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CONTENTS

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SEVERE CYTOMEGALOVIRUS INFECTION AND IMMUNOSUPPRESSIVE THERAPY IN PEDIATRIC LIVER TRANSPLANTATION*

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Summary: Pehlivanoğlu E, Ament M.E, Spolidoro J.V.N, Vargas J, Busuttil R, Berquist W.E. (Departments of Pedatrics, Marmara University Faculty of Medicine, Istanbul, Turkey, and University of California, Los Angeles, USA). Severe cytomegalovirus infection and immunosuppressive therapy in pediatric liver transplantation. Turk J Pediatr 32: 3-11, 1990.

Twenty-two post-orthotropic liver transplant (OLT) recipients were studied to investigate the clinical, laboratory and histopathological differences between rejection and CMV infection. The mean age at the time of transplantation was five years. Nine of 22 (41 %) patients developed positive CMV, CF – IgG and IgM antibody titers and cultures for CMV following surgery, and three (group 1a) developed interstitial pneumonitis. CMV specific inclusion bodies were found in lung and liver biopsies. Two patients in group 1a were treated successfully with DHPG and decreasing immunosuppressive treatment, while the third died. Clinical presentation of rejection episodes were similar in all groups. CMV infected patients (group 1) received more transfusions of blood and blood products than the non-infected patients (group 2). Rejection episodes occurred sooner and more frequently in group 1a than in group 1b (CMV infected-asymptomatic) and group 2 (non-infected). Group 2 received fewer steroid boluses as well as azathioprine and OKT 3. A percutaneous liver biopsy with routine stains helped detect CMV when inclusion bodies were seen. We conclude that culture proven CMV infection is common post-OLT.

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Severe CMV infection occurred more frequently in those who had received greater doses of immunosuppressive therapy for possible graft rejection. Monitoring CMV infection following OLT is absolutely necessary. After OLT, decreasing the immunosuppressives and using antiviral agents are important in the management of CMV infection. ***Key words: cytomegalovirus infection, liver graft rejection, differential diagnosis, risk factors, treatment.***

Severe cytomegalovirus (CMV) infection is frequently detected in the immediate post - operative period following organ transplantation, at a time when the patient is subject to high - dose immunosuppressive therapy [1-8]. In liver transplant patients, the clinical manifestations of CMV infection may mimic liver graft rejection. Graft rejection, however, is treated with higher doses of immunosuppressive drugs. Since CMV viral replication and infection may be enhanced under these circumstances, the need for rapid and early detection of infection is necessary.

The aims of this study were (1) to determine the clinical and laboratory manifestations of CMV infection (2) to learn how CMV infection differs from liver graft rejection (3) to indicate the risk factors for developing CMV infection, and (4) to record the management and treatment of both conditions in post – orthotropic liver transplant (OLT) patients.

Material and Methods

Twenty-two patients who received OLT were retrospectively studied in the Department of Pediatrics, University of California, Los Angeles (UCLA) from March, 1984 to May, 1986. The mean age at the time of transplantation was five years and two months (range: seven months to 16 years). There were thirteen females and nine males. Pre-operative diagnoses of liver diseases were: biliary atresia (14 patients), alfa-1 antitrypsin deficiency (three patients), familial cholestasis syndrome (two patients), cryptogenic cirrhosis (one patient), hepatoblastoma (one patient) and leiomyoma with liver metastasis (one patient). All the patients were evaluated for CMV infection by serologic methods (complement fixation-IgG and CMV specific antibody) and/or urine, blood and throat cultures pre-operatively. If the patients developed clinical and/or biochemical evidence of graft rejection post-operatively, CMV serology was similarly obtained, as well as urine, throat, blood, and/or bronchia lavage for CMV cultures. Percutaneous liver biopsy was performed as indicated for diagnosis and management of presumed graft rejection. The biopsy, stained with hematoxylin and eosin, was also evaluated for CMV by routine light microscopy. The biopsies of the patients who had unexplained liver dysfunction, positive CMV cultures or interstitial pneumonitis were studied for CMV using the immunoperoxidase technique (Enzo Biochemical Inc, New York). All biopsy slides were reviewed by two pathologists to determine features of rejection and CMV infection.

Open lung biopsy and cultures were also performed in two cases who had positive cultures for CMV, poor response to anti-rejection therapy, and interstitial pneumonitis.

Rejection episodes were diagnosed clinically by the presence of fever, fatigue, jaundice, hepatomegaly, and right upper quadrant tenderness; biochemically by progressively increasing levels of SGOT (normal = 10-40 1 U/L), SGPT (normal = 15 1 U/L), total bilirubin (normal = 0-1.5 mg/dl), alkaline phosphatase (normal = 55-363 1 U/L), and histopathologically by liver biopsies revealing infiltration of portal tracts with plasma cells, lymphocytes, polymorphonuclear leukocytes, cholestasis, bile duct changes, cytoplasmic vacuolization, inflammatory infiltrate, centrilobular necrosis and vascular injury.

Initially all patients received methylprednisolone (20 mg/kg/day) as well as intravenous cyclosporine (2-3 mg/kg/day) before and after transplantation. The maintenance dosages for oral cyclosporine were 10-20 mg/kg/day, and for prednisone 1-2 mg/kg/day. The treatment regimen for rejection included either methylprednisolone pulses (15-20 mg/kg/day), Ortholone OKT 3 (monoclonal antibody for T cell; Ortho Pharmaceutical Corp, New Jersey) (2-5 mg/day i.v. bolus) or azathioprine (1-2 mg/kg/day). Routine immunosuppression and anti-rejection treatments were assessed for each patient. Treatment with 9-(1,3 dihydroxy-2 propoxymethyl) guanine (DHPG) (Syntex Research, Palo Alto, California) in a dose of 2.5 mg/kg q 8 hr for 10 days was given for CMV infection if the patient had CMV viremia and CMV related disease, such as interstitial pneumonia proven by lung biopsy.

The duration of hospitalization was determined for each patient following OLT.

Results

Forty-one percent of all patients (nine of 22; group 1) developed positive cultures (urine, blood, throat) 14 to 51 days (mean 22 days) following OLT. The number of patients in the infected and non-infected groups, and age and sex distributions are given in Table I. Three patients (13.5 %) in group 1 a (symptomatic group), also had a poor response to treatment during rejection episodes, and developed interstital pneumonitis 12 to 48 days after transplantation. One had an unexplained maculopapular skin rash. CMV specific inclusion bodies were found

TABLE I: Patient Profile

	Group 1 CMV infected	Group 2 Non-infected
Number	9	13
Age-mean (SD)	3.0 ±3.3	6 ±5.4
Sex-male/female	4/5	5/8

in the lung and liver biopsies of two cases. All the patients had fever (38-39 °C) with each rejection episode without positive cultures for infectious agents other than CMV. One patient developed gastrointestinal bleeding and became septic due to *E. coli and Pseudomonas*. She died four months after OLT, secondary to sepsis, gastric perforation and bleeding, and liver dysfunction. She had not received any anti-CMV treatment. The other two patients were treated with DHPG successfully for 10 days and steroid boluses were discontinued. Based on therapeutic blood levels, the oral cyclosporine dosage was 20-30 mg/kg/day and oral prednisone 1-2 mg/kg/day. In these patients clinical signs of pneumonia and skin rash improved markedly, and serum transaminase and bilirubin levels dropped to normal in 10 ten days, without additional immunosuppressive medication.

Six patients (group 1b; asymptomatic group) were found to have positive cultures from one or more sites. In four patients, the blood and saliva cultures were positive, whilst urine cultures were positive in all six patients. They did not develop CMV-related pneumonia, and neither was CMV detected in the liver tissue by culture or immunoperoxidase methods. All patients in group 1 had elevated complement-fixing antibody (CF) titers for CMV. Following DHPG treatment, two patients developed markedly higher titers than the pre-treatment levels.

Thirteen patients (group 2) did not have positive cultures for CMV. Laboratory data including culture and serology results, and mean values of liver function tests obtained during rejection episodes are given in Tables II and III. Group 1 patients received 59 ± 35 units of blood or blood products as compared with 25 ± 12 units in group 2 patients; these products were not tested for CMV.

TABLE II: Laboratory Data of Post-OLT Patients

	CMV infected		Non-infected
	Symptomatic	Asymptomatic	
	n:3	n:6	n:13
Cultures*	3	6	0
CF G* Pre-transplant	2	1	2
Post-transplant	3	6	3
IgM*	3	2	0

* No. of positive

TABLE III: Laboratory Data of Post-OLT Patients During Rejection Episodes*

	CMV infected		Non-infected
	Symptomatic	Asymptomatic	
	n:3	n:6	n:13
WBC (X 1000/mm^3)	11.3 ± 5.4	9.2 ± 3.9	14.4 ± 7.4
Serum albumin (g/dl)	3.0 ± 0.6	3.2 ± 0.3	3.5 ± 0.3
SGOT (1 U/L)	390 ±402	336 ±496	204 ±125
SGPT (1 U/L)	409 ±254	383 ±496	354 ±203
Total bilirubin (mg/dl)	4.4 ± 3.3	5.9 ± 5.2	4.2 ± 3.8
Conjugated bilirubin (mg/dl)	3.3 ± 2.9	4.8 ± 4.1	3.6 ± 3.1

* (mean SD)

Rejection episodes occurred in group 1a earlier, and more frequently, than in groups 1b and 2. CMV culture negative patients (group 2) received fewer steroid boluses as well as azathioprine and OKT 3. The data showing the number and onset of the rejection episodes, and the immunosuppressive therapy given for each patient in each group is shown in Table IV.

Clinical presentation of rejection episodes were similar in the three groups. All had fever, fatigue, right upper quadrant tenderness or hepatomegaly. In both groups 1b and 2 steroid boluses or OKT 3 relieved discomfort and fever, but in two patients in group 1, fever was elevated immediately following treatment.

Three types of rejection were found biochemically: 1) both transaminase and bilirubin levels elevated, 2) transaminase levels elevated predominantly, 3) bilirubin levels elevated predominantly. The patients with CMV in the liver mostly showed a Type I rejection pattern.

TABLE IV: Clinical Characteristics of Post-OLT Patients

	Group 1 CMV infected		Group 2 Non-infected
	Symptomatic	Asymptomatic	
	n:3	n:6	n:13
Onset of rejection episodes* (day)	5 ±1.0	7.5 ±2.0	8.5 ±5.0
No. of rejection episodes*	6.3 ±0.6	3.7 ±3.0	3.4 ±2.0
No. of steroid pulses*	5.7 ±0.5	3.5 ±3.0	3.3 ±2.0
No. of OKT 3 treated patients	3	2	4
No. of azathioprine treated patients	3	1	3

* mean (SD)

The liver biopsy findings given in Table V were not diagnostic for CMV in any of the groups unless CMV specific inclusion bodies were detected by immunoperoxidase. Intraparenchymal PMN clusters without surrounding inclusion bodies were found in one case from group 1, which is not typically seen in rejection. Hospitalization was longer in groups 1a and 1b than in group 2 (105 days; 57 days; 33 days, respectively).

TABLE V: Histologic Features of Liver Biopsies of Post-OLT Patients

	Group 1 CMV infected		Group 2 Non-infected
	Symptomatic	Asymptomatic	
	n:3	n:6	n:13
Portal infiltration	3	6	13
Cholestasis	3	6	6
Bile duct proliferation	–	1	2
Hepatocellular degeneration	3	2	1
Parenchymal mononuclear infiltration	1	2	1
Intraparenchymal polymorphonuclear leukocyte infiltration clusters	2	–	1
Inclusion bodies	2	–	–
Peroxidase staining	3	–	–

Discussion

The frequency of CMV infection following kidney transplantation has been reported to be up to 60 percent[9]. Comparable data for liver transplantation was not available until recently. Three centers, including our own, have recognized this complication, with one third of the patients infected. However, serious life-threatening infection is seen in 10-15 percent of patients[1-3].

The differentiation of liver rejection from CMV infection is very difficult because both conditions have similar symptoms and laboratory abnormalities. Since all OLT patients receive immunosuppressive medication to prevent rejection, they are more susceptible to acquire or reactivate CMV infection. Failure to correctly diagnose CMV infection may result in incorrect use of more immunosuppressive therapy which may result in complicated disseminated CMV infection and/or death.

Although there was no statistically significant difference in age between the infected and non-infected groups, the latter appeared older. This could be explained by the presence of protective antibodies for CMV from previous CMV infections in the older group. However, this condition may be a risk factor if the patient has been carrying the virus because of the possibility of reactivation of infection due to immunosuppression in the post-OLT period.

The level of immunosuppression was markedly higher in the patients who became infected with CMV. Although all transplant patients received cyclosporine, which acts on T cells and may promote CMV infection, group 1a also received a great number of methylprednisolone pulses and/or monoclonal antibody. The latter is recognized to promote CMV infection in transplant patients by increasing immunosuppression. In this study there was a correlation between the degree of immunosuppression and CMV infection. Another characteristic of those with CMV infection was the use of a fourth immunosuppressive agent, azathioprine. Although none of our patients had a positive culture for CMV prior to transplantation, two patients in group 1a had positive CMV specific CF titers, and were transfused with multiple units of blood and blood products, which are potential sources of CMV[10-12]. In our program, these products were not routinely tested for CMV.

In a comparable situation seen in renal transplantation, CMV infection is most often caused by a virus transferred by a transplanted kidney from a CMV antibody positive donor[13]. Knowing the donor's CMV status is important in order to predict the possibility of this complication.

Serologic tests can be useful in the diagnosis of CMV. Complement-fixing antibodies are typically elevated in infected children. However, they do not discriminate between passively acquired immunity and active infection[14]. In an immunocompromised patient, the antibody response to CMV infection will be different[15]. Only one-third of renal transplant patients produce CMV specific IgM antibodies with recurrent infections which can be useful in diagnosing active infection[16,17]. In our series, steadily increasing CF titers and positive IgM antibodies were found in all symptomatic patients with CMV disease; CF titers rose markedly following antiviral treatment with decreased immunosuppression. An accurate diagnosis of CMV in immunocompromised patients requires a combination of serologic markers and viral isolation[14,18].

During CMV infection, there are a wide range of histopathological changes which occur in the liver and are related to the immune status of the donor[8,15]. Although cytomegalic inclusion bodies were detected in two of our patents, who had clinical CMV disease, it was a late phenomenon[19,20]. The immune status of the patient, rapid degeneration of the hepatocytes, delayed diagnosis and sampling error in needle biopsies may be the factors explaining their absence[21]. CMV specific immunoperoxidase stain may be helpful in detecting CMV in tissues. Another specific diagnostic feature of a liver infected with CMV is granuloma-like clusters of polymorphonuclear leukocytes surrounding infected hepatocytes[19]. One of .our patients had such intraparenchymal PMN accumulation without inclusion body bearing cells. Although CMV has been reported as a cause of granulomatous hepatitis, none of our patients had this finding[15,22]. The

morphology of mild rejection episodes is no different from the changes observed in CMV infection, portal inflammation and cholestasis.

Clinical signs of rejection, fever, jaundice and fatigue, are indistinguishable from CMV infection. None of our infected patients developed retinitis but three of them had interstitial pneumonia which is common in serious CMV infection.

Laboratory manifestations of rejection episodes are similar to those of CMV hepatitis. Both conditions may cause elevated transaminase and bilirubin levels. In our CMV infected patients, who had CMV-related disease, the rejection reaction was different from the non-infected group. There was an abrupt elevation of transaminase and bilirubin levels with rejection that could be attributed to CMV. Several drugs and medical agents such as acyclovir, DHPG, hyperimmunoglobulin, and immunization have been used for treatment of CMV infection[23,24]. On the other hand, anti-rejection treatment affects the immune system and increases the possibility of exacerbation of the latent infection in those who carry the virus. When a patient has an active CMV infection, immunosuppressive treatment should be reduced, and administration of anti-viral drugs should be started to enable the patient to overcome the infection.

It is essential to know the status of the donor and monitor the recipient during pre-and post-transplant periods in order to decrease complications of immunosuppressive treatment. The ability to distinguish between CMV infection and rejection early in their course is an important factor in starting appropriate treatment and preventing unnecessary complications and death.

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CLINICAL AND IMMUNOLOGICAL ASPECTS OF HYPER–IgM SYNDROME*

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Summary: Ersoy F, Sanal Ö, Tezcan İ. (Immunology Unit, Hacettepe University Institute of Child Health, Ankara, Turkey). Clinical and immunological aspects of hyper–IgM syndrome. Turk J Pediatr 32: 13-20, 1990.

Eight patients with Hyper–IgM syndrome were subjected to clinical and immunological evaluation. There were seven males and one female. All the patients had recurrent pyogenic infections; one had lymphoid hyperplasia with centrally necrotic granulomas, and one had gingivitis with neutropenia. Isohemagglutinin titers were either high or normal in all the patients and five had group 0 blood. The percentage of IgM-bearing cells were normal in five patients. The percentage of T cells were normal in all the patients, helper T cells were decreased in two patients, and suppressor T cells were increased in four patients. These results suggest that at least in some patients, the imbalances of T cell subsets may play a role in the pathogenesis of the disease rather than it being attributed to an intrinsic B cell defect. *Key words: immunodeficiency, Hyper-IgM, lymphocyte subpopulations.*

Immunodeficiency with hyperimmunoglobulinemia M (hyper–IgM) is a dysgammaglobulinemia which was first described by Rosen et al[1] in 1961, and is recognized by the World Health Organization to be one of the primary immunodeficiency syndromes[2]. This syndrome is characterized by very low or absent serum IgG and IgA levels and normal or more frequently elevated IgM concentration. The clinical manifestations of this disorder are usually similar to those of agammaglobulinemia, with frequent infections and increased risk of neoplasms at an early age[1-7]. Recurrent neutropenia, hemolytic anemia or aplastic anemia have been reported in some patients[8]. Although the disorder has been reported to occur mostly in males, and inherited in an X–linked fashion, both autosomal dominant and recessive forms, a form following congenital rubella, and acquired forms have also been described[3-9]. The immunopathogenetic mecha-

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nisms of this syndrome appear to be varied. Excessive suppressor T cell activity, abnormal B cell differentiation[5,10], lack of helper T cells[11], and failure to switch from IgM to IgG[6,12,13] have been shown in various studies. In this report, we describe the clinical and immunological data of eight patients with Hyper–IgM syndrome.

Material and Methods

The clinical diagnosis of patients was based on the history of recurrent infections, the pattern of immunodeficiency with low IgG, and IgA, normal or elevated IgM in the serum, and the presence of isohemagglutinins which conformed with the criteria of the World Health Organization for immunodeficiency and Hyper–IgM[2].

Skin tests: delayed hypersensitivity reaction in vivo was evaluated by skin reactivity to several antigens: Candida (prepared at 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) 3 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 described by Jondal et al[14]. In vitro blastogenic response was performed according to a previously published method[15].

Serum immunoglobulins (IgG, IgM, IgA) were determined by using the Behring–Werke immunodiffusion plates.

B lymphocytes bearing membrane Ig (Smig) were identified by direct immunofluorescence using commercial antisera against Ig isotypes (polyvalent, IgG, IgM, IgA; Behring–Werke Inst)[16].

Evaluation of T lymphocyte subsets: Pan T ($CD3^+$) cells, helper T ($BD4^+$) cells and suppressor T ($CD8^+$) cells were examined by monoclonal antibodies (OKT 3, OKT 4, OKT 8; Behring–Werke Inst) according to the standard technique[17].

İsohemagglutinins were determined using standard methods.

Results

Clinical findings of the patients with Hyper–IgM syndrome are shown in Table I. Only one out of eight patients was a girl (RS), whose family history did not suggest any immunodeficiency diseases. She had pneumonia at six months of age followed by recurrent infections and chronic suppurative otitis. She had developed bronchiectasia. There were no signs of congenital rubella. The parents were first cousins and healthy. She had a healthy brother.

Two of our patients were siblings (ER, EK) from one family and three were siblings (OF, AF, FF) from another family. The parents in each family were unrelated. While a pattern of X–linked inheritance was determined in six patients (three families), there was no evidence of familial occurrence in two (Table I). Five

TABLE I: Characteristics of Patients With Hyper–IgM Syndrome

Family No	Patient No	Name	Age/Sex (yrs)	Consanguinity of Parents	Familial Occurrence	Clinical Findings
1	1	RS	4.5/F	First cousins	–	Growth retardation, chronic otits recurrent pneumonia, bronchiectasia
2	2	DH	4/M	First cousins	+	Growth retardation, chronic diarrhea, chronic otitis
3	3	EK	12/M	–	+	Recurrent pneumonia, cervical and mediastinal lymphadenopathy
3	4	EK	14/M	–	+	Sinopulmonary infections
4	5	OF	4/M	–	+	Gingivitis, aphthous stomatitis, growth retardation, neutropenia
4	6	AF	6 mo/M	–	+	Chronic diarrhea, malnutrition, bronchopneumonia, hepatomegaly,
4	7	FF	10 mo/M	–	+	Diarrhea
5	8	HK	8/ mo/M	First cousins	–	Malnutrition, sinopulmonary infection

patients had recurrent respiratory infections, two had chronic suppurative otitis, two developed hepatomegaly, and one had aphthous stomatitis with neutropenia prior to gammaglobulin therapy (OF). One patient (EK) was admitted to our hospital presenting with fever, dyspnea, and bilateral neck and mediastinal masses. The lymph node biopsy from the supraclavicular region revealed centrally necrotic granulomas. There were lymphocytes and neutrophils in the centers. Scattered follicles and plasma cells were also noted. These enlarged lymph nodes disappeared after the beginning of gammaglobulin therapy.

One of the patients (AF), who had hepatomegaly and icterus, died at home. His brother (OF) developed malabsorption due to intractable giardiasis and hepatomegaly at six years of age. There are also twin siblings in this family, a boy and a girl. The male twin was diagnosed as having Hyper-IgM syndrome at 10 months of age. The girl is healthy.

Immunological findings of the patients are shown in Table II. Total lymphocyte counts of all the patients were within normal limits. Only one patient (OF) had neutropenia. The percentages of E-rosette forming cells were found to be within normal limits in all patients. Delayed hypersensitivity skin tests were negative and the in vitro PHA response was low in three patients.

TABLE II: Immunological Findings of the Patients With Hyper-IgM Syndrome

No	Patient	Total lymphocyte count/ mm^3	Skin Tests	E-rosettes (%)	In vitro PHA response	Immunoglobulins (mg/dl) Serum IgG	IgM	IgA	Blood group	Isohemagglutinins
1	RS	2600	–	64	Low	22	290	0	B	Anti A:1/32
2	DH	4800	–	59	Low	160	392	0	Nd	
3	EK	2600	+	65	Normal	22	345	0	0	Anti A:1/156 Anti B:1/512
EK	EK	6000	+	71	Normal	22	483	0	A	Anti B:1/256
5	OF	7200	+	69	Normal	120	215	0	0	Anti A:1/512 Anti B:1/64
6	AF	4000	–	66	Low	102	58	0	0	Anti A:1/4 Anti B:1/2
7	FF	7200	+	68	Nd	103	59	0	0	Anti A:1/64 Anti B:1/32
8	HK	6160	+	64	Nd	55	483	0	0	Anti A:1/128 Anti B:1/512

Nd: not done.

The serum IgG and IgA levels were either very low or absent in all the patients. The IgM levels were found to be increased in six patients and within normal limits in two.

Isohemagglutinin titers were either normal or increased in all the patients; five patients had blood group 0.

Subpopulations of T cells and surface immunoglobulin bearing B cells were studied in seven of the patients and the results are shown in Table III. The percentage of $CD3^+$ cells (pan T cells) was found to be within normal limits in all patients. $CD4^+$ cell (helper T cells) percentages were below two standard deviations of normal values in two patients (DH, EK). There was a slight increase in the percentages of $CD8^+$ (suppressor T cells) in four patients (DH, EK, EK, HK), and the $CD4^+$ / $CD8^+$ cell ratio was found to be reversed in two (DH, EK). While the percentages of total immunoglobulin and IgM bearing cells were normal, IgG and IgA bearing cells were either absent or low in all the patients studied.

TABLE III: Lymphocyte Subpopulations of the Patients With Hyper–IgM Syndrome (%)

No.	Patient	$CD3^+$	$CD4^+$	$CD8^+$	CD4/CD8 Ratio	Polyvalent	$SigG^+$	$SigM^+$	$SigA^+$
1	RS	73	35	25	1.4	14	4	7	1
2	DH	78	27	41	0.7	15	0	8	0
3	EK	69	37	38	1	17	0	11	0
4	EK	64	31	42	0.7	22	Nd	Nd	Nd
5	OF	75	52	18	2.9	19	1	10	1
6	AF	63	38	32	1.2	26	Nd	Nd	Nd
7	FF	Nd	Nd	Nd	Nd	Nd	Nd	Nd	Nd
8	HK	82	40	40	1	8	1	8	1
Normal values		66.9±13.3	45.6±5.2	27±6.9	1.8±0.5	22.2±5	9.1±3.6	8.2±4.2	4.5±3.1

Discussion

A variety of clinical features have been described in Hyper–IgM syndrome; the most consistent being recurrent pyogenic infections. Although the initial description of this disorder reported a pattern of X–linked inheritance, other genetic and nongenetic forms have been described[3-9]. Our study population consisted of eight patients from five families. There were seven males and only one female. Six of the eight patients exhibited X–linked inheritance. In three out of five families the parents were first–degree relatives. All our patients had recurrent pyogenic infections including otitis media, bronchopneumonia, and chronic diarrhea, usually beginning during the first year of life. Stomatitis and mouth ulcers

with neutropenia have been reported in some patients[4,8,18]. One of our patients (OF) had gingivitis and aphthous stomatitis with neutropenia which disappeared after intramuscular gammaglobulin therapy.

Marked enlargement of the tonsils, cervical lymph nodes, spleen and liver are common manifestations of this syndrome. The presence of lymphoid hyperplasia in this condition often diverts the physician from a diagnosis of immunodeficiency[2,18,19]. One patient (EK) was admitted to our hospital with dyspnea caused by cervical and mediastinal masses. Histopathology of the lymph node biopsy revealed centrally necrotic granulomas. Goldstein et al[7] have reported a patient with the acquired form of Hyper–IgM syndrome who presented striking cervical lymphadenopathy which contained necrotizing granulomas. They suggested that this histopathologic picture may represent either an unusual inflammatory response in a patient with impaired humoral immunity or may be secondary to some unknown agent capable of impairing the patient's humoral immune system and affecting the reticuloendothelial system in such a way as to stimulate production of nonspecific necrotizing granulomas. Since our patient had the X–linked form of Hyper–IgM syndrome, lymphoid hyperplasia containing necrotizing granulomas was suggested to be secondary to the humoral immunodeficiency disease.

Hyper–IgM syndrome is characterized by elevated or normal serum IgM levels and very low or undetectable quantities of IgG and IgA. Although thymic dependent lymphoid tissues, T cell subpopulations and their functions are usually normal in most of the patients. Some impairment of cellular immunity as shown by abnormal results in skin tests, in the in vitro blastogenic response to PHA, increased T cell suppression or lack of helper T cells have been reported[4,10,11,19,20]. The findings of this study reflect the heterogeneity in this respect. While total lymphocyte counts, percentages of E–rosette forming cells and $CD3^+$ cells were normal in all patients, skin tests were found to be negative and the in vitro PHA response was low in three patients. The percentage of helper T cells was low in two patients, and suppressor T cells were increased in four. The helper/suppressor T cell ratio was found to be low in four of seven patients and reversed in two. Although most of the previous studies in patients with this syndrome have suggested that the defect is intrinsic to the B cell, the imbalances of T cell subsets detected in the present study may play a role in the pathogenesis of the disease. In fact, Mayer et al[13] described a type of T cell, derived from a patient with a Sezary–like syndrome which can induce IgG and IgA secretion in B cells from patients with Hyper–IgM syndrome regardless of the pattern of inheritance or acquisition. This data has suggested that the defect, at least in some patients with this syndrome, may be exogenous to the B cell and may reflect a defect in switch T cells.

The total number of immunoglobulin bearing cells and IgM bearing cells was found to be normal in our study and conformed with the findings of previous studies[5,12,19].

Five out of seven patients were blood group 0 and all the patients had normal levels of isohemagglutinins. Similarly, since most of the cases reported previously have been blood group 0 and positive for isohemagglutinins A and B of the IgM type, investigators have suggested that this disorder might be genetically linked to the 0 blood group[4].

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GAMMA–GLUTAMYL TRANSFERASE IN NEONATAL NON–HEMOLYTIC INDIRECT HYPERBILIRUBINEMIA*

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Summary: Yurdakök M, Yılmazoğlu G. (Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Gamma-glutamyl transferase in neonatal non-hemolytic indirect hyperbilirubinemia. Turk J Pediatr 32: 21-23, 1990.

Serum gamma-glutamyl transferase (GGT) activities were determined on the third day of life in healthy controls (n:15) and in infants with non-hemolytic hyperbilirubinemia (n:16). GGT activities were 39.6±28.4 units/ml and 46.6±26.7 units/ml, respectively. There was no statistical difference between both groups (p>0.05).

Key words: gamma glutamyl transferase, newborn, hyperbilirubinemia, serum.

Gamma-glutamyl transferase (GGT) is a peptidase transfer enzyme that hydrolyzes gamma-glutamyl amides and peptides, and catalyzes the transfer of gamma-glutamyl groups to other peptides and amino acids. It is present in many mammalian tissues and body fluids, and has been shown to be a sensitive enzyme in various conditions, especially in obstructive and infiltrative hepatic disorders[1-5]. It has been reported that serum GGT activities are high in neonatal jaundice[6]. Thus, we decided to study GGT activity in newborns with non-hemolytic hyperbilirubinemia in order to determine whether this enzyme activity is a valuable indicator of the development of hyperbilirubinemia.

Material and Methods

Thirty-one infants admitted to the Hacettepe University Children's Hospital comprised the study. The infants were either born in our hospital or transferred from other hospitals. Their gestational ages were more than 37 weeks. They were all in good health except for the infants with non-hemolytic hyperbilirubinemia, who were selected as subjects for the study group. Gestational ages were determined from the mothers'menstrual histories, and neonatal assessment by

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external and neurological criteria. The infants in the study group did not require exchange transfusion. Their mean peak serum indirect bilirubin levels were 14.9±3.3 mg/dl.

Blood samples were drawn from a peripheral vein of each infant on the third day of life and collected in tubes. The serum was immediately separated by centrifugation at 2000 rpm for five minutes. The samples for GGT assays were stored at-18°C for not more than seven days. Gamma-glutamyl transferase activities were determined by the method described by Naftalin et al[7] (Procedure 545) using Sigma Diagnostics (Sigma Chemical Co., St. Louis, Mo 63178 USA). The results were expressed as the mean ± standard deviation and Student's *t* test was used for comparisons.

Results

There were eight males in the control group (n:15) and nine in the study group (n:16). The rest were females. Their birth weights were 3223±603 g and 3195±578 g, respectively ($p>0.05$).

GGT activities were recorded as 39.6±28.4 units/ml in the control group and 46.6±26.7 units/ml in the study group. There was no statistical difference between the two groups ($p>0.05$).

Discussion

Gamma–glutamyl transferase is one of the key enzymes in the gamma-glutamyl cycle. Its primary catalytic functions appear to be the cleavage of glutathione into glutamic acid and cysteinlyglycine and, acting as a transpeptidase, catalyzes the transfer of gamma-glutamyl groups to other peptides and amino acids. The amino acids so formed enter the amino acid pool of the cell for reutilization. Reduced glutathione is reformed in the gamma-glutamyl cycle, and acts as a co-enzyme in several intra-cellular enzymatic reactions[1-5].

Gamma-glutamyl transferase is found mainly in the membranes of cells that show high secretory or absorptive capacity: the epithelial cells lining the biliary tract, hepatic canaliculi, proximal renal tubules, pancreatic acinar tissue, pancreatic ductules, intestinal brush border cells. The liver is the source of most GGT activity in serum. The kidney, pancreas, and intestines contribute little to the normal activity in serum. Gamma-glutamyl transferase is cleared by the liver and excreted in the bile; a small amount is catabolized by the kidneys[1-5].

Measurement of GGT in serum is an extremely sensitive test for disorders that affect the excretory capacity of the structural integrity of the liver. It has also been demonstrated that membrane-bound GGT is induced in the liver during cholesta-

sis, and the fact that various drugs increase the GGT content of hepatocytes by this mechanism is probably the reason for microsomal induction of GGT synthesis. Persistent cholestasis caused primarily by biliary cirrhosis or other liver diseases, kidney, lung, pancreatic, and myocardial disorders, hyperlipidemia, malignancies, diabetes mellitus, hyperthyroidism, rheumatoid arthritis and also various drugs, can produce an enormous increase in serum GGT[1-5].

Although it has been reported that there is a significant correlation between serum GGT activity and bilirubin levels in neonatal indirect hyperbilirubinemia and that elevated GGT levels in the neonate may show hepatic microsomal damage with subsequent impairment of bilirubin conjugation[6], we did not find any increase in GGT activities in the newborns with non-hemolytic anemia.Increased GGT activities may play an important role, however, in the other causes of hyperbilirubinemia.

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PERCUTANEOUS TRANSLUMINAL BALLOON PULMONARY VALVULOPLASTY : IMMEDIATE AND MEDIUM-TERM RESULTS*

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Summary: Özme Ş, Çeliker A, Özkutlu S, Özer S, Baysal K. (Pediatric Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Percutaneous transluminal balloon pulmonary valvuloplasty: immediate and medium-term results. Turk J Pediatr 32: 25-31, 1990.

Ten patients with pulmonary stenosis, (six males and four females) whose ages ranged between five and ten years (mean age 7 years) underwent cardiac catheterization and balloon valvuloplasty. Right ventricular systolic pressure before valvuloplasty ranged from 90 to 200 mm Hg (mean 133.5±33.3 mm Hg). It fell to 50-90 mm Hg (mean 64.5±13.8 mm Hg) immediately after the procedure. The peak systolic gradient across the pulmonary valve before valvuloplasty ranged from 70 to 180 mm Hg (mean 114.5±35.4 mm Hg) and decreased significantly to 30-70 mm Hg (mean 43.0±13.8 mm Hg) immediately after dilation. Doppler echo studies confirmed these results. At repeat cardiac catheterization in three patients, five to 15 months after valvuloplasty, restenosis was noted in one patient while there was no change in the others. All patients had been followed up by Doppler echocardiography. Patients with isolated valvular pulmonary stenosis can be adequately and safely treated with balloon valvuloplasty which results in excellent immediate and medium-term results. *Key words: balloon valvuloplasty, pulmonary valvular stenosis, children, immediate and medium-term results.*

Percutaneous transluminal balloon pulmonary valvuloplasty is widely used for the treatment of moderate to severe pulmonary valvular stenosis in children[1-3]. This invasive method, which was found to be effective by long-term follow-up studies,

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has a very low complication rate[2,3] and is now used for palliative therapy of congenital cyanotic heart disease with pulmonary valvular stenosis[4].

In this article, we report our experience in treating ten cases with pulmonary stenosis by using balloon valvuloplasty. We comment particularly on the effectiveness of this method, and we review the related literature.

Material and Methods

During an 18 month period, ending in October 1988, ten patients aged between five and 15 years (mean age 7.0±3.7 years) underwent therapeutic percutaneous balloon pulmonary valvuloplasty in the Pediatric Cardiology Unit of Hacettepe University Children's Hospital. The patients were diagnosed by physical examination, electrocardiography and telecardiography. Pulmonary valvular stenosis was evaluated by Doppler echocardiography and finally cardiac catheterization and angiography. Continuous wave Doppler flow velocity recordings from the right ventricular outflow tract and main pulmonary artery were obtained as previously described. The systolic peak flow velocity from three consecutive beats were measured and averaged. A Doppler estimate of the transvalvar gradient was calculated by using the modified Bernoulli equation[1]. The diameter of the pulmonary annulus was measured by two - dimensional echocardiography. The patients, who had a 60 mm Hg or higher transvalvar gradient, underwent cardiac catheterization. Trefoil balloon catheters were used for the pulmonary valvuloplasty. The size of the catheter depended on the size of the pulmonary valve annulus which was measured on the angiogram. This technique is similar to that used by other investigators[2,3].

The patients were followed up by Doppler echocardiography. Three patients underwent a second cardiac catheterization at five to 18 month (mean 13.0±6.8 months) intervals following balloon valvuloplasty. Student's *t* test was used to compare data obtained prior to and following balloon valvuloplasty. The level of statistical significance was set at $p<0.05$.

Results

Nine patients showed good results following balloon valvuloplasty (Fig. 1). The peak systolic gradient across the pulmonary valve before valvuloplasty ranged between 70 – 180 mm Hg (mean 11.4±35.4 mm Hg) and decreased significantly to between 30 and 70 mm Hg (mean 43±13.8 mm Hg) immediately after dilation ($p<0.001$). Right ventricular peak systolic pressure before valvuloplasty ranged between 90 and 200 mm Hg (mean 133.5±33.3 mm Hg) and this value fell to 50 – 90 mm Hg (mean 64.5±13.8 mm Hg) immediately after the procedure ($p<0.001$; Table I).

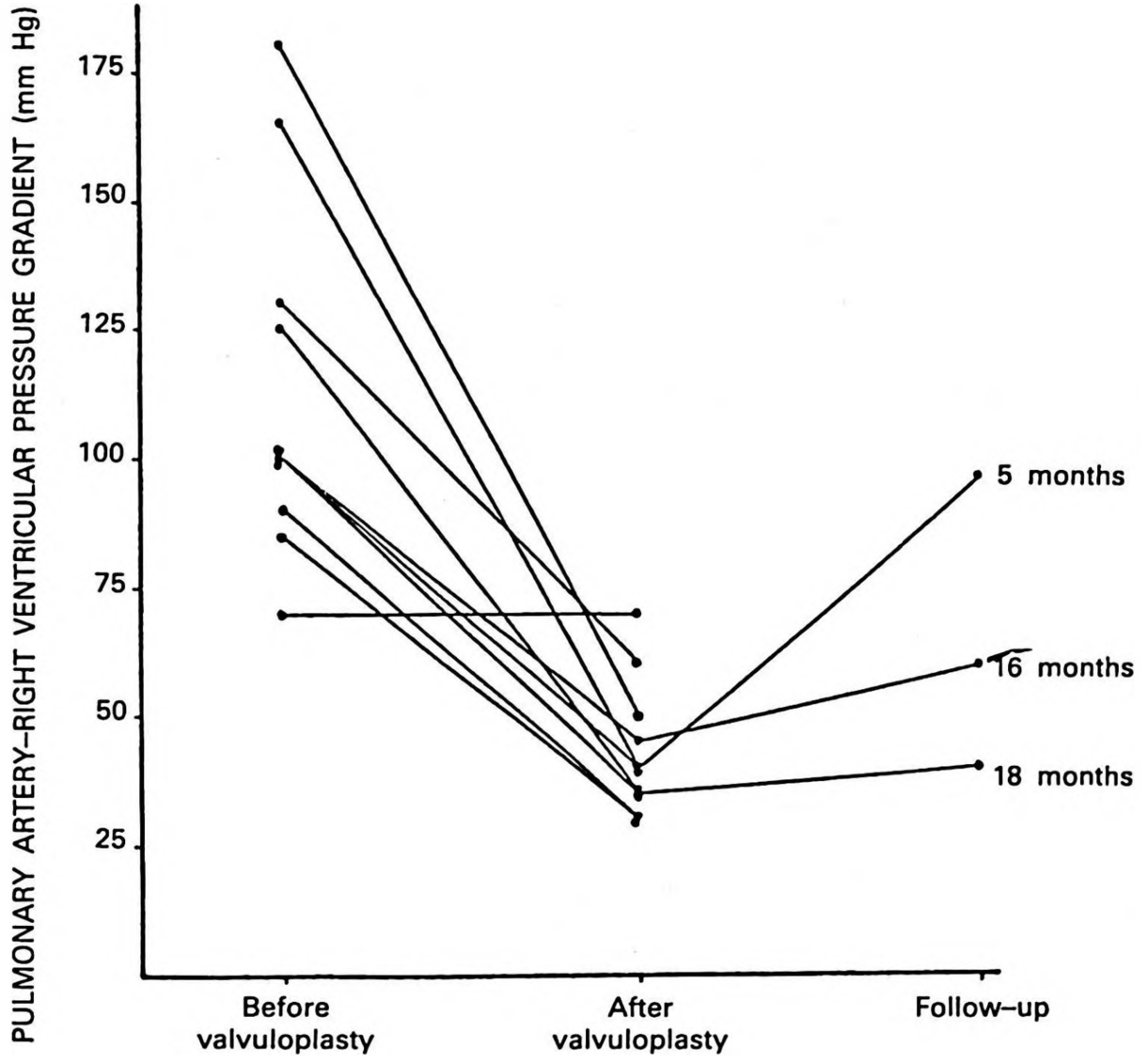

Fig. 1: Pulmonary valve peak systolic pressure gradients in ten patients with catheterization data. Note the fall in the gradient immediately after dilation. In one patient, the gradient remained unchanged. In the repeat study, the gradient increased and restenosis developed in one patient.

TABLE I: Balloon Pulmonary Valvuloplasty-Hemodynamic Data

		Before Valvuloplasty	After Valvuloplasty	
Right ventricular peak systolic pressure (mm Hg)	Range	90 – 200	55 – 90	$p < 0.001$
	mean ± SD	133.5 ± 33.3	64.5 ± 13.8	
Pulmonary artery right ventricular pressure gradient (mm Hg)	Range	70 – 180	30 – 70	$p < 0.001$
	mean ± SD	114.5 ± 35.4	43.0 ± 13.8	

In the subgroup of patients (three patients), in which long term catheterization (five to 18 months) follow – up data were available, one presented with restenosis (Fig. 1), and in the remaining two patients minimal changes were observed. Echo Doppler follow – up data were available in all patients. The duration of follow – up was three to 18 months (mean 7.0±5.2 months). Transvalvar gradients before valvuloplasty fell from 55 – 160 mm Hg (mean 97.3±37.21 mm Hg) to 30 – 51 mm Hg (mean 50.6±17.84 mm Hg) ($p<0.001$) (Fig. 2; Table II). Six patients with a long-term follow-up showed the same results after balloon valvuloplasty (Fig. 2).

Pulmonary insufficiency was detected in one patient by Doppler echocardiography while in the remaining patients there were no findings associated with this complication.

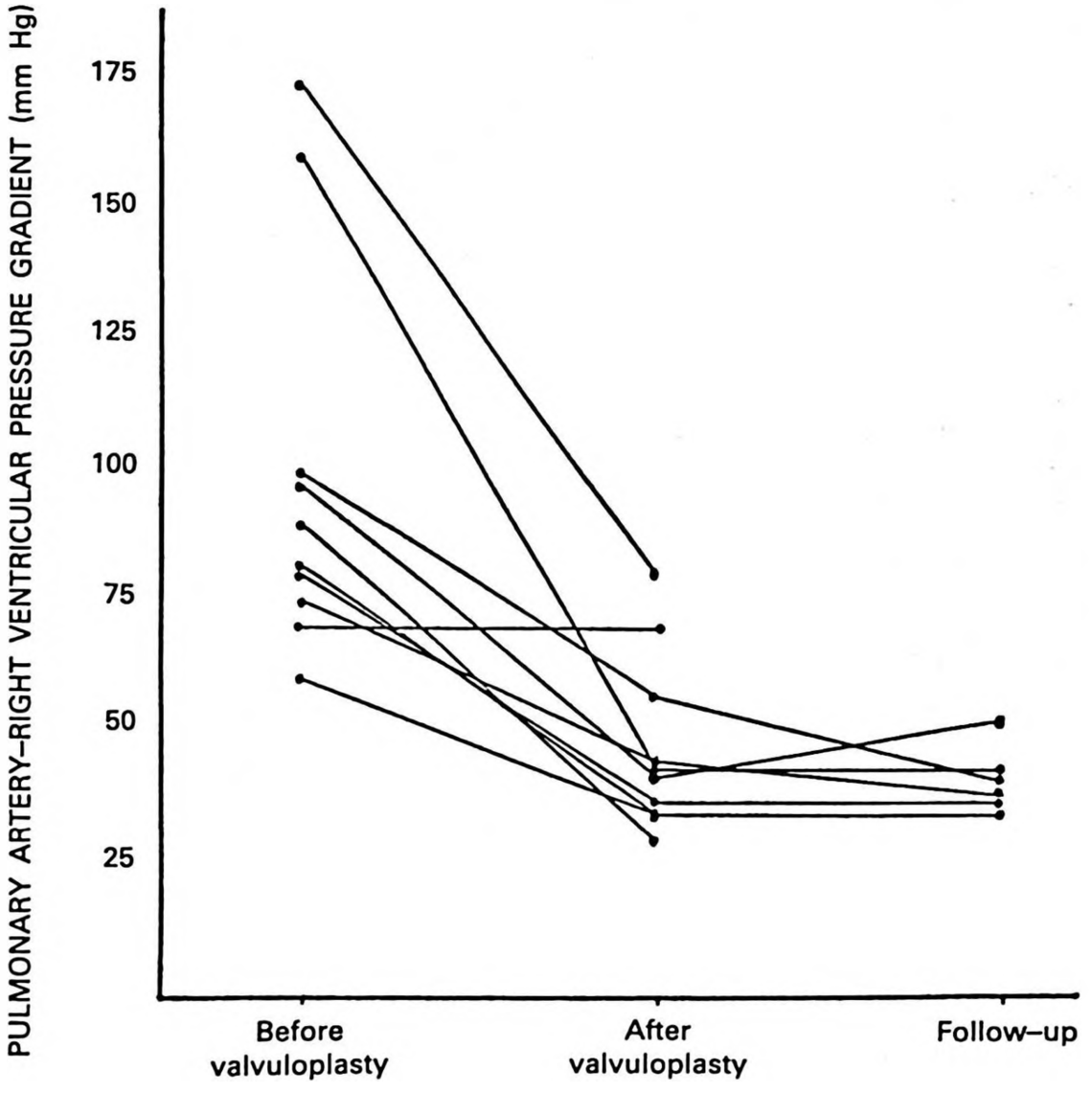

Fig. 2: Pulmonary artery-right ventricular pressure gradient before, immediately after, and at follow-up (six patients) following balloon dilatation. Doppler echocardiographic data.

TABLE II: Balloon Pulmonary Valvuloplasty: Doppler Echo Data

		Before Valvuloplasty	After Valvuloplasty	
Pulmonary artery right ventricular pressure gradient (mm Hg)	Range	55 – 160	30 – 81	
	mean ± SD	97.3 ± 37.21	50.6 ± 17.84	$p < 0.001$

Discussion

The degree of obstruction and right ventricular dysfunction represent the indications for surgical therapy in pulmonary valvular stenosis[1]. Since the mortality rate of 3 percent and the non-fatal complications rate of 12 percent are not low[1], less complicated techniques have been investigated. Kan et al[5] performed balloon valvuloplasty for the treatment of pulmonary valvular stenosis in 1985. This effective and safe technique has been employed in the Pediatric Cardiology Unit of Hacettepe University Children's Hospital since April 1987.

Ten patients with moderate to severe pulmonary valvular stenosis underwent balloon valvuloplasty in which immediate success was achieved in all but one patient who had infundibular stenosis. Balloon dilation with appropriate size balloons was attempted in this patient, but failed.

After balloon valvuloplasty, the patients were followed up by Doppler echocardiograpy and cardiac catheterization. In various studies restenosis has been detected in some patients[2,3,6,7]. These patients underwent repeat balloon dilation with a larger balloon, and successful results were obtained[2,3]. Infundibular stenosis can also be reduced to a lower degree by a repeated dilation[2]. Our three patients were followed up by cardiac catheterization; one of them had restenosis. This patient will undergo a repeat valvuloplasty.

Doppler echocardiography has been reported to be a simple and accurate non-invasive technique for quantitating the pressure gradient[8-11], and two-dimensional echocardiography has been used to evaluate the anatomical and functional status of the pulmonary valve after balloon dilation[7-9]. Kveselis et al[8] confirmed that after balloon valvuloplasty, Doppler echocardiographic studies produced results similar to cardiac catheterization.

Six patients were followed up with Doppler echocardiography at long-term intervals; the late results were consistent with the immediate results. We suggest that Doppler echocardiography be employed to follow-up patients who undergo balloon valvuloplasty.

Pulmonary insufficiency may be detected by physical examination and Doppler echocardiography[2,3,6,7]. Of a total 30 patients. Rao et al[2] reported pulmonary insufficiency in 12 patients clinically, and in 21 patients using Doppler echocardiography. Doppler evidence of pulmonary insufficiency was detected in one of our patients.

The balloon size is the most important factor in determining the success of valvuloplasty[1-3]. In their report, Rao et al[2] recommended that for effective valvuloplasty, the size of the balloon be from 1.2 to 1.4 times the pulmonary valve annulus. If restenosis is present, excellent results can be obtained by attempting a repeat dilation with a larger balloon[2]. Appropriate balloons were used for our patients, and the results were satisfactory. Infundibular stenosis and dysplastic pulmonary valves are usually the reasons for unsuccessful balloon valvuloplasty[2,6].

In conclusion, percutaneous balloon pulmonary valvuloplasty used in the treatment of moderate to severe pulmonary valvular stenosis is a very successful technique[2,3,7]. Long-term noninvasive studies, such as Doppler echocardiography seem to accurately detect hemodynamic improvement following balloon pulmonary valvuloplasty[2,8]. Despite these positive results, follow-up data taken over a much longer period (five to ten years) are necessary to further confirm the long-term effectiveness of balloon pulmonary valvuloplasty for relief of valvular pulmonary stenosis.

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ZINC AND COPPER IN CONGESTIVE HEART FAILURE*

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Summary: Atlıhan F, Söylemezoğlu T, Gökçe A, Güvendik G, Satıcı O. (Department of Pediatrics, Dicle University Faculty of Medicine, Diyarbakır, Turkey). Zinc and copper in congestive heart failure. Turk J Pediatr 32: 33-38, 1990.

In this study serum zinc (Zn) and copper (Cu) levels in children with congestive heart failure (CHF) were evaluated. The mean serum Zn levels of the patients with CHF were 92.9±18.9 μg/100 ml, and they showed a significant decrease when compared to controls ($p<0.05$). The mean serum Cu levels, which were 173.6±26.6 μg/100 ml, showed a significant increase when compared to controls ($p<0.001$). After digoxin therapy, a significant increase in Zn levels and a significant decrease in Cu levels were observed. *Key words: congestive heart failure, zinc, copper.*

Zinc (Zn) has a key role in many essential enzyme systems including carbonic anhydrase, alkaline phosphatase, carboxypeptidases and glutamic dehydrogenases. It is also essential in the metabolism of nucleic acid, in the synthesis of proteins and collagen, and is concentrated in cardiac tissue[1-3].

Like Zn, copper (Cu) is also an essential trace element. The role of Cu in maintaining collagen integrity is well established and deficiency of this metal has been shown to produce myocardial friability and necrosis. Copper is concentrated in ventricular muscular tissues. In the heart, the major Cu-containing enzyme is cytochrome oxidase[1,3].

In recent years, attention has been drawn towards such trace elements as Cu and Zn in the myocardium which are involved in the maintenance of myocardial integrity. The role of Cu and Zn in acute myocardial infarction in adults has been reported by many workers. In the pediatric age-group there are only a few investigations on the relation of these trace elements to myocardial ischemia and congestive heart failure[4]. The present study was therefore undertaken to explore the diagnostic and prognostic significance of serum Cu and Zn in congestive heart failure (CHF) of children

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Material and Methods

Twenty-nine cases of CHF admitted to the Pediatric Clinic of Dicle University Hospital constituted the material for the present study. Eleven healthy subjects matched according to age and sex served as controls.

The diagnosis of CHF was based on the physical examination. The patients had only received digoxin therapy for CHF. The doses were 0.06 mg/kg for patients under two years of age and 0.04 mg/kg for patients above two years of age. In each case blood was taken to determine the Zn and Cu levels and was kept in a polypropylene tube free of trace elements. After centrifugation the serum was kept at –5°C. In every patient two samples were obtained, one before the initiation of digoxin therapy and the other after the end of the therapy.

Serum Zn and Cu levels were measured by using the Atomic Absorption Method with the Varian Techtron Model 1300 spectrophotometer[1]. The results were expressed as the Mean ± Standard Deviation. Student's *t* test (dependent or independent) was used for statistical analysis[5].

Results

The ages of the patients with CHF ranged between one month and eleven years, with a mean age of 2.3±1.5 years. The ages of the controls were between three months and ten years, with a mean age of 3.1±2.8 years ($p>0.05$). Forty-one percent of the patients were girls and 59 percent were boys. Forty-five percent of the controls were girls and 55 percent were boys ($p>0.05$).

The cause of CHF was pneumonia in twenty patients; cardiomyopathy in three; rheumatic carditis in four, and pericarditis in two. The duration of therapy was between 5-12 days, with a mean 6.8±1.8 days.

The serum Zn and Cu levels of the patients with CHF were evaluated before and after therapy and were compared with the control group (Table I).

The mean serum Zn levels before therapy were 92.9±18.9 μg/100 ml, and they showed a significant decrease in the cases of CHF when compared to the

TABLE I: Serum Zn and Cu Levels* in Patients with CHF Before and After Therapy

Groups	n	Serum Zn** (μg/100 ml)	Serum (μg/100 ml)
t Control	11	107.5±15.7	113.9±16.2
I CHF before therapy	29	92.9±18.9**	173.6±26.6***
II CHF after therapy	29	107.4±17.2***	151.4±27.3***

* Mean±SD
Comparison with controls **$p<0.05$, ***$p<0.001$.

controls ($p<0.05$). After therapy, the mean serum Zn levels were 107.4±17.2 μg/100 ml. No statistically significant difference was observed when compared to the controls ($p>0.05$).

The serum Zn levels of the patients with cardiac failure showed a significant increase after therapy when compared to the levels before therapy ($p<0.001$; Figs. 1 and 2).

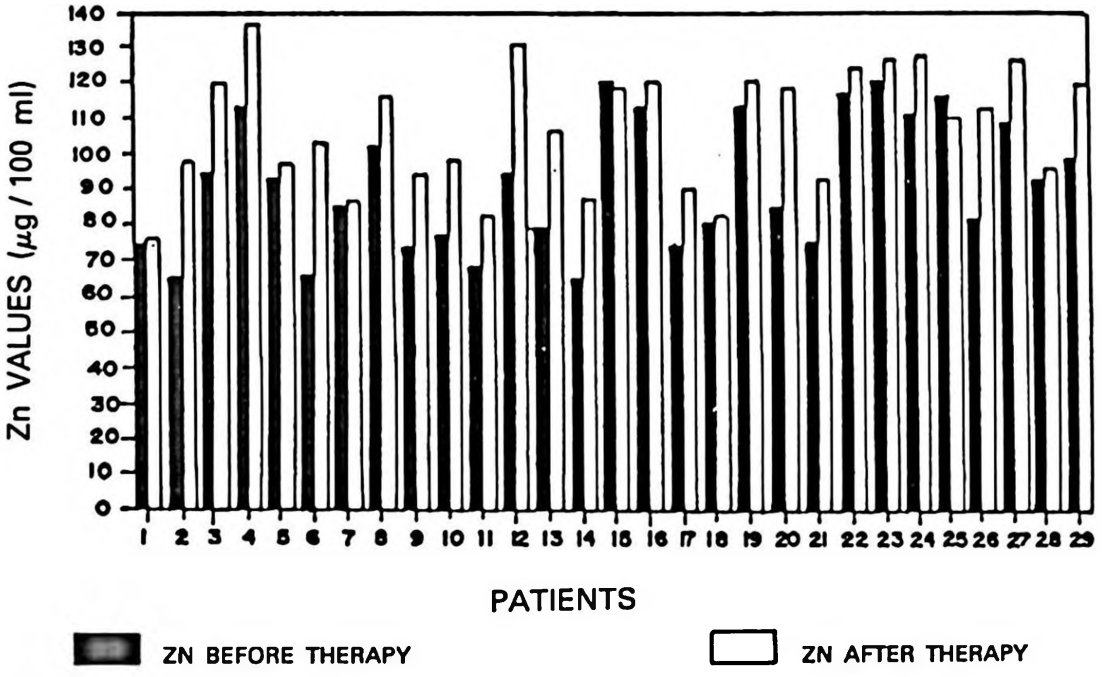

Fig. 1: Zn levels before and after therapy

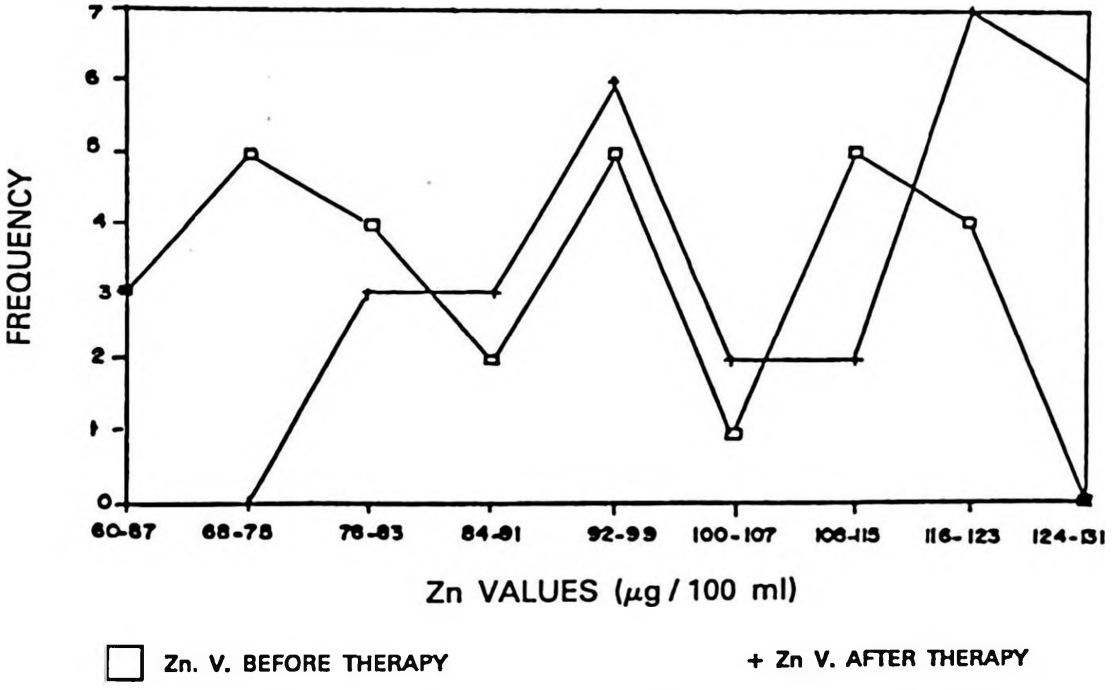

Fig. 2: Distribution of Zn levels before and after therapy

The mean serum Cu levels of the patients with CHF before digoxin therapy were 173.6±26.6 μg/100 ml. The mean serum Cu levels were significantly elevated when compared to the controls ($p<0.001$). After the therapy the mean serum Cu levels were 151.4±27.3 μg/100 ml. A significant difference was still present when compared to the controls ($p<0.001$). The serum Cu levels showed a significant decrease in the patients with CHF after therapy when compared to the levels before therapy ($p<0.001$). Copper levels before and after therapy, and the distribution of Cu levels are given in Figs. 3 and 4.

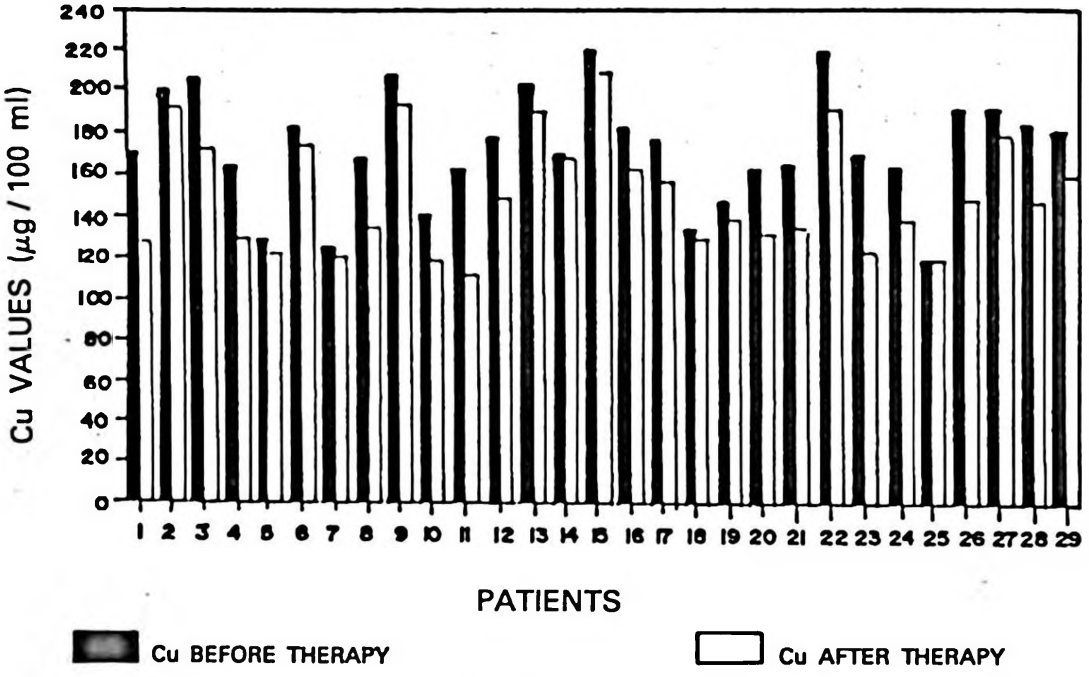

Fig. 3: Cu levels before and after therapy

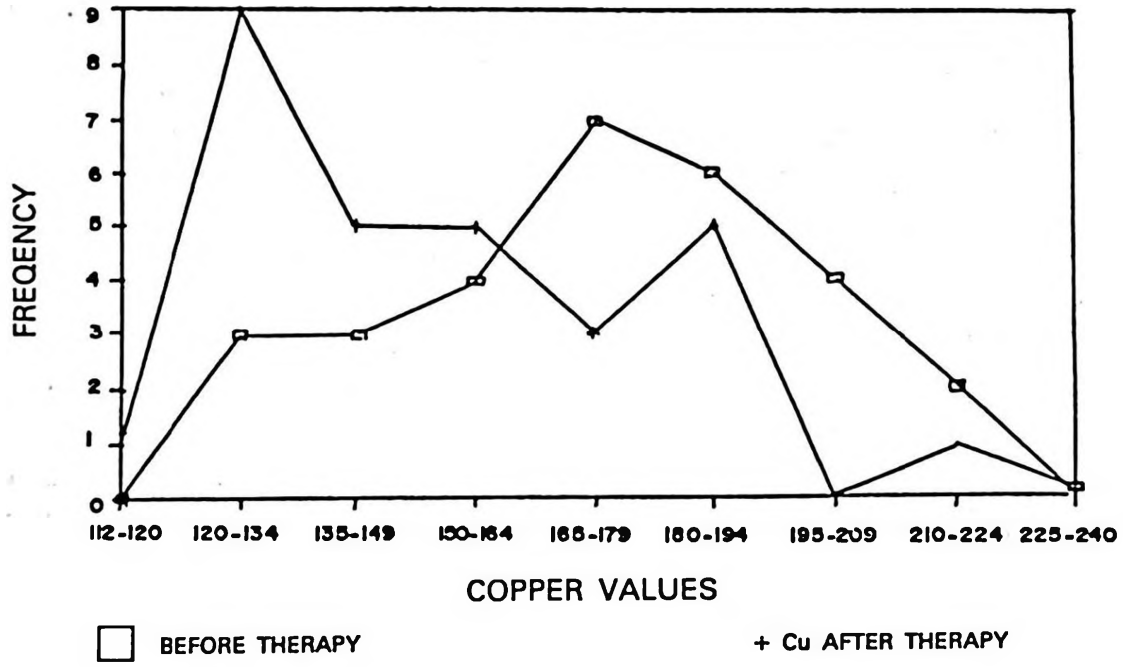

Fig. 4: Distribution of copper levels before and after therapy

Discussion

The role of Zn and Cu in enzymatic reactions has been examined critically as a potential key factor in cardiovascular diseases. In acute myocardial infarction decreased plasma Zn levels have been reported. In myocardial ischemia, however, slightly higher than usual serum Zn levels suggest that the net effect of cardiac ischemia is a release of Zn[1,3,6-9].

However, not much data is available regarding the relationship of Cu with cardiac disease. Elevated Cu levels have been reported in rheumatic heart diseases, CHF and atheriosclerotic heart diseases[1,6,7,10,11].

In the present study, we observed that serum Zn levels were significantly lower in CHF. The precise origin of the decrease in serum Zn concentration following CHF is not known. Hypoxic injury of myocardial tissue may increase the activity of leukocyte endogenous mediator (LEM) which mediates the hepatic uptake and sequestration of circulating Zn[1,3,12]. It is not known whether infectious or inflammatory stress precipitates a drop in circulating Zn levels. In CHF secondary to pneumonia, the reason for the decrease can be explained by infection but Zn levels were also decreased in cases of CHF due to cardiomyopathy and rheumatic carditis.

Serum Cu levels were significantly higher in CHF. Increased synthesis or decreased breakdown of ceruloplasmin by the liver has been suggested as an explanation for the increase of Cu in CHF. A rise in cerulaplasmin and hence serum Cu is related to the passive congestion in the liver[10,13].

Further investigations are needed to explain the variations in serum and tissue Zn and Cu levels in CHF.

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The Turkish Journal of Pediatrics 32: 39-41, 1990

ACUTE LYMPHOBLASTIC LEUKEMIA IN A CHILD WITH HEMOGLOBINS S AND Q–IRAN *

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*Gülersu Irken MD****, Çidem Altay MD****

Summary: Gürgey A, Özsoylu Ş, Hiçsönmez G, Irken G, Altay Ç. (Pediatric Hematology Unit, Department of Pediatrics, Hacettepe Universty Faculty of Medicine, Ankara, Turkey). Acute lymphoblastic leukemia in a child with hemoglobins S and Q-Iran. Turk J Pediatr 32: 39-41, 1990.

A 13-year-old girl with acute lymphoblastic leukemia is presented. The peripheral smear showed, in addition to lymphoblasts, marked anisocytosis, poikilocytosis, and polychromasia. In vitro sickling test was positive. Hemoglobin electrophoresis at pH 9.0 on starch gel revealed the presence of hemoglobin A, hemoglobin S, and a band with a mobility of hemoglobin A_2. Structural analysis revealed the presence of hemoglobin S and an alpha-chain variant, hemoglobin Q-Iran. The patient attained remission with the initial therapy administered but a relapse occurred five months later. Our study indicates the need for detailed investigation of leukemia patients in which abnormal hemoglobins are prevalent. *Key words: acute lymphoblastic leukemia, hemoglobin S, hemoglobin Q-Iran.*

Recently, hematologic malignancies in patients with hemoglobinopathies have been reported[1,2]. However, to our knowledge, the association of acute lymphoblastic leukemia (ALL) with hemoglobins S and Q-Iran has not been reported in the literature. Therefore, the purpose of this paper is to present such a case with leukemia in whom hemoglobinopathy was detected.

Case Report

A twelve-year-old girl from Southern Turkey with a diagnosis of ALL was referred to the Hacettepe University Children's Hospital for treatment of the disease. On physical examination the child appeared wasted and had a generalized petechial rash. The liver and spleen were palpated three cm and six cm below the respective costal margins.

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Laboratory studies revealed a hemoglobin level of 5.85 g/dl, mean corpuscular volume 92 fl, white blood cell count 150,000/ml. The peripheral smear showed 26 % blasts and thrombocytopenia with marked anisocytosis, polychromasia and poikilocytosis of red blood cells. The sickling test was positive and glucose -6-dehydrogenase activity was normal. The diagnosis of ALL (L 3 by FAB classification) was made by examination of the bone marrow. Since the patient showed signs of hemolysis, hemoglobin electrophoresis was performed which revealed hemoglobin A, hemoglobin S, and a variant with a mobility similar to that of hemoglobin A_2 on starch gel at pH 9.0. The diagnosis of hemoglobin Q-Iran ($\alpha^{75}{}_{B_2}$ Asp → His) and hemoglobin S was made by the structural analysis of abnormal hemoglobins. The child had obtained the hemoglobin S gene from her father, and the hemoglobin Q-Iran gene from her mother (Fig. 1). Remission was achieved with combination chemotherapy of prednisone, vincristine and L-asparaginase followed by cranial x-ray prophylaxis. However, she had a relapse five months later.

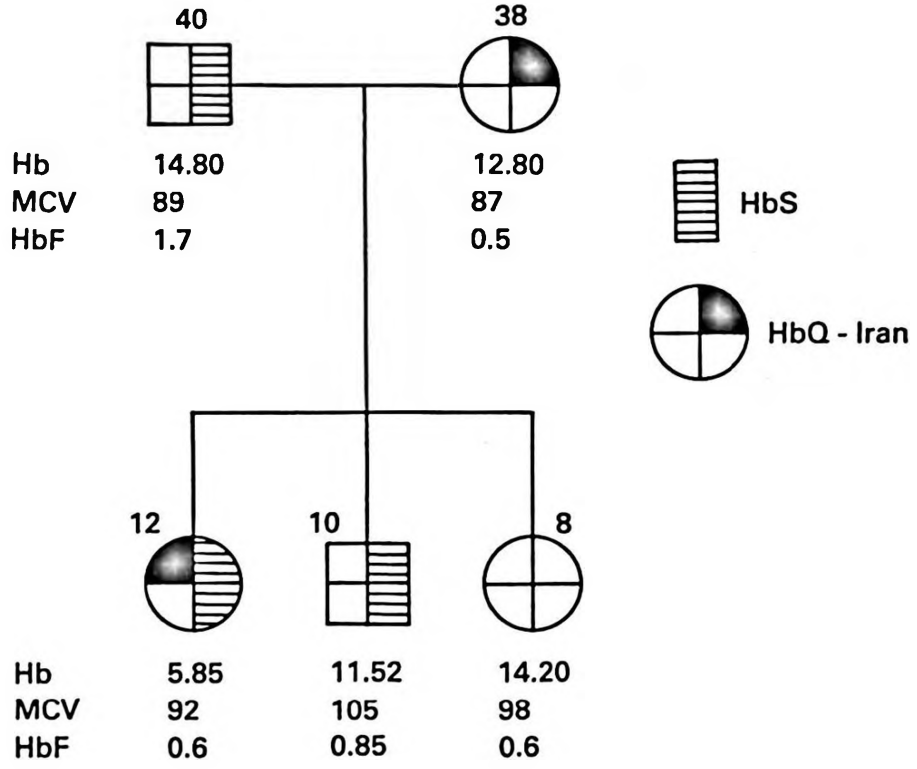

Fig 1: The family pedigree: hemoglobin (Hb; g/dl), mean corpuscular volume (MVC), hemoglobin F (HbF; %).

Discussion

Hemoglobin S and other hemoglobin abnormalities have been encountered in Southern Turkey[3]. Recently, two other families with hemoglobin Q-Iran were also reported from this part of the country[4].

Between 1975 and 1987, 1062 children were diagnosed as having acute leukemia at the Hacettepe University Children's Hospital. Hemoglobin electrophoresis was performed in twenty-two cases, and hemoglobinopathy was noted in three patients; one had Hb-E Saskatoon, another had sickle cell trait, and the third Hb H disease[5,6]. Acquired hemoglobin H disease may be observed in patients with leukemia[7]. In a two-year-old patient that we studied with hemoglobin H, it was impossible to ascertain whether this hemoglobin variant was related to her disease since a family study could not be performed. There are few reports in the literature concerning patients with a hemoglobin abnormality who have developed leukemia.

In the future, routine screening of patients for hemoglobinopathies may disclose whether or not subjects with hemoglobinopathies are more susceptible to developing leukemia than normal children.

Acknowledgement

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The Turkish Journal of Pediatrics 32: 43-47, 1990

A CASE OF LATE PRESENTING CHRONIC GRANULOMATOUS DISEASE*

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*Nuran Salman MD****, Sema Anak MD****

Summary: Yalçın I, Güler N, Öneş Ü, Salman N, Anak S. (Department of Pediatrics, Istanbul University Faculty of Medicine, Istanbul, Turkey). A case of late presenting chronic granulomatous disease. Turk J Pediatr 32: 43-47, 1990.

An eleven-year-old boy with a history of severe lung infection which had been resistant to antibiotic therapy for a period of six months demonstrated a functional leukocyte defect similar to that found in children with chronic granulomatous disease (CGD). X – ray findings suggested a hilar mass, and granulomatous lesions developed on the thorax wall. The documentation of this case suggests that there may be a late presenting form of CGD.
Key words: chronic granulomatous disease, late onset.

Chronic granulomatous disease (CGD) is a syndrome of recurrent bacterial or fungal infections associated with defective microbicidal capacity of the phagocytic cells and an abnormal oxidative metabolic response during phagocytosis. It occurs both in males and females, and usually during the first two years of life[1-4]. This report describes an unusually late presenting case of CGD and summarizes the related literature.

Case Report

An eleven-year-old boy, whose parents were first degree relatives, was admitted to our hospital with complaints of failure-to thrive, a cough, fever, and sweating which had developed about six months prior to his admission. The child had been examined by various physicians in several hospitals. He was diagnosed as having pneumonia and was treated with various antibiotics. In spite of all the antibiotic and anti-tuberculous drug regimens used, there was no clinical or radiological response, thus the patient was referred to our hospital for further evaluation and treatment.

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Physical examination revealed an underweight child (below third percentile) in respiratory distress. His subcutaneous tissue was wasted away and pallor was prominent. He had hyperthermia and clubbing of the fingers. There was cervical and axillary microlymphadenopathy. His liver and spleen were not palpable. On auscultation the lung fields showed fine crepitant rales on both bases. There was some intercostal retraction, with a respiratory rate varying from 25 to 30/min. The rest of the physical examination was unremarkable.

Urinalysis was normal; blood and sputum cultures yielded no bacterial growth. The delayed hypersensitivity skin test with PPD (5 and 250 TU) was negative. Remarkable laboratory findings were a high blood cell count with segmented neutrophil preponderance, and an elevated erythrocyte sedimentation rate.

Chest X-ray demonstrated parahilar and paracardiac diffuse, nonhomogenous interstitial infiltrates bilaterally which were considered to be nonspecific broncho-pneumonic infiltration.

Upon repeated chest X-ray, the infiltrates became homogenous and dense, similar to the characteristic X-ray findings of atelectasis. The chest X-ray findings also suggested a hilar mass. Computer tomography of the lungs and bronchoscopy revealed no further diagnostic evidence.

Since there was no clinical or radiological response to the treatment, a thoracotomy was performed which revealed pneumonia and a lung abscess. Almost simultaneously, two subcutaneous abscesses each 4 x 5 cm in diameter appeared on the thorax wall along the two sides of the sternum. After surgical drainage, a culture of the aspirate yielded *S. aureus.*

The diagnosis of CGD was considered because of the clinical features of the case and because the patient failed to respond to routine antibiotic therapy. Tests for humoral and cell-mediated immunity and for qualitative defects of phagocytes were performed (Table I). The nitroblue tetrazolium test (Slide test) was negative and bacterial killing index (for *S. aureus*) showed defective killing. Serum immunoglobin levels were high. Other tests were normal.

TABLE I: Immunological Evaluation of the Case

A – Test of humoral immunity

1) Serum concentrations of immunoglobulins
   Ig G: 2410 mg/dl (N: 700 – 1650 mg/dl)
   Ig M: 448 mg/dl (N: 50 – 260 mg/dl)
   Ig A: 558 mg/dl (N: 29 – 270 mg/dl)
2) Isohemagglutinins:
   1): 128 (Anti – A)
3) Anti – Streptolysin – 0 titer (ASO):
   200 Todd Units

B – Tests for cell – mediated immunity

1) E – rosette forming cells: 54 %
2) Delayed hypersensitivity skin tests: PHA – Positive
   PPD – Negative

C – Tests for qualitative defects of phagocytes

1) Nitroblue Tetrazolium Test (NBT): 0 %
2) Stimulated Nitroblue Tetrazolium Test with *E. Coli* endotoxin: 0 %
3) Bacterial Killing Index: 0.21 (Defective killing)
4) Rebuck Skin Window Test: Positive response

Discussion

CGD is a rare disease most often inherited as an X-linked trait but 20-40 percent of patients have been found to have an autosomal recessive pattern of inheritance[3]. Recognition and phagocytosis of bacteria occur normally in phagocytic cells, but the ingested microbes are not killed. Defects in oxydative metabolism and production of reactive oxygen radicals during phagocytosis are the essential defects in CGD. NADH and NADPH oxydases are present in phagocytic cells, but increased activity is not stimulated during phagocytosis[1,4,5].

Nearly all males with CGD and X-linked genetics have absent or grossly abnormal cytochrome b which is required for electron transport and reduction of oxygen to superoxide[6-9].

Several clinical pictures suggest CGD. Any patient with recurrent lymphadenitis should be suspected of having the disease. In addition, a patient with bacterial hepatic abscesses, osteomyelitis at multiple sites in the small bones of the hands and feet, and a family history of recurrent infections demands an investigation of the immunologic status[2]. Granulomata, characterized by phagocytes and giant cells sometimes loaded with pigmented lipid material, can develop in virtually any organ system. The mechanism of granuloma formation in CGD is unknown. It has been postulated that because of the defective respiratory burst in phagocytes, there is persistent inflammation. In our case, microlymphadenopathy, several episodes of pneumonia, subcutaneous and lung abscesses with *S. aureus* were the main features. Our patient's age was unusual for CGD, but similar cases have been reported[10,11].

The diagnosis of CGD is made by the NBT test. In the most common forms of the disease, NBT reduction is not observed in any of the cells[12]. The results of our case were also negative. One of the major criteria for classifying CGD is the cytochrome b spectrum[13,14]. But we could not determine it. The bacterial killing index for staphylococci is also defective in cases of CGD. Other laboratory

findings include anemia, neutrophil leukocytosis, an elevated erythrocyte sedimentation rate, raised immunoglobulin levels, normal antibody responses and tests for cell-mediated immunity.

The laboratory results of our case correlated with all the above-mentioned findings such as an absence of NBT reduction, a defective bacterial killing index for *S. aureas,* anemia, neutrophil leukocytosis, an elevated erythrocyte sedimentation rate, raised immunoglobin levels, normal tests for cell-mediated immunity, and extremely abnormal chest X-rays.

Since bone marrow transplantation is the only known cure for CGD, vigorous supportive care is important. Cultures must be obtained as soon as infection is suspected, since unusual organisms are commonly the source of infection. Recent studies suggest that gamma interferon can be used as an adjunct to antimicrobial therapy during acute infections in CGD[15].

Treatment which requires the administration of effective concentrations of bactericidal antibiotics may be continued for as long as two to four months because most antibiotics do not penetrate the neutrophils and, therefore, phagocytized bacteria are protected from their action. Rifampicin penetrates living cells, but unfortunately staphylococci rapidly become resistant to this drug, thus, its clinical usage in CGD may be less successful than in vitro tests suggest[16]. We used several antibiotics including rifampicin, but no successful results could be obtained.

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The Turkish Journal of Pediatrics 32: 49-52, 1990

A CASE OF MUCOPOLYSACCHARIDOSES TYPE I WITH HEART INVOLVEMENT DURING INFANCY*

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*Rana Olguntürk MD*****, Sedef Tunaoğlu MD**, Deniz Oğuz MD******

Summary: Demirsoy S, Gücüyener K, Olguntürk R, Tunaoğlu S, Oğuz D. (Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey). A case of mucopolysaccharidoses type I with heart involvement during infancy). Turk J Pediatr 32: 49-52, 1990.

We report a case of mucopolysaccharidoses I with severe cardiac involvement, which was diagnosed on the basis of clinical and laboratory findings even though, symptoms begin to occur in mucopolysaccharidoses after the first year of life. In our case cardiac failure occurred in the third month of life, which resulted in the patient's death after one month. *Key words: mucopolysaccharidoses, heart, infancy.*

The mucopolysaccharidoses (MPS) are a group of inherited disorders caused by incomplete degration and storage of acid mucopolysaccharides in various organs, including the heart[1].

We report a case of mucopolysaccharidoses type I with severe heart involvement during infancy, which resulted in death.

Case Report

A three-month-old girl was admitted to the Department of Pediatrics of Gazi University Faculty of Medicine with complaints of respiratory difficulty which had been present since birth, and cyanosis and vomiting which had been present for two days. Her parents were not related.

Physical examination on admission revealed an extremely agitated infant with pallor, peroral cyanosis and coarse facies. Her temperature was 38.3 °C, respiratory rate 60/min, pulse rate 200/min, and blood pressure 70/30 mm Hg. She had stridulous breathing and intercostal retractions. The liver was palpable four cm below the costal margin.

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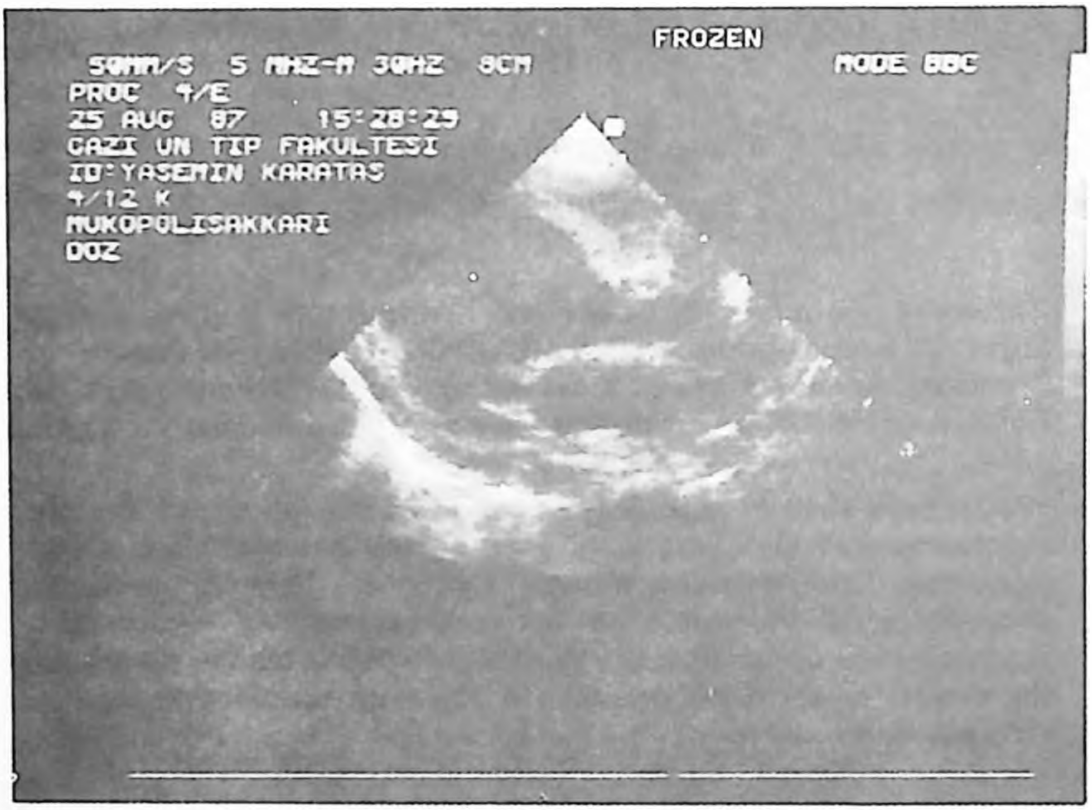

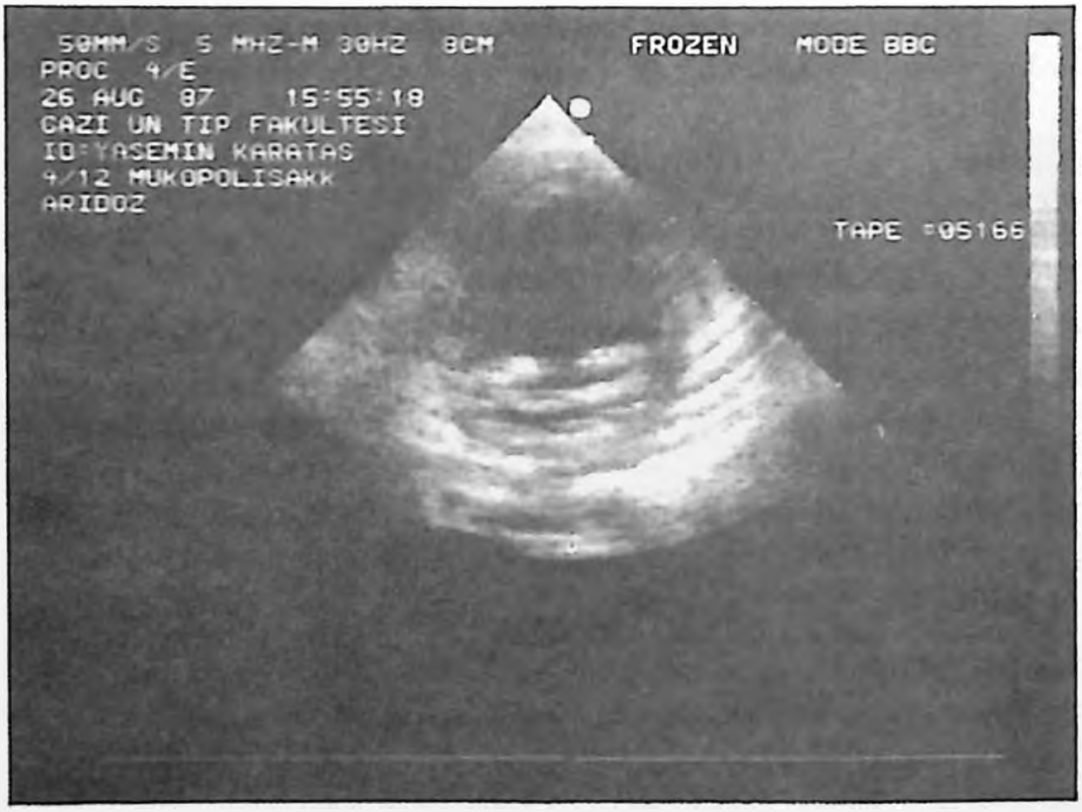

Fig. 1: Thickening in mitral valve leaflets (longitudinal A and horizontal B).

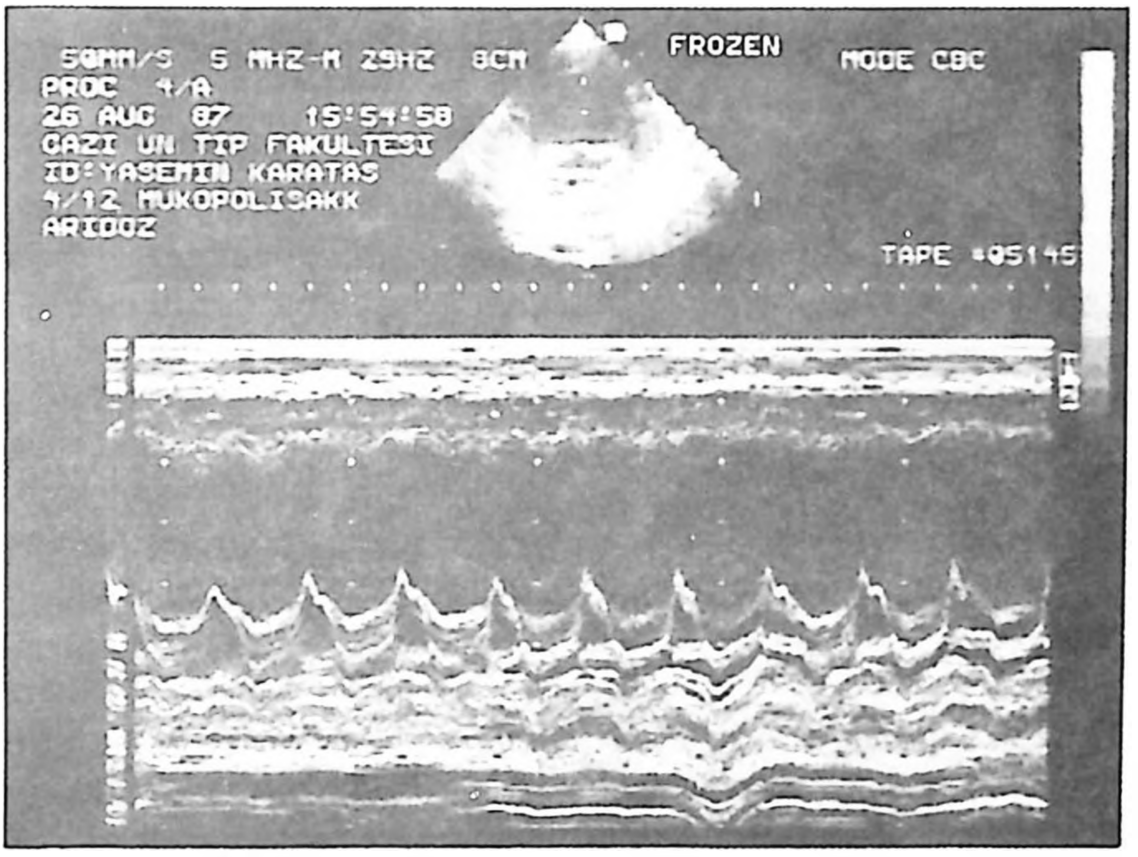

Fig. 2: Echocardiogram shows mitral valve prolapse.

Laboratory studies, including a complete blood count, urinalysis, and liver and kidney function tests were within normal limits. Moderate cardiomegaly was detected on the telecardiogram, and the L 1 vertebral body appeared more rounded and immature than usual in the dorsolumbar graph. Electrocardiography revealed left ventricular hypertrophy.

The echocardiogram was recorded using a Hewlett Packard Ultrasonoscope (Model 77 020 A) with a 3.5 MHz transducer. Utilizing the echocardiographic measurements and Bi-plane Ellipse Method, ventricular functions (ejection fraction and fractional shorting) were found to be decreased. There was a profuse thickening and restriction in the mitral valve leaflets during diastole (Figs. 1 a, b). A prolapse in the anterior leaflet of the mitral valve was observed (Fig. 2). The left atrial dimensions were slightly increased. The aortic, pulmonary and tricuspid valves were normal.

Because of the presence of coarse facies, cardiomegaly, hepatomegaly and noisy breathing, the diagnosis of mucopolysaccharidoses was suspected and urinary excretion of mucopolysaccharides was investigated. Total mucopolysaccharides were 97 mg/dl (normal: up to 85 mg/dl) with 20 % heparan sulfate (normal: 0), 63 % dermatan sulfate (normal: 0-20 %), and 17 % hyaluronic acid (normal: 10-20 %). Institution of appropriate therapy resulted in moderate clinical improvement, and the patient remained in stable condition for the next month. On her

second hospital admission, physical examination revealed an infant in poor health with symptoms of severe cardiac failure. She died five hours after admission.

Discussion

Deficiency of ten specific lysosomal enzymes has been demonstrated in various mucopolysaccharidoses[1]. The clinical manifestations of mucopolysaccharidoses have some common symptoms. Generally, the clinical course in all the mucopolysaccharidoses is one of apparent normal development in the first years of life, and progressive deterioration beginning at some time thereafter[1,2]. Death usually occurs before the age of ten in the prototype disorder, Hurler's syndrome, which carries the gravest prognosis among all the mucopolysaccharidoses[3]. On the other hand, patients with the Scheie and Hunter syndromes have survived way into their sixties, and even longer. No specific treatment is available for any of these disorders[1].

In our case, stridulous breathing, coarse facies, cardiomyopathy, hepatomegaly, immature vertebrae and excessive amounts of dermatan sulfate and heparan sulfate in the urine were the criteria used for the diagnosis of mucopolysaccharidoses[1]. The interesting aspect of our case was the early severe cardiac involvement which resulted in the patients's death due to cardiac failure. Cardiac involvement occurs in at least eighty percent of patients but only half show clinical incidence of cardiovascular problems. Cardiomegaly may be detected without evidence of organic murmur, as in our case. Thickening of the mitral annulus and the leaflets may be due to infiltration of mucopolysaccharides, as previously described[4]. Fifty percent of patients die either from cardiac failure or suddenly. Early death is the usual outcome[5].

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MASSIVE PARAESOPHAGEAL HIATUS HERNIA CONTAINING COLON AND STOMACH WITH ORGANO–AXIAL VOLVULUS IN A CHILD*

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Summary: Şenocak ME, Büyükpamukçu N, Hiçsönmez A. (Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Massive paraesophageal hiatus hernia containing colon and stomach with organo-axial volvulus in a child. Turk J Pediatr 32: 53-58, 1990.

Paraesophageal hiatus hernia is a very rare entity in children. The majority of cases remain asymptomatic and some are diagnosed incidentally. The clinical course of a massive paraesophageal hiatus hernia containing colon and stomach in a five-year-old boy is presented. *Key words: paraesophageal hiatus hernia, gastric volvulus, hiatus hernia.*

Paraesophageal hiatus hernia (PEHH) is an exceedingly rare disorder. It has been found in 3.5-5.1 percent of adult patients with hiatus hernia[1-3] but the actual incidence is unknown in children. A case of PEHH in a child is presented and the treatment is discussed.

Case Report

A five-year-old boy with a history of intermittent vomiting since he was seven months of age and failure-to-thrive was admitted to the Hacettepe University Children's Hospital.

Physical examination revealed that the child was below the third percentile for weight. The other physical findings were unremarkable, except for mild hypochromic anemia. A routine chest radiograph showed two air-fluid levels, one beneath the left hemidiaphragm, and the other within the right hemithorax (Fig. 1). An upper gastrointestinal series demonstrated a giant PEHH. The cardia and pylorus were below the diaphragm, and concomitant organo-axial gastric volvulus was observed. There was also evidence of partial obstruction of the stomach (Fig. 2 a). A barium enema revealed that a portion of the transverse colon was

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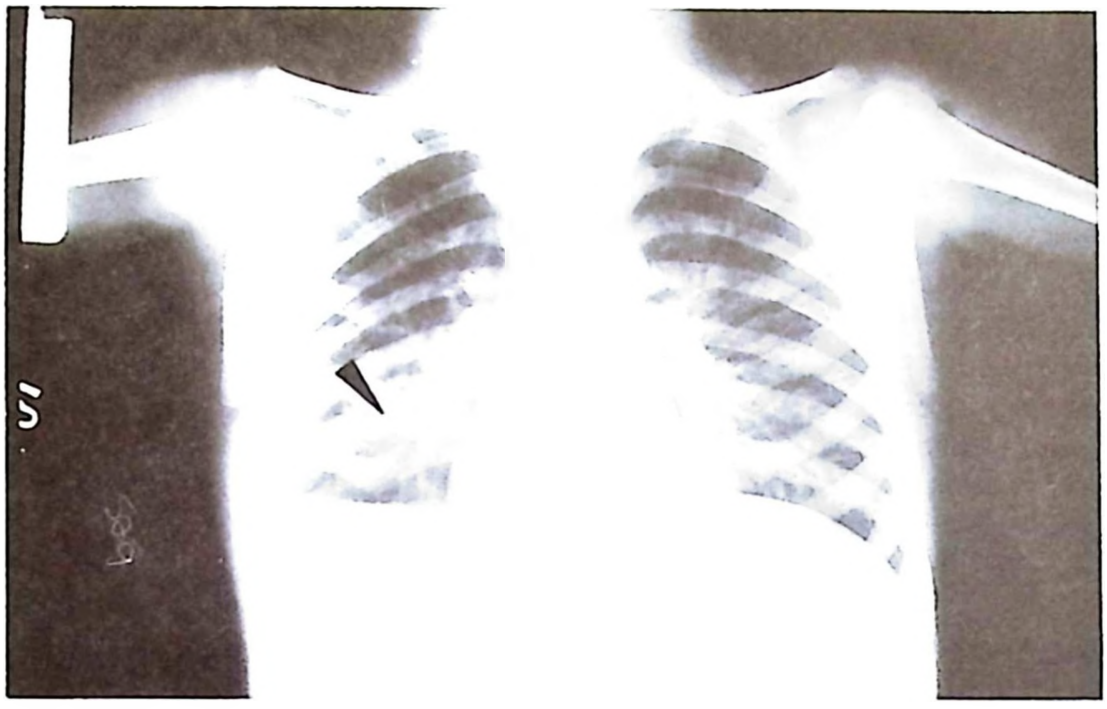

Fig. 1: Pre-operative routine chest x-ray showing the intrathoracic segment of the stomach completely filled with fluid and gas (black arrow).

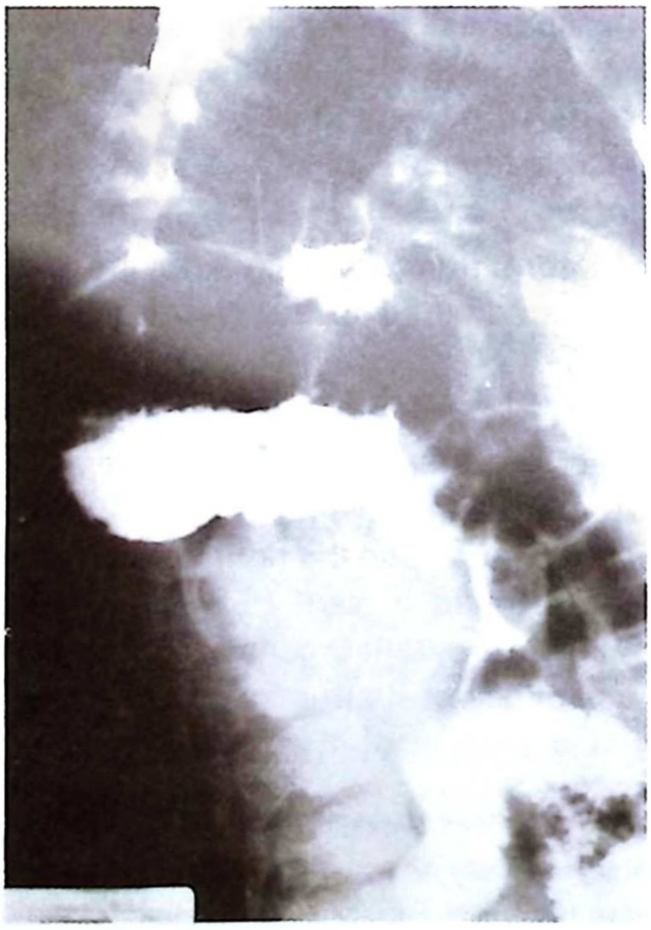

Fig. 2: a) Upper gastrointestinal series and b) barium anema in the same patient. The entire stomach is in the chest and has undergone OA volvulus. A large segment of the transverse colon is also in the thorax.

displaced into the chest (Fig. 2 b). The esophageal mucosa appeared normal at endoscopy.

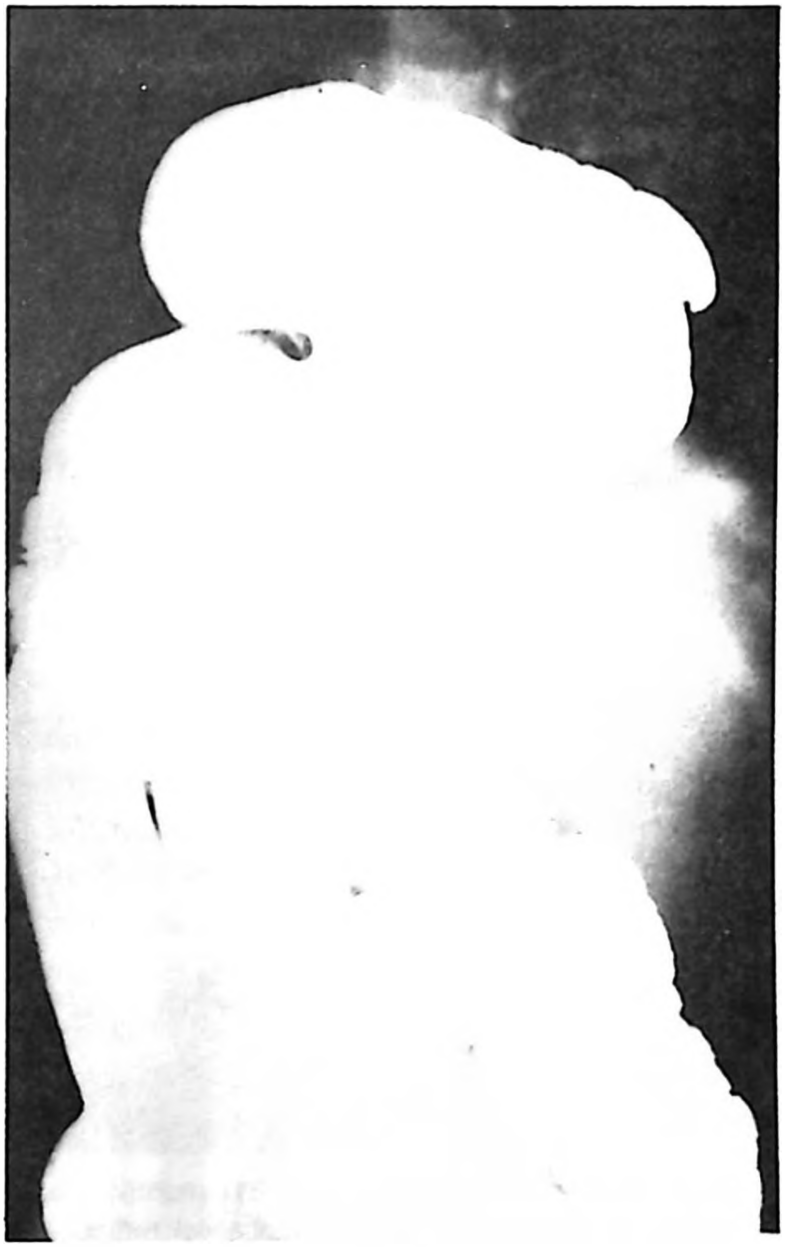

Fig. 2b:

At laparotomy, the stomach was found to be displaced into the thorax but the transverse colon was intraabdominal. The stomach was reduced and the organo-axial (OA) volvulus was corrected. The paraesophageal defect measured approximately 15 cm in diameter. The esophagogastric junction was in its normal position. The defect was closed posterior to the esophagus with minimal dissection. Then an anterior gastropexy was performed.

The patient's post-operative course was uneventful. Six months postoperatively, a barium swallowing showed no evidence of gastroesophageal reflux (GER), and the stomach was in its normal position (Fig. 3).

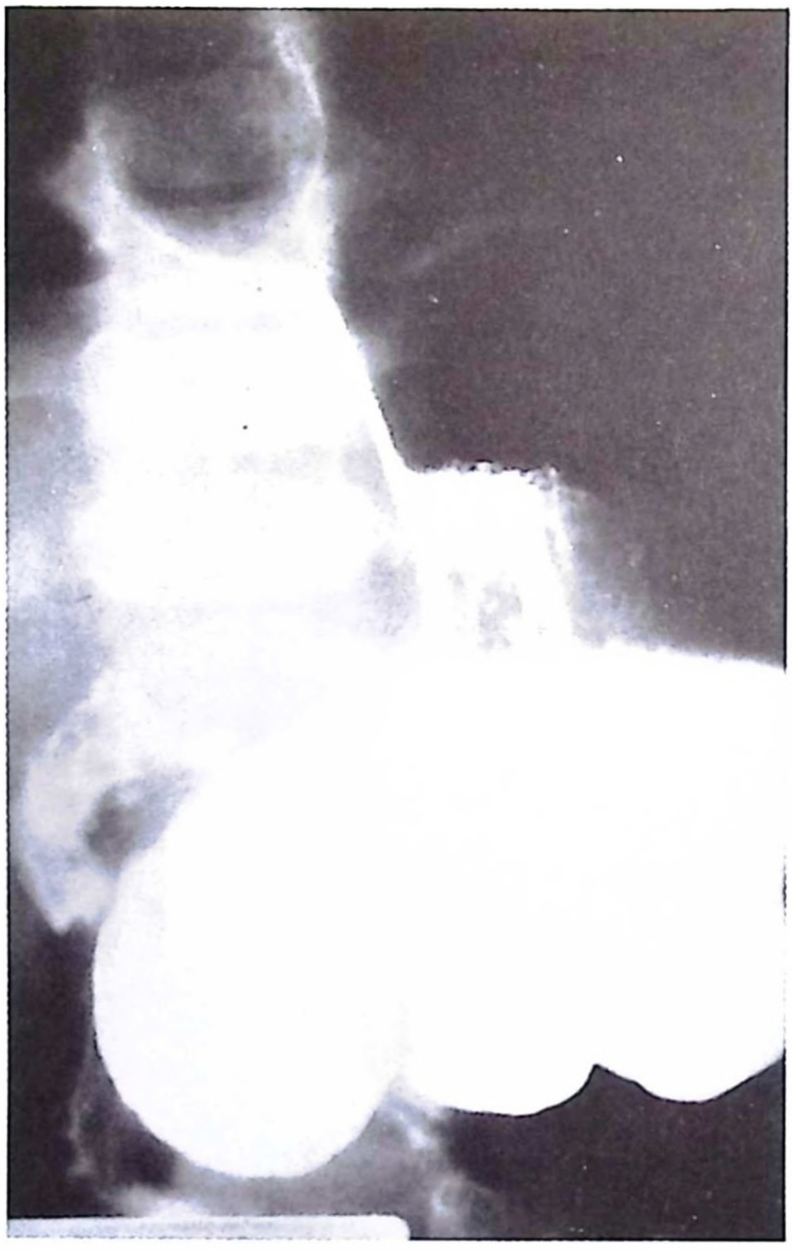

Fig. 3: An upper gastrointestinal series taken six months after surgery shows no evidence of gastro-esophageal reflux.

Discussion

Paraesophageal hiatus hernia is an uncommon disorder which is distinctly different from the much more common sliding hiatus hernia[1,4,5]. The cause of PEHH remains unknown. It may be a congenital condition but symptoms usually develop in adults which suggest that other factors may play a role in its occurrence[1].

In PEHH the gastric fundus rolls up anteriorly and may progress to complete gastric herniation with OA volvulus (upside-down stomach) through the widened esophageal hiatus into the chest. The esophagastric junction is often near its normal position, thus, it remains competent and most patients do not suffer from gastroesophageal reflux[1,5,6].

Intermittent womiting, aspiration pneumonia and malnutrition are the major symptoms of this disorder in children[7]. In many patients, chronic iron deficiency anemia may develop due to occult bleeding[3,6-8].

Radiologic examination provides the basis for proper diagnosis. All cases suspected of having PEHH should be evaluated by routine chest radiograms[5,9]. We believe that a barium swallow is mandatory for a definite diagnosis. Esophagoscopy has relatively little diagnostic value in this entity[10].

This type of hernia may remain completely asymptomatic for many years, and most are usually diagnosed incidentally. Since PEHH has a high risk of serious complications, the defect should be corrected immediately after diagnosis[6,9]. Otherwise, the hernia may become incarcerated, and the patient may require emergency surgery without preparation which has high morbidity and mortality[4,8,11,12].

Reduction of the herniated organs and repair of the defect are the main principles in the surgery[5]. A transthoracic or transabdominal approach has been recommended[1,3,5,13,14] as operative procedures. We believe, however, that the latter is quite satisfactory in children. Extensive dissection of the distal esophagus is unnecessary and should be avoided. The defect can be closed anterior or posterior to the esophagus[14,15]. Surgical intervention should be completed with subsequent simple left anterior gastropexy. If there is a mobile distal esophagus, lax phrenoesophageal ligament or massive herniation, an antireflux operation is necessary after closing the defect[6].

Surgical results are excellent and no mortality has been reported in elective cases[2]. An upper gastrointestinal series should be obtained after the operation to determine the end results and the presence of gastroesophageal reflux.

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SOTOS SYNDROME PRESENTING WITH EPILEPSY*

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Summary: Büyükgebiz A, Kınık E. (Hacettepe University Institute of Child Health, Ankara, Turkey). Sotos syndrome presenting with epilepsy. Turk J Pediatr 32: 59-63, 1990.

A fourteen and a half year-old boy of tall stature presenting with epilepsy was diagnosed as having Sotos syndrome (cerebral gigantism) at the Hacettepe University Children's Hospital. Since EEG abnormalities are known manifestations in this syndrome, a case presenting with epilepsy is very rare. We believe that a presumed cerebral defect could create convulsions and would thus be the cause of cerebral gigantism whose etiology is still unclear. Thus patients with this syndrome should be followed up for the risk of epilepsy. *Key words: Sotos syndrome, epilepsy.*

Sotos syndrome (cerebral gigantism) was first described as a syndrome by Sotos and co-workers[1] in 1964. A hypothalamic defect has been suggested as a cause, but this has not been demonstrated functionally or at necropsy. Thus, the etiology of the disease remains unknown[1-4]. In 1983, Ashcraft et al[5] described an unidentified growth factor in the serum of patients with this syndrome. This factor also stimulated the erythroid precursor cells of a Laron-type dwarf whose cells were unresponsive to growth hormone. But the authors claimed that although this factor could be responsible for the altered somatic growth observed in this condition, the physiologic role of this growth factor in normal man as well as its pathogenic role in subjects with the syndrome remains to be established. In this paper, we report a case of Sotos syndrome presenting with epilepsy and review the literature.

Case Report

A fourteen and a half year old boy of tall stature was diagnosed as having epilepsy and was referred to the Hacettepe University Children's Hospital for further investigation. His past history revealed that he had graduated from a private school for mentally retarded children and was unable to continue his education.

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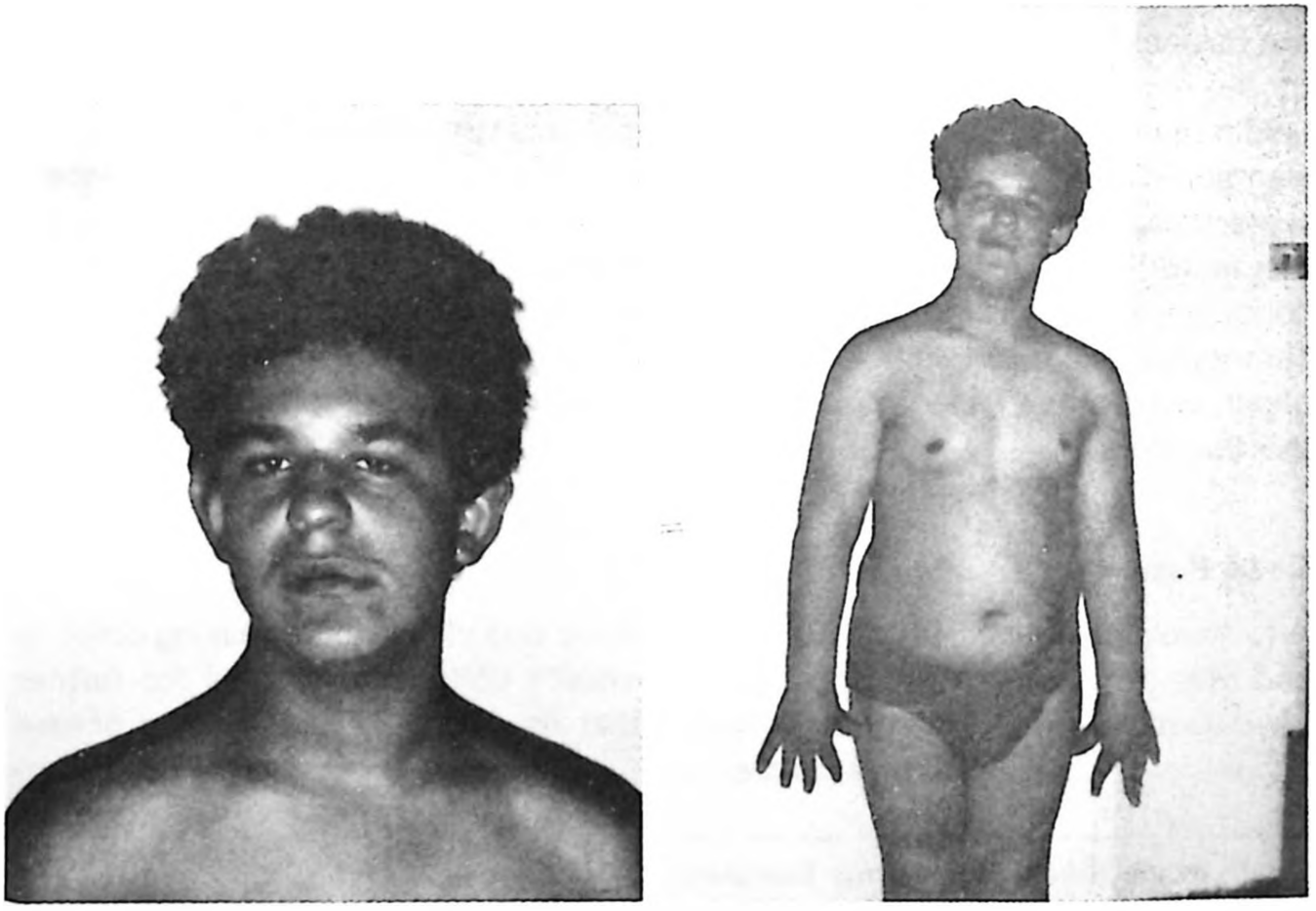
He had been having generalized convulsions for five years, and the diagnosis of epilepsy with abnormal EEG findings was established. Diphenylhydantoin therapy was initated in a daily dose of 5 mg/kg, and he responded well to treatment. Two years ago his enlarged hands and feet were noticed by his family.

Physical examination revealed a boy whose weight was 95 kg (above 95th percentile) and whose height was 177 cm (above 90th percentile). He had an arm span of 179 cm, an upper/lower ratio of 0.9 and a head circumference of 63 cm. He had a large head, prominent jaw and forehead, large hands and feet (Figs. 1,2), and wore a size 45 shoe. His sexual development was Tanner Stage IV. He was mentally retarded, had an awkward gait and his skeletal age was 15 years. Radiographs (Figs. 3-5) showed a large skull, no signs of increased intracranial pressure, and the sella turcia and clinoid processes were of normal contour. Radiographs of the hands showed them to be large and there was slight tufting of the terminal phalanges[5]. Lateral foot radiographs showed thickening of the soft tissue from the calcaneus. Computerized axial tomography demonstrated no enlarged ventricles.

Repeated fasting growth hormone levels were 0.50, 1.49, and 0.87 ng/ml (normal, 0-10 ng/ml). The oral glucose tolerance test yielded normal results.



Figs. 1, 2: General appearance of the patient; note the large head, prominent jaw and forehead, and large hands.

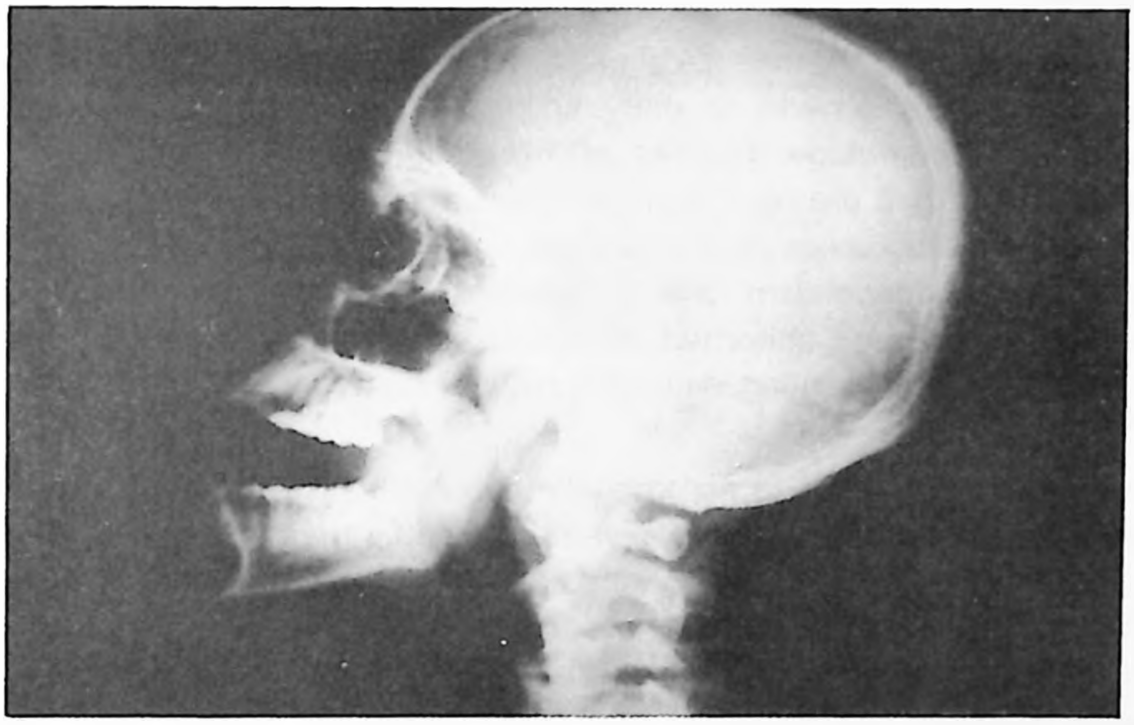


Fig. 3: Skull radiogram of the patient (lateral view); note the absence of signs of increased intracranial pressure and the normal appearance of sella turcica and clinoid processes.

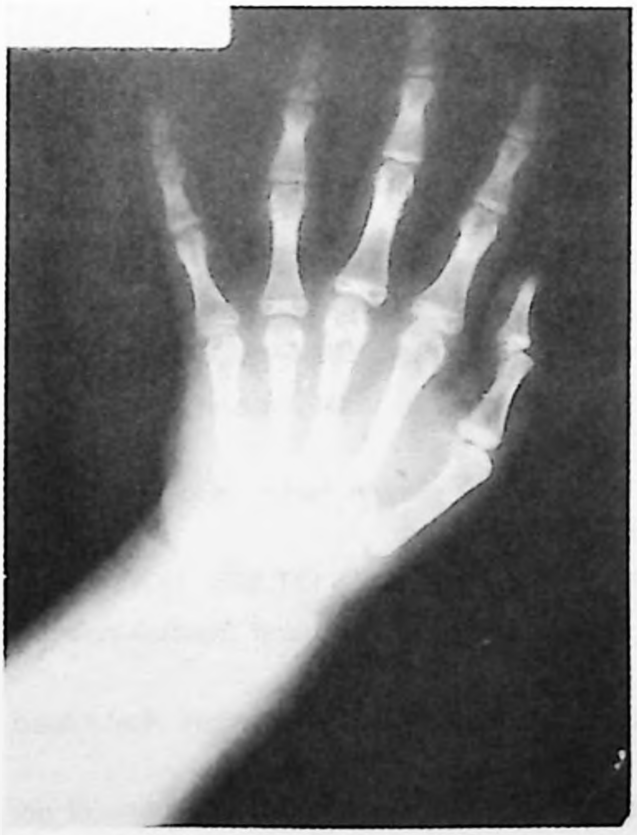


Fig. 4: Wrist X-ray demonstrating bone age of 15 years; note enlarged hand.

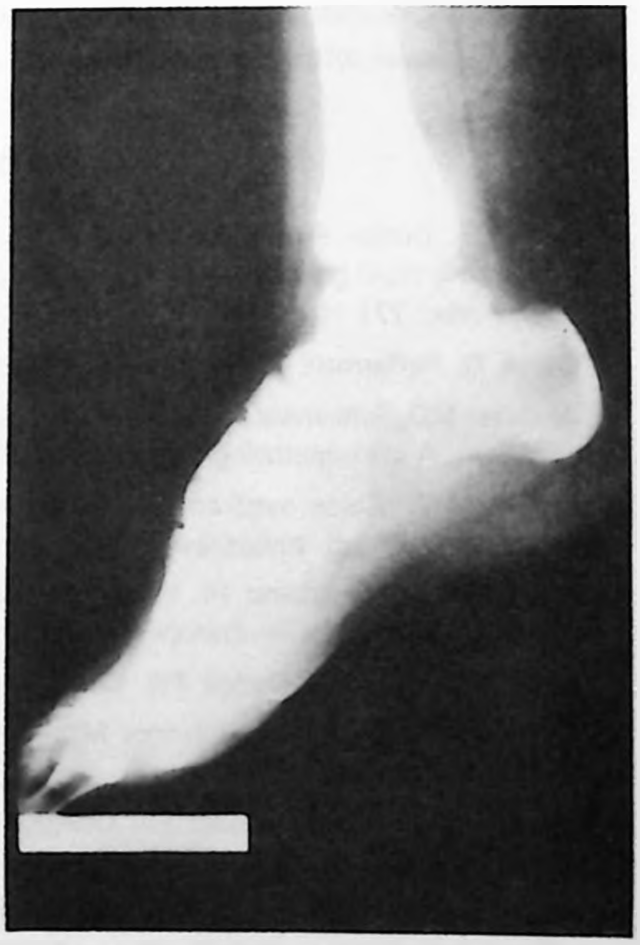


Fig. 5: X-ray of foot shows enlargement.

Discussion

According to Sotos et al[1], the typical pattern of cerebral gigantism is characterized by excessive rapid growth in early childhood, acromegalic features, and a non-progressive neurologic disorder with mental retardation. Mental retardation and an awkward gait are mostly present in patients with Sotos syndrome[1,4,6]. Several reports emphasize endocrinological abnormalities including thyrotoxicosis, primary hypothyroidism and a fourteen percent incidence of glucose intolerance[7-9]. Although abnormal electroencephalograms are common, to our knowledge a case presenting with epilepsy as the initial symptom is extremely rare[14].

Our case presented definite acromegalic characteristics, mental retardation an awkward gait, and epilepsy. There were no signs of intracranial pressure but since EEG abnormalities are known manifestations in this syndrome, a presumed cerebral defect in our patient could create convulsions[1-4]. His generalized convulsions responded well to 5 mg/kg diphenylhydantoin therapy. Although advanced osseous maturation is said to accompany cerebral gigantism, our patient did not show any osseous maturation[1-4].

Patients with Sotos syndrome may be at high risk for developing neoplasia, hepatic carcinoma and Wilms' tumor[10,11]. Therefore, at follow-ups, patients should be evaluated for these risk factors including epilepsy.

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