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EXPERIENCE WITH DIARRHEAL DISEASE IN A UNIVERSITY PEDIATRIC HOSPITAL*

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Summary: Uzel N, Oğuz F, Uğur S, Sıdal M, Neyzi O. (Istanbul University Institute of Child Health at Çapa, Istanbul, Turkey). Experience with diarrheal disease in a university pediatric hospital. Turk J Pediatr 32: 233-240, 1990.

In 1987, 3227 diarrhea cases, half of which were infants, presented at the Out-patient Department of the Istanbul University Children's Hospital. An examination of these cases showed that in 1,066 cases diarrheal disease (DD) was accompanied by a coexisting infection or other disease. The cases with severe dehydration, shock or severe systemic disease were immediately hospitalized. All the remaining cases were administered oral rehydration therapy (ORT) in the Diarrhea Unit, and 94.7 percent of them were successfully rehydrated with ORT. Severe dehydration, shock, severe systemic infection, abdominal distention, failure of rehydration by the enteral route, severe protein energy malnutrition (PEM), and the presence of convulsions were the indications for i.v. therapy. The overall mortality rate was 11 percent.

Our experience with DD indicates that widespread implementation of ORT in diarrheal disease and the establishment of Diarrhea Units in large hospitals will contribute not only to saving more lives but will also have an economic impact by reducing the number of admissions. *Key words: diarrhea, dehydration, oral rehydration therapy, infantile diarrhea, diarrhea mortality.*

Diarrhea is one of the major presenting symptoms in the pediatric age group, ranking second to upper respiratory tract infections which top the list. It has been reported that the frequency of diarrheal episodes per child under two years of age is two to three per year in industrialized countries[1,2]. In developing countries the mean number of yearly diarrheal episodes per child ranges between six and ten[3-6]. Unlike the situation in industrialized countries, in areas where malnutrition and infectious diseases prevail, diarrheal disease is a major cause of death in infants and young children[3,5,6].

Diarrheal disease also frequently occurs in Turkey. A national survey conducted in 1986 by the Turkish Ministry of Health showed that depending on the area, 10 to 57 percent of children between 0-5 years of age had suffered from at least one

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episode of diarrhea within the previous fortnight[7]. According to data furnished by the Turkish Government, diarrhea ranks third as a cause of all infant deaths in the first year of life (9.3%), and second (13.4%) as a cause of death between the ages of one and four[8]. In this paper, our experience with diarrheal disease in a children's hospital, based on the examination of patient records accumulated in 1987, is presented.

Material and Methods

Since 1983, oral rehydration therapy (ORT)[9] has been used instead of parenteral fluid therapy in the Istanbul University Children's Hospital at Çapa, as routine treatment for mild-moderate dehydration due to diarrhea. Routine management of these patients by residents practicing in the Out-patient Department necessitates that they grade patients according to a slightly modified World Health Organization (WHO) criteria[9].

Thus, Grade 1 includes diarrheal disease (DD) cases with no clinical symptoms except for diarrhea (mild cases); Grade 2 includes DD cases with vomiting or history of severe purging and/or mild to moderate dehydration; Grade 3 includes DD cases with moderate dehydration accompanied by high fever, with or without symptoms of coexisting disease, and Grade 4 includes DD cases with severe dehydration with or without symptoms of other disease and also cases who are not severely dehydrated but have a severe coexisting disease. All the cases in Grades 1, 2 and 3 are transferred to the Diarrhea Unit (DU). Following reevaluation Grade 3 patients may be kept in the DU or sent to the Emergency Care Unit for admission. WHO standard ORS with 90 mmol/L sodium has been used in oral rehydration therapy.

Grade 1 patients are kept in the DU for only one hour, providing their condition is improving and the purging is not severe, during which time they are administered ORT. The mothers of the patients are then given a demonstration on how to administer the solution at home, the feeding routine, and are cautioned about watching for danger signs. Grade 2 and Grade 3 cases are administered ORT and are monitored closely for any vital signs, vomiting, fever, tolerance of ORT, and the rate of purging for a minimum period of four hours. At the end of this period, the patient may be kept in the Unit for another four hours, hospitalized in the Emergency Care Unit, or sent home, depending on the clinical assessment of the patient and also on whether or not the mother is capable of following instructions as to the administration of the therapy at home. All Grade 4 cases are admitted directly to the Emergency Care Unit. All the diarrheal disease cases who presented at the General Out-patient Department of the Istanbul University

Children's Hospital at Çapa from January to the end of December 1987, were studied.

A special form is filled for all diarrheal cases which includes the following: patient's age, duration of diarrheal episode, degree of dehydration, coexisting disease, route of administration of fluids, purging rate, reasons for resorting to nasogastric or i.v. administration of fluids, nutritional state, and if hospitalized, reasons for hospitalization and outcome. An etiological approach was not considered in this study.

Results

Out of a total of 54,242 patients seen at the General Out-patient Department of the Hospital in 1987, diarrhea ranked second to upper respiratory tract infections as the presenting symptom. The number of diarrhea cases was 3,227 (6 % of total outpatient cases). In 1,066 DD patients (33%), the diarrhea was accompanied by a coexisting infection or other disease, while in 2,161 patients (67%) all the symptoms and signs were diarrhea-related. The lowest number of cases was seen between January and May, while a peak was observed in August (Fig. 1).

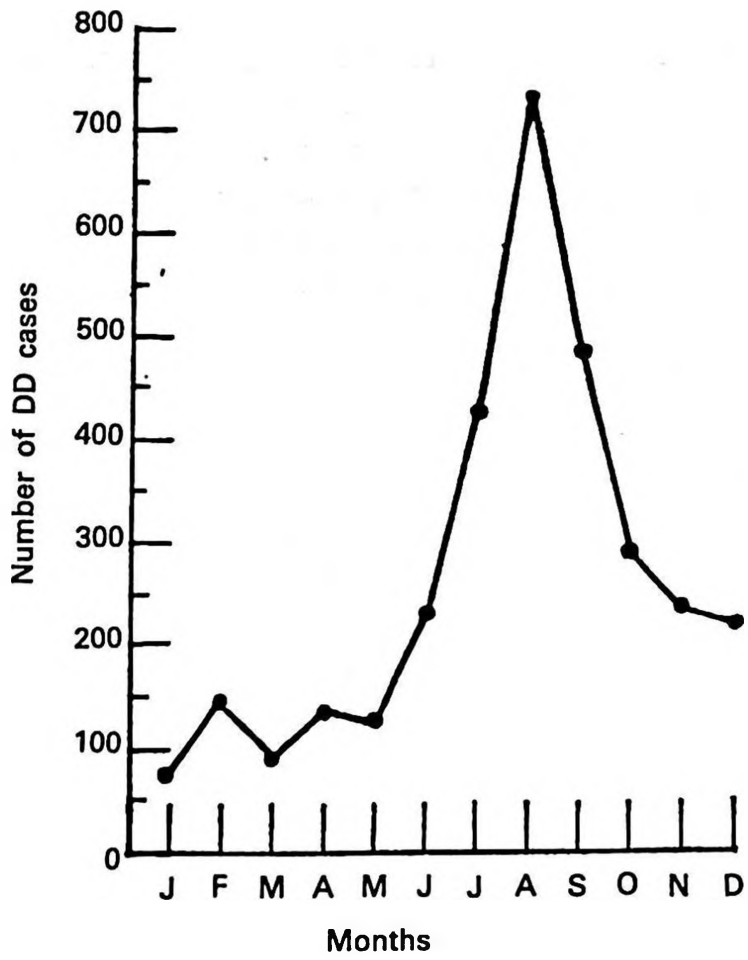

Fig. 1. Seasonal distribution of DD cases

As shown in Table I, about half of the patients were in the 0-1 year-old age group. The degree of severity of the diarrhea was found to be related to age. While the ratio of Grade 4 cases was 5.2 percent of the total group, this ratio was 15 percent for the youngest infants and showed a stepwise decrease with age (Table I).

TABLE I: Classification of DD Cases According to Age Group

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
Age Group	n	%	n	%	n	%	n	%	n	% (of total group)
0-3 mo	248	59.1	61	14.5	48	11.4	63	15.0	420	13.0
4-12 mo	906	74.5	151	12.4	92	7.6	67	5.5	1216	37.7
13 mo-4 yrs	916	85.1	77	7.2	52	4.8	32	3.0	1077	33.4
≥5 yrs	442	85.9	33	6.4	31	6.0	8	1.6	514	15.9
TOTAL	2512	78.0	322	9.9	223	6.9	170	5.2	3227	100.0

Table II gives the body weight distribution of the group. Weight was below the 3rd percentile for age in 3.4 percent of the cases, and below the 10th percentile in 16.2 percent of the cases.

With the exception of the cases with severe dehydration, shock or severe systemic disease, all the patients in the Diarrhea Unit were administered ORT. Rehydration with ORT was successful in 94.7 percent of these cases. In the remaining cases, i.v. fluid administration had to be resorted to. The two major indications for changing to parenteral therapy in this group of patients was the development of abdominal distention and the worsening of the dehydration.

TABLE II: Nutritional Status of the Patients

Weight for age percentile	n	%
< 3	110	3.4
3 – 10	413	12.8
> 10	2704	83.8

A total of 333 patients were hospitalized directly or as transfers from the DU. The hospitalization rate was 100 percent for the total group and was inversely correlated with age, being highest (24.3%) for infants under three months of age (Table III).

TABLE III: Rate of Hospitalization According to Age Group

Age group	n	Rate of hospitalization %
0 – 3 mo	102	24.3
4 – 12 mo	146	12.0
13 mo – 4 yrs	50	4.6
⩾ 5 yrs	35	6.8
TOTAL	333	10.0

The reasons for hospitalization were severe dehydration and/or shock, severe systemic infection, abdominal distention, failure of rehydration by the enteral route, severe protein energy malnutrition (PEM) and convulsions, respectively. All these patients received fluids parenterally. Indications for i.v. administration are shown in Table IV.

In 70 (21%) of these cases, it was possible to change to ORT at the end of a four-hour period.

TABLE IV: Reasons for I.V. Therapy in Hospitalized DD Cases

Reasons	n	%
Severe dehydration / shock	223	67.0
Severe infections except diarrhea	77	23.1
Abdominal distention, paralytic ileus	16	4.8
Severe PEM	10	3.0
Convulsion	7	2.1
TOTAL	333	100.0

Overall mortality rate was 11 percent (37 hospitalized cases), and it was highest in young infants (Table V).

The causes of death are given in Table VI. Weight for age was below the third percentile for age in 35 out of 37 fatal cases with severe PEM in eight[10].

TABLE V: Mortality in DD Cases According to Age Group

Age	n	Mortality rate (per 1000)
0 - 3	22	52
4 - 12 mo	11	9
13 mo - 4 yrs	3	3
> 5 yrs	1	2
TOTAL	37	11

TABLE VI: Cause of Death in Fatal DD Cases

	n
Sepsis and septic shock (Paralytic ileus in one)	15
Severe PEM	8
Bronchopneumonia	7
Acute renal failure	4
Encephalitis	2
Immune deficiency (Thymic hypoplasia at autopsy)	1
TOTAL	37

Discussion

Although the aim of this study was not epidemiological, the high frequency of diarrhea occurring among the children brought to our Out-patient Department, many in a dehydrated state, stresses the importance of DD as a major pediatric problem in a large city of Turkey.

Our experience with this group of patients shows once again that dehydration resulting from diarrhea can be successfully treated with ORT in the large majority of cases[11,12]. Thus, most of our patients were kept in the DU, and the rate of hospitalization in this group was much lower (10%) as compared to the years before the advent of ORT as routine treatment for DD in our hospital. The rate of admission of diarrheic patients seen in our Out-patient Department was 38 percent in 1981[13].

This study also documents that diarrhea, complicated by severe coexisting disease and/or severe dehydration with consequent need for parenteral therapy and

hospitalization, occurs more frequently in young infants. As reported by other workers, neonates and young infants are more prone to developing severe dehydration in a relatively short period of time, and the microorganisms responsible for the diarrhea may also cause systemic severe infection in this age-group[14-17]. Young infants are also more prone to undesirable effects of oral rehydration such as abdominal distention, hypernatremia and/or persistent diarrhea[17]. The particular importance of close observation and careful follow-up in this vulnerable age group cannot be overemphasized.

An overall mortality rate of one percent associated with DD is reported in non-industrialized countries[18,19]. In a recent report, it was stated that 500 pediatric deaths from DD occur annually in the U.S.A., 400 of which are infants under one year[20]. According to data furnished by the Turkish Ministry of Health[8], approximately 30,000 deaths occur annually from diarrhea in Turkey. Overall mortality in this series was one percent. Since this is a selected group of cases, consisting of children brought to the hospital, the said high mortality rate does not reflect overall diarrhea mortality in Istanbul. Indeed, the risk of death was ten-fold in patients who presented with diarrhea complicated by severe dehydration and/or metabolic disorders, or accompanied by the late stage of a severe coexisting infection. Age and nutritional state were also factors influencing prognosis. Almost all the deaths occurred in malnourished infants under one year of age.

In conclusion, our experience with DD indicates that a Diarrhea Unit should be an indispensable part of a hospital in areas where diarrhea is a major pediatric problem. The establishment of such units will contribute not only to saving more lives, but will also have an economic impact, in that the number of admissions will be less.

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X – LINKED AGAMMAGLOBULINEMIA: CLINICAL AND IMMUNOLOGIC EVALUATION OF SIX PATIENTS*

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Summary: Ersoy F, Sanal Ö, Tezcan I, Berkel A I. (Immunology Unit, Hacettepe University Institute of Child Health, Ankara, Turkey). X-linked agammaglobulinemia: clinical and immunologic evaluation of six patients. Turk J Pediatr 32: 241-247, 1990.

The clinical and immunologic features of six patients with X-linked agammaglobulinemia (XLA) are presented. The most common presenting manifestations were respiratory and gastrointestinal tract infections. On admittance to the hospital, one patient had a history of recurrent meningitis, another had a dermatomyositis-like syndrome, and still another had a history of recurrent arthritis. *Key words: agammaglobulinemia, Bruton's disease, T lymphocyte sub-populations.*

X-linked agammaglobulinemia (XLA) is a rare, sex-linked congenital immunodeficiency disease characterized by recurrent bacterial infections starting in infancy or early childhood, profoundly depressed serum immunoglobulins, a paucity of lymphoid tissue, and absence of B cells[1-3]. Pre-B lymphocytes are found in normal numbers in the bone marrow, peripheral blood or lymph nodes, suggesting a maturation defect in the differentiation of pre-B cells to B cells[4]. Cellular immunity is uniformly normal.

The aim of this report is to review the clinical and immunologic features and complications of XLA, and also to present the common and rare clinical presenting manifestations of this disorder.

Material and Methods

Six patients with XLA diagnosed between the ages of 20 months and six years were followed up in the Immunology Unit of the Hacettepe University Institute of

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Child Health. The diagnosis of each case was based on the following criteria of the World Health Organization for Immunodeficiency and XLA[5]. 1. Male sex, 2. Onset of disease in infancy or early childhood, 3. Paucity of lymphoid tissue, 4. Serum concentration of IgG less than 200 mg/dl and IgM and IgA concentrations less than 5 mg/dl, 5. Normal T cell numbers and normal proliferative response to T cell mitogens, 6. Very low number of B cells in the peripheral blood.

Delayed hypersensitivity reaction was evaluated by several antigens: Candida (prepared at the Hacettepe University Pediatric Allergy Labs) of a 1:10 dilution, phytohemagglutinin (PHA-P, Burroughs-Wellcome Labs) 10 μg/0.1 ml, PPD (Refik Saydam Hygiene Inst., Ankara) 5 U/0.1 ml, streptokinase-streptodornase (SKSD, Lederle Labs) 50/12.5 U/0.1 ml.

E-rosette forming cells were measured by the method of Jondal et al[6]. In vitro blastogenic response to PHA was studied according to a previously published method[7]. Serum immunoglobulins (IgG, IgM, IgA) were determined by using Behring-Werke immunodiffusion plates.

B cells were identified by direct immunofluorescence using commercial antisera against immunoglobulin isotypes (polyvalent, IgG, IgM, IgA; Behring-Werke Inst.)[8]. T lymphocyte subsets–pan T, helper T, and suppressor T–were determined by monoclonal antibodies (OKT3, OKT4, OKT8; Behring Werke Inst.) according to the standard indirect immunofluorescence technique[9].

Results

The clinical findings of our six patients are shown in Table I. Of the six males fulfilling the diagnostic criteria, only one patient (UYS) had a possible family history of the disease. His brother, who had recurrent infections beginning at the age of six months, died of meningitis at 13 months of age.

TABLE I: Clinical Features of XLA Patients

Case no.	Age at onset of symptoms	Age at diagnosis	Clinical manifestations at diagnosis	Present age
1.UYS	17 months	20 months	Dermatomyositis-like syndrome	6 years
2.AAR	9 months	22 months	Recurrent pneumonitis	19 years
3.OBC	10 months	2 years	Arthritis	7 years
4.EC	2 years	5 years	Recurrent meningitis	8 years
5.AO	4 years	6 years	Recurrent pneumonitis Chronic diarrhea Polio sequela	9 years
6.HB	1 year	5 years	Recurrent pneumonitis	exitus

The five remaining patients neither had male siblings nor symptoms of an immunodeficiency disease in their maternal uncles. Onset of symptoms was between the ages of 9 months to four years (mean age: 20 months). The mean age of the diagnosis of agammaglobulinemia was 3.6 years.

Infections were the major presenting feature. Three out of six patients had recurrent pulmonary infections. Patient UYS presented with a dermatomyositis-like syndrome and showed a dramatic response to gammaglobulin therapy, and patient EC had recurrent meningitis. The data of these two patients are published in other reports[10,11]. Recurrent arthritis was the presenting symptom in patient OBC.

Four patients had recurrent enteritis during the follow-up period and *Giardia lamblia* was isolated from the stools of these patients. One of these patients (OBC) developed malabsorption, hypoproteinemia, and edema due to giardiasis. Patient AO had hepatomegaly, and biopsy material revealed chronic active hepatitis. This patient had poliomyelitis two years prior to admittance to our hospital. During the follow-up period, patient AAR developed recurrent polyarthritis but no causative agent was identified from the synovial materials. The family of patient HB did not arrange for him to be given gammaglobulin regularly, and he died of pneumonia and sepsis. The immunological findings of our patients are shown in Table II. All the patients had a positive reaction to delayed hypersensitivity skin tests, and the percentages of E-rosette forming cells and in vitro blastogenic response to PHA were found to be within normal limits. Serum IgG levels were profoundly low (42-116 mg/dl),and IgA and IgM levels were undetectable. The percentage of Ig bearing cells (B cells) was very low (1-7 %). $CD3^+$ T cell percentages were above one standard deviation of normal levels in all

TABLE II: Immunologic Features of XLA Patients

Case No.	Delayed hypersensitivity skin test	Blastic transformation to PHA (SI)*	E-rosette formation** (%)	Serum immunoglobulins (mg/dl) IgG	IgM	IgA
1.UYS	+	42	72	42	0	0
2.AAR	+	57.4	68	144	0	0
3.OBC	+	59.9	81	92	0	0
4.EC	+	ND***	76	23	0	0
5.AO	+	31.7	65	46	0	0
6.HB	+	52	80	116	0	0

* Stimulation index (normal value for our lab: > 20)
** E-rosette formation (normal: 69 ± 5.6)
*** Not done

the patients (mean: 89±4.3) (Table III). $CD4^+$ T cells were found to have decreased in four patients and $CD8^+$ T cells to have increased in five. The helper/suppressor T cell ratio was found to be inverted in these five patients.

TABLE III: Lymphocyte Subsets of XLA Patients

Case No.	T Cell Subsets (%)				sIg⁺ (B) Lymphocytes (%)			
	$CD3^+$	$CD4^+$	$CD8^+$	CD4/CD8 ratio	sIg^+ polyvalent	$sIgG^+$	$sIgM^+$	$sIgA^+$
1.UYS	89	30	47	0.6	4	1	0	0
2.AAR	90	38	47	0.8	7	5	0	1
3.OBC	83	21	50	0.4	1	3	0	0
4.EC	95	54	27	2	2	0	0	0.5
5.AO	89	28	40	0.7	3	3	0	0
6.HB	82	25	49	0.5	4	2	2	1
Controls	66.9±13.3	45.6±5.2	27.0±6.9	1.8±0.5	22.2±5.0	9.1±3.6	8.2±4.2	4.5±3.1

Discussion

X-linked agammaglobulinemia (XLA) is a congenital antibody deficiency disease. Since Bruton's recognition of the first case of X-linked agammaglobulinemia in 1952, several terms (infantile panhypogammaglobulinemia, Bruton's disease, congenital agammaglobulinemia) have been used to describe this disease. Recently, the term "XLA" has been used to designate this entity[3]. Carrier detection can be done by using X-linked restriction fragment length polymorphism[12-14].

The histories and clinical presentations of patients with XLA vary. But respiratory and gastrointestinal tract infections, frequently in combination, are the most common presenting manifestations[1,2]. These symptoms were present in all our patients during the follow-up period. In the series of Lederman and Winkelstein[2], respiratory and intestinal infections were reported in 91 percent of the patients. These investigators indicated that infections in XLA are either recurrent or chronic, and that they occur on more than one site of the body and in combination. Gastrointestinal infections are the major presenting manifestations (35%) of the disorder. *Giardia lamblia* and viral pathogens (e.g. rotavirus) may cause chronic diarrhea[15,16]. We observed diarrhea in four of our patients and detected *Giardia lamblia* upon examination of the stool. Malabsorption, protein-losing enteropathy and disaccaridase deficiency have been described in agammaglobulinemic states[15,17,18]. In one of our patients (OBC), chronic diarrhea persisted for four weeks, and protein-losing malabsorption, hypoproteinemia and edema developed. Another one of our patients presented with recurrent meningitis, and another had a bout of meningitis at the time the diagnosis was made. It has been reported that meningitis occurred in 16 percent of patients in a larger series[2].

Patients with XLA are susceptible to chronic enterovirus infections[19-21]. Particularly chronic echo virus infections of the central nervous system have become evident, and often fatal, in patients with agammaglobulinemia. A dermatomyositis-like syndrome, a rare presenting manifestation, was seen in one of our patients. We observed muscle weakness in this patient, who responded dramatically to gamma globulin therapy. Electron microscopic examination of the muscle biopsy revealed virus-like particles. This clinical presentation might be a consequence of a systemic enterovirus infection[19].

Arthritis, which can be present during the clinical course of XLA, was observed at the follow-up of two of our six patients, and it was a presenting sign in another. No microorganism was identified from the synovial materials of these patients. Chronic middle ear infections were seen in four of the patients even after gamma globulin prophylaxis was initiated.

It has been reported that hearing loss due to chronic middle ear infection or a central nervous system infection occurs in approximately 32 percent of XLA patients[2]. Hearing loss was detected in one of our patients at the age of 15.

Rash, fever, anaphylactic-like reactions, and acrodynia have been described as complications of intramuscular gamma globulin therapy[1]. We observed a gamma globulin-induced anaphylactic reaction in only one of our patients.

During the follow-up period, hepatomegaly developed in one patient (AO), and, the biopsy material revealed chronic active hepatitis. This patient had poliomyelitis and developed sequela two years before admittance to our hospital.

In XLA, the common causes of death are cardiorespiratory failure as a consequence of recurrent pulmonary infections and severe viral infections[1-3]. All of our patients were diagnosed during early childhood, and gamma globulin treatment was given regularly, except for one patient. Chronic, obstructive lung disease and cor pulmonale were not observed during the patients clinical courses. One patient did not receive gamma globulin therapy regularly, and died of pneumonitis and sepsis.

In XLA, serum immunoglobulin concentrations are either very low or absent[22, 23]. In our patients, the serum concentration of IgG was very low, while serum IgA and IgM could not be detected. Lymphoid tissue is hypoplastic and lymph nodes do not have germinal centers. Peripheral B lymphocytes are absent or very low, and examination of the bone marrow reveals absent plasma cells which indicates that there is a differentiation defect between pre-B cells and B cells. This defect may not be complete and may be at more than one stage of maturation[24-27]. In all the patients, the number of surface immunoglobulin positive total B cells was markedly reduced. There were no surface IgM bearing lymphocytes in the peripheral blood in five of the patients and very few (2%) in one. Although

the number of IgM and IgD bearing lymphocytes in peripherial blood varies among patients, the percentage of circulating surface immunoglobulin positive B cells is always markedly low[24-27].

Cell-mediated immunity is intact in XLA. Although circulating T cells and T cell subsets are normal, minor alterations in the number and proportion of T cell subsets have been reported[28]. The alterations of T cell subsets and the $CD4^+$ / $CD8^+$ ratio, which we observed in our patients, might be related to recurrent infections or gamma globulin therapy.

The time period between the onset of symptoms and diagnosis has been reported to be (familial and non-familial forms) one year. In our series, it was 22 months. Since patients with XLA are susceptible to recurrent respiratory, gastro-intestinal and central nervous system infections, those patients presenting with these clinical manifestations should be immediately suspected of having this disease. Early diagnosis and treatment can prevent the development of early or late complications resulting from infections.

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LONG – TERM PROGNOSIS OF ACUTE RHEUMATIC CARDITIS WITH COMBINED AORTIC AND MITRAL REGURGITATION*

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Summary: Onat, T, Ahunbay G. (Pediatric Cardiology Unit, Department of Pediatrics, Istanbul University Cerrahpaşa Faculty of Medicine, Istanbul, Turkey). Long-term prognosis of acute rheumatic carditis with combined aortic and mitral regurgitation. Turk J Pediatr 32: 249-258, 1990.

Thirty-one patients with acute rheumatic carditis associated with aortic (AR) and mitral regurgitation (MR) who received corticosteroid anti-inflammatory therapy for an average of nine weeks were followed up for 332 patient-years (mean: 10.71 years). The age of onset was 9.34 (1 SD = ± 1.94) years. The patients were classified according to degree of left ventricular volume overloading (LVH), duration of pre-treatment interval and regularity of penicillin prophylaxis. The probability of the yearly disappearance of MR, AR and both lesions were calculated for the total group and in relation to affecting subgroups. The mean yearly rate of disappearance of AR was 2 percent after a 10 percent probability in the first year. This rate was 6.83 percent per year for MR, and it increased to 10.15 percent per year in the patients in whom therapy was initiated in less than three weeks, and decreased to 3.14 percent in the patients in whom therapy was initiated after three weeks. The disappearence of both AR and MR was observed in only two patients (about 1% per year); MS developed in two patients (6.45%) and the mortality rate was 3.2 percent in 332 patient-years (0.0001/year). *Key words: acute rheumatic fever, penicillin prophylaxis, prognosis.*

In acute rheumatic fever, aortic regurgitation (AR) is usually combined with mitral regurgitation (MR). The occurrence of MR in patients with AR is reported to vary between 50[1] and 93 percent[2], most reports ranging between 71 and 92 percent. These incidences vary greatly in studies because a portion of the data has been obtained from the records of patients who have experienced initial attacks, have had recurrences, or who have been over-diagnosed for AR in some centers[3-5].

Long and short-term studies reporting the incidence of residual heart disease (ResHD) have neglected to differentiate the outcome of each lesion when they co-exist[1-8]. Information regarding the prognosis of each lesion has been obtained from patients with either isolated MR or AR, or from a combination, which

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includes mitral stenosis (MS) with MR. In general, isolated MR has a better prognosis than isolated AR. It is not known, however, whether this also applies if the lesions occur together because studies have been planned to determine ResHD. Thus, MR, having a better prognosis and a greater probability of disappearing, is obscured by such an analysis, i.e., in case of persistent AR.

The prognosis of valvular lesions depends on such factors as severity of the lesion, presence of congestive heart failure (CHF), prevention of recurrences, and time of onset of effective treatment[9]. We therefore present our follow-up results of 332 patient-years of each lesion in 31 patients in whom AR and MR coexisted, whereby factors influencing the prognosis such as degree of left ventricular volume overloading, presence of CHF, regularity of penicillin prophylaxis (PP) and the duration of the pre-treatment interval were considered.

Material and Methods

The study population comprised 31 children who had an initial attack of MR and AR due to rheumatic fever[10], and who had been hospitalized in the Department of Pediatric Cardiology, Cerrahpaşa Faculty of Medicine, between 1964-1984. Their laboratory studies were complete with regard to the methodologies presented below. They were followed up for 2-21 years by the same pediatric cardiologist (T.O.), who was informed of the past histories of the patients and who had prospectively carried out the follow-ups at the Out-patient Department of the unit.

The course and prognosis of the condition were evaluated with respect to 1) pre-treatment interval; 2) adherence to penicillin prophylaxis (PP);3) presence of congestive heart failure (CHF), and 4) presence of valvular lesion and degree of left ventricular hypertrophy (LVH).

1) *Pre-treatment interval.* The pre-treatment interval was considered as the time which had elapsed between the onset of symptoms attributed to acute rheumatic fever (ARF) and the initiation of antiinflammatory therapy. If proper therapy was instituted more than three weeks after the onset of the initial symptoms, these patients were classified as the "late group", in contrast to the "early group".

2) *Adherence to penicillin prophylaxis.* Following the initial ten days of penicillin therapy, penicillin prophylaxis, consisting of benzathine penicillin in a dose of 1,200,000 units, was initiated on the eleventh day. The patients who showed strict adherence to the regimen every 3-4 weeks were classified as the "regular PP" group, while those who had neglected to take the drug for a few months or for a longer period, but who had later resumed taking it on a regular basis, were classified as the "irregular" group. All the patients received prednisone in a dose of 2 mg/kg/day for a duration of three weeks, which was followed by a gradual reduction of dosage for another six weeks.

3) *Presence of congestive heart failure.* Patients with carditis were considered to have CHF, if dyspnea not caused by a respiratory infection was present, and if cardiac enlargement was not due to pericarditis. Thus, false positive diagnoses of CHF, which are most common, were avoided.

4) *Presence and degree of valvular lesion.* A newly observed pansystolic murmur maximum at the apex of grade II-IV intensity, transmitted towards the axilla during the hospitalization period, was accepted as MR. An early diastolic decrescendo murmur maximum at the 2nd and 3rd left parasternal intercostal space was accepted as AR. The valvular lesion was considered healed if the specific murmur had disappeared and was also undetectable after exercise, including subsequent check-ups.

The degree of severity of both valvular lesions can be assessed from the degree of left ventricular volume overloading[11,12], which can in turn be evaluated from electrocardiographic voltage dependent LVH criteria[12] and also from the cardiothoracic ratio (CTR) using p.a. teleradiography. Both methods used simultaneously reduce the false negativity or false positivity of either system. The CTR can be false positive in pericardial effusion and in the expiratory phase[13]. A right diaphragmatic level of one intercostal space higher in the same individual leads to a mean increase of 7 percent in CTR[13]. In comparing the values in the same subject and in classifying CTR values, a correction was made according to Onat[13], which was designated to standardize all CTR values to a right diaphragmatic arc's level of under the 5th anterior rib.

In order to correct the false positive cardiac enlargement, due to pericarditis, which was observed on the chest x-ray, the values that were used as an index were those obtained after the serial clinical detection of pericarditis, and not those which had been obtained at the initial examination.

Taking into account the above-mentioned points, left ventricular volume overloading (LVH) was graded into three groups of severity[9].

Follow – up of patients: The prognosis of acute rheumatic carditis associated with MR and AR was based on the monitored 332 patient-years of the 31 subjects studied. Of the initial 31 patients, 21 were followed up for ten years or more. The mean follow-up period was 10.7 years and the median value 11 years. Ninety-four percent were followed up for four years, 81 percent for six years, 77 percent for seven years, 68 percent for ten years, 23 percent for 13 years, and 13 percent for 20 years. Of the ten patients who were unable to be followed up for ten years, two were followed up for two years, four for four years, and four for seven years.

The distribution of the data of patients "lost to study" in a longitudinal study can lead to biased results if it is significantly different from that of the subjects remaining in the study. Therefore, a chi-square test was performed to determine the differences in the qualifications of the subjects who were lost to study in

different years in relation to the degree of severity of LVH, percentage of patients with CHF (10% vs. 19%), pre-treatment interval (60% vs. 50%) and percentage of patients with regular PP (50% vs. 52%). The distribution of the data of the cases lost to study did not differ significantly from the distribution of the data of the initial material. Thus, the yearly rate of disappearance of MR or AR in our subjects was considered unbiased data.

Linear regressions estimating the yearly rate of disappearance of MR, AR and of both lesions were calculated from the yearly percentage of patients without the specific lesion/total patients studied for that year.

Results

The number of patients in the above-specified subgroups of the classification system and their age and sex distribution are presented in Table I.

The age of onset of carditis was 9.34 years, with a range from 4.7 to 13.1 years. The well known male preponderance in patients with AR is 67.7 percent, which was significant when compared with the 42 percent male incidence observed in our 86 isolated MR patients[9] ($x^2=5.134$; $p<0.025$). Although early onset of treatment was more often (65%) associated with regularity in the continuation of PP, as compared with late onset of treatment (36%), this difference was not significant ($x=1.553$; $p>0.20$).

The mean severity of LVH, graded from I-III was 1.82 in patients with a short pre-treatment interval as compared to 2.07 in patients with a longer than three week interval. Likewise, 42 percent of patients with LVH (groups II-III) were in the early treated group. The difference was not statistically significant ($x^2=0.120$;

Table I: Number of Patients in the Classification System and their Age and Sex Distribution

Left Ventricular Overloading	Penicillin Prophylaxis	Onset of Therapy Early*	Late**	CHF***	Sex male	Sex female	Age mean SD
none or moderate	regular	10	3	1	9	4	9.19 1.80
	irregular	5	6	1	8	3	
severe	regular	1	2	1	3	–	9.88 2.37
	irregular	1	3	3	1	3	
Total	regular	11	5	2	12	4	9.34 1.94
	irregular	6	9	4	9	6	
		17	14	6	21	10	

* "Early" denotes a pre-treatment interval of less than three weeks.
** "Late" denotes a pre-treatment interval of more than three weeks.
*** CHF: Congestive heart failure.

$p>0.70$). The incidence of regularity with regard to continuation of PP was not significantly different in those with or without LVH ($x^2=0.013$, $p>0.80$).

Disappearance of AR: The pulse and diastolic pressure were normal in three patients. The diastolic pressure was below 55 mmHg in 13 patients and below 35 mmHg in 15 patients. Thus, celer pulse and low diastolic pressure were present in 28 of the 31 patients. Of the 25 patients followed up for six years, AR disappeared in four patients in the first year, in one patient in four years, and in one patient in five years, which constitutes a 25 percent rate of disappearance of AR. After six years, there was no disappearance of AR in any of the patients. Of the six patients who recovered from AR, none had severe volume overloading. Five patients were receiving continuous PP and had no recurrence, while one patient, who was receiving irregular PP, did. The yearly rate of disappearance of AR can be estimated from the regression presented in Table II, Fig. 1. This rate is about two percent per year, after a 10 percent probability in the first year. However, if there is no LVH present at onset, the probability of AR disappearing is about 15 percent in the first year, and 3.5 percent per year in the following years.

In 24 patients in groups I and II, i.e., with either no or moderate LVH, the recovery rate of AR was found to be 29 percent in five years and 30 percent in ten years.

The yearly rate of disappearance of AR was 2.01 percent, 3.4 times less than MR (Table II, Fig. 1).

Table II: Linear Regressions of Yearly Disappearance Rates of Rheumatic Valvular Lesions

		Regression analysis for disappearance of valvular lesions in MR and AR	
	No. of Patients	Disappearance of MR (%)	Disappearance of AR (%)
Total	31	6.83 (years) − 3.82	2.01 (years) + 8.82
Late**	14	3.14 (years) + 1.90	1.82 (years) + 3.12
Early*	17	10.15 (years) − 8.95	2.18 (years) + 13.60
LVH:			
None or moderate	24	7.19 (years) − 1.73	2.31 (years) + 11.90
severe	7	3.41 (years) − 5.68	0.00 (years) + 0.0
		Disappearance of both MR and AR (%)	
	31	0.93 (years) + 0.55	

* "Early" denotes a pre-treatment interval of less than three weeks.
** "Late" denotes a pre-treatment interval of more than three weeks.

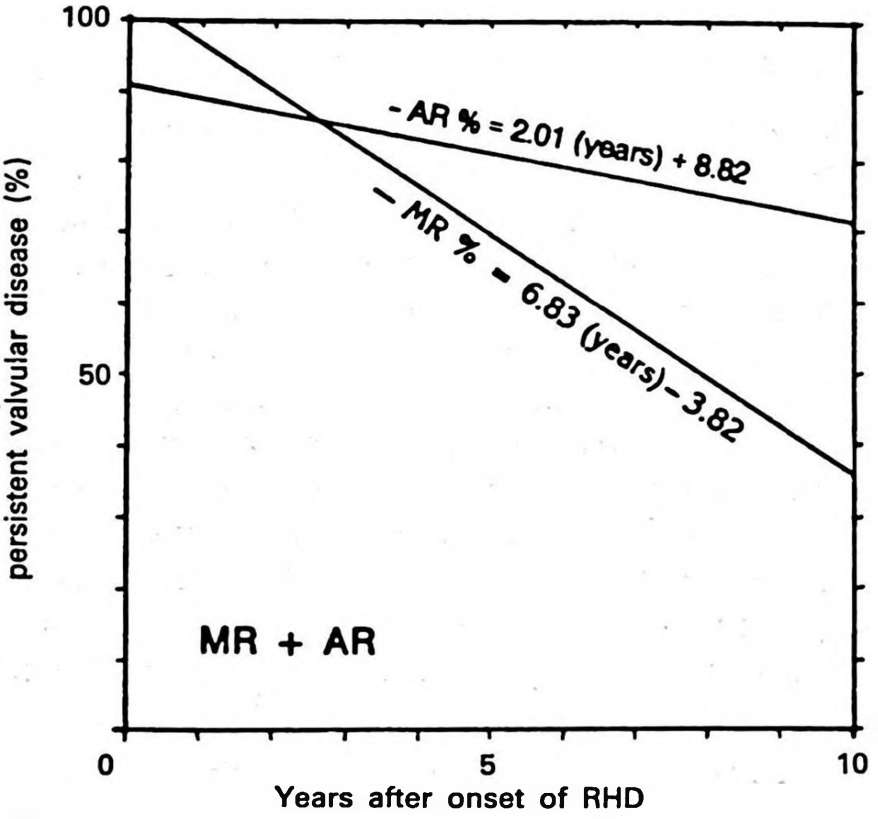

Fig. 1: The percentage of patients with persistent aortic regurgitation (AR) and mitral regurgitation (MR) in relation to years after onset. The regression equations are presented in percentage of disappearance of AR (−AR%) and MR (−MR%), whose slopes represent the yearly probability of disappearance of regurgitation. Note that the chances of recovery are higher in MR than in AR. The slopes represent a yearly percentage of disappearance of 6.83 as compared to 2.01, respectively. But note that the recovery rate in the first years is higher in AR than in MR.

Disappearance of MR: The yearly probability rate of disappearance of MR was 6.83 percent. The expected median time of disappearance was 7.9 years. This tendency of recovery decreased to 3.41 percent per year in the group with severe LVH, while it increased to 7.78 percent in those with or without moderate LVH (Table II).

The yearly rate of disappearance of MR was 10.5 percent in patients in whom therapy was initiated in less than three weeks, and 3.14 percent in patients in whom therapy was initiated after three weeks (Table II; Fig. 2). The higher rate of disappearance of MR observed, in the earlier treated group, was not significant in five years ($x^2=0.588;p>0.40$) but significant in ten years after the onset of rheumatic heart disease ($x^2=5.86;p<0.025$).

Disappearance of both AR and MR: Both AR and MR disappeared in only two patients: one in the second and another in the fifth year, which constitutes nearly a 0.93 percent chance of complete recovery per year (Table II). Congestive heart failure was present in six patients (19%) at onset. Treatment started after three weeks in five patients, and in less than three weeks in one. There were no

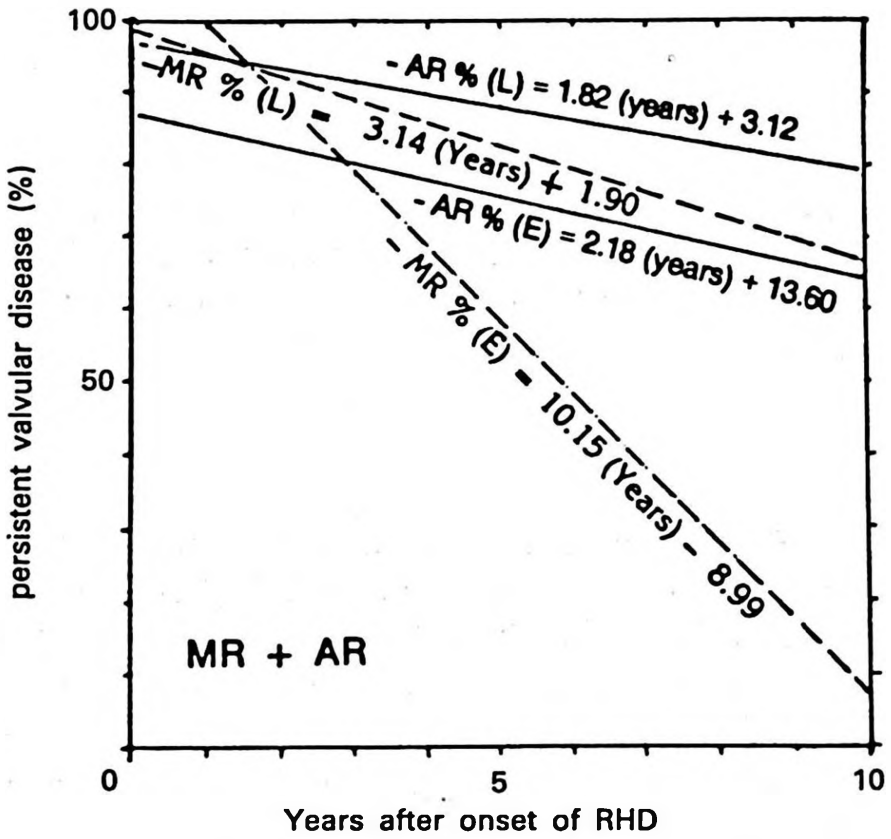

Fig. 2: Same coordinates as in Figure 1. The rate of disappearance of MR (broken lines) and AR (continuous lines) are divided into two groups in relation to onset of therapy before or after three weeks. Note that the chances of recovery are higher in the earlier (E) treated groups as compared to the later (L) treated groups.

patients with CHF at onset without ResHD after ten years, and no patients who had recovered from AR. The development of MS was observed in a female patient with CHF and in a male patient (6.45%). In the latter, AR disappeared in the second year and MS developed in the fourth year after the onset of MR.

Course of patients with ResHD after ten years: In one patient without LHV, AR and MR persisted without LVH developing in 20 years. In the group with moderate LVH, MR disappeared in one patient after 12 years and persisted in another patient for 14 years, without LVH developing. AR was still present after 21 years in two patients, and in three other patients after 16, 14 and 13 years, respectively. In one male patient from the group with severe LVH, after two recurrences in the sixth and seventh year (despite regular PP), MR disappeared 16 years after its onset, however, AR, was still present after 21 years.

Recurrences (R): Of the 12 cases with recurrences, there was only one patient who recovered from AR (8.5%) and six from MR (50%). Of the 19 patients without recurrences, five recovered from AR (26%) and 11 from MR (58%). In the regular PP group, the recurrence rate was 2.42% per year in 165 patient-years (four in three patients' 41 years and no R in 13 patients' 124 years) and 8.67 percent per year in the 150 patient-years of the irregular PP group. The differences

in recurrences between the groups receiving regular and irregular PP was significant ($x^2 = 3.950$; $p<0.05$), but differences were much more significant in our 730 patient-years of isolated MR cases[9].

Mortality: One patient, who discontinued PP, died in the fourth year during a recurrence of pancarditis. The mortality rate was therefore calculated as 3.2 percent of the total AR and MR patients in 332 patient-years (0.001/year) and 17 percent of the patients with CHF who were followed up for 54 patient-years (0.003/years).

Discussion

The prognosis of MR and AR differed in the same patient, in that the recovery rate in MR was lower in the first two years and much higher in the years thereafter (Table II, Figs. 1, 2). It is evident from Fig. 1 that the slope representing the disappearance of MR is 3.4 x higher but the intercept is negative, 3.8 as compared to a positive 8.8 in AR.

The chance of recovery from AR is around 20-25 percent. This becomes, however, less probable after two years of onset and much less after five years.

The results reported in the "Joint Study"[4,5] with regard to the first year are consistent with our findings. The investigators, however, reported data from one center where AR had been over-diagnosed, and the rates of disappearance of AR were extremely high as compared to all the other centers (24/33=73%). Therefore, they excluded the results of this center[5]. However, only 12 patients remained from 11 centers, and only three of these recovered (25%), which is consistent with our findings obtained after ten years. Bland and Jones[6] have observed that if the intensity of the AR murmur is grade I, the probability of it disappearing is 33 percent (9/27) while, if the intensity of the AR murmur is grade II or higher, the probability of it disappearing is nil.

Wilson and Linn[14] found that in 96 adult patients with isolated AR,the murmur did not disappear. However, the intensity of the murmur regressed in 15 percent of the patients and remained constant in 85 percent.

From the eight isolated and 17 combined AR patients that Thomas[15] studied, all revealed significant AR, and the condition did not disappear in five years, while in the cases with slight AR, 8/10 disappeared.

In our subjects, the rate of disappearance of AR plus mitral valve disease was 13.1 percent (9/69), as compared to 45.7 percent in isolated AR (19/35) in the series of Feinstein et al[7]. This was reported as two percent (1/49) in another publication describing the same patient series[8]. The rates of disappearance were given for both lesions but not for each. No differentiation was made between MR and MS

with respect to prognosis of combined valvular lesions. In their patients with isolated AR, the rate of disappearance was 27.8 percent (5/18).

We conclude, that in patients with rheumatic carditis and combined mitral and aortic regurgitation the chance of recovering from AR is about 10 percent in the first year and 19 percent in five years. On the other hand, the chance of recovering from MR is much better; 30 percent and 65 percent in five and ten years, respectively. But the chance of complete recovery from both valvular lesions is only 6.5 percent in ten years or more. This is the reason why isolated AR is found much more frequently in adult patients.

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INTRACRANIAL CALCIFICATION IN DIHYDROPTERIDINE REDUCTASE DEFICIENCY*

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Summary: Coşkun T, Besim A, Özalp İ, Eryılmaz M. (Departments of Pediatrics and Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Intracranial calcification in dihydropteridine reductase deficiency. Turk J Pediatr 32: 259-264, 1990.

We described the clinical status and computerized tomographic findings of two patients with tetrahydrobiopterin (BH_4) deficiency due to impaired BH_4 regeneration. In addition to an unfavorable course, cranial computerized tomography scans demonstrated severe cortical and subcortical atrophy and bilateral corticomedullary and basal ganglia calcifications in these two cases. The occurrence of calcification in the same distribution following the use of methotrexate, a folic acid antagonist, supported the hypothesis that there is a link between the metabolism of pterins and folate. *Key words: dihydropteridine, reductase deficiency, hyperphenylalaninemia, intracranial calcification.*

Tetrahydrobiopterin (BH_4) is a specific cofactor for phenylalanine (Phe), tyrosine (Tyr) and tryptophan (Trp) hydroxylases. The deficiency, therefore, of this cofactor results in hyperphenylalaninemia associated with low levels of the monoamine neurotransmitters dopamine, norepinephrine and serotonin. BH_4 deficiency may be either due to a defect in regeneration of BH_4 from quinonoid dihydrobiopterin (qBH4) or in its biosynthesis. Dihydropteridine reductase (DHPR) catalyses the regeneration reaction of BH_4, whereas 6-pyruvoyl tetrahydropterin synthase (PTPS) and GTP-cyclohydrolase have a role in BH_4 biosynthesis. The clinical picture of hyperphenylalaninemias due to BH_4 defects differs from that of other hyperphenylalaninemias, in that they show a progressive neurological deterioration despite early and adequate dietary therapy[1].

In this report, we describe the cerebral computed tomographic (CT) findings of two patients with DHPR deficiency of which very few cases have been reported in the literature[2-6]. Our results draw attention to the association of this type of hyperphenylalaninemia with intracranial calcification.

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Case Reports

Case 1

Patient E.K., a five-year-old girl, was born weighing 3100 g. Pregnancy, labor and delivery had been uncomplicated. The parents were unrelated. Her blood samples were screened for hyperphenylalaninemia because her elder sister had been diagnosed as having hyperphenylalaninemia due to DHPR deficiency. Her blood Phe level rose gradually and reached 15 mg/dl by the seventh day of life. Subsequent urinary pterin analysis and measurement of DHPR activity in the erythrocytes confirmed the diagnosis of DHPR deficiency. On the eighth day of life, a restricted Phe diet was initiated. L-Dopa/Carbidopa and 5-OH-tryptophan were instituted as neurotransmitter precursors. Her blood Phe level was well under control. Her psychomotor development was normal until seven months of age, when she first experienced a convulsive attack. Myoclonic seizures continued to occur despite the combined anticonvulsive therapy administered. There was also evidence of progressive neurological deterioration. The first CT brain scan, taken at two years of age, demonstrated the presence of cortical atrophy of the brain and multiple foci of calcification at the level of the basal ganglia. Folinic acid was added to the therapeutic regimen but no clinical improvement was evidenced. A repeat CT scan, at five years, revealed dilatation of the hemispheric cortical sulci, ventricles and cisterns due to severe cortical and subcortical atrophy. Bilateral, symmetric cortico-medullary junction and basal ganglia calcifications were also observed (Fig. 1 a, b).

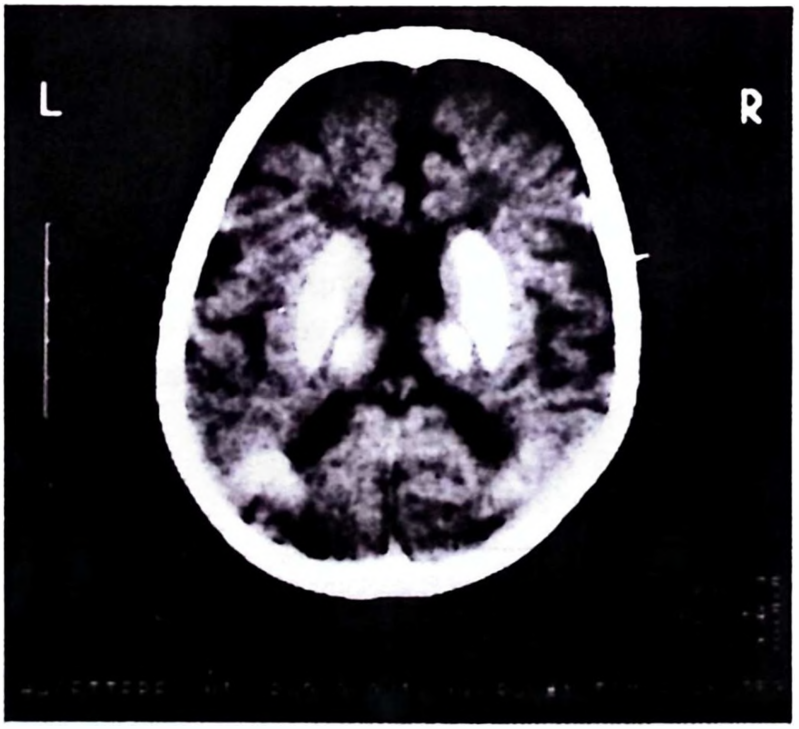
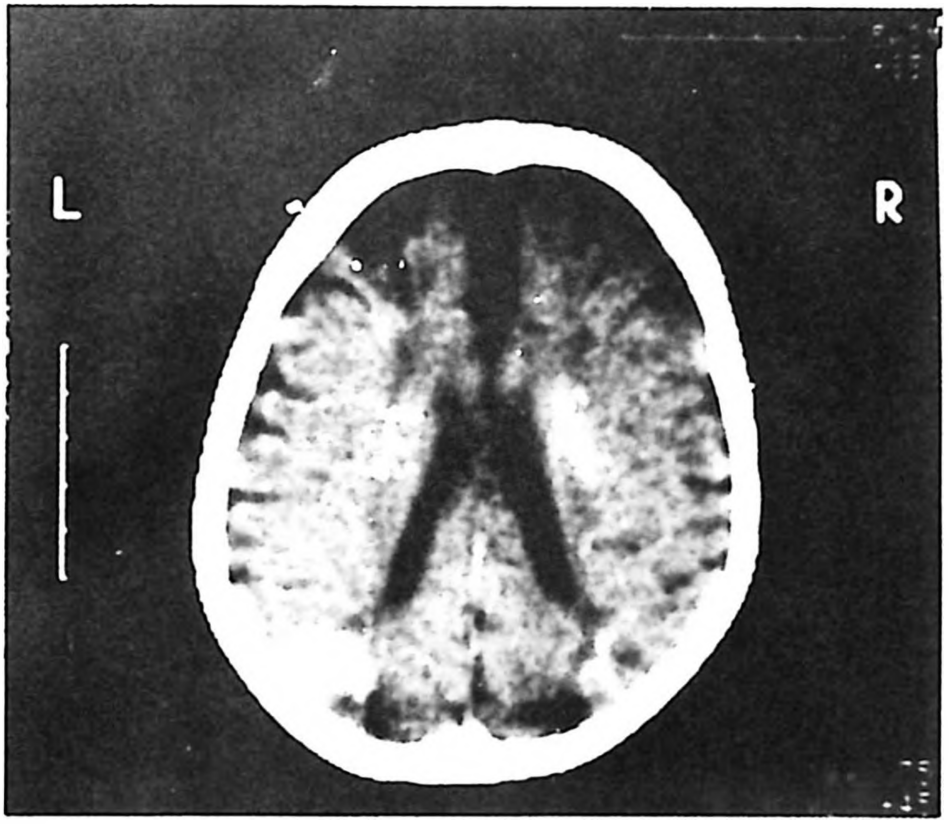


Fig. 1 a, b: The CT images, which are not enhanced, show bilateral symmetric calcification of lentiform and thalamic nuclei and of the cortico-medullary junction in the parieto-occipital lobes (Case 1).

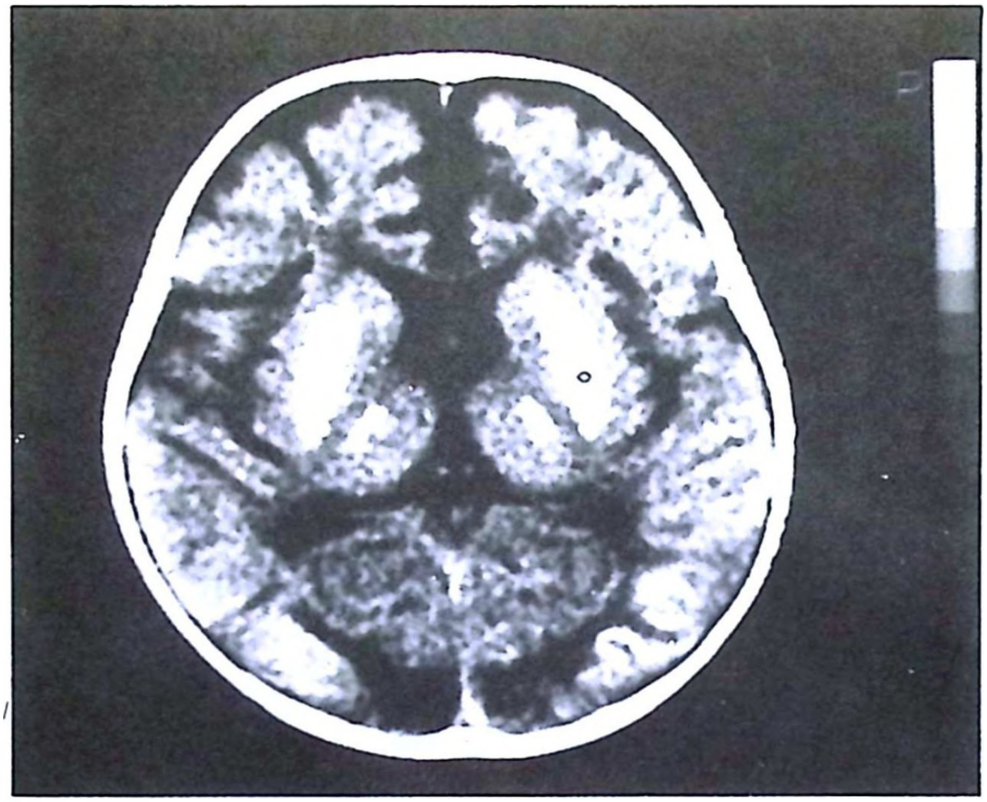


b

Case 2

Patient B.Y., a 13-month-old girl, was brought to Hacettepe University Children's Hospital with the chief complaints of developmental delay and spasticity. Pregnancy and delivery were both uneventful. The parents were first cousins. The first born child, a 1.5-year-old girl, had died demonstrating the same clinical signs and symptoms.

Physical examination revealed that the patient was below the 5th percentile for weight (5700 g) and at the 5th percentile for height (70 cm). Her head circumference of 41 cm was below the 5th percentile. She was unable to recognize her mother, sit unaided, and was not interested in her surroundings. Her extremities were extremely spastic and there was truncal hypotonia. Laboratory investigations revealed that the blood Phe level was 13.8 mg/dl. The results obtained from urinary pterin analysis and from measuring DHPR activity were consistent with the diagnosis of DHPR deficiency. A CT brain scan demonstrated the same features as Case 1 (Fig. 1 c, d). The patient was given a low Phe diet and the neurotransmitter precursors L-Dopa and 5-OH-tryptophan shortly after confirmation of the diagnosis.



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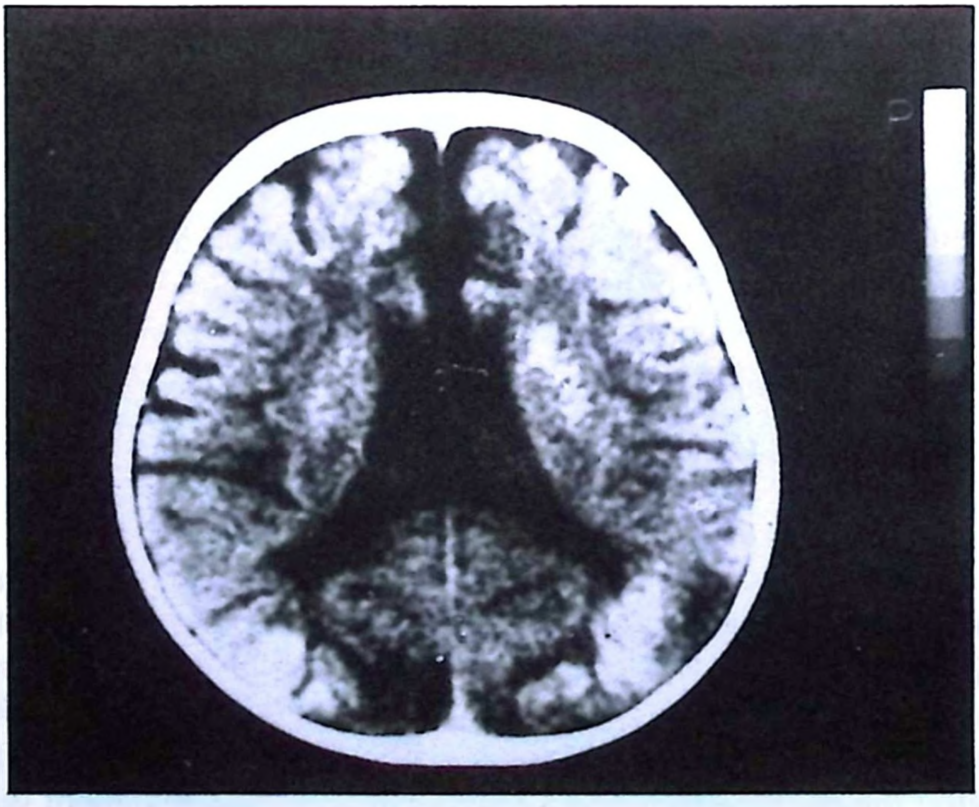

d

Fig. 1 (c, d): The ventricles and hemispheric cortical sulci are dilated because of cortical and subcortical atrophy (Case 2).

Discussion

Deficiency of DHPR, an enzyme involved in the regeneration of the cofactor BH_4, is one of the three inborn errors of metabolism causing BH_4 deficiency. Since BH_4 is a cofactor not only of phenylalanine hydroxylase, but also of Tyr and Trp hydroxylase, an atypical form of phenylketonuria (PKU) with progressive neurological symptoms which are unresponsive to a Phe restricted diet, develops when there is a defect either in BH_4 regeneration or in its biosynthesis[1].

Neuroradiological studies in children with classical PKU have demonstrated only cerebral atrophy, probably due to demyelinization[7]. In CT scans of our two patients with DHPR deficiency, there were intracranial calcifications at the cortico-medullary junction and the basal ganglia, in addition to cerebral atrophy. Basal ganglia calcification occurs under a wide range of conditions[4]. The number of recognizable metabolic derangements described in association with basal ganglia calcification has increased in recent years with the availability of computed tomography. In our cases, an abnormality in calcium metabolism was excluded by routine biochemical tests. Few previous reports have noted the presence of intracranial calcifications in DHPR deficiency[2-6]. The mechanism responsible for intracerebral calcification in DHPR-deficient patients has not yet been fully clarified. In addition to the cases which have been previously reported,our two cases add further support to the hypothesis that the presence of intracerebral calcification in DHPR deficiency is not a coincidental finding.

In fact, there have been reports of cases ascribing the development of intracerebral calcifications in DHPR deficiency to folate deficiency in the central nervous system (CNS) resulting from the loss of the folate conservative effect of DHPR in CNS[3,5]. In addition, the pattern of calcification and atrophy seen in our cases is exactly the same as that observed in cases of mineralizing microangiopathy which occurs in children treated with cranial irradiation and methotrexate, a folic acid antagonist[8].

In conclusion, we believe that the presence of intracerebral calcifications in DHPR-deficient children is not just a mere coincidence but points to a common mechanism. We, therefore, propose that DHPR deficiency should be included in the list of causes of intracerebral calcifications visualized by CT scans in children. Awareness of this possibility will lead to performance of necessary laboratory investigations in a child with hyperphenylalaninemia characterized by progressive neurological deterioration which is unresponsive to dietary therapy alone.

Acknowledgement

We wish to thank Dr. N. Blau, Zürich, Switzerland, for the measurement of DHPR activity in the erythrocytes and for determining pterins in the urine.

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The Turkish Journal of Pediatrics 32:265-271, 1990

FIBROMUSCULAR DYSPLASIA OF THE RENAL ARTERIES TREATED WITH PERCUTANEOUS TRANSLUMINAL RENAL ANGIOPLASTY : A CASE REPORT*

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*Umman Şanlıdilek MD*****

Summary: Yalçınkaya F, Tümer N, Ekim M, Şanlıdilek U. (Pediatric Nephrology Unit, Department of Pediatrics, Ankara University Faculty of Medicine, Ankara, Turkey). Fibromuscular dysplasia of the renal arteries treated with percutaneous transluminal renal angioplasty: a case report. Turk J Pediatr 32: 265-271, 1990.

A nine-year-old girl with renovascular hypertension is presented. The diagnosis of fibromuscular dysplasia was established by selective renal angiography, and percutaneous transluminal renal angioplasty was performed. After successful dilation, the blood pressure returned to normal. The patient has been followed for a year and there is no evidence of hypertension. *Key words: fibromuscular dysplasia, percutaneous transluminal renal angioplasty.*

The incidence of secondary hypertension in the pediatric population has been reported to be high[1]. Renal and renovascular diseases account for nearly 80 percent of secondary hypertension in children, and approximately 70 percent of children with renovascular hypertension have fibromuscular dysplasia (FMD)[2].

In this report, we describe a patient with hyperreninemic hypertension and angiographically diagnosed FMD. Since the patient's hypertension could not be controlled with medication, a percutaneous transluminal renal angioplasty (PTRA) was performed.

Case Report

A nine-year-old girl was admitted to the hospital with epistaxis. Physical examination revealed a blood pressure of 160/130 mmHg. She was a well developed child and had normal physical findings, including funduscopic examination.

Laboratory findings revealed a hemoglobin of 14 g/dl, hematocrit 46%, white blood cell count 12,000/m^3 with 60% neutrophils, 38% lymphocytes, 2%

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monocytes, and a normal platelet count. Urinalysis, BUN, serum creatinine, electrolytes, total protein, albumin and creatinine clearance were within normal limits. Urine cultures were negative. The chest radiograph, electrocardiogram, intravenous pyelography and abdominal ultrasound examinations were also normal. Urinary excretion of catecholamines and vanilmandelic acid (VMA) were found to be within the normal range. The peripheral plasma renin activity and aldosterone concentrations were high. In a supine position, the plasma renin activity was 4.5 ng/ml/hr (normal: 0.2-2.7 ng/ml/hr) and in an upright position it was 5.5 ng/ml/hr (normal: 0.4-3.2 ng/ml/hr). Plasma aldosterone concentration was 700 pg/ml (normal: 20-200 pg/ml).

Medical therapy was initiated which consisted of methyldopa (10 to 20 mg/kg/day), propranolol (2 to 5 mg/kg/day), captopril (1 to 1.5 mg/kg/day), prazosine (1 mg/kg/day) and hydrochlorothiazide (2 to 4 mg/kg/day) in increasing doses with various combinations for a year. But her blood pressure could not be controlled.

Intravenous digital subtraction angiography (DSA) was performed on the patient, and evidence of a possible stenosis was detected in the dorsal branch of the right main renal artery. To evaluate this stenosis further, selective renal angiography was performed which revealed a focal stenosis of the dorsal branch of the right main renal artery with its poststenotic dilation (Fig. 1). The luminal diameter of this branch measured 2.4 mm, and the stenotic segment 0.4 mm, indicating high grade stenosis of the renal artery (Fig. 2). These angiographic findings were found to be characteristic of the focal type of FMD.

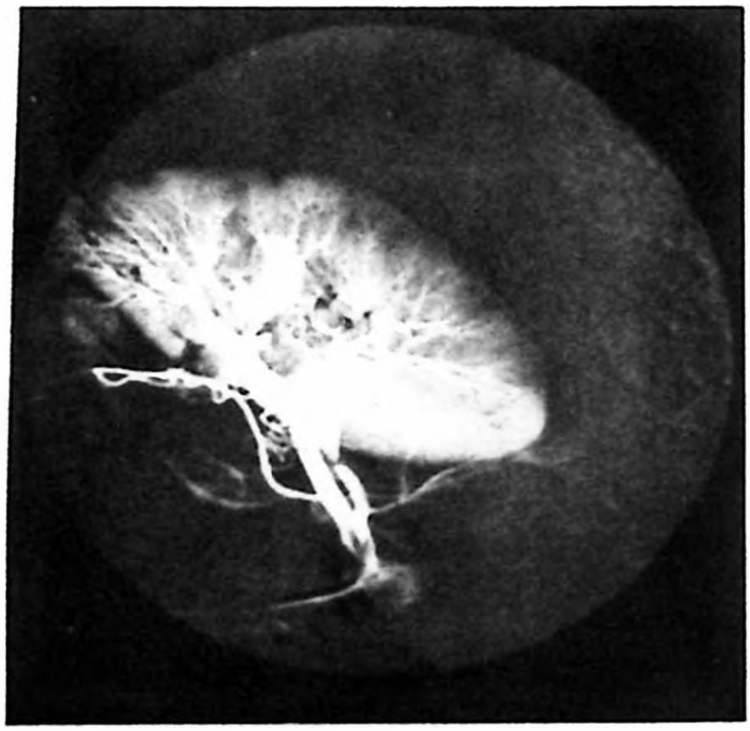

Fig. 1: Stenosis and post-stenotic dilatation of the right renal artery.

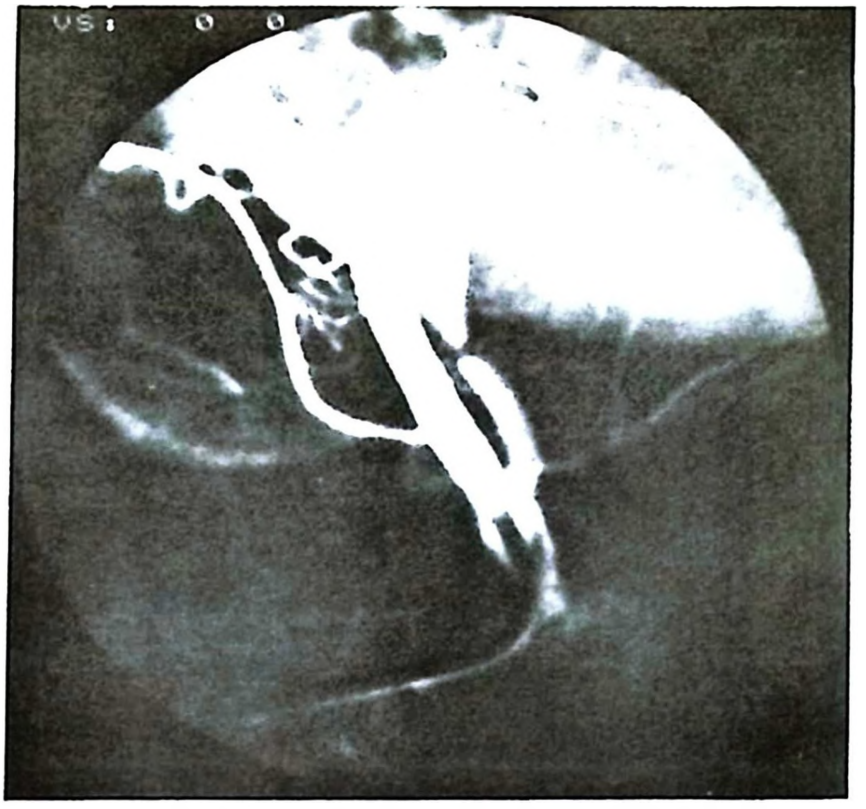

Fig. 2: High-grade stenosis of right renal artery.

Her right stenotic side (R_1), left nonstenotic side (R_2), inferior vena cava (IVC), and plasma renin activities (R_3) were 3.9 ng/ml/hr, 1.3 ng/ml/hr, and 2.3 ng/ml/hr, respectively. The renal vein renin data were analyzed by using the plasma renin activity ratio (PRA) and suppression index. The PRA ratio is the ratio of PRA of the stenotic side to the nonstenotic side, and values equal to or greater than 1.5 are considered significant. The suppression index is the ratio of PRA of the nonstenotic side to PRA of IVC. If the values are equal to or less than one, it can be assumed that contralateral renin secretion is suppressible[3,4]. Thus, our patient's PRA ratio values which were (R_1/R_2 = 3.9/1.3) greater than 1.5 and the suppression index which was (R_2/R_3 = 1.3/2.3) less than one were considered significant (Table I).

Since there are various technical difficulties and risks involved in surgical intervention, PTRA was performed on the patient. A successful dilation, using local anesthesia was carried out by introducing an inflatable balloon-tipped catheter over the guide wire percutaneously (Figs. 3, 4). After PTRA, the blood pressure returned to normal, and anti-hypertensive therapy was discontinued. The patient has had normal blood pressure for a year without the use of any medication.

TABLE I: Plasma Renin Activity (PRA) and Suppression Index in Our Patient

PRA Stenotic / PRA non-stenotic R1 R2 (PRA Ratio)	PRA non-stenotic / PRA IVC R2 R3 (Suppression index)
3.9 / 1.3 > 1.5	1.3 / 2.3 < 1

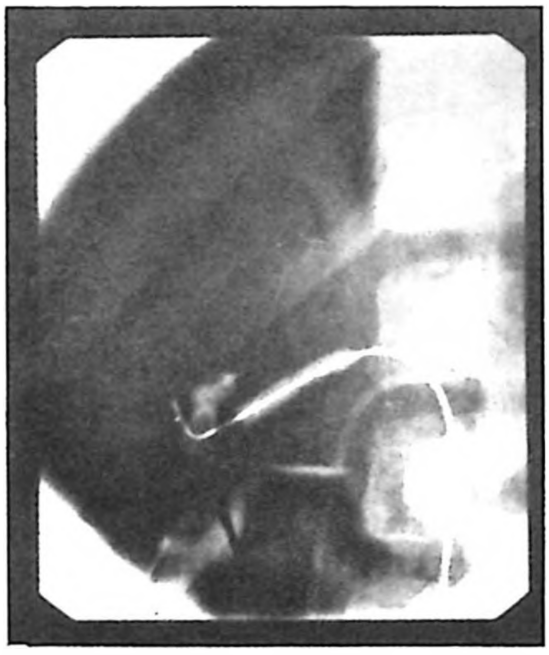

Fig. 3: Inflatable balloon catheter in right stenotic artery.

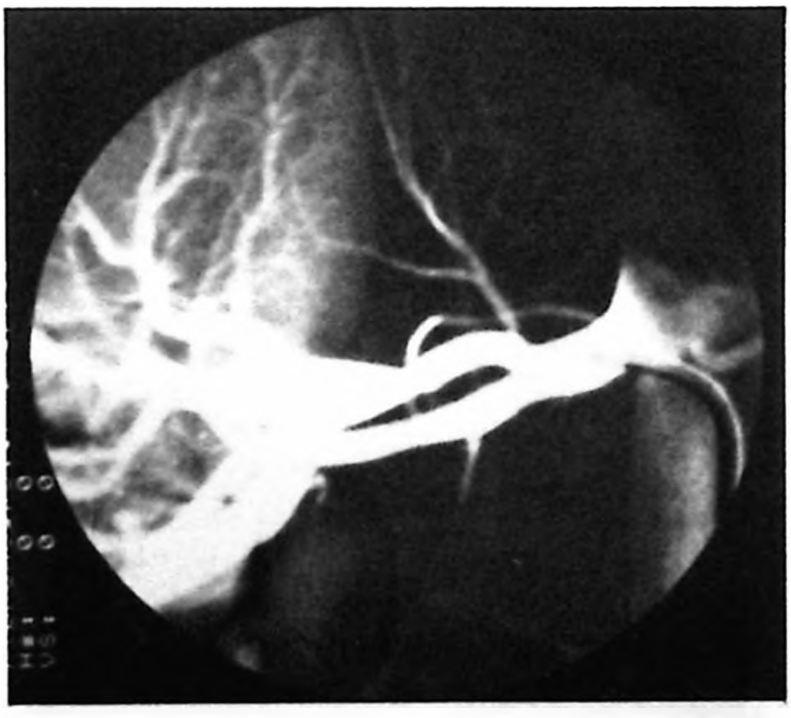

Fig. 4: Dilatation of right stenotic artery after PTRA and collaterals.

Discussion

FMD is a well known angiopathy primarily involving the aortic branch arteries. The disease was originally described in the renal arteries in 1938[5]. But, later, it was reported that it could also affect carotid, celiac, mesenteric, iliac, splenic, hepatic, subclavian, and even the coronary arteries[5-7]. Recently, involvement of the aorta has also been documented[5]. Involvement of the renal arteries is the most common manifestation of FMD. It has been reported that half of the patients with bilateral renovascular disease show additional extrarenal FMD[5].

Although FMD may be seen at any age, and in both sexes, it is known as the disease of young women, and the frequency in children remains low. The ages of patients range from five years to 69 years in large group studies[6,8,9].

Usually the middle and distal third of the main stem of the renal artery is involved, but extension into the branches of the renal artery can occur. The disease may be bilateral or unilateral, and nearly 80 percent of unilateral lesions occurs on the right side[6-9]. Our patient had a high grade stenosis in the dorsal branch of the right main renal artery. Collaterals can be demonstrated in 17 to 93 percent of lesions[6,9]. The second angiography performed on our patient revealed renal arteries with collaterals (Fig. 4).

The etiology of FMD is still unknown. Many hypotheses have been proposed stressing the importance of genetic and humoral factors and the role of arteriolar spasm[5-7]. Renal ptosis is common among patients with renal artery lesions: It has been postulated that traction due to ptotic kidneys (the right kidney larger than the left) may also be an etiologic factor.

Arteriographic findings of the lesions are pathognomonic for the diagnosis. FMD is classified as focal, multifocal, tubular and mixed, according to the angiographic findings[6,8,10]. The most common form is the multifocal type, which is also known to have a "string of beads" appearance[2,6,8,10]. The angiographic findings of our patient revealed that she had the focal type of FMD.

Histopathologically, these lesions can be classified as medial, intimal and periarterial, according to the arterial wall layer in which they predominate[7,8]. In some cases, the angiographic appearance of the lesions shows an excellent correlation with the pathological findings. It is known that medial fibroplasia represents the most common dysplastic lesion (nearly 85%) found in pediatric patients[7].

FMD is considered to be a persistent and often progressive abnormality[8,10]. Unilateral FMD may progress to involve the contralateral renal artery[7]. Recently, it has been reported that spontaneous improvement may occasionally occur[11,12].

Three different therapeutic approaches are being used in patients with renovascular disease: medical therapy, surgical intervention, and PTRA. It has been reported that more favorable results of curative interventions, other than pharmacotherapy, have been obtained in unilateral renal artery stenosis with a significant PRA ratio and, in particular, in those with suppression of renin secretion in the contralateral kidney[3,4]. Our patient's PRA ratio and suppression index were 3 and 0.5 respectively, and these results were considered significant.

Renal angioplasty is a balloon dilatation technique and reconstructive procedure. Following its first description in 1978, PTRA soon became the established technique for the treatment of almost all forms of renal artery stenosis in adults, proving to be both effective and safe, since there is no need for general anesthesia, surgery or prolonged hospitalization[13,14]. This technique also has certain applications in the treatment of renovascular hypertension in children, and satisfactory results have been reported following the development of smaller catheters and proper patient selection[15-17].

PTRA has been reported to be technically successful in 66-87 percent of patients with FMD. After successful dilatation, the overall benefit (cure and improvement of hypertension) has been found to be 94 percent[14,15]. The results of many studies document the good, long-term effect of PTRA on blood pressure and kidney function in patients with renal artery stenosis.[14,17,18]. The occurrence of restenosis has been reported to be 22 percent in patients with FMD[15]. The frequency of complications has been reported to range between 3-10 percent, and only 2-4 percent of major complications has been found to be directly related to PTRA[19]. Finally, the reported mortality rates have been found to be much lower with PTRA (1-3%) than with surgery (11%)[5,19].

Our patient was treated medically with combinations of various antihypertensive drugs for a year, but her hypertension did not respond to the therapy. After PTRA, her blood pressure returned to normal.

We suggest that PTRA can be the treatment of choice in renovascular FMD in children because of its high cure and low complication rates and its long-term beneficial effect on renal functions.

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HYPER – IgE SYNDROME: A CASE REPORT*

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Summary: Sanal Ö, Göçmen A, Tezcan İ, Ersoy F, Adalıoğlu G. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Hyper-IgE syndrome: a case report. Turk J Pediatr 32: 273-278, 1990.

A four-year-old-girl with hyper-IgE syndrome is presented. She had a coarse facial appearance, pruritic dermatitis, recurrent skin abscesses, pulmonary infection, spontaneous bone fractures, and an elevated serum IgE concentration. She has been treated with cimetidine, ascorbic acid and trimethoprim-sulfamethoxazole for the last two years and there has been no evidence of a severe infection. *Key words: hyper-IgE syndrome, bone fractures, cimetidine, vitamin C.*

The hyper-IgE syndrome (HIES) is a rare disorder characterized by pruritic dermatitis, recurrent staphylococcal skin abscesses, lung infections with pneumatocele formation, extreme elevations in serum IgE levels and generally normal or near-normal serum concentrations of the other immunoglobulins[1-3]. The coarse facial appearance, the defects in cellular and humoral immunity, and variable polymorphonuclear (PMN) leukocyte chemotactic abnormalities have also been reported in this syndrome[1].

We present a four-year-old girl who had dermatitis and recurrent superficial and deep bacterial infections in association with raised IgE levels.

Case Report

The patient (Y.T.) was first hospitalized at 18 months of age for numerous skin abscesses and fever. Her medical history revealed persistent dermatitis localized on the scalp, face and retroauricular areas, which started at 20 days of age, and also recurrent pneumonia, pustular skin lesions, diarrhea and oral candidiasis. She did not have any unusual reactions following routine immunizations and neither

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was there any clinical evidence of parasitic infestation, history of respiratory allergy or asthma. The parents were first degree cousins and healthy. Physical examination revealed a coarse facial appearance (Figs. 1, 2). Her weight was above the 15th percentile and her height was above the 25th percentile. There were numerous skin abscesses on her scalp, face and right buttock. Cultures of the abscesses yielded *Staphylococcus aureus*. The lesions responded to surgical drainage and two weeks of oral trimethoprim-sulfamethoxazole therapy. Laboratory examinations showed hypochromic anemia and a peripheral leukocyte count of 20,400 per mm^3 with 75% neutrophils. Total peripheral eosinophil count was 550 per mm^3. Serum IgE level was above 2,500 kU/lt. Other serum immunoglobulin levels were within normal limits (IgG: 1560 mg/dl; IgM: 123 mg/dl; IgA: 77.7 mg/dl). Delayed hypersensitivity skin tests were positive with PHA, Candida and PPD but negative with SKSD. The percentage of E-rosette forming cells was normal (60%). Lymphocyte blastogenic response to PHA, NBT reduction test, and total complement (CH_{50}: 47 u) were found to be normal. Serum anti-A and anti-B titers were 1/64 and 1/512, respectively. In vitro neutrophil chemotaxis value using Boyden's chamber and Zymosan activated serum (ZAS) as a chemoattractant was 57.4% of the healthy control.

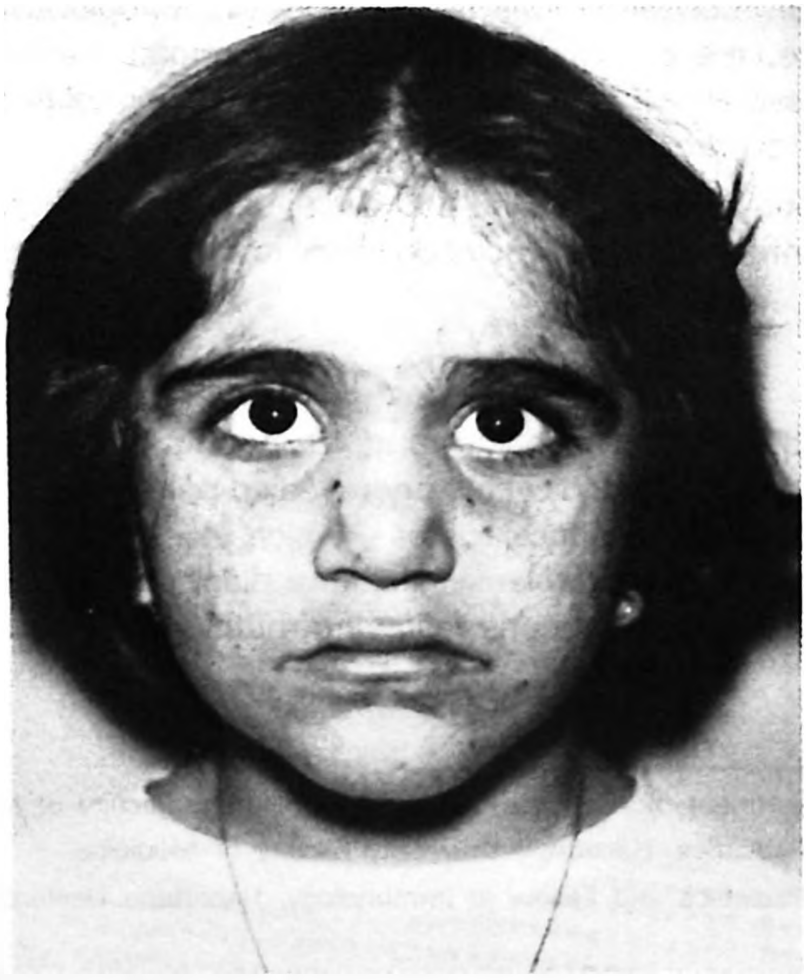

Fig. 1: Coarse facial appearance

Fig. 2: Skin infection and pruritic dermatitis

In view of the clinical picture and laboratory findings, the patient was diagnosed as having hyper-IgE syndrome. She was administered cimetidine (as a histamine-receptor blocking agent) and trimethoprim-sulfamethoxazole.

At 19 months of age, the infant was hospitalized for the second time, and the diagnosis of pneumonia was established. She had a fracture of the third metatarsal bone with no history of trauma. We learned that after she had been discharged from the hospital, she had not been receiving trimethoprim-sulfamethoxazole and cimetidine on a regular basis.

Pneumatocele formation with air-fluid levels were noted on the chest roentgenogram. Despite the administration of anti-staphylococcal antibiotic therapy, a massive pleural effusion developed and tube drainage was performed. Cultures of the pleural fluid grew *Staphylococcus aureus.* Intravenous antistaphylococcal therapy was continued for 3 weeks. Pleural effusion disappeared but the pneumatocele persisted. She was discharged and ascorbic acid was prescribed in addition to the cimetidine and trimethoprim-sulfamethoxazole. She did well for the next 8 months. At 2 1/2 years of age, she was hospitalized again because of a fracture of the left radius-ulna bone, resulting from a relatively slight trauma. A chest x-ray revealed that the pneumatocele had disappeared.

Repeated scalp abscesses and recurrent middle ear infections, although less severe and less frequent, developed during the follow-up period. The in vitro neutrophil chemotaxis value was 91 percent of the healthy control when evaluated during ascorbic acid treatment.

The patient had no major skin or lung infection but a chronic middle ear infection was present.

Discussion

This patient, who had dermatitis in the newborn period, numerous superficial and deep skin abscesses located especially on the scalp, face and neck, multiple bouts of staphylococcic pneumonia complicated with empyema and pneumatocele formation and a marked elevation of the serum IgE level, was diagnosed as having HIES.

Since Buckley's[2] first description of two patients with HIES in 1972, several cases have been reported[3-6]. Pruritic (not atopic) dermatitis, skin infections, especially on the scalp and face, recurrent episodes of pneumonia complicated by empyema, lung abscesses, pneumatocele formation, and a coarse facial appearance are the major clinical features seen in this syndrome. Infections of the ears, eyes, oral mucosa, sinuses and joints can also be present in HIES. Most patients do not have histories of allergic rhinitis or asthma.

Kirchner[7] emphasized recurrent bone fractures in some of the patients with HIES. Our patient had a bone fracture twice during the follow-up period. Leung et al[8] suggested that the monocytes from HIES patients cause osteopenia. The spontaneous release of prostaglandin E_2 (PGE_2) may induce the monocytes to resorb bone. The familial nature of HIES has been documented[9,10]. Both sexes are said to be affected. IgE levels are reported to be normal in non-affected family members[10].

The major immunologic feature of HIES is a marked elevation of serum IgE levels. An elevated concentration of IgD has been found in most patients[1]. It has been reported that IgA antibodies to *Staphylococcus aureus* are deficient in some patients[11]. High levels of IgE antibodies to staphylococcus aureus antigen were found by Buckley[1] and Dreskin[11]. Berger et al[12] and Scmitt et al[13] observed high titers of IgE antibodies to tetanus toxoid and Candida antigens. They concluded that there might be an abnormal IgE immunoregulation.

Buckley[1] et al observed negative delayed hypersensitivity skin reactions to Candida and SKSD in half of their patients. Our patient had a positive delayed hypersensitivity skin reaction to three out of four antigens tested. In Buckley's series, the lymphocytes from most of the patients with HIES had a normal proliferative response to mitogens but no, or a very low response to Candida antigen and tetanus toxoid[1].

Impaired neutrophil chemotaxis has been noted by several authors[1,3,4,6,9,14]. It has been suggested that high levels of histamine cause cyclic GMP elevation in the neutrophils from patients with HIES. A chemotactic inhibitor factor might also be responsible for the defective neutrophil chemotaxis[4,15]. Our patient's neutrophil chemotaxis was 57.4 percent of the healthy control. Hill et al[16] studied the effects of the H_2-receptor blocking agent to PMN leukocyte chemotaxis in vitro. They observed an improvement in neutrophil chemotaxis from HIES exposed in vitro to burimamide (H_2-receptor blocking agent). Defective neutrophil chemotaxis is not consistent and may vary even in the same patient. Our patient's in vitro neutrophil chemotaxis was normal during the follow-up period. This might be related to the ascorbic acid treatment or a spontaneous alteration that is seen in HIES. Buckley[1] emphasized that chemotactic abnormalities were more suggestive of atopic dermatitis than HIES. PMN leukocyte phagocytosis, killing and nitroblue tetrazolium dye-reduction were found to be normal in their patients.

Job's syndrome (JS), characterized by recurrent "cold" staphylococcal abscesses and pulmonary infections was described in 1966[3,17]. A high serum concentration of IgE was demonstrated later. There are some clinical similarities between JS and HIES. While some authors consider JS to be within the spectrum of HIES, others say it is an entirely different entity. At present, the relationship between JS and HIES is not clear.

The primary defect in HIES is unknown, therefore, definitive therapy is not possible. Several investigators have studied the effects of normal plasma transfusions, histamine-2-receptor blocking agents, transfer factor, levamisole and interferon-alpha in the treatment of HIES[3-5,9,14,18,19].

Although treatment using transfer factor or levamisole has not resulted in any significant improvement in clinical or laboratory findings, normal plasma transfusions, cimetidine and ascorbic acid are said to improve the chemotactic abnormalities of neutrophils in these patients. Mawhinney et al[18] did not observe any severe infections in their patient during the administration of cimetidine. Souillet et al[19] reported that the administration of interferon-alpha for four weeks resulted in the reduction of the serum IgE level and eczema in a HIES patient.

Lifelong antibiotic therapy seems to be useful in preventing infections in these patients, and a favorable therapeutic response to trimethoprim-sulfamethoxazole has been reported[1-5].

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The Turkish Journal of Pediatrics 32:279-282, 1990

NEONATAL SMALL LEFT COLON SYNDROME: A CASE REPORT*

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Summary: Gündoğdu H, Tanyel FC, Besim A, Büyükpamukçu N. (Departments of Pediatric Surgery and Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neonatal small left colon syndrome: a case report. Turk J Pediatr 32: 279-282, 1990.

A newborn infant with neonatal small left colon syndrome is presented, and the relevant literature regarding the etiology of the disorder, its diagnosis and follow-up treatment is reviewed. *Key words: small left colon, colonic dysfunction, neonatal, transient.*

An infrequent cause of intestinal obstruction in the neonate is distal colonic obstruction which commonly results from Hirschsprung's disease [1]. Other causes of intestinal obstruction which are even more rarely encountered are colonic stenosis and atresia, meconium plug, and small left colon syndrome.

Small left colon syndrome (SLCS), first described as a distinct entity by Davis et al[2] in 1974, causes transient colonic obstruction in the newborn infant. To date, approximately 58 cases of SLCS have been reported[1-4]. In this paper, we wish to present the first case of SLCS diagnosed in our hospital, and as far as we know, no other such case has been previously reported in our country.

Case Report

A male infant with a birth weight of 3200 g was born to a multi-parous mother after an uneventful delivery. The newborn was admitted to the Hacettepe University Children's Hospital at 72 hours of age because of increasing abdominal

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distension, failure to pass meconium, and vomiting bilious material. A high blood sugar level had been detected in the mother during pregnancy, but she had received no treatment, except for a diet.

A plain erect abdominal radiograph taken immediately after admission suggested low colonic obstruction (Fig. 1). Barium enema roentgenogram showed a uniformly, narrowed small left colon from the anus to the splenic flexure, at which point there was an abrupt zone of transition (Fig. 2). The entire colon filled readily without evidence of obstruction at any point. Following the barium enema, the patient passed meconium in a large amount. His distension progressively disappeared and no more bowel difficulties were encountered. Oral feeding was started on the following day. After the patient was observed in our neonatal surgical unit for five days, he was discharged in good condition with no defecation problems. The patient was regularly followed up in our out-patient department for one year, and during that period no problems in defecating were evidenced. Barium enemas, which were repeated in the first and third months of the follow-up, revealed progressive normalization of the caliber of the colon in the narrow segment (Figs. 3, 4).

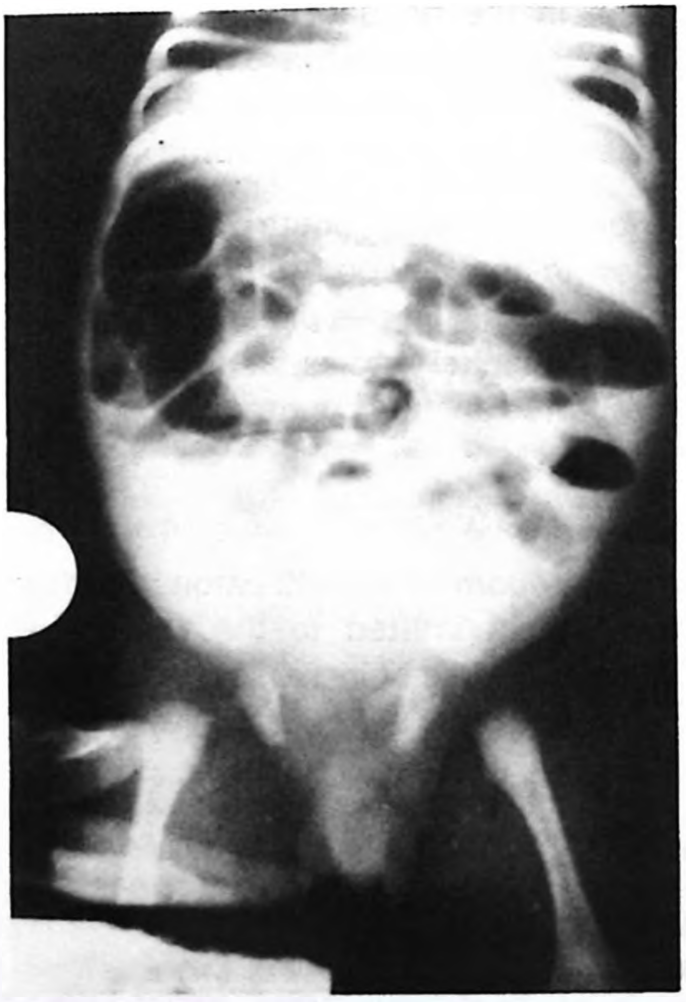

Fig. 1: Plain erect radiogram on admission.

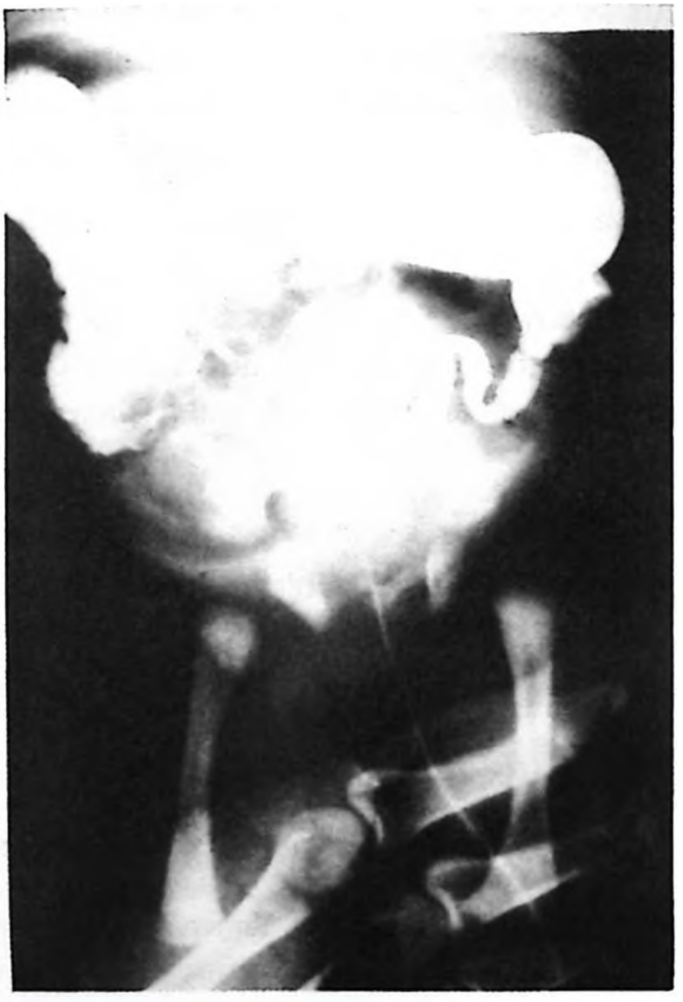

Fig. 2: Barium enema on admission showing the typical appearance of small left colon syndrome.

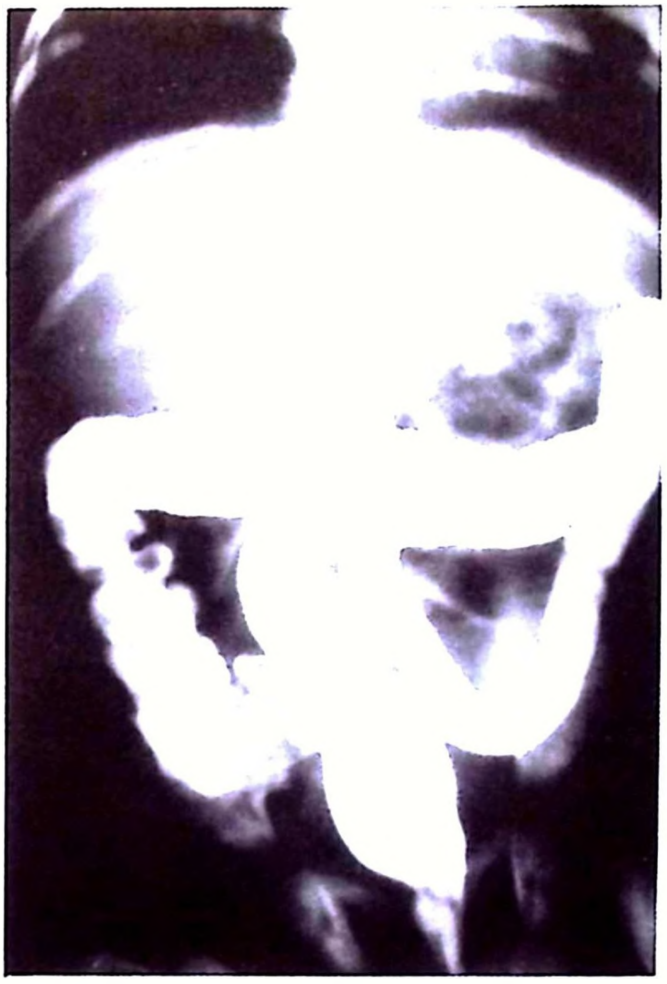

Fig. 3: Barium enema after a month, revealing dilatation of the narrow segment.

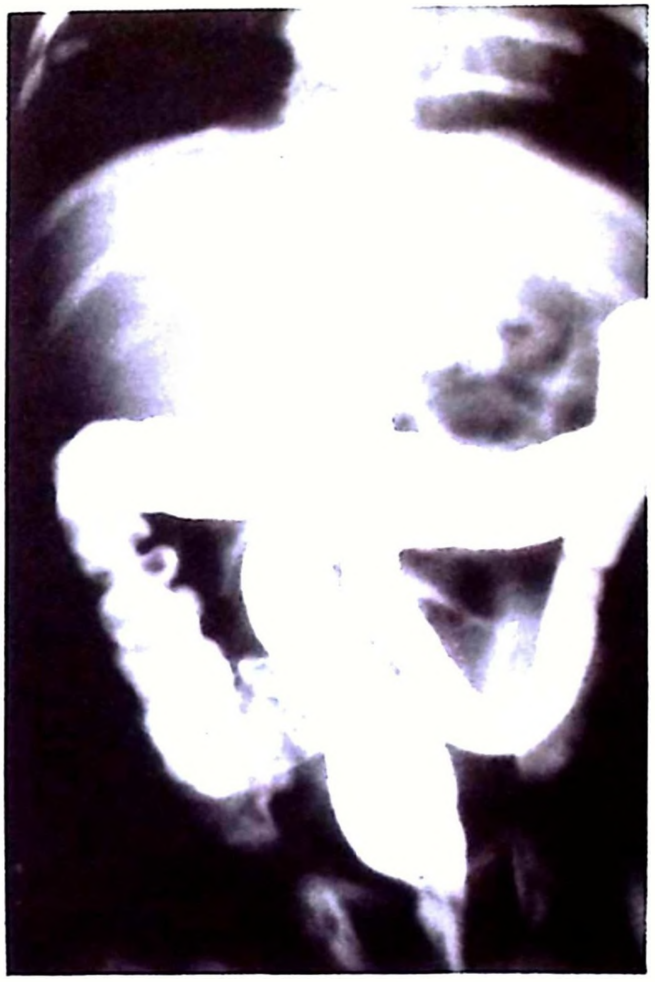

Fig. 4: Barium enema after three months, revealing normal colonic caliber.

Discussion

Although the etiology of neonatal left colon syndrome remains unknown[1-4], a history of maternal diabetes is reported to be present in 50 percent of SLCS patients[5,6], a fact which may shed light on the cause of the disorder. The history of a high blood sugar level in the mother of our patient was a clue in diagnosing SLCS in our patient.

It is difficult to distinguish SLCS from Hirschsprung's disease. In Hirschsprung's disease, the aganglionic segment may extend to splenic flexure in 20 percent of cases[1].

In SLCS, the narrow left colon extending to the splenic flexure is somewhat smaller, and there is an abrupt dilatation without a transition zone at the proximal portion. While in Hirschsprung's disease there is a transition zone, and dilatation at the proximal ganglionic segment may not be very obvious until the age of six weeks[1].

The symptoms of low colonic obstruction are relieved following barium enema in SLCS, but persist in Hirschsprung's disease. Repeated barium enemas reveal widening of the narrow segment in SLCS. If the clinical symptoms and barium enema findings disappear, the patient can be followed safely. However, if any doubt exists, further investigation, such as a biopsy, should be performed to evaluate Hirschsprung's disease[1].

In our patient not only did the clinical but also the radiologic findings disappeared, and therefore, further investigation such as biopsy was not needed. Since there have been patients erroneously diagnosed as having Hirschsprung's disease, to avoid unnecessary surgical procedures, SLCS should always be considered in patients with a history of maternal diabetes and if a narrow segment extending to the splenic flexure is seen during barium enema examination.

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