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INBORN ERRORS OF BIOTIN METABOLISM*
Clinical and Laboratory Features of Eight Cases

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SUMMARY: Coşkun T, Tokatlı A, Özalp I. (Nutrition-Metabolism Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Inborn errors of biotin metabolism: clinical and biochemical features of eight cases. Turk J Pediatr 1994; 36: 267-278.

There are two genetically determined biotin-dependent disorders. The first is holocarboxylase synthetase (HCS) deficiency and the second biotinidase deficiency. HCS catalyzes the reaction in which active holocarboxylases are synthesized from inactive apocarboxylases. Biotin is required for this synthesis. Biotinidase facilitates the release and recycling of free biotin. Deficiency of either HCS or biotinidase is characterized by certain neurological, cutaneous and biochemical abnormalities.

In this paper, six patients with biotinidase and two patients with HCS deficiency are described. Among the most common neurological findings were hypotonia (6/8), seizures (2/6) and optic atrophy (2/8). Dermatitis and conjunctivitis were present in three and four patients, respectively. All patients had low blood pH bicarbonate levels. Serum lactate was increased in all and pyruvate in six cases. Two patients with biotinidase deficiency presented earlier than the mean age of onset previously reported in the literature.

Detection of eight cases during the past few years at a single metabolic unit indicates that biotinidase deficiency is not rare in Turkey, where the frequency of some other metabolic disorders has also been reported to be high. We suggest that biotin-dependent disorders should be considered in all infants with neurological symptoms, particularly those with jerks, even if other signs such as alopecia, seborrheic dermatitis and acidosis are not evident, regardless of the age of presentation. *Key words: biotin-dependent disorders, holocarboxylase synthetase deficiency, biotinidase deficiency.*

Biotin is a water-soluble, B-complex vitamin that acts as a cofactor for four mammalian carboxylases: pyruvate carboxylase, acetyl CoA carboxylase, propionyl CoA carboxylase and 3-methyl crotonyl CoA carboxylase. Biotin binds covalently to the apoprotein of these carboxylases in order to render them active in a reaction catalyzed by holocarboxylase synthetase (HCS). The active holocarboxylases are degraded by proteases in the course of normal cellular turnover. The end-products of this degradation reaction are not amino acids, unlike the situation with other proteins. The reaction is stopped when it reaches the small peptide biocytin (biotinyl-lysine) that contains biotin. Biotinidase is an

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enzyme found in serum and most body tissues, and is essential for the release of biotin from biocytin and for the recycling of free biotin. Deficiency of either HCS or biotinidase results in malfunction of all carboxylases and in organic acidemia[1-3].

In this report, we describe the clinical and laboratory features of eight cases (six with biotinidase deficiency and two with HCS deficiency) in order to draw attention to the facts that the clinical expression of biotin-dependent disorders varies and it is no longer tenable to differentiate biotinidase deficiency from HCS deficiency simply based on the relatively later age of onset of the former.

Case Reports

Clinical and laboratory features are summarized in Tables I and II. Of the following eight cases, three (Cases 1, 3 and 4) have previously been reported elsewhere[4,5].

Table I: Clinical Characteristics of Six Patients with Biotinidase Deficiency and Two Patients with Holocarboxylase Synthetase Deficiency

	Biotinidase-Deficient Cases						Holocarboxylase Synthetase Deficient Cases	
Clinical Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age of onset	30 mos	18 mos	91 days	70 days	6 mos	Newborn	5.5 mos	3.5 mos
Sex	F	M	M	F	M	M	M	F
Consanguinity	—	—	+	+	+	—	—	—
Hypotonia	—	—	+	+	+	+	+	+
Seizures	—	—	+	+	—	—	—	—
Dermatitis	+	+	+	—	—	—	—	—
Alopecia	+	+	+	+	+	—	+	—
Conjunctivitis	+	+	+	—	+	—	—	—
Optic atrophy	—	—	+	—	+	—	—	—
Stridor	+	—	—	—	—	—	—	—
Biotin treatment (mg / day)	Init. 20 Maint. 5	Init. 20 Maint. 5	Init. 10 Maint. 5	Init. 10 Maint. 5	Died before specific diagnosis	Died before specific diagnosis	Init. 20 Maint. 40	Init. 20 Maint. 40
Follow-up	doing well at 5.5 yrs	had only gait problems at 3.5 yrs	doing well at 11 mos with abnormal BAEP	doing well at 10 mos	died at 6 mos	died on the 13th day	doing well at 3 yrs	lost to follow-up

M: male, F: female, Init.: initial, Maint.: maintenance, Yrs: years, Mos: months.

Table II: Laboratory Characteristics of Six Patients with Biotinidase Deficiency and Two Patients with Holocarboxylase Synthetase Deficiency

	Biotinidase-Deficient Cases						Holocarboxylase Synthetase Deficient Cases	
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Blood pH	7.35	7.42	7.25	6.98	7.31	7.32	7.30	7.31
HCO_3	14.20	13.50	7.30	3.40	8.80	14.10	13.20	12.00
LA (mg / dl)	41.80	65.00	94.30	79.30	72.00	28.10	45.80	32.00
PA (mg / dl)	1.60	4.00	6.00	5.60	2.80	1.00	1.30	0.78
NH_3 (microg / dl)	50.00	60.00	84.00	118.00	53.80	180.00	140.00	152.00
Amino acids								
serum	Alanine ↑	Alanine ↑	Alanine ↑	N	N	N	N	N
urine	Alanine ↑	Alanine ↑	Alanine ↑	Alanine ↑	N	N	N	N
Organic acids in urine	ND	ND	typical for a biotin depend. disord.	ND	typical for a biotin depend. disord.	typical for a biotin depend. disord.	typical for a biotin depend. disord.	typical for a biotin depend. disord.
EEG	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	ND	ND
CT	ND	N	ND	N	Abnormal	ND	ND	ND
MRI	ND	N	ND	N	ND	ND	Abnormal	N
VEP	Abnormal	Abnormal	Abnormal	Normal	ND	ND	ND	ND
BAEP	N 5.5 yrs	Abnormal problems at 3.5 yrs	Abnormal 11 mos with abnormal BAEP	Abnormal 10 mos	ND	ND day	ND 3 yrs	ND

LA: lactic acid, PA: pyruvic acid, EEG: electroencephalogram, CT: computerized tomography, MRI: magnetic resonance imaging, VEP: visual evoked potentials, BAEP: brainstem evoked potentials, N: normal, ND: not done, Depend.: dependent, Disord.: disorder.

Case 1

A 30-month-old girl was admitted to our hospital because of acute spastic laryngitis. At 10, 18 and 29 months of age, she had developed a noisy breathing pattern diagnosed as bronchitis, which persisted for several weeks. She had developed erythematous skin lesions involving the whole body and lost her hair seven months and 20 days prior to her admission to the hospital, respectively. Her parents were nonconsanguineous, and one elder sister had been healthy.

On physical examination, the patient was severely ill and had dyspnea with a respiratory rate of 46 / min, hoarseness and inspiratory stridor. Her hair texture was sparse, with the occipital region being totally alopecic. There was bilateral blepharoconjunctivitis.

Laboratory investigations revealed a metabolic acidosis (blood pH 7.35 and bicarbonate 14.2 mmol / L). Lactic and pyruvic acidemia were found (lactic acid

41.8 mg / dl, normal 10-14 mg / dl; pyruvic acid 1.6 mg/ dl, normal 0.5-1.0 mg / dl), associated with increased serum and urine concentrations of alanine demonstrated by paper chromatography. Blood ammonia was 50 µg / dl (normal 20-120 µg / dl). Upon testing with Bayley's scale, the patient was found to be slightly retarded. An electroencephalogram (EEG) displayed paroxysmal abnormalities, while visual evoked potentials (VEP) showed prolonged latencies.

Organic pathology of the larynx was excluded by direct laryngoscopy. Biochemical abnormalities coupled with neurological and cutaneous findings suggested biotinidase deficiency, and biotin was administered orally (20 mg / day in two divided doses). Both respiratory and metabolic abnormalities were normalized within three hours of initiating therapy. Biotinidase activity in whole blood was subsequently shown to be deficient. The biotin dose was gradually decreased to 5 mg / day. When last seen, the patient was 5.5 years of age and symptom-free.

Case 2

An 18-month-old boy was referred to our hospital because of respiratory difficulty and unconsciousness after having been hospitalized for about 22 days with the diagnosis of encephalitis at another institution. His parents were nonconsanguineous. An eight-month-old female sibling had reportedly been healthy.

On examination, seborrheic-type dermatitis involving mainly the perianal and gluteal area was detected. The patient had very little hair and bilateral blepharoconjunctivitis. He was responsive to painful stimuli.

Laboratory investigations revealed a blood pH of 7.42 and bicarbonate 13.5 mmol / L. Both serum lactate (65 mg / dl) and pyruvate (4.0 mg / dl) were elevated. Blood ammonia was normal (60 µg / dl). Alanine concentration was increased in serum and urine samples. An EEG showed diffuse irregular slow activity. Prolongation of latencies was detected on VEP and brainstem auditory evoked potential (BAEP) studies. Computed tomographic scan (CT) and magnetic resonance imaging (MRI) of the brain were interpreted as normal. Biotinidase activity in serum was found to be absent.

A diagnosis of acrodermatitis enteropathica was considered, but normal serum zinc concentrations made this possibility unlikely. Biotin therapy (20 mg / day in two divided doses) was initiated, and the patient responded dramatically within hours. Blood pH and bicarbonate returned to normal and the patient regained consciousness. The dermatitis and conjunctivitis disappeared within 10 days.

When last seen, the patient was 3.5 years old and doing well under biotin therapy (5 mg / day). Neurological examination still revealed weakness in the lower extremities and gait disturbance. Repeated VEP and BAEP studies gave normal results.

Case 3

A 91-day-old male infant was brought to our hospital with the chief complaints of difficulty in feeding and a generalized squamous rash. The patient had started experiencing tonic-clonic muscle jerks when he was one month old, and these had increased in frequency and severity with time. Infantile spasms were diagnosed at another institution, and he was given corticotropin and phenobarbital with some relief. Ten days after discharge, the patient was admitted to our hospital. His parents were first-degree relatives. One sibling had died at the age of five months after persistent convulsions.

On examination, lethargy, hypotonia, hyperpnea and frequent muscle jerks were noted. Generalized alopecia of the scalp and seborrheic dermatitis were also evident. Ophthalmologic examination revealed optic atrophy and keratoconjunctivitis of both eyes.

Laboratory investigations revealed a blood pH of 7.25 and bicarbonate 7.3 mmol /L. Serum lactic (94.3 mg / dl) and pyruvic (6.0 mg / dl) acid levels were increased. Blood ammonia was 84 µg / dl. Alanine concentration was increased in serum and urine samples. BAEP showed no response on the left side and only a low amplitude response on the right side. VEP showed prolonged P1 latencies on both sides. EEG showed the presence of a multifocal epileptiform abnormality. Gas chromatography-mass spectrometry (GC-MS) analysis of the urine sample was found to be typical for a biotin-dependent disorder.

A presumptive diagnosis of biotinidase deficiency was made, and biotin therapy was initiated (10 mg / day). The patient's condition responded dramatically to the administration of biotin. Blood pH and bicarbonate values were normalized within six hours. The seborrheic dermatitis improved shortly after treatment and disappeared at the end of 10 days. Biotinidase activity was later shown to be absent.

On follow-up examination at 11 months of age, the patient was doing well and had not experienced any convulsions while receiving biotin (5 mg / day). Neurological examination revealed no abnormalities.

Case 4

A 70-day-old female infant was referred to our hospital because of intractable convulsions. She began having jerky movements at one month of age. She was

hospitalized at another institution and given phenobarbital and sodium valproate, which had no effect on the convulsions. The diagnosis of infantile spasms was then made, and corticotropin was started. The frequency of convulsions decreased under such therapy, and the patient was referred to our hospital for further evaluation. The parents were third-degree relatives and had a nine-year-old healthy daughter.

Physical examination revealed a lethargic and hypotonic child with sudden jerky movements of the limbs. Scalp hair was sparse. She developed acidotic respirations on the tenth day of hospitalization.

Laboratory investigations revealed the following: blood pH 6.98 and bicarbonate 3.4 mmol / L; increased serum levels of lactic (79.3 mg / dl) and pyruvic (5.6 mg / dl) acid; and serum ammonia level of 118 µg / dl. BAEP showed no response on either side, and VEP studies were normal. EEG showed a generalized chaotic baseline pattern and paroxysmal activity in the left hemisphere. CT and MRI of the brain were both normal. The urine alanine level was increased.

Biotinidase deficiency was considered as a diagnostic possibility, and biotin was administered orally (10 mg / day), resulting in abatement of the acidosis within hours.

On follow-up examination at 10 months of age, the patient's physical and neurological findings were normal while receiving 5 mg / day biotin. The patient is currently receiving no anticonvulsant drug and is free of convulsions. A repeat BAEP was found to be unresponsive on the left side, while only a low-amplitude response could be obtained on the right side.

Case 5

A six-month-old male infant was brought to our hospital because of hypotonicity since birth. His developmental milestones were delayed. The parents were first-degree relatives, and their first three children had died of unknown causes between one and two months of age. They also had three healthy children.

On examination, the patient was generally unresponsive, not fixing or following, and was profoundly hypotonic. His hair was sparse, thin and fragile. Bilateral optic atrophy and keratoconjunctivitis were also noted.

An EEG revealed a diffuse bioelectrical abnormality with paroxysmal activity which was more marked in the left hemisphere. A CT scan revealed severe atrophy of the cerebral and cerebellar hemispheres, and dilatation of the third and lateral ventricles. Blood lactate and pyruvate concentrations were both elevated (72 and 2.8 mg / dl, respectively). Blood ammonia was normal (53.8 µ / dl). Blood pH was 7.31 and bicarbonate 8.8 mmol / L. Serum and urine amino acid patterns and immunological studies were found to be normal.

The absence of developmental progress from birth in the presence of lactic acidosis suggested a defect in pyruvate metabolism. The patient died on the tenth day of hospitalization despite all supportive measures. Urine organic acids collected just before his death revealed a pattern compatible with biotinidase deficiency which was subsequently confirmed.

Case 6

This boy was born at 36 weeks gestation by cesarean section with intrauterine growth retardation (birthweight 1750 g) due to the presence of severe preeclampsia and placental insufficiency in the mother. The parents were nonconsanguineous. The first pregnancy had resulted in a spontaneous abortion.

The patient was transferred to the neonatal intensive care unit and experienced hypoglycemia in the first few days of life (blood glucose 20-40 mg / dl). Glucose infusions at a rate of 4-6 mg / min were given. On the third day of life, he became more hypotonic and developed sclerema. Sepsis was suspected, and antibiotic treatment along with immunoglobulin infusions were instituted. On the eighth hospital day, acidotic respiration was noted. Blood pH was 7.32 and bicarbonate 14.1 mmol / L. Serum lactate and pyruvate concentrations were found to be slightly increased (28.1 and 1.0 mg / dl, respectively). Blood ammonia was 180 µg / dl, and paper chromatography of serum and urine samples was found to be normal. An EEG showed the presence of paroxysmal activity in the right hemisphere and a generalized burst suppression pattern. He died on the 13th day of hospitalization.

GC-MS analysis of the urine sample collected just before his death disclosed a pattern seen in biotin-dependent disorders. Serum biotinidase activity was subsequently measured and found to be absent.

Case 7

A 5.5-month-old male infant was first brought to our hospital because of developmental delay. He was the first child of a nonconsanguineous couple. He was seen at our hospital for the second time at the age of 12 months.

On examination, his skin was normal and he had sparse hair growth. He was profoundly hypotonic and unable to hold up his head, sit unaided or walk.

An MRI of the brain demonstrated cerebral cortical atrophy associated with demyelination of the cerebral white matter in the occipital lobes. Blood pH was 7.30 and bicarbonate 13.2 mmol / L. Blood ammonia was slightly increased (140 µg / dl). Serum lactate (45.8 mg / dl) and pyruvate (1.3 mg / dl) concentrations were moderately increased. The urinary organic acid profile was typical for a

biotin-dependent disorder. Serum biotinidase activity was measured and found to be normal.

Biotin (20 mg / day) therapy was initiated and the dose increased to 40 mg/day. The patient began to make developmental progress and, when last seen at three years of age, his development was appropriate.

Case 8

A 3.5-month-old female infant was referred to our hospital for evaluation of hypotonia, noisy respiration and difficulty in swallowing with the suspected diagnosis of Werdnig-Hoffman disease following a hospitalization period of 15 days and having been fed by nasogastric tube at another institution. She had been doing well during the first three months of life, but then began to have feeding and swallowing difficulties. Her parents were nonconsanguineous and had three other healthy children.

On examination, the patient was extremely hypotonic and was unable to hold up her head. Organic pathology of the larynx and nasopharynx was excluded by direct endoscopic examination.

Laboratory investigations revealed a blood pH of 7.31 and bicarbonate 12 mmol / L. A slight increase in serum lactate concentration was detected (32 mg / dl). Serum pyruvate concentration was normal (0.78 mg / dl) as were serum and urine amino acid concentrations and magnetic resonance imaging of the brain. Blood ammonia was slightly increased (152 µg / dl). GC-MS analysis of the urine sample was found to be compatible with a biotin-dependent disorder. Biotinidase activity in serum was normal.

On the grounds of these clinical and laboratory findings, one of the congenital lactic acidoses, particularly Leigh's encephalomyelopathy, was considered. Typical urinary organic acid profile and normal serum biotinidase activity led us to the diagnosis of holocarboxylase synthetase deficiency, and biotin at a dose of 20 mg / day was initiated. The dose of biotin was increased to 40 mg / day. The patient showed clinical improvement, began to tolerate oral feeding and became more active within 20 days. She was discharged from the hospital in good clinical condition but did not return to our unit for follow-up visits.

Discussion

There are two genetically determined biotin-dependent disorders. The first is HCS deficiency, the second a deficiency of biotinidase. These two conditions share some signs and symptoms. Patients with a deficiency of HCS present during the neonatal period with a life-threatening illness, whereas biotinidase

deficiency usually presents after three months of age[1-7]. The age of onset in HCS deficiency varies from one day to eight months[8]. In accordance with those reported in the literature, our patients with HCS deficiency had presented at 5.5 and 3.5 months. The age of the patients with biotinidase deficiency at the time of diagnosis ranged from the first few days of life to 30 months. Since the clinical course was complicated by sepsis in the case diagnosed within the first week of life (Case 6), it is difficult to say to what extent the metabolic defect had played a role in the development of clinical manifestations, although Collins et al.[9] reported a case that was symptomatic from birth. Contrary to the common belief that biotinidase deficiency usually presents later in the first year of life, two patients in our series (Cases 3 and 4) became symptomatic at 70 and 91 days of life, respectively[1-9].

Most children affected by a biotin-dependent disorder exhibit hypotonia, seizures and alopecia[1-12]. Of the six patients with biotinidase deficiency, four were hypotonic as were the two patients with HCS deficiency. Seizure was the initial symptom to bring two biotinidase-deficient patients (Cases 3 and 4) to our attention. The seizures are typically infantile, myoclonic or generalized, and usually do not respond to anticonvulsant therapy, as in the two patients presented[1-12]. Hair was sparse in all patients with biotinidase deficiency, except for the case detected in the newborn period, and in one of the patients with HCS deficiency.

Keratoconjunctivitis and optic atrophy may be noted in biotin-dependent disorders[1-12]. Keratoconjunctivitis was present in two patients (Cases 3 and 5) in our series. Affected children commonly exhibit skin rash in the form of eczema or seborrhea or severe desquamating lesions[1-12]. Such lesions were present in half of our cases with biotinidase deficiency. Patients may have respiratory problems such as apnea, stridor and hyperventilation[1-4,13]. In our series, Case 1 had laryngeal stridor as the initial symptom of the disease, and another (Case 2) had respiratory problems complicated by apnea.

As the children grow older and remain untreated, they will experience loss of vision and hearing of neurosensory type as demonstrated by VEP and BAEP studies[1-12]. Both of these studies were found to be abnormal in two of our patients (Cases 2 and 3) whereas one case (Case 1) had only VEP abnormalities and another (Case 4) only BAEP abnormalities. In the remaining half of the patients, VEP and BAEP studies could not be done. EEG abnormalities, including a burst suppression pattern, have been reported in patients with a biotin-dependent disorder[1-3]. Bioelectric abnormalities were detected on EEG tracings of all of our patients with biotinidase deficiency. The CT scan and MRI of the brain may show hypomyelination[1-3]. These two neuro-imaging studies were performed in

three patients. One CT (Case 5) and one MRI (Case 7) were interpreted as abnormal.

Patients with a biotin-dependent disorder may present with episodes of acidosis or with chronic compensated acidosis[1-3, 10-12]. Acidosis was present in all patients in our series as evidenced by low blood pH and bicarbonate. Both lactic and pyruvic acid are usually found to be elevated in serum and cerebrospinal fluid samples[1-3, 10-12]. A two- to seven-fold increase in serum lactate was present in our cases, whereas pyruvate was increased in all but two cases (Cases 6 and 8). Therefore, patients diagnosed as having primary lactic acidosis should always be evaluated by organic acid analysis to detect these conditions. A characteristic organic aciduria is seen in biotin-dependent disorders[1-3]. In addition to lactic aciduria, excretion of 3-methylcrotonyl glycine, 3-hydroxy-isovaleric acid, 3-hydroxypropionic acid and 2-methylcitric acid is indicative of a biotin-dependent disorder. GC-MS analysis of urine samples showed this typical organic acid pattern in five of our cases (Cases 3, 5, 6, 7 and 8) and prompted us to measure serum biotinidase activity, which was found to be absent in all six cases with biotinidase deficiency.

Hyperammonemia may be found during the acute metabolic episode, particularly in HCS-deficient patients[1-3]. Except for the newborn with biotinidase deficiency complicated with sepsis (Case 6), blood ammonia levels were within normal limits in our biotinidase-deficient patients. Two HCS-deficient patients, however, had slightly increased blood ammonia concentrations similar to what has been reported in the literature.

Amino acid chromatography was done in all patients. Half of the patients showed no abnormality in serum and urine amino acid patterns. Three patients (Cases 1, 2 and 3) had elevated serum and urine concentrations of alanine, and one patient (Case 4) had an increased urine alanine concentratilon. Alanine is known to be increased in conditions associated with lactate and pyruvate accumulation in serum, such as biotin-dependent disorders[14].

Children with these disorders may exhibit feeding problems[1-3]. Cases 3 and 8 in our series presented with swallowing difficulty necessitating nasogastric tube feeding in addition to hypotonia. Harmful effects of lactic acidosis on the nuclei of cranial nerves in the brainstem have been implicated in the pathogenesis of nasopharyngeal and laryngeal functional abnormalities[15].

The clinical picture of a biotin-dependent disorder may resemble that of many other diseases, such as acrodermatitis enteropathica, congenital lactic acidosis, intractable infantile seizures, intermittent maple syrup urine disease, seborrheic dermatitis, severe combined immune deficiency, Leigh's encephalomyelopathy

and Werdnig-Hoffman disease[2]. In our series, acrodermatitis enteropathica in Case 2, infantile spasms in Cases 3 and 4, congenital lactic acidosis and immune deficiency disease in Case 5, and Werdnig-Hoffman disease and Leigh's encephalomyelopathy in Case 8 were initially considered. To confirm the diagnosis, infections as well as true cardiorespiratory and gastrointestinal problems should be excluded, GC-MS analysis of the urine sample should be performed and biotinidase activity measured.

All symptomatic patients may respond well to pharmacologic doses of biotin[1-3,10-12]. We started with a daily total dose of 20 mg in two (Cases 1 and 2) and 10 mg in another two cases (Cases 3 and 4) with biotinidase deficiency. All patients displayed a dramatic response to the treatment, as evidenced by the disappearance of neurological and cutaneous symptoms and correction of metabolic acidosis. Only Case 2, who had a relatively long period of coma, developed gait disturbance, and Case 4 displayed BAEP abnormalities as sequelae of the disease. Biotinidase-deficient patients were doing well on a maintenance dose of 5 mg biotin / day. The response to 20 mg / day biotin treatment was partial in two HCS-deficient patients, and the dose of biotin was doubled subsequently as recommended in the literature[1-3, 10-12].

Biotin-dependent disorders affect both males and females, and consanguinity has been reported in 20 percent of cases[2]. There were five males and three females in our series, and of the eight affected cases, three (Cases 3, 4 and 5) were products of consanguineous marriages. The combined incidence of profound and partial deficiencies of biotinidase is 1 in 61,067 live births[2]. Detection of eight cases at a single metabolic unit during the last few years indicates that biotin-dependent disorders are not rare in our country, where the frequency of other metabolic disorders is also known to be high[16].

In conclusion, it can be said that biotinidase and HCS deficiencies share certain nonspecific signs and symptoms that suggest an infectious disease or cardiorespiratory and gastrointestinal problems. In countries such as Turkey where the frequency of metabolic diseases is high, both biotinidase and HCS deficiencies should be considered in children who experience infantile spasms, especially when they do not respond to anticonvulsive therapy, as well as in children with immunologic dysfunction, unexplained breathing abnormalities, skin rash and / or hair loss, regardless of the age of onset.

Thus, a high index of suspicion of a biotin-dependent disorder in such cases should lead to the measurement of urinary organic acids and serum biotinidase activity and to the initiation of biotin therapy before irreversible central nervous system damage occurs.

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BRAINSTEM AUDITORY EVOKED POTENTIAL, VISUAL EVOKED POTENTIAL AND NERVE CONDUCTION VELOCITY AND THEIR RELATION WITH HbA_{1c} AND β_2 MICROGLOBULIN IN CHILDREN WITH INSULIN DEPENDENT DIABETES MELLITUS*

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SUMMARY: Akıncı A, Deda G, Karagöl U, Teziç T. (Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Brainstem auditory evoked potential, visual evoked potential and nerve conduction velocity and their relation with HbA_{1c} and β_2 microglobulin in children with insulin dependent diabetes mellitus. Turk J Pediatr 1994; 36: 279-287.

Brain stem auditory evoked response (BAER), visual evoked response (VER) and nerve conduction velocities (NCV) were studied in 18 insulin-dependent diabetic children between the ages of 3.5 and 16 years (mean 9.0 ± 3.2 years). The results were compared with those of age-matched controls. The VER latencies of the diabetic children in the right eye and left eye were significantly prolonged when compared with the control group. NCV of n.peroneus and the latency of sensorial n.medianus were significantly impaired when compared with the control group.

Although the latencies of waves III, IV and V of the right ear and the interpeak latencies of I-III, I-V, III-V of both ears were prolonged, the comparison with the control group was not significant. The β_2 microglobulin levels of the diabetic patients were significantly higher than those of the control group. There was a positive correlation between the β_2 microglobulin and the BAER interpeak latencies of wave III-V in both ears ($r: 0.51$ $p < 0.01$). There was also a positive correlation between NCVs of n.peroneus and n.medianus (motor and sensorial) with β_2 microglobulin ($r: 0.52$ $p < 0.01$) and between VER latencies ($r: 0.52$ $p < 0.01$) of both eyes separately.

In our study the prolonged latencies of VER and BAER were detected in the absence of clinical abnormalities in visual and hearing systems. Due to our findings, we conclude that prolongation of latencies of VER and BAER are mostly the first signs of central nervous system (CNS) involvement in insulin-dependent diabetes, and the procedures are easy to perform as well as harmless to patients. *Key words: brainstem auditory evoked potential, visual evoked potential, HbA_{1c}, β_2-microglobulin, insulin dependent diabetes mellitus.*

Neuropathy is the most precocious and frequent complication of diabetes mellitus. All the clinical and diagnostic studies on diabetic neuropathy have concerned only peripheral and autonomic nerve impairment. Very few data exist on the involvement of the central nervous system (CNS) in diabetes, especially in children[1].

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Although the true incidence of diabetic neuropathy has never been rigorously established in a population-based study, the prevalence of neuropathy appears to correlate with the duration and severity of hyperglycemia in both insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus[2]. The pathogenesis of diabetic neuropathy remains largely unresolved. The suggested pathogenetic scheme is summarized in Fig. 1[3]. Hyperglycemia generates rheologic changes to increase endoneural vascular resistance and reduce nerve blood flow (NBF). It also reduces the transport of myoinositol (MI) into nerve and increases nerve glucose, fructose and sorbitol by activating the polyol pathway. The possible effect of hyperglycemia on inducing capillary changes is speculative but of crucial importance. Similarly speculative are other mechanisms (such as genetic and immune mechanisms) of capillary damage. Endoneural hypoxia is secondary to NBF reduction and increased endoneural vascular resistance. Once hypoxia is established, it is postulated that it may start a vicious cycle of further capillary damage and escalating hypoxia. Endoneural hypoxia may impair axonal transport of structural proteins and impair nerve Na-K-ATPase activity. Both mechanisms are postulated to reduce nerve conduction velocity, the former by inducing axonal atrophy and the latter by reducing membrane current density. Nerve MI is also suggested to cause Na-K-ATPase hypoactivity[3] (Fig. 1).

Our investigation aimed to evaluate the degree of early alterations of the optic pathways and hearing system detected by visual evoked response (VER) and

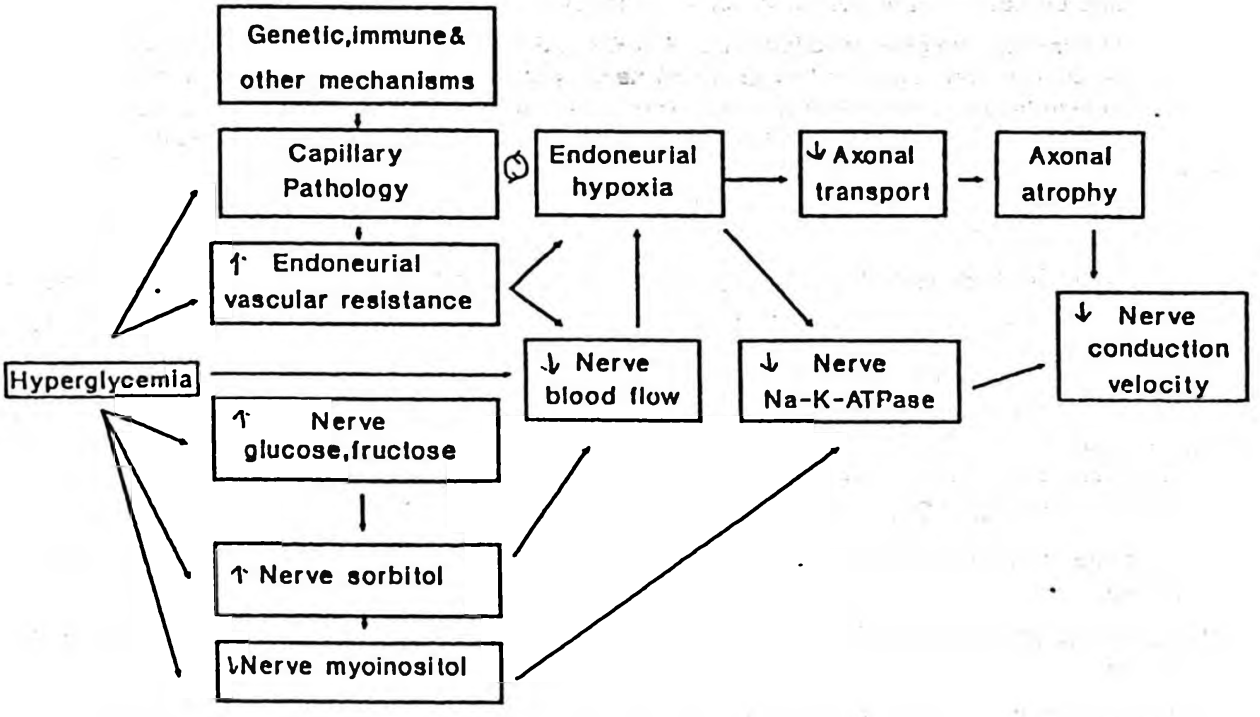

Fig. 1: Suggested pathogenesis of diabetic neuropathy.

brainstem auditory evoked response (BAER) techniques as well as any correlation between VER, BAER and clinical and metabolic parameters of the disease and paraclinical parameters of polyneuropathy in a population of diabetic children without retinopathy or any clinical hearing loss.

Material and Methods

We studied 18 diabetic patients (10 boys, 8 girls), mean age 9.0 ± 3.2 years (range 3.5-16 years) with a mean duration of disease since diagnosis being 38.3 ± 13.1 months (range 20-59 months). All patients were under conventional insulin therapy, regular insulin + NPH insulin twice per day. The mean insulin dosage was 0.6 ± 0.25 IU / Kg / day (0.4-1.1).

The control of diabetes were investigated by regular measurements of HbA_{1c} and blood glucose. None of the patients had visual or hearing impairment.

The control group consisted of nine healthy subjects for BAER with a mean age of 7.2 ± 2.8 years (range of three to 12 years), 10 healthy subjects for VER with a mean age of 7.6 ± 2.8 years (range of three to 12 years) and 16 healthy subjects for nerve conduction velocities (NCVs) of n.peroneus, n.medianus and the latency of n.medianus (sensorial) with a mean age of 8.2 ± 2.83 years (range of 2.5-12 years).

HbA_{1c} and β_2 microglobulin were also studied both in diabetics and in the 18 healthy subjects.

The patients were evaluated for retinopathy by angiography and none displayed evidence of it.

Evoked potential studies:

Visual evoked potentials were recorded in a dark room. Both eyes were stimulated separately and binocularly at full field by a checkboard pattern reversal with a 16 x 16 mm check size at 1 Hz. The amplitude and latency of the positive wave (P100) were calculated.

Brainstem auditory evoked responses were recorded in a shielded, sound-attenuated room with stimulus at an intensity of 90 decibels normal hearing level (nHL) in both ears at 10 cps. During BAER recording, silver surface electrodes were applied at the vertex (explorer), the forehead (ground) and the auricular lobe (common) with standard electrode paste as conductive medium. Acoustic alternating transients were presented monoaurally through shielded earphones. The computer average of 2000 clicks was obtained for each ear. Wave I through V individual latencies, and interpeak latencies between waves I-III, I-V and III-V were measured. The latency was evaluated from the electrical onset of the click at the earphone to the peak of the wave. Wave I latency

values are considered to be the index of peripheral transmission, while wave I-V interpeak latency represents an index of central transmission time. Wave I is generated primarily by the portion of nerve VIII that is contiguous with the spiral ganglion in the mastoid bone, while wave II represents cochlear nuclei (pons), wave III represents superior olivary, wave IV represents lateral lemniscus and wave V represents inferior colliculus (midbrain)[4].

Motor nerve conduction velocities were evaluated from n.peroneus and n.medianus. Sensorial latency of n.medianus was also detected using a Nihon Kohden Neuropack 2 device according to Thompson[5].

β_2 microglobulin was measured by the radioimmunoassay method with Pharmacia double antibody.

HbA_{1c} was studied with chromatographic spectrophotometry (Biosystem, ion-exchange).

Statistical analysis: Student's t test, paired t test and correlation analyses were used.

Results

There was no significant difference between the ages of diabetic patients and the control groups ($p > 0.05$).

Table I: Latencies of Brainstem Auditory Evoked Response (msec)

Wave	Diabetic Patients	Control Group	
Left Ear	90 dB	90 dB	P
I	1.41 + 0.28	1.76 + 0.40	> 0.05
II	2.47 + 0.23	2.75 + 0.49	> 0.05
III	3.63 + 0.32	3.96 + 0.45	> 0.05
IV	4.80 + 0.33	5.12 + 0.42	> 0.05
V	5.78 + 0.44	5.84 + 0.51	> 0.05
I-III	2.26 + 0.20	2.19 + 0.14	> 0.05
III-V	2.05 + 0.48	1.83 + 0.21	> 0.05
I-V	4.30 + 0.44	4.07 + 0.19	> 0.05
Right Ear			
I	1.56 + 0.27	1.54 + 0.51	> 0.05
II	2.82 + 0.20	2.73 + 0.59	> 0.05
III	3.93 + 0.46	3.73 + 0.59	> 0.05
IV	5.05 + 0.38	4.70 + 0.60	> 0.05
V	6.00 + 0.58	5.71 + 0.80	> 0.05
I-III	2.36 + 0.52	2.23 + 0.44	> 0.05
III-V	2.10 + 0.18	1.97 + 0.47	> 0.05
I-V	4.47 + 0.62	4.16 + 0.69	> 0.05

In our study the latencies of waves III, IV and V of the right ear and the I-V, I-III, III-V interpeak latencies of both ears were prolonged in the diabetic patients

but were not statistically significant when compared with the control group. Pattern-shift visual evoked responses (PSVER).

Table II: Visual Evoked Potentials

	Diabetic Patients	Control Group	P
P100 latencies (ms.)			
Left eye	113.83 + 10.09	93.47 + 4.31	< 0.001
Right eye	111.41 + 10.72	94.17 + 4.11	< 0.001
Binocular	109.92 + 16.32	108 + 6	> 0.05
Amplitudes (uV)			
Left eye	11.12 + 4.40	6.9 + 2.3	
Right eye	10.90 + 3.75	6.6 + 2.3	

There was a significant increase in the P100 latencies of the right and left eye separately ($p < 0.01$) (Fig. 2). With binocular stimulation there was no significant increase in P100 latency ($p > 0.05$). None of these patients had retinopathy. There was no correlation between PSVEP and age, duration of diabetes, or HbA_{1c} using correlation analysis, but there was a positive correlation between β_2 microglobulin and the P100 latencies (Fig. 3) (r: 0.52, $p < 0.01$) of both eyes separately; there was also a positive correlation between motor nerve conduction velocity of n.peroneus and P100 latency of the left eye.

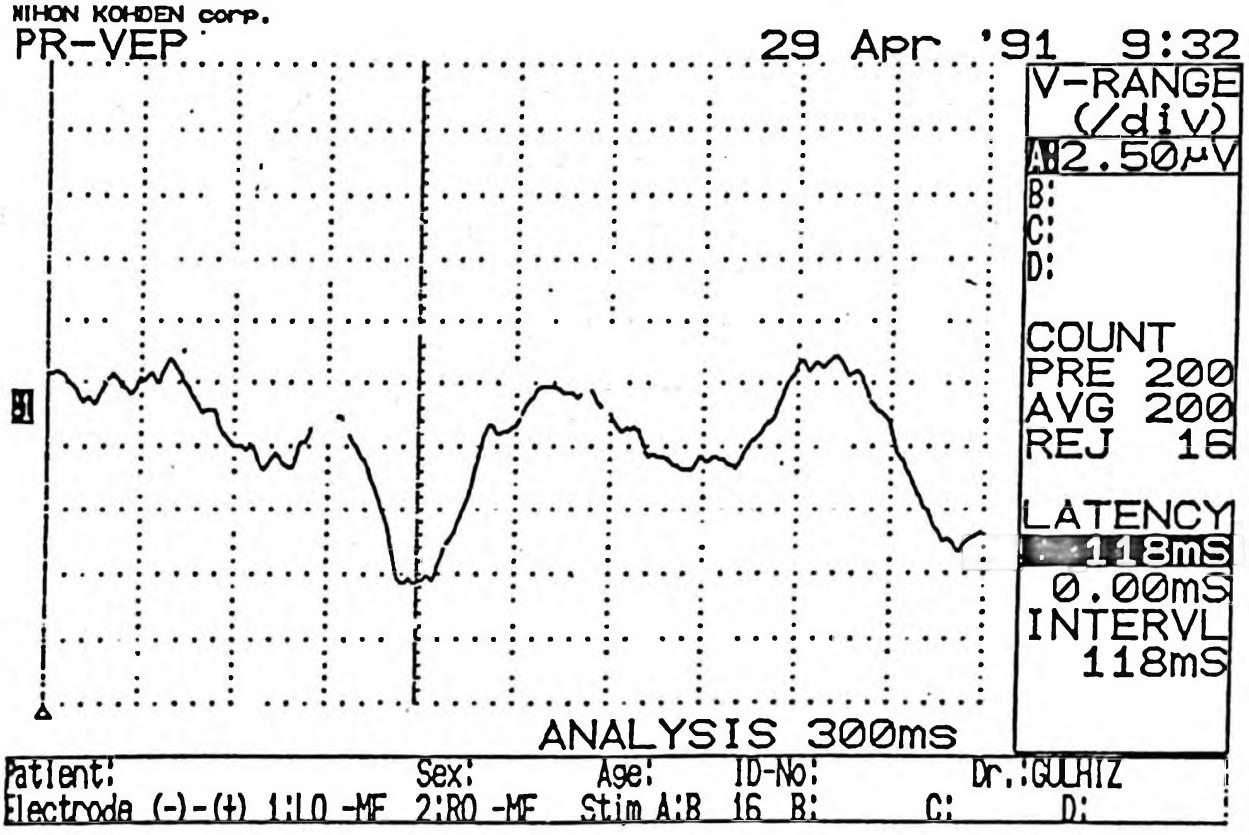

Fig. 2: VER Recorded From a Diabetic Patient.

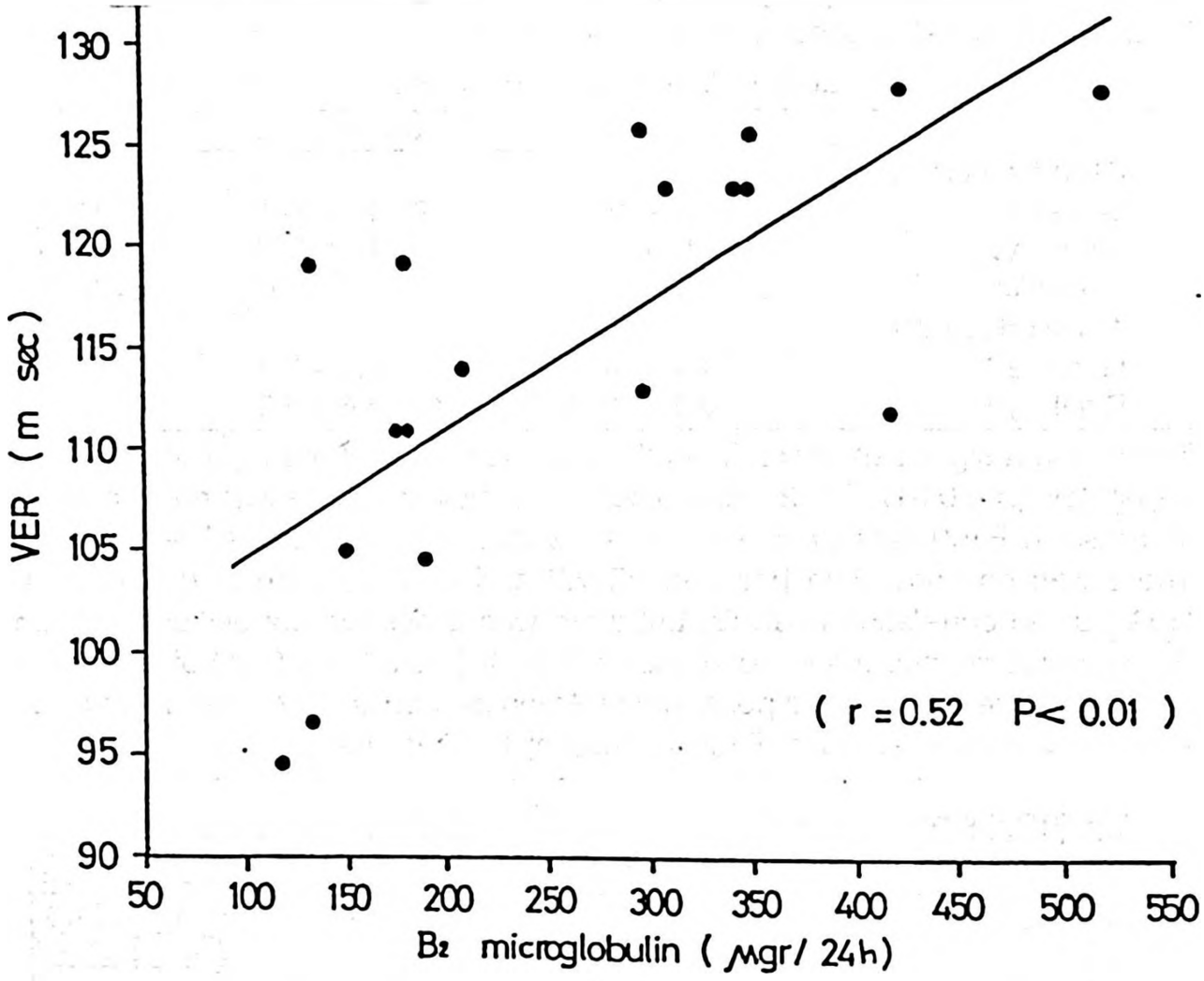

Fig. 3: Correlation between β_2-microglobulin in urine and P100 latencies of left eye in diabetic patients.

Table III: Nerve Conduction Velocities

	Diabetic Patients	Control Group	P
Motor NCV (m/sec)			
N.medianus	54.53 + 10.56	57.25 + 6.88	> 0.05
N.personeus	46.38 + 11.38	54.27 + 6.89	< 0.05
N.medianus sensorial Latans (msec)	2.30 + 0.38	2.73 + 0.83	< 0.05

Motor nerve conduction velocity of n.peroneus correlated positively with the duration of diabetes (Fig. 4) (r: 0.49, $p < 0.05$) and with β_2 microglobulin (r: 0.52, $p < 0.01$).

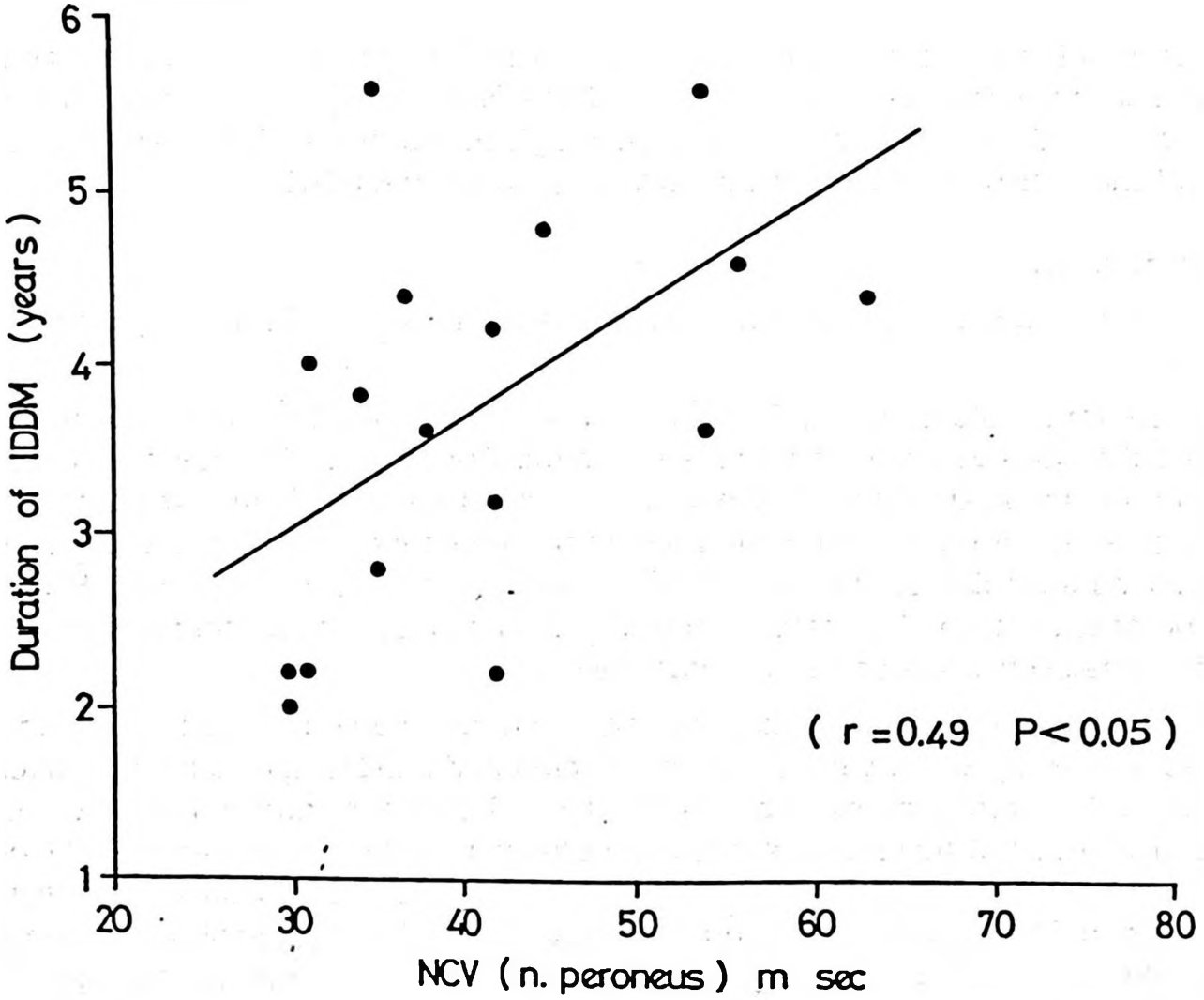

Fig. 4: Correlation between duration of diabetes and motor nerve conduction velocity of n.peroneus in diabetic patients.

Table IV: HbA_{1c} and β_2-microglobulin

	Diabetic Patients	Control Group	P
HbA_{1c} (g / dl)	11.8 + 2.4	5.42 + 0.80	< 0.001
β_2-microglobulin (µg / 24 hours)	311.28 + 56.78	89.96 + 20.35	< 0.001

The HbA_{1c} level of the diabetic patients was between 8.5 and 15 g / dl (mean 11.8 ± 2.4), and the HbA_{1c} level of the control group was between 4.5 and 6.9 g / dl (mean 5.42 ± 1.80). The difference between HbA_{1c} concentrations in diabetic patients and the control group was statistically significant ($p < 0.01$).

The β_2 microglobulin levels in the diabetic patients were between 196 and 711 µg / 24 hours (mean 311.28 ± 56.78), while the control group ranged from 72 to 135 µg / 24 hours (mean 89.96 ± 20.35). There was a significant difference between these two groups ($p < 0.01$).

Although there was no correlation between HbA_{1c} and motor nerve conduction velocities of n.medianus, n.peroneus and sensorial latency of n.medianus, there was a positive correlation between β_2 microglobulin and the NCV of n.peroneus and the sensorial latency of n.medianus (r: 0.52, $p < 0.01$).

Discussion

Our results demonstrate abnormalities in the PSVER and BAER of subjects with IDDM.

Since wave I latency of BAER was normal in our patients, it must be concluded that the observed abnormalities are central. Abnormal BAER has also been reported by other authors[1-6]. Whether these changes result from primary neural involvement or represent neural dysfunction secondary to vascular involvement remains speculative. Our study failed to show any correlation between BAER and age, duration of diabetes and HbA_{1c}. In one study[6] the authors also found no correlation between these parameters.

The mean latency of PSVERs of the right and left eye separately in our study group were significantly prolonged when compared with the age-matched control group. No correlation existed between PSVER and age, duration of diabetes and HbA_{1c}, but there was a positive correlation between the motor NCV of n.peroneus and P100 latency of the left eye. There was also a positive correlation between P100 latencies of both eyes separately and β_2 microglobulin. In most of the studies there was also prolongation of P100 latency in diabetic patients[7-10]. Our diabetic patients had no complaints related to the eye, their visual acuity was near normal and they showed no signs of retinopathy. Yet an appreciable delay of conduction in the optic nerve occurred in our patients. The delay was bilateral, suggesting that the visual pathway was diffusely affected. Since β_2 microglobulin is an indicator of control of diabetes, the increased amount of this indicator indicates poor control of diabetes, as in our study. Because of the correlation between β_2 microglobulin and P100 latencies of VER, we may say that the prolonged VER latencies were due to poor control of diabetes. Prolongation in the optic nerve parallels peripheral nerve conduction[10], which correlates with our study.

In our study NCV of n.peroneus correlated positively with the duration of diabetes, a finding confirmed by other studies[11].

Although NCV is associated with both the duration of diabetes and β_2 microglobulin, the III-V interpeak latency of both ears had a positive correlation with only β_2 microglobulin. β_2 microglobulin levels in our study group were significantly higher than those of the control group, but according to the literature[12] it is at the upper limit of normal values. Increased β_2 microglobulin

is the first sign of degeneration of renal tubular cells[13]. As β_2 microglobulin and latencies of BAER and VEP correlate positively, we may speculate that the degeneration of cells of the urinary and nervous system probably occur at the same time.

In our study the prolonged latencies of VER and BAER were detected in the absence of clinical abnormalities in the visual and hearing systems. Thus we can say that prolongation of latencies of VER and BAER are the first signs of CNS involvement in IDDM. These techniques are easy to perform and harmless to the patient. We recommend that these investigations be done in every diabetic patient, regardless of the duration of the disease.

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SERUM FERRITIN AND HEMOGLOBIN LEVELS OF MOTHERS AND THEIR NEWBORNS*

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*Mukadder Selimoğlu MD******, *Meltem Energin MD****

SUMMARY: Altınkaynak S, Alp H, Bastem A, Selimoğlu M, Energin M. (Department of Pediatrics, Atatürk University Faculty of Medicine, Erzurum, Turkey). Serum ferritin and hemoglobin levels of mothers and their newborns. Turk J Pediatr 1994; 36: 289-293.

In this study, hemoglobin, serum ferritin, serum transferrin, transferrin saturation, serum iron and total iron-binding capacity were measured in venous blood taken from 52 primiparous mothers approximately one hour before delivery and in cord blood from their newborns after birth. The mean maternal serum ferritin level was 12.9 ± 8.9 ng / ml. This value was lower than that of healthy women. The mean serum ferritin level of cord blood was 103.0 ± 54.1 ng/ml. While we found no correlation between maternal and cord blood hemoglobin values, we observed a significant positive correlation between serum ferritin values in maternal and cord blood. Only the serum ferritin levels of mothers whose iron stores had been depleted were significantly reflected in their babies' levels ($p < 0.001$). There was no statistically significant difference in other parameters ($p > 0.05$). It is concluded that serum ferritin levels, which are affected earlier than hemoglobin levels, should be measured for the diagnosis of occult iron deficiency. *Key words: hemoglobin, ferritin, mother, newborn.*

Iron components keep their balance in the body with construction and usage and can be categorized into two groups. The first group of components includes those having enzymatic and metabolic functions, of which hemoglobin is the most important. The second group comprises components related to iron supplementation and transportation.

Iron bound to apoferritin is stored as ferritin in iron stores. Ferritin and hemosiderin together comprise 20 percent of total body iron. Serum ferritin is mainly an intracellular protein and a useful indicator of iron stores. A serum ferritin level of 1 ng/ml reflects 8 mg of stored iron. Serum ferritin levels that are less than 10 ng/ml in children and 12 ng / ml in adults suggest that iron stores have been depleted[1-3].

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Iron deficiency anemia is the most commonly encountered type of anemia in childhood, even in developed countries. In our developing country, especially in our region, this problem clearly needs more attention. In our country, the nutritional status of pregnant women and children is inadequate; sensitive tests reflecting the amount of iron stores are affected by the iron status of the body before the hemoglobin level decreases. These tests are used to detect mild anemia in our country.

We planned this study to investigate the value of serum ferritin levels compared to hemoglobin levels for diagnosing occult iron deficiency in newborns and their mothers.

Material and Methods

This study included 52 primiparous mothers without complications and their neonates born at Atatürk University Faculty of Medicine Gynecology and Obstetrics Department between January and October, 1990. Blood samples were taken from mothers' peripheral veins one hour before delivery and from newborns' umbilical cords. Hemoglobin levels were measured by semi-automatic hematologic analyzer Cell. Dyn 1500; serum ferritin by Ferritin Enzyme Testing Kits of Medix Biotech Inc; and serum transferrin by Hitachi-705 autoanalyzer. The serum iron-binding capacity was calculated using the following formula: Total Iron Binding Capacity = Unsaturated Iron Binding Capacity + Serum Iron Level. Data were assessed by Student's t test, and linear regression analyses were made[4].

Results

The fifty-two mothers in this study were between the ages of 18 and 39 years, with a mean age of 26 ± 5.3 years. The mean birth weight of the newborn infants was 3136 g (2500-4400 g), with gestational ages of 38-40 weeks. Twenty-seven of the newborns were female (52%) and 25 were male (48%). The ratio of girls to boys was 1.1.

Hemoglobin, serum ferritin, serum transferrin, transferrin saturation, serum iron and total iron-binding capacity levels from the venous blood of mothers and the cord blood of newborns are shown in Table I.

Newborns of mothers whose iron stores had been depleted (< 12 ng/ml) ($p < 0.001$) had significantly lower levels of serum ferritin (76.5 ± 27.7 ng/ml) as compared to the levels of newborns of mothers with adequate iron stores (153.2 ± 56.8 ng/ml) (Table II). Statistical differences between other parameters were not significant ($p > 0.05$).

Table I: Values Detected from Venous Blood of Mothers and Cord Blood of Their Newborns (n: 52)

	Mother X ± SD	Newborn X ± SD	Mother, Newborn t	p
Hemoglobin (g/dl)	12.2 ± 1.4	16.0 ± 1.5	13.2	< 0.001
Serum Ferritin (ng/ml)	12.9 ± 8.9	103.0 ± 54.1	11.8	< 0.001
Serum Transferrin (mg/dl)	280.8 ± 31.3	205.1 ±37.6	11.2	< 0.001
Transferrin Saturation (%)	12.4 ± 2.3	45.0 ± 10.5	21.8	< 0.001
Serum Iron (µg/dl)	42.6 ± 7.0	110.4 ± 10.6	38.4	< 0.001
Total Iron Binding Capacity (µg/dl)	348.1 ± 50.7	260.3 ± 53.7	8.6	< 0.001

Table II: Hemoglobin, Serum Ferritin Values and Other Parameters of Mothers Whose Iron Stores are Depleted (Group IIA), of Their Newborns (Group IIB), and of Mothers Who Have Adequate Iron Stores (Group IA) and of Their Newborns (Group IB).

	Group I A (n: 18)	Group I B (n: 18)	Group II A (n: 34)	Group II B (n: 34)	Group IB vs IIB	
	$\bar{X}$ ± SD	$\bar{X}$ ± SD	$\bar{X}$ ± SD	$\bar{X}$ ± SD	t	p
Hb (g / dl)	13.1 ± 0.7	16.1 ± 1.3	11.6 ± 1.4	5.9 ± 1.6	0.1	> 0.5
S.Ferritin (ng/ml)	20.2 ± 12.1	153.2 ± 56.8	9.1 ± 1.7	76.5 ± 27.7	5.7	< 0.001
S.Transferrin (mg / dl)	279.0 ± 33.6	208.8 ± 30.4	281.8 ± 30.2	203.2 ± 41.2	0.2	> 0.05
Transferrin Sat (%)	14.4 ± 1.1	44.8 ± 8.1	11.3 ± 2.0	45.0 ± 11.7	0.1	> 0.05
Serum Iron (µg/dl)	49.2 ± 5.2	111.2 ± 11.3	39.2 ± 5.1	110.0 ± 10.4	0.2	> 0.05
T.I.B. Capacity (µg/dl)	348.3 ± 33.4	256.3 ± 38.4	348.1 ± 58.3	257.7 ± 60.6	0.3	> 0.05

Discussion

The incidence of iron-deficiency anemia is higher in developing countries and during pregnancy and childhood. Moreover, children of mothers with iron deficiency are at risk of developing iron-deficiency in early childhood. In diagnosing occult iron deficiency, serum ferritin measurements that show the status of iron stores provide accurate information[2, 5-11].

During pregnancy, the fetus' only iron source is the plasma iron of the mother. Even when the mother's reserve of iron is used up, the fetus can obtain sufficient iron for erythropoiesis from his mother. For that reason, hemoglobin levels of newborns are not affected by occult iron deficiency or empty iron stores of mothers[3, 10, 12]. Although 34 of 52 mothers had empty iron stores, their babies had normal hemoglobin levels (15.9 ± 1.6 g/dl).

When iron deficiency develops, iron stores are depleted before hemoglobin levels significantly decrease. The most reliable and sensitive indicator of the mother's iron status is her serum ferritin level[1, 10, 13]. In our study, the mean value of the mother's serum ferritin was 12.9 ng/ml. In some other studies, this level

ranged from 17.3 to 29.1 ng/ml[8, 10, 12-15]. We concluded that our low values reflected irregular ingestion of iron by mothers during pregnancy and low socioeconomic levels in our region. Only six mothers in our study took iron regularly.

We found that the difference between the mean hemoglobin values of mothers and newborns was statistically significant ($p < 0.001$). While MacPhail et al[12] stated that there was a positive correlation between hemoglobin values of maternal blood and umbilical cord blood, other investigators stated the opposite[9, 10, 15]. We did not see a positive correlation between them.

The mean serum ferritin values of the newborns' cord blood was 103 ± 54.1 ng / ml, which was similar to that cited in the literature[6, 10, 12, 16, 17]. There was a significant positive correlation between the mean serum ferritin value of mothers

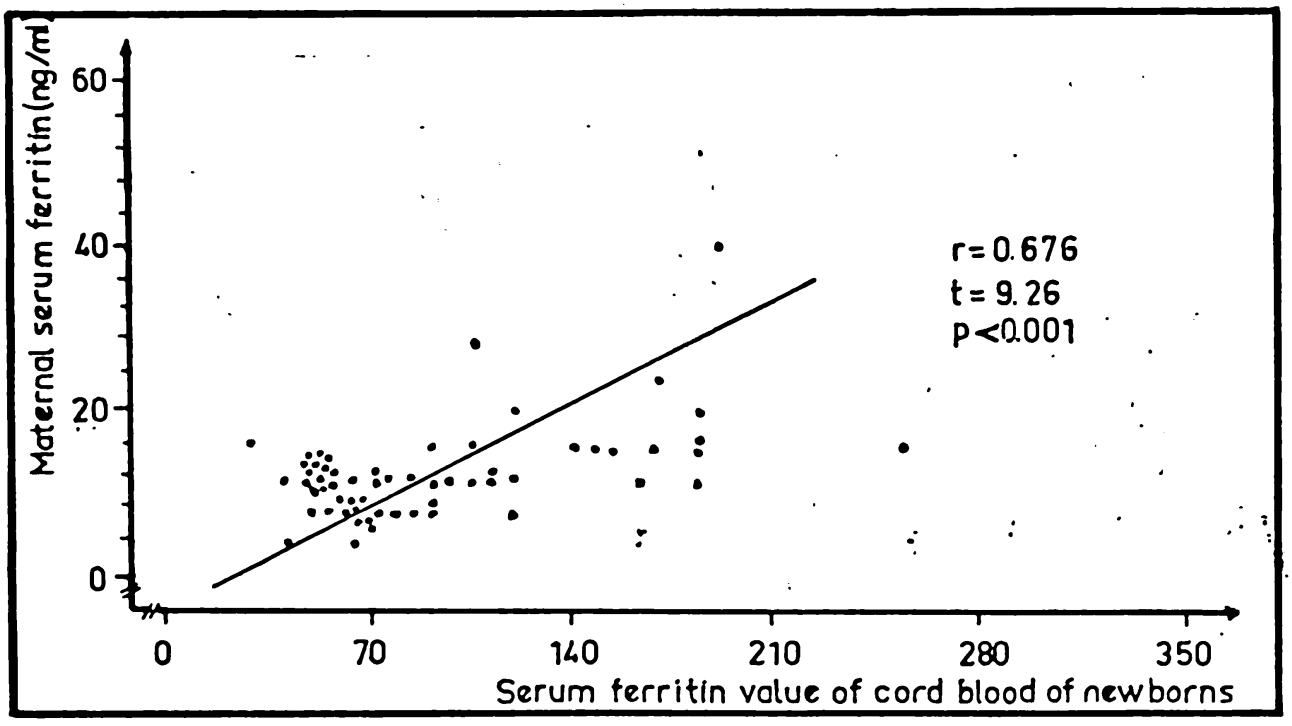

Fig. 1: Correlation between serum ferritin values in maternal and cord blood.

and of newborns-again similar to that cited in the literature[9, 10, 13] (Fig. 1). In our study, only the serum ferritin levels of mothers whose iron stores had been depleted were reflected in their babies' levels ($p < 0.001$). We did not find such a statistically significant difference in other parameters, as shown in Table II.

In conclusion, because we found no correlation between the hemoglobin values of mothers and children, we recommend that serum ferritin levels, which are

affected earlier than hemoglobin, be measured for the diagnosis of occult iron deficiency.

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MESENTERIC AND OMENTAL CYSTS IN CHILDREN*

Analysis of Nineteen Cases

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SUMMARY: Şenocak ME, Gündoğdu H, Büyükpamukçu N, Hiçsönmez A. Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Mesenteric and omental cysts in children: analysis of nineteen cases. Turk J Pediatr 1994; 36: 295-302.

Mesenteric and omental cysts are infrequently encountered, benign, intraabdominal tumors. Nineteen new patients were analysed. The most common presenting symptoms were abdominal distension (74%) and abdominal pain (63%). A palpable abdominal mass was found in 58 percent of cases. A correct preoperative diagnosis was established in 91 percent of the patients who were examined by abdominal ultrasonography. Of 19 cases documented at laparotomy, 14 patients (74%) had mesenteric, and five patients (26%) omental cysts. Eleven of the former were located in the small bowel mesentery. All of the cysts were completely removed, and in eight of them bowel resection was required. Subtotal gastrectomy was performed in one case. The mortality rate wase 0%. After a mean follow-up period of five years, no recurrence was observed. Our study showed that abdominal ultrasonography by experienced professionals is the most reliable diagnostic tool for detecting these lesions. *Key words: mesenteric cysts, omental cysts, intraabdominal cysts, intraabdominal cystic lymphangiomas.*

Mesenteric and omental cysts are uncommon, clinically confusing, unilocular or multilocular, endothelium-lined, intraabdominal, benign lesions that contain either chylous or serous fluid[1].

Many etiologic theories propose that these cysts arise from a congenital developmental abnormality of the lymphatic system, which results in ectopic lymphatic tissue that proliferates and collects fluid owing to a lack of communication with the central lymphatic system1.

Because these cysts are seen so infrequently, very little information about them is available[2]. Only a few cases are documented in the literature. For these reasons, our relatively large surgical experience with these cysts has been reviewed to aid other clinicians in the diagnosis and treatment of these uncommon pathologies.

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Table I: Clinical Summary of the Patients

Case No.	Age (Year)	Sex	Presenting Complaints	Palpable Mass	Type	Localization	Surgical Procedures	Complications and treatment	Results
1	8/12	M	Abdominal pain	Present	MC	Descending colon	Resection and anastomosis	Early adhesive ileus, Adhesiolysis	Recovered
2	6	F	Abdominal distension	Present	MC	Ileum	Simple excision	–	Recovered
3	6	F	Abdominal pain and distension	Absent	MC	Ileum	Simple excision	–	Recovered
4	4	F	Abdominal pain	Absent	MC	Jejunum	Resection and anastomosis	–	Recovered
5	14	F	Abdominal distension	Present	MC	Ileum	Resection and anastomosis	–	Recovered
6	3	M	Abdominal distension	Present	OC	Omentum major	Simple excision, Subtotal gastrectomy	Pyloric obstruction, Pyloroplasty	Recovered
					OC	Omentum minus			
7	2 1/2	M	Abdominal distension	Absent	MC	Sigmoid colon	Resection and anastomosis	–	Recovered
8	3	F	Abdominal pain, vomiting	Present	MC	Ileum	Resection and anastomosis	–	Recovered
9	3 1/2	M	Abdominal pain and distension	Present	OC	Omentum major	Simple excision	–	Recovered
10	1 1/2	M	Abdominal pain and distension	Present	MC	Ileum	Simple excision	–	Recovered
11	12	M	Abdominal pain and distension	Absent	OC	Omentum major	Simple excision	–	Recovered
12	7	M	Abdominal distension	Present	MC	Ascending colon	Simple excision	–	Recovered
13	12	F	Abdominal pain, vomiting	Absent	MC	Ileum	Resection and anastomosis	–	Recovered
14	4	F	Abdominal pain and distension	Present	MC	Jejunum	Resection and anastomosis	–	Recovered
15	8 1/2	M	Abdominal pain	Absent	MC	Jejunum	Simple excision	–	Recovered
16	3	M	Abadominal pain and distension	Absent	OC	Omentum major	Simple excision	–	Recovered
17	6	M	Abdominal pain and distension, vomiting	Present	OC	Omentum major	Simple excision	–	Recovered
18	6	M	Abdominal distension	Absent	MC	Jejunum	Resection and anastomosis	–	Recovered
19	9	M	Abdominal distension	Present	MC	Jejunum	Simple excision	–	Recovered

Abbreviations: MC, mesenteric cyst; OC, omental cyst.

Material and Methods

Nineteen patients with mesenteric (n = 14) and omental (n = 5) cysts treated in the Pediatric Surgery Department of Hacettepe University Faculty of Medicine between January 1973 and January 1989 have been reviewed. Twelve patients were male and seven were female. The ages of the patients ranged between 8 months and 14 years, with a median age of 5.87 ± 1.81 years. The clinical history of the disease was learned from the parents and the patients themselves.

After a general physical examination and routine laboratory studies (e.g. complete blood count, urinalysis, plain radiographs of the abdomen and chest), intravenous pyelography (IVP) and barium enema were obtained to rule out the existence of a mass originating from the gastrointestinal (GI) or genitourinary tract. Abdominal ultrasonography has been performed as a first diagnostic study since 1983 and was used in 11 cases presented here.

All of the patients underwent laparotomy, and all of the cysts were removed completely. Clinical data of the cases are summarized in Table I.

Results

According to the statistical records, there were approximately 1,471,968 admissions to Hacettepe University Children's Hospital between 1973 and 1989. Nineteen patients with mesenteric and omental cysts were treated during this 16-year period.

Abdominal distension and pain were chief presenting symptoms in 14 and 12 of the patients, respectively, while these symptoms coexisted in seven patients. One patient presented with an acute mechanical obstruction of the small bowel as a result of firm adhesions between the intestinal segments and omental cyst. Two patients presenting with intermittent vomiting had partial intestinal obstruction due to compression of the bowel stretched over the cyst in the ileal mesentery.

On physical examination, an abdominal mass could be palpated in 11 of the 19 patients (58%). Nine of those (82%) had protuberant abdomens.

Plain radiographs of the abdomen showed a mass effect that is gasless, homogenous, and of water density displacing the intestinal tract gases in three (16%) patients (Fig. 1a). Abdominal calcification was not observed in any case. IVP was obtained in 10 cases and was interpreted as normal. Only two of the nine barium enemas revealed intraabdominal mass effect, displacing the sigmoid and ascending colon (Fig. 1b); the others were completely normal. Abdominal ultrasonography delineated the cystic mass in 10 of 11 patients examined (Fig. 2a-b).

On laparotomy, 14 mesenteric and six omental cysts were found. (One patient

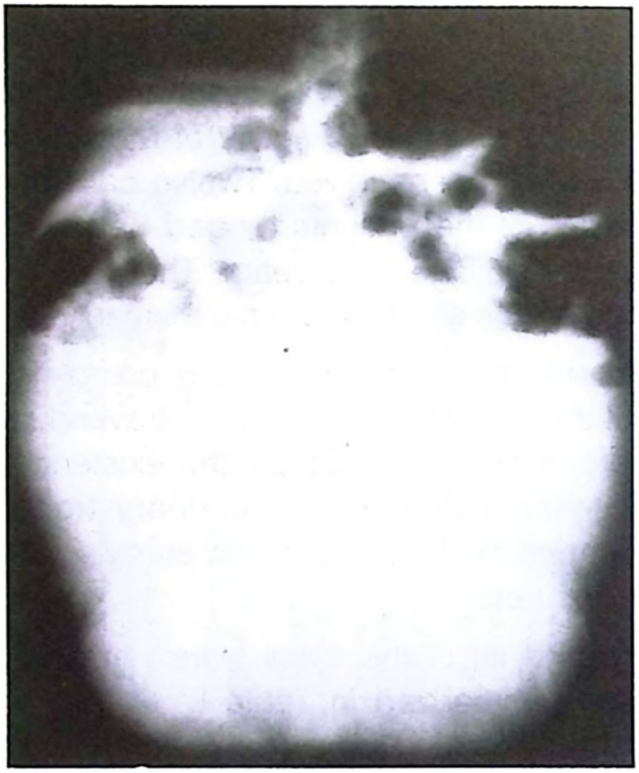


Fig. 1a) Plain abdominal radiograph showing space-occupying mass effect displacing the bowel gases.

Fig. 1b) The barium enema demonstrating an extrinsic mass impinging on the sigmoid and ascending colon.

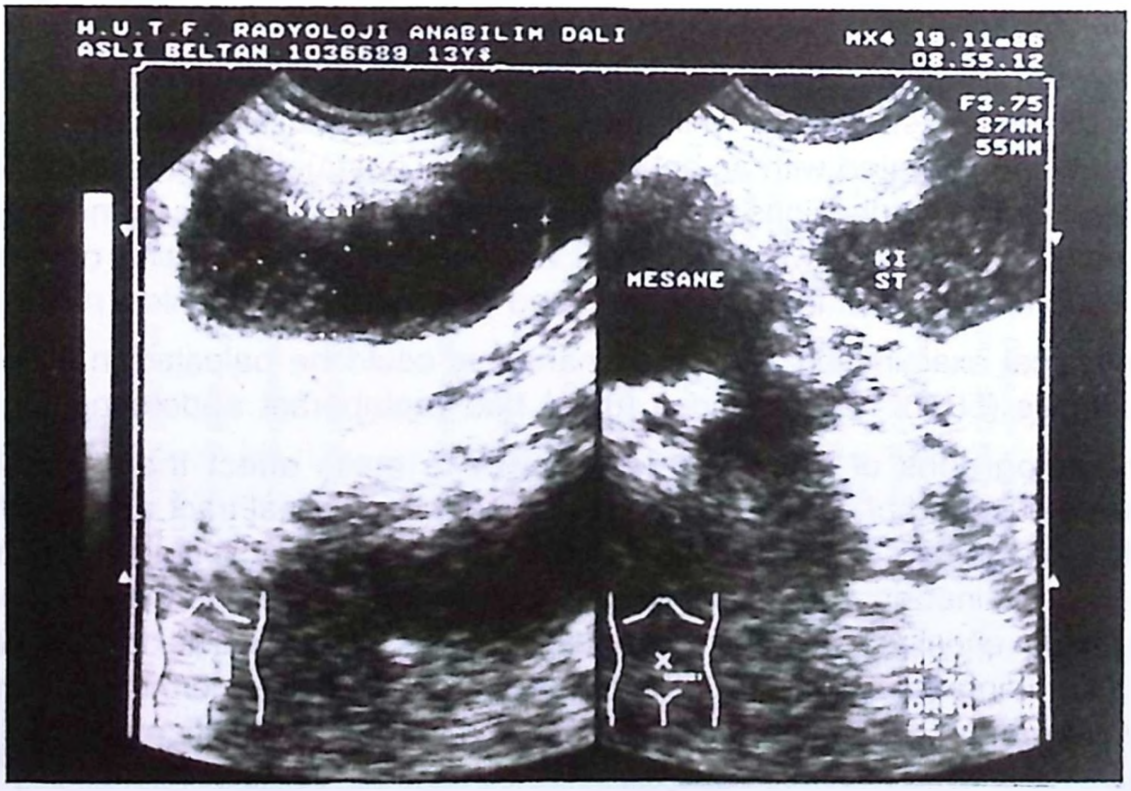


Fig. 2a) Abdominal ultrasonography showing an intraabdominal cystic mass filled with fluid.

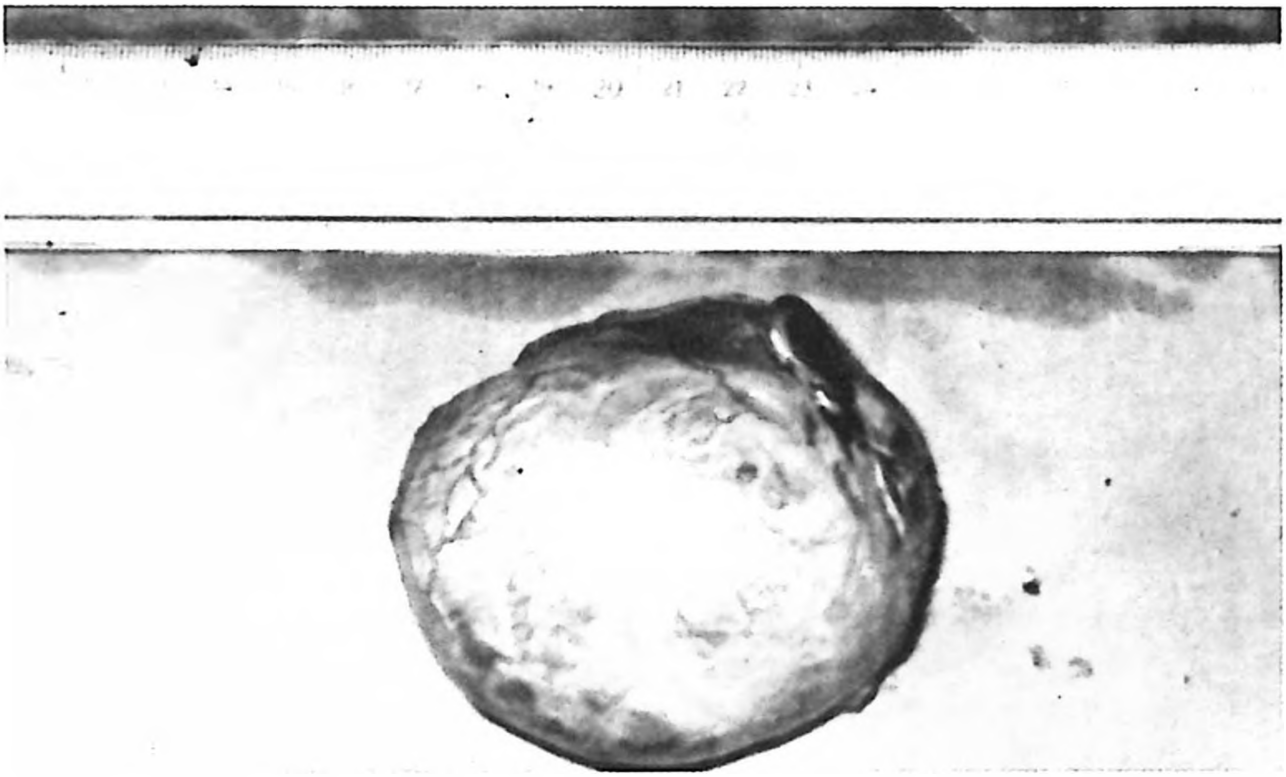


Fig. 2b) Gross surgical specimen of the same patient: the mesenteric cyst has been totally excised with adjacent bowel segment.

had two omental cysts in the omentum minus and major). Of the mesenteric cysts, six were ileal, five were jejunal, and three were in the large bowel mesentery (Table I). All of the omental cysts were serous. Two of the mesenteric cysts contained chylous fluid (Fig. 3 a-b).

Five omental and six mesenteric cysts were simply excised. In eight cases, the overlying bowel was resected along with the cyst, and primary end-to-end anastomosis was performed. Subtotal gastrectomy was performed to remove the cyst located in the omentum minus in one case. Seventeen of the patients had uneventful recoveries. Early adhesive ileus requiring surgical intervention developed in one patient on the seventh postoperative day, and adhesiolysis was performed. Another patient who had a subtotal gastrectomy was readmitted with evidence of pyloric obstruction 16 days after the initial operation, and pyloroplasty was performed. None of the patients developed a recurrence of the cyst and required a second operation after a mean follow-up period of five years.

Microscopic examination of the specimens showed simple cysts with a lining composed of either fibrous tissue or single-layered endothelial cells in all cases. Cyst wall calcification was not detected in any of the patients, and none of the cysts was malignant.

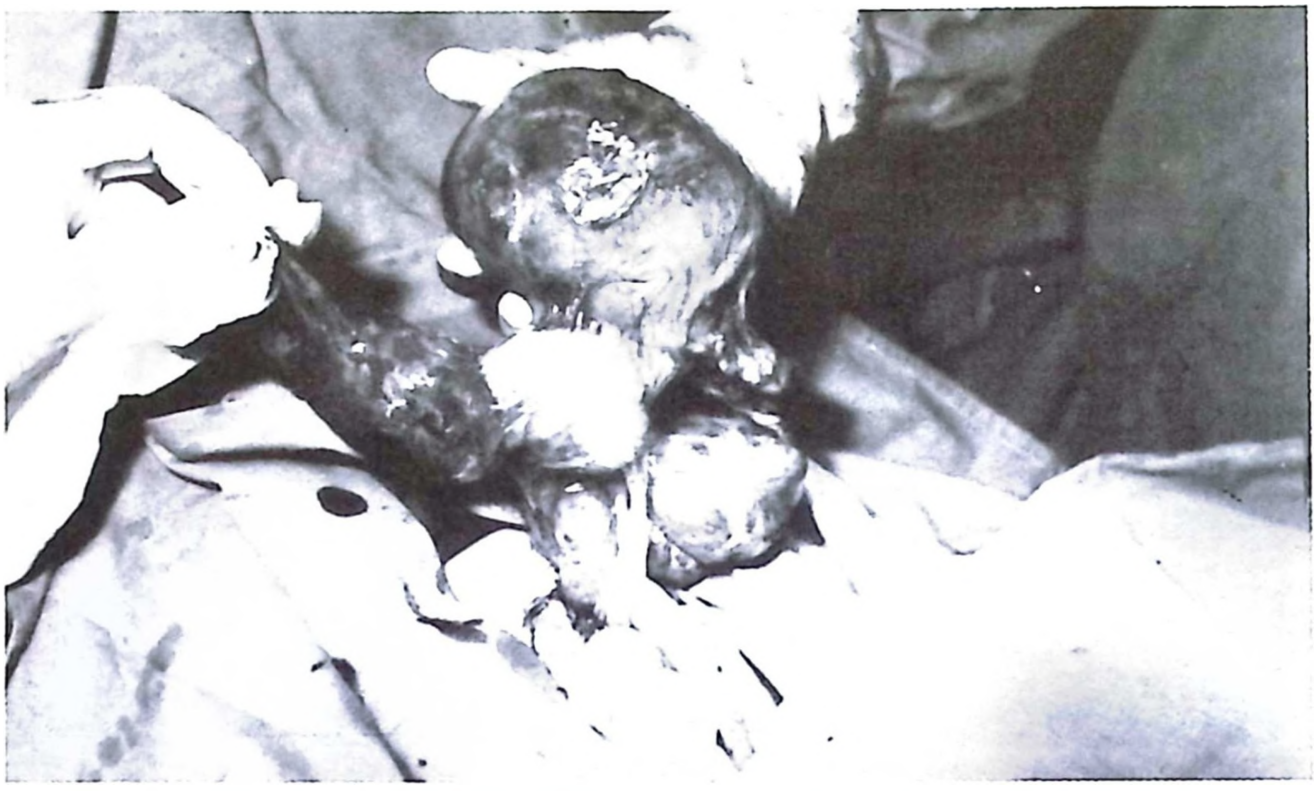
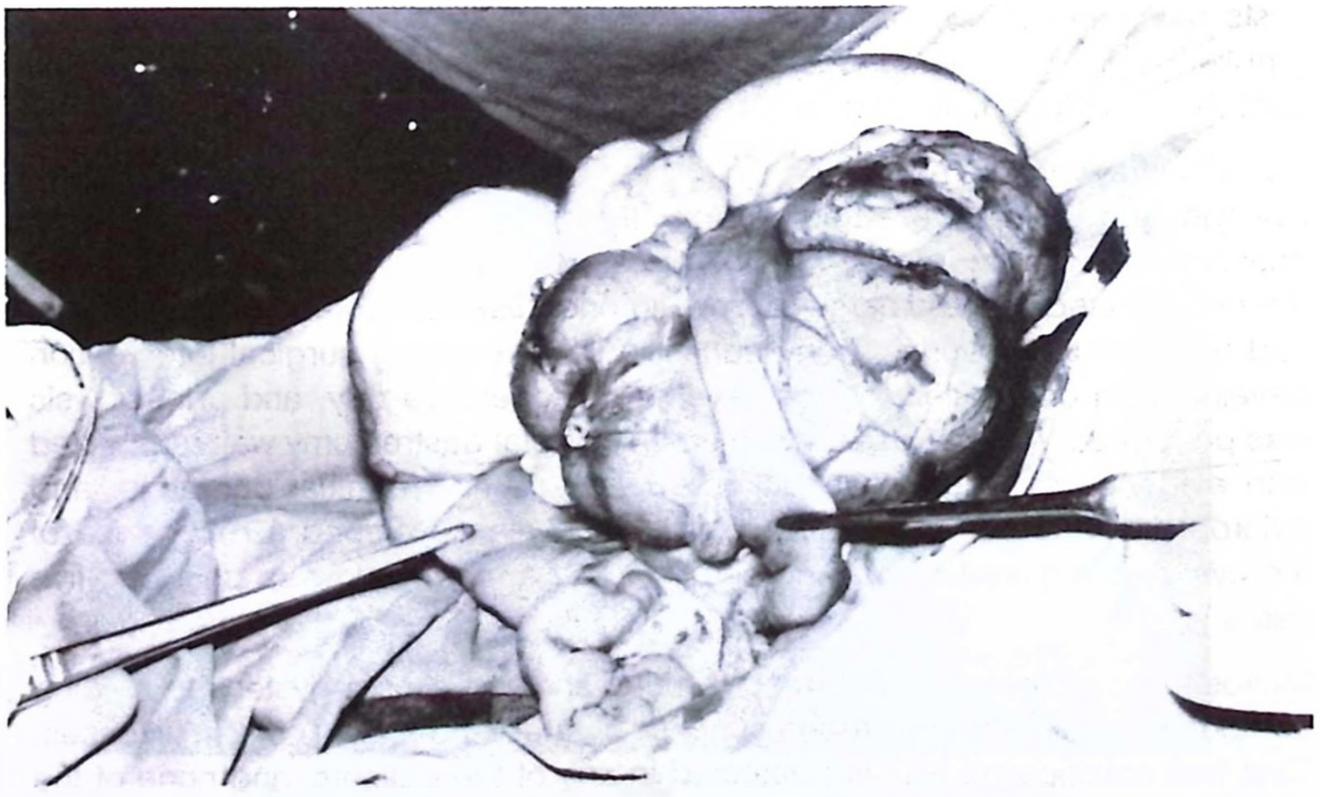


Fig. 3: a) Operative view of a multiloculated omental cyst causing intestinal obstruction.



b) A huge multiloculated mesenteric cyst containing chylous fluid.

Discussion

Mesenteric and omental cysts are infrequent intraabdominal lesions. Several series have indicated that 25 percent of reported cases have been in children[1]. The estimated incidence in our series (1 / 77,472) is quite similar to the previously reported incidences[2-4].

There are no pathognomonic signs and / or symptoms of mesenteric and omental cysts[2]. They may be asymptomatic or may cause abdominal distension and / or pain or may present acute symptoms secondary to complications such as obstruction (volvulus, extrinsic compression or entrapment in pelvis), rupture, hemorrhage into cyst, or infected cyst or abscess[1,3]. The clinical history and findings on physical examination may suggest the possibility of a cyst. Although these findings are nonspecific, when the patient also presents with a long duration of symptoms, an intraabdominal mass should be suspected. Abdominal pain and distension have been reported as the most common presenting symptoms[2]. In our series, abdominal distension was present in 74 percent of the cases and abdominal pain in 63 percent. Only one of the patients presented with acute symptoms due to intestinal obstruction.

The cysts may be located anywhere within the abdomen. Mesenteric cysts are most common in the small bowel mesentery, especially in the ileum[3]. We also identified a great number of mesenteric cysts (79%) in the small bowel mesentery.

Some of the lesions (such as large ovarian cysts, pancreatic, choledochal cysts or enteric duplication) and ascites (if loculated in the midabdomen) may be difficult to differentiate from these cysts. Only one patient with an extremely large omental cyst had been misdiagnosed with ascites. A correct preoperative diagnosis was made in only 25 percent of previously reported cases[2]. In our series. 79 percent of the patients were diagnosed preoperatively. This result has been attributed to the existence of a palpable mass in 58 percent of patients. Plain radiographs of the abdomen infrequently show nonspecific abnormalities, such as intraabdominal calcifications and / or displacement of the bowel gases, suggesting a space-occupying mass. GI tract contrast studies (upper GI series, barium enema) may reveal an extrinsic mass effect in a small number of cases, but these are not more efficient than plain radiographs of the abdomen. IVP may also exclude genitourinary cysts and tumors. With these studies, the diagnosis of an intraabdominal mass was made in five of the patients (26%) in our series. According to our experience, abdominal ultrasonography is the most reliable diagnostic study in experienced hands; 91 percent of our patients were correctly diagnosed by ultrasonographic examination. In suspected cases, the diagnosis should be confirmed with computed tomography (CT). We had no need for CT.

The surgical goal is complete excision of the cyst. Simple excision is feasible in many patients; however, resection of the adjacent bowel may also be required in some mesenteric cysts in intimate contact with the bowel. We removed all of the cysts completely, and bowel resection with the cyst was necessary in 57 percent of patients. With succesful excision, recurrence is exceedingly rare. We had no recurrence in a mean follow-up period of five years.

Malignant neoplasm of the cyst wall is also extremely rare, but several cases of sarcoma and a few cases of adenocarcinoma have been reported in only adults[2,3]. Among our cases, no cyst wall malignancy was encountered.

Currently, expected mortality has been reported as zero to eight percent with simple excision and three to 15 percent with accompanying bowel resection[3]. Our mortality rate (0%) is also in agreement with the literature.

Finally, we emphasize that mesenteric and omental cysts are uncommon though not rare lesions. With a high index of suspicion and the use of ultrasonography and CT, the correct preoperative diagnosis may be made in almost all cases.

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PSYCHOSOCIAL CONSIDERATIONS IN THE MANAGEMENT OF LATE - DIAGNOSED MALE PSEUDOHERMAPHRODITISM*

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SUMMARY: Alkın T, Büyükgebiz A, Baykara A. (Departments of Psychiatry and Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Psychosocial considerations in the management of late-diagnosed male pseudohermaphroditism. Turk J Pediatr 1994; 36: 303-308.

Male pseudohermaphroditism (MPH), which causes ambiguous genitalia, rarely presents during adolescence. Herein we report two siblings diagnosed with MPH at the ages of 16 and 12 years and raised unambiguously as girls. Individuals with MPH provide caregivers the opportunity to observe the complex interaction between the biologic and psychosocial forces which shape gender identity. Factors which contribute to gender identity and the management of sex assignment may differ between cultures with regard to dominating sociocultural attitudes towards masculinity and femininity in a given society. The decision to perform feminizing surgery on both patients was made in consideration of these issues. *Key words: pseudohermaphroditism, gender identity, adolescence, pseudohermaphroditism-psychology.*

Male pseudohermaphroditism (MPH) is the result of incomplete virilization of the 46, XY individual with testes, and patients with this condition have ambiguous genitalia[1]. The diagnosis of MPH is generally made at birth, and treatment must be initiated immediately in order to prevent physical and psychosocial consequences[2, 3]. If the diagnosis is not made until puberty, virilization occurs as a result of stimulated hormonal activity[1, 3, 4]. This may lead to severe sexual identity confusion. Given the fact that body awareness increases at puberty, at this time the choice of gender must be considered very carefully. Herein we report two siblings diagnosed with MPH at the ages of 16 and 12 years and raised unambiguously as girls.

Case Reports

The patients were the second and third children in a family. The other two sisters were healthy. The mother and father were close relatives. The patients' maternal uncle also had MPH and was reassigned as a male at the age of 12 years.

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Case 1

A. was 16 years old and had been raised as a girl. Her complaints were having "double genitalia", deep voice and no breast development. Two years earlier she had discovered by herself that her genitalia were different from her sisters'. Preoccupied with this matter, she had withdrawn and become depressed with an overwhelming shame. After a year, her apathetic and morose behavior as well as voice were noticed by her parents. She reluctantly agreed to seek medical help.

On physical examination, stage I breast development and stage III public hair growth were found. There was incomplete labioscrotal fusion and urogenital sinus opening.

Bilaterally palpable testes were present in the inguinal canal under the labiosacral folds. This finding was confirmed with ultrasonography (USG), which also revealed that there was no uterus or ovaries. X-ray examination of the internal genitalia showed a rudimentary vagina with no uterus. Chromosomal analysis proved a 46, XY karyotype. Laboratory data revealed a plasma-free testosterone of 8.6 pg/ml, total testosterone of 283.9 ng / dl and dihydrotestosterone level of 1.5 ng/dl. Follicle stimulating hormone (FSH) was 64 IU/ml, luteinizing hormone (LH) 10.3 IU / ml, estradiol 48 pg /ml, dehydroepiandrosterone sulfate (DHEAS) 185 mg / ml and 17-OH progesterone was 1.4 ng/ml. All of these values were within the normal range for boys. Human chorionic gonadotropin (HCG) stimulation test denoted a normal response of testosterone and dihydrotestosterone.

In conjunction with these diagnostic procedures, psychiatric assessments were made. During the first interview, A. was almost whispering in order to conceal her masculine voice. Her head was covered by a scarf indicating a strong religious belief. Being fully aware of what was happening to her body, she was severely depressed at the time of evaluation and cried throughout the interview. The pressure of growing pains related to her sexual identity confusion lowered her self-esteem tremendously. As a result, she had become detached and fairly passive in her interpersonal relations. As expected, she took a considerably long time to think about the issue. Considering the sex reassignment as intolerable, A. decided not to change her female gender. In a determined manner, she stated that if she could not be a female, she would commit suicide. She had plans for suicide in the case of a masculinizating operation against her consent.

A battery of psychological tests consisting of the Sentence Completion test, Minnesota Multiphasic Personality Inventory (MMPI), Beck Depression Inventory (BDI) and the Draw-a-person test were performed. According to the results, the

patient was unusually sensitive, rigid and pessimistic. She was also expressing fears concerning her future sexual life. Her identification with the female sex was apparent in her drawings and wishes of becoming an aunt, a grandmother and a nurse. Subtle implications of negative identification with men were present. Her BDI score was 28, indicating a depressive episode.

A. had grown up in a village located in a rather conservative, rural area of Turkey. She had completed elementary school in the village and had not continued her education. Shortly thereafter, her family migrated to a metropolitan area and resided in a peripheral part of the city. She was treated unambiguously as a girl within the family. She was quiet, unaggressive, obedient and restricted in fancifulness. Traditional sex role expectations and stereotypes were adopted very rigidly by the family. Her parents consistently reinforced sex-appropriate behaviors. The patient busied herself with domestic chores. Under these sociocultural upbringing conditions, she identified completely with the female gender identity. A had strong sexual inhibitions and had not experienced any cross-sex friendship.

In a six-month follow-up period after surgical reinforcement of female genitalia, A. was relieved of her depression, gradually became more sociable and began to work in a factory. It was obvious that she had overcome her sexual-identity confusion.

Case 2

B., sister of A., was a 12-year-old girl with a four-month history of a deepening voice. When she was a baby, the family questioned whether her genitalia were normal, but the physician who examined her had confirmed that she was normal.

At the age of nine years, on second examination, it was said that she had a right-sided inguinal hernia and a repair operation was performed. Following A.'s diagnosis, B. was examined once again in our hospital.

B. also had ambiguous genitalia. Stage I-II pubic hair growth, stage I breast development and an absence of axillary hair were noted. A palpable gonad was present only in the left inguinal canal. Instead of a penis she had a small clitoris. There was also a urogenital sinus opening. There was no genital pigmentation. Neither uterus nor ovaries were seen on pelvic USG examination. Genitography visualized a rudimentary vagina. Her hormonal profile was completely normal for boys. According to laboratory data, free testosterone was 1.5 pg / ml, total testosterone 30.3 ng / dl, basal dihydrotestosterone 12 ng / dl, FSH 17.6 IU / ml, LH 2.9 IU / ml, estradiol 32 pg / ml, DHEA-S 251 mg / ml and 17-OH progesterone was 1.1 ng / ml. Following HCG stimulation, normal responses of testosterone and dihydrotestosterone were elicited.

On psychiatric evaluation, B. seemed to be an intelligent, stable and conforming school girl. She was popular within her peer group. Night fears were the only psychological complaint that she reported. She was somewhat uninterested in and less affected by the existing problem. Her mood was euthymic; however, she regretted that her problem saddened her parents. Psychological testing data provided evidence that B. had a sense of being female and no interest in sex. She was well adjusted to the "cheerful girl" image which was a part of her "self." Highly influenced by her sister's gender choice, B. was also determined to live as a female. Six months after the feminizing surgery, she was continuing to function well psychosocially.

Discussion

Both cases were diagnosed as incomplete testicular feminization. Experiencing shame and guilt feelings, the parents left the decision of gender choice to the physicians and patients.

After a multidisciplinary team approach, the decision was made to perform feminizing surgery on both patients. In a final meeting with the participation of pediatricians, endocrinologists, radiologists, pediatric surgeons, medical geneticists and psychiatrists, the issues of gender role, gender identity, sex of rearing and the anatomy of the genitalia were carefully evaluated. Nevertheless the most influential factor in making the final decision was the gender identity which was tenaciously defended by both patients. Gender identity is acquired by postnatal psychosocial experiences as well as prenatal hormonal influences[1, 3-5]. Individuals with ambiguous genitalia, such as MPH, provide health care providers the opportunity to observe the complex interaction between these two forces.

Gender role change during adolescence has been noted in MPH individuals[4,6,7]. Imperato-McGinley et al.[4] described 18 MPH patients with 5-alpha-reductase deficiency who were raised as girls; at puberty, after virilization had occurred, 17 out of 18 changed to the male gender. These data have been interpreted as the effect of testosterone, which predominantly influences sexual identity and overrides the effects of rearing as girls. In another study, MPH individuals with 17-beta-hydroxysteroid dehydrogenase enzyme deficiency, contrary to having been raised as girls, mostly preferred to become male after puberty[7]. Nonetheless, subtle sociocultural factors may have been involved in both of these studies[1, 5, 7].

Presumably, sex reversal at puberty may create medical, psychological, social and moral problems. Surgical interventions, such as reinforcement of gender or reassignment, is difficult and multistage[8]. Even early surgical interventions

were not able to prevent psychosocial injuries to personality and gender role, which were the results of parent-child and environment-child interactions[9]. As shown by Money et al.[10], childhood stigmatization originating from either family or peers was the most important factor significantly correlated to later gender transposition such as bisexualism, lesbianism or sex reassignment to live as male in a group of MPHs who were assigned as female at birth. This implies the critical importance of socio-cultural factors, whether subtle or overt.

Cultural generalizations and expectations about sex-typed behaviors shape an individual's sexual orientation and sex roles[5, 11]. To complete the discussion, it is crucial to take into account our patients' culture-bond status. In Turkey, strictly defined sex roles and separate social networks exist[12, 13]. Dealing with domestic chores, child care and the home are the women's duties. Thus, in contrast to men, women are restricted to a home-bound and inferior status. As Kandiyoti[12] noted, "This status difference is reflected in a stereotypic definition of sex roles as well as the custom of physical and social segregation." Because of well-differentiated sex roles, socialization into a female world occurs and same-sex social networks develop[12, 13]. Together with the strict social control, these networks are the sources of submissive role identification of women.

Noting that these values also dominated in our patients' patriarchal nuclear family, gender role change was a real threat for their already established sexual and social identity. It would have necessitated changing all of their networks and losing their most intimate relationships. Neither was ready for the traditional "bread-winner" role of men. In both patients, the preference for surgical reinforcement after considering all the implications of management was the result of fears related to these future uncertainties and challenges. Although fertility is very important for both sexes and gives an opportunity to increase women's status in the Turkish family[14], and being a male has advantages in the community[12, 13], both patients prefered to be sterile females rather than become dysfunctional males. Such a sacrifice is the product of the culture and is contrary to certain western social values[7]. In addition, our report defies oversimplifications such as, "In underdeveloped countries, males enjoy a higher status than females, even if imperfect"[3].

As suggested by previous researchers[1-3], early diagnosis of ambiguous genitalia before gender identity establishment is imperative, and prompt surgical treatment should be initiated. In both cases, gender identity and sex role identifications had been developed rigidly by the time of diagnosis. Under the aforementioned circumstances, the future risks associated with sex-reassignment were greater than the price the patients had already paid. In conclusion, these cases suggest the relative importance of sociocultural forces–at least in some societies–on the classic "nature versus nurture" debate. In different societies, depending on the power of cultural values and norms, individuals may differ in their choices of gender identity.

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NONCARDIOGENIC PULMONARY EDEMA IN CHILDHOOD*

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Pulmonary edema is caused by transudation of fluid from pulmonary capillaries into the alveolar spaces and the bronchiolus. It is most frequently secondary to either increased pulmonary capillary hydrostatic pressure (cardiogenic pulmonary edema) or increased pulmonary capillary permeability (noncardiogenic pulmonary edema). Numerous systemic and pulmonary insults are capable of damaging the capillary endothelium and / or alveolar epithelium, resulting in noncardiogenic pulmonary edema. Although clinically similar, the presence of noncardiogenic pulmonary edema requires a different therapeutic approach from that of cardiogenic pulmonary edema.
Key words: noncardiogenic pulmonary edema, childhood, etiology, management.

A commonly encountered problem in the pediatric intensive care unit setting is pulmonary edema (PE) (pulmonary fluid overload)[1, 2]. An understanding of the etiopathogenesis of PE and its treatment requires an appreciation of the physiology of water and protein clearance. Although progressively more complex models are being developed, the traditional principals of Starling are still accepted. The Starling[1] equation states that the flow of fluid across a semipermeable membrane is governed by the driving pressures and barrier conductance.

$$Q = Kf\ [(P_{cap} - P_{int}) - r\ (X_{cap} - X_{int})], \qquad [1]$$

where Q is the net rate of flow across the surface area of the capillary; Kf is the liquid conductance of the microvascular barrier; P is the hydrostatic pressure in the capillary lumen (cap) and in the perimicrovascular interstitial liquids (int); r is the reflection coefficient; and X is the capillary colloid osmotic pressure in the capillary lumen and perimicrovascular liquids.

Although there are many possible causes of PE, a simple analysis of the Starling equation suggests that there are only two major mechanisms of PE, though they may coexist in the same patient[3, 4]. The first mechanism is cardiogenic pulmonary edema (CPE), which develops in patients with heart failure due to

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increased pressure in the pulmonary capillaries. This form of PE is associated with a normal microvascular barrier and preserved selective capillary membrane permeability for proteins[4] (transudative PE). The second mechanism, noncardiogenic pulmonary edema (NCPE), is caused by increased permeability of the pulmonary capillaries with or without loss of integrity of the capillary endothelium and / or alveolar epithelium. In CPE the time course of fluid accumulation is generally slow and is related to the increased hydrostatic pressure in the capillaries. The fluid itself has a low protein concentration. Alternatively, when there is capillary injury resulting in increased permeability, the onset of edema can be very rapid even in the face of normal hydrostatic pressure. The increased capillary permeability allows leakage of large molecular weight compounds; thus the protein concentration is higher in NCPE than in CPE[5].

When NCPE develops, the airspace is flooded due to leaky pulmonary vessels and alveolar membranes, which impedes oxygen transfer from the airspace into the blood[6]. This sequence of events results in hypoxemia, reduced oxygen delivery, hypoxia, and eventually hypercapnia and death if corrective therapy is not applied[7]. Although the resulting clinical syndrome is frequently associated with adult respiratory distress syndrome (ARDS), this syndrome has the following strict criteria[8,9]: 1) a major antecedent precipitating event; 2) the sudden onset of respiratory distress; 3) hypoxemia refractory to a high concentration of inspired oxygen (PaO_2 < 50% with FiO_2 > 0.60) with increased shunt fraction and dead space ventilation; 4) the presence of diffuse patchy infiltrates on the chest radiographs; 5) a decrease in static lung compliance (overall compliance < 50% normal, usually 20 to 30% normal); and 6) the exclusion of cardiogenic pulmonary edema and chronic pulmonary disease. ARDS is characterized histologically by diffuse alveolar epithelial and endothelial damage and includes characteristics of an acute inflammatory reaction located primarily in the lung[10].

NCPE is a catastrophic and frequently unanticipated complication of an acute illness. A major concomitant of the ARDS, NCPE may affect more than 250.000 patients annually in the United States and is likely associated with greater than a 50 percent mortality rate[11]. The ability to distinguish NCPE from CPE is vitally important, since management, beyond initial stabilization, is radically dissimilar.

In this review, the circumstances under which NCPE most frequently develops will be described, and those methods available to the clinician which may assist in the differentiation of this syndrome from the more common type of edema, CPE, will be reviewed.

Etiology

Since, in addition to many systemic disease processes, variable factors such

as smoke lead to an excessive amount of water in the lung, there are numerable causes of pulmonary edema[8, 12]. An abbreviated listing is provided in Table I.

Table I: Etiopathogenesis of Noncardiogenic Pulmonary Edema

Edema Due to an Increased Pressure Gradient Across the Microvasculature

Hydrostatic interstitial pressure becomes more negative
- Acute atelectasis (drowned lung)
- Rapid re-expansion of hydro- or pneumothorax

Microvascular colloid osmotic pressure decreased
- Hypoalbuminemia due to liver or renal disease
- Starvation

Edema Secondary to Injured Endothelium or Epithelium

Infectious agents: Viruses, mycoplasma, other (especially in immunocompromised patients)

Inhaled substances

Gases: oxygen, nitrogen dioxide, sulfur dioxide, smoke and other noxious gases

Liquid aspiration: gastric contents, salt and fresh water drowning

Ingestants

Chemotherapeutic agents: azothioprine, BCNU, bleomycin, busulfan, chlorambucil, cytosine arabinoside, cytoxan, melphalan, methotrexate, mitomycin

Other medications: amphotericin B, colchicine, gold, hydrochlorothiazide, nitrofurantoin, salicylate, penicillamine

Shock, pancreatitis, trauma and sepsis

Radiation

Neurogenic: hypoxic encephalopathy, head trauma, subarachnoid hemorrhage

Unilateral pulmonary edema occasionally may be seen after rapid reexpansion of a previously atelectatic lung or lobe secondary to the rapid removal of air or fluid from the pleural space[4, 13, 14]. This phenomenon is reported most in adult patients whose involved lung has been collapsed for at least three days or at least two liters of pleural fluid has been removed rapidly[4]. Although edema usually presents acutely, its radiologic appearance may be delayed for up to 24 hours[4]. Pulmonary edema may be produced by a decrease in interstitial pressure. Normal values for interstitial pressures have been estimated as between -5 to -10 mmHg, but during certain circumstances they may increase to -80

mmHg[8], such as during increased respiratory effort associated with an obstructed upper airway. Upper airway obstruction leading to PE was recognized predominantly in children as a consequence of acute epiglottitis or foreign body aspiration[15, 16]. Also, this complication may be associated with conditions such as tonsillar or adenoidal hypertrophy and post-extubation laryngospasm[17, 18].

A decrease in the plasma colloid osmotic pressure results in a tendency toward edema formation. Although hypoproteinemia alone seldom leads to pulmonary edema, patients with hypoproteinemia are more likely to present with pleural effusion[19]. This is seen in hypoproteinemic conditions such as nephrotic syndrome, protein-losing enteropathy and malnutrition. Although this condition is a NCPE, it is not due to increased permeability because the microvascular barrier is intact.

A permeability injury to the pulmonary microvasculature may occur from either the epithelial or endothelial side of the barrier membrane. Injury from the epithelial side of the membrane directly disrupts the alveole-capillary barrier, although a subsequent "inflammatory" response may potentiate the increase in permeability. Injury from the endothelial side is due to a cascade of events likely initiated by complement activation and characterized by entrapment of neutrophils within the microvasculature[11].

Injury to the pulmonary vasculature is the presenting feature in a variety of insults. Pulmonary and extrapulmonary infections, severe systemic insults, different toxins and drugs, or a combined cause leading either to direct injury to the lung or to secondary injury to the lung, are associated with NCPE[2, 19, 20]. In terms of the Starling equation, this amounts to an increase in the filtration coefficient and a decrease in the reflection coefficient, which results in relatively protein-rich edematous fluid[8].

Respiratory distress due to pulmonary edema occurring in conjunction with cerebral injury is a well-recognized but poorly understood phenomenon. Neurogenic PE is associated with a major central nervous system insult such as subarachnoid hemorrhage, intracranial bleeding, seizure and head trauma[21, 22]. Hemodynamic monitoring has shown transient increases in systemic and pulmonary blood pressures, considered to be secondary to the increased adrenergic output during central nervous system dysfunction[8, 23].

Clinical and Laboratory Findings

Although the diagnosis of PE generally is not difficult, differentiation between the cardiogenic and noncardiogenic froms of edema may not be made easily[4].

The initial presentation of both CPE and NCPE is remarkably similar to that of interstitial edema. Findings of pulmonary edema on physical examination vary

according to the severity of respiratory distress and the underlying cause of edema. Some degree of respiratory distress is generally manifested by an increased respiratory rate, labored breathing, intercostal retractions and use of accessory muscles of respiration[8, 24]. Since in NCPE the time course of fluid accumulation is generally faster than in cardiogenic pulmonary edema, the clinical picture develops more acutely. Cyanosis may be noted, and there may be crackles on auscultation. Excessive frothy, pink-tinged sputum is noted in fairly severe pulmonary edema with alveolar flooding. Wheezing has also been noted early in the course of pulmonary edema in children, along with pulmonary hyperexpansion[8].

It is worthwhile to remember that NCPE is invariably associated with an underlying disease which may or may not be readily apparent. Therefore, the diagnosis of NCPE often depends on a high index of suspicion for secondary probabilities; for example, acute respiratory distress and pulmonary edema in a patient with documented peritonitis or pancreatitis must primarily evoke concern for NCPE. Furthermore, NCPE is uncommonly associated with a well-defined cardiac event. Thus, there is no essential prerequisite that NCPE be diagnosed only when there is lack of objective evidence for an acute cardiac event[11]. In contrast to CPE, NCPE is usually a hyperdynamic illness, clinically apparent as a warm, vasodilated periphery. CPE complicating an acute cardiac illness is frequently a low-flow state, with a cool mottled periphery. Auscultation may aid in making a diagnosis. CPE is usually associated with traditional evidence of left ventricular failure, such as an S_3 gallop. Unless complicated by concurrent volume overload, patients with NCPE will not manifest such physical signs[11].

In summary, although there will usually be a number of subtle findings which should alert the clinician to the etiology of PE, in any given situation which is potentially of a noncardiac variety[11], the history and physical examination cannot be relied upon to distinguish NCPE from CPE. In the critically ill patient managed in the intensive care unit, right ventricular catheterization with measurement of pulmonary capillary wedge pressure (PCWP) is frequently used to help differentiate CPE from other forms of PE[11, 25]. With CPE, a reduction of PCWP to less than 18 mmHg usually will be accompanied by significant clinical and radiographic improvement within 24 hours[4].

PE fluid suctioned from an intubated patient may be used to help distinguish noncardiogenic PE from CPE. A PE fluid protein to plasma protein ratio of greater than 0.7 is considered diagnostic of increased permeability edema, whereas a ratio less than 0.5 is characteristic for CPE[11, 26, 27].

There is considerable controversy regarding the ability of the plain chest radiograph to differentiate cardiogenic from NCPE[11, 28, 29]. NCPE is usually

characterized by a patchy, frequently peripheral nongravitational distribution of edema with a normal distribution of pulmonary blood flow, normal vascular pedicle width and cardiac size. Septal lines are not seen and peribronchial cuffing and pleural effusions are rare. Although these findings are helpful to distinguish NCPE, they are not specific.

Scintigraphy of the lung following an injection of I^{131} - HSA shows increased extravascular accumulation in NCPE compared to CPE. Extravascular lung water, measured by the thermal-greendye technique, demonstrates a greater quantity of extravascular lung water in NCPE. Due to the investigative nature of the last two techniques, their routine use is prohibited[25].

Management

Treatment of NCPE in children is directed toward the initial insult as well as to ongoing support of cardiopulmonary function[8, 30]. Treatment of the participating illness and management of temperature, serum electrolyte balance, glucose levels, acid-base status, hematocrit and nutrional status, along with appropriate monitoring are required[31]. Aggressive chest physiotherapy and pulmonary toilet are also important[25].

The main goals of therapy are two-fold: to maintain systemic arterial oxygenation and to decrease the sum of pressures causing liquid filtration. Patients who require more than 50% FiO_2 to maintain arterial oxygen pressures greater than 50 mmHg and those who develop acute hypercapnia ($PaCO_2$ greater than 50 mmHg) benefit from mechanically assisted ventilation. An important adjunct to this form of therapy is positive end-expiratory pressure (PEEP)[30]. PEEP is desired to maintain alveolar patency, thereby minimizing intrapulmonary shunt and hypoxemia as well as poor lung compliance associated with progressive alveolar collapse and atelectasis.

Some studies have found that for patients unresponsive to conventional ventilation, use of pressure control ventilation with inverse inspiratory-to-expiratory ratio (2:1 or longer) results in improved oxygenation. Other patients who have unremitting respiratory failure despite maximal medical management have been managed successfully with high frequency oscillation or with extracorporeal membrane oxygenation[31].

Since O_2 transport is governed by arterial O_2 content and cardiac output, optimizing these two parameters is crucial[25, 32]. Cardiac output can be increased by increasing preload or contractility and decreasing afterload. To optimize O_2 content, hemoglobin should be maintained between 11 and 13 g/dl and hypophosphotemia prevented to reduce its impact on the position of the oxyhemoglobin dissociation curve[25].

Fluid therapy in a patient with NCPE must be monitored closely to avoid compounding pre-existing abnormal pulmonary capillary permeability characteristics. Although in experimental NCPE (caused by oleic acid) furosemide has been reported by some to be beneficial, other studies contradict this finding[33, 34]; thus it is reasonable to decrease lung microvascular pressure. Though no specific recommendations are available regarding the optimum rate of fluid administration, each patient's hemodynamic status must be monitored closely and enough fluids administered to maintain adequate cardiac output[20].

If the adequacy of perfusion or of the volume status of the child is in doubt, central venous pressure (CVP) should be measured[30]. When therapy for poor peripheral perfusion includes pressor agents or vasodilators, a Swan-Ganz thermodilution catheter may help in assessing the effects of those treatments on cardiac output and vascular resistance. Similarly, when more than 10 cmH_2O of PEEP is administered with the ventilator, cardiac output monitoring may allow clinicians to better assess the efficacy of aggressive treatments for NCPE[30].

Prevention, detection, and treatment of complications (such as nosocomial pneumonia, catheter sepsis, stress ulceration, air leak syndromes and multiple organ system failure) are vital in reducing morbidity and mortality. Pulmonary and abdominal sepsis may be particularly insidious, with a high associated mortality rate[31].

Recent studies have shown that high-dose corticosteroids do not enhance recovery from ARDS, and their use is no longer recommended[25, 32]. However, other drugs such as vasodilators, nonsteroidal anti-inflammatory agents, inhaled nitric oxide and prostaglandin E are still undergoing clinical trials in ARDS[25, 32]. Immunotherapy with monoclonal antibodies has been developed against endotoxin and tumor necrosis factor and may prove to be a major form of treatment for ARDS[35]. Replacement therapies with artificial surfactant and liquid ventilation with perfluorocarbon for treatment of ARDS are also being investigated[31, 36].

Conclusion

Expedient differentiation of NCPE from CPE is important since diagnostic and therapeutic objectives are so radically dissimilar in these two diseases. NCPE is merely a clinical "marker" of an underlying and usually ominous disease. Its successful management can only be anticipated in pediatric intensive care units with the support of cardiopulmonary functions and therapeutic resolution of the underlying disease (e.g., a septic focus).

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KIDNEY PATHOLOGY IN A PATIENT WITH SEVERE COMBINED IMMUNODEFICIENCY DISEASE*

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SUMMARY: Sanal Ö, Çağlar M, Ersoy F, Coşkun Y, Tezcan İ. (Immunology and Pathology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Kidney pathology in a patient with severe combined immunodeficiency disease. Turk J Pediatr 1994; 36: 319-323.

A 2-month-old SCID patient with mesangial sclerosis of the kidney is presented. Although the ADA status of the patient is unknown, the parents' RBC-ADA levels seemed to be in the heterozygote range. *Key words: severe combined immunodeficiency disease, adenosine deaminase, mesangial sclerosis.*

Severe combined immunodeficiency disease (SCID) represents a heterogeneous group of congenital disorders manifested by profound deficiencies of both B- and T-cell immunity. A great diversity and alterations in clinical, laboratory and pathological findings and genetic inheritance have been observed in SCID[1-7]. An inherited deficiency of adenosine deaminase (ADA) has been shown to be responsible for a substantial proportion of autosomal recessive SCID cases. Several findings in non-lymphoid organs have been described in ADA-deficient SCID patients[5, 8]. Recently mesangial sclerosis of the glomeruli has been reported in a few patients[8].

We present a SCID patient with unknown ADA activity and associated with kidney pathology. However, the parents' red blood cell (RBC)-ADA activity was found to be compatible with the heterozygote range, the determination of which was made after the patient died.

Case Report

A two-month-old girl was admitted to Hacettepe Children's Hospital with complaints of respiratory difficulty, cyanosis and coughing. She was a product of a marriage between first cousins and had an 18-month-old healthy sister.

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The patient's history included a pulmonary infection at one month of age. Her weight, height and head circumference were 3,700 g, 49 cm and 36.5 cm, respectively. The physical examination and x-rays revealed bronchopneumonia. Although antibiotics and gammaglobulin were given, her condition gradually worsened and she died on the 14^{th} hospitalization day.

Laboratory findings: In the peripheral blood there was marked lymphopenia ($< 400/mm^3$), monocytosis and neutrophilia. The serum IgG level was 100 mg/dl, while IgM and IgA were undetectable. Delayed hypersensitivity skin tests were positive for phytohemagglutinin (PHA), and negative for candida. The percentage of E-rosette-forming lymphocytes was very low (3%). Proteinuria was not documented. Although the ADA activity of the patient was unknown, the RBC-ADA activities of the parents determined after the patient's death fell in the heterozygote range (46 and 13 μmol/uric acid/hour/g Hb) [normal values (n = 30) 106 ± 34, range 61-185]. Chest x-rays showed a lung infiltrate on the right. No thymic shadow or bone abnormality could be visualized.

Pathological findings: Postmortem histopathological examination revealed thymic dysplasia, mesangial sclerosis in glomeruli, bronchopneumonia, fatty liver, and congestion in the adrenal medulla, lung and central nervous system.

The thymus weight was 0.2 g. There was no differentiation between cortex and medulla and no clearly identifiable Hassal's corpuscles. Lymphoid cells were rare and sparse. The connective tissue separating thymic lobules was decreased (Fig. 1).

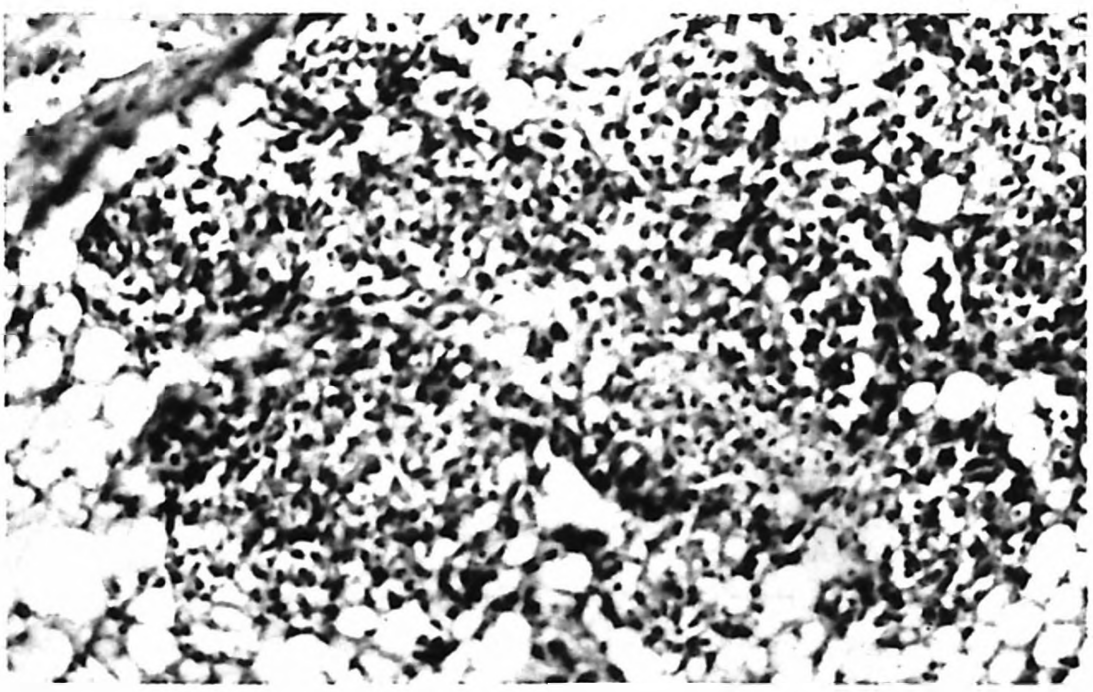

Fig. 1: Microscopic appearance of thymus gland (H + E, x 20).

The peripheral lymphoid tissues were not well developed and lymph nodes were devoid of lymphoid cells. Plasma cells were absent (Fig. 2).

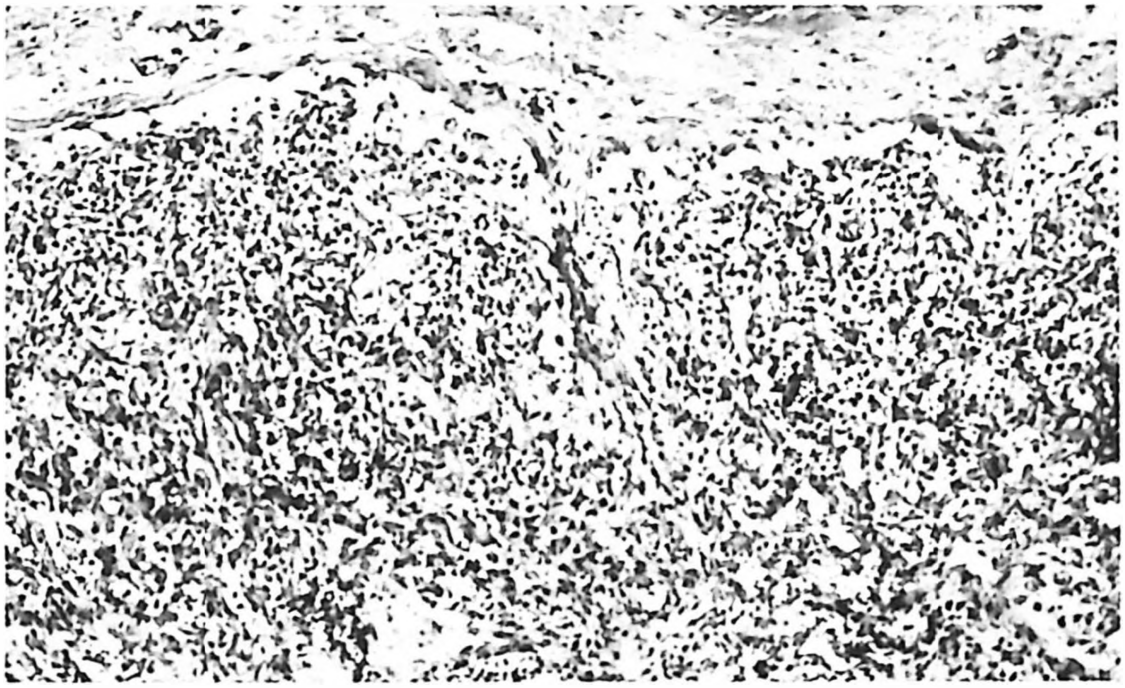

Fig. 2: Lymphoid tissue with no lymphoid or plasma cells (H + E, x 20).

By light microscopy, the kidneys showed increased mesangial fibrillar matrix (mesangial sclerosis) of varying degrees unassociated with cellular proliferation in almost all glomeruli (Fig. 3).

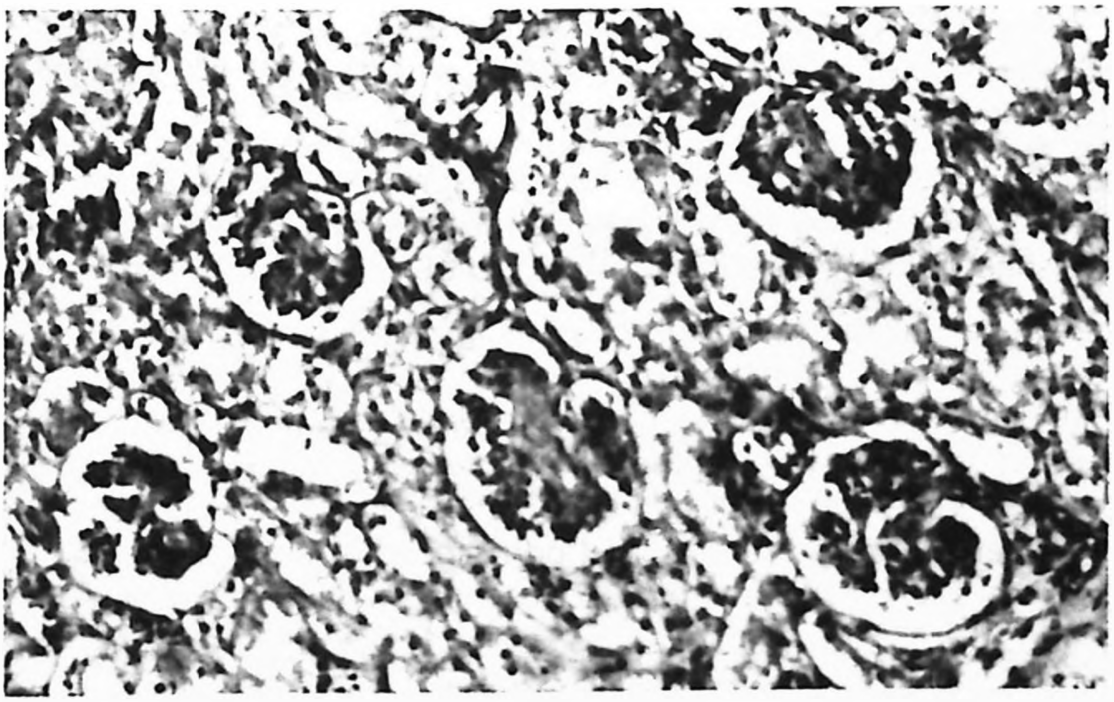

Fig. 3: Kidney pathology characterized by increased mesangial sclerosis (H + E, x 20).

Discussion

SCID cases may occur sporadically, in autosomal recessive form or X-linked form. ADA deficiency has been reported to be present in 25-40 percent of the autosomal recessive cases.

The description of individual cases with SCID shows considerable heterogeneity in immunological findings[1,3,4]. Our patient's serum immunoglobulin levels and E-rosette-forming T-lymphocyte count were very low, consistent with SCID. Further immunological tests could not be performed.

In addition to the histopathological findings consistent with SCID in the thymus and lymphoid tissue on postmortem histopathologic examination, the patient had glomerular sclerosis. Several findings in non-lymphoid tissues have been observed in ADA-deficient SCID cases[6-9]. These include mesangial sclerosis in the kidney, adrenal gland cortical sclerosis and typical alterations in chondro-osseous tissue[8]. Few patients have been reported with kidney pathology associated with ADA-deficient SCID[8]. Ratech et al.[8] reviewed the postmortem pathological findings of non-lymphoid organs in eight patients with ADA-deficient SCID and noticed mesangial sclerosis of the glomeruli in seven out of eight patients. They suggested that the toxic metabolites resulting from the specific enzyme defect may play a role in these pahological changes in the kidneys as in bones and adrenal glands[8-10]. Diffuse mesangial sclerosis is a rather uncommonly encountered clinicopathological entity and is one of the unique subsets of primary-type nephrotic syndrome (NS) occurring in the first year of life[11]. Diffuse mesangial sclerosis may also be an associated nephropathy in syndromic conditions like Drash syndrome (pseudohermaphroditism, Wilms' tumor, glomerulopathy)[12].

The renal pathological finding was not associated with clinical nephropathy in our patient. The fact that NS is a common manifestation of ADA-deficient SCID distinguishes the renal lesion in ADA-deficient SCID from nephrotic syndrome[8].

Our patient had no histopathologic or radiologic abnormality in chondro-osseous tissue, which is an associated finding in ADA-deficient SCID. Although histopathological findings have not been reported in all cases, radiographic changes of bones are not present in all patients with ADA-deficient SCID. Furthermore, bone abnormalities in two ADA-deficient SCID patients reported by Ratech et al.[8] could not be found on histopathological examination. These two patients had been treated with bone marrow transplantation.

Unfortunately we could not determine the ADA activity of the patient, but the parents had RBC-ADA levels compatible with the heterozygote range, indicating that the patient may have had ADA-deficient SCID.

At the present time, it is not known whether the non-lymphoid pathological changes are unique to ADA deficiency. More SCID patients with or without ADA deficiency should be examined to clarify this issue.

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CRANIAL COMPUTED TOMOGRAPHIC FINDINGS IN A PATIENT WITH HYPERTENSIVE ENCEPHALOPATHY IN ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS*

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SUMMARY: Saatçi I, Topaloğlu R (Departments of Radiology and Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Cranial computed tomographic findings in a patients with hypertensive encephalopathy in acute poststreptococcal glomerulonephritis. Turk J Pediatr 1994; 325-328.

A 13-year-old girl with a severe headache, blurred vision, altered mental status, seizures, high blood pressure, edema and hematuria is presented. With a previous history of upper respiratory tract infection, acute onset of edema, gross hematuria, high ASO and low C_3 levels, she was diagnosed with acute poststreptococcal glomerulonephritis (APSGN) and hypertensive encephalopathy. Computed tomography (CT) revealed symmetric hypodense areas representing edema in the parieto-occipital regions. As noted in previous reports, these CT findings are of value in establishing the diagnosis of hypertensive encephalopathy. In this particular case the CT appearance and the subsequent clinical improvement without any neurological deficit supported the diagnosis of hypertensve encephalopathy due to APSGN. We emphasize that awareness of the CT findings of hypertensive encephalopathy may facilitate in making the correct diagnosis in symptomatic hypertensive patients, especially in cases with an unusual presentation or clinical course. *Key words: CT findings, hypertensive encephalopathy, acute poststreptococcal glomerulonephritis.*

Encephalopathy refers to a non-infective cause of brain dysfunction. A wide spectrum of conditions including hypertension can cause encephalopathy[1,2].

Hypertension is found in over 75 percent of acute poststreptococcal glomerulonephritis (APSGN) cases, but hypertensive encephalopathy due to APSGN has been reported rarely in children[3].

We present a 13-year-old girl with hypertensive encephalopathy due to APSGN and the cranial computed tomographic (CT) findings.

Case Report

A 13-year-old girl was admitted to the hospital with altered mental status. Her past history revealed a sore throat and fever about 20 days prior, and after a latent period of ten days, she developed edema, nausea, vomiting and gross

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hematuria. She was referred to Hacettepe Children's Hospital when she developed a severe headache, blurred vision, altered mental status, seizures and high blood pressure (180/110 mmHg) one week after the onset of edema and hematuria.

Physical examination revealed a blood pressure of 150/110 mmHg and a stuporous state with (+) Babinsky sign on the left side. The fundoscopic examination showed bilateral minimal papilledema.

Laboratory findings revealed a hemoglobin of 15 g/dl, hematocrit 44% and white blood cell count of 8500/mm^3 with 54% neutrophils and 46% lymphocytes. Urine analysis showed a specific gravity of 1025, 1+ proteinuria, numerous erythrocytes and 5-6 leukocytes per high power field in urinary sediment. BUN, serum creatinine, electrolytes, total protein, albumin, SGOT, SGPT and alkaline phosphatase levels were within normal limits. Urine and throat cultures were negative. The chest and abdominal ultrasonography were unremarkable. Antistreptolysine-O (ASO) titer was 500 U, C-reactive protein (CRP) + erythrocyte sedimentation rate 50 mm/hr, C_3 30 mg/dl, C_4 20 mg/dl, and antinuclear antibody (ANA) was negative. The evaluation of cerebrospinal fluid (CSF) was normal. EEG demonstrated paroxysmal activity in the right posterior hemisphere with a slow background rhythm. CT examination performed four days after the onset of acute signs and symptoms demonstrated symmetric hypodense areas in the parieto-occipital regions bilaterally (Fig. 1).

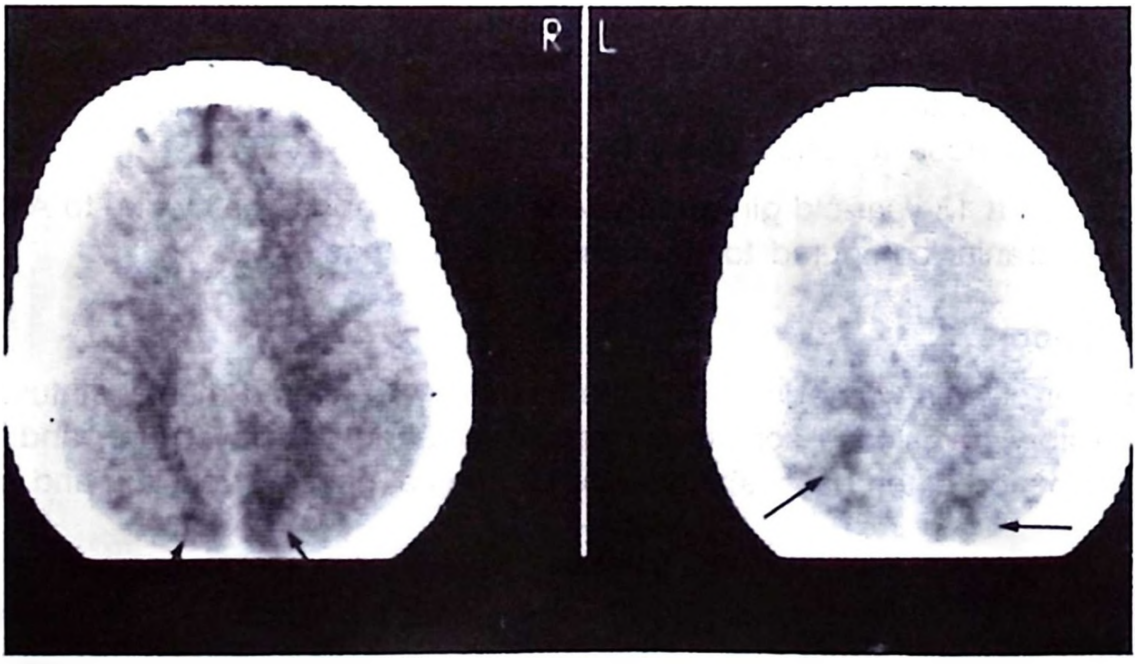

Fig. 1: Contiguous axial non-contrast CT images reveal bilateral parieto-occipital areas with decreased attenuation, more obvious on the right side.

Discussion

Hypertensive encephalopathy is a neurologic syndrome characterized by headache, visual disturbances, seizures, altered mental status and focal neurologic signs[1,2]. Various neurologic conditions such as stroke, intracranial hemorrhage, venous thrombosis and encephalitis can mimic hypertensive encephalopathy[4]. These were excluded with the CSF analysis and CT in the present case. Even after controlling the patient's blood pressure, her stuporous state and agitation persisted, arousing the suspicion of systemic lupus erythematosis (SLE) or other vasculitic syndromes. SLE and other vasculitic syndromes were ruled out with the normal C_4 level, negative ANA and lack of signs and symptoms related to vasculitis. With the typical history and classical clinical presentation of APSGN of acute onset of edema, hematuria, high ASO titer and low C_3 level, the patient was diagnosed with APSGN and hypertensive encephalopathy.

Hypertension is found in over 75 percent of APSGN cases. Hypertension is usually mild to moderate and not accompanied by the retinal alterations of malignant hypertension[5]. Hypertension is usually more evident at or near the onset of the renal disease and subsides promptly with the onset of diuresis. Encephalopathy is occasionally a complication of APSGN in children[3].

Hypertensive encephalopathy is a subacute phenomenon requiring several days of increasing pressure to manifest. The susceptibility of the posterior circulation to the lesions of hypertensive encephalopathy is well-known[6]. The theory of the regional heterogeneity of the sympathetic vascular innervation has been proposed for the posterior predilection of the lesions in hypertensive encephalopathy[7]. Schwartz et al.[8] noted that the imaging findings in hypertensive encephalopathy are distinct from those in acute as well as chronic hypertension. Acute hypertensive crises may result in cerebral hemorrhage or infarction, whereas in chronic hypertension multiple small infarctions and focal hemorrhages are frequently seen in the basal ganglia, thalamus, centrum semiovale and, less commonly, the pons and cerebellum. In their series of 14 patients with hypertensive encephalopathy, all displayed edema in the cortex and subcortical white matter of the occipital lobes.

In consistency with the previous reports, bilateral hypodensity representing edema in the parieto-occipital area as well as the subsequent clinical improvement of the patient without any neurological deficit supported the diagnosis of hypertensive encephalopathy due to APSGN in this particular case.

The present case report is intended to emphasize that awareness of the CT appearance of hypertensive encephalopathy may facilitate in making the correct diagnosis in symptomatic hypertensive patients, particularly those who have an atypical presentation or clinical course.

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WHISTLING FACE (FREEMAN-SHELDON) SYNDROME IN TWO SIBLINGS*

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SUMMARY: Bekir N, Bayraktaroğlu Z, Coşkun Y, Karaaslan C. (Departments of Ophthalmology and Pediatrics, Gaziantep University Faculty of Medicine, Gaziantep, Turkey). Whistling face (Freeman-Sheldon) syndrome in two siblings. Turk J Pediatr 1994; 329-332.

Two siblings with typical manifestations of whistling face (Freeman-Sheldon) syndrome (WFS) born to unaffected parents are presented. In Case 1, deep-set eyes, epicanthus, blepharophimosis, right lid ptosis, strabismus, anti mongoloid slant, small mouth, mask-like face, high-arched palate, nasal speech, dysphagia, kyphosis and minimal scoliosis were noted, while Case 2 displayed blepharophimosis, mask-like face, long philtrum, high-arched palate, scoliosis, bilateral post-axial polydactyly of the feet and pes varus. We corrected the blepharophimosis in Case 1 by bilateral canthotomy and canthoplasty.

This syndrome is usually inherited as an autosomal dominant trait; however, some authors have reported an autosomal an autosomal recessive form of this syndrome similar to our cases. Nevertheless, this could be explained by genetic expression of the mutant gene. *Key words: whistling face syndrome, blepharophimosis, canthotomy, canthoplasty, genetic heterogeneity.*

This disorder was described by Freeman and Sheldon in 1938[1]. The most common manifestations of Freeman-Sheldon syndrome are midface flatness with small mouth giving a "whistling" appearance, deep-set eyes, epicanthal folds, strabismus, ulnar deviation of fingers, blepharophimosis and talipes equinovarus[2].

Although the occurrence of autosomal dominant inheritance has been clearly established, the recessive form of this syndrome has yet to be definitively evaluated[3].

We describe here two siblings with whistling face (Freeman-Sheldon) syndrome (WFS) born to unaffected parents, and we present our surgical approach to lid deformities.

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Case Reports

The phenotypically normal parents with consanguinity (marriage between cousins) had four children, two of them unaffected. The mother and father were 27 and 29 years old, respectively.

Case 1

This seven-year-old boy had typical manifestations of WFS (Fig. 1): deep-set eyes, epicanthus, blepharophimosis, right lid ptosis, strabismus, anti-mongoloid slant, small mouth, mask-like face, high-arched palate, nasal speech, dysphagia, kyphosis and minimal scoliosis. Vertical lid distance of the right eye was 6 mm for downward gaze and 7 mm for upward gaze, while horizontal lid distance was 22 mm. Vertical lid distance of the left eye was 8 mm for downward gaze and 9 mm for upward gaze; horizontal lid distance was 23 mm. Lateral canthotomy and canthoplasty were performed on the patient's lids.

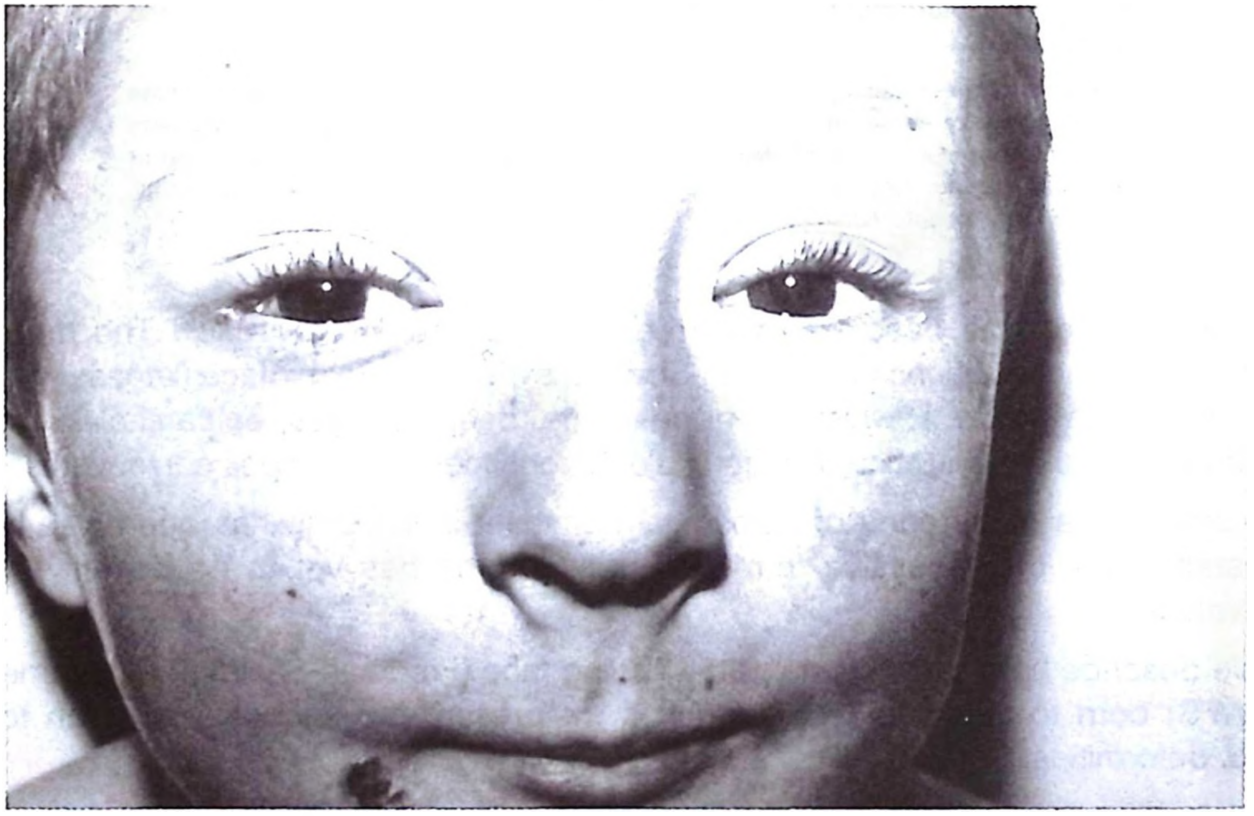

Fig. 1: The typical "whistling face" appearance of Case 1.

Case 2

The three-year-old sister of Case 1 (Fig. 2) had abnormal features of extremity and face which included blepharophimosis, mask-like face, long philtrum, high-arched palate, scoliosis, bilateral post-axial polydactyly of the feet and pes varus. Vertical lid distance of the right eye was 6 mm for downward gaze and 7 mm for upward gaze, with a horizontal lid distance of 20 mm. Vertical lid distance

of the left eye was 7 mm for downward gaze and 8 mm for upward gaze; horizontal lid distance was 21 mm. In this case polydactyly of both feet was correted.

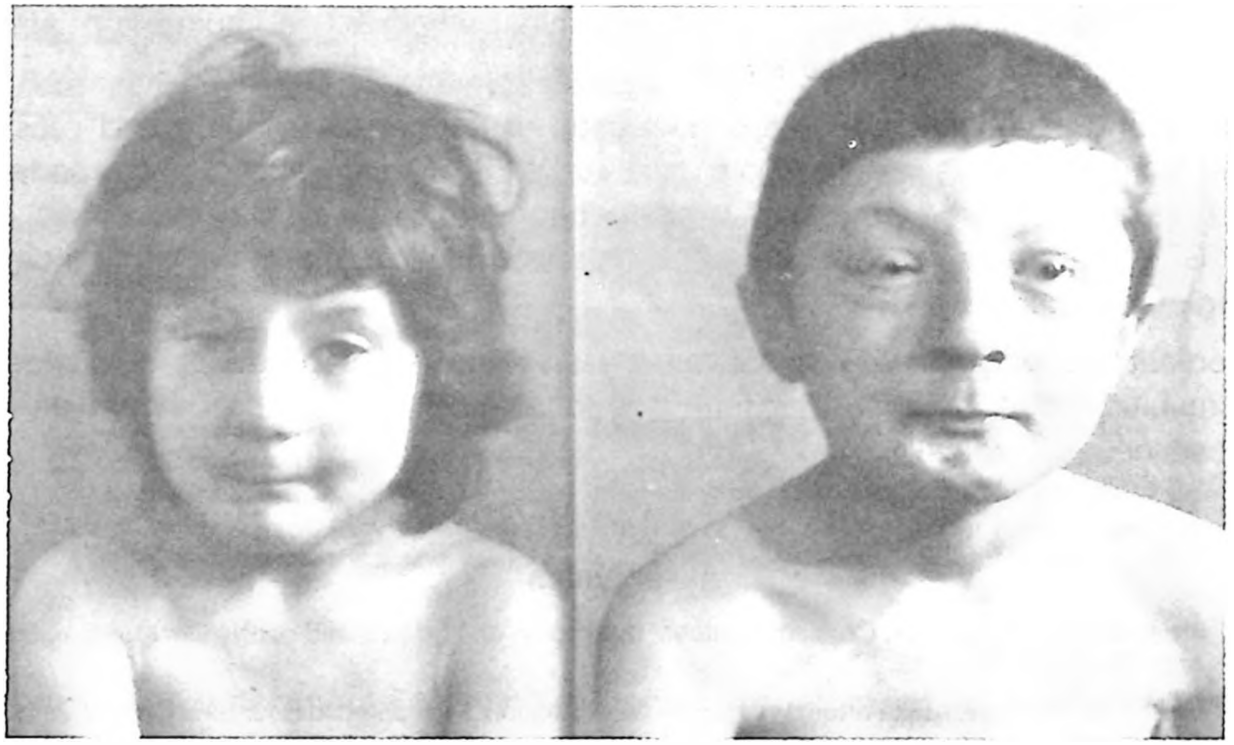

Fig. 2: Photograph of Case 2.

Discussion

Patients born to normal consanguineous parents often have characteristic manifestations of WFS[1,4]. Although there is general agreement in the literature that genetic inheritance of WFS is autosomal dominant[3], some reports suggest an autosomal recessive transmission of this syndrome[5-8]. The two siblings reported here are likely to have had autosomal recessive inheritance because of consanguineous unaffected parents; however, we found no clue in differentiation of their phenotype and clinical severity of the disease from patients with the autosomal dominant from. This evidence suggests that genetic heterogeneity including variable expressivity of the mutant gene or gonodal mosaicism can be seen in WFS, as in our cases. Some authors reported similar cases, indicating an autosomal recessive form of WFS, but they did not observe phenotypical and clinical differences from the autosomal dominant form of the disease[8,10]. In conclusion, since there is no agreement regarding the occurrence of autosomal recessive inheritance in WFS, it is more convenient to consider this form of genetic transmission in practical implications and genetic counselling. A new aspect of WFS was reported by Vanek et al.[11] They observed two cases of WFS with severe abnormalities of the extremities but only slight anomalies

of the face and claimed that the primary cause of the deformities was related to myopathy, classifying this syndrome as a separate type of myopathic arthrogryposis. Bilateral post-axial polydactyly of the feet in Case 2 is an unusual finding in this syndrome; however, it is unclear whether this finding is related to WFS or is a coincidental matter.

Guyuron and Winkler[12] reported correction of congenital upper eyelid ptosis and bilateral commissuroplasty in a case with WFS. Guzzanti et al.[13] also reported orthopedic aspects concerned with the locomotor apparatus in two cases of WFS. We corrected the blepharophimosis in Case 1 by bilateral canthotomy and canthoplasty.

Medical treatment for WFS is not available, and prenatal diagnosis of the disease is insufficient at present. It is beneficial to correct some of the deformities of these cases surgically.

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TOTAL CORRECTION FOR TETRALOGY OF FALLOT AFTER BROCK-TYPE OPERATION*

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SUMMARY: Yurdakul Y, Arsan S, Peker O, Yücekaya E, Özkutlu S. (Departmenmt of Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Total correction for tetralogy of Fallot after Brock-type operation. Turk J Pediatr 1994; 333-336.

We present a case of tetralogy of Fallot who had previously undergone a graded Brock-type operation. The post-operative development of pulmonary arteries and pulmonary trunk after the Brock operation were very suitable for total correction, which was then performed successfully. In contrast to shunt, in Brock-type operations enlargement of the outflow tract induces symmetrical growth of hypoplastic pulmonary arteries without the risk of acquired pulmonary obstruction or peripheral stenosis at the site of anastomosis. After palliative operations, the repair can be deferred until the pulmonary arteries are of a suitable size. *Key words: tetralogy of Fallot, hypoplastic pulmonary arteries, two-stage repair, Brock-type operation.*

Patients with tetralogy of Fallot and unfavorable anatomy of the right ventricular outflow tract or hypoplastic pulmonary arteries may require primary palliation and subsequent repair (two-stage repair). The concept of palliation includes improvement of the pulmonary arterial perfusion and reduction of systemic hypoxia, usually by means of some type of arterio pulmonary arterial shunt or, rarely, a Brock-type operation[1]. Brock-type operations carry the risk of pulmonary hypertension, however the increase of pulmonary blood flow may stimulate the growth of primarily hypoplastic pulmonary arteries and train the frequently smaller-than-normal left ventricle[1]. In contrast to a shunt, enlargement of the outflow tract induces symmetrical growth of hypoplastic pulmonary arteries without the risk of acquired pulmonary obstruction or peripheral stenosis at the site of anastomosis[2].

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Case Report

The patient was a 14-year-old girl whose previous medical history included two operations and three catherizations. In 1981 at the age of two years, a catheterization showed that the pulmonary artery diameter was one-fourth of the aortic diameter. Exploratory surgery was performed by left posterolateral thoracotomy, revealing many collaterals but no pulmonary artery, and the thoracotomy was closed.

In 1990 when the patient was 11 years old, she underwent another catheterization. The pulmonary arteries and trunk were found to be very hypoplastic (Fig. 1), and the decision was made to do a Brock operation. Intraoperatively, infundibular band resection and pulmonary valve commissurotomy were performed. Here, we performed graded enlargement of the outflow tract. In 1992 a third catheterization displayed well-developed pulmonary arteries and pulmonary trunk (Fig. 2), with a pulmonary artery pressure of 18 mmHg. In January 1993, total correction was performed. We used a patch for the ventriculotomy and outflow tract. The postoperative status of the patient was very good, requiring the use of no positive inotropic agent, and the patient was discharged on the eighth postoperative day.

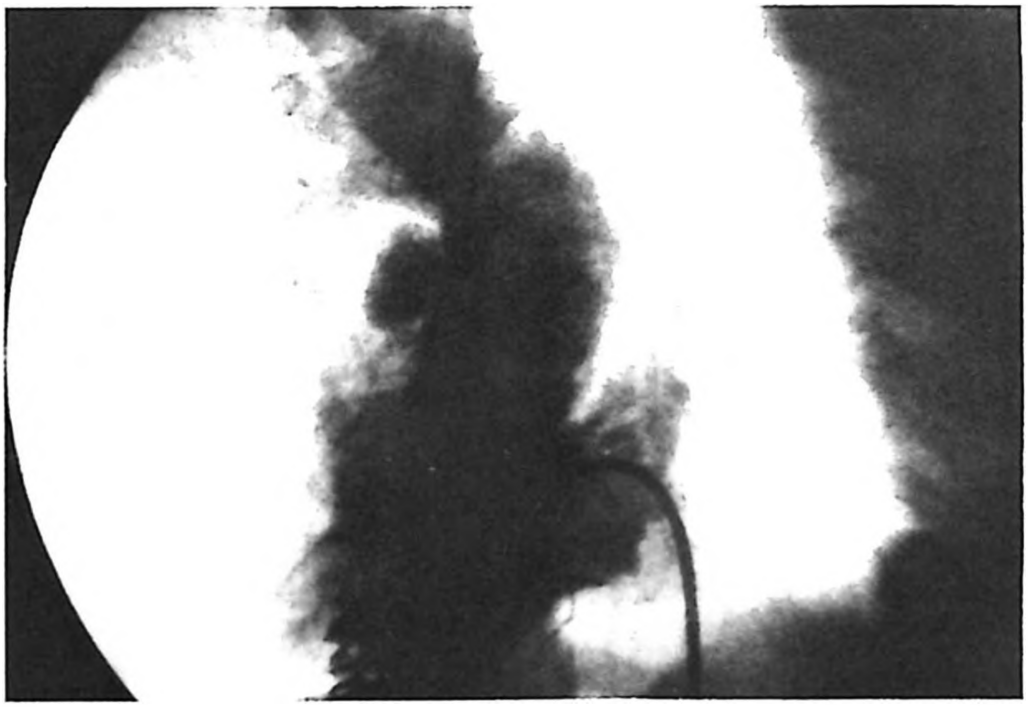

Fig. 1: The angiographic film of the pulmonary arteries before Brock-type operation.

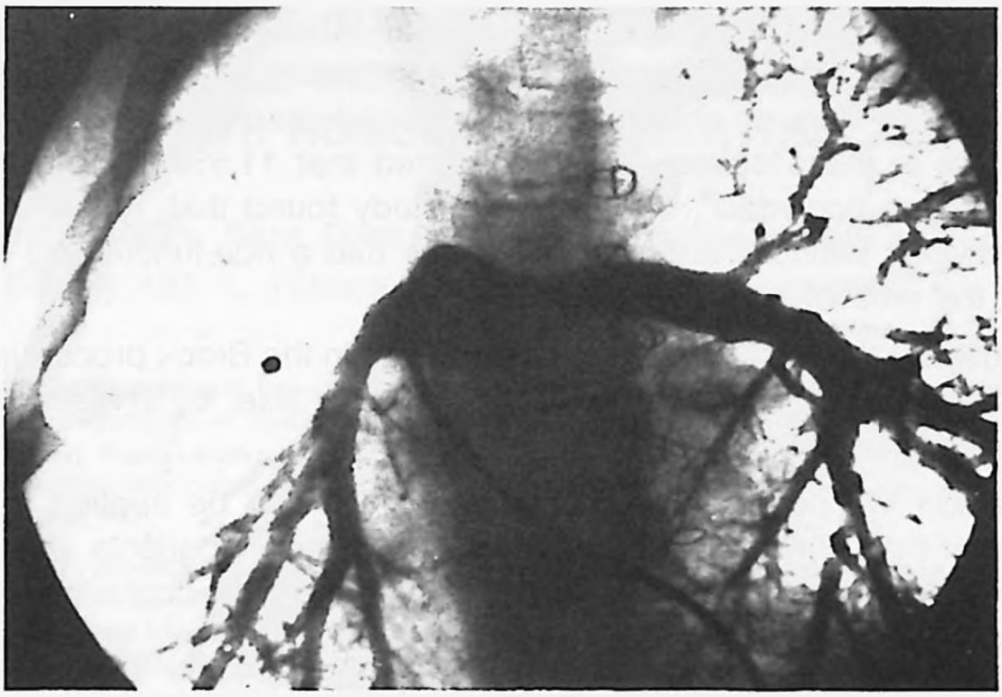

Fig. 2: The angiographic film of the pulmonary arteries before total correction.

Discussion

Several teams have published their experiences regarding the growth of pulmonary arteries after one method our palliation[3]. In this case report we review a patient who had a two-stage operation: Brock operation followed by total correction. After Brock-type palliative operations, no specific surgical problems are typically anticipated at definitive repair except for dissection of the intrapericardial adhesions; however, a previously constructed aortopulmonary shunt must be closed before starting total correction[1].

After Blalock-Taussig operation, the ipsilateral pulmonary artery predominantly increases in size without significant growth of the pulmonary vascular ring and pulmonary trunk. The Brock procedure induces a significant and symmetrical growth of the pulmonary arterial system by improving proximal flow in the pulmonary vascular system[2]. The repair can be deferred until the pulmonary arteries are of a suitable size. The relative diameter of the right pulmonary artery should be at least 30 percent of the diameter of the ascending aorta[4].

Palliative operations should not only reduce the symptoms of hypoxia but should also induce the growth of the pulmonary vascular tree, thereby creating improved anatomy for complete repair[2].

In patients with critically hypoplastic pulmonary arteries, we prefer the graded enlargement of the outflow tract because of its beneficial effects on pulmonary vascular growth[2]. We do not prefer shunt procedures because of the high risk of occlusion in these cases. One report cited that 11.5% of Blalock-Taussig shunts became occluded[4], while another study found that 18.4% of patients with a previous Blalock-Taussig anastomosis had a non-functioning occluded shunt at the time of definitive repair[1].

Enlargement of the right ventricular outflow tract in the Brock procedure should be to approximately one-half of the appropriate size, otherwise pulmonary hypertension may develop.

In conclusion, we prefer shunt procedures which can be applied to patients more easily than Brock-type procedures. However, in patients with critically hypoplastic pulmonary arteries and a high risk of shunt occlusion, we prefer Brock-type operations.

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PLASMA EXCHANGE IN REFRACTORY AUTOIMMUNE ANEMIA IN A CHILD WITH SYSTEMIC VASCULITIS ASSOCIATED WITH HOMOZYGOTE BETA THALASSEMIA*

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SUMMARY: Beşbaş N, Özen S, Bakkaloğlu A, Gürgey A, Kanra T, Saatçi Ü. (Nephrology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Plasma exchange in refractory autoimmune anemia in a child with systemic vasculitis associated with homozygote beta thalassemia. Turk J Pediatr 1994; 337-340.

A four-year-old girl presenting with fever and purpuric lesions was diagnosed with systemic vasculitis based on her clinical and laboratory findings. She also had homozygote beta thalassemia. Oral steroids were administered and during the course of her treatment she developed necrotizing lesions on her extremities along with severe myalgia and an autoimmune refractory anemia. Autoantibodies against the Rh antigen causing a persistent hemolysis of her erythrocytes were detected in her serum. Since no improvement in her skin lesions and autoimmune hemolytic anemia was achieved with bolus methylprednisolone therapy and cyclophosphamide, plasma exchange was performed. After three sessions of plasma exchange, her immune complex and autoantibody levels gradually declined and a remission in her clinical and laboratory findings was achieved. We suggest the use of plasma exchange along with conventional therapy for similar cases with ongoing immunologic injury. *Key words: refractory autoimmune anemia, plasma exchange, autoantibodies, vasculitis.*

In most cases of vasculitis there is indirect evidence of immune complex disease, although the inciting antigen (Ag) is often not found[1,2]. In various types of vasculitis, autoantibodies may be involved in these immune complexes with an abnormal imbalance and interaction of viral, genetic and immunologic factors[3]. The presence of circulating serum autoantibodies with no organ specificity may also be expected. Plasma exchange is an effective way of reducing the amounts of circulating antibody and/or immune complexes in patients with antibody-mediated or immune complex-mediated disease[2,4]. We present a four-year-old

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patient with systemic vasculitis in whom we attempted to modify the primary disease and clear the autoantibodies against Rh system (D) Ag by plasma exchange therapy.

Case Report

This four-year-old girl was admitted to our hospital with persistent fever in the previous few months and recent maculo-papular eruptions. She had been hospitalized for fever in a local hospital. She also complained of swelling and pain in the dorsum of the right hand and arthritis in the lower extremities. Her parents were first cousins. The first child of the family had received multiple blood transfusions for his thalassemia and had died at the age of two years. One other sibling was healthy and six years old.

Physical examination on admission revealed a pale child with palpable purpuric lesions and livedo reticularis over the extremities and abdomen. Her body temperature was 38.5°C, pulse rate 156/min, and blood pressure 100/50 mmHg. The liver and spleen were enlarged by 5 cm and 4 cm, respectively. She had severe myalgia in the lower extremities with arthritis of the knees.

Laboratory examination revealed the following: hemoglobin 6.35 g/dl, hct 18%, WBC count 18,000/mm^3, and thrombocyte count 272,000/mm^3. The blood smear showed anisocytosis, poikilocytosis, hypochromia and microcytosis. Reticulocyte count was 6.6%. Her blood type was 0 Rh+. Direct Coombs test was positive and anti-complement Coombs test was negative. Plasma Hb level was 26.3% and haptoglobulin was 0. Hemoglobin electrophoresis was compatible with homozygote beta thalassemia: HbA2 2.4%, HbF 76%; starch electrophoresis A+, F4+, A2 normal; agar electrophoresis A+, F4+. Urine examination was normal. The renal and liver function tests were within normal limits. Creatinine phosphokinase was 79 u (N: 20-191). Complement 3(C3) and C4 levels were 50 mg/dl (N: 60-120) and 18 mg/dl (N: 20-55), immune complexes were 275 ug/ml (high), and the CH50 level was within normal limits. Antinuclear antibodies and anti-DNA titers were negative. Immunoglobulin levels were all increased. The electromyography and the muscle ultrasonography were compatible with myopathy/polymyositis.

During the hospital course, severe myalgia and fever dominated the patient's clinical course. Marked digital ulcerations and pain characteristic of polyarteritis nodosa (PAN) developed on the first and second fingers of the right hand. Cutaneous lesions consistent with vasculitis and the accompanying systemic findings were interpreted to be related to a vasculitis syndrome. Soon after steroid treatment was initiated at a dose of 2 mg/kg/day, improvement of symptoms was noted and the patient was discharged with a diagnosis of systemic vasculitis.

Six weeks later the steroid dosage was reduced. One week later the patient was readmitted with high fever, rash, cough and severe abdominal pain. On physical examination her body temperature was 40°C and she had bronchopneumonia and arthritis in the left distal interphalangeal joints. She again had a Coombs (+) hemolytic anemia, and occult blood was detected in her stool. Antineutrophil cytoplasmic antibodies (ANCA) (diffuse staining) were detected by indirect immunofluorescence.

Antibiotics were administered for her pneumonia. Although the pneumonia resolved with antibiotics, her fever persisted and a gradual decline was observed in the hemoglobin level. Bone marrow aspiration was normal. Autoantibody detected in the serum and eluate showed anti-D (Rho) specificity at a titer of 1/32. Necrotizing purpuric lesions recurred. A combined treatment including pulse methylprednisolone therapy at a dose of 30 mg/kg/day +cyclophosphamide 2.5 mg/kg/day +dipyridamole 3 mg/kg was initiated. However, the patient's anemia progressed, necessitating multiple blood transfusions in a single day, with no improvement in the severe symptoms nor in serological findings. Plasma exchange was hence performed. Double-filtration plasma exchange was carried out using a cellulose diacetate hollow fiber. Fresh frozen plasma was used as substitute plasma. The blood was circulated from the internal shunt at a rate of 40 ml/min, and the replacement plasma was substituted at one-fifth that rate (8-10 ml/min). After the first sesson, the autoantibody titer against Rh decreased to 1/8 and the Hb level remained stable for 72 hours. On the fourth day the Hb level again decreased to 3 g/dl, and the autoantibody level was again elevated to 1/32. Two additional sessions of plasma exchange were performed with an interval of three days. Oral low-dose steroid and cyclophosphamide were also continued. At the end of this treatment period, the autoantibody level declined, the Hb level was stabilized and there was a decline in the immune complex level. Clinically the patient's myalgia and skin lesions resolved. The family then migrated to another country.

Discussion

Systemic vasculitis is an immune-complex-mediated and/or autoantibody-mediated disease[3,4]. Therapeutic approaches consist mainly of high-dose corticosteroid and a number of cytotoxic drugs. A diagnosis of systemic vasculitis was accepted in the presented patient given the clinical and serological findings along with the positive ANCA result. Since it is believed that circulating ANCAs may contribute to the injurious effects of infiltrating leukocytes in the tissue, the beneficial effect of plasma exchange is obvious in the acute stages when the ANCA titer is high[5].

Retrospective studies on patients with vasculitis have shown improved survival

with administration of the combination of steroids plus cyclophosphamide or azathioprine[1]. The addition of intravenous methylprednisolone, methotrexate or plasma exchange to conventional immunotherapy (high-dose steroids and cytotoxic drugs) has also been reported to have some beneficial results[1,2,5]. Whether the combination of these drugs with plasma exchange therapy is of additional benefit is currently being evaluated in various clinical settings[4,5]. The rationale for the use of plasma exchange in vasculitis is that antibodies and mediators that cause the vascular damage by deposition in the arteriolar walls can be thus removed[5,6]. Plasma exchange should be considered in cases with rapidly progressing vascular disease with evidence of ongoing immune complex process[1]. Turner et al.[2] reported excellent results in seven of their eight patients with severe refractory cutaneous vasculitis. The indication for plasma exchange is also strengthened in cases like ours with detrimental effects of an autoantibody which cannot be controlled by conventional immunotherapy. Bernstein et al.[6] also reported a beneficial effect with plasma exchange in an idiopathic case of refractory acute autoimmune hemolytic anemia. Our case manifested an autoantibody against Rh antigen causing the hemolysis of erythrocytes. To our knowledge this is the first report of such autoantibodies in a systemic vasculitis case. The association of vasculitis with thalassemia major has not been previously reported either.

Since plasma exchange may induce a rebound of antibody formation which may exacerbate the disease, a combination of cytotoxic drugs is recommended to reduce this rebound effect[1]. We also applied this approach. After three sessions of plasma exchange, we achieved a consistent decrease in the autoantibody and immune complex titer and were able to arrest the hemolytic process in the patient. A regression in the symptoms of vasculitis was also observed. On the other hand, in renal vasculitis the results of plasma exchange therapy are reported to be less promising[4]. Overall, however, the association of plasma exchange with conventional immunotherapy has significantly reduced mortality in severe vasculitis[5]. This case report emphasizes the beneficial effect of this form of therapy in cases with ongoing immunologic injury indicated by immune complexes and autoantibodies.

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INVASIVE PULMONARY ASPERGILLOSIS IN CHRONIC GRANULOMATOUS DISEASE: RESPONSE TO SYSTEMIC PREDNISOLONE TREATMENT AND LOCALLY APPLIE AMPHOTERICIN B*

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*Ülker Öneş MD****

SUMMARY: Güler N, Yalçın I, Salman N, Öneş Ü. (Department of Pediatrics, Istanbul University Faculty of Medicine, Istanbul, Turkey). Invasive pulmonary aspergillosis in chronic granulomatous disease: response to systemic prednisolone treatment and locally applied amphotericin B. Turk J Pediatr 1994; 341-345.

A five-year-old boy with deforming and destructive invasion of pulmonary aspergillosis to the thoracic cage was diagnosed as having chronic granulomatous disease. Conventional antifungal therapy failed in this patient. Prednisolone therapy was added and rapidly improved the general condition of patient but deterioration had already been very rapid. The failure of systemic therapy prompted us to give amphotericin B locally to the granulomatous lesions through the bronchocutaneous fistula. This application yielded a good clinical response with closure of fistula. Despite this improvement the patient died from septicemia. We believe that systemic prednisolone treatment is useless in such cases, but local application of amphotericin B into the granulomatous lesions together with systemic therapy during the earlier stages of infection can contribute to a change in prognosis. *Key words: pulmonary aspergillosis, chronic granulomatous disease, local amphotericin B.*

Quantitative and qualitative neutrophil defects are the most frequent risk factor for opportunistic fungal infections[1]. Chronic granulomatous disease (CGD) is a rare inherited disease characterized by a decreased or absent ability of neutrophils and monocytes to kill microorganisms that have undergone phagocytosis. In addition to infectious complication, obstructive lesions resulting from granuloma formation compressing vital structures have been major sources of morbidity and mortality in patients with CGD[2]. This report describes a child with CGD and invasive pulmonary aspergillosis in whom conventional antifungal therapy had failed.

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Case Report

A five-year-old boy was transferred from another hospital to ours with a three-month history of bronchopneumonia resistant to antibiotic therapy and progression of the disease to the chest wall. His past medical history revealed recurrent pustulosis on the skin which had been treated with oral antibiotics in the first year of life. The parents of the child were unrelated and healthy. The first-born child of the family had died of diarrhea at five months of age.

Physical examination revealed a cachetic child (weight 14.5 kg, height 120 cm). The child was pale, weak and febrile. The chest wall was deformed with bulging masses on the anterior right side and on the back. There were inspiratory crackles over both lungs. The liver and spleen were palpated two centimeters and one centimeter below the costal margings, respectively.

Hematologic values on admission included: hematocrit 27%, leukocyte count 15,000/mm^3 with 40% mature neturophils and 8% band forms, and erythrocyte sedimentation rate of 60 mm/h. Bacterial cultures of numerous tracheal aspirates and sputum specimens grew only normal flora, and cultures for mycobacteria were negative. A chest x-ray showed diffuse infiltrates in the right upper and left lower lobes. Upper right ribs were also deformed. Computerized tomography of the lungs demonstrated a solid tumoral mass 10 cm in diameter in the upper lobe of the right lung and destruction of ribs. Pleural space was also involved on the left side. On immunologic investigation, polymorphonuclear leukocytes revealed an inability to reduce nitroblue tetrazolium dye, and the bacterial killing index suggested defective killing of test organism (S.aureus). CGD was diagnosed based on these clinical and laboratory findings. Biopsy of the granulomatous lesion on the right posterior chest wall revealed Aspergillus sp in granuloma tissue.

Antifungal therapy with a combination of amphotericin B and 5-fluorocytosine was effective initially. Both lung infiltrates and abscesses healed within three months of this treatment, but deformity of the ribs did not change. One month after therapy was stopped, the same lesions in the lungs became active again. Over the ensuing month, administration of the drugs was continued, with no response observed this time. Prednisolone at a dose of 2 mg/kg/day was added to this treatment. Within two weeks a dramatic clinical improvement occurred. Granulomatous lesions penetrating the chest wall became smaller and pus formation stopped, but the radiologic picture of the lungs did not change markedly. The initial prednisolone dosage was continued for three weeks and then tapered during the following two weeks. At the end of this period, the child's general condition deteriorated and the lesions on the chest wall progressively showed paraspinal infiltration with the destruction of the vertebral

bodies between T1 and T11. Paraplegia had developed with the compression of the medulla spinalis (Figs. 1, 2). Excessive formation of pus and loculations in abscesses had been demonstrated, and a bronchocutaneous fistula was diagnosed with instillation of methylene blue. Although no organism was identified by routine microbiologic invastigation, antibiotics were initiated empirically.

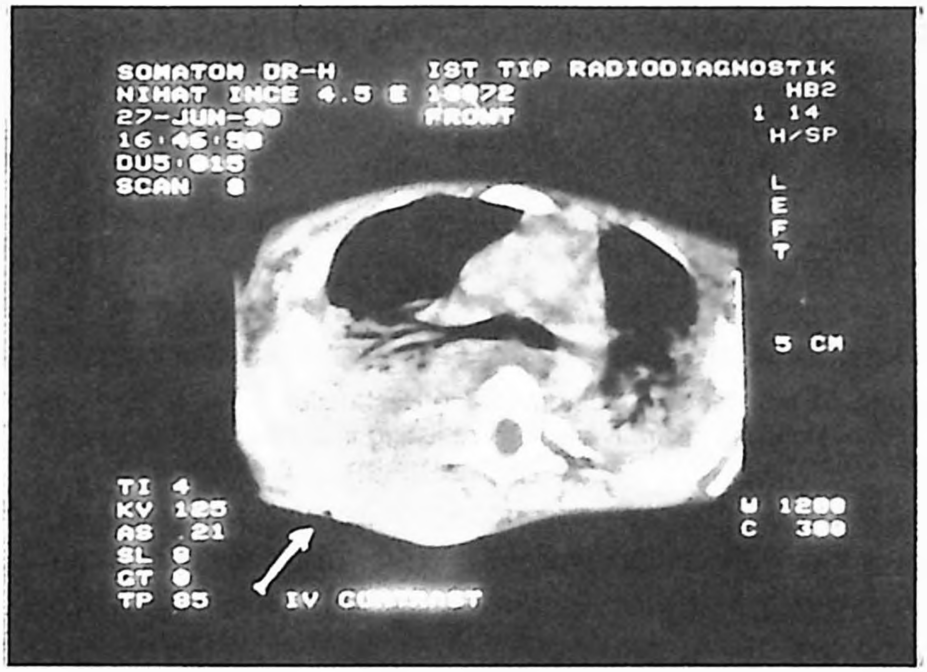

Fig. 1: Computed tomography of patient showing the invasion of granulomatous lesions to the lungs, ribs and vertebrae. The external opening of the bronchocutaneous fistula is shown with an arrow.

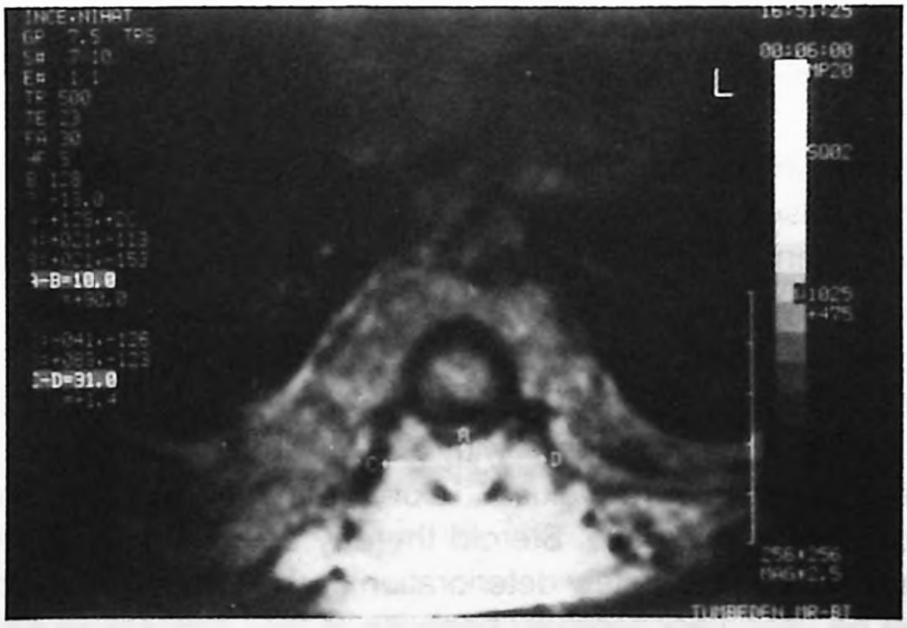

Fig. 2a: Magnetic resonance imaging of the spine demonstrating paraspinous mass.

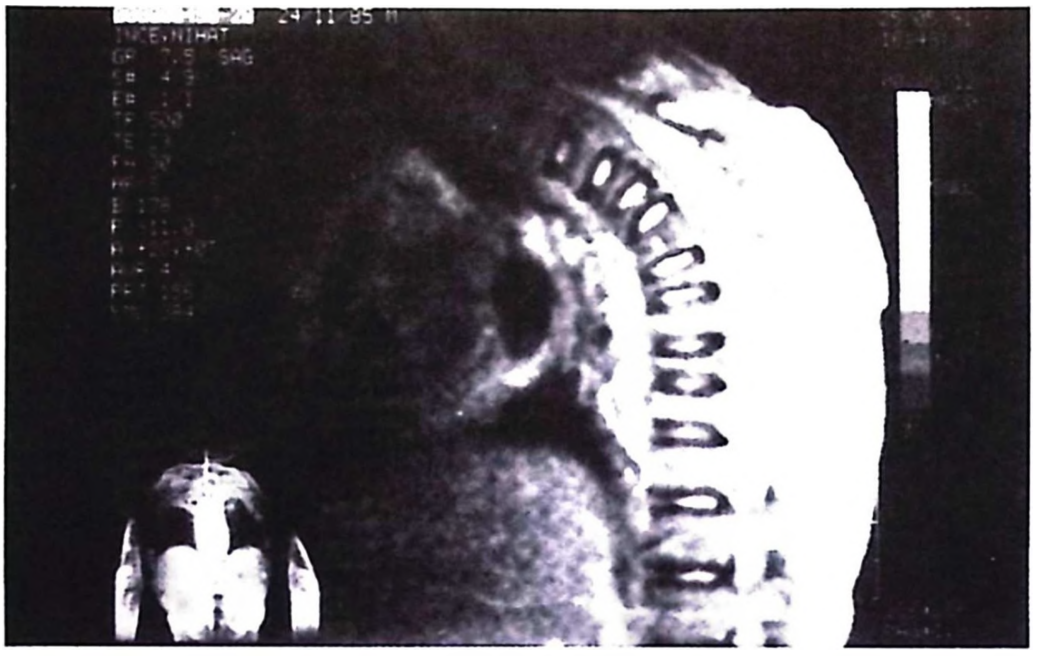

Fig. 2b: Magnetic resonance imaging showing destruction of the thoracic vertebrae and paravertebral infiltrative lesions resulting in epidural compression.

The failure of systemic therapy prompted us to give an antifungal drug locally. After sterilizing the skin, a catheter was advanced into the abscess cavity and amphotericin B was administered slowly at a dose of 15 mg/day. This procedure was repeated every day for two weeks. With this therapy, a cough was provoked in the first days, due to a bronchocutaneous fistula. After several days, this symptom disappeared and the patient began to improve with closure of the fistula. The size of the thorax wall decreased and pus formation gradually diminished. Despite this improvement, the clinical picture of septicemia developed and the patient died.

Discussion

Although opportunistic aspergillus infection is seen relatively frequently in immunocompromised patients and almost always arises from the respiratory route with involvement of the lungs, invasion to the chest wall is extremely rare[1,3-5].

This case presented with bronchopneumonia rapidly progressing to the chest wall.Conventional antifungal therapy failed in this patient. Corticosteroids have been used successfully in patients with CGD to treat obstructive lesions when antimicrobial therapy is of no value[6,7]. Our experience in corticosteroid usage was not promising in this case. Steroid therapy acted rapidly in improving the patient's status, but unfortunately deterioration had also been very rapid. Steroids in CGD must be used very carefully because of their supressive effects on host defenses[8].

Transbronchial hyphal invasion of pulmonary arterioles usually results in ischemic necrosis of the lung. This histopathologic picture of vascular invasion may explain clinical features such as cavitation and fistulae[9].

Progressive deterioration despite systemic treatment, absence of other focuses in other parts of the body and abundant purulant discharge through the bronchocutaneus fistula prompted us to give amphotericin B locally to the granulomatous lesion. There have been several reports describing the use of intracavitary therapy to treat pulmonary aspergilloma with rapid improvement[10]. Rapid effectiveness of amphotericin B is probably due to its irritative and sclerosing properties. We also observed sclerosis and closure of the fistula. Local application of amphotericin B had a palliative effect on symptoms but did not affect the outcome of the patient, probably because it was initiated at the terminal stage of the disease. We believe that early administration of local therapy along with systemic amphotericin B may affect the prognosis of such patients.

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HYPOGLOSSIA-HYPODACTYLIA (HANHART'S) SYNDROME WITH SENSORINEUROL HEARING LOSS*

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SUMMARY: Tüysüz B, Erginel A, Unutmaz T, Cenani A. (Department of Pediatrics, Istanbul University Cerrahpaşa Faculty of Medicine, Istanbul, Turkey). Hypoglossia-hypodactylia (Hanhart's) syndrome with sensorineural hearing loss. Turk J Pediatr 1994; 347-352.

Hanhart's syndrome, an uncommon disorder characterized by severe micrognathia, hypoglossia and absence of the extremities, belongs to the oromandibular-limb hypogenesis group of diseases.

Our patient was admitted with the complaints of abnormality of the mouth and absence of the upper extremities. Physical examination revealed severe micrognathia, a small tongue adhered to the base of the mouth, absence of bone, muscle and skin tissue at the lower edge of the right humerus and at the middle zone of the left ulna and radius. According to these findings, the diagnosis of hypoglossia-hypodactylia (Hanhart's) syndrome was made. At the age of 1 1/2 years, tympanometric examination revealed conductive hearing loss due to dysfunction of the eustachian tube. Auditory brainstem responses also revealed bilateral severe sensorineural hearing loss.

A literature search revealed two cases of Hanhart's syndrome with conductive hearing loss, but no report of sensorineural hearing loss as part of this entity. Therefore, we present this case of Hanhart's syndrome with severe sensorineural hearing loss. *Key words: Hanhart's syndrome, hypoglossia-hypodactylia, aglossia-adactylia, sensorineural deafness.*

Cases presenting with absence of the extremities and oral cavity malformations have, since the beginning of this century, been reported under various names, including aglossia-adactylia syndrome, hypoglossia-hypodactylia syndrome, glosso-palatine ankylosis, ankyloglossia superior syndrome, and Hanhart's syndrome[1,2]. The syndrome, which is one of the diseases grouped under the name of oromandibular limb hypogenesis, was described by Hanhart[2] in 1947 and is characterized by severe hand and/or foot defects together with oral abnormalities.

Oral malformations consist of extreme micrognathia, hypoglossia-to-aglossia, adhesion of the tongue to the law and fibrous bands between the upper and lower jaws[2,4,5]. There may also be paralysis of cranial nerves III, V, VI, VII, IX

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and XII[4,6]. Hearing loss is rare in Hanhart's syndrome[5], but two cases with conductive hearing loss have been reported[7,8]. In this report, a case of Hanhart's syndrome with bilateral sensorineural hearing loss is presented.

Case Report

A three-day-old boy was admitted because of absence of upper extremities and abnormality of the mouth. He was born at term. His birth weight was 2310 gr (< 3rd percentile), length 49 cm (25th-50th percentile) and the head circumference 36 cm (90th percentile). He was the first child of unrelated healthy parents (mother 20, father 26 years old). The mother had previously had a spontaneous abortus at two-and-one-half months of gestation. There was no similar case in the family. During pregnancy the mother had received no drugs, was not x-rayed and had no illness with fever and rash.

Severe microretrognathia, a defect in the symphysis of the jaw and hypoplasia of the tongue were detected (Fig. 1). The tongue was adhered to the base of the mouth and the palate was high-arched. Two hemangiomas (3×5 cm) were

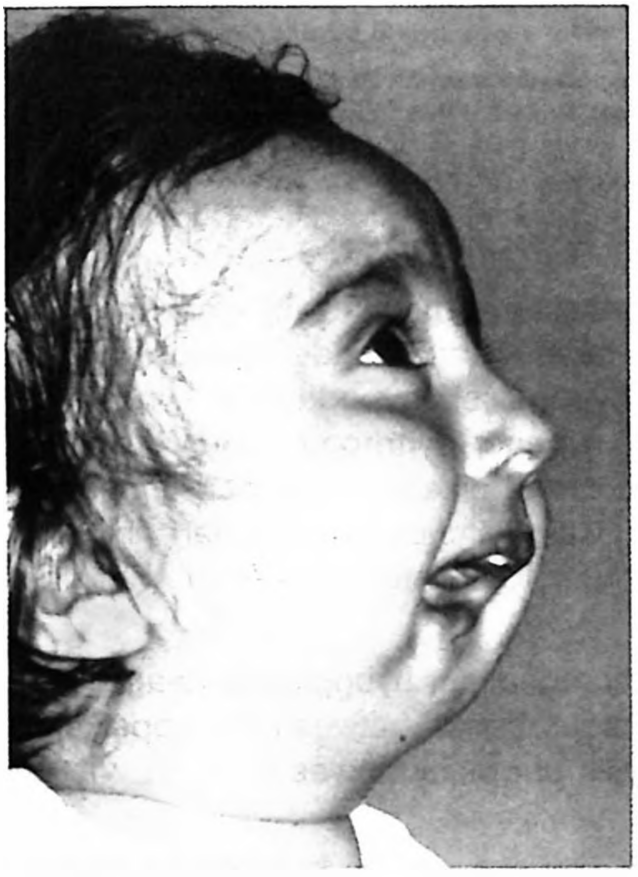

Fig. 1: Lateral view of the patient displaying severe microretrognathia, defective jaw and hypoplastic tongue.

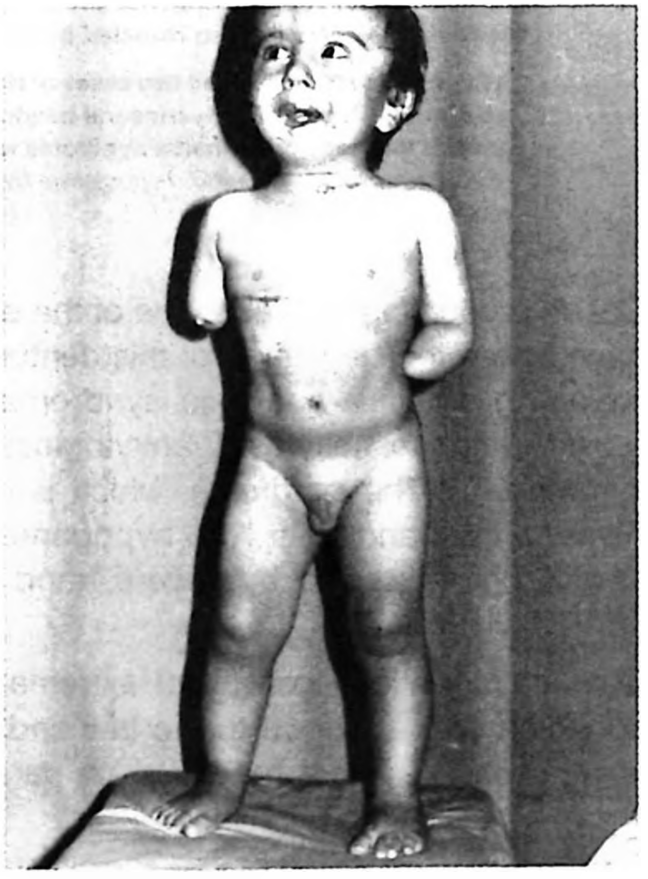

Fig. 2: Photograph displaying the absence of the distal end of the right humerus and part of left forearm.

present between the right eyelid and eyebrow and on the forehead. The eyes and ears were not malformed. Bone, muscle and skin tissues were absent at the distal end of the right humerus and in the middle of the left radius and ulna. There was a rudimentary finger at the end of the right arm consisting of skin and subcutaneous tissue (Fig. 2). No malformation of the lower extremities was noted. Neurologic examination revealed no paralysis of the cranial nerves. The eyes and the other systemic findings were normal.

Complete blood count and urinalysis were normal. Biochemical findings of the blood were normal. Humoral and cellular immunological studies were normal. Chest x-ray, electrocardiography, abdominal ultrasonography and intravenous pyelography revealed no congenital malformations. Cranial computed tomography was normal except slight dilatation of the ventricles. The karyotype was 46XY by G-banding technique.

The patient was considered to be a case of Hanhart's syndrome. When he was admitted again at the age of one and a-half years, his weight was 11 kg (25th-50th percentile) and his height was 78 cm (25th percentile). He had six hypoplastic and irregular teeth. His neuromotor development was reported to be normal. His speech was limited to a few words. Denver test revealed that fine and gross motor skills were compatible with his age. Speech development was compatible with 14 months.

Tympanometric evaluation revealed a conductive hearing loss which was due to dysfunction of the eustachian tube. Auditory brainstem responses were evaluated. Wave responses to acoustic stimulations of 80 decibel intensity in both ears were examined; configuration of the waves was irregular and the fifth wave was not observed. In conclusion, severe bilateral sensorineural type hearing loss was detected.

The patient was referred to the plastic surgery department. The defect in the mandibula was repaired and the tongue was surgically released.

Discussion

In 1976, Hermann et al[6] evaluated seven personal and 62 previously reported cases of oromandibular-extremity hypoplasia. Patients with oro-acral malformations accompanied by nuclear agenesis of the cranial nerves and pectoral defects were classified as having Poland-Mobius syndrome. Patients with ocular hypertelorism, cleft-palate and variable degrees of hypodactyly of hands and feet were classified as having Charlie-M syndrome. Cases of distal agenesis of the extremities and severe micrognathia-microglossia and sometimes cranial nerve palsy were classified as having Hanhart's syndrome. There is considerable overlap between these syndromes. In the same study, 35 patients

with Hanhart's syndrome were coded according to the severity of the clinical findings: Grade-0: no pathology in the extremities; Grade-I: partial or complete cutaneous syndactyly, with or without short digits; Grade-II: presence of oligodactylia; Grade-III: complete or partial agenesis of the hands and/or feet; Grade-IV: complete or partial transverse agenesis of a forearm or leg; Grade-V: partial or complete hemimelia. According to this classification, our patient was compatible with Grade-V. In this study, severe micrognathia was observed in 26 cases while five cases had slight micrognathia. Four patients lacked this pathology. The anterior two-thirds of the tongue was absent in 21 cases. Even though some authors name Hanhart's syndrome as "aglossia-adactylia", the tongue is expected to exist, and rudimentary or not, it adheres to the base of the mouth. In our case the tongue was hypoplastic, adhered to the base of the mouth and there was a defect in the symphysis of the jaw. In Hanhart's syndrome, the palate is narrow and high-arched, maybe cleft, and the teeth are hypoplastic and irregular[1-5]. In our patient, the palate was high-arched, and the teeth were irregular and hypoplastic.

Chandra-Sekhar et al.[7] reported two patients: one of them had atresia of the external auditory canal and temporal bone, and the other had bilateral conductive hearing loss. Our patient had no malformation in the external ear but he had conductive hearing lose due to dysfunction of the eustachian tube and severe bilateral sensorineural hearing loss determined by auditory brainstem responses. It is known that paralysis of cranial nerves. III, V, VI, VII, IX, XII might be present in Hanhart's syndrome[4,6]. The tests to determine whether our patient's sensorineural hearing loss was due to paralysis of the eighth cranial nerve or whether there was an accompanying cochlear pathology cannot be done in this age group.

Our patient was born at term and was small for gestational age. In the literature [1-8], most of the cases were also born small for gestational age.

Congenital heart and renal disease, cryptorchidism and anal atresia are other possible features of the syndrome[1-6], but none of them was present in our patient. Cases with hydrocephaly and porencephaly have been reported[4,8]. In our patient physical examination revealed no increase in intracranial pressure, and cranial tomography revealed only minimal ventricular dilatation. A case of Hanhart's syndrome with colobomatous microphthalmia has been reported[9]; however, examination of the eyes was normal in our patient.

Most of the reported patients had normal intelligence[1-6]. Even with hypoglossia, speech is surprisingly good. In our patient the Denver test results revealed that fine and gross motor skills were in accordance with his age at 18 months, while speech development was compatible with a child of 14 months.

The prevalence of the disease has been reported by two different authors to be one in every 500,000 births and less than one in every 20,000 births [4,10].

The etiology of Hanhart's syndrome is not clearly understood. Thirty-five cases which were analyzed by Herman et al.[6] were all sporadic, chromosome analyses were normal and the parents were not relatives. Tunçbilek et al.[11] reported three cases whose parents were relatives and suggested that the syndrome might be autosomal recessive. However, in Turkey the incidence of consanguineous marriages is high and this condition might be a coincidence. Temtamy[12], McKusick[13] and later Scott[14] determined dental malformations in first-degree relatives of patients and suggested that an autosomal dominant gene with low penetrance might play an etiological role. In our case the karyotype was normal. Similar cases and consanguineous marriage were not reported in the family history.

Many investigators[11,15-18] have suggested that between the 5th and 7th weeks of gestation, thrombosis or vasoconstruction of the vessels caused by drugs or other teratogenic factors resulted in these clinical malformations of the Meckel cartilage, the tongue and the extremities developing from the same embriological region. In our patient the mother had not been exposed to any teratogenic agent.

Prognosis is usually good if aspiration due to malformations of the mouth does not occur[1,5,6,19].

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The Turkish Journal of Pediatrics 36: 353-355 1994

AN ALTERNATIVE METHOD FOR PERICARDIAL PATCH CLOSURE*

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To the editor,

Primary closure of the pericardium may lead to cardiac tamponade in cases having an extracardiac conduit or outflow patch, especially in cases of Fallot's tetralogy[1-4]. In such cases the pericardium may be closed to the mediastinal pleura with prepericardial fat tissue as described below to protect the retrosternal cardiac structures, conduits or patches during sternal reentry without the potential disadvantages of primary closure[2,3].

Technique: At the end of surgery, the right or left pleura spaces are longitudinally opened beneath the sternum (Fig. 1a). The mediastial pleura itself is first incised horizontally along the phrenic nerve, and dissection is then continued medially toward the right or left border of the pericardium. The trapezoidal mediastinal pleural flap with fat tissue is thus formed broad-based on the right or left border of the pericardium. The graft may be used as described above or may be used with dissection completely from the pericardium as a free graft. If the pedunculated graft is used, it is reversed and sutured to the other side of the pericardium and thymic tissue (Fig. 1b); if the free graft is used, it is sutured to both the pericardial border and thymic tissue.

We believe that the surgical risk of elective reoperation does not differ from that of primary operations, particularly if the pericardium had been closed during the first operation. If primary closure of the pericardium is impossible, different prosthetic materials and heterologous pericardial substitutes may be used to cover the heart[3], or the pericardium may be closed using patch mediastinal pleura as an alternative material for closure with no cost. The patient's own tissue is more resistant to mediastinal infections, and the elasticity of such a graft is superior to that of others. This new technique has been used for two years on nearly 50 patients without complications such as tamponade or construction; however two patients required reoperation on postoperative day

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12 and 14 because sternal instability and viability of the free graft were detected. We believe that the new technique described in this letter is applicable to all congenital cases, particularly in cases having an extracardiac conduit or outflow patch.

Fig. 1a:

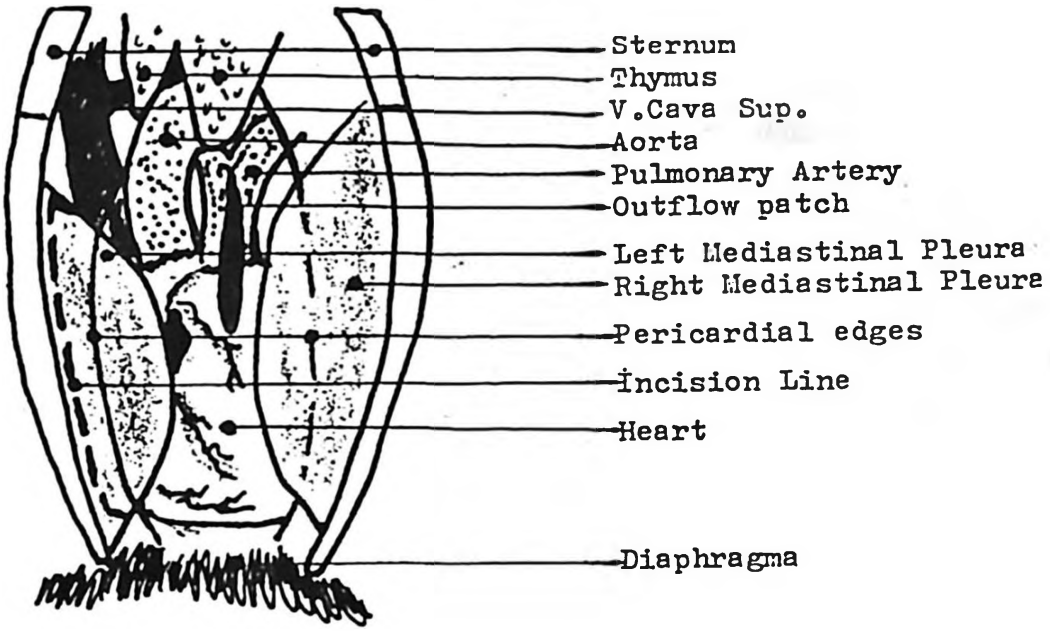
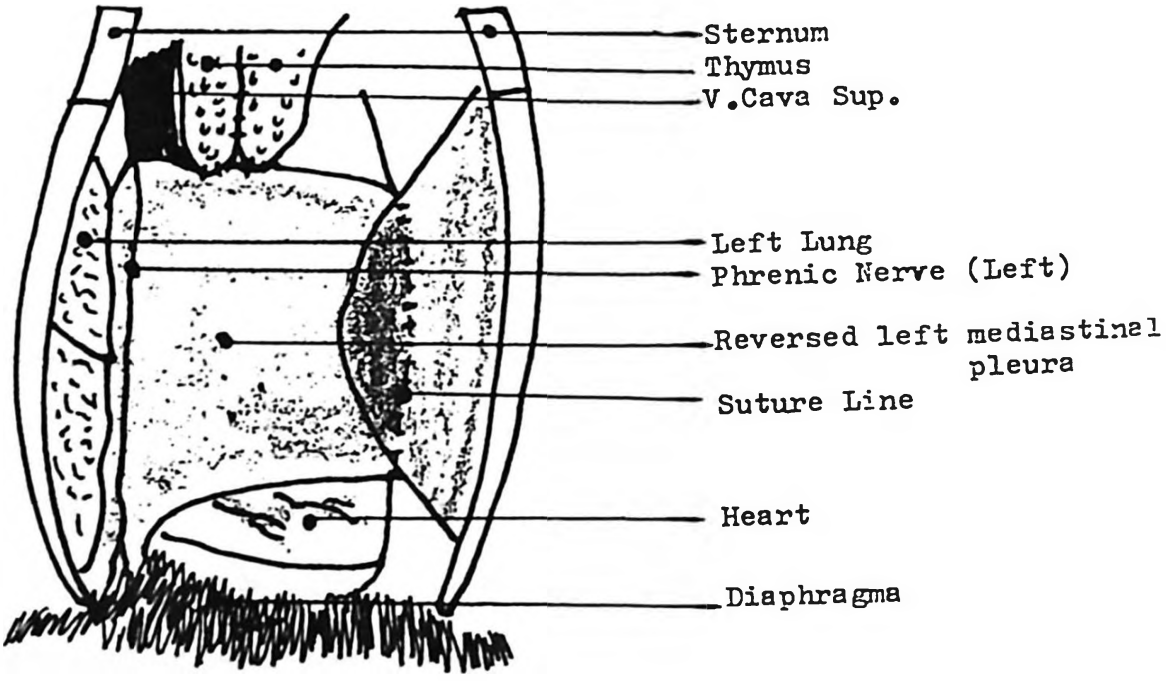


Fig. 1: Schmatic drawing of the closure of the pericardium.
(a) showing the left pleural incision (just beneath the sternum); (b) showing the suture line between the reversed left mediastinal pleura and right pericardial edge.

Fig. 1b:



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