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GLOBAL CHILD HEALTH: CHALLENGES AND GOALS IN THE 1990s*

*Richard S. Reid***

Mr. President of the Republic honorable minister of health and education, Prof. DOĞRAMACI, I stand here before you as an adopted son of Turkey, buoyed by warm memories and the recollection of prodigious beginnings in child health that took place in this very hall. Particularly the 1985 Turkish National Immunization campaign which was launched here. And I bring you the greetings of another adopted son, the Executive Director of UNICEF, Mr. James P. Grant.

Mr. President, your presence here with us today, and the informed and concerned statement you just made, will send a strong signal across Turkey and to the countries represented here about the importance this country attaches to child health.

The pediatricians of ten countries are gathered here today, along with child health experts from international organizations. Most of us tend in our work to think of children, particularly those in developing countries, as the vulnerable, fragile cohorts of their societies, rather than as sturdy building blocks of national development in the making. It is this focus on children as short-term objects of protection that I want to challenge today, because such a view excludes the social and economic payoff that healthy and well-educated children can bring to their countries when they grow up. This payoff can often capture the attention of politicians and natural leaders (whose support we vitally need) more than arguments based only on compassion and morality.

If you asked economists on political scientists anywhere to name the world's most serious problems undermining development, they would probably say population, poverty and the environment. Asked to name the most serious of those three, they would probably say population, with poverty the second-most serious. Runaway population guarantees poverty because of the competition for diminishing resources; poverty drives people to have more children; population pressure and poverty both ruin the environment, which is to say the earth, our increasingly battered spaceship.

What does this have to do with UNICEF's mandate–the survival and development of children–consider a moment! There are two million more people in the world (mainly in the poor countries) every week: the deserts are expanding a hundred kilometers a year; the forests are disappearing, the rivers are being made foul, and one of every five people in the world is living on a dollar a day or less.

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This is a desperate picture that cries out for remedies, for solutions. We as responsible people should be urgently seeking those solutions—whatever country we come from. Finding solutions by isolating the causes. But what can the conditions of children have to do with this? Surely the suffering children—35,000 dying a day around the world—surely their hunger and deaths and illness and poor or absent education are a symptom of the desperate straits. The developing countries are not a cause, not a key to a solution. We should protect children and come to their aid when we can, certainly, but in doing so we are obviously addressing a symptom, not getting at a cause of our worst problems. This is what our intuition may tell us.

But we in UNICEF argue that this intuition is wrong. If children are given real priority, they can be the main key to a country's rise from poverty and its escape from the population trap and an easing of pressure on the land, the forests, and the rivers. Except for the few developing countries that are extravagantly rich from oil, an absolute priority concentration on children, the indispensable foundation of human resource development, is probably the surest way to grow out of underdevelopment. One only has to look at the East Asian countries, at Thailand, South Korea, Taiwan, and Singapore, as examples. Thirty years ago they were poor, but they were also sacrificing and deferring the consumer gratification of the elites and disciplining themselves in order to give their children, all of their children (girls and boys), good nutrition, good health care, and a rigorous primary and secondary education. They made family planning services available to all parents. And in doing this, they broke the "inner cycle" of poverty. Better health care and hygiene, immunization, clean water supply, and sanitation meant that many fewer children died from the childhood killer diseases, and their survival gave parents confidence to have fewer babies. State-supported nutrition programmes meant bigger, stronger young people more productive at the workplace, less of a drag on the health system. Because they were almost never stalled. Sound basic education meant a better-trained and more skilled workforce. These countries put children at the center of their national agendas a generation and a half ago, and have kept them there, and this has been a main force in lifting them out of underdevelopment. The formula for such a lift for the "great ascent" described by Robert Heilbroner based on social development, human development, and rooted in the protection and development of the under-five-year-old child, is not complex. It should be of interest to all of you here from the newly independent states.

Since the early 1980s, more and more countries have raised the priority of children, seeing them as the fundamental care of national growth. This process was built upon the 1976 Alma-Ata (Kazakhstan) conference, which defined primary health care and proclaimed health for all by the year 2000, and the 1979 International Year of the Child.

From the mid-1980s onward, there came the amazing rush of child survival progress that cut under-five death rates by a third to half in less than 10 years, and saw most of the developing countries move ahead of Europe and North America in immunization of under-ones. It may not be surprising that our host city, Ankara, and today Calcutta, India, Lagos, Nigeria, and Mexico City have far higher levels of immunization than do New York City or Washington, D.C.

The countries that have made these immunization achievements that have sharply cut their child mortality rates and whose heads of state participated in the 1990 World Summit for children and committed themselves to that meeting's end-of century goals all learned four rules:

I. Hospitals do not mean health. Eighty percent of the childhood illnesses that reach hospitals for treatment can be prevented by primary health care by clinics or by community health workers at the village or community level. We all learned this in 1976 at Alma-Ata when primary health care (PHC) was enshrined as a basic operating principle for all countries. In any case, there are the disproportionate social and economic factors inherent in large hospitals, particularly teaching hospitals; they are rarely accessible to more than ten percent of the population of developing countries, and they sometimes absorb as much as 80 percent of the national health budget. This is an imbalance that favors rich and influential urban elites, and it takes political courage to correct it and advance toward "health for all". An example of such political courage was the decision taken in the 1980s by the government of Pakistan to build several hundred light health structures—village-level clinics—with funds that would otherwise have been used to build a single large teaching hospital, whose construction was backed by powerful medical and other interests. This difficult decision has no doubt averted tens of thousands of child deaths and countless cases of permanently handicapping illness.

II. National wealth does not make health. There are many countries whose "overachieving" or less-than-capacity performances in taking care of their children prove this rule. Financially poor countries such as China, Guatemala, and Sri Lanka are doing very well by their children; their child nutrition, mortality, and school-finishing records rank with the best in the world. Some relatively wealthy countries, on the other hand, are doing poorly against the same indicators despite their high GNP per capita circumstances. It is clearly a matter of political will and social commitment, a decision on priorities rather than a matter of money.

III. Three-fourths of all childhood deaths and illness come from a handful of controllable diseases and deficiencies. Some of these diseases (measles, whooping cough, and tetanus) are vaccine-preventable and cheaply eliminated (roughly $10 per child). A fourth, diarrhea, perennially the main cause of child death and malnutrition, can be controlled at less than $1 per bout by oral

rehydration therapy that a village health worker or a mother can administer. The case management of a fifth, pneumonia (acute respiratory infection), can be handled by trained health workers through such antibiotics as oral ampicillin and cotrimoxizol for $5 per case or less. Two major deficiences, those of breastmilk and vitamin A, can also be corrected with relative ease, the first through concerted awareness, raising campaigns championing the indispensability of breastfeeding, and the second through the distribution of low-cost capsules. Put together, these seven protections can lead the way to a country's halving of its child mortality rates. This has happened in less than ten years in a number of countries in this region.

IV. To control these main causes of childhood death and illness, the health services alone are not enough, a broad mobilization of all sectors of society is needed. A good example of such a mobilization is our host country, Turkey, which immunized 4,200,000 under-fives in 1985 and sharply cut down its child mortality in a four-month campaign which saw the direct involvement of 370,000 people: health workers, school teachers, Intercom Ministry officials, imams, medical students, media staff, celebrities, members of Rotary, and others. I know that one of the N.I.S. countries represented here, Kazakhstan, put on its own mobilization against pneumonia in the winter of 1992-1993.

Today the N.I.S. States, the six Turkic countries represented here, with an aggregate population of 60 million, are suffering, by my rough estimate, about 150,000 preventable child deaths a year. Could you emulate Turkey in mobilizing against these deaths? Could you set for yourselves now, and reaffirm at your Tashkent meeting a year from now, the goal of reducing these deaths by at least one-third by the end of 1995?

The World Health Organization and UNICEF will be ready to stand by you in this effort. For the period 1993-1994, as many of you know, UNICEF has committed an average of some $4 plus-million, for a total of $2 million for the six countries. Our UNICEF area representative for the five Central Asian republics, Mr. Ekrem Birerdinç, is aware of this meeting and is ready to work with and advise you.

Pediatricians have always been the most socially engaged and politically aware members of the medical profession. Pediatricians have historically concerned themselves with broad issues of public well being and public policy far beyond the borders of their private practice. I hope that this meeting will ring a bell of appeal to all of you to redouble your efforts and work in your countries to project not only the sad and true message of child malnutrition, illness, and death, but also the message of child well-being as the indispensable foundation of your country's social and economic future. There is a home truth in this message that no country can afford to ignore.

Thank you, Mr. President.

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PERIPHERAL NEUROPATHY IN CHILDREN WITH INSULIN-DEPENDENT DIABETES MELLITUS*

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SUMMARY: Fıçıcıoğlu C, Aydın A, Haktan M, Kızıltan M. (Departments of Pediatrics and Neurology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey). Peripheral neuropathy in children with insulin-dependent diabetes mellitus. Turk J Pediatr 1994; 36: 97-104.

Peripheral somatic nerve function was studied in 38 unselected diabetic children and 31 age and sex-matched healthy controls. Thirteen of the 38 diabetics had abnormal peripheral somatic nerve function tests (more than 3 SD below the mean for normals). Five of the 13 diabetic children had only abnormal peripheral nerve function (early asymptomatic neuropathy); seven of these 13 were abnormal both in neurologic examination and peripheral nerve function (asymptomatic neuropathy). Only one of the 13 patients showed neuropathic symptoms as well as an abnormal neurologic examination and impaired peripheral nerve function tests (symptomatic neuropathy). Both motor and sensory peripheral somatic nerve abnormalities were related to poor glycemic control (HbA_{1c}) and duration of diabetes. Individual peripheral nerve tests correlated with HbA_{1c} (fibular motor, $p<0.001$; sural sensory, $p<0.05$) or duration of diabetes (fibular motor, $p<0.01$; median motor, $p<0.01$). These results emphasize the importance of metabolic control and duration of diabetes in the pathogenesis of diabetic neuropathy. The findings suggest that peripheral neuropathy is common in young, insulin-dependent diabetics. Being easy to conduct and sensitive, regular follow-up of nervous function test results may help to achieve good metabolic control and prevent diabetic complications. *Key words: Insulin-dependent diabetes, peripheral neuropathy, peripheral somatic nerve tests.*

Diabetic neuropathy is a frequent complication of diabetes mellitus; approximately two out of three adult patients are thought to be affected, even though nerve involvement is often mild and detectable only by electrophysiological tests[1].

The classical signs of peripheral neuropathy are rarely found in children with insulin-dependent diabetes mellitus (IDDM)[2]. The frequency of electrophysiological abnormalities and peripheral neuropathy varies widely, from 9% to 72%, in

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different studies reported on diabetic children[2-9]. These discrepancies can be attributed both to the heterogeneity of cases and the variety of electrophysiological tests; in addition, in none of these papers were there common criteria, accepted by all investigators for the diagnosis of diabetic neuropathy.

Having considered these difficulties, Dyck[10] from the Mayo Clinic suggested some precise criteria for the diagnosis of diabetic neuropathy in 1988.

The aim of this study was to evaluate the prevalence of symptomatic and asymptomatic peripheral neuropathy in an unselected group of children with IDDM by using the minimal criteria suggested by Dyck for the diagnosis of diabetic neuropathy, and to investigate the relation between peripheral neuropathy and some relevant parameters, such as duration of diabetes and metabolic control.

Material and Methods

The study group consisted of 38 children from 3.5 to 18 years of age (mean ± SD: 10.5 ± 3.2) in whom the duration of diabetes ranged from 2 months to 12 years (mean ± SD: 3.1 ± 2.8), and 31 nondiabetic children from 3 to 18 years of age (mean ± SD: 10.2 ± 2.8). The diabetic children were treated with two daily injections of human insulin, the dosage of which was adapted according to blood glucose monitoring with Dextrostix (Ames) and a glucometer. Their normally balanced diets were divided into up to six separate meals. No patients were treated with isoniazid, and none had a history of drug dependence. None of them had a family history of hereditary neuropathic disorders.

HbA_{1c}, as the degree of metabolic control, was measured by the colorimetric technique originally described by Fluckiger et al[11].

Determination of the amplitude, conduction velocity and distal latency of the motor fibers of the fibular and tibial nerves in both lower extremities and of the median and ulnar in one upper extremity, and sensory amplitude conduction velocity and distal latency of the median and sural nerves were made on the patients and healthy children by the same observer with a Medelec MSG electromyograph.

A complete neurological examination was performed by a neurologist on all the children. Muscle strength was evaluated according to the principles suggested by the Medical Research Council. Tendon reflexes were evaluated in biceps brachii, triceps brachii, brachioradialis, quadriceps and gastrocnemius soleus muscles.

Sensory deficit was evaluated at three different points from distal to proximal on each extremity.

Cotton wool was used to assess touch-pressure. Disposable pins and a 25 cm long, 28 Hz tuning fork were used for pain and vibratory sensation testing, respectively.

Sense of joint position was tested by manually displacing the great toe or finger.

The findings of the neurologic examination were scored as to neurological symptoms and neurological disability[10].

Criteria for diagnosis and staging of diabetic neuropathy (Table I):

Table I: Staging of Diabetic Neuropathy

	EMG*	NE**	NS***
Stage 0-No Neuropathy	−	−	−
Stage Ia-Early Asymptomatic Neuropathy	+	−	−
Stage Ib-Asymptomatic Neuropathy	+	+	−
Stage II-Symptomatic Neuropathy	+	+	+
Stage III-Disabling Neuropathy	+	+	++

* EMG-Electromyography.
** NE-Neurologic examination.
*** NS-Neuropathic symptoms.

Stage 0-No Neuropathy :

Stage I a-Early Subclinical (asymptomatic) Neuropathy: abnormality of amplitude or nerve conduction (more than 3SD below the mean for normals) or distal latency (more than 3SD above the mean for normals) of one or more attributes in two or more nerves and not due to a disease other than IDDM or to faulty electrode placement or low nerve temperature.

Stage I b-Subclinical (asymptomatic) Neuropathy: abnormalities both of peripheral nerve test and neurologic examination (abnormality of one or more of muscle strength, tendon reflexes or sensation, judged to be due to diabetic neuropathy).

Stage II-Symptomatic Neuropathy: two or more abnormalities of nerve conduction, neurologic examination or neuropathic symptoms. Neuropathic symptoms present but of lesser severity than in Stage III.

Stage III-Disabling Neuropathy: two or more abnormalities of peripheral nerve test, neurologic examination or neuropathic symptoms. Disabling neuropathic symptoms present.

Analysis : Standard statistical tests were used throughout. Results in the text are expressed as mean ± standard deviation.

Results

Glycemic Control : In the 38 diabetics, the mean HbA_{1c} was 14.4±4.7% (range: 7.8-21). There was a significant correlation between plasma glucose and HbA_{1c} ($r=0.65$, $p<0.001$).

Clinical Features : With one exception, no patients had symptoms of somatic neuropathy and only eight showed abnormal clinical findings; seven had diminished and one had absent tendon reflexes. Three had general muscle weakness and one had diminshed pin-prick sensation to the level of the ankles. All eight of these patients had abnormal results of peripheral electrophysiologic nerve tests in two or more nerves (Table II).

Table II: Frequency of Symptoms and Signs of Peripheral Neuropathy in Diabetic Children (n = 38)

Symptoms/Signs	n	%
Decreased deep tendon reflexes	7	18.4
Absent deep tendon reflexes	1	2.6
Muscle weakness	3	7.8
Paresthesia/pain/cramp	1	2.6
Loss of pain sensation	1	2.6
One or more signs and/or symptoms	8	21

Peripheral Somatic Nerve Tests : The mean amplitude, nerve conduction velocity and distal latency values in diabetic children were slower than those in the normal control group. However, the difference was statistically significant only for fibular nerve amplitude; fibular, tibial and median nerve motor conduction velocity (MCV) and distal latency; and sural and median nerve sensory conduction velocity (SCV), amplitude and distal latency (Table III).

One of the 38 diabetic children studied satisfied our criteria and was diagnosed as having symptomatic diabetic neuropathy, giving a prevalence of 2.6%. Seven other patients (18.4%) had both abnormal peripheral somatic electrophysiologic nerve test results in two or more nerves and pathologic findings in the neurologic examination (asymptomatic neuropathy). Five of the 38 diabetic children diagnosed as having early subclinical neuropathy had only abnormal electrophysiological test results in one or more attributes of two or more nerves.

The diabetic patients with asymptomatic and symptomatic neuropathy had a statistically significant longer duration of diabetes and higher HbA_{1c} value than those of the non-neuropathic children (Table IV).

The correlation between conduction velocities and the duration of diabetes and HbA_{1c} are presented in Table V.

The duration of diabetes showed a strong correlation with median and fibular motor conduction velocities ($r = 0.44$; $p < 0.01$, $r = 0.42$; $p < 0.01$), but there was no correlation with median and sural sensory conduction velocities.

Table III: Mean Electrophysiological Measurements and Significance

	Nerves	Normal n: 31	Diabetic n: 38	Significance
Compound muscle action potential amplitude CMAP (millivolts)	Fibular	4.6 ± 1.8	3.5 ± 2	$p<0.01$
	Tibial	6.05 ± 2.5	6.17 ± 2.4	NS*
	Median	8.24 ± 3.7	8.97 ± 3.2	NS
	Ulnar	7.3 ± 3	7.1 ± 2.4	NS
Motor Conduction Velocity MCV (m/s)	Fibular	48.5 ± 6	43 ± 7.5	$p<0.001$
	Tibial	45.7 ± 5.4	40.8 ± 6.5	$p<0.001$
	Median	56 ± 5.7	52.2 ± 8.7	$p<0.05$
	Ulnar	56.5 ± 9	52.3 ± 9.4	NS
Distal latency (m/s)	Fibular	3.5 ± 1.1	4.5 ± 1.4	$p<0.001$
	Tibial	3.3 ± 0.7	4.3 ± 1.4	$p<0.001$
	Median	2.75 ± 0.4	3.2 ± 0.7	$p<0.001$
	Ulnar	2.3 ± 0.4	2.6 ± 0.8	NS
Sensory nerve action potential amplitude SNAP (microvolts)	Sural	18.1 ± 4.6	14.3 ± 5	$p<0.001$
	Median	69.6 ± 20.2	54.8 ± 17.8	$p<0.01$
Sensory conduction velocity SCV (m/s)	Sural	54.3 ± 3.7	50.1 ± 5.7	$p<0.001$
	Median	59.5 ± 8.9	54.6 ± 9.5	$p<0.05$
Distal latency (m/s)	Sural	3.45 ± 0.6	4.32 ± 1.1	$p<0.001$
	Median	2.8 ± 0.36	3.17 ± 0.6	$p<0.05$

* NS: not significant.

Table IV: Mean Value of HbA_{1c} and Duration of Diabetes in Diabetic Subjects with and Without Neuropathy

	Group with Asymptomatic-Symptomatic Diabetic Neuropathy n = 13	Group Without Diabetic Neuropathy n = 25	Significance
HbA_{1c} (%)	20.7 ± 4.9	13.9 ± 3.8	$p<0.001$
Duration of diabetes (yr)	6.1 ± 3.4	2.3 ± 2.1	$p<0.001$

Poor balance of diabetes, based on HbA_{1c}, also correlated with fibular motor conduction velocity ($r=0.75$; $p<0.001$) and sural sensory conduction velocity ($r=0.31$; $r<0.05$); however, no correlation was found between HbA_{1c} and median motor and sensory conduction velocities.

Table V: Correlation of Nerve Conduction Parameters with HbA_{1c} and Duration of Diabetes

	Correlation Coefficient	Significance
Duration of diabetes		
Median, MNCV	0.44	$p<0.01$
Fibular, MNCV	0.42	$p<0.01$
Median, SNCV	0.20	NS*
Sural, SNCV	0.18	NS
HbA_{1c}		
Median, MNCV	0.22	NS
Fibular, MNCV	0.75	$p<0.001$
Median, SNCV	0.21	NS
Sural, SNCV	0.31	$p<0.05$

* NS: not significant.

Discussion

The present study investigated peripheral neuropathy in IDDM. We found that 12 of the 38 diabetic children (31.5%) had subclinical neuropathy and confirmed that impaired peripheral nerve function is not a rare complication of diabetes in childhood.

Studies of peripheral somatic nerve function have been reported in diabetic children before, but the results are difficult to compare with ours because wide age ranges were included, either motor or sensory conduction studies alone were evaluated, variations in normal values throughout the childhood period were not taken into account, and a variety of diagnostic criteria were used.

Our findings are not concordant with those reported by Hoffmann[12], whose relative data emphasize a strong contrast between adult and child populations, and who concludes that peripheral neuropathy is a rare complication in children.

Despite the strict diagnostic criteria used in our study, the following investigators have reported data which agree with this study: Eeg-Olofsson et al[2] 9%, Gamstrop et al[3] 10%, Kaar et al[4] 30%, Lawrence at al[5] 19%, Young et al[6] 72%, Dorchy et al[7] 36%, Eng et al[8] 30%, Gallai et al[9] 32%, Marcus et al[13] 25%, and Hoffmann et al[14] 40%.

We have shown that disturbances of motor and sensory peripheral somatic nerve function in young, type 1 diabetics are related to both glycemic control, as assessed by HbA_{1c}, and the duration of diabetes.

In diabetic children, those with definite evidence of peripheral neuropathy have been shown to have a longer duration of diabetes. A correlation was found between abnormal fibular and median motor conduction velocities and the duration of diabetes, but not between sural and median sensory conduction velocities and the duration of diabetes.

In many studies reported, it was found that the longer the duration of diabetes, the higher the frequency of peripheral neuropathy[2-4,8,13,14]. Although this correlation is clear in the adult population, it was not possible to find any relation between diabetic neuropathy and the duration of diabetes in some of the studies reported on children[6,7,9].

Gallai et al[9] explained this discrepancy by the shorter duration of diabetes in a juvenile population, which obviously does not permit a correlation to be verified due to the limited number of years in question.

The level of HbA_{1c} was also higher in diabetic children with peripheral neuropathy than in children without neuropathy.

The motor conduction velocity of the fibular nerve and sensory conduction velocity of the sural nerve were dependent on the balance of diabetes based on HbA_{1c}.

In light of these findings, the motor abnormalities we have demonstrated in the median and fibular nerves are related predominantly to the duration of diabetes and are probably permanent because of repeated metabolic insults over the years; on the other hand, abnormalities in sensory conduction of the sural nerve although electrophysiologically similar, may still be reversible, and hence correlated only with the HbA_{1c}.

The data found in our study confirm the importance of hyperglycemia in the etiology of diabetic neuropathy and point to the net combined effects of metabolic control and the duration of diabetes.

In electromyographic (EMG) studies; amplitude indicates axonal function, whereas motor and sensory conduction velocity measurements reflect predominantly Schwann cell damage.

In our study, although we could not find any denervation finding such as fibrillation, the measurements of sensory and motor potential amplitudes in the lower extremities were decreased when compared with those of the control group. We also found a marked decrease in motor and sensory conduction velocities. Our results therefore imply that there is little axonal but extensive Schwann cell malfunction in young diabetic patients who are free of clinically detectable neuropathy.

In conclusion, according to our data it is possible to suppose that diabetic neuropathy is not a rare complication of diabetes in children and that the reduction

of amplitude, conduction velocity and distal latency values is influenced by the degree of glycemic control and the duration of diabetes.

Being easy to conduct and sensitive, peripheral nerve tests may be suggested for diabetic children at regular intervals after the onset of the disease in order to achieve good metabolic control and to find and follow abnormalities in peripheral nerve function.

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A PRELIMINARY STUDY ON IL4 LEVELS IN EXTRINSIC ATOPIC ASTHMATIC CHILDREN*

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SUMMARY: Akçakaya N, Sözer V, Çokuğraş H, Söylemez Y, Yılmaz G. (Department of Pediatrics, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey). A preliminary study on IL4 levels in extrinsic atopic asthmatic children. Turk J Pediatr 1994; 36: 105-110.

Interleukin 4, (IL4) known as a lymphokine secreted by type II helper T-cells, is thought to regulate IgG and IgE secretions. Therefore, elevated IL4 levels are expected in atopic allergic disesase and parasitoses.

The purpose of this study was to determine IL 4 levels in allergic asthmatic children. In 50 extrinsic atopic children (19 females, 31 males, mean age 8±4), IgE and IL 4 were found to be 469±296 U/L and 0.318±0.09 ng/ml, respectively. In seven control cases, IgE and IL4 levels were 62±25 and 0.106±0.017, respectively.

Comparison of the two groups disclosed statistically significant differences in IL4 and IgE levels, suggesting the ability of IL4 to augment IgE production. *Key words: helper T cell, lymphokine, interleukin 4, atopic asthma.*

T-lymphocytes regulate immunoglobulin production via lymphokines, soluble immunomodulator substances. These T-cell-derived, multifunctional lymphokines adjust the activation, growth and differentiation of multiple cell types[1,2].

A subgroup of the T-lymphocytes, helper T-cells are classified according to the lymphokines they secrete. Type I helper T-cells (THI) secrete interleukin 2, interferon, granulocyte and macrophage colony stimulating factors and interleukin 3; type II helper T-cells release interleukin 3, interleukin 4, mast cell and T-cell growth factors[2,3].

The subject of this study, interleukin 4, (IL4) also named B-cell stimulating factor 1 (BSFI), was first described in 1982 as a cofactor. In vivo and in vitro studies have since shown that IL4 is a potent stimulator of IgG and IgE production[3,4].

The human condition most commonly associated with increased IgE antibody production is atopy, the common familial allergic disorder of immediate-type

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hypersensitivity to environmental allergens. In vivo studies have demonstrated that IgE production is critically dependent on IL4.

The present study was designed to determine IL4 levels and the association between IgE and IL4 in children with allergic asthma and a healthy control group.

Material and Methods

This study involved 50 extrinsic atopic asthmatic children attending Cerrahpaşa Faculty of Medicine-Immunology and Allergy out-patient clinics. Seven similar-aged healthy children chosen from the outpatient clinic as healthy children without a history of atopy comprised the control group.

The diagnosis of atopic asthma fit the related criteria[5]. Blood samples for IgE and IL4 determinations were collected at the time of first enrollment in the study. Nineteen of the patients were girls and 31 were boys each of them having a serum IgE level of 50 IU or more. IgE and IL4 levels were measured with RIA technique (Pharmacia), and ELISA assay (Genzym, human IL4 Elisa test strips), respectively.

The IL4 Elisa test kit is a solid phase enzyme immunoassay employing the multiple antibody sandwich principle. A murine monoclonal antibody specific for human IL4 was attached to microtiter wells in a 96 well plate. IL4 present in standard samples and unknown specimens was captured by the solid phase monoclonal. A rabbit polyclonal anti-human IL4 antibody was added to bind to multiple epitopes on the IL4 contained on solid phase. A third antibody, biotin labelled goat anti-rabbit Ig, was then applied to bind to the rabbit polyclonal antibody already attached to IL4.

Also added was a horseradish peroxidase conjugated streptavidin reagent, which binds to biotinylated goat anti-rabbit Ig. This enzyme acts with a peroxide and OPD containing substrate buffer to produce increased absorbance, indicating the presence of IL4. This reaction was halted at the appropriate point by the addition of a stop reagent.

Immunoreactive IL4 could then be quantitated by an ELISA reader. The measured absorbance was proportional to the concentration of IL4 that was present in the sample. A reference curve was obtained by plotting the IL4 concentrations of several dilutions of standard versus absorbance. Since the IL4 concentrations used to produce the standard curve were known, the amount of IL4 in the experimental samples could be determined by comparing their absorbance to that produced by the standards. Values between 0.025-2 ng/ml were the range that could be read by this system.

Student's t test was used for statistical analysis and a level of $p<0.05$ was considered significant.

Table I: Age, Sex Differences, IgE and IL4 Levels of the Patients

No	Name	Age (yrs)	Sex	IgE (IU/100 ml)	IL4 (ng/ ml)
1	B.O.	6	M	226	0.25
2	E.A.	8	F	462	0.30
3	B.T.	3	F	605	0.4
4	E.T.	3	M	319	0.3
5	S.M.	3	F	374	0.3
6	B.G.	7	F	231	0.3
7	S.K.	4	M	814	0.4
8	H.Ö.	6	M	550	0.35
9	O.G.	3	M	352	0.3
10	U.A.	7	M	154	0.2
11	A.Ç.	3	M	616	0.3
12	O.E.	4.5	M	200	0.3
13	Ö.Ç.	6	F	148	0.5
14	E.T.	6	M	330	0.3
15	S.B.	7	M	286	0.2
16	İ.Ş.	6	M	308	0.3
17	G.K.	3.5	F	429	0.3
18	S.K.	7	M	440	0.2
19	M.A.	3	M	550	0.3
20	Ö.A.	12	M	218	0.3
21	Ç.K.	9	M	134	0.3
22	İ.A.	12	M	978	0.45
23	A.K.	9	M	253	0.3
24	H.S.	13	M	550	0.2
25	N.O.	10	F	286	0.45
26	K.K.	7	M	297	0.5
27	N.B.	8	F	506	0.5
28	C.A.	14	M	566	0.3
29	F.Ç.	7	M	143	0.5
30	M.K.	10	F	385	0.2
31	T.K.	15	M	695	0.3
32	M.T.	11	M	1650	0.45
33	Ş.O.	10	M	660	0.3
34	Y.P.	14	F	664	0.3
35	Ü.Ç.	11	F	616	0.3
36	E.Ö.	6	F	1144	0.5
37	B.F.	11	M	814	0.35
38	M.P.	4	M	148	0.2
39	E.B.	8	F	462	0.3
40	E.B.	6	M	616	0.3
41	M.I.	4	F	145	0.2
42	B.G.	5	M	396	0.2
43	M.Ş.	12	M	682	0.2
44	Y.Y.	10	M	127	0.2
45	F.K.	13	F	264	0.3
46	İ.G.	13	F	527	0.35
47	G.H.	9	F	374	0.3
48	F.B.	14	F	1034	0.45
49	G.G.	7	F	248	0.3
50	F.E.	7	M	374	0.3
Mean		8±4	19 Female 31 Male	469±296	0.318±0.09

Results

Age, sex distribution, IgE and IL4 levels of the patients and the control group are illustrated in Tables I and II. The mean age of the 50 asthmatic children was 8±4 years. Mean concentrations of IL4 and IgE of the patient population were found to be 0.318±0.09 ng/ml and 469±296 U/L successively (Table I). For the control group, the mean age was 4.2±2 years and the mean concentration of IL4 was 0.106±0.017 and of IgE was 6.2±25 U/L (Table II).

Table II: Age, Sex Distribution and IgE and IL4 Levels of the Control Group

No	Name	Age (yrs)	Sex	IgE (IU/100 ml)	IL4 (ng/ml)
1	A.Y.	6	M	16	0.09
2	T.Y.	7	F	46	0.12
3	P.A.	6	F	82	0.085
4	Z.D.	2	M	70	0.095
5	E.E.	2	F	72	0.12
6	H.E.	4	F	57	0.105
7	T.Y.	3	M	90	0.13
Mean		4.2±2	4F 3M	62±25	0.106±0.017

The presence of limited IL4 test samples restricted the number of control cases. None of the atopic patients revealed an IgE level considered to be normal in our laboratory (0-50 IU/L).

The assessment of IgE and IL4 levels between the asthmatic and control cases disclosed statistically significant differences ($p<0.001$) (Table III).

Table III: Comparison of the Study Group with the Control Group

	n	Mean Age (yrs)	IgE (IU/100 ml)	IL4 (ng/ml)
Asthmatic patients	50	8±4	469±296	0.318±0.09
Control group	7	4.2±2	62±25	0.106±0.017
			t: 3.6	t: 5.34

Discussion

During the past several years, it has become clear that regulation of the growth of both T-cells and B-cells involves signals not only from antigen-specific cell surface receptors but also from lymphokines. The understanding of the mechanism by which lymphokines affect the growth of lymphocytes is crucial in evaluating the regulation of immune responses.

The subject of this study, IL4, was first described in 1982 as a co-factor in the proliferation of resting B-cells stimulated through the cross-linkage of their membrane Ig by anti-Ig antibodies[6]. IL4, a 20,000 dalton glycoprotein produced by some activated T-cells, has gained popularity especially after Mosmann et al's work[7-9]. These investigators indicated the existence of two broad classes of mouse T-lymphocytes, designated as T_{H1} and T_{H2}, and stated that IL4 is produced by the T_{H2} subgroup.

It has now become clear that IL4 acts on resting B-cells as well as late G_1 B-cells, T-cells, and multiple hematopoietic cell lineages[10-12].

IL4 is a potent stimulant of IgG_1 and IgE secretion by B-cells[13,14]. Experimental studies show that in vivo production of IgE is highly dependent on IL4. Mice infected with the larvae of the nematode Nippostrongylus brasiliensis display a striking increase in serum IgE. Administration of monoclonal anti-IL4 antibodies to these animals markedly inhibits this increase[15].

Likewise, injection of anti-IgD antibodies into mice causes a strong polyclonal activation of B-cells, which results in a marked increase in both serum IgG_1 and serum IgE levels. Purified monoclonal anti-IL4 antibody inhibits the increase in IgE completely, suggesting that anti-IgD induced IgE production is modulated at least in part by T-cell mediated IL4 production[16]. In our clinical study carried out on atopic asthmatic children, this fact is confirmed, implying that a correlation exists between IL4 secretion and IgE production.

Recently it has been shown that IL4 has the capacity to regulate the so-called VCAM-1 expression on endothelial cells, which is a very important clue in the early events after an allergen challenge in asthmatics[17]. It has again been shown in biopsy specimens from patients with asthma that pre-formed IL4 can be localized to mast cells[18]. These events provide an important link between mast cell activation, regulation of adhesion molecules and chemotaxis priming.

In certain diseases, B-cells could be induced to switch to IgE-producing cells in response to IL4. In common variable immunodeficiency, it is demonstrated that peripheral blood mononuclear cells could be induced to produce IgE[19].

Obviously, on the basis of this study, we do not presume to draw conclusions about the pathogenesis of atopy and of other diseases characterized by the hyperproduction of IgE. Future studies on the mechanisms underlying defective IgE synthesis, as in patients with immunodeficiencies, might contribute to the understanding of IgE production in both normal and allergic individuals.

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INTRACRANIAL CALCIFICATION IN CHILDREN ON COMPUTED TOMOGRAPHY*

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SUMMARY: Erdem E, Ağıldere M, Eryılmaz M, Özdirim E. (Departments of Adult Neurology, Pediatrics and Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Intracranial calcification in children on computed tomography. Turk J Pediatr 1994; 36: 111-122.

Pathological intracranial calcifications detected on computed tomography of 83 children during a six-year period were reviewed. The common causes in our series were tuberous sclerosis and intracranial tumors. Other conditions associated with calcification were Sturge-Weber syndrome, neurofibromatosis, Cockayne's syndrome, hypoparathyroidism, arteriovenous malformations, vein of Galen aneurysm, encephalomalacia, cerebral infarcts, subdural hematoma, cerebral infections, birth asphyxia and dihydropteridine reductase deficiency. In two cases (2%), calcifications were idiopathic. The distribution and location of the calcifications in these conditions are discussed. *Key words: Intracranial calcification, computed tomography.*

Computed tomography (CT) detects intracranial calcification more sensitively than do plain X-rays[1]. Intracranial calcification may be of diagnostic importance or may guide etiological study; however, it may also be an incidental finding[1-3].

Studies of the diagnoses of children with intracranial calcifications in the hospital setting are rare[3]. In this investigation, intracranial calcifications on the CTs of 83 patients in the pediatric age-group from the years 1985 to 1990 were studied retrospectively.

Material and Methods

The patients' ages ranged from 2.5 months to 17 years. All CT studies were done with third generation CT scanners. Only the pathological intracranial calcifications on CT were studied. The calcifications were assessed in regard to their appearance as described by Holland et al[4] and their locations.

The calcifications were divided into five categories based on CT appearance:

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linear, punctate, homogeneous fine, homogeneous dense-partial, and homogeneous dense-total. Deposits of calcium large enough to be individually identified but less than 2 mm in diameter were designated as punctate. Homogeneous fine calcification was defined as many minute calcifications resulting in a stippled increase in density with no single deposit large enough to be seen individually. The category of "homogeneous dense, partial" was defined as any calcification larger than 2 mm but forming a component of the lesion; the category "homogeneous dense, total" was defined as any calcification encompassing the entire lesion.

Laboratory tests were selected depending on the clinical features of the patients. Serum calcium, phosphorus and alkaline phosphatase activity were determined in all cases of basal ganglia calcification. In an epileptic patient with depigmented nevi and adenoma sebaceum, a diagnosis of tuberous sclerosis was made, and subependymal calcifications seen on CT were supportive.

Results

In nine patients, there were basal ganglia calcifications; in 64 patients, calcifications, were in other parts of the brain. In eight, calcifications were both on basal ganglia and in other parts. The results are summarized in Table I.

In all cases of intracranial tumors (Case 26-41), histopathological study was performed. In Cases 42-45, a solitary mass was visualized, but neither biopsy nor autopsy could be done because either the patient succumbed before surgery or the family did not permit the operation or the autopsy. CT was the first-performed diagnostic investigation when neurological symptoms developed acutely or subacutely (usually in cases of intracranial tumor or cerebrovascular disease). However, CT findings in tuberous sclerosis were particularly invaluable when cutaneous features were absent; in that case, biochemical studies were performed. In five cases of mental and motor retardation (Cases 72-76), despite extensive investigation no definite cause of the retardation could be demonstrated. Laboratory studies including muscle biopsy were not fruitful in Case 77, a 17-year-old female with cerebellar syndrome. Case 80 presented with secondarily generalized partial seizures, and the CT features suggested a previous hematoma. As no previous history of neurological dysfunction was obtained, the CT abnormality may have been related to an intrauterine hemorrhage. Case 81 was a patient with epilepsy whose developmental and neurological examination were normal, and no cause could be found for the epilepsy. In two cases (Case 82, 83), calcifications were incidental. CT was requested in Case 82 because of convulsions and in Case 83 because of premature thelarche. In both, basal ganglia calcification was found.

Table I: CT Findings of the Patients

CASE	DIAG	CALCIFICATION		OTHER CT FINDINGS
		basal ganglia	other	
1-22	TS	unilateral dense total in caudate nucleus in 2 cases	subependymal dense total in 6 cases; periventricular dense total in 21 cases; dense total in other sites in 12 cases	hypodensities in various sites in 12 cases
23-24	Sturge-Weber syndrome		left F dense partial; bilateral F dense total; bilateral P dense total; O dense total	left F and P serpiginous enhancement; bilateral O enhancement in the other case
25	neurofibromatosis		right O dense total, left T dense total, right cerebellar dense total	left O, right F homogeneous enhancement, left F and right O craniotomy defects
26-41	brain tumors 3 astrocytomas; 1 astrocytoma associated with tuberous sclerosis; 1 glioma; 1 mixed glioma; 1 glioblastoma, multiforme; 1 meningioma; 1 medulloblastoma; 2 craniopharyngiomas; 1 chordoma; 1 dermoid tumor; 1 malign teratoma; 1 pinealoblastoma; 1 malign primitive ectodermal tumor		focal in 2 and dense partial in 1 of 3 astrocytomas; periventricular dense total and dense partial in 1 astrocytoma associated with tuberous sclerosis; dense total in 1 glioma and 1 mixed glioma; linear in 1 meningioma; dense partial in 1 glioma multiforme, 1 medulloblastoma, 2 craniopharyngiomas, 1 chordoma, 1 dermoid tumor, 1 malign teratoma, 1 pinealoblastoma, 1 malign primitive ectodermal tumor	masses with other features of a brain tumour, usually suggestive of the diagnosis
42-45	solitary masses		dense partial	masses of which 3 enhances after contrast injection and 1 is cystic
46	Cockayne's syndrome	bilateral focal in putamen, globus pallidus and caudate nucleus		cerebral atrophy
47	hypoparathyroidism	bilateral dense total in putamen, globus pallidus and caudate nucleus	multiple dense total in bilateral centrum semiovale	
48-50	AVM		right O dense partial; dense partial in mesencephalon; dense partial intraventricular in both cases posterior midline (linear and dense partial)	O, mesencephalic, thalamic AVMs, in 1 triventricular hydrocephalus exists posteriorly extending enhancement between the lateral ventricles in 1 case
51-52	vein of Galen aneurysm			
53-54	encephalomalacia		right OP dense total; right P dense total, right F dense total, right O dense partial	right O encephalomalacia in both cases, cerebral atrophy in 1 case
55	cerebral infarct		left TP dense partial	left TP old infarct
56	sickle-cell anemia old cerebral infarcts		dense total in right sulcus precentralis	right OP infarct, lacunar infarct in right centrum semiovale, cerebral atrophy

CASE	DIAG	CALCIFICATION basal ganglia	CALCIFICATION other	OTHER CT FINDINGS (continued)
57	subdural hematoma		F-P-O linear	left F-P-O subdural effusion
58	tuberculoma		dense partial	mass with annular enhancement extending from right thalamus to TO region
59-68	TORCH	bilateral dense total in globus pallidus in 2 cases, in putamen in 4 cases, in caudate nucleus in 2 cases, bilateral focal in caudate nucleus in 1 case, unilateral dense total in caudate nucleus in 1 case	dense total P; focal, dense total in capsula interna; focal, dense total periventricular; subcortical dense total; subependymal dense total; O dense total; FP dense total; cerebellar dense total; multiple intracerebral focal, dense total; dense total in bilateral centrum semiovale	cortical atrophy in 3, subcortical atrophy in 1 cases, cavum septum pellucidi et Vergae in 3 cases
69-71	birth asphyxia	bilateral focal in putamen in 1 case	periventricular dense total in 1 case; bilateral partial in thalamus in 1 case	cortical and subcortical atrophy in 1 case
72-76	MMR	bilateral focal in putamen in 2, unilateral dense partial in putamen in 1, in caudate nucleus in 1 case	subependymal, linear around the ventricles in 1; F partial and O partial in 1 case	cortical atrophy in 2; subcortical atrophy in 1 case; megacisterna magna in 1 case
77	cerebellar syndrome	bilateral focal in putamen in 1 case		
78-79	DHPR deficiency	in both cases bilateral dense total in putamen, globus pallidus and caudate nucleus	bilateral P-O dense total in both cases	cortical and subcortical atrophy in both cases
80-81	epilepsy		left F partial obliterating the lateral ventricle in 1 case; focal in bilateral basal ganglia, capsula interna, left P and F white matter in the other	left F hypodense area in 1; prominent left Sylvian fissure in the other case
82-83	idiopathic	bilateral focal in globus pallidus, bilateral dense total and bilateral focal in putamen in the other case		

ABBREVIATIONS:

AVM: arteriovenous malformation DIAG: diagnosis
DHPR: dihydropteridine reductase F: frontal
MMR: mental and motor retardation O: occipital
P: parietal T: temporal TS: tuberous sclerosis

Discussion

Intracranial calcification is detected more sensitively by CT than by plain X-rays[1]. There is only one study on the incidence of the pathological calcification in children; the incidence was found to be 1.6 percent in 18,000 patients[3]. Intracranial calcification can be of diagnostic importance and can guide etiological study[1-3]. However, it may be an incidental finding, without any relation to a disease process[1-3]. Pathological intracranial calcifications have been described in a great number of diseases. Harwood-Nash et al[2] classified these in groups of "developmental, inflammatory, neoplastic, vascular, endocrine, and toxic" diseases. After the advent of CT, pathological calcification in some other diseases was described with CT demonstration (Table II).

Table II: Classification of Pathological Intracranial Calcifications in Infants and Children[2,15,16,23-31].

Developmental abnormalities, inherited diseases	
Tuberous sclerosis	Lipoid Proteinosis
Sturge-Weber syndrome	Basal cell nevus syndrome
Neurofibromatosis	Lissencephaly
Cockayne's syndrome	Wilson's disease
Fahr syndrome	Kearns-Sayre syndrome[24]*
MELAS syndrome[25]*	Adrenoleukodystrophy[26,3]*
Krabbe's disease[27]*	Infantile neuroaxonal dystrophy[3]*
Down syndrome[28]*	
Dihydropteridine reductase deficiency[3,23]*	
Osteopetrosis, associated with type-II carbonic anhydrase deficiency[29]*	
Inflammatory	
Systemic lupus erythematosis	
Infectious diseases	
Cytomegalic inclusion disease	
Herpes Simplex	
Congenital rubella	
AIDS[30]*	
Congenital toxoplasmosis	
Bacterial infections	
Pyogenic meningitis	
Tuberculous meningitis	
Tuberculoma	
Other parasitic infections	
Cysticercosis	Trichinosis
Paragonimiasis	Coccidioidomycosis
Echinococcosis	
Neoplastic	
Craniopharyngioma	Medulloblastoma
Teratoma	Corpus Callosum Lipoma
Dermoid tumors	Secondary retinoblastoma
Astrocytoma	Pituitary adenoma
Ependymoma	Chordoma
Oligodendroglioma	Meningeal leukemia
Meningioma	Meningeal neuroblastoma
Choroid plexus neoplasm	Undifferentiated neuroectodermal tumors
Acute lymphocytic leukemia[31]*	
Postradiation calcification	

Table II:

Vascular	
Subdural hematoma	Aneurysm
Extradural hematoma	Vascular hamartoma
Intracranial hematoma	Anoxia
Arteriovenous malformation	Vessel wall
Vein of Galen aneurysm	Therapeutic radiation
Cerebral infarcts[15-16]*	
Endocrine	
Hyperparathyroidism	
Hypoparathyroidism	
Pseudohypoparathyroidism	
Pseudopseudohypoparathyroidism	
Toxic	
Carbon monoxide poisoning	
Lead poisoning	
Vitamin D intoxication	
Hypercalcemia	
Intrathecal methotrexate	

*: described after the advent of CT, with CT demonstration

Tuberous sclerosis was the most common disease in our series. The distribution of calcifications in tuberous sclerosis includes periventricular and subependymal[5]; besides the calcifications, hypodensities representing demyelination or cortical and subcortical tubers may be seen (Fig. 1)[6-7]. The subependymal calcifications are characteristic of tuberous sclerosis and constitute an important diagnostic aid in cases without any positive finding on physical and neurological examination. In Sturge-Weber syndrome (Fig. 2) contrast enhancement resulting from the

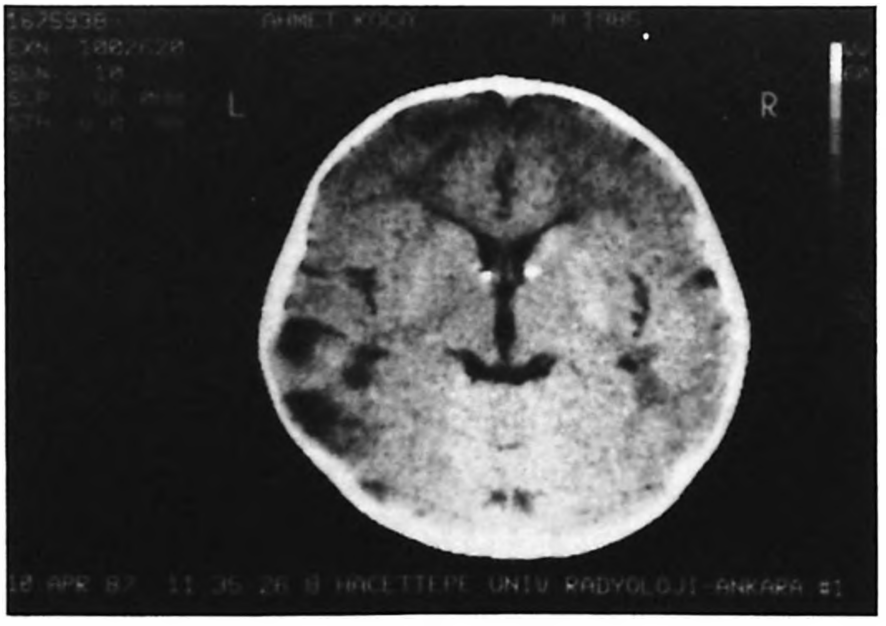

Fig. 1: Tuberous sclerosis, 2-year-old male infant (Case 11). There are subependymal calcifications and left temporal hypodensities representing the tubers.

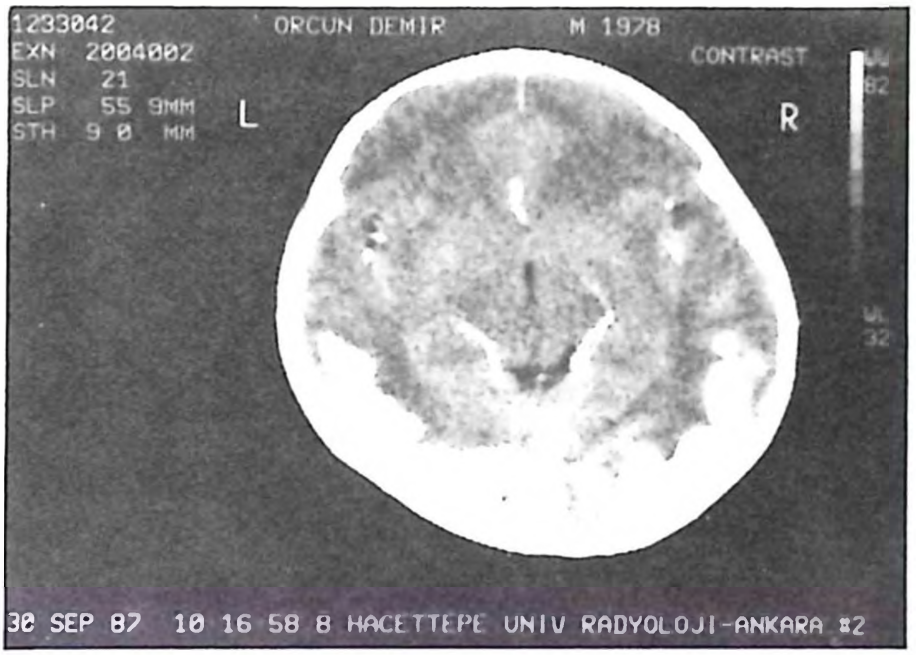

Fig. 2: Sturge-Weber syndrome. 9-year-old boy (Case 24). Bilateral occipitoparietal calcification. Contrast enhancement does not extend beyond the calcified areas.

angiomatosis extends beyond the calcified field[8]. There may be subependymal calcifications thought to be related to glial tissue proliferations in neurofibromatosis besides the acoustic (and less frequently other cranial nerve) neurinomas[9]. Calcification in intracranial tumors is well documented. The appearance of the calcification and the location within the tumor are highly suggestive, being an important feature for differential diagnosis (Fig. 3)[10-11].

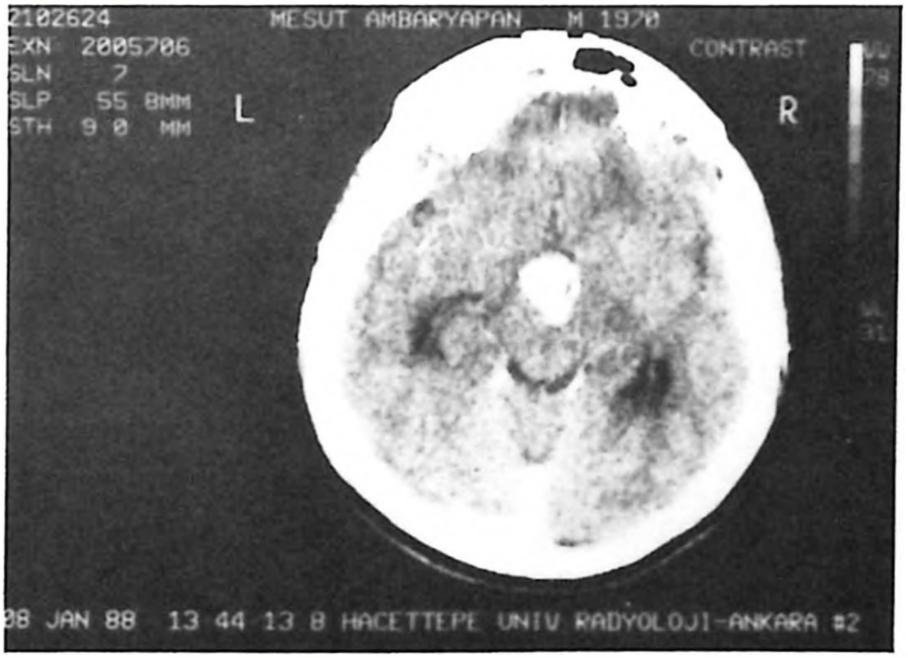

Fig. 3: Craniopharyngioma. 17-year-old boy (Case 35). Calcified mass with posterior enhancement in the location of the supracellar cistern.

In hypoparathyroidism, there may be extensive calcifications involving the cerebral gray and white matter and the dentate nucleus (Fig. 4)[12].

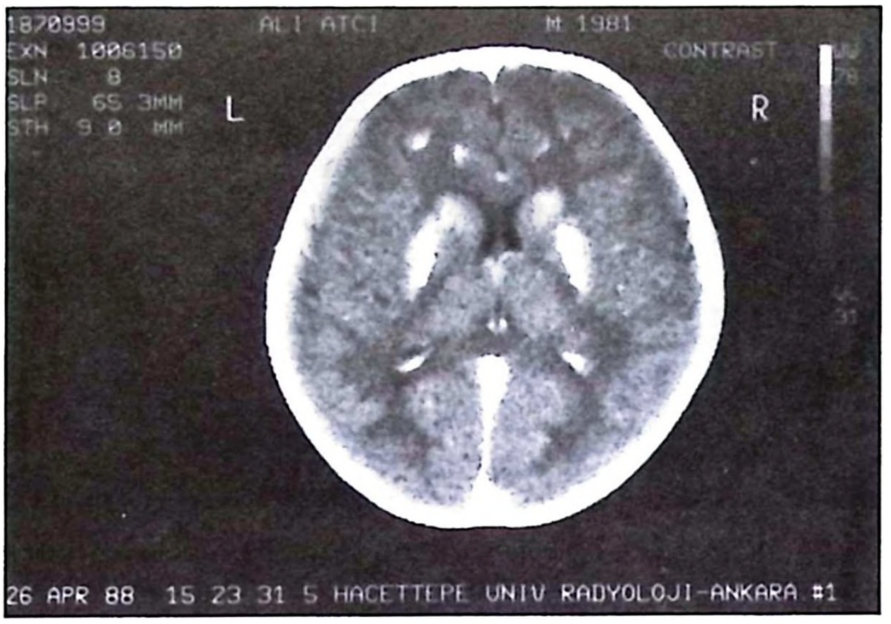

Fig. 4: Hypoparathyroidism. 7-year-old boy (Case 47). Calcifications are seen in the basal ganglia and left frontal white matter.

Calcifications may be seen within the globus pallidus, putamen and cerebellum in Cockayne's syndrome. In the only case in our series, bilateral calcification occurred at these sites[13].

Calcifications scattered in the cerebral white and gray matter may be found in vein of Galen aneurysms and are attributed to the secondary hypoxic effect of the aneurysm[14].

Calcifications may develop several months after cerebral infarcts[15-16]. Small infarcts may develop during the neonatal or infancy period; when they are clouded by other clinical symptoms or are in the clinically silent areas of the brain, they may remain undetected for years. When radiologic verification is absent at the time of the infarct development, the detected hypodensities may be related to previous hematomas or infections besides the infarction. Encephalomalacia is the appropriate term for cases with hypodensities on CT in which there is significant loss of brain tissue[17]. The cases with encephalomalacia in our series were not investigated with CT at the onset of symptoms, and the large tissue loss which appeared on CT in two cases (Case 53 and 54) may be ascribed to previous infarctions, considering the clinical and CT features of the cases.

Subdural hematomas may calcify months later. The calcification is usually peripheral[18].

Calcification of the meninges at the base of the brain was demonstrated in 48 percent of the patients, 18 months to three years after tuberculous meningitis[19].

In tuberculomas, calcifications may be seen as a target sign of central calcified nidus surrounded by a ring of enhancement. The calcification of the case in our series was an example of tuberculomas.

In TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes) infections, calcifications are usually periventricular, but they may be scattered in the basal ganglia and in other parts of the brain (Fig. 5)[20-22]. Other CT findings, hydrocephalus, cortical and subcortical atrophy are usually present, and clinical findings aid in making the diagnosis. As cytomegalovirus and herpes infections are rather prevalent in the population, serological tests are only helpful if used in the acute stages of the infections. Calcifications are seen not only in the congenital form, but also after the infections in later years.

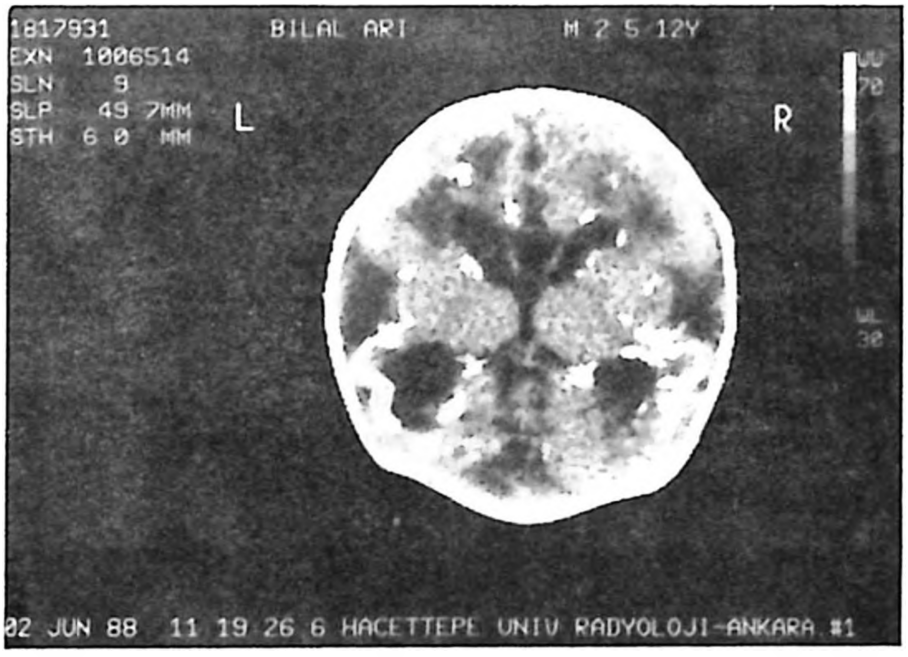

Fig. 5: Congenital toxoplasmosis. 2.5-month-old male infant (Case 68). Calcifications are scattered throughout the brain.

Calcifications associated with birth asphyxia are usually seen in the basal ganglia or in the thalamus[3].

In dihydropteridine reductase (DHPR) deficiency, calcifications have been demonstrated in the basal ganglia and deep hemispheric white matter. Kendall et al[3] emphasized the linkage between the metabolisms of pterins and folate as well as the development of intracranial calcifications following the use of methotrexate, a folic acid antagonist. We observed calcifications in the basal ganglia and in the corticomedullary junction in two cases with DHPR deficiency (Fig. 6). These two cases were previously reported by Coşkun et al[23].

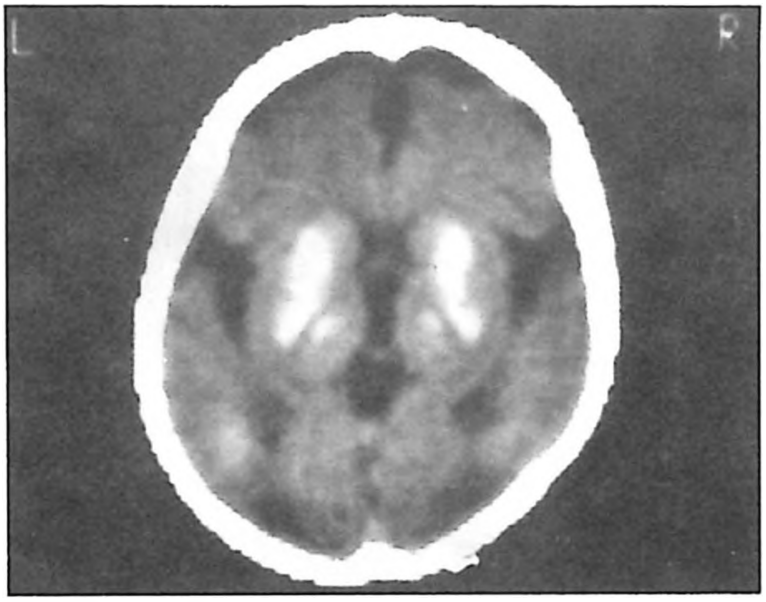

Fig. 6: Dihydropteridine reductase deficiency. 5-year-old girl (Case 79). Bilateral basal ganglia calcification and left occipital calcification in the corticomedullary junction.

In five cases with mental and motor retardation, no cause could be found despite extensive etiological investigation (Fig. 7). In Case 77, clinical (cerebellar syndrome) and CT features were suggestive of mitochondrial myopathy, but biochemical studies and muscle biopsy were not positive.

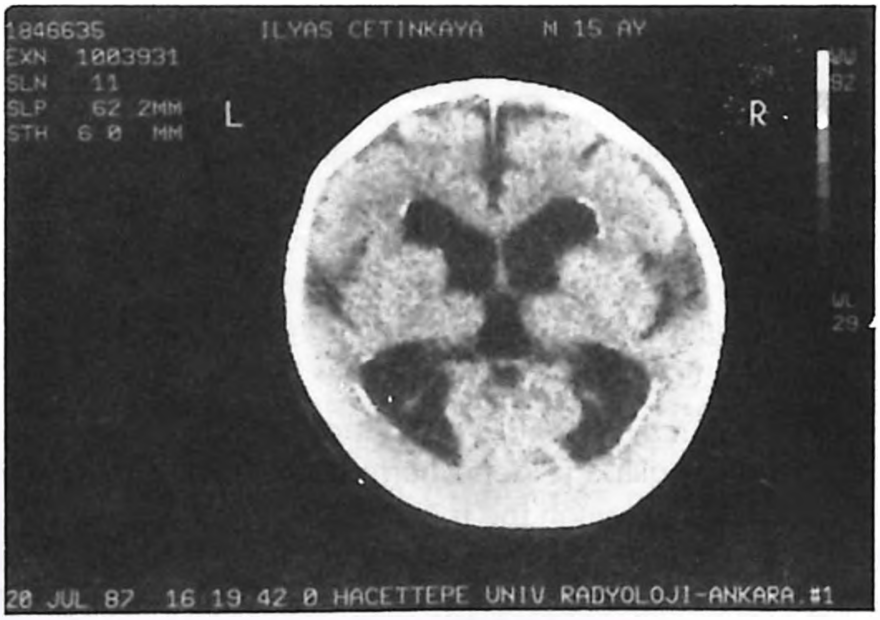

Fig. 7: Case of mental and motor retardation. No definite cause could be identified. 15-month-old male infant (Case 75). Frontal and occipital periventricular linear calcifications.

In two Cases (Cases 82, 83), CT scans were done because the first had a seizure and the second had premature thelarche. In both cases, basal ganglia calcifications were found. The basal ganglia calcifications in these cases did not have any relation with the clinical symptomatology, and we believe that they were idiopathic.

Intracranial calcification on CT offers an important aid in differential diagnosis. However, the calcification may also be an incidental finding without any relation to a disease process.

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LEUKOCYTE BLOOD PICTURE IN EARLY NEONATAL PERIOD IN ANTALYA REGION OF TURKEY*

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*Olcay Yeğin MD***

SUMMARY: Gür Güven A, Göl B, Oygür N, Yeğin O. (Department of Pediatrics, Akdeniz University Faculty of Medicine, Antalya, Turkey). Leukocyte blood picture in early neonatal period in Antalya region of Turkey. Turk J Pediatr 1994; 36: 123-132.

In two hundred neonates, white cell counts and peripheral blood smears were evaluated at birth, and after the 24th, 48th and 72nd hours of delivery to compare the differential counts of leukocytes with the values of other investigators. Parity between neutrophils and lymphocytes was observed on the third day, which was earlier than the time reported previously by other investigators. The total white cell counts were similar to those generally observed, but absolute total neutrophil counts, absolute total immature neutrophil counts and immature-to-total neutrophil ratio were found to be higher than those values previously reported in the literature.

Environmental factors during delivery and in early postnatal life may play a role in the dynamics of leukocytes. These differentials should be taken into account when the diagnosis of early neonatal infections is considered. *Key words: leukocyte counts, neonate, reference values.*

Peripheral white blood cell (WBC) counts and differentials display wide variations in the first few days of postnatal life. The patterns of sequential total neutrophil counts, immature neutrophil counts, immature-to-total neutrophil ratio and calculated absolute cell counts are becoming more valuable indices in the early diagnosis and outcome of bacterial infections in neonates[1-8].

There are several factors affecting the blood picture at birth and thereafter. The local, hygienic, environmental and even genetic factors may affect the neonate's response.

This study was planned to determine whether neonates in the Antalya region have different reference values for WBC counts and differentials than the previously reported results.

Material and Methods

The study population consisted of 91 female and 109 male, full-term, healthy neonates consecutively delivered at Antalya Maternity Hospital in Antalya, Turkey.

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The healthy neonate was defined as one without maternal complications (fever during the last 24 hours of delivery, use of intrapartum antibiotics, presence of hypertension or diabetes, prolonged labor, severe pain), intrapartum complications (early membrane rupture, use of oxytocin, midforceps rotation, fetal bradycardia, meconium stained amniotic fluid), neonatal complications (hyaline membrane disease, transient tachypnea, sepsis, TORCH infections, hemolytic disease, nonphysiologic hyperbilirubinemia, use of phototherapy, suspected or confirmed periventricular or subarachnoid hemorrhage, hypoglycemia, seizures, gastrointestinal complications, meconium aspiration syndrome, pneumothorax, pneumonia, meningitis) and also with normal physical examination at the time the blood samples were collected.

Out of 200 neonates, 23 were delivered by cesarean section. The birth weight, postnatal age (hours) and gestational age (determined by Dubowitz Score) were recorded on each subject.

Samples for hematologic analysis were obtained from a free-flowing heel prick at birth and in the postnatal 24^{th}, 48^{th} and 72^{nd} hours of life. On sectio-delivered babies, samples from the 120^{th} hour were added to the study. WBC count was measured by the classical method[9]. On Wright-stained blood smears, two sets of 100 cells were counted by the same physician (BG). A neutrophil was defined as having lobes connected by a thread or filaments. A band was defined as a neutrophil in which the isthmus between the lobes was wide enough to reveal two distinct margins with nuclear material in between.

All bands and cell forms less mature than bands were classified together as immature neutrophils. The absolute number of total neutrophils (ATN) included both mature and immature forms and was calculated by the following formula;

$$ATN = \frac{\text{Total WBC Count/Percent of Total Neutrophils}}{100}$$

The absolute number of total immature neutrophils (ATIN), total lymphocytes (ATL), total monocytes (ATM) and total eosinophils (ATE) were calculated using the same formula. A proportion expressing the fraction of immature to total neutrophilic forms (I/T) was calculated by the following formula:

$$I/T = \frac{ATIN}{ATN}$$

Statistical Analysis :

All values were evaluated according to the postnatal age and sex and the mode of delivery. The median, mean 1 SD, 5^{th} percentile and 95^{th} percentile values were

estimated. Nonparametric Mann-Whitney U test was used to compare the data on Amstrad 6128.

Probabilities of <0.05 were considered significant.

Results

The mean gestational age was found to be 39 ± 1.1 weeks and the birth weight was 3300 ± 509 g.

The WBC counts were shown in Fig. 1. The peak value was detected at birth, and the median, 5th and 95th percentile values were found to be decreased during the first five days. Daily decrement was statistically significant in the first three days ($p<0.05$).

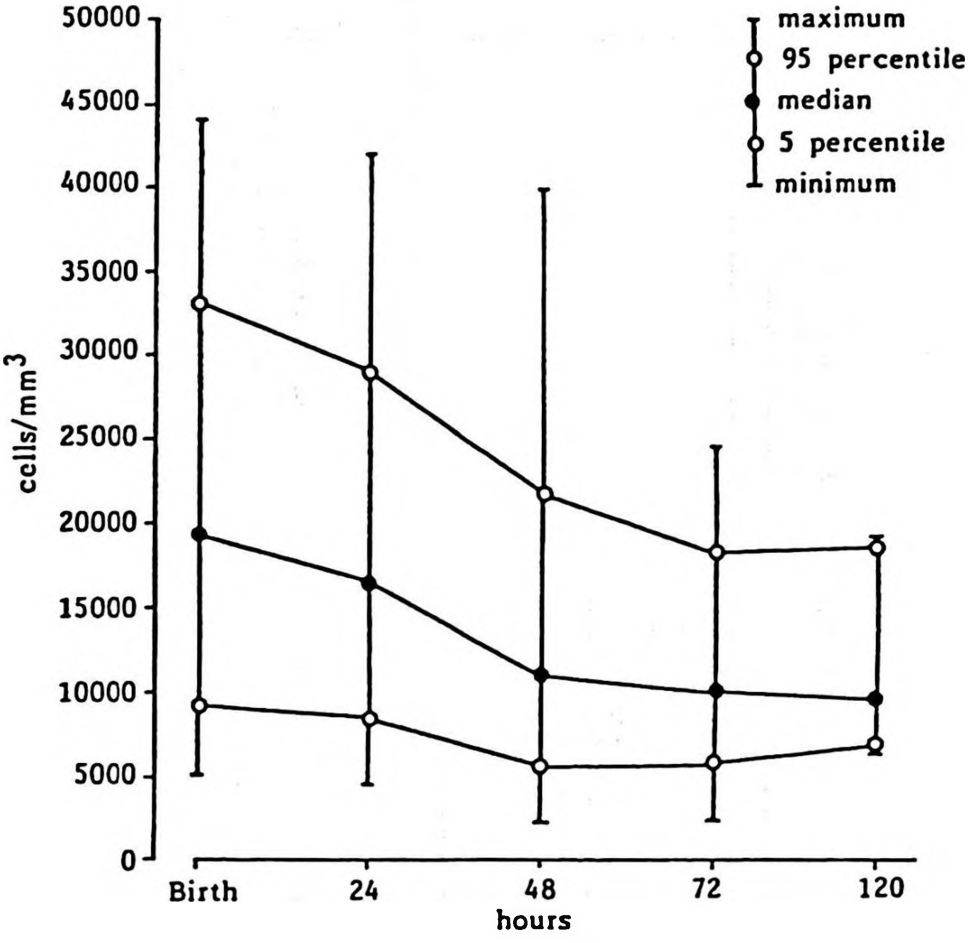

Fig. 1: Total white blood cell counts.

The ATN counts also gradually decreased and reached the lowest values in the 5th day of life (Fig. 2).

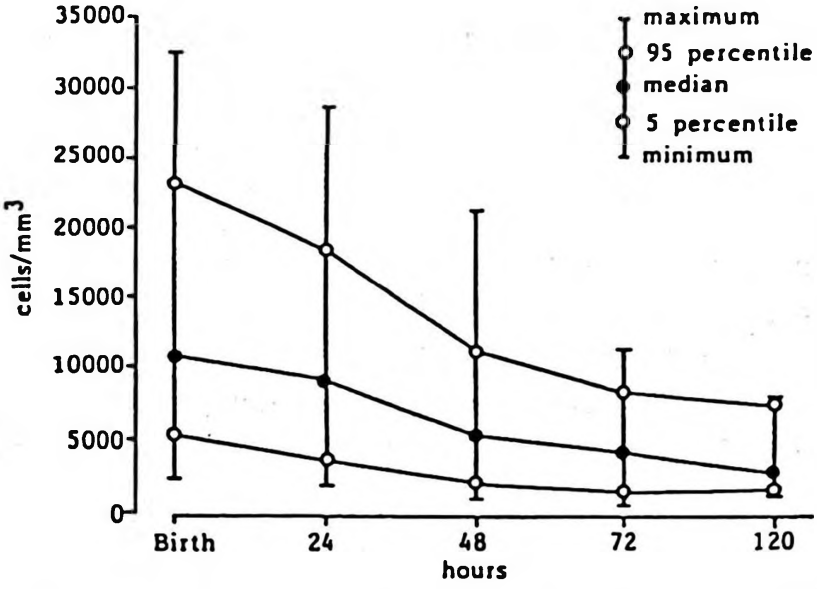

Fig. 2: Absolute total neutrophil counts.

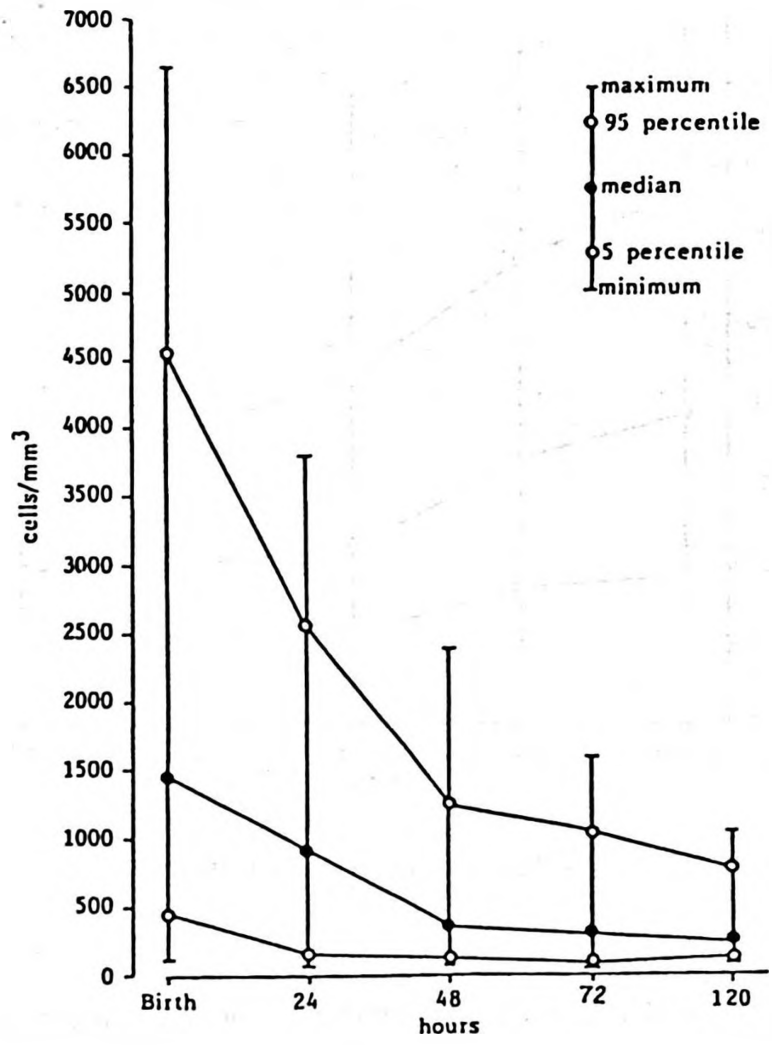

Fig. 3: Absolute total immature neutrophil counts.

For ATIN counts (Fig. 3), the most impressive decrease was observed the first day. This parameter showed stable values after 48 hours of life.

The I/T ratios showed a rapid decrease in the first 48 hours and a slide increase thereafter (Fig. 4). The progression in the ATL profile was very similar to I/T ratios (Fig. 5).

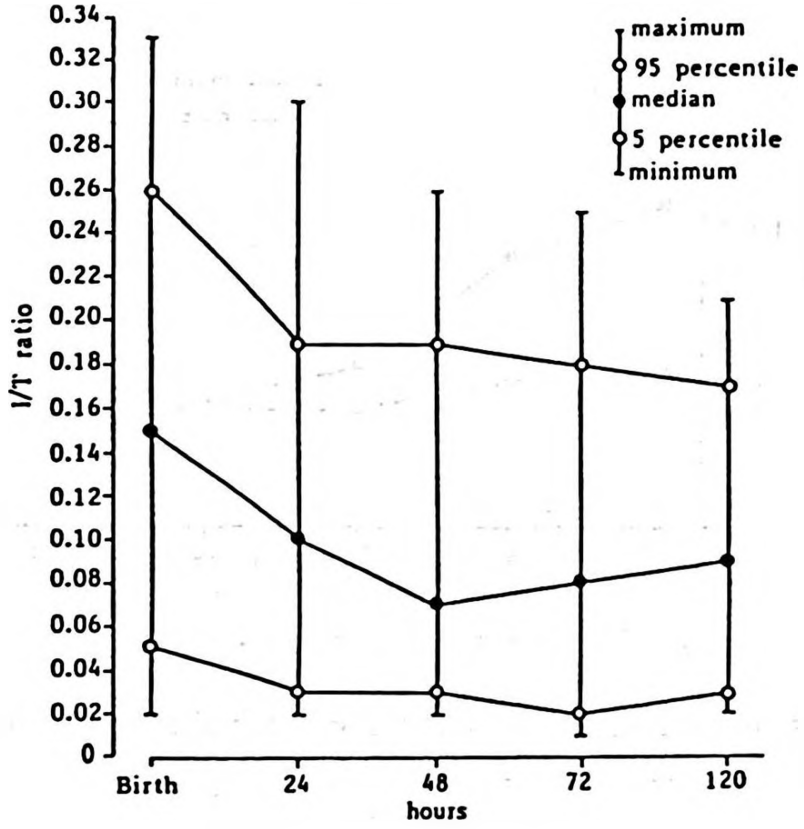

Fig. 4: Pattern of I/T ratios.

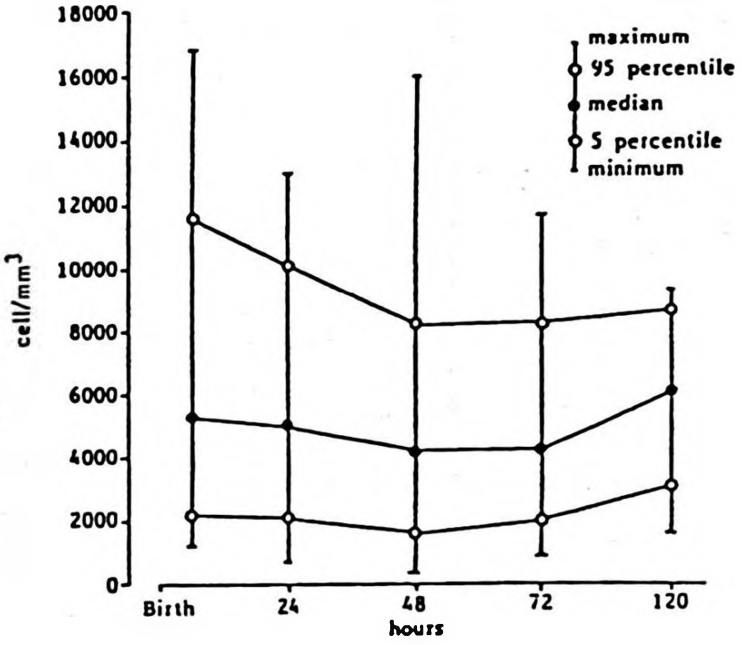

Fig. 5: Absolute total lymphocyte counts.

The parity between neutrophils and lymphocytes was observed on the third day (Fig. 6). The percentage of lymphocytes was higher than the neutrophils in 65% of subjects in the 72nd hour and in 87% of subjects in the 120th hour of life.

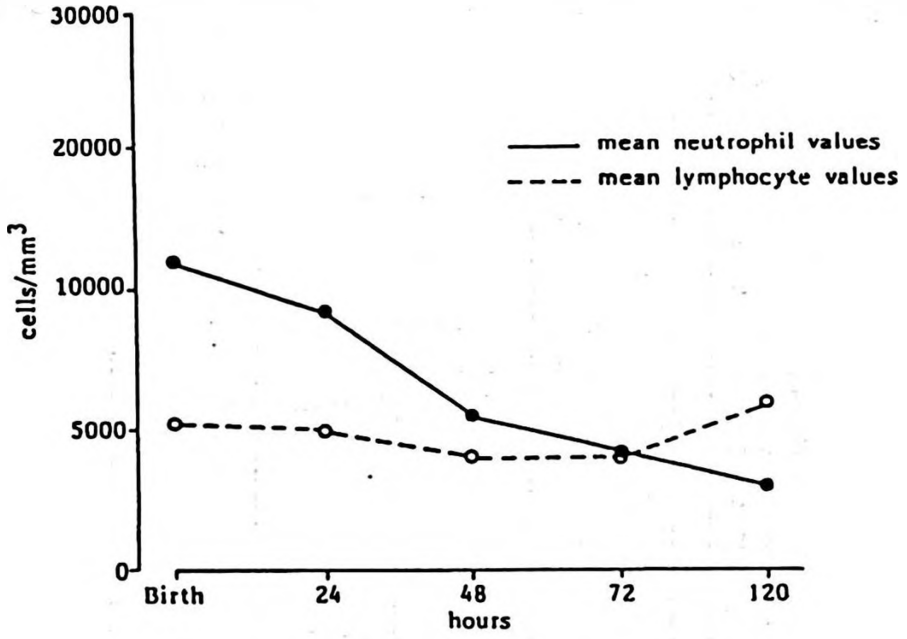

Fig. 6: The parity between neutrophils and lymphocytes.

Absolute total monocyte (ATM) counts were higher in the first 24 hours and remained stable thereafter (Fig. 7).

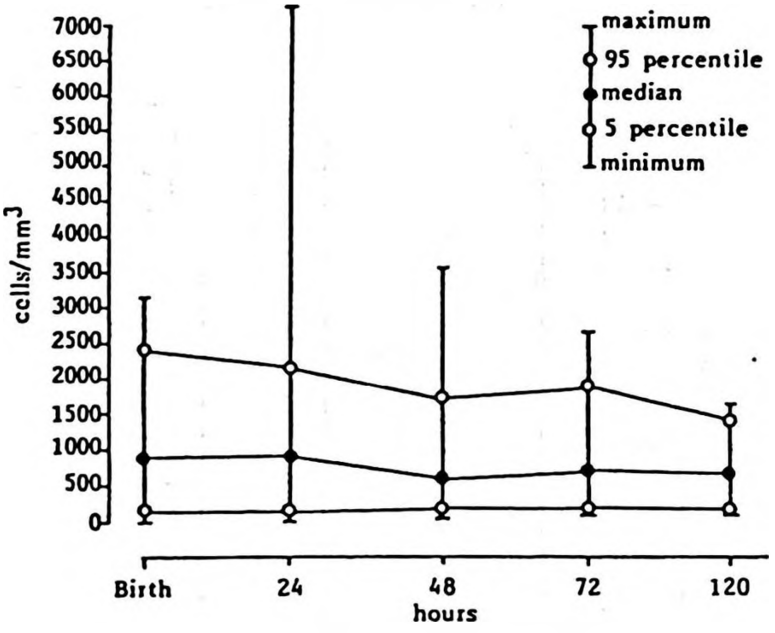

Fig. 7: Absolute total monocyte counts.

Absolute total eosinophil (ATE) counts showed a wide range among subjects, but the median values were constant during the study period (Fig. 8).

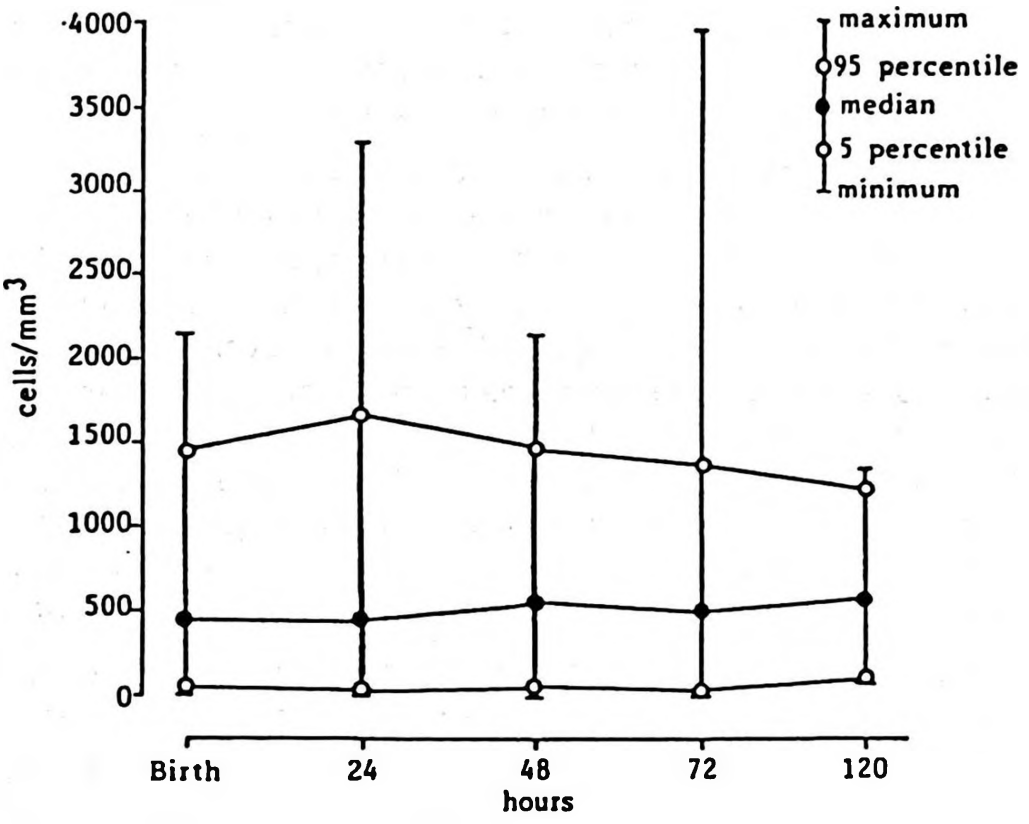

Fig. 8: Absolute total eosinophil counts.

In all these parameters, there was no significant difference between girls and boys, and between the babies who were delivered by sectio and were not. Sectio babies presented significantly higher monocyte counts in the 72nd hour and lower eosinophil counts in the 48th hour ($p<0.05$).

Discussion

It is generally accepted that the neutrophil profile is a useful screening technique for the early diagnosis of neonatal sepsis[4,6,10-14]. Although the reference ranges for the neutrophil values in normal neonates have been extensively documented in the literature, whether the different ethnic groups or regions present different patterns for sequential analysis of leukocytes in the early neonatal period is not known. In our study, total WBC counts showed a peak value in the first 24 hours and rapidly decreased after the first day. Fifth percentile values of 5423/mm^3 and 90th percentile values of 33080/mm^3 were similar to the values published in the literature[1,2,5].

The absolute total neutrophils also showed a gradual decrease in median values after birth. The peak value of 32560/mm^3 occurred at birth and the lowest value of 720/mm^3 in the third day of life. The reference values of ATN counts were found to be 1243/mm^3 for the 5th percentile and 2341/mm^3 for the 95th percentile in our study. Our results were different from Manroe's[5] and Xanthou's[2] studies and were similar to the results of Kuchler[8].

Maternal neutrophils gradually increase due to high estrogen levels and increased muscle function during the gestational period and reach a high level in labor, so the WBC and ATN counts obtained soon after birth generally project the maternal peripheral blood cell picture[15-17]. The neutrophil counts were found to be higher in babies whose mothers had prolonged labor and/or severe pain. This temporary increase in neutrophils may be due to the releasing of cells from the vascular bed to the circulation[18]. The etiopathology of those changes is explained by the sum of the effects of hormonal factors such as adrenalin and hydrocortisone colony stimulating factors, and marginal pool-bone marrow pool interactions of the mother. Neonates with a history of prolonged labor and/or severe maternal pain were excluded from our study in order not to change the accuracy of the values.

Soon after birth, a variety of perinatal and postnatal problems, mostly infections, may be associated with an abnormal neutrophil profile[3-5,19,20].

The increases in immature neutrophil counts and in the immature-to-total neutrophil ratio have generally been accepted as sensitive markers for neonatal sepsis[3-6,10,12]. Knowledge of the upper-normal limits of immature total neutrophil values is important. As far as the 95th percentile of ATIN values is concerned, our study showed the counts of 4531/mm^3 at birth, 2560/mm^3 in the 24th, 1249/mm^3 in the 48th, 1031/mm^3 in the 72nd and 765/mm^3 in the 120th hour of life (Fig. 2). Our results were higher than the results of Manroe[5] and Akenzua[4] but very similar to the results of Kuchler[8]. In our study, the I/T ratios were higher than others' reference values[2,5]. Our 95th percentile values were 0.26, 0.19, 0.19, 0.185 and 0.17 respectively (Fig. 4). The patterns of ATIN and the I/T ratio can be considered as the reference values for us.

As far as the ATL values are concerned, the significant decrease was reported on the 3rd day by Xanthou et al[2], on the 5th day by Weinberg et al[21] and more than 5 days by others[1]. In our study, the median lymphocyte values were 5298/mm^3 in the 24th, 4193/mm^3 in the 48th, 4216/mm^3 in the 72nd and 6032/mm^3 in the 120th hour of life (Fig. 5). A significant decrease in ATL values was observed in the 48th hour of lifeşearlier than was cited in previous reports.

The crossing between neutrophils and lymphocytes was generally reported on the 5th-7th days of life[2,5,22]. In our infants, this occurred on the 3rd day. This was the most important observation of our study. It may show the earlier accomodation and stabilization of leukocyte dynamics in our neonates.

In our infants, the median ATM values were relatively stable and were similar to the observations of Xanthou et al[2].

Absolute total eosinophil counts were 450/mm^3 at birth and slightly increased thereafter (Fig. 7). Our results were lower than the results of Xanthou[2], but higher than Weinberg[21] and Barbero[23].

Considering the range of leukocyte dynamics boys and girls had values similar to those reported by other investigators[2,11,21,24].

In conclusion, we believe that it will be more suitable to establish the reference values for our country by doing similar investigations in different regions of Turkey and to use these reference values in the diagnosis of sepsis and other infectious diseases.

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PLASMA FREE CARNITINE LEVELS IN CHILDREN WITH MALNUTRITION*

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SUMMARY: Tanzer F, Uzunsel S, Atalay A. (Department of Pediatrics, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Plasma free carnitine levels in children with malnutrition. Turk J Pediatr 1994; 36: 133-137.

In this study, plasma free carnitine and albumin levels were measured in children with protein-energy malnutrition (PEM). A total of 71 children with malnutrition were studied. The control group consisted of 20 healthy children. The mean plasma carnitine level was 78.4±1.94 nmol/ml in the control group. Marasmus and kwashiorkor patients displayed lower plasma free carnitine values, which were found to be statistically significant when compared to those of the control ($P<0.001$). However, the values were significantly lower in kwashiorkor patients than in marasmic cases (29.7>5.46). There was no correlation between serum albumin and free carnitine levels in cases with kwashiorkor. *Key words: malnutrition, plasma carnitine.*

L-carnitine plays an essential role in mitochondrial oxidation of long-chain fatty acids, facilitating their transfer across the mitochondrial membrane. The endogenous synthesis of carnitine from lysine and methionine occurs mainly in the liver, from which free and acylcarnitines are released into the blood and transported to other tissues. Cardiac and skeletal muscles depend greatly on fatty acid oxidation as an energy source and have a high requirement for carnitine[1-7].

Protein-energy malnutrition. (PEM) develops as a result of a lack of calories and protein and is usually associated with various infections[8]. Marasmus results mainly from an inadequate intake of calories in other words, starvation. A lack of calories causes an increase in catabolism, and naturally carnitine intake decreases in children with PEM.

In kwashiorkor, protein intake in particular is very limited. Likewise, the essential amino acids, such as lysine and methionine, are also deficient; consequently in sufficient endogenous synthesis of carnitine occurs. As a result, a fatty liver develops. Since carnitine plays an essential role in the oxidation of fatty acids, the deficiency of carnitine may provide an explanation for the accumulation of fats in the liver of these patients.

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There are limited data in the literature on carnitine metabolism in children with PEM[6-7]. Since studies of serum carnitine may aid in the understanding of metabolic changes occurring in PEM[9-12] and may be of potential value as regards therapy, the purpose of the present investigation was to determine carnitine and albumin concentrations in serum of children suffering from this disease in the Sivas region of Turkey.

Material and Methods

This investigation was carried out at the Department of Pediatrics at Cumhuriyet University Hospital on 71 children suffering from malnutriton and 20 healthy controls enjoying normal development.

Plasma carnitine and albumin levels were examined in 20 controls and 14 children suffering from kwashiorkor, 41 children suffering from marasmus and 16 children who were apparently healthy but had body weights which were 60-80 percent of the standard weight for Turkish children of that age[13] and hence were judged as undernourished[14]. For all groups the age range was 9-24 months.

Plasma albumin fraction was estimated by Biotrol kits using RA 1000 autoanalyzer. Plasma free carnitine determination was made by an enzymatic method, using a Beckman model Spectrophotometer and recorder with electronic temperature control[15].

Statistical evaluations were made in accordance with standard deviation, correlation Kruskal Wallis's analysis and real significance difference method.

Results

The mean ages, heights, weights and types of malnutrition of the 71 patients and 20 healthy controls are shown in Table I.

Table I: Mean Weights and Heights of Children with Malnutrition and Healthy Controls

		Age (month)	Weight (kg)	Height (cm)
Groups	n	$\bar{X}$ Sx	$\bar{X}$ Sx	$\bar{X}$ Sx
Control	20	23.25 ± 4.02	11 ± 1.04	75.3 ± 3.65
Undernourished	16	16.2 ± 2.47	7 ± 0.46	71.5 ± 2.26
Marasmus	41	12.49 ± 1.57	5.6 ± 0.31	67.44 ± 1.49
Kwashiorkor	14	9.6 ± 2.62	6.4 ± 0.57	69.4 ± 2.52

Albumin levels were significantly lower in the plasma of children suffering from kwashiorkor as compared to control children (Table II).

Table II: Plasma Free Carnitine and Albumin Levels of Control and Malnourished Children

Groups	Number	Carnitine (nmol/ml)	Albumin (g/dl)
Control	20	78.40 ± 1.94	4.29 ± 0.15
Undernourished	16	67.75 ± 1.38	4.04 ± 0.09
Marasmus	41	58.97 ± 0.94	4.09 ± 0.08
Kwashiorkor	14	48.70 ± 1.91	2.10 ± 0.15
			KW = 36.76
			p < 0.001

There was no correlation between serum albumin and free carnitine levels ($r = 0.22$, $r = 0.16$, $r = -0.05$, $r = 0.45$, $p > 0.01$).

Following measurements of plasma free carnitine values in marasmus and kwashiorkor patients, the mean values were found to be 69.75 ± 1.38 nmol/ml in undernourished children and 58.97 ± 0.94 in those with marasmus. The mean obtained in patients with kwashiorkor 48.7 ± 1.91 nmol/ml. All these values were significantly lower than those of the healthy controls (Table III, $P < 0.001$). However, values were significantly lower in kwashiorkor patients than in marasmic cases (29.7 > 5.46, Table III).

Table III: Plasma Free Carnitine Levels of Control and Malnourished Children

Groups	Number	Carnitine (nmol/ml)	Analysis
Control[a]	20	78.4 ± 1.94	KW = 67.56
			p > 0.001
Undernourished[b]	16	69.75 ± 1.38	
Marasmus[c]	41	58.97 ± 0.94	
Kwashiorkor[d]	14	48.70 ± 1.91	

Statistical Analyses: a vs b, a vs c, a vs d, b vs c, b vs d, c vs d; $p < 0.05$.

Discussion

Factors such as sex, age[16-18], nutritional status[19], fasting[20-21], and disease[22-24] have been cited as influencing plasma carnitine levels in man. Recently there have

been several reports about the impact of diet on plasma carnitine levels in various species[25]. Less has been published on plasma carnitine levels in man[19,26].

The present study clearly demonstrates a decrease in serum carnitine in children with PEM, especially kwashiorkor, as compared to well-nourished controls. This finding is consistent with the observations of Khan et al[6] and Hammod et al[7]. The low levels of carnitine reported here for children with PEM, may be associated with reduced intake of carnitine itself, together with a deficiency of the precursor amino acids lysine and methionine, giving rise to inadequate endogenous synthesis[27-30]. Deficiency of other nutrients, such as iron and vitamin C, as well as enzymes required for the biosynthesis of carnitine may also be involved. This clearly accounts for the low level of carnitine leading to fatty liver in kwashiorkor.

This condition is an indicator of fatty acid catabolism disorder. In marasmic cases without fatty liver, the plasma free carnitine level was higher than that of the kwashiorkor cases. This finding stresses the significance of endogenous carnitine achieved by the liver.

The fact that no correlation between serum albumin and free carnitine levels was observed in the cases investigated in this study has been attributed to varying dysfunctions in the control mechanism in cases with kwashiorkor. The findings obtained clearly indicate that further investigations on carnitine concentration at the tissue level are essential in PEM for more effective oral management of carnitine deficiency.

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LIPIDOSIS WITH SEA-BLUE HISTIOCYTES*
Report of Two Siblings with Lung Involvement

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SUMMARY: Göğüş S, Göçmen A, Koçak N, Kiper N, Küçükali T, Yüce A, Büyükpamukçu N. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Lipidosis with sea-blue histiocytes. Report of two siblings with lung involvement. Turk J Pediatr 1994; 36: 139-144.

Two siblings, an eight-year-old girl and a three-year-old boy with lipid storage disease, most likely non-neuropathic Niemann-Pick disease (NPD) with sea-blue histiocytes, are presented. Both of them had foamy and sea-blue histiocytes in their bone marrow smears and reticulo-nodular appearance of both lungs on their chest X-rays. Case 1 had diffuse, biopsy-proven, pulmonary involvement associated with sea-blue histiocytes. Although diffuse reticulo-nodular pulmonary infiltration of non-neuropathic NPD (type B) is frequently detected on chest X-rays, to our knowledge there is only one reported adult case of lipidosis resembling NPD in which severe pulmonary involvement associated with pigmented histiocytes and Niemann-Pick cells were demonstrated at autopsy. *Key words: non-neuropathic Niemann-Pick disease, adult Niemann-Pick disease, sea-blue histiocyte syndrome.*

Histiocytes containing distinctive blue-green intracytoplasmic granules were first reported in a splenic aspirate by Moeshlin[1] in 1947. Later they were detected in the bone marrow of some patients with hepatosplenomegaly, and it was suggested that this might represent a specific syndrome with a benign course[2-4]. But it is now clear that they can be seen in a variety of conditions including inborn errors of lipid metabolism[5-15].

We report here two siblings with lipid storage disease, most likely non-neuropathic Niemann-Pick disease (NPD) with sea-blue histiocytes. One of them had diffuse biopsy-proven pulmonary involvement associated with sea-blue histiocytes. Although diffuse reticulo-nodular pulmonary infiltration of non-neuropathic NPD (type B) is frequently detected on chest X-rays, to our knowledge there is only one reported adult case of lipidosis resembling NPD in

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which severe pulmonary involvement associated with pigmented histiocytes and Niemann-Pick cells were demonstrated at autopsy[9-11,15-18].

Case Reports

Case 1

An eight-year-old girl was admitted to Hacettepe Children's Hospital for the evaluation of a diffuse reticulo-nodular appearance of both lungs on chest X-ray and splenomegaly. She had been underweight since infancy. When she was seen at the same hospital at the age of 14 months because of failure to thrive, iron-deficiency anemia and urinary tract infection were detected. She did not have hepatosplenomegaly at that time. Her parents were healthy and distantly related. Her three-year-old brother had also had failure to thrive since infancy.

The patient was 108 cm in length (< 5th percentile) and weighed 17 kg (< 5th percentile). Her spleen was palpable 8 cm below the costal margin. The liver was not palpated. The neurological examination was normal, and there was no evidence of intellectual impairment. Laboratory tests (including whole blood count and liver function tests) were found to be within normal limits. The chest X-ray showed a diffuse reticulo-nodular pattern in both lungs (Fig. 1). An open lung biopsy was performed because of a suspicion of miliary tuberculosis. Microscopic examination of the formalin-fixed lung tissue revealed many nodular clusters of oil-red O and Sudan-black B positive foamy histiocytes in the alveoli, located prominently in the perivascular, peribronchial and subpleural areas (Fig. 2). Some cells had cytoplasmic, faint yellow-brown pigments that were blue-green in color, with Giemsa stain giving them an appearance of sea-blue histiocytes. These granules were PAS-positive after diastase treatment and iron-stain-negative. An

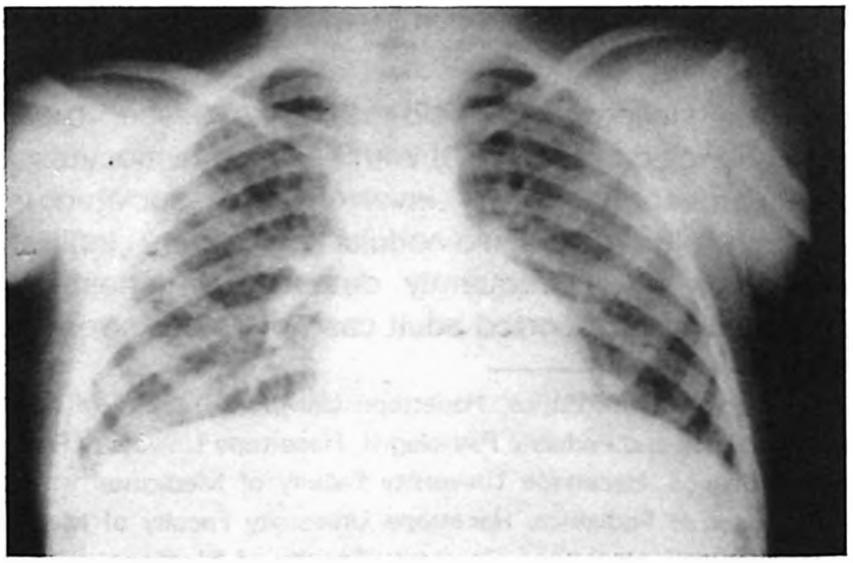

Fig. 1: Case 1- Chest X-ray showing reticulo-nodular appearance of lung fields.

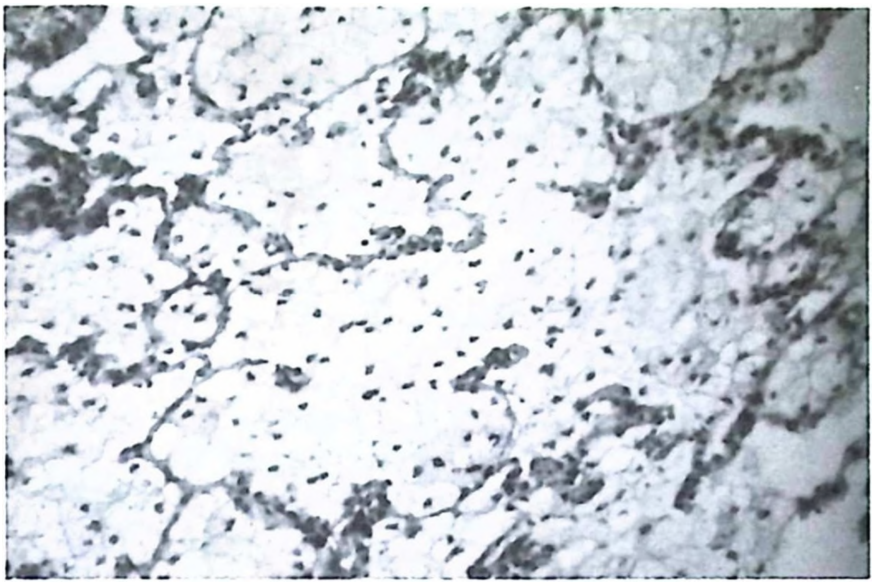

Fig. 2: Case 1- The alveolar spaces are filled with foamy histiocytes in the lung (H + E x 400).

electron microscopic study with formalin-fixed tissue was attempted. Ultrastructurally the intracytoplasmic-stored material was represented by either lamellated membranous bodies or fine granular materials (Figs. 3, 4).

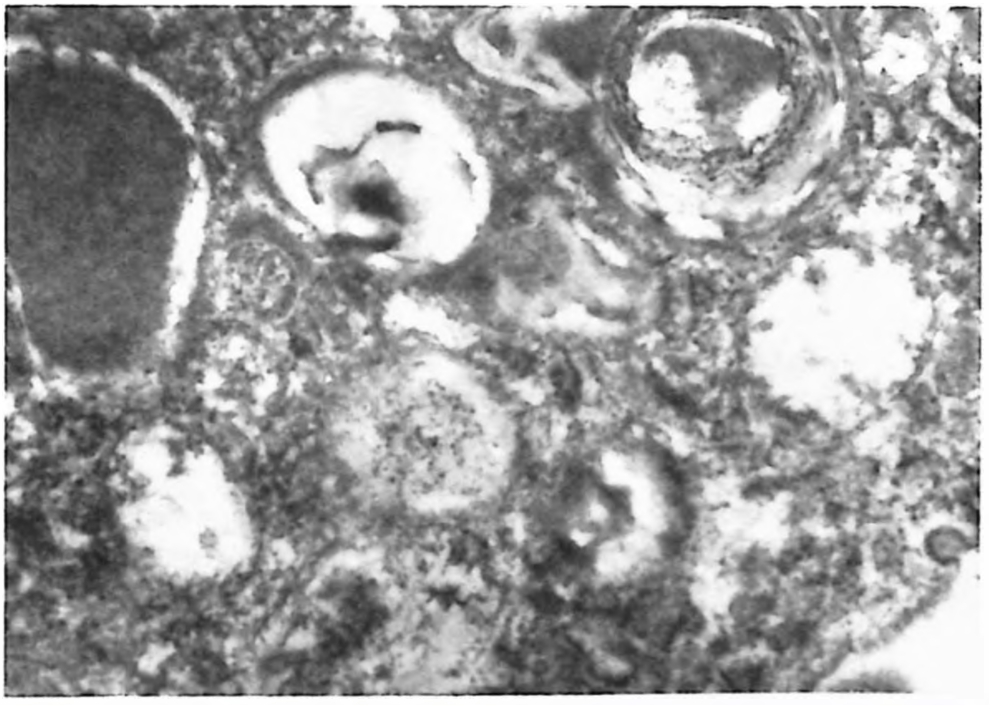

Fig. 3: Case 1- Electron micrograph of lung biopsy. Lamellated membranous material in the histiocytes (x 8300).

A bone marrow specimen stained with Wright stain also showed many sea-blue histiocytes and foamy histiocytes similar to Niemann-Pick cells (Fig. 5).

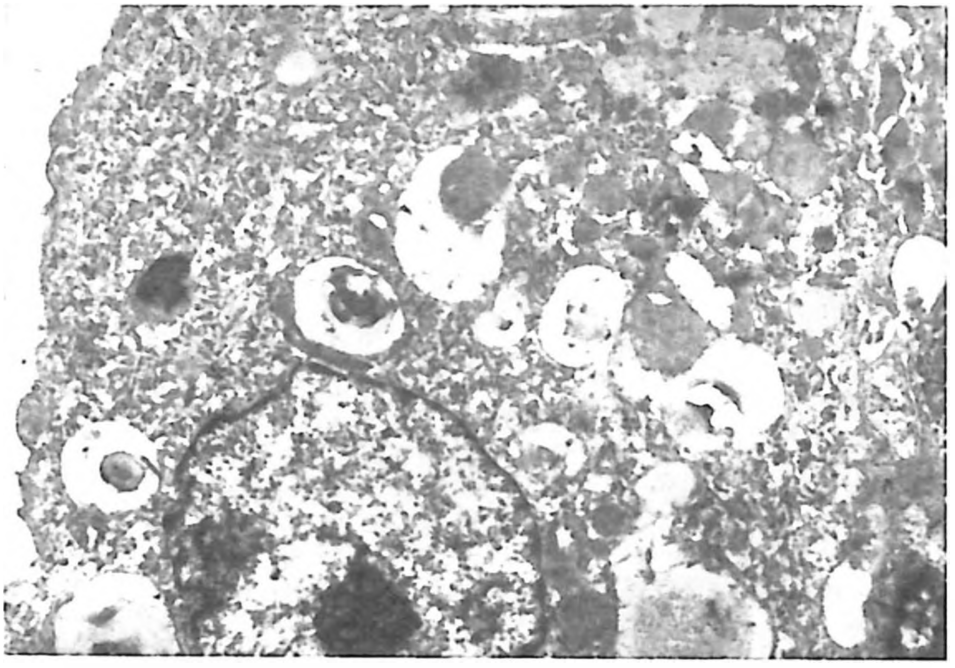

Fig. 4: Case 1- Electron micrograph of lung biopsy. Fine granular material in the histiocytes (x 8300).

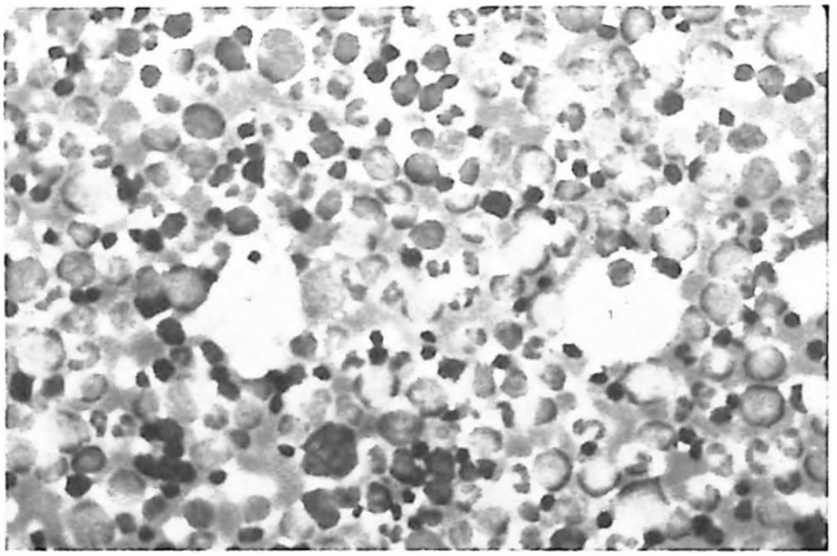

Fig. 5: Bone marrow of Case 1 showing foamy histiocyte (Wright x 650).

Case 2

The three-year-old brother of Case 1 was called for examination. He was 90 cm tall (10^{th} percentile) and weighed 13.5 kg (25^{th} percentile). His liver and spleen were palpated 2.5 cm below the respective costal margins. The neurological examination was normal. Bone marrow examination revealed many foamy histiocytes similar to Niemann-Pick cells and sea-blue histiocytes. The chest X-ray

showed a fine reticular appearance in both lung fields. Other routine laboratory tests were all within normal limits.

Despite the same appearance of their chest X-rays, the patients had no complaint during the follow-up of two and one-half years.

Discussion

Sea-blue histiocytes have been associated with a variety of systemic, hematological and neurological syndromes[6-15]. The primary syndrome is quite rare[8]. Recently, many authors have suggested that this term should be discarded, as it leads to confusion[6,7]. They recommended that the presence of such cells in abundance should initiate a search for an underlying defect because it is becoming clear that variants of NPD are common causes of this uncommon clinical picture in adults and children[6-13]. The actual origin of sea-blue histiocytes is unknown. Though the precise biochemical defect cannot always be identified, it seems reasonable to suggest that in most instances, a structurally defective or partially or completely absent enzyme leads to an accumulation of its natural substrate within the cell. It is shown that the sea-blue color on Giemsa stain is due to the presence of ceroid[9].

Sea-blue histiocytes have been reported in many forms of NPD (types B, C, D, E, F)[6,9-13,15]. They have been observed in the bone marrow, spleen, liver or lymph nodes in nine of 17 cases of well-documented chronic non-neuropathic NPD (type B) in the literature[9]. The age ranges of these patients varied from two to 17 years. They all had hepatosplenomegaly associated with moderate anemia and sometimes thrombocytopenia. A reticulonodular appearance was noted on the chest X-rays in seven of the cases. None of the patients had abnormal neurological signs or mental impairment. NPD type B is manifested by a subacute or chronic course and hepatosplenomegaly. The chronic form, however, may reveal only slight visceromegaly, sometimes only splenomegaly, and may take an inapparent and rather benign course[10]. Chronic forms frequently contain a conspicuous amount of ceroid, thereby hindering diagnosis and misleading one to the diagnosis of the sea-blue histiocyte syndrome[10]. The incidence of this form is low. However, because of the absence of neurologic changes, the diagnosis may be unsuspected clinically. Traumatic rupture of an enlarged spleen is frequently the first sign. It is important, therefore, for the pathologist to recognize this condition in surgically removed spleens or at autopsy.

Clinical, histopathological and electron microscopic findings of Case 1 and the clinical and bone marrow findings of Case 2 revealed a lipid storage disease, most likely non-neuropathic NPD type B with sea-blue histiocytes. To our knowledge, this is the first reported lung-biopsy-proven case of lipid storage disease with sea-blue histiocytes. We were not able to do biochemical investigations nor could

we confirm the diagnosis by enzyme assays; however, we believe the diagnosis can be established with reasonable certainty from formalin-fixed tissue. Because of the reticulo-nodular appearance of its pulmonary involvement, NPD must be considered in the differential diagnosis in countries where tuberculosis and consanguinity are fairly common.

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I-CELL DISEASE*
A Case Report and Review of the Literature

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SUMMARY: Güngör N, Coşkun T, Akçören Z, Çağlar M. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). I-cell disease: a case report and review of the literature. Turk J Pediatr 1994; 36: 145-152.

A four-month-old female infant having developmental delay, coarse facial features and dysostosis multiplex is reported with a special emphasis on the differential diagnosis among I-cell disease (ICD), Hurler syndrome and GM1 gangliosidosis. The lysosomal enzyme studies in cultured skin fibroblasts and serum sample of the patient certified the diagnosis of ICD.

Foamy cell infiltration of some organs, including the lungs, and microgyria formation were also noted. Genetic counselling was provided and prenatal diagnosis was offered to the couple to detect ICD in the next pregnancy. *Key words: I-cell disease dysostosis multiplex, microgyria, prenatal diagnosis.*

I-cell disease (ICD, mucolipidosis type II) is a rare. autosomal recessive lysosomal storage disorder. It was first described in 1967, and coarse cytoplasmic inclusions in the cultured skin fibroblasts (designated inclusion cell or I-cell) of two children were noted[1]. This disorder has been well defined clinically[1-6]. Manifesting at birth or in the first few months of life, ICD is characterized by developmental delay, short stature, coarse facial features with hyperplastic gums, and dysostosis multiplex clinically[2,3,5,6]. Affected patients may also have congenital dislocation of the hips, inguinal hernias, restricted motion in the shoulders, generalized hypotonia, thick and tight skin, and hepatomegaly[5,6]. The disease has a progressive clinical course resulting in a fatal outcome at 2-8 years of age (approximately 4 years). Death usually occurs due to intractable heart failure and/or pulmonary infection[1,2,6].

Histologically, vacuolation of cells is the most characteristic feature in patients with ICD, and this vacuolation is seen in various types of cells, such as myocardial fibers, hepatocytes, epithelial cells of renal glomeruli, renal tubular cells, splenic cells and neurons of the brain[2].

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In this report, because of its rarity, a case of ICD with its clinical, biochemical, and histological features is described and the relevant literature is reviewed.

Case Report

A four-month-old infant girl was admitted to Hacettepe University Children's Hospital because of difficulty in breathing, coughing and vomiting. She was born at full-term with a birth weight of 2000 g ($<5^{th}$ percentile) following an uncomplicated delivery. The child's psychomotor development was mildly delayed; head control was achieved at two months and she was able to recognize her mother at three months. She was the third child of the family. The parents were first cousins. The first child of the family was a five-year-old healthy female and the second child had died due to sepsis at 17 days of age.

On physical examination, the patient was 45 cm ($<5^{th}$ centile) in length and 3000 g ($<5^{th}$ percentile) in weight. Her head circumference was 33 cm ($<5^{th}$ percentile). Her general status was not good with mild lethargy and hypoactivity. Her skin was pale and cold with cutis marmoratus. Perioral and acral cyanosis was noted. She had coarse facial features characterized by bilateral mild exophthalmos, low-set ears, upturned nostrils, a long philtrum and hyperplastic gums (Fig. 1). She had a high-arched palate. The patient was tachypneic and had intercostal

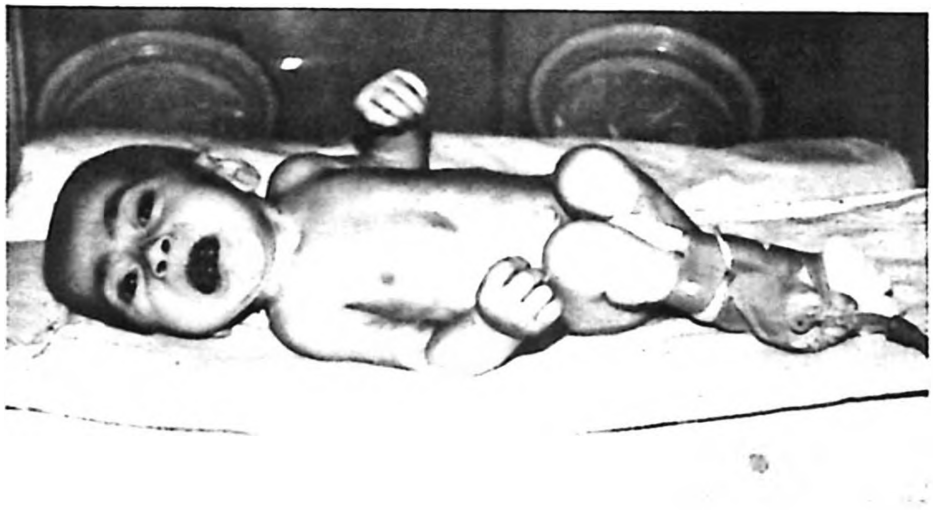

Fig. 1: The patient with coarse facial features, exophthalmos, low-set ears, upturned nostrils, long philtrum and hyperplastic gums.

and subcostal retractions. Crepitant rales were heard over the pulmonary fields. A III/VI degree systolic murmur was heard in the third and fourth left intercostal spaces. Diastasis recti was present. The liver was palpable 3 cm below the right costal arch. The abduction of both hip joints was limited. Bilateral pes equinovalgus deformity was present. Cortical fisting and crossing of legs were observed with hypoactive Moro reflex and poor suck.

The complete blood count revealed a hemoglobin value of 9.2 g/dl and a hematocrit value of 27% with hypochromia and anisocytosis in erythrocyte morphology. Mild leucocytosis (13.000/µl) with a predominance of polymorphonuclear cells and stabs was present. Granulation was observed in the cytoplasm of lymphocytes. The mean corpuscular volume and transferrin saturation were below normal, indicating iron deficiency anemia. The urinalysis and serum electrolytes were within the normal range. The chest roentgenogram revealed cardiomegaly and a diffuse pulmonary infiltration. The EKG revealed findings compatible with right ventricular hypertrophy and ST and T changes. Echocardiography displayed 58 mm of systolic gradient in the mitral valve. Urinary mucopolysaccharide excretion was normal. Serum and urine amino acids were normal. Skin specimens for fibroblast culture were obtained. Lysosomal enzyme studies were performed in cultured skin fibroblasts. The lysosomal enzyme activities were found to be high in serum and low in fibroblasts (Table I).

Table I: Lysosomal Enzyme Studies in The Patient

	Activity (mU/mg)	
Enzyme		
FIBROBLASTS	Patient	Normal Range
o-Iduronidase	0.046	1.36-4.40
β-Glucuronidase	0.464	3.05-7.65
α-Galactosidase	0.109	7.53-14.3
SERUM		
o-Ac-α-Glucosamin	0.9844	0.183-0.697
β-Glucuronidase	13.4236	0.281-1.991
α-Fucosidase	19.6403	1.017-11.13
α-Mannosidase	17.8642	0.109-1.173
Hexosaminidase A	10.7205	1.125-4.249
Total Hexosamin	423.694	8.916-27.07

The patient had interesting skeletal findings which may be grouped together under the term "dysostosis multiplex". Except for the skull bones, the skeleton was characterized by a low density and an abnormal texture which gave a fibrillar or lacunar appearance to the bones. The roentgenographic findings of the patient will now be summarized, beginning from the proximal:

Skull : The skull was microcephalic with a mildly deep posterior fossa. There was sclerosis in the skull base.

Spine : The anteroposterior diameter of the lumbar bodies was small. The bodies were longer posteriorly than anteriorly. The end-plates of the vertebral bodies were convex. The second lumbar body was hypoplastic with a "hook" configuration. There was slight concavity at the anterior borders of the vertebral bodies of L2 and L3 (mild hook configuration). There was thoracal scoliosis.

Pelvis : Bilateral hip dislocation with supraacetabular constriction was observed. The iliac wings were flared.

Long Tubular Bones : The shaft of the long bones had a poorly defined contour (a contour with a double line image, resembling periosteal apposition). Especially in both femurs and tibiae, the double outline (cloaking) involved almost the entire shaft. The cortices were thin and the medullary canals were enlarged (Fig. 2).

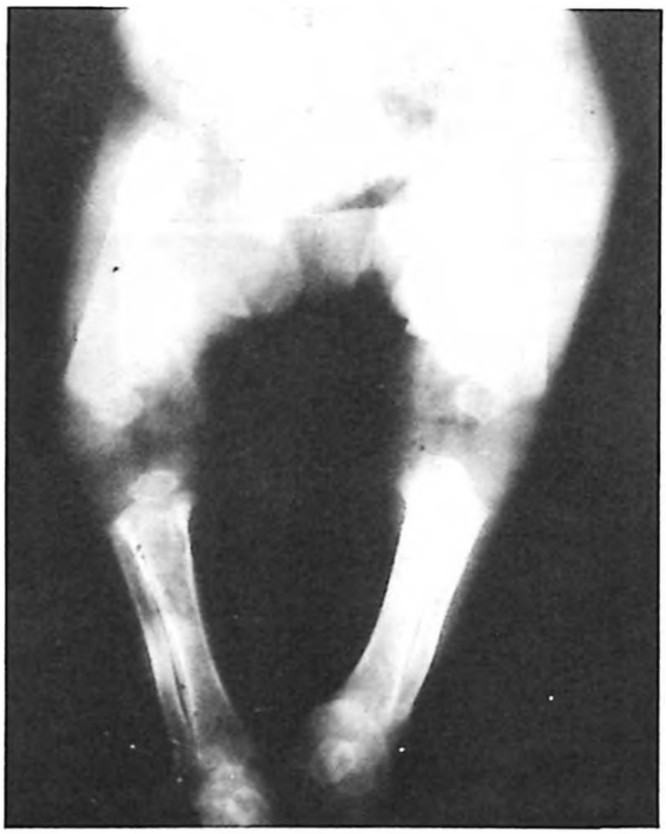

Fig. 2: Cloaking of both femurs and tibiae with enlarged medullary canals.

Hands and Feet : The metacarpal and metatarsal bones were shortened and rectangular in shape with coned proximal ends. The proximal and middle phalanges were shortened and bullet-shaped. Distal phalanges were markedly hypoplastic. The cortex of these bones was inapparent and their texture was fibrillar or lacunar (Fig. 3).

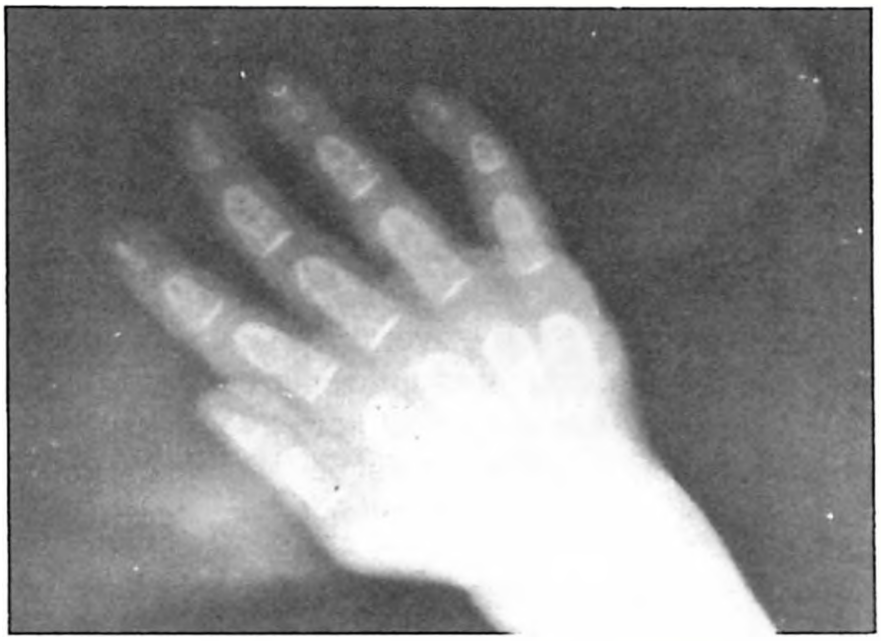

Fig. 3: Short and rectangular metacarpal bones with coned proximal ends. Bullet-shaped proximal and distal phalanges and hypoplastic distal phalanges.

Ribs : The ribs were oar-shaped with widening of the lateral and anterior part (Fig. 4).

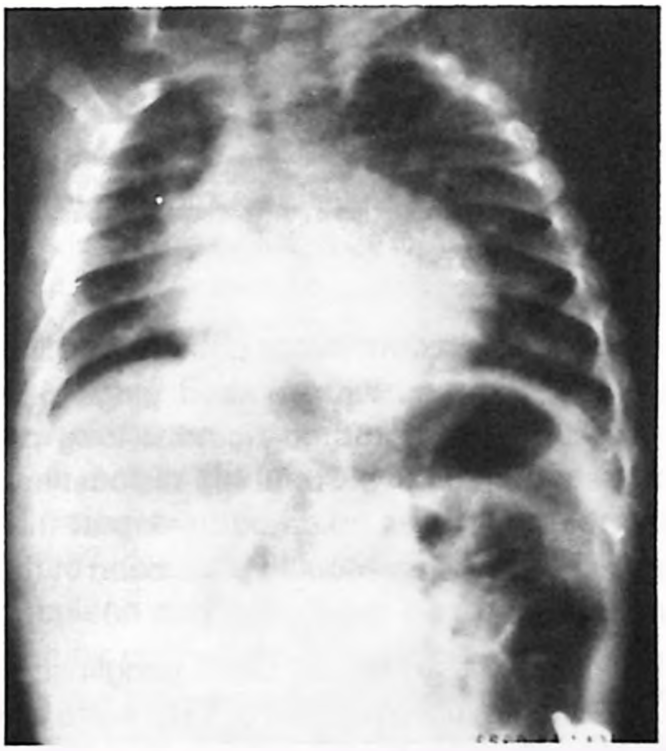

Fig. 4: Thoracal scoliosis and oar-shaped ribs. This figure also reveals the cardiomegaly of the patient.

Proper alimentation (first oral then intravenous), antibiotics, digitalization, supportive therapy and ventilation were administered. The patient's clinical status worsened daily, and she died following a cardiopulmonary arrest on the eighth day of hospitalization. Permission for autopsy was given by her parents.

On histopathological examination, congestion and hemorrhage in some alveolar spaces and findings consistent with interstitial pneumonitis were observed. Some of the macrophages in the alveolar spaces were vacuolated and stained light blue with Hale's colloidal iron[9] (Fig. 5). The liver displayed fatty degeneration. In the kidneys, some of the glomerular epithelium displayed foamy changes and were also stained light blue with Hale's colloidal iron. In addition there were foci of mononuclear cell infiltration revealing interstitial nephritis. There was no other marked histopathological change in the other organs and tissues.

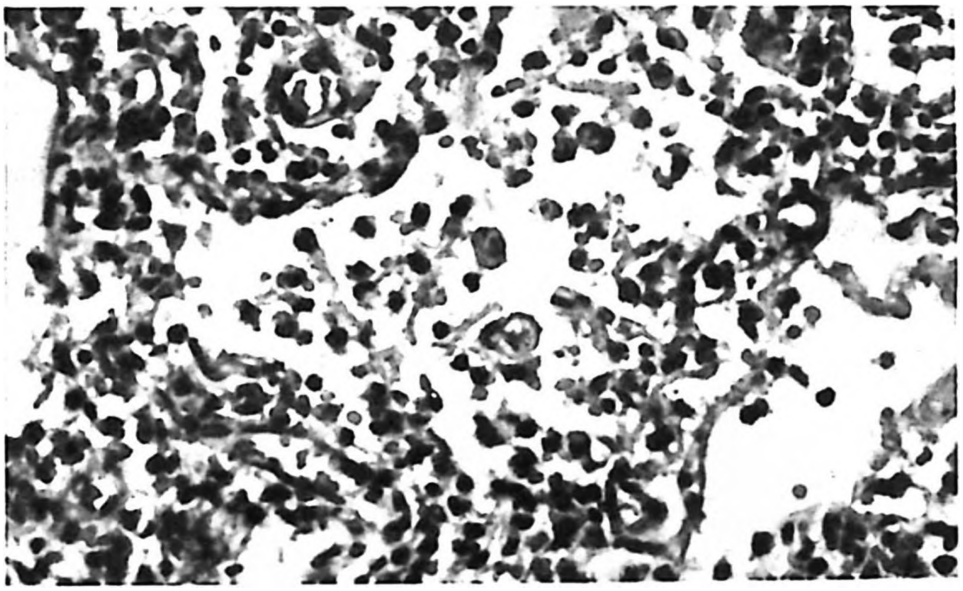

Fig. 5: The vacuolated macrophages in the alveolar spaces. (H+, x100).

Discussion

The major clinical abnormalities present in our patient were developmental delay, microcephaly, coarse facial features with marked gingival hyperplasia, bilateral mild exophthalmos, low-set ears, upturned nostrils, long philtrum, high-arched palate, diastasis recti, hepatomegaly, bilateral hip dislocation and pes equinovalgus deformity. At first, these features made us think that the patient might have an inborn error of metabolism. This error could have been in the mucopolysaccharide (MPS) or lipid metabolism.

Mucolipidosis type II (I-cell disease, ML-II). GM1 gangliosidosis, and mucopolysaccharidosis type I (Hurler syndrome, MPS I-H) were the main issues for differential diagnosis. Patients with Hurler syndrome appear normal at birth, and during the first year of life only slight developmental delay is noted. Infants with

MPS I-H usually have macrocranium and they are usually tall (in contrast to our patient), but the coarse facial features are also seen in Hurler syndrome. Presence of a marked gum hypertrophy and the detection of normal excretion of urinary mucopolysaccharides made this diagnostic consideration less likely. The radiographic findings in our patient were consistent with dysostosis multiplex. The early onset of clinical findings and no detection of a cherry red spot in the macula were against the diagnostic consideration of GM1 gangliosidosis in our patient. As GM1 gangliosidosis presents with the same skeletal changes as mucolipidosis type II, radiologic differentiation between these conditions was not possible.

Biochemically, elevated serum levels of many lysosomal enzymes, decreased intracellular activities of some of them and normal excretion of urinary mucopolysaccharides characterizes I-cell disease (ICD)[3,4]. The primary defect in ICD is a deficiency of a specific N-acetylglucosamine phosphotransferase. This enzyme phosphorylates newly formed lysosomal enzymes and generates the common phosphomannosyl recognition markers of lysosomal enzymes. Thus, lacking these phosphate groups that serve as a recognition marker, the newly synthesized enzymes do not enter the lysosomes but are excreted from the cell. This explains the striking elevation in the serum levels of lysosomal hydrolases and their deficiency in fibroblasts associated with ICD. Other body fluids (tears, amniotic fluid, etc.) also show this increased activity of several lysosomal enzymes. On the other hand, some cells and tissues do not express the lysosomal enzyme deficiency (leukocytes) and others express it partially (liver, brain)[3,6].

For the definite diagnosis and differentiation of the two conditions (GM1 Gangliosidosis and ICD), lysosomal enzyme studies were required in cultured fibroblasts, culture medium and serum. When this enzymatic study was performed, the lysosomal enzyme activities were found to be high in serum and low in fibroblasts. The diagnosis of ML-II (ICD) was confirmed in our patient in this way.

The death of patients with ICD occurs mostly due to intractable pulmonary infections or cardiac failure[2,6]. The same occurred in our patient despite the effort to cure her. No cardiac abnormality was detected in our patient except for a systolic gradient of 58 mm in the mitral valve. On the other hand, the relation between histological changes in the lungs and the cause of death in ICD patients is still being investigated[2]. Characteristic foamy changes in the organs such as the heart, kidneys, liver, spleen and brain have been reported in the literature[2]. The changes in the glomerular epithelium of the patient's kidneys were in accordance with those reported in the literature. Foamy changes in the alveolar epithelium of the lungs is a relatively rare finding in the literature which attracts attention especially when recurrent respiratory infections are being considered as a major cause of death in ICD; this rare finding is also found in our patient. In addition,

marked microgyria formation was observed in the frontal lobe of the cerebrum of our patient. To the best of our knowledge, this finding has not before been reported in ICD patients; this may be a new finding in ICD patients.

The importance of recognizing the index case in metabolic diseases is once more emphasized by this case report. This family was provided with thorough genetic counseling; thus the next pregnancy was evaluated in utero. Since the fetus was found to be affected, the pregnancy was terminated.

Acknowledgements

We are thankful to Dr. M. Beck of Kinderklinik Johannes Gutenberg University. Mainz, Germany, for the enzyme studies in serum and skin fibroblasts. We also wish to thank to Dr. A. Besim and M. Ünsal of Hacettepe University's Radiology Department for their help in interpreting the roentgenograms.

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The Turkish Journal of Pediatrics 36: 153-156, 1994

CLASSICAL PHENYLKETONURIA ASSOCIATED WITH GOLDENHAR'S SYNDROME*

A Case Report

*Ayşegül Tokatlı MD**, Turgay Coşkun MD**, Can Naci Kocabaş MD***
*İmran Özalp MD****, Sevim Balcı MD****

SUMMARY: Tokatlı A, Coşkun T, Kocabaş CN, Özalp İ, Balcı S. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Classical phenylketonuria associated with Goldenhar's syndrome. A case report. Turk J Pediatr 1994; 36: 153-156.

Classical phenylketonuria (PKU) and Goldenhar's syndrome were diagnosed in a six-month-old male infant who was referred to Hacettepe Children's Hospital for evaluation of developmental delay. There had been epibulbar dermoids in his left eye, strabismus, bilateral multiple preauricular appendices, malar hypoplasia, micrognathia, hemifacial microsoma and high palatal vault. In addition to congenital anomalies and developmental delay, blond hair, fair skin and unusual urinary odor were noted. Ferric chloride test on his urine sample was positive, and the plasma phenylalanine level was high (34 mg/dl). Based on these clinical and biochemical findings, the diagnoses of phenylketonuria and Goldenhar's syndrome were made. To our knowledge, this is the first case with PKU and Goldenhar's syndrome. *Key words: classical phenylketonuria, Goldenhar's syndrome.*

Classical phenylketonuria (PKU), resulting from a deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH), has been reported in association with some genetic and non-genetic diseases[1-9].

Goldenhar's syndrome (oculoauriculo-vertebral dysplasia) is characterized by epibulbar dermoids, preauricular appendages and pretragal fistulas. Several congenital defects have been reported with Goldenhar's syndrome[10-15].

This is the first report of PKU associated with Goldenhar's syndrome.

Case Report

The patient was the second child of healthy, non-consanguineous parents and born after an uneventful pregnancy and delivery with a birthweight of 2500 g. His sister was healthy. Certain anomalies were noted at the time of birth. There were small, round, creamy-white epibulbar dermoids in the medial limbus of the left

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eye, strabismus, bilateral multiple preauricular appendices, malar hypoplasia, micrognathia, hemifacial microsoma and high palatal vault (Figs. 1, 2). At six months of age, he was referred to Hacettepe Children's Hospital for evaluation of developmental delay. His weight was 7150 g. (75^{th} percentile), length 69 cm (75^{th} percentile) and head circumference 43 cm (25^{th} percentile). On physical examination, in addition to congenital anomalies and developmental delay, blond hair, fair skin and unusual urinary odor were noted. Ferric chloride test on his urine sample yielded a strongly positive reaction. The plasma phenylalanine level was

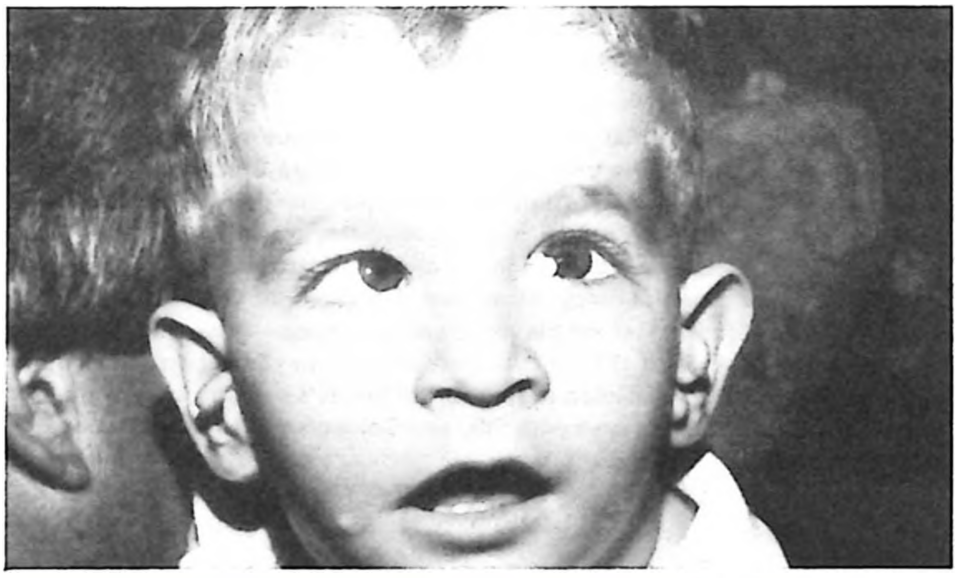

Fig. 1: Patient at 15 months. Note epibulbar dermoid in the left eye and bilateral preauricular appendages.

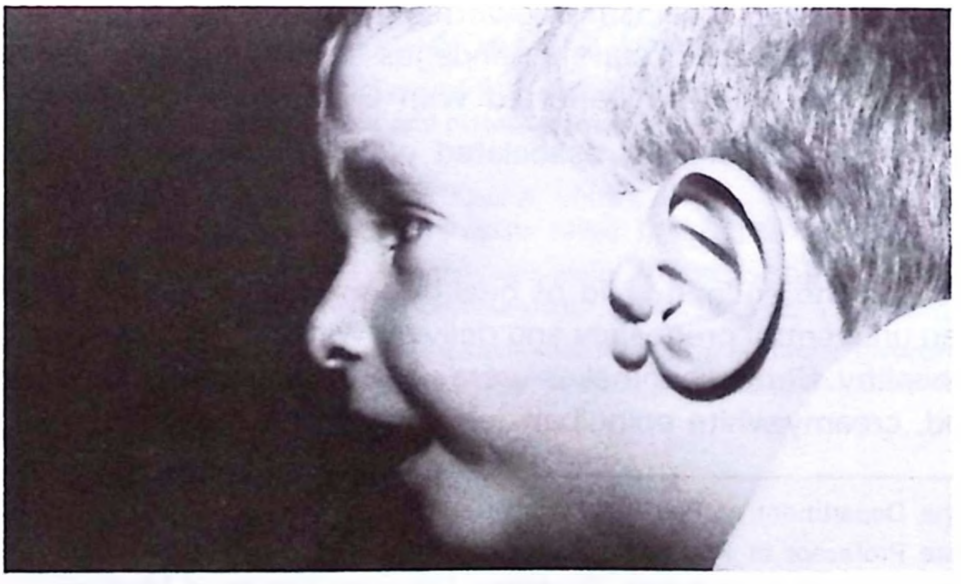

Fig. 2: The combination of malar hypoplasia and micrognathia gives the patient's profile a characteristic appearance.

34 mg/dl. Based on these clinical and biochemical findings, the diagnoses of phenylketonuria and Goldenhar's syndrome were made.

He was put on a low phenylalanine diet and benefitted from the dietary therapy. He was able to walk unaided when last seen at 18 months of age.

Discussion

Goldenhar's syndrome, described by Goldenhar in 1952[10], is characterized by epibulbar dermoids, preauricular appendages and pretragal fistulas. Preauricular appendages are one of the most consistent findings of the syndrome, with unilateral involvement usually being reported. But, there are numerous exceptions, including our case. Epibulbar dermoids and lipodermoids occur unilaterally in half of the patients with Goldenhar's syndrome. In our case, epibulbar dermoids were in the patient's left eye. Lipodermoids do not occur as frequently as do epibulbar dermoids, and were not found in this case. Several ocular and vertebral anomalies are described later that have not been reported in the original cases. Hydrocephalus, mental retardation, cardiovascular, kidney, parotid and parotid duct, urethral, rectal and oral abnormalities, inguinal hernias, hemangiomas, rectovaginal fistulas and clubfoot are other less-frequently associated defects[10-15]. Among these only mental retardation was found in our case, although it was not clear to what extent PKU had played a role in the development of developmental delay.

Several vertebral anomalies and bony defects of the skull were reported in more than 50 percent of the cases in the literature. Skull and vertebral X-rays did not reveal any abnormality in our case. However, the computerized tomography of the brain showed a lipoma in the corpus callosum and some calcifications of the falx cerebri. The calcifications of the falx cerebri were described in Mellor's case[11]. The phenotypical features of untreated PKU, including blond hair, very lightly pigmented skin and "musty" odor, were found on physical examination in our case. Since the serum phenylalanine level exceeded 20 mg/dl and the ferric chloride test was positive, there was no doubt about the diagnosis of classical PKU.

Goldenhar's syndrome is sporadic. No evidence of any hereditary pattern was found in any of the reported cases with the exception of Krause and Summitt's[16,17], who described the syndrome in the same family. In contrast, PKU is inherited autosomal recessively and is the most commonly seen metabolic disorder in Turkey. The incidence of PKU is 1/4370 in our country the highest among the reported surveys[18].

We cannot say whether these two conditions occurred together by chance or as a result of genetic linkage. The reporting of further cases will clarify the association.

Developmental delay or mental retardation is a component of several syndromes. If children with these syndromes are not screened for preventable causes of mental retardation, such as PKU and hypothyroidism, they will become more retarded. The purpose of the present report, therefore, was not only to document the simultaneous occurrence of two conditions, PKU and Goldenhar's syndrome, but also to emphasize that metabolic screening tests must cover all children, especially in countries like Turkey where the incidence of metabolic disease is high. The overlap of clinical symptoms may lead to a delay in the diagnosis of certain treatable diseases.

Acknowledgement

We thank Dr. Nihal Tanrıöğer, Alanya, Antalya, for referring the patient to us.

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The Turkish Journal of Pediatrics 36: 157-162, 1994

HOLOPROSENCEPHALY ANOMALY WITH NASAL AND PREMAXILLAR AGENESIS*
(Possibly Autosomal Recessive Type)

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*M. Arif Akşit MD***, Nilüfer Tel MD*****

SUMMARY: Aydoğdu Durmuş S, Yakut A, Öner Ü, Akşit MA, Tel N. (Departments of Pediatrics and Pathology, Anadolu University Faculty of Medicine, Eskişehir, Turkey). Holoprosencephaly anomaly with nasal and premaxillar agenesis. Turk J Pediatr 1994; 36: 157-162.

A one-day-old male infant with cleft lip and palate, microcephaly, hypotelorism, microphthalmia and absence of the nose is presented. The intermaxillar segment and nasal bone structure were not seen on radiological examination of the skull. Chromosome examination showed a 46, XY karyotype. On postmortem examination, the cerebrum was seen to be a single lobe. Olfactory nerves, corpus callosum and nasal formation, besides the septum were absent. The first and second ventricles were formed as a single ventricle. These findings were compatible with alobar holoprosencephaly. *Key words: holoprosencephaly, nasal and premaxillar agenesis.*

Holoprosencephaly is a malformation complex in which impaired midline cleavage of the embrionic forebrain is the basic feature[1]. The term "arhinencephaly" was used in 1882 by Kundrat because of the hypoplasia or absence of the olfactory bulbs and tracts[2] DeMyer and Zeman[3] used the term "holoprosencephaly" and classified this condition according to the degree of severity as alobar, semilobar and lobar formation.

The true incidence of holoprosencephaly is unknown. In the study by Cohen[4] the prevalence was given as 0.56/10,000-0.63/10,000 in live births.

In this article, a male infant with alobar holoprosencephaly associated with nasal agenesis, which is seen very rarely, and premaxillar agenesis, who exhibited normal karyotype is presented. Related literature is reviewed.

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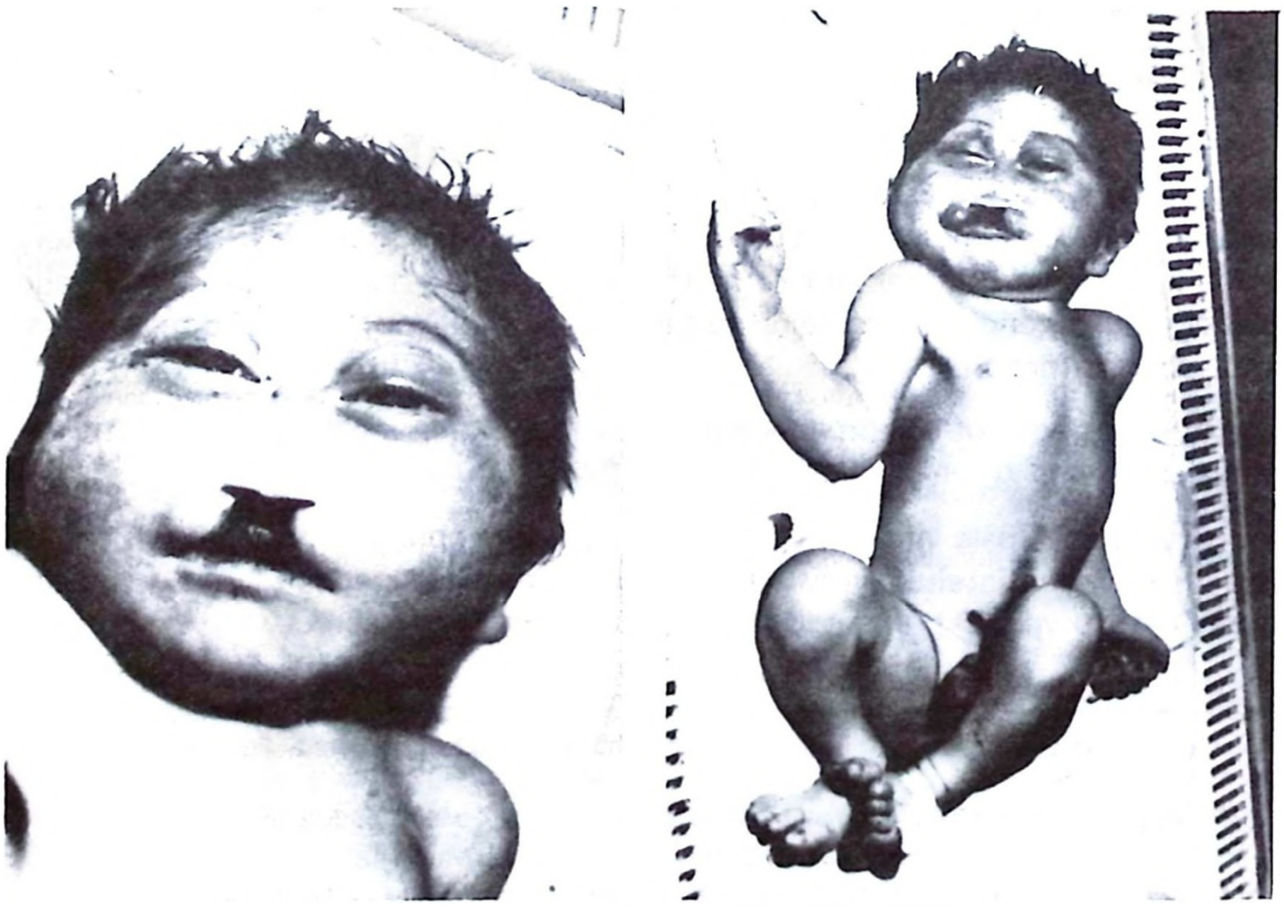
Case Report

A one-day-old male infant was admitted to the hospital because of cleft lip and palate and hypotelorism. He was born at 38 weeks gestation with an uncomplicated delivery as the product of the first pregnancy of a 22-year-old mother. His parents were first-degree relatives. There was no history of congenital anomaly in the family. The parents had a normal female baby after this child.

Physical examination revealed that his weight was 2800 g. length was 49 cm, and head circumference was 31 cm. He had a narrow forehead, hypotelorism, bilateral proptosis and microphthalmia, a short neck, low-set ears with folded auricula on the right side, and complete cleft lip and palate. There was no outer nose formation, but the nasal septum could be seen when looked through the mouth (Figs. 1 and 2). The patient had tachypnea, and crackling rales were heard on auscultation. The Moro reflex was diminished bilaterally.

Laboratory examination revealed that complete blood count, blood glucose, serum electrolytes and calcium were normal. On urinalysis, (+ +) proteinuria and 3-4 leucocytes and granular cylinders were displayed. Proteus (100,000/mm^3)

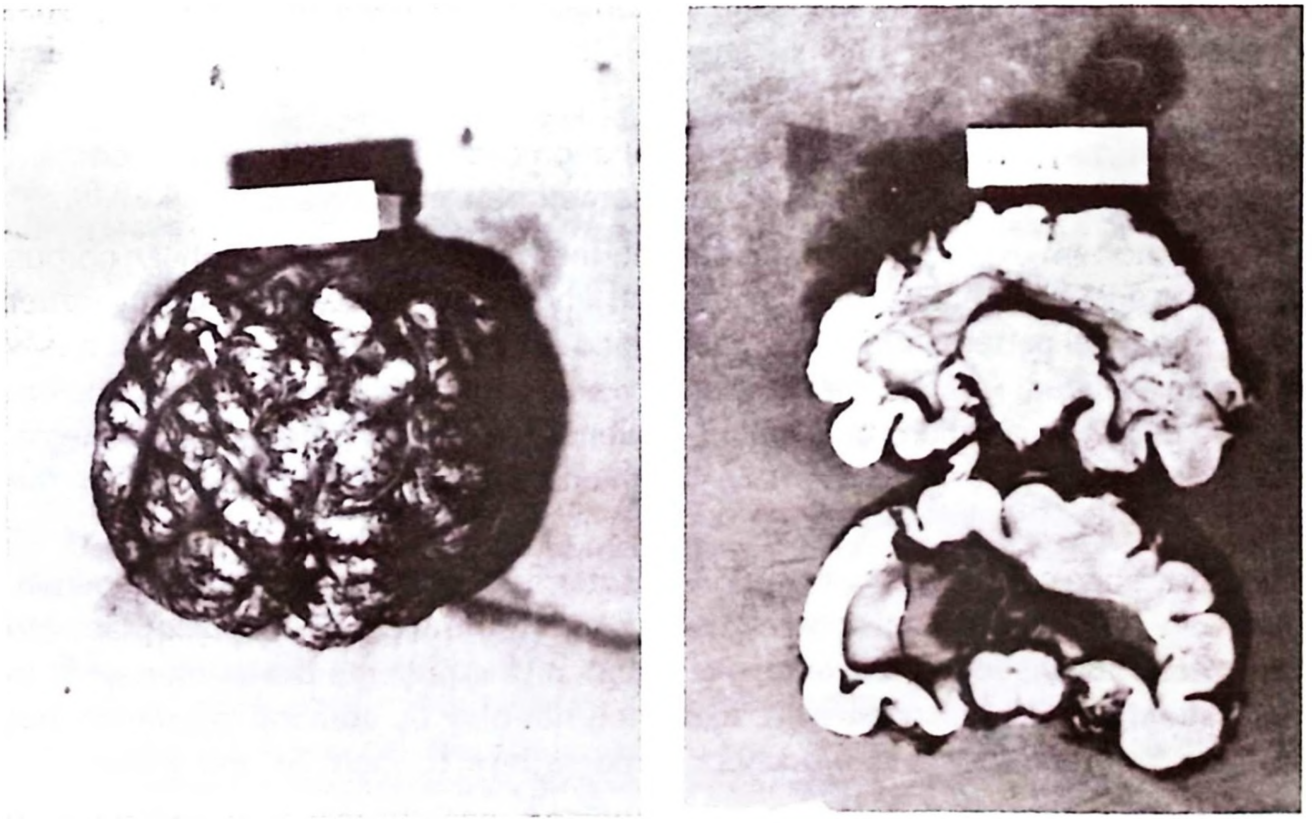


Figs. 1, 2: Face and general appearance of the patient.

was isolated in the urine culture. Craniography showed an absence of the intermaxillar segment and nasal bone structure. The skeletal survey was normal. A chest X-ray demonstrated bilateral bronchopneumonic infiltration. Intravenous pyelography and electrocardiogram were normal. Electroencephalogram showed diffuse irregular activity. Chromosomal examination demonstrated 46, XY karyotype.

During the patient's hospital stay, he was fed by nasogastric tube. Penicillin G. and gentamicin were given for respiratory and urinary tract infections. The patient gradually exhibited difficulty breathing, so nasogastric feeding was stopped. He also had generalized convulsions. The infant's condition deteriorated, and despite supportive treatment he died on the 10^{th} day of hospitalization.

The post-mortem examination revealed severe central nervous system malformations. The cerebrum consisted of a single lobe, with a decreased gyral pattern. Frontal lobes were atrophic. There were no olfactory nerves. There was corpus callosum agenesis. No distinction in grey-white substance was observed. The ventricles were not formed properly; the lateral and third ventricles were formed as a single ventricle. The lower portion of the third ventricle was present, but the upper part consisted only of meningeal membranes which formed a sac. The fourth ventricle was absent (Figs. 3 and 4). Besides cerebral malformations the



Figs. 3, 4: Brain as a single lobe and ventricular abnormalities.

right lung consisted of two lobes. In addition, hemorrhagic bronchopneumonia and a slight thymic involution were observed.

Discussion

Holoprosencephaly has been defined as a medial facio- cerebral developmental abnormality. Cerebral malformations may vary according to the severity of the defect. The term alobar holoprosencephaly or holotelencephaly may be more appropriate in the most common of severe cases, in which the telencephalon remains a single sphered structure but the diencephalon is somewhat less affected[5].

In this anomaly, the olfactory bulbs and tracts are nearly always absent. The term semilobar holoprosencephaly is used to describe a brain with rudimentary hemispheric lobes, an incomplete interhemispheric fissure, and arhinencephaly. The brain with lobar holoprosencephaly has well-formed hemispheric lobes, a distinct interhemispheric fissure, and the third ventricle is continuous with the lateral ventricles[2,3,6,7].

Holoprosencephaly has rarely been associated with several other central nervous system anomalies such as anencephaly, encephalocele, spina bifida and agenesis of cranial nerves[2,8]. Anomalies of other organs are present in 50-60% of patients with holoprosencephaly. The most common anomalies are congenital heart disease, lung anomalies, diaphragmatic defects, omphalocele, hepatic malformation and double vaginae. Endocrine disturbances such as diabetes insipidus, hypoplastic thyroid, and nonexistance of the pituitary gland have also been seen[2,7,8].

Although it may be true that severe facial anomalies can predict a concomitant brain anomaly, facial abnormalities are sometimes mild or absent[2,6,7,9,10].

On post-mortem examination of our patient, tele ventricle, arhinencephaly, corpus callosum agenesis, and atrophy of frontal lobes were observed. On the other hand, the gyral patterns were decreased, and gray-white matter could not easily be differentiated. All of the findings were compatible with alobar holoprosencephaly. In addition, our patient exhibited nasal and premaxillar agenesis. Nasal agenesis is a rare anomaly, with only a few cases reported in the literature[11,12].

Clinically, apneic episodes, convulsions, motor and mental retardation, anosmia, spasticity, hemispheric asynchrony and spikes in the electroencephalogram are most commonly seen in this anomaly[2]. Most of the patients die in infancy[2,6]. In our patient, apneic episodes were explained not only by cerebral anomalies but also by lung anomaly and bronchopneumonia due to cleft lip and palate.

Holoprosencephaly is a heterogenous condition, and the cause is unknown in most cases[2,6,7]. Holoprosencephalic malformations have been produced ex-

perimentally with vitamin D, vinblastine, alcohol and Veratrum Californicum[1,2,7]. Barr et al[13] reported that holoprosencephaly is increased in children of diabetic mothers.

Although holoprosencephaly is usually sporadic and familial autosomal dominant, autosomal recessive and X-linked transmission have also been reported[2,3,6,7,14-17]. On the other hand, numerous chromosomal abnormalities have been described in holoprosencephaly, especially, together with extracranial anomalies such as trisomy D, trisomy 18, Down's syndrome, 18 p^- syndrome, and 13 q syndrome[2,3,6,7,18,19]. Our case had extracranial anomalies and a normal karyogram. Holoprosencephaly has also been associated with other syndromes, such as DiGeorge syndrome, Meckel syndrome, and Kalman's syndrome[27].

Possible autosomal recessive-type holoprosencephaly was detected in our patient. For this reason, genetic counselling is important because of the 25% chance of anomaly in every pregnancy. Prenatal diagnosis can be done by ultrasonography. In Turkey, Balcı et al[20-22] reported cases with autosomal recessive cyclopia/holoprosencephaly anomaly who were diagnosed by ultrasonography at 18 weeks gestation.

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CONGENITAL ABSENCE OF THE PULMONARY VALVE ASSOCIATED WITH PULMONARY STENOSIS, LARGE DUCTUS ARTERIOSUS AND INTACT VENTRICULAR SEPTUM*

Case Report

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*Sema Özer MD*****, Arman Bilgiç MD******

SUMMARY: Yurdakul Y, Atasoy Ş, Sarıosmanoğlu N, Özer S, Bilgiç A. (Departments of Thoracic and Cardiovascular Surgery and Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Congenital absence of the pulmonary valve associated with pulmonary stenosis, large ductus arteriosus and intact ventricular septum. Case report. Turk J Pediatr 1994; 36: 163-169.

A six-day-old neonate was diagnosed with a severe form of the syndrome of absent pulmonary valve associated with pulmonary stenosis, aneurysmal dilatation of the pulmonary artery and rare findings including an intact ventricular septum and large ductus arteriosus. The patient underwent surgical repair by closed technique. Cardiac catheterization data, hemodynamic and clinical findings, and surgical technique are reported.

Congenital absence of the pulmonary valve is a rare cardiac anomaly. An especially severe form occurs with ventricular septal defect and pulmonary stenosis. The usual findings are respiratory distress, aneurysmal dilatation of the pulmonary arteries and pulmonary stenosis. *Key words: congenital absence of pulmonary valve, intact ventricular septum, closed surgical technique.*

Absent pulmonary valve is a rare congenital heart defect usually associated with ventricular septal defect, patent ductus arteriosus, endocardial cushion defect, double outlet right ventricle and Marfan's syndrome[1,2].

Pulmonary insufficiency and massive or aneurysmal dilatation leading to tracheobronchial tree compression are the common features of absent pulmonary valve syndrome[3-5].

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In infants and neonates, absent pulmonary valve syndrome is associated with severe respiratory problems, often due to tracheobronchial tree compression, and can cause respiratory and cardiac failure. Treatment of this syndrome can include medical and surgical approaches. Surgical treatment includes aneurysmorrhaphy, aneurysmectomy, division of right pulmonary artery and tubular graft reconnection with the main pulmonary artery or anastomosis with the superior vena cava[2]. In older patients, some physicians do not recommend pulmonary valve replacement[6], while others do recommend this procedure in order to prevent pulmonary regurgitation[7].

Case Report

A six-day-old male neonate weighing 3100 g was cyanotic, tachypneic and in moderate respiratory distress. Cardiac findings included increased right ventricle impulse, loud and single S_2, and grade 2-3/6 systolic and diastolic murmur at the left upper sternal border. Chest X-ray showed mild cardiomegaly.

Echocardiography showed no ventricular septal defect, dilated pulmonary arteries, a 20 mm diameter main pulmonary artery, stricture in pulmonary annulus and no pulmonary valve (Fig. 1-a).

Cardiac catheterization data revealed 63 mm Hg pressure in both the right and left ventricles, an intact ventricular septum, aneurysmal dilatation of the main pulmonary artery, and large ductus arteriosus (Fig. 2).

The infant underwent surgical repair on the sixth day of life. Using left posterolateral thoracotomy, we reached the pericardium. After opening the pericardium 1 cm above and parallel to the left phrenic nerve, we were faced with an aneurysmal, dilated, main pulmonary artery. We proceeded by placing double oval shaped purse sutures on the main pulmonary artery. After pulmonary arteriotomy using a straight clamp, we enlarged the pulmonary annulus in two steps, so as to allow pulmonary flow and minimize bleeding. Then, we resected the pulmonary artery aneurysm using a partial occluding vascular clamp, and the arteriotomy was sutured. Patent ductus arteriosus was ligated (Figs. 3-4).

On the sixth postoperative day, the main pulmonary artery measured 9 mm in diameter by echocardiograpy (Fig. 1-b).

The patient remained symptom-free during a one-year postoperative follow-up period, and normal-sized pulmonary arteries were seen on chest X-ray (Fig. 5) and echocardiography (Fig. 1-c).

Discussion

Since Cheever's report in 1847, 306 cases of congenital absence of the pulmonary valve have been reported. Most of the patients had a ventricular septal

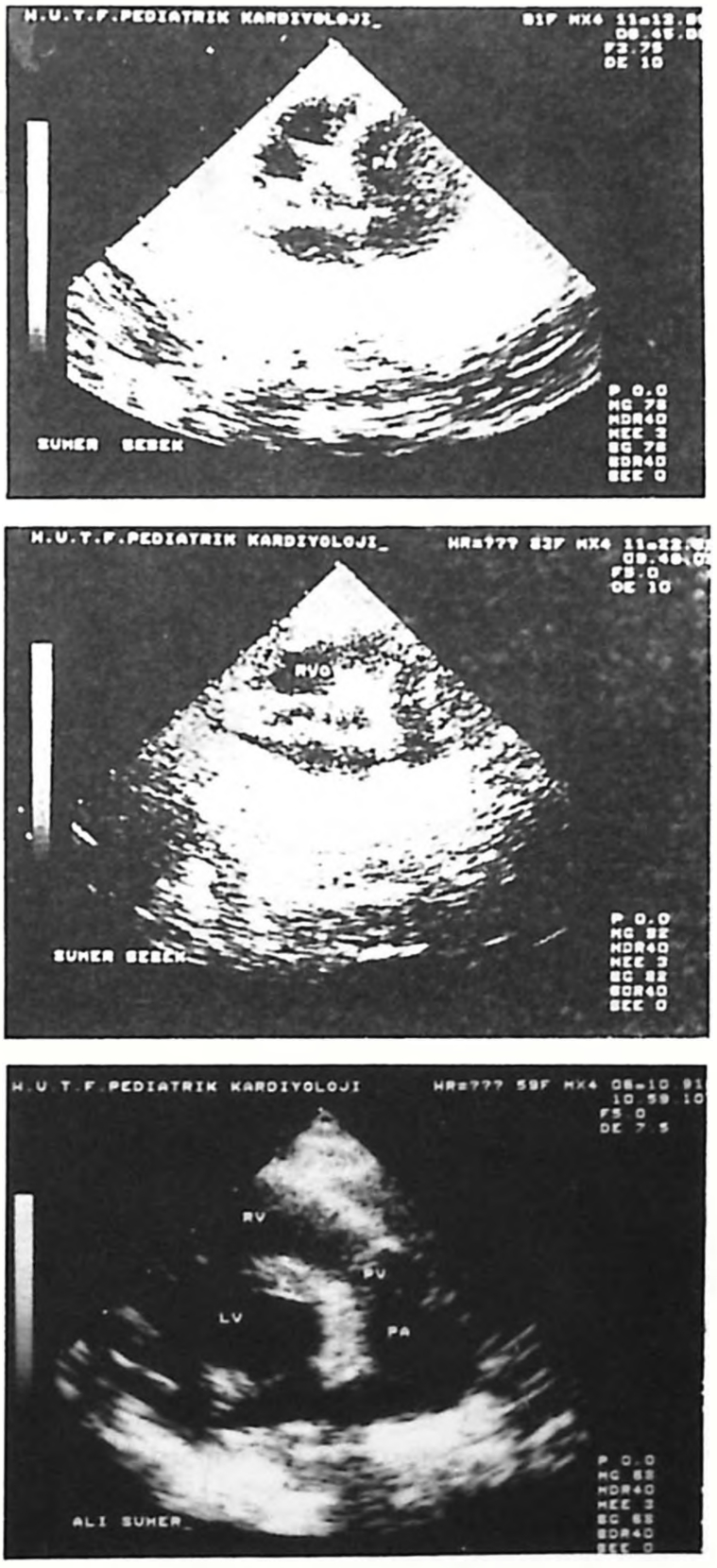

Fig. 1: Two-dimensional echocardiography (a) preoperatively showing no pulmonary valves and 20 mm main pulmonary artery, and (b) post-operatively on the sixth day showing the pulmonary artery 9 mm in diameter, and (c) after one year of follow-up showing normal pulmonary artery. (AO: Aorta, PA: Pulmonary artery, RV: Right ventricle, LV: Left ventricle, RVOT: Right ventricular outflow tract PV: Pulmonary valve annulus).

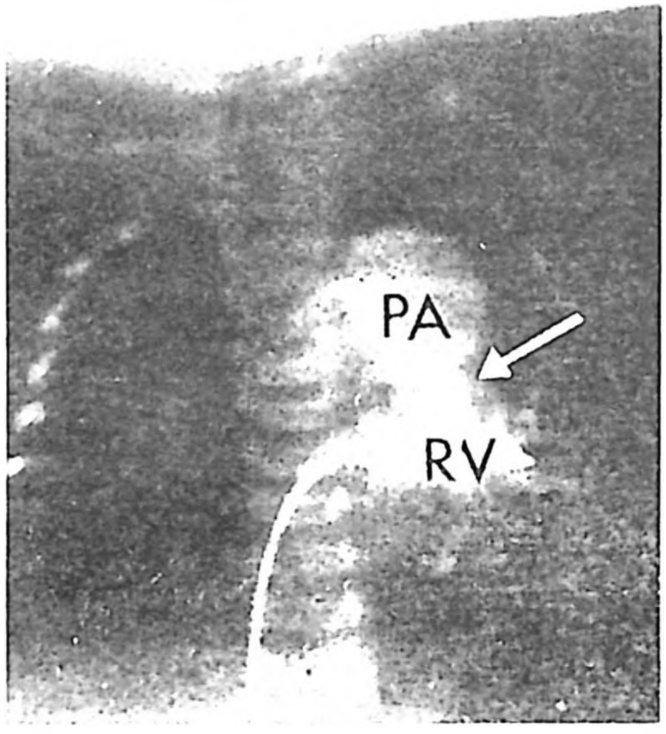

Fig. 2: Antero-posterior view of selective right ventriculogram showing aneurysmal dilatation of the main pulmonary artery. PA: Pulmonary artery, RV: Right ventricle.

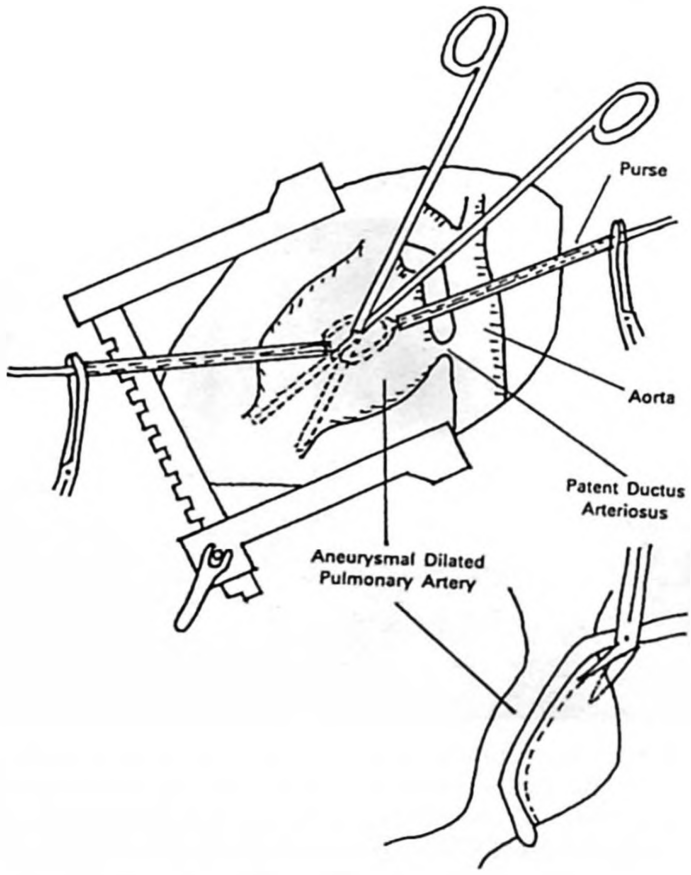

Fig. 3: Illustration of dilatation of the pulmonary annulus and resection of aneurysm.

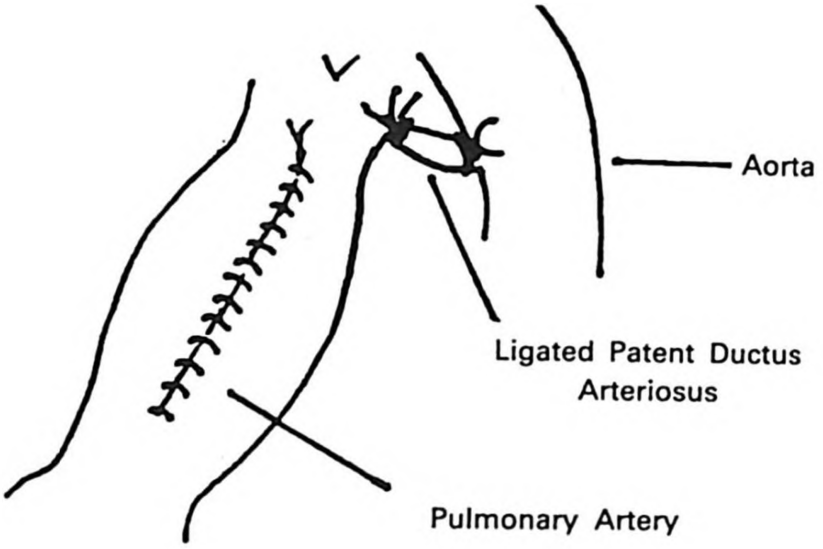

Fig. 4: Illustration showing the last image at the end of surgery.

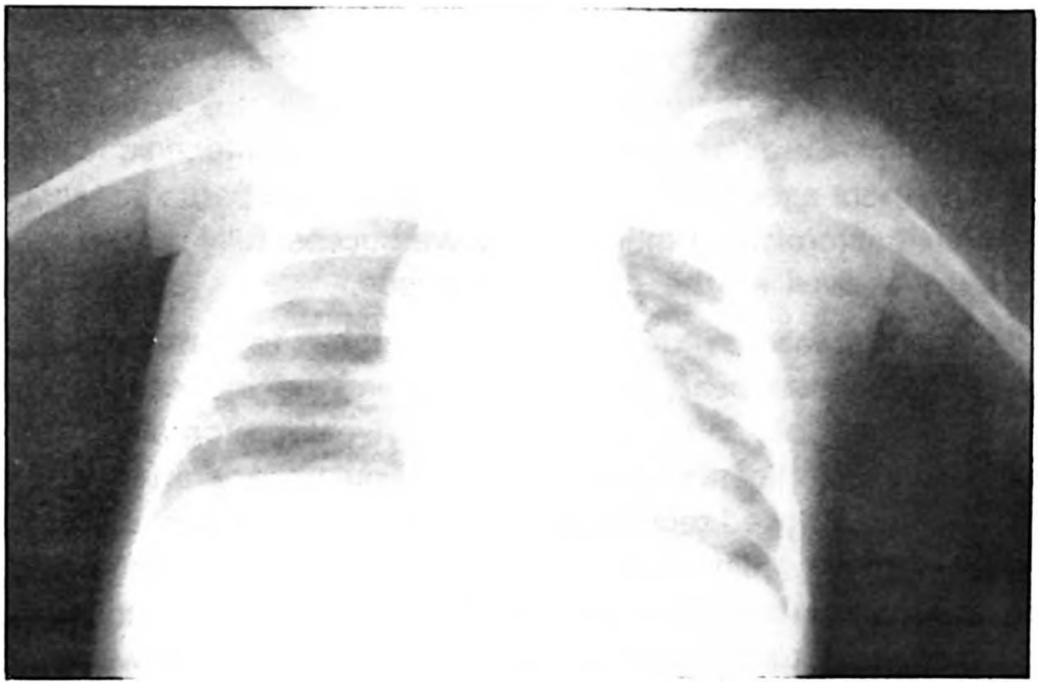

Fig. 5: Postero-anterior chest X-ray showing the normal-sized pulmonary artery.

defect, pulmonary stenosis and aneurysmal dilated pulmonary arteries. The occurrence of an intact ventricular septum with an absent pulmonary valve is very rare[1].

When the pulmonary valve is absent, severe problems arise soon after birth. Tracheobronchial compression resulting in atelectasis and obstructive emphysema cause severe respiratory distress[1].

There are several causes of aneurysmal dilatation of the pulmonary arteries, the most important of which are pulmonary stenosis and pulmonary insufficiency.

Pulmonary insufficiency increases the right ventricular stroke volume which, coupled with pulmonary stenosis results in pulmonary dilatation[3,5]. However, if the degree of stenosis is too severe, blood flow cannot produce pulmonary dilatation[8].

Patients born with absent pulmonary valves can be divided into two groups: patients in group I present with severe cardiorespiratory distress in infancy, while patients in group II display mild symptoms in infancy[3]. Our patient was in the first group.

The most important aspects of surgical management are: (1) reducing the pulmonary artery aneurysmal dilatation, (2) relieving pulmonary stenosis, and (3) performing intracardiac repair if any intracardiac anomaly is present[3,6].

A surgical approach can involve open or closed heart surgery. In open heart surgery, total correction can be achieved, while in closed technique a palliation can usually be done (e.g., pulmonary artery binding, or Blalock-Taussig shunt) depending on the cardiac anomaly.

In our case a closed technique was chosen because of the absence of intracardiac anomaly other than pulmonary stenosis and patent ductus arteriosus. In open heart surgery, a midline sternotomy is not so effective a technique for reaching the pulmonary artery aneurysmal dilatation to perform a partial resection. In this case, using left posterolateral thoracotomy we successfully reached the pulmonary aneurysm as well as the ductus arteriosus.

In absent pulmonary valve syndrome, the surgeon has to think carefully whether or not to perform open heart surgery to correct the intracardiac anomaly, if present, whether to use aortic valve homograft or heterograft to prevent the pulmonary artery insufficency and secondary pulmonary artery dilatation, or whether to employ a closed technique according to the present cardiac anomaly. Reports showed that a satisfactory result can be obtained by using an aortic valve homograft or heterograft in older patients[5-7]. A palliative operation can be used with infants to facilitate the normal development of their airways.

In case the reported patient may face residual pulmonary stenosis in the future, but we believe that elective total repair of pulmonary stenosis and insufficiency later will result in a lower risk of mortality[4].

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A CASE OF COMMON TRUNCUS ARTERIOSUS WITH RARE CARDIAC ABNORMALITIES*

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SUMMARY: Ören H, Özkan H, Ören B, Küpelioğlu A, Çevik N. (Departments of Pediatrics and Pathology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). A case of common truncus arteriosus with rare cardiac abnormalities. Turk J Pediatr 1994; 36: 171-174.

Truncus arteriosus communis is a well-known, congenital, cardiac abnormality. In this report, we describe a very rare variant in which the truncus arose from the right ventricle, the atrial and ventricular septa were intact, the left ventricle was hypoplastic and the small right atrium was draining to the truncus arteriosus through a fibrose tunnel-like connection. *Key words: common truncus arteriosus, congenital heart disease, hypoplastic left ventricle.*

Truncus arteriosus communis is defined as a congenital cardiovascular malformation in which one major artery arises from the base of the heart and gives origin to the coronary, pulmonary and systemic arteries[1,2],

In this report, we present a very unusual variant in which the truncus arteriosus arose from the right ventricle, the ventricular and atrial septa were intact, the left ventricle was hypoplastic, and the small left atrium was draining to the truncus arteriosus through a fibrose tunnel-like connection.

Case Report

A three-day-old white male was seen in the emergency clinic for severe cyanosis and respiratory failure. He had a history of mild cyanotic episodes which disappeared spontaneously in a short time. He went into cardiopulmonary arrest immediately after admission to the clinic. He did not respond to cardiopulmonary resuscitation. The electrocardiogram displayed the full pattern of asystoli. No further laboratory investigations, such as chest X-ray, echocardiogram or hemodynamic studies, were performed, as the patient dead on admission.

At necropsy the systemic and pulmonary venous connections were seen to be normal. There was a common arterial trunk, guarded by a three-leaflet common

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valve which originated solely in the right ventricle. The trunk gave rise to the ascending aorta and, in its posterior aspect, to both pulmonary artery branches and a stenotic arterial duct continuous with the left-sided descending aorta. Two coronary arteries were present, arising from the anterior sinuses. The left atrium was small and the left ventricle was diminutive and poorly developed (Fig. 1). The mitral valve was also rudimentary. The enlarged right atrium was connected to a dominant hypertrophied right ventricle (Fig. 2). The tricuspid valve was dysplastic.

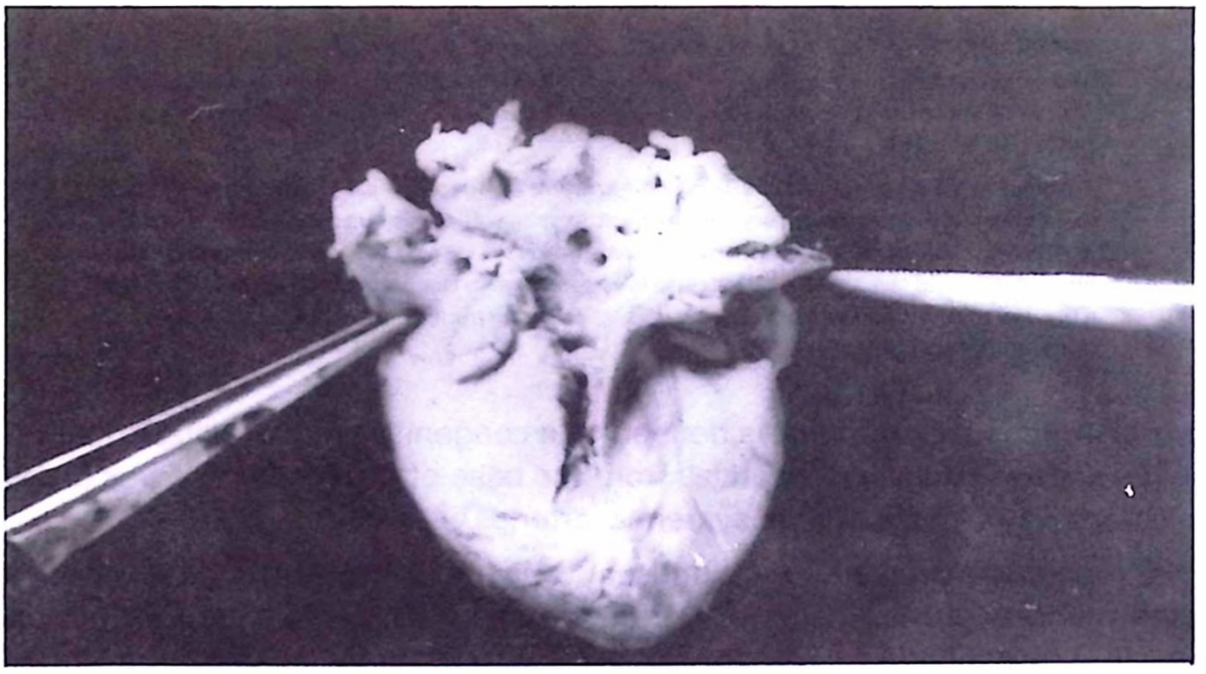

Fig. 1: The general appearance of the heart and hypoplastic left ventricle.

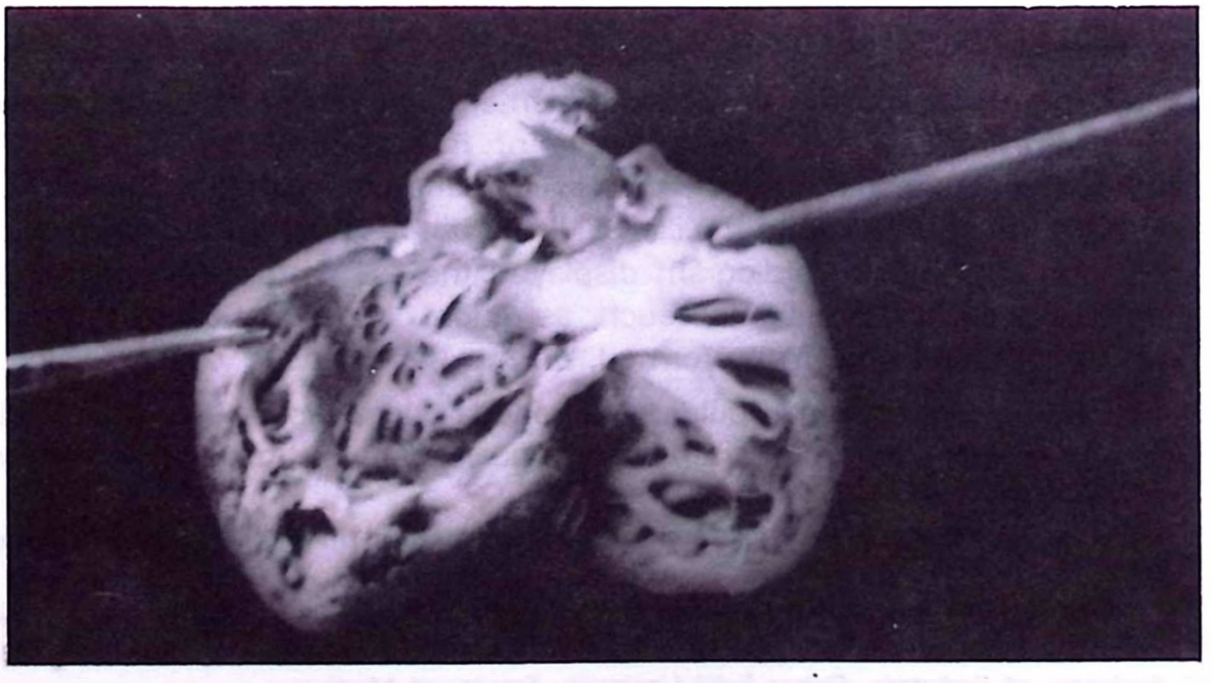

Fig. 2: The enlarged right atrium and the hypertrophied right ventricle.

The atrial and ventricular septa were intact; the small left atrium was draining into the truncus arteriosus at the level of the ascending aorta where the pulmonary arteries left the truncus through an exterior fibrose tunnel-like connection from the postero-inferior wall of the left atrium (Fig. 3).

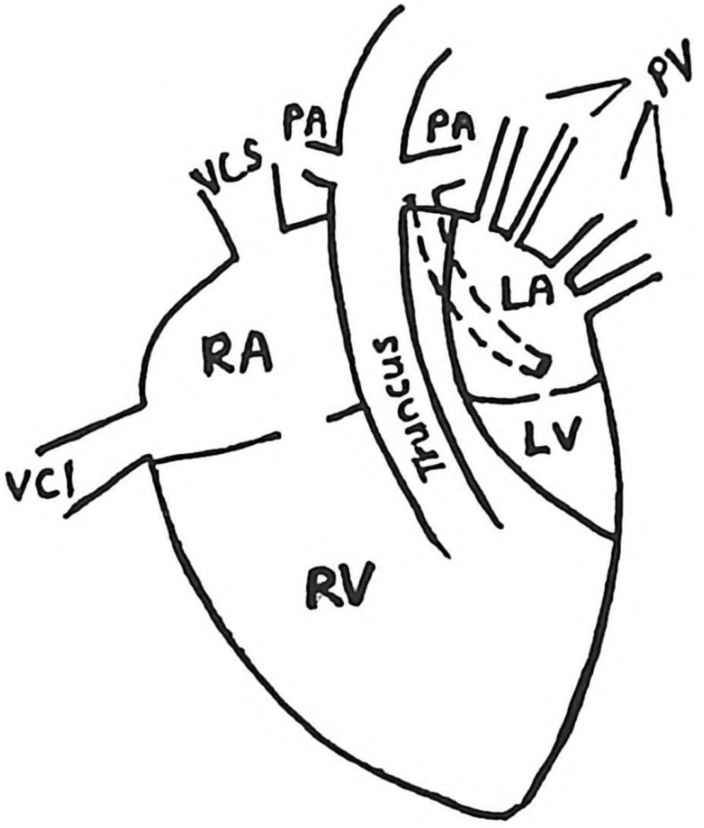

Fig. 3: Demonstration of fibrose tunnel-like connection draining left atrium to the truncus.

Discussion

Truncus arteriosus communis is a rare congenital abnormality, accounting for approximately 1-3% of the largest pathological series of all congenital heart defects and usually accompanied by other intracardiac malformations[3,4]. In our case, truncus arteriosus communis occurred together with hypoplastic left ventricle, intact ventricular and atrial septa, and the left atrium draining to the truncus through a fibrose tunnel-like connection.

No similar case presentation was found, even in the largest series recently reported[2,5,6], endorsing the rarity of this cardiac abnormality. A case of a common arterial trunk arising from the right ventricle with hypoplastic left ventricle, intact ventricular septum and absent left atrioventricular connection was reported by Alves et al in 1987[3], but in their case, there was an atrial septal defect. In our case the atrial septum was also intact and the small left atrium draining into the truncus arteriosus through an exterior fibrose tunnel-like connection was extraordinary. The case is presented because of its unusual nature.

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AN UNUSUAL ASSOCIATION: FIBROEPITHELIAL POLYP AND CONTRALATERAL NEPHROLITHIASIS IN A CHILD*

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SUMMARY: Kızılcan F, Şenocak ME, Göğüş S, Hiçsönmez A. (Departments of Pediatric Surgery and Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). An unusual association: fibroepithelial polyp and contralateral nephrolithiasis in a child. Turk J Pediatr 1994; 36: 175-177.

A 12-year-old boy presented with fever and flank pain bilaterally. Intravenous pyelogram revealed multiple stones and hydronephrosis in the right kidney and an obstructive filling defect at the left upper ureter. Exploration of the left ureter revealed a fibroepithelial polyp. The presented case was an example of the unreported association between fibroepithelial polyp and contralateral nephrolithiasis. *Key words: ureter, fibroepithelial polyp, nephrolithiasis.*

Fibroepithelial polyp of the ureter is very uncommon in children, with fewer than twenty cases reported in the literature to date[1]. The association between ureteric polyp and ipsilateral nephrolithiasis has been reported[2], but as far as we know the occurrence of the polyp with contralateral nephrolithiasis has not. The presented case is an example of this unusual occurrence.

Case Report

A twelve-year-old boy was admitted to the hospital with fever and bilateral flank pain of two weeks duration. Medical history revealed right pyelolithotomy which had been performed elsewhere six years prior to admission. The family history was negative with respect to urolithiasis.

On physical examination, it was found that the patient had a fever of 39°C and bilateral costovertebral angle tenderness with otherwise normal findings. Urinalysis showed abundant white blood cells per high power field. An intravenous pyelogram revealed multiple stones and hydronephrosis in the right kidney as well as an obstructive filling defect at the left upper ureter (Fig. 1). The latter could not be demonstrated ultrasonographically.

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In surgery, the left upper ureter was opened, revealing a polyp with dimensions of 0.5 x 1.5 cm and numerous finger-like projections. After excision of the polyp, end-to-end ureteroureterostomy was performed. Removal of the stones from the right kidney was postponed. The postoperative course was uneventful. The histopathological examination revealed that it was a fibroepithelial polyp (Fig. 2).

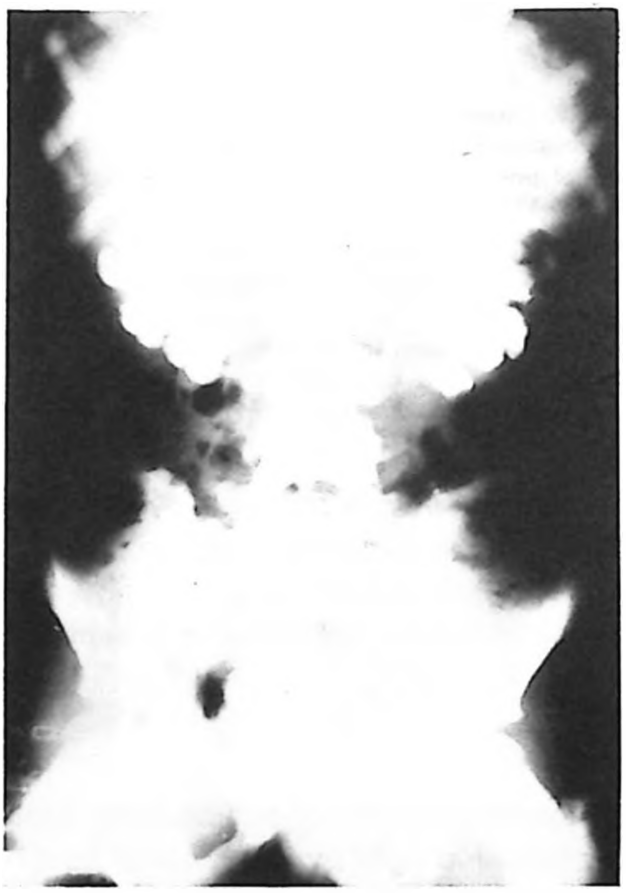

Fig. 1: Intravenous pyelogram showing obstructive filling defect in the left ureter and contralateral nephrolithiasis associated with bilateral hydronephrosis.

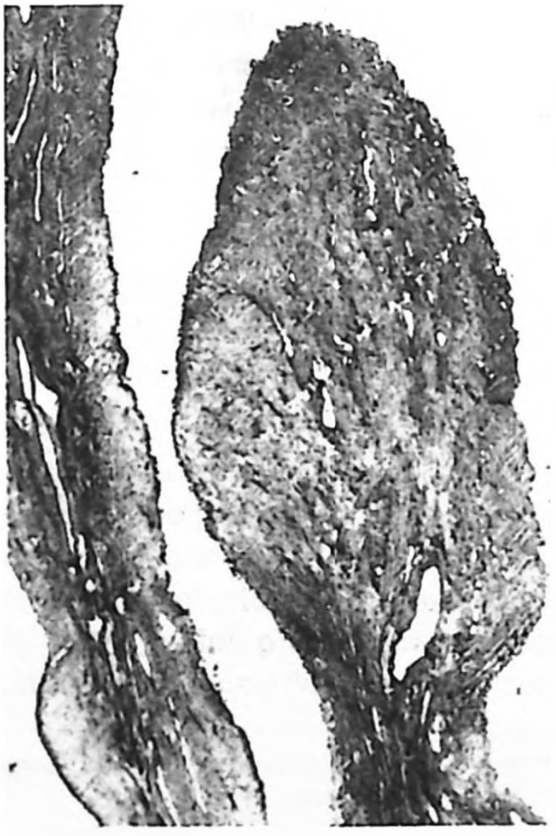

Fig. 2: Microscopic section of the ureteric polyp, made of fibrous stroma, covered by normal transitional epithelium (H + E, x 30).

Discussion

Patients with fibroepithelial polyps usually present with hematuria or flank pain and sometimes urinary tract infection[3]. The intravenous pyelogram usually reveals an intraluminal, non-opaque, smooth, space-occupying lesion, with a lack of severe upper urinary tract obstruction[1]. There is preferential involvement of the left ureter, usually in its upper third and at the ureteropelvic junction[4].

The differential diagnosis of hematuria and a ureteral filling defect includes ureteral tumors, opaque and non-opaque stones, thrombus and inflammatory lesions. It is difficult to establish a diagnosis of ureteral polyp preoperatively despite preoperative evaluation. A long history of non-specific loin pain, with or without hematuria, accompanied by an intraluminal filling defect detected by intravenous pyelogram is suggestive of a ureteral polyp. However, a stone is the most probable cause of ureteral obstruction, and the possibility of a polyp is seldom considered in the patient with contralateral nephrolithiasis.

An association between fibroepithelial polyp of the ureter and ipsilateral nephrolithiasis is the usual finding[2]. Therefore obstruction, infection and chronic irritation have been proposed as the etiologic factors of the fibroepithelial polyp[4,5]. Alternatively, fibroepithelial polyp may be the cause of urinary stasis and infection resulting in nephrolithiasis. In contrast, an association between ureteral polyp and contralateral nephrolithiasis has not been reported in the literature. This unusual association may be a coincidental finding in this patient, or ipsilateral small stones may have been passed silently and undetected previously.

Fibroepithelial polyp of the ureter presents a diagnostic challenge because of its rarity. The difficulty in diagnosis increases further when the polyp is associated with ipsilateral or contralateral nephrolithiasis. Therefore, fibroepithelial polyp should be considered as a possible diagnosis in all cases of upper ureteral obstructions.

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ANNOUNCEMENTS

MEETINGS

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PHENYLKETONURIA: PAST, PRESENT, FUTURE

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İSTANBUL, 19 - 25 JUNE 1994

IXth TURKISH ANTIBIOTICS AND CHEMOTHERAPY CONGRESS

Inquiries to : Prof. Dr. Yavuz Bozfakıoğlu
İstanbul University
Faculty of Medicine
Department of General Surgery
34390 Çapa - İstanbul
TURKEY

AMSTERDAM, 25 - 28 SEPTEMBER 1994

XXVIIIth ANNUAL SYMPOSIUM OF THE EUROPEAN SOCIETY FOR PAEDIATRIC NEPHROLOGY

Inquiries to : XXVIIIth Annual Meeting of the
European Society for Paediatric Nephrology
c/o: Conference Management
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3437 RP Nieuwegein
NETHERLANDS

SHATIN, NEW TERRITORIES, 11 - 14 NOVEMBER 1994

III[rd] COMMONWEALTH CONFERENCE ON DIARRHOEA AND MALNUTRITION

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Organizing Secretary
Department of Paediatrics
Prince of Wales Hospital
Shatin, New Territories
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