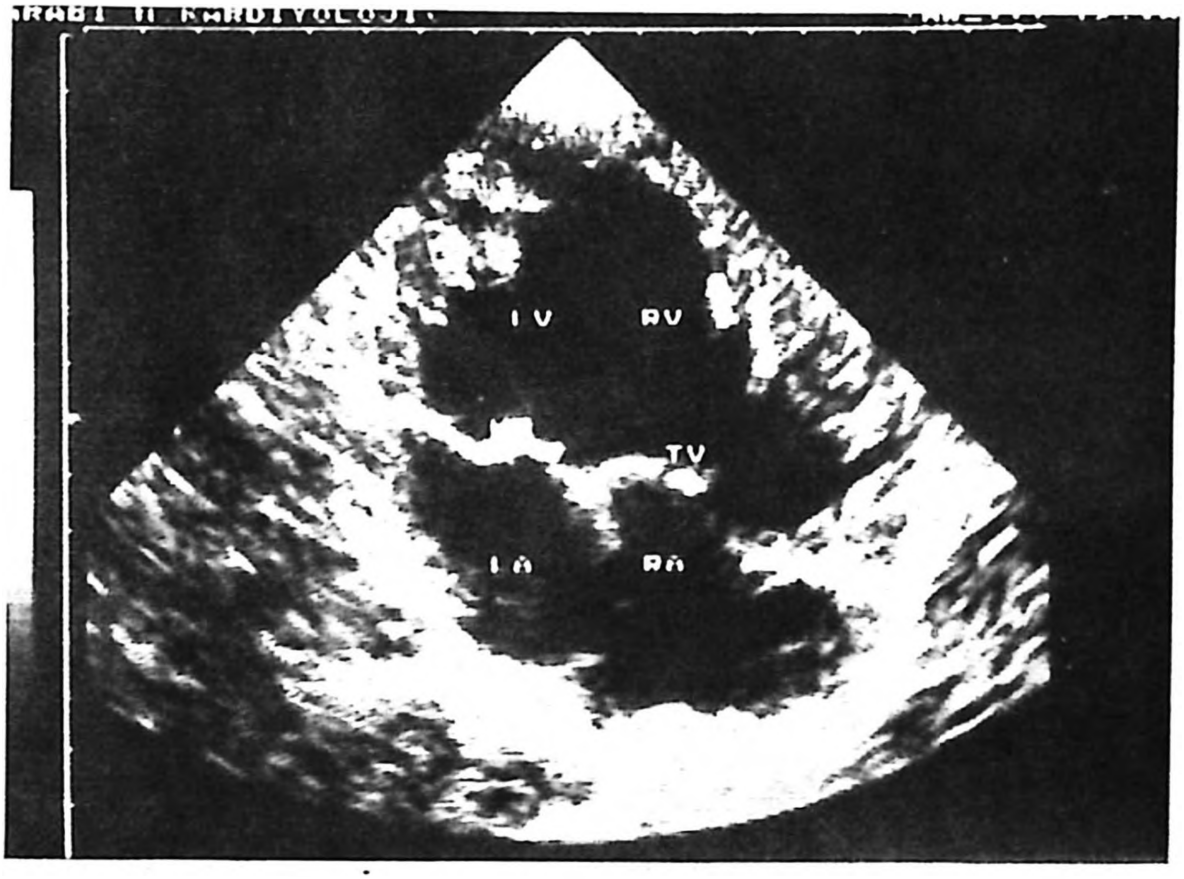

Fig. 2: Echocardiogram of Case 1 showing absence of the ventricular septum.

Case 2

A nine-month-old girl was referred to our clinic for evaluation of striking asymmetric facies when crying, intermittent cough and tachypnea. The patient was the product of her mother's third, full-term, uncomplicated pregnancy. She had two healthy male siblings and her motor mental development was normal.

The physical examination yielded the lack of downward contraction of the right angle of the mouth when crying, suggesting weakness of the right DAOM. Her pulse was 110/min, and respirations were 44/min. On the left lung, the percussion note was increased, breath sounds were reduced and a mild wheeze was heard. The heart sounds were best heard at the right sternal border. The other system examinations were normal.

Anteroposterior chest x-ray showed an over distended hyperlucent left-upper lobe with mediastinal and cardiac shift, and herniation of the left lung into the right hemithorax with compression of the right lung (Fig. 3). suggesting congenital lobar emphysema (CLE). The chest tomography findings were similar to those of the chest x-ray. Bronchography demonstrated incomplete distal filling of the left-upper bronchi. ENMG suggested the diagnosis of hypoplastic right DAOM.

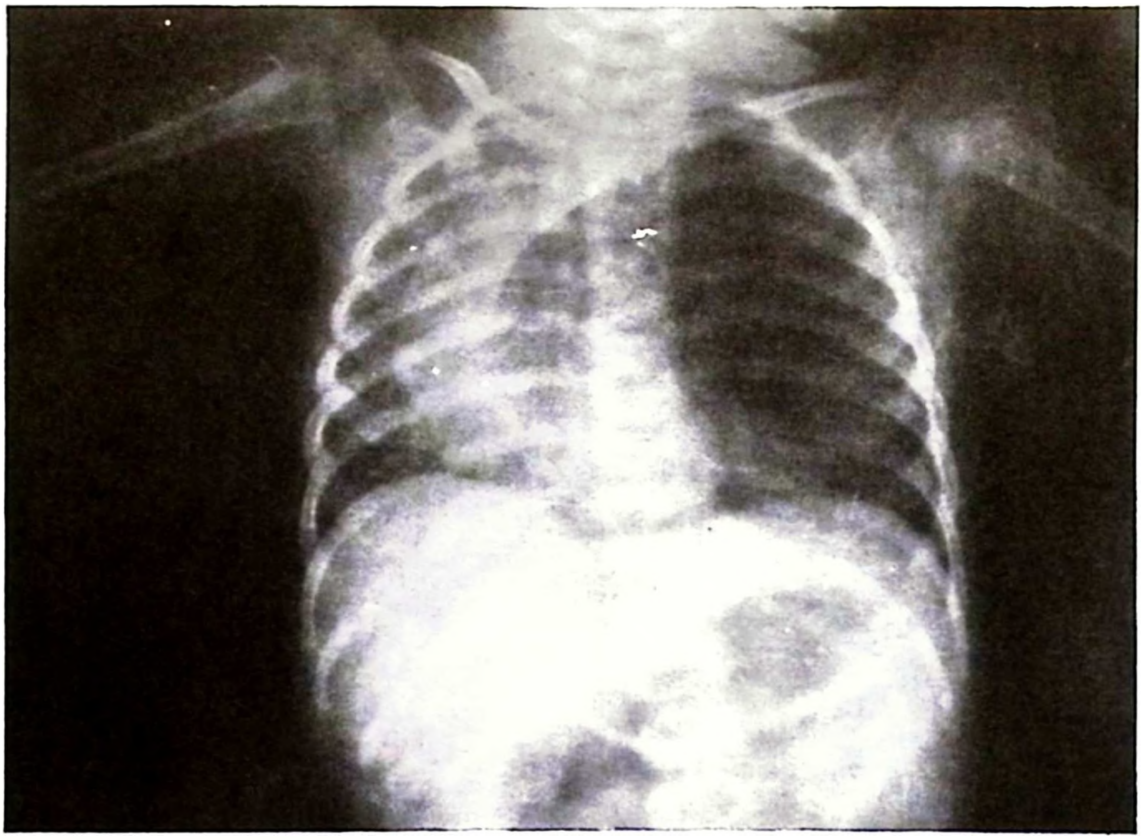

Fig. 3: Chest x-ray of Case 2 showing an overdistended, hyperlucent left-upper lobe with mediastinal and cardiac shift, and herniation of the left lung into the right hemithorax.

The patient's pulmonary disease was treated with medical and supportive therapies for three months without improvement; then she was operated on and a left-upper lobectomy was performed. Macroscopic and microscopic examination of the excised material suggested the diagnosis of CLE. After surgery demonstrated near-normal total lung functions.

Case 3

A two-day-old male infant was admitted to our clinic with the complaint of multiple anomalies. He was his mother's first child and the product of a full-term uncomplicated gestation, labor and delivery. His parents were healthy and first-degree relatives.

Physical examination revealed left-sided ACF. His weight was 3400 g and length was 50 cm. He had micrognathia, cleft plate, short neck, bilateral high-set scapula and barrel thorax (Fig. 4). The rest of the physical examination findings were normal. ENMG suggested the diagnosis of hypoplastic left DAOM. The other investigations were normal.

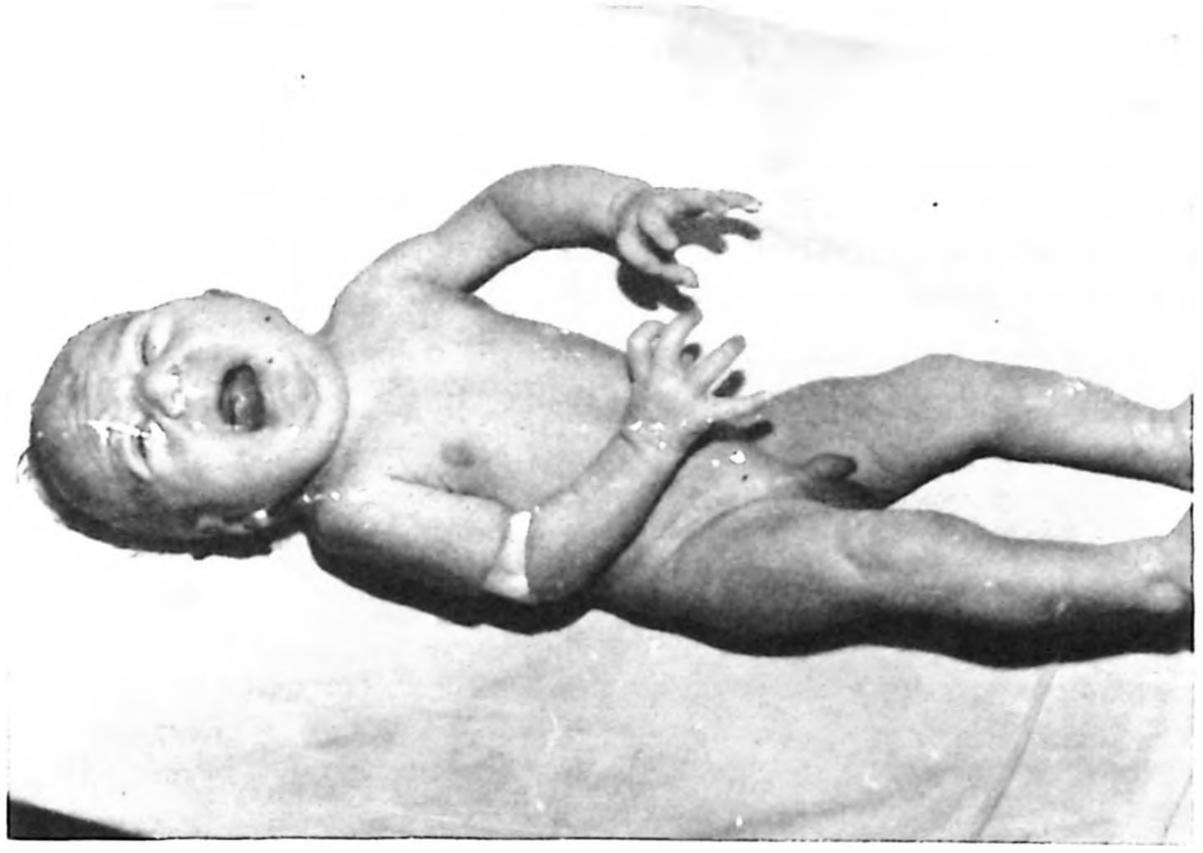

Fig. 4: Photograph of Case 3 showing ACF, micrognathia, short neck, high-set scapula and barrel thorax.

Discussion

Congenital hypoplasia of the DAOM is a rare congenital anomaly which is sometimes confused with congenital facial palsy[4]. The etiology of this anomaly, which causes ACF in an infant, is still debated[5]. It is proposed that it has a polygenic inheritance[5]. Its frequency, as calculated in two large newborn surveys, varies from 1/122 to 1/155[4]. The diagnosis of ACF is basically clinical. It is necessary to make a differential diagnosis of the paralysis of the seventh cranial nerve using electrophysiological techniques[2].

The interesting aspect of this abnormality lies in the frequently associated malformations. First Cayler[6] described the association of ACF with congenital heart defects, and proposed the name "Cardiofacial Syndrome" for this new condition. A number of associated anomalies other than cardiac have been subsequently observed in patients with ACF. Urogenital, musculoskeletal, respiratory and cervicofacial defects are most frequently associated[1,2,5,6]. In 1987, de Echaniz et al.[2] stressed the high incidence of an association with congenital malformations (eight times that in the general populations). Therefore it is suggested that ACF can be used as an index of congenital anomalies[1,7,8], and there is evidence that the condition is genetically determined[5].

The presence of a single ventricle is a rare congenital heart disease. As far as we know, two cases with ACF associated with a single ventricle have been reported to date[6]. We also report here an infant with ACF and a single ventricle.

Congenital lobar emphysema in infants is characterized by severe overinflation of the pulmonary lobe, usually causing severe respiratory distress[9]. A familial occurrence has been reported[9]. Our Case 2 may be the first reported case in the literature with the combination of ACF and CLE.

Cleft palate has been previously reported in a few cases with ACF[5], but micrognathia, short neck, high-set scapula and barrel thorax are reported here for the first time (Case 3).

Finally, in light of the literature, we suggest that all children with ACF be carefully investigated for other congenital anomalies.

REFERENCES

1. Pape KE, Pickering D. Asymmetric crying facies: an index of other congenital anomalies. J Pediatr 1972; 81: 21-30.
2. de Echaniz EL, Narbona GJ, Gracia CC, Villa EI. Asymmetric crying facies syndrome. An Esp Pediatr 1987; 27: 199-204.
3. Kayamori R, Takahashi S, Orii K, et al. Electrophysiological study of congenital facial paralysis. No To Shinkei 1988; 40: 157-161 (Eng. Abstr.).
4. Nelson KB, Eng GD. Congenital hypoplasia of the depressor anguli oris muscle: differentiation from congenital facial palsy. J Pediatr 1972; 81: 16-20.
5. Silengo MC, Bell GL, Biagioli M, et al. Asymmetric crying facies with microcephaly and mental retardation. An autosomal dominant syndrome with variable expressivity. Clin Genet 1986; 30: 481-484.
6. Cayler GG. Cardiofacial syndrome. Congenital heart disease and facial weakness, a hitherto unrecognized association. Arch Dis Child 1969; 44: 69-75.
7. Fiocchi A, Amadio C. The "asymmetric crying facies": an indication of other malformations? Minerva Pediatr 1988; 40: 195-198.
8. Sanklecha M, Kher A, Bharucha BA. Asymmetric crying facies: the cardiofacial syndrome. J Postgrad Med 1992; 38: 147-148, 150.
9. Stern RC. Emphysema and overinflation. In: Behrman RE, Kliegman RM (eds). Nelson Textbook of Pediatrics (14th ed). Philadelphia: W.B. Saunders Co; 1992: 1094-1095.

The Turkish Journal of Pediatrics 1996; 38: 277-280

KLIPPEL – TRENAUNAY – WEBER SYNDROME WITH HEMIMEGALENCEPHALY*

Report of a Case

*Faruk Alpay MD***, *A.Emin Kürekçi MD***
*Selçuk Güneşli MD****, *Erdal Gökçay MD*****

SUMMARY: Alpay F, Kürekçi AE, Güneşli S, Gökçay E. (Department of Pediatrics, Gülhane Military Medical Academy, Ankara, Turkey). Klippel-Trenaunay-Weber syndrome with hemimegalencephaly: report of a case. Turk J Pediatr 1996; 38: 277-280.

A case of Klippel-Trenaunay-Weber Syndrome (KTWS) in a 2.5-year-old girl with congenital hemihypertrophy, nevus flammeus and liver hemangioma is presented. In addition, this report describes the rare association of hemimegalencephaly with KTWS.
Key words: hemihypertrophy, nevus flammeus, Klippel-Trenaunay-Weber syndrome, hemimegalencephaly.

The syndrome of a macular vascular nevus (nevus flammeus), bony and soft tissue hypertrophy, and venous varicosities was described in 1900 by Klippel and Trenaunay[1]. Weber[2] added another component, arteriovenous fistula, in 1907. These findings are also present in the clinical presentations of several other syndromes (Beckwith-Wiedeman, Silver-Russel, Sturge-Weber, Rubinstein-Taybi, Cobbs, etc.) and malignancies (Wilms' tumor, hepatoblastoma, etc.)[3,4]. Hemimegalencephaly, or unilateral megalencephaly, is caused by abnormal neuronal proliferation and migration during the second trimester, and results in overgrowth and secondary polymicrogyria of one cerebral hemisphere. The association of this entity with Klippel-Trenaunay-Weber syndrome (KTWS) is extremely rare. Cerebral and cerebellar hemihypertrophy have been reported previously[5], but magnetic resonance imaging (MRI) was not done in that case. We present a case of KTWS and her striking MRI findings with hemimegalencephaly.

Case Report

A 2.5-year-old girl was admitted to Gülhane Military Medical Academy Hospital with the findings of anemia, cervical lymphadenitis, macrosomic appearance, hemihypertrophy involving the left upper and lower extremities, nevus flammeus

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on the trunk, face, upper right extremity and lower extremities, hypopigmented skin lesions, and mental and motor subnormality (Fig. 1). Her height was at the 50th, weight at the 90th, chest circumference at the 75th, and head circumference above the 97th percentile. The hemoglobin was 4.5 g/dl, hematocrit 13 percent, platelet count 434,000/mm^3, and red cell indices revealed iron deficiency anemia [mean corpuscular volume (MCV) 56 cubic microns, mean corpuscular hemoglobin (MCH) 22 pg/cell, red-cell distribution width (RDW) 39.4]. The serum iron was 21 µg/dl, total iron binding capacity 342 µg/dl and ferritin 46 ng/ml, and occult blood was negative in the stool. Plain skeletal films showed cranial hemihypertrophy. The bone age was delayed (6 months-1 year). Bone scintigraphy confirmed the presence of soft tissue hemihypertrophy. Total body venography was normal except for left vesicoureteral reflux. Abdominal ultrasonography revealed diffuse enlargement of the liver, and computed tomography showed hemangioma in the liver (Fig. 2). Magnetic resonance imaging of the brain revealed dysmyelinization, left lateral ventricle dilatation. (particularly in the frontal and occipital horns), and hemimegalencephaly (Fig. 3). Skin biopsy verified the diagnosis of nevus flammeus, and skin fibroblast culture showed no mosaicism.

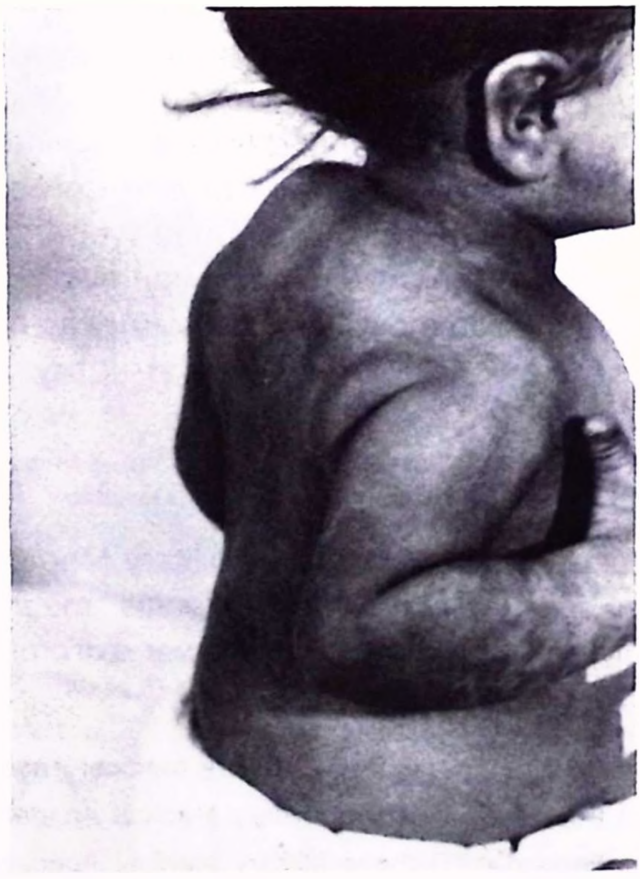

Fig. 1: Nevus flammeus on the trunk and arm.

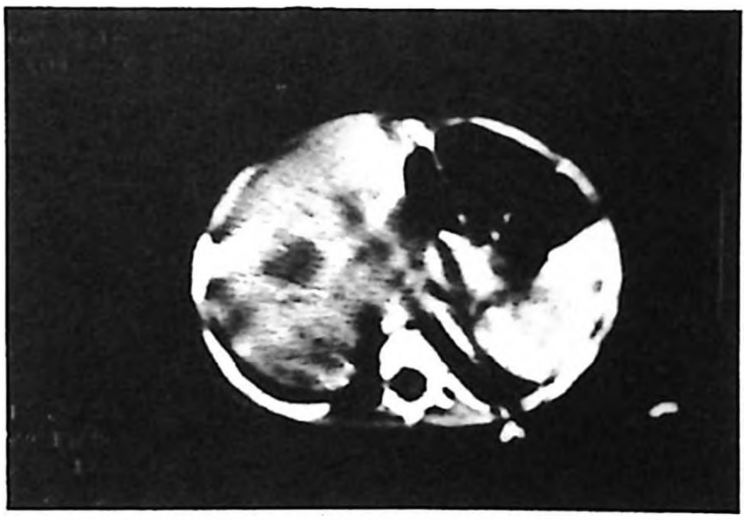

Fig. 2: Computed tomographic appearance of liver hemangioma.

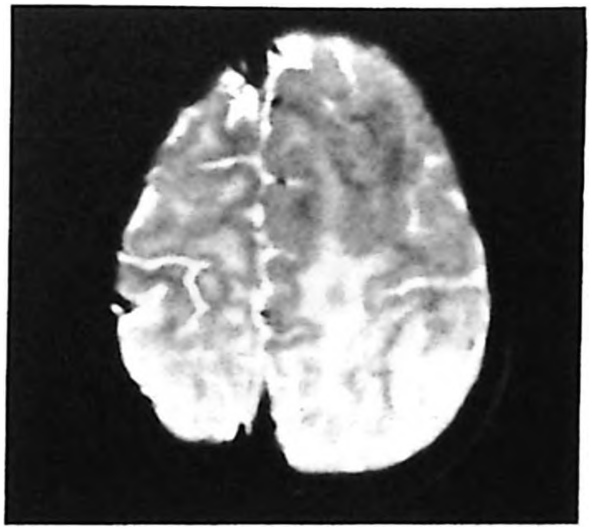

Fig. 3: Magnetic resonance imaging of hemimegalencephaly.

Discussion

Klippel-Trenaunay-Weber Syndrome consists of a port-wine nevus in combination with bony and soft tissue hypertrophy and venous varicosities. The association of hemimegalencephaly, hypopigmented skin lesions and the absence of bony hypertrophy are uncommon in this nonheritable disorder. Although some of its features resemble those of Hypomelanosis of Ito (i.e., hypopigmented macules, mental retardation, and craniofacial dysmorphism), the lack of chromosomal abnormality, scalp abnormalities, triphalangeal thumbs, inflammatory cells in the dermis, and pigment incontinence distinguish it from KTWS[6,7]. Several syndromes may mimic the clinical and laboratory features of KTWS. Of these, Maffucci syndrome has enchondromas in long bones[8], and Bannayan syndrome has

symmetrical macrocephaly, lipomatosis and angiomatosis[9] in association with hemihypertrophy. The lack of a porencephalic cyst with cerebral atrophy seen in Haberlund encephalocraniocutaneous lipomatosis and the absence of exostoses with characteristic cerebriform masses involving the palmar or plantar surfaces in Proteus syndrome exclude these syndromes in the differential diagnosis[10,11]. Cranial hemihypertrophy is a relatively rare component of KTWS[12,13]. Therefore, we believe that our patient is an interesting instance of KTWS exhibiting many unusual manifestations.

REFERENCES

1. Klippel M, Trenaunay P. Du naevus variqueux osteo-hypertrophique. Arch Gen Med 1900; 185: 641-672.
2. Parkes-Weber F. Angioma formation in connection with hypertrophy of limbs and hemihypertrophy. Br J Dermatol 1907; 19: 231-235.
3. Roberts LJ. Dermatologic diseases. In: Oski FA, De Angelis CD, Feigin RD, Mc Millan JA, Warshaw JB (eds). Principles and Practice of Pediatrics (2nd ed). Philadelphia: J.B. Lippincott Company, 1994: 486-494.
4. Esterly LB. Vascular lesions. In: Behrman RE, Kliegman RM, Nelson WE, Vaughan VC (eds). Nelson Textbook of Pediatrics (14th ed). Philadelphia: WB Saunders Company, 1992: 1629-1633.
5. Anlar B, Yalaz K, Erzen C. Klippel-Trenaunay-Weber syndrome: a case with cerebral and cerebellar hemihypertrophy. Neuroradiology 1988; 30: 360.
6. Donnai D, McKeown C, Andrews T, Read AP. Diploid/triploid mixoploid and hypomelanosis of Ito. Lancet 1986; i: 1443-1444.
7. Thomas IT, Frias JL, Cantu ES, et al. Associations of pigmentary anomalies with chromosomal and genetic mosaicism and chimerism. Am J Hum Genet 1989; 45: 193-205.
8. Norman ME. Osteochondrodysplasias with anarchic development of cartilagenous or fibrous tissue. In: Behrman RE, Kliegman RM, Nelson WE, Vaughan VC (eds). Nelson Textbook of Pediatrics (14th ed). Philadelphia: WB Saunders Company, 1992: 1740-1741.
9. Happle R. Lyonization and the lines of Blaschko. Hum Genet 1985; 70: 200-206.
10. Haberlang C, Perou M. Encephalocraniocutaneous lipomatosis. Arch Neurol. 1970; 22: 144-155.
11. Samlaska CP, Levin SW, James WD, et al. Proteus syndrome. Arch Dermatol 1989; 125: 1109-1114.
12. Viljoen DL. Klippel-Trenaunay-Weber syndrome (angio-osteohypertrophy syndrome). J Med Genet 1988; 25: 250-252.
13. Stephan MJ, Hall BD, Smith DW, Cohen MM. Macrocephaly in association with unusual cutaneous angiomatosis. J Pediatr 1975; 87: 353-359.

To The Editor

About Salmonella Typhi Infections

I have read Seçmeer et al.'s paper in the recent issue of the Journal (1995; 37: 339-344).

The authors mentioned that "16 cases were males and 9 were females". Was sex not recorded in two cases?

The authors also stated that 11 (40.7%) patients were seen in the second five-year period (1988-1992). Would it not be more convenient to state that about 41 percent of the patients in stead of 40.7 percent, since a patient cannot be less than one?

Much more importantly, antimicrobial resistances between 1988-1992 were given as 23.5, 17.6 and 17.1 percent to ampicillin, chloramphenical and trimethoprim-sulfamethoxazole, respectively, in Table VI. From this Table, 2.5, 1.94 and 1.88 patients should have resistance to the above antibiotics since there were only 11 patients in this period. This is not logical(!).

Was any of the patients unable to be treated with the above antibiotics?

Although one of the contributors (GK) was among the authors of a paper emphasizing granulocytosis in typhoid fever, especially in patients under five years of age, nothing was mentioned in this study to support or refute the previous finding.

Dr. Şinasi ÖZSOYLU

REFERENCES

1. Çağlar MK, Özsoylu Ş, Kanra G. Relative granulocytosis in childhood typhoid fever. J Pediatr 1983; 102: B 603-604.

Reply

I thank Dr. Özsoylu for bringing to our attention the errors in the number of the patients and in Table VI. There were 11 females, not 9. The percentages of the isolates resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole were 27.2% (3 patients), 18.1% (2 patients), and 18.1% (2 patients), respectively.

Dr. Özsoylu also suggested that it would be more convenient to say 41% of the patients instead of 40.7%. I do not agree with him. Those numbers are the percentages (not the numbers), which are found by dividing the number of observations in a given class by the total number of observations and then multiplying by 100[1]. For the second five-year period in our study, the percentage is 40.7% (11/27 X 100) (rounded to one decimal place).

If sepsis is suspected, initial treatment depends on epidemiological and microbiological considerations, and then the choice is based on the isolates' antibiotic sensitivity pattern. Because the patients infected by resistant isolates had not improved with trimethoprim-sulfamethoxazole, ampicillin or chloramphenicol before admission to the hospital, we started treatment with third-generation cephalosporins in our patients.

Although Dr. Özsoylu stated that a paper emphasizing granulocytosis in typhoid fever[2] was not mentioned, another paper by the same authors about hematological findings in typhoid fever[3] was cited in the article.

Dr. Gülten SEÇMEER

REFERENCES

1. Dawson-Saunders B, Trapp RG. Basic and Clinical Biostatistics (2nd ed). Appleton and Lange, New Jersey, 1994.
2. Çağlar MK, Özsoylu Ş, Kanra G. Relative granulocytosis in childhood typhoid fever. J Pediatr 1983; 102: 603-604.
3. Çağlar MK, Özsoylu Ş, Kanra G. Çocukluk çağında tifoda hematolojik bulgular: relatif granülostoz. Çocuk Sağlığı ve Hastalıkları Dergisi 1983; 26: 67-72.

To The Editor

Rice for Diarrhea

Drs. Yurdakök and Yalçın have shown once more the positive effect of rice in the treatment of diarrhea in their recent paper in the Journal (1995; 37: 315-321).

The authors discussed very wisely how rice-ORS is more effective than simple ORS. I would like to add that rice may also inhibit cAMP of intestinal crypt epithelium, which is one of the main factors in secretory diarrhea. This issue was mentioned recently in Yeni Tıp Dergisi (1995; 12: 328).

Dr. Şinasi ÖZSOYLU

REFERENCE

1. Macleod RJ, Bennett HPJ, Hamilton JR. Inhibition of intestinal secretion by rice. Lancet 1995; 346: 90-92.

Erratum

The following is a correction to the article entitled, "Galactosialidosis in Two Siblings", which appeared in the January-March 1996 issue of The Turkish Journal of Pediatrics (1996; 38: 85-89).

The symbols α and β were inadvertently switched, as noted below:

Location	Error	Correction
1. p.85, Summary, Line 6	α-galactosidase, β-neurominidase	β-galactosidase α-neurominidase
2. p.85, Introduction, Line 2	α-galactosidase, β-neurominidase	β-galactosidase α-neurominidase
3. p.87, Line 2	α-galactosidase	β-galactosidase
4. p.87, Case 2, Line 6	α-galactosidase	β-galactosidase
5. p.88, Line 3	α-galactosidase	β-galactosidase
6. p.88, Line 4	β-neurominidase	α-neurominidase
7. p.89, Line 2	α-galactosidase	β-galactosidase

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Ege University Faculty of Medicine
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e-mail: mutafp@cakabey.ege.edu.tr

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