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From the Editor

Dear Readers,

As we have the honor of completing the 35th year of our Journal, which has been published since 1958, we would like to inform you that some changes have been made in the administration and the Editorial Board of the Journal. We, the new editors, would like to thank the previous editors, associate editors and editorial board members for bringing the Journal to the level of entering the international index.

We do not plan to make major changes in the Journal's editorial policies, However, more space will be allocated for educational articles, the topics and authors of which will be identified by our editors. Furthermore, a new section called "Letter to the Editor" will be established, with the aim of assuring that readers' views can reach you.

One of our goals is to give feedback in a timely manner to authors who submit articles for publication. We will try to reply within two months of receiving all articles. In order to publish all qualified articles in the order they are received, before the data therein become outdated, it is possible that our Journal will be published more frequently. Also, authors whose articles are published most will be awarded.

We are beginning our new positions, given to us by the Council of the Hacettepe University Child Health Institute, we remind you that we are always awaiting your contributions, ideas and recommendations. We thank you in advance for your cooperation.

Editor and Associate Editors

The Turkish Journal of Pediatrics 35: 245-247, 1993

ETHICS IN PEDIATRIC RESEARCH*

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Ethics, a vital component of medical practice ever since Hippocrates drafted his code almost 2500 years ago, has become a particularly crucial issue because of the great strides in medical science and technology that have been witnessed during our century – as research became an important component of our work.

In the case of adults, the consent of the patient is required whenever research is undertaken. But what makes moral dilemmas particularly difficult in the pediatric setting is the child's inability to weigh the options and risks often connected with medical matters, and to make free and informed decisions. Thus, the awesome responsibility for what are sometimes irrevocable decisions must be shifted onto others. Decisions of such magnitude are always painful, but when they must be made on someone else's behalf, they can be excruciating. Consider, for example, life-prolonging measures. An adult can decide for himself to discontinue such measures if the pain and discomfort are such that his life becomes meaningless. But how do you decide for someone else? And what about organ transplants? What happens when a child's very life depends on receiving the kidney of a sibling too young to provide "informed" consent?

İt is this issue of "informed" consent that makes research using children as subjects fraught with ethical problems. No one questions the benefits of such research on medical grounds. We are all well familiar with the immense successes of medical research – virtual eradication of smallpox in our world; elimination for all practical purposes in the industrialized countries of tetanus, diphtheria, poliomyelitis, measles, and infantile gastroenteritis, leading causes of child mortality and morbidity; the discovery of a simple and effective (though unfortunately inadequately implemented) treatment for diarrhea – still the foremost cause of death among children in the developing world.

Research has led to significant progress in treating certain forms of cancer as well as leukemia and osteosarcoma. In Wilms's tumor, the survival rate has been pushed from zero to about 90 percent over the past half century.

We also know that the use of adult subjects in research on diseases of children is inappropriate, as data obtained on adults cannot be extrapolated to children because of important pharmacologic differences in absorption, distribution, and

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metabolism, essential differences in fluid and electrolyte requirements, and because the factor of growth and development is vulnerable to toxic action. Attempts to modify adult dosages to suit children based on body weight and surface area are not always effective and have sometimes proved fatal.

But even if gains from a *medical* standpoint are indisputable, is it *ethical* to use uncomprehending young children – children incompetent to consent – in research that may conceivably put them at risk? Do parents have the right to enlist their child in an activity, no matter how praiseworthy, that may jeopardize him? Does this not constitute a *breach* of parental duty to protect? How can we reconcile the seeming contradiction of medical research's duty to vanquish disease on the one hand, with the moral imperative to protect to the utmost each individual child patient on the other? Stated differently, how can we reconcile the potential future good for many against a possible risk for a few?

Before proceeding further, let us distinguish between therapeutic reseach (undertaken in the course of treatment for the direct benefit of the subject) and non-therapeutic research (where benefits, if any, are long-term and would accrue to others). In the first case, greater risk may be justified by the potential benefit, particularly when all other treatment possibilities have been exhausted. There is broad consensus concerning the moral validity of this research, despite the absence of "informed" consent. It is the second case that raises the ethical questions, and it is this case that shall engage our attention.

It is in the nature of ethics to stretch hypothetical situations to their outer limits, to pose alternatives as starkly as possible, in order to highlight the dilemmas and the awesome dimensions of the choices. But, in fact, non-therapeutic research covers a wide range of situations – from research on children with debilitating or fatal diseases who are themselves beyond cure, to the collection of baseline data on normal, healthy children. Much of non-therapeutic research is of a decidedly prosaic nature, involving simple procedures such as physical examinations, minor changes in diet, the recording of infant weights and measurements, monitoring feeding practices, non-invasive sample collections such as urine, feces, saliva.

Invasive sample collection, including blood, cerebrospinal fluid, biopsy tissue, is of course more problematical, although it seems to me that there is little legitimate cause for objecting to taking quantities slightly larger than required in routine procedures, or to taking samples during surgery, provided the research being undertaken aims at advancing the diagnosis or treatment of childhood diseases.

The point is that in assessing the ethical validity of non-therapeutic reseach, it is very important to have a very good idea of what the risks involved may be. Thre is always at least a hypothetical risk factor in research. The goal is to assess it as realistically as possible, and to weigh it against possible gains.

In this regard, I think we can dismiss arguments of so-called purists who consider unethical all research using children as subjects on the grounds that it violates their autonomy or integrity. Such an attitude, it seems to me, is absolutely self-defeating, indirectly penalizing the very children it claims to protect. Elimination of non-therapeutic research would make it impossible to control clinical testing of new procedures and drugs, which could actually harm children, by leading to the introduction of untested substances. The thalidomide tragedy, and the blinding of infants through excessive oxygen administration, are just two examples of disasters that could have been minimized by controlled clinical research. Further, the prohibition of research using child subjects would remove all hope for overcoming cancer, leukemia, and other diseases that continue to prey upon children.

For research using children as subjects, the standard practice is to recognize the right of the parent or guardian to decide on behalf of the child. Yet there are cases of abuse, and the parents may not fully comprehend the risks involved in the research. This is why the child's consent, wherever feasible, is increasingly becoming an essential requirement. In this regard, it seems absurd to lump together into one category all those who are legally classified as "children". Many of those who are children in the eyes of the law are by no means incompetent to consent.

For research involving infants and very young children, parental consent would be acceptable only after it had been established with reasonable certainty that the parent was responsible and fully committed to the child's well-being. The project and all attendant risks would have to be fully explained in laymen's terms to the parent by the research team.

For research projects involving those children who have reached an age at which they could reasonably be expected to make decisions, informed parental consent must be supplemented by the child's own consent, with the age at which this is possible varying with the individual child. It should be emphasized that consent does not mean seeking "rubber-stamp approval. "The researchers must explain fully, in terms appropriate to the subject's age, the reason for the research, its importance, and the procedures involved, inluding all possible discomforts and risks. If the child objects, his or her decision would be absolutely final.

These are some reflections on the topic of ethics in research on children. In many cases, a well-balanced ethics committee in a hospital has to make the final decision, especially in cases where the research procedures are invasive and not directly aimed at improving the child's own health.

The Turkish Journal of Pediatrics 35: 249-256, 1993

THE ASSOCIATION BETWEEN HENOCH – SCHÖNLEIN SYNDROME AND RENAL AMYLOIDOSIS: A PROPOSAL OF A PATHOGENIC MECHANISM*

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SUMMARY: Tınaztepe K, Güçer Ş, Bakkaloğlu A, Tınaztepe B. (Nephropathology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The association between Henoch-Schönlein syndrome and renal amyloidosis: a proposal of a pathogenic mechanism. Turk J Pediatr 1993; 35: 249-256.

The clinicopathological analysis of 250 pediatric cases that had been tissue-diagnosed with renal amyloidosis revealed three patients associated with Henoch-Schönlein syndrome (HSS). The renal biopsies revealed AA-type amyloidosis in all three cases. Case 2 displayed focal and segmental proliferative glomerulonephritis in the same renal biopsy. No evidence of well-known diseases and / or conditions for the development of AA-type amyloidosis except for familial Mediterranean fever (FMF) existed in these particular cases. On the other hand, the frequency of the association between FMF and HSS has been reported extensively in the literature; thus, common etiological factors can be considered. The mechanism involved in amyloid deposition in these cases may be related to HSS-associated chronic antigenemia and / or FMF through a mechanism that is, to date, unknown. Further studies are needed to clarify this causal relationship. *Key words: Henoch-Schönlein purpura, renal amyloidosis, familial Mediterranean fever, childhood.*

Amyloidosis refers to a group of diseases characterized by an accumulation of an extracellular eosinophilic and hyaline subtance in various organs[1]. Though it is a relatively rare disease, renal involvement is frequent and is the major cause of death[1]. Cases of childhood amyloidosis are usually secondary to chronic inflammatory and infective disorders and familial conditions, many of which have been extensively studied[2,3]. On the other hand, there also reports of diseases rarely associated with amyloidosis which should be investigated[4-6]. In the majority of these diseases, chronic antigenic stimulation is most likely one of the causative factors in the complex pathogenesis of AA-type amyloidosis.

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The aim of this study is to present three cases with Henoch-Schönlein syndrome (HSS) and renal amyloidosis determined from investigated cases of tissue-diagnosed renal amyloidosis and biopsy-proven Henoch-Schönlein nephritis, and to discuss possible mechanisms and the relationship involved in the amyloidogenesis of this association.

Material and Methods

Three patients were found to have Henoch-Schönlein syndrome and renal amyloidosis during the analysis of 250 tissue-diagnosed renal amyloidosis and 38 biopsy-proven Henoch-Schönlein syndrome pediatric cases between 1966 and 1992 in the Pathology Department of Hacettepe Children's Hospital. Clinical charts and all pathological materials were used in the diagnostic evaluation. The diagnosis of HSS was based on the presence of at least two of the four criteria recommended by the American College of Rheumatology[7] :

1) Palpable purpura.
2) Age below 20 years at onset.
3) Abdominal pain (bowel angina).
4) Microvasculitis with granulocytic infiltration in the biopsy.

Renal biopsies from all three patients, were available while in Case 2, liver and lesional skin biopsies were also available. For light microscopic examination, renal tissue sections were stained with hematoxylin and eosin (HE), periodic acid Schiff (PAS), Jones' silver, Masson's trichrome, trichrome light green and Congo-red stains. The presence of amyloid was confirmed in Congo-red stained sections by demonstration of apple-green birefringence under polarized light. In all cases, AA-type amyloidosis was confirmed by potassium permanganate reaction[8].

The clinical signs and some pertinent laboratory findings of these three cases are presented in Table I.

Case 1

A 12-year-old girl was admitted to the hospital with the complaints of swelling of the hands, feet and eyelids. Four years earlier, she was diagnosed with HSS; she presented then with abdominal pain and skin lesions which were interpreted as palpable purpura as she began to experience intermittent episodes of fever, arthralgia and swelling of the joints. During the last eight months, she developed edema of the eyelids and feet.

Physical examination revealed blood pressure of 120 / 90 mmHg and pitting edema in both legs. The liver was palpated 2 cm and the spleen 1 cm below the costal margin.

Laboratory examination revealed a hemoglobin of 9.2 g / dl, white blood cell count 12,200 / mm^3, erythrocyte sedimentation rate (ESR) 140 mm / h total serum

Table I: Pertinent Clinical and Laboratory Data of Three Patients with Henoch-Schönlein Syndrome and Renal Amyloidosis

	CASES		
	1	2	3
Age (year) / sex	12, Female	11, Male	16, Male
Edema	+	+	+
Abdominal pain	+	+	++
Palpable purpura	+ (past history)	+ (on admission)	+ (past history)
Arthralgia	+	+	+
Hepatomegaly	+	+	–
Splenomegaly	+	+	–
Hematuria	–	–	+
Hypertension	–	–	+
ESR (mm / hour)	140	110	54
Hemoglobin (g / dl)	9.6	8.6	15
White blood cell count (per mm^3)	12000	8000	13600
BUN (mg / dl)	46	12	10
Creatinine (mg / dl)	–	0.6	0.8
Total protein (g / dl)	4.1	4.4	5.2
Albumin (g / dl)	2.0	2.3	1.6
Cholesterol (mg / dl)	236	280	134
Creatinine clearance (ml / min / 1.73 m^2)	–	46	91
Urinary loss of protein (g / 24 hours)	–	4.9	3.5
Renal biopsy	Amyloidosis AA-type	Amyloidosis AA-type and FSPGN*	Amyloidosis AA-type
Liver biopsy	–	Amyloidosis AA-type	–
Skin biopsy	–	LCV**	–

* FSPGN: Focal and segmental proliferative glomerulonephritis.
** LCV : Leukocytoclastic vasculitis.

proteins 4.1 g / dl, serum albumin 2.0 g / dl, cholesterol 236 mg / dl, and blood urea nitrogen (BUN) 46 mg / dl. Urinalysis showed proteinuria but no glucose. The urinary sediment contained 2-3 leukocytes as well as hyaline and granular casts. A diagnosis of amyloidosis was established by renal biopsy.

Case 2

An 11-year-old boy was admitted to the hospital for evaluation of joint pain, purpuric lesions in the gluteal areas and on the limbs, and edema of the feet. He had a six-year history of transient attacks of pain involving the ankles, knees and hips. During the ten days, before hospital admission, he began to experience painful swelling of the wrists, ankles and knees, and developed a purpuric rash in the gluteal areas and on the limbs.

Physical examination revealed a blood pressure of 100 / 70 mmHg. Painful pitting edema was noted in the fingers, wrists, ankles and knees. Palpable purpura was present on both legs and in the gluteal areas. The liver was palpable 4 cm and the spleen 2 cm below the costal margin.

Laboratory examination revealed a hemoglobin of 8.6 g / dl, white blood cell count 8000 / mm^3, ESR 110 mm / h total serum proteins 4.4 g / dl, serum albumin 2.1 g / dl, cholesterol 280 mg / dl, total lipids 1120 mg / dl, BUN 12 mg / dl, creatinine 0.6 mg / dl, and creatinine clearance 46 ml / min / 1.73 m^2. Tests for HBsAg, antinuclear antibody and rheumatoid factors were all negative. Urinalysis showed proteinuria, a specific gravity of 1020, hyaline and granular casts, and fat bodies in the sediment.

Lesional skin biopsy revealed the characteristic appearance of leukocytoclastic vasculitis (LCV). Liver biopsy showed fatty changes with AA-type amyloid deposition on the vascular walls. The kidney biopsy revealed AA-type renal amyloidosis and additional focal segmental proliferative glomerulonephritis. Colchicine therapy at a dose of 0.25 mg / day was initiated, and the patient was discharged on the 36th day of hospitalization. Five months later, he was still on colchicine with pretibial pitting edema and persistent proteinuria. One year after discharge, he died at home.

Case 3

A 16-year-old boy was referred to the hospital because of left knee pain, edema of the feet, and proteinuria. A diagnosis of HSS had been established ten years prior to hospital admission, at which time the patient had presented with abdominal pain, palpable purpura and arthralgia. He was followed up at regular intervals. Three days prior to this hospital admission, the patient developed pain in his left knee and slight swelling of the feet. Physical examination was unremarkable except for pitting edema at the ankles. His blood pressure was 110 / 70 mmHg on admission.

Laboratory examination revealed a hemoglobin of 16 g / dl, white blood cell count 9400 / mm^3, ESR 77 mm / h total serum proteins 5.2 g / dl, serum albumin 1.6 g / dl, BUN 10 mg / dl, creatinine 0.6 mg / dl, cholesterol 224 mg / dl, total lipids 458 mg / dl, and creatinine clearance 91 ml / min / 1.73 m^2. Urinalysis showed proteinuria with 3-4 leukocytes and 1-2 erythrocytes per high-power field.

On the second day of admission, a renal biopsy was performed to determine the cause of the proteinuria, and a diagnosis of renal amyloidosis was established. The patient was discharged on the tenth day of hospitalization and colchicine therapy was started. In the third year of follow-up, the child was noted to be hypertensive and was treated medically. Ten years later, he was in good health and had nearly normal renal function.

Renal Biopsy Findings

On light microscopic examination, Case 2 revealed a segmental deposition of amyloid in the glomeruli, while diffuse amyloid depositions of the glomeruli were present in Case 1 and 3. AA-type amyloidosis was demonstrated in all cases with potassium permanganate reaction. Additionally, in Case 2 the glomeruli displayed varying degrees of focal and segmental mesangial cell proliferation. Between these proliferative changes, small masses of amyloid deposits in the mesangial areas were easily recognized (Fig. 1).

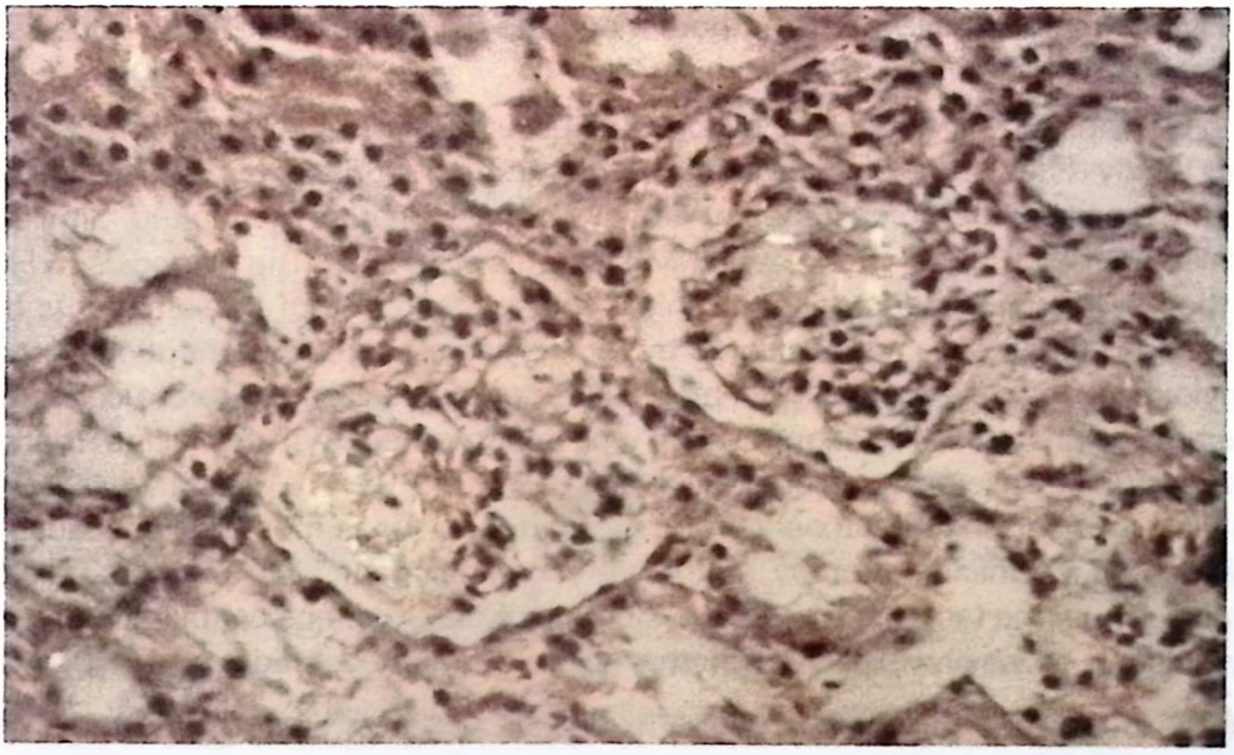

Fig. 1: Spicule-type minute masses of amyloid depositions showing apple-green birefringence and varying degrees of mesangial proliferation are seen in the glomeruli under partially polarized light (Congo-red stain, x 250).

Discussion

Henoch-Schönlein syndrome (HSS) is a type of microvasculitis which mainly involves the skin, gastrointestinal tract and kidneys[9]. Although it can occur in adults, it is a common childhood disease[10]. Renal involvement is the most serious complication and varies from minimal glomerular involvement to focal and diffuse proliferative glomerulonephritis[11]. On the other hand, renal amyloidosis is a rare disease in childhood and is associated mostly with juvenile rheumatoid arthritis, chronic infections and familial Mediterranean fever (FMF)[3,12-14].

In our earlier study of a pediatric series of 174 cases with renal amyloidosis, we found that FMF was the primary disease in the majority of cases (48%), and a minority of cases had juvenile rheumatoid arthritis (6.9%) and chronic suppurative infections (2.8%). In 32 percent of the cases, the underlying disease as a cause of AA-type renal amyloidosis was not clearly demonstrated[14]. However, in the latter cases it was concluded that phenotype II FMF may have been an underlying disease. Overall in 80 percent of the above-mentioned series, FMF may have been the main cause of renal amyloidosis.

Recently, several isolated cases of diseases demonstrated to be associated with renal amyloidosis have been reported[4,6]. On the other hand, until now an association between HSS and biopsy-proven renal amyloidosis has not been presented in the literature, though the association of Henoch-Schönlein syndrome and FMF has been reported[15-17]. Flatau et al[16], described eight cases of FMF with severe HSS. The authors made the diagnosis of HSS on the basis of clinical findings.

Skin biopsies of four patients and kidney biopsies of two patients were available in their study. Focal mesangial proliferative glomerulonephritis was seen in the two kidney biopsies, but no evidence of amyloid deposition was mentioned. Similarly, Schlesinger et al[17], reported seven FMF patients with HSS. The diagnosis of HSS in their series was based only on clinical findings, and one of these patients had proteinuria which was not evaluated by renal biopsy. There is no mention of renal amyloidosis in these studies or in previous reports, possibly due to the colchicine therapy given to FMF patients. It is well-documented that colchicine therapy prevents the development of amyloidosis[18]. If FMF is the causative factor in amyloidogenesis in HSS, absence of amyloid deposition is most likely because of the use of colchicine therapy at the very beginning of FMF patients' clinical course. Thus, the fact that there is no mention of the presence or absence of renal amyloidosis is easily explained in the above-mentioned studies.

Furthermore, in large series, renal amyloidosis has never been reported to be associated with HSS[19,20]. A pathogenic mechanism, chronic antigenemia involving immune complexes such as IgA, viral, bacterial and food antigens, as well as drug-related immune complexes, can play a role in triggering the

development of renal amyloidosis as it does in Henoch-Schönlein nephritis[9,11]. However, many types of chronic antigenemias are apparently not strong enough to cause amyloidosis, as there have been no reports of amyloidosis associated with HSS.

Kidney biopsy of Case 2 of our study showed focal and segmental endocapillary proliferative changes in the glomeruli, which is an unusual finding in renal amyloidosis[1]. The glomerular changes we observed were caused by both amyloidosis and Henoch-Schönlein nephritis. On the other hand, some of the overlapping findings of HS purpura and FMF appeared to be unrelated to FMF in Cases 1 and 3, since there was no clinical and familial history of FMF. The development of renal amyloidosis in these patients could be related to phenotype II FMF, because the patients exhibited no clinical findings of FMF. Thus, amyloidosis represents the initial feature of this disease. It is also possible that if chronic antigenemia, which is present in HSS, is a causative predisposing factor in the development of renal amyloidosis, it could be an accelerating and / or summation factor in amyloidogenesis in type-II FMF patients who are naturally prone to developing renal amyloidosis.

In conclusion, our cases presented the association of HSS with FMF-related renal amyloidosis. To our knowledge, these are the first cases of biopsy-proven renal amyloidosis associated with HSS to be reported in the literature. To enlighten these speculations, further studies on a molecular basis could provide the primary field of research.

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The Turkish Journal of Pediatrics 35: 257-265, 1993

THE FREQUENCY OF MULTIPLE BIRTHS IN CENTRAL ANATOLIA*

*İzzet Duyar***, *Nilüfer Güntay - Ayaz****

SUMMARY: Duyar İ, Güntay - Ayaz N. (Department of Physical Anthropology, Ankara University Faculty of Language and History-Geography, and the Ministry of Environment, Ankara, Turkey). The frequency of multiple births in central Anatolia. Turk J Pediatr 1993; 35: 257-265.

The purposes of the present study were to contribute additional data regarding the frequency of multiple births in Ankara, and to reassess both the relation between maternal age and twinning, and the inter-relation between twinning and seasonality. The frequency of twinning was found to be 0.0084858 ± 0.00028 (0.85%), triplets 0.0001087 ± 0.000031 (0.011%), and quadruplets 0.000009 (0.0009%). It is observed that there is a correlation between the frequency of twinning, maternal age and parity, and that the rate of twinning increases with maternal age. The twinning rate varies according to the month of the year in which birth takes place. Accordingly, the frequency of twin births is greater between May and August, and lower between September and December. *Key words: multiple births, frequency, Ankara.*

In Turkey, research on multiple birth frequency began with Tunakan's two studies[1,2], in which we see that only the incidence of twinning was examined. Later, Atabey and Gizer[3], Önder[4], Çanga and Yavuz[5], and Bilgin and Yılmaz[6] studied the influence of maternal age and parity on twinning, in addition to its frequency. Research separating dizygotic (DZ) and monozygotic (MZ) twinning was done by Topçuoğlu and Serim[7], Kişnişçi and Ayhan[8], and Say et al[9]. In Say et al's study, DZ and MZ rates were determined with the help of blood group, placentas, chorions and amnions. In former research, it was not stated how the DZ and MZ rates were ascertained. Finally, a common and important aspect of the above-mentioned studies is that they were done only in one health center.

The main purpose of this study was to determine the frequency of multiple births in Ankara. Also, we examined the relationship betwen twin births and maternal age, parity and seasonality.

Material and Methods

The data for the study was obtained from five state and three maternity hospitals in Ankara and mostly dated back to 1987 and 1988 (Table I). In these health

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Table I: Multiple Births From Hospitals

Hospitals	Period	Number of Pregnancy	Twins n	Twins (%)	Triplets n	Triplets (%)	Quadruplets n	Quadruplets (%)
Gülhane	1970 - 88*	23905	223	0.93	2	0.008	–	–
Numune	1984 - 88	2915	43	1.47	2	0.07	–	–
Zübeyde Hanım Maternity	1986 - 89**	33364	278	0.83	2	0.006	–	–
SSK Ulucanlar Maternity	1987 - 89**	23462	118	0.50	–	–	–	–
Ankara	1987 - 88	2933	28	0.95	1	0.03	–	–
Gazi University	1987 - 88	1164	21	1.80	–	–	–	–
Dr. Z.T. Burak Maternity	1988	21370	217	1.01	5	0.02	1	0.005
Ankara University	1988	1306	9	0.69	–	–	–	–
		110419	937	0.85	12	0.011	1	0.0009

* The data for 1984 cannot be obtained.
** The first three months of 1989 is included.

institutions, 110,419 deliveries were studied with respect to multiple births. As for geographical distribution, 60.94% of the twin births were delivered by mothers born in Central Anatolia. If we consider the province of Çorum, from which migration to Ankara is still quite intensive, this ratio increases to 66.7%.

In this study, to determine the rate of DZ and MZ, the mathematical formula of Gittelson and Milham developed in 1964 was used[10]:

$$\hat{\theta} = \frac{2\underline{b}}{1 - (\underline{a} - \underline{c})^2}$$

According to this formula, $\hat{\theta}$ is DZ, $\underline{a}$ male-male twins, $\underline{b}$ male-female twins, and $\underline{c}$ female-female twins. Rate of MZ is derived from the formula:

$$MZ = 1 - DZ.$$

Results and Discussion

1. Twin Births

Of 110,419 pregnancies, 937 resulted in twins. According to this figure, the frequency of twin births is 00084858 ± 0.0028. In other words, the percentage of twinning is 0.85%. Among studied twins, the probability of DZ is 0.6368, and MZ probability is 0.3632. As for total births in the sample, the ratio of DZ is 0.54%, while MZ is 0.31%. Only one *conjoined twin* was found among the 937 twin births. The distribution of twinning according to health institutions is given in Table I.

The results of twin research already done in Turkey is shown in Table II. If we consider the frequency of twinning in general, the value we found is the lowest ratio except in the study of Atabey and Gizer[3]. However, discordant values are

Table II: The Data of Monozygotic (MZ) and Dizygotic (DZ) Twinning Frequencies in Turkey

Region	Period	n	Twins (%)	DZ	MZ	Researcher
Marmara	1945 - 56	26174	1.27	–	–	Tunakan 1959
Marmara	1955 - 65	21241	1.74	1.45	0.29	Topçuoğlu and Serim 1967
Marmara	1957 - 65	47509	0.74	0.53	0.21	Atabey and Gizer 1965
Central Anatolia	1952 - 54	17460	1.35	–	–	Tunakan 1955
Central Anatolia	1947 - 62	9802	1.35*	1.03	0.32	Çanga and Yavuz 1967
Central Anatolia	1956 - 65	8592	1.21*	0.97	0.24	Önder 1966
Central Anatolia	1965 - 66	10000	1.49	–	–	Say et al. 1967
Central Anatolia	1971 - 75	7617	1.21	0.85	0.36	Kişnişçi and Ayhan
Aegean	1975 - 85	35964	0.98	–	–	Bilgin and Yavuz 1985

* Rates of DZ and MZ were calculated by the authors.

seen among the results of these studies. It can be said that MZ twinning, in general, is clustered about 0.30, however, DZ twinning rates vary widely.

When the results from other populations are compared to our results (Table III), the values for India and Spain are approximately the same as ours. As we can see in Table III, the highest value of twinning and the highest ratio of DZ is found among people of African descent. The lowest twinning rate was found in Japan[11], where the DZ rate is lower than in the other populations, but the MZ rate is higher. Imaizumi and Inouye[12] pointed out that this phenomenon is peculiar to the Japanese.

1.1. *The Correlation Between Maternal Age and Twinning* : The distribution of 937 twin births according to maternal age is given in Table IV and Figure 1. From mothers between the ages of 20 and 29 delivered 69.16% of twins. It is observed

Fig. 1: Twinning rates according to maternal age.

Table III: The Rate of Twinning in Various Populations*

Country	Period	Twins (%)	DZ	MZ
Romania	1936 - 38	1.56	–	–
Turkey	1965 - 66	1.49	–	–
Denmark	1946 - 55	1.42	–	–
Germany	1950 - 55	1.24	0.91	0.33
Italy	1949 - 55	1.23	0.86	0.37
Norway	1946 - 54	1.21	0.83	0.38
Belgium	1960 - 61	1.20	0.78	0.42
Sweden	1946 - 55	1.17	0.86	0.32
Switzerland	1943 - 48	1.17	0.81	0.36
USA (Whites)	1922 - 36	1.13	0.74	0.39
USA (Whites)	1922 - 30	1.13	–	–
Austria	1952 - 56	1.09	0.75	0.34
Belgium	1950	1.09	0.75	0.34
France	1946 - 51	1.08	0.71	0.37
Spain	1951 - 53	0.91	0.59	0.32
Nigeria	–	4.49	3.99	0.50
South Africa	–	2.72	2.23	0.49
USA (Blacks)	1922 - 54	1.36	0.98	0.38
China	1950 - 53	1.085	0.42	0.67
India	1950 - 53	0.86	0.52	0.34
Japan	1926 - 31	0.71	0.27	0.43

* Source: Susanne and Corbisier 1967.

Table IV: The Distribution of Twinning According to Maternal Age

Age Groups	Twins	(%)	Percentage of DZ in Each Age Group
x - 20	76	8.11	0.48
20 - 24	282	30.10	0.64
25 - 29	366	39.06	0.65
30 - 34	152	16.22	0.68
35 - 39	50	5.34	0.76
40 - x	11	1.17	0.18
Total	937	100.00	

that the frequency of twin-bearing mothers increases until age 30, and rapidly decreases after this age. It is important to note that the frequency of birth overall also decreases to a great extent in mothers older than 30. In the study of Topçuoğlu and Serim[7], the rate of twin pregnancy reached its highest point in the 25-30 year age range. Atabey and Gizer[3], who used ten-year interval grouping, stated that a large proportion of twinning occurred in women between the ages of 26 and 35. If we examine the subject with respect to DZ twinning, the rate increases until the age of 40, and after this age it decreases sharply (Fig. 2). The reason for the increase in the rate of DZ with age is not clearly understood, but a possible reason may be the stimulation of FSH (follicle stimulating hormone) from the pituitary gland in aging females[13,14].

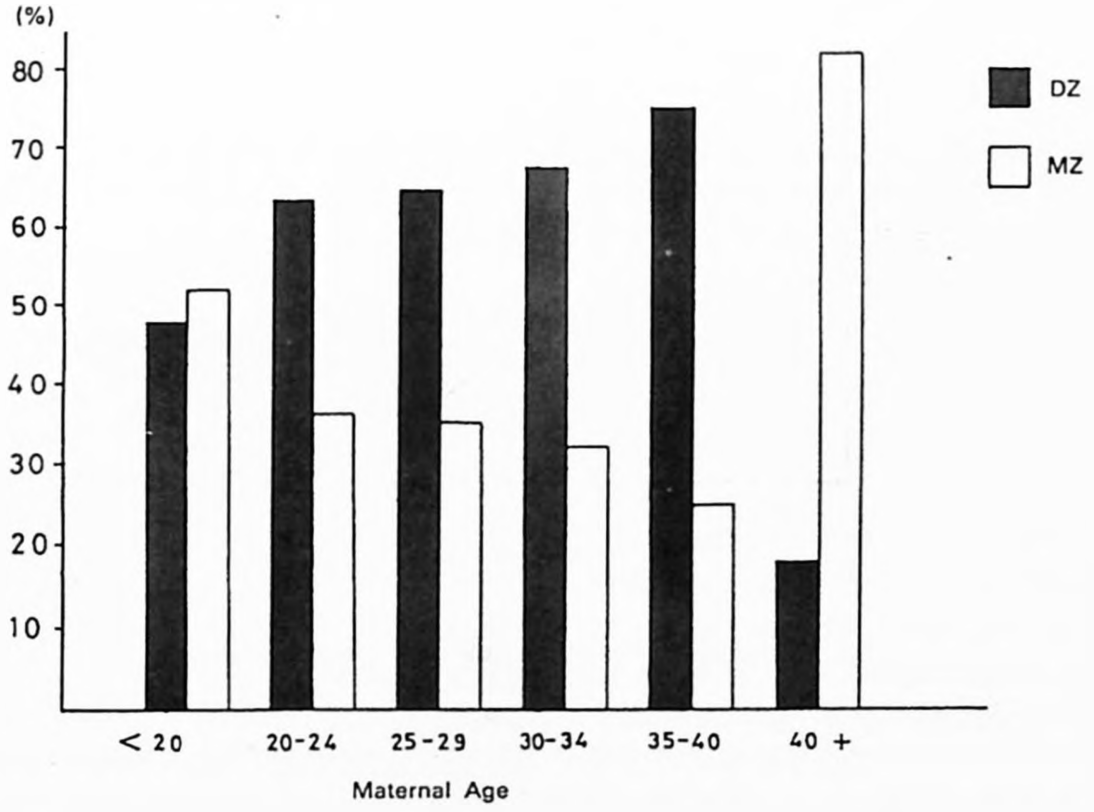

Fig. 2: The rates of DZ and MZ twinning in each maternal age groups.

1.2. *Maternal Parity and Twinning* : Some researchers have pointed out that there is a relation between twinning and parity[10,14,15]. In our study we were able to collect the data on this subject only from Gülhane and Numune hospitals, where 26.3% of 226 studied twin mothers were primiparous but 73.7% were multiparous (Fig. 3). The results of various research on maternal parity are summarized in Table V. Excluding the study of Önder[4], the values are similar. If we consider this table, we can see that the probability of twin pregnancy is higher in multiparous females, and peaks in the third pregnancy.

Table V: The Results on Maternal Parity in The Research in Turkey

Researcher	Primiparous	(%)	Multiparous	(%)
Atabey and Gizer 1965	104	29.9	244	70.1
Topçuoğlu and Serim 1966	94	25.4	277	74.6
Önder 1966	46	43.8	59	56.2
Çanga and Yavuz 1967	30	28.4	104	77.6

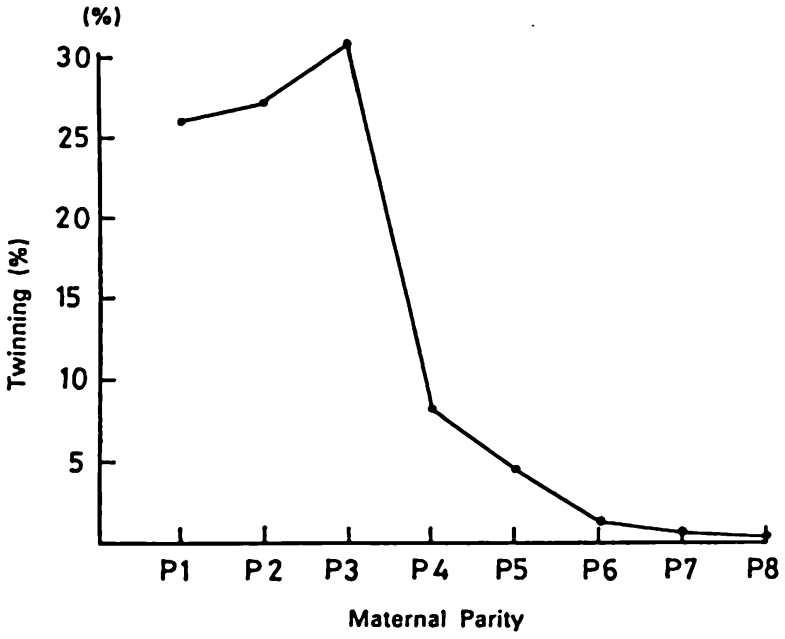

Fig. 3: Twinning rates according to maternal parity.

1.3. *The distribution of twinning according to birth months* : Some researchers suggest that there is a relation between change of season and twinning[14]. According to these researchers, exposure to continuous sunlight (for six months), e.g. in Finland, causes multiple ovulation. Regarding the distribution of twinning according to months (Fig. 4), it is observed that the ratio increases between May and August, and decreases to the lowest level between September and December. There is a discrepancy between the months in which twinning occurs most frequently and the months in which deliveries are most frequent.

According to the results of "1966-1967 Demographic Survey"[16], in urban areas the occurrence of births is at its lowest level between May and July. However, it reaches its highest level between February and April. James[17] has reported a similar situation: In England, deliveries occur frequently in March, while twin births peak in October.

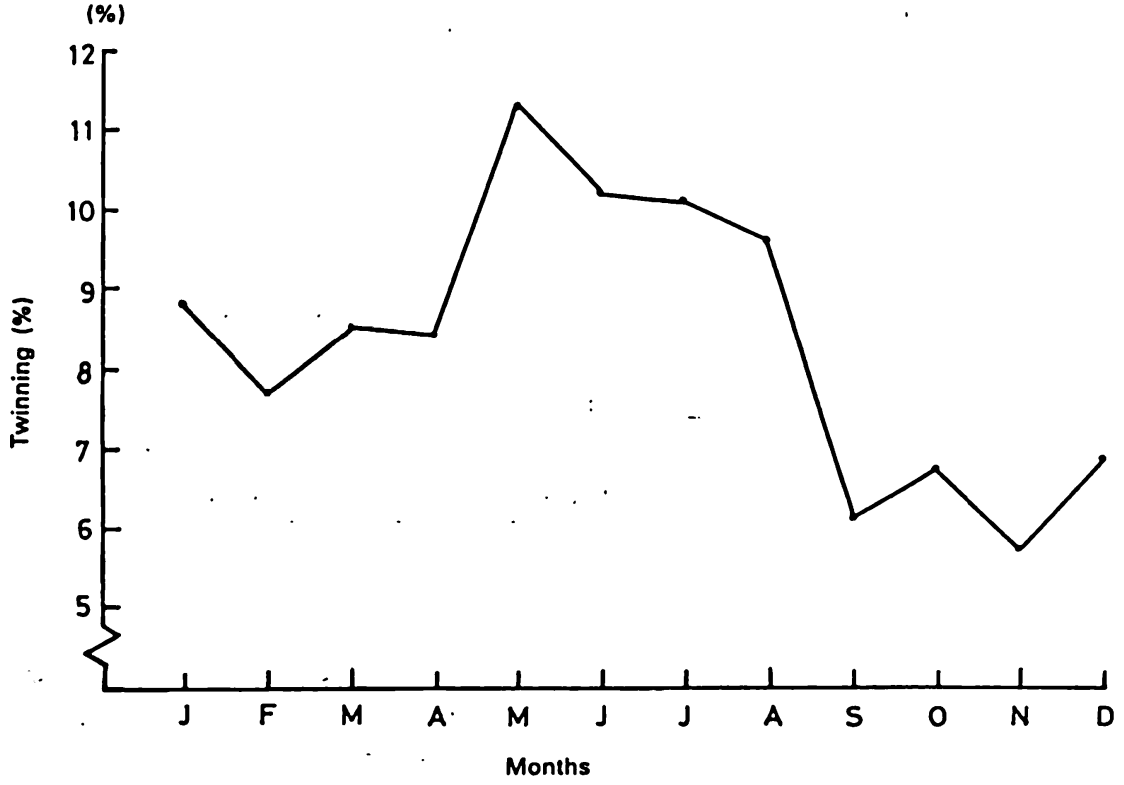

Fig. 4: Seasonal trends in twin births.

2. Triplets and Quadruplets

Taple I displays the frequency of triplet and quadruplet births in the present study. The frequency of triplets was 0.0001087 ± 0.000031 (0.011%) and the frequency of quadruplets was 0.000009 (0.0009%). In other words, one out of 2901 pregnancies resulted in triplets, and one out of 110,419 pregnancies yielded quadruplets. If we compare our figures with Hellin's rule*, we may observe that our triplets were rarer, and quadruplets were more frequent.

Among the studies on the frequency of triplets in Turkey, our results have values similar to Topçuoğlu and Serim[7] and Önder[4], as shown in Table VI.

If we consider the number of pregnancies and triplets together with the data of previous researchers and recalculate the frequency of triplets, the resulting rate is

$$(50 / 323{,}203) = 0.0001547.$$

* According to this rule, one of every 80 births is twin; if the frequency of twin pregnancy is shown as $\underline{a}$, triplets $1 / a^2$, quadruplets $1 / a^3$, quintuplets $1 / a^4$ and so on.

Table VI: The Data From Research on Triplets in Turkey

Region	Pregnancies	Triplets	(%)	Researcher
Marmara	26460	10	0.038	Tanakan 1959
Marmara	47509	8	0.017	Atabey and Gizer 1965
Marmara	21241	2	0.009	Topçuoğlu and Serim 1966
Central Anatolia	17460	5	0.029	Tunakan 1955
Central Anatolia	8592	1	0.012	Önder 1966
Central Anatolia	9802	2	0.020	Çanga and Yavuz 1967
Central Anatolia	7617	3	0.039	Kişnişçi and Ayhan 1977
Aegean	35964	7	0.019	Bilgin and Yılmaz 1985

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The Turkish Journal of Pediatrics 35: 267-270, 1993

IS L – CARNITINE PROTECTIVE IN HYPOXIC CEREBRAL EDEMA IN NEWBORN MICE?*

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SUMMARY: Yurdakök M, Hazıroğlu R, Coşkun T. (Department of Pediatrics, Hacettepe University Faculty of Medicine, and Department of Pathology, Ankara University Faculty of Veterinary Medicine, Ankara, Turkey). Is carnitine protective in hypoxic cerebral edema in newborn mice? Turk J Pediatr 1993; 35: 267-270.

The value of carnitine in the prevention of cerebral edema due to acute severe hypoxia in 38 newborn mice was studied. Twenty-nine animals received normal saline (0.25 ml) or carnitine (16 mmol / kg) intraperitoneally, thirty minutes before exposure to 0% oxygen in inspired air for two minutes. Nine mice received no drug and were exposed to room air. After hypoxic insult, brain water content was measured and was found to be similar in all groups. These findings suggest that carnitine pretreatment does not prevent brain edema associated with cerebral hypoxia in newborn mice. *Key words: carnitine, hypoxia, cerebral edema, mice.*

L-carnitine is necessary for the transformation of acyl-compounds (free long-chain fatty acids) to acyl-carnitines, and for their transport from the cytosol into the mitochondrial matrix. Beta-oxidation of these compounds precedes their entry into the Krebs cycle, where energy production occurs[1]. When beta-oxidation is impaired in various conditions including cellular hypoxic-ischemic damage, L-carnitine may relieve the pathological acumulation of acyl-CoA esters by extracting the acyl-compounds from coenzyme A. Excess acyl-carnitine esters may then be transported out of the mitochondrion and the cell, and excreted in the urine as acyl-carnitine esters. This peculiar detoxifying activity of L-carnitine may cause a relative deficiency of carnitine in cells. In the absence of L-carnitine, the accumulation of free fatty acids in the cytoplasm produces a toxic effect on the cell, and an energy deficit arises from the unavailability of fatty acids within the mitochondria[2].

Asphyxia represents a major cause of brain injury in the newborn. In the premature infant, asphyxia is often complicated by cerebral hemorrhage and death, but neonatal death or later neurological disability is also seen in the term infant[3]. Studies have shown that hypoxic brain injury is seen in nearly all infants dying within the first days of life[4].

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Fatty acid oxidation is virtually non-existent in the adult brain, but it can be detected in the fetal and neonatal brain where it supplies 25% of the metabolites required in the Krebs cycle. Since fatty acid oxidation and ketogenesis are critical steps for neonatal survival and development, an adequate supply of carnitine at this stage of life is essential[5].

The present study was carried out to assess the value of carnitine in the prevention of cerebral edema due to acute severe hypoxia in newborn mice, although reduced carnitine or increased acyl-Coa levels has not been reported in hypoxic cerebral damage.

Material and Methods

The maturation level of a newborn mouse's brain is similar to that of a newborn infant's brain at 36 weeks gestation. One-day-old newborn mice (n = 38) weighing 25.4 ± 3.9 g (mean ± SD) were therefore studied. Throughout the study, the animals were kept in three plastic chambers with an air temperature of 37 °C.

The animals were randomly divided into three groups. Nine mice were separated as the control group, received no drug and were exposed to room air. Twenty-nine animals in the study group received either normal saline or carnitine intraperitoneally (i.p.) prior to hypoxia. Fourteen mice were injected (i.p.) with 0.25 ml of saline (injectable form, pH 7.0). Fifteen mice in the study group were injected (i.p.) with 16 mmol / kg of carnitine as a 20% (wt / vol) solution in water. L-carnitine (injectable form, pH 7.0) was purchased from Sigma Co. Thirty minutes after the injections, all animals in the study group were exposed to hypoxia for two minutes. Hypoxia was established with 0% oxygen in inspired air by substituting O_2 with N_2.

After hypoxic insult, all animals were sacrified by cervical dislocation. The brains (including brainstem and cerebellum) were quickly dissected and placed in pre-weighed 5 ml glass vials and weighed on a microanalytical balance. Subsequently, the tissue specimens were desiccated at + 70 °C for 48 hours. Vials were re-weighed to ascertain the brain dry weight (DW), and by subtraction from the total brain weight (TW), the wet weight of the tissue was obtained. Brain water content (BWC) was determined as a percentage of total brain weight according to the following formula:

$$\text{Water content } (\%) = [(TW - DW) / TW] \times 100$$

Values were expressed as means ± SD. Differences were analyzed by Student's *t* test and considered statistically significant when $p < 0.05$.

Results

Brain water contents of animals are displayed in Table I. BWC was higher in hypoxic animals than in controls (86.60 ± 1.90% and 85.03 ± 1.58% respectively, $p < 0.02$). But in animals with pretreated carnitine before hypoxic insult, BWC was the same as in animals that did not receive any drug (86.49 ± 1.13% and 86.60 ± 1.90% respectively, $p > 0.05$). According to these findings, carnitine pretreatment does not prevent brain edema associated with cerebral hypoxia in newborn mice.

Table I: Effect of L-carnitine on Brain Water content (BWC) in Newborn Mice Challenged with Hypoxia

Group	Treatment	BWC (%)
Control	None (n = 9)	85.03 ± 1.58[a]
Hypoxic	Saline (n = 14)	86.60 ± 1.90[b]
Hypoxic	Carnitine (n = 15)	86.49 ± 1.13[c]

a vs b: $p < 0.02$, b vs c: $p > 0.05$, a vs c: $p < 0.05$

Discussion

Carnitine deficiency secondary to defects of intermediary metabolism, systemic disease, drug therapy or ischemia (especially of the heart and skeletal muscle) is common. Ischemia causes carnitine depletion in affected tissues and is particularly evident in heart and skeletal muscle, where energy production depends mainly on the utilization of fats and is therefore most likely to suffer from deficient mitochondrial transport of long-chain fatty acids. Although the plasma carnitine level may be in the normal range in the presence of severe tissue deficiency, increased acyl-carnitine in the urine is also an indication of possible tissue carnitine deficiency[6-8]. Abnormally high concentrations of acyl-Coa esters also occur in the myocardial cells during ischemia, the consequence of reduced fatty acid oxidation due to lack of oxygen. Myocardial fatty acid accumulation has been presented as a cause of both conduction disturbances and ventricular arrhythmias. The potential beneficial effects of L-carnitine therapy in these conditions have been demonstrated in careful experiments[2 6].

We made such an experimental study by giving L-carnitine in the prophylaxis of cerebral edema in newborn mice exposed to acute severe hypoxia. Although cerebral acyl-Coa and L-carnitine levels could not be determined in this study, our findings indicate that L-carnitine pretreatment was ineffective in protecting cerebral edema induced by hypoxia.

It has been reported that i.p.-administered L-carnitine accumulates preferentially in the brain[9]. Controversy exists as to regulation of the ability of L-carnitine to cross the blood-brain barrier. According to an earlier report, the passage of L-carnitine to the brain from blood in vivo is slow[10] indicating that L-carnitine may not cross the brain-blood barrier readily. Hearn et al[11] also reported that L-carnitine crosses the blood-brain barrier at a slow rate. So it is not clear whether the increase in L-carnitine content of brain observed in this study is sufficient to protect animals against cerebral edema due to hypoxia.

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TREATMENT OF CONSTITUTIONAL DELAYED PUBERTY WITH A COMBINATION OF TESTOSTERONE ESTERS*

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SUMMARY: Büyükgebiz A. (Division of Endocrinology, Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Treatment of constitutional delayed puberty with a combination of testosterone esters. Turk J Pediatr 1993; 35: 271-275.

Thirteen boys with constitutional delayed puberty (CDP) were treated with a combination of short and long-acting testosterone esters (testosterone propionate, testosterone phenylpropionate, testosterone isocaproate). Mean age at the onset of treatment was 14.9 ± 0.6 years and bone age delay was −2.7 ± 0.9 years. The dose of testosterone used was 200 mg intramuscularly four times at three week intervals, and the treated CDP boys were followed for two years. All the boys with CDP entered puberty after the last dose (testicular volume ≥ 4 ml), and growth rate increased from 4.5 ± 0.5 cm / year, pretreatment, to 8.4 ± 1.6 cm / year, posttreatment, at the two year follow-up. Height for bone age SD score did not change significantly from a mean of −1.1 before treatment to −1.3 after treatment, nor did predicted height before treatment (173.5 ± 6.6 cm) and after treatment (173.3 ± 4.9 cm). Combination of testosterone esters in a given dose and schedule is a safe and effective treatment for prepubertal boys with constitutional delayed puberty. *Key words: constitutional delayed puberty (CDP), testosterone treatment, predicted adult height.*

Constitutional delayed puberty (CDP) is the most common cause of short stature and delayed development in adolescent boys[1]. Boys with CDP have delayed sexual maturation and delayed skeletal bone ages, and are shorter than age-matched controls[1-3]. For psychological reasons, different drugs have been used for pubertal advancement and short-term growth increment in these adolescents with CDP[2-5]. One of drugs used widely for CDP is testosterone enanthate, a long-acting testosterone ester found to be effective and safe especially in small doses[5-7].

A combination of short-and long-acting testosterone esters (20 mg testosterone propionate, 40 mg testosterone phenylpropionate, 40 mg testosterone isocaproate in a 100 mg ampule) was used for our CDP patients, and they were longitudinally followed for two years in an attempt to investigate the physiological responses.

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Material and Methods

Thirteen boys between the ages of 14.2 and 15.4 were referred to our pediatric endocrinology clinic for evaluation of short stature or delayed puberty. They fulfilled the criteria for CDP (no endocrine or systemic disease, height below the 3rd percentile, testicular volume below 4 ml and showing symptoms of psychological disturbance). Two hundred mg of testosterone esters was administered intramuscularly four times at three week intervals, and the patients were then followed up for two years. Clinical data from 13 patients with CDP are shown in Table I. Statistical analyses were performed by *t* test for matched pairs and Wilcoxon signed ranked test where appropriate. P values less than 0.05 were accepted as statistically significant.

Growth was measured by using a Harpenden stadiometer, and bone age was measured by the method of Tanner et al[8]. Testicular volume was assessed by using a Prader orchidometer by the same observer, and predicted adult height was assessed by TW2 method[8,9].

Table I: Data For Subjects Treated with Testosterone

		Posttreatment	
	Pretreatment	3 months	2 Years
Chronological age (years)	14.9 ± 0.6		16.9 ± 0.6
Bone age delay (years)	−2.7 (−3.8 to 0.1)		
Height (cm)	147.6 ± 7.7	150.9 ± 8.8	164.4 ± 7.7
Growth rate (cm / year)	4.5 ± 0.5		8.4 ± 1.6
Predicted adult height (cm)	173.5 ± 6.6		173.3 ± 4.9
Height SDS for BA	−1.1(−2.7 to +1.5)		−1.3(−3.2 to +1.4)
Test. volume (ml)	3.2 ± 0.7	4.3 ± 0.4	11.3 ± 2.5
Pubic hair (Tanner stage)	1	2	4
CA / BA	1.24		1.18

SDS : Standard deviation score.
BA : Bone age.
CA : Chronological age.

Results

After three months of testosterone therapy, all thirteen CDP boys entered puberty (testicular volume 4.3 ± 0.4 ml and pubic hair stage 2) and no regression was detected at their two year follow-up (Fig. 1). Growth rate, which was 4.5 ± 0.5 cm / year, increased to 8.4 ± 1.6 cm / year after two years of follow-up in CDP boys ($p < 0.001$) (Fig. 2).

No significant difference was demonstrated in height SD score for bone age between pretreatment and posttreatment two years ($p > 0.05$). Predicted adult heights, a very important consideration in testosterone treatment, did not vary significantly before testosterone treatment (173.5 ± 6.6) and after treatment (173.3 ± 4.9) ($p > 0.05$). None of the boys experienced adverse reactions during the course of treatment.

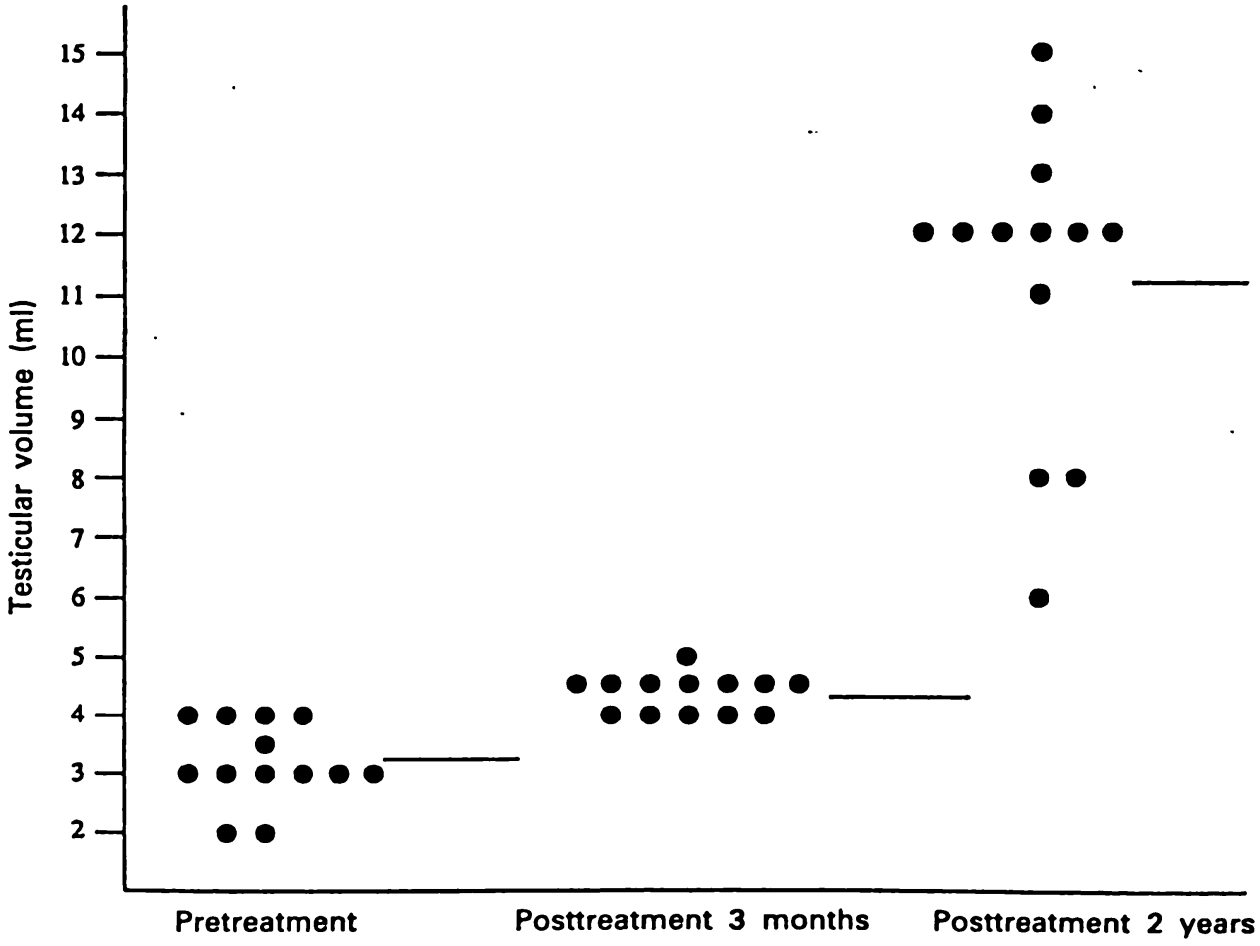

Fig.1: Effect of testosterone therapy on testicular volume in CDP boys. Horizontal line represents the mean value.

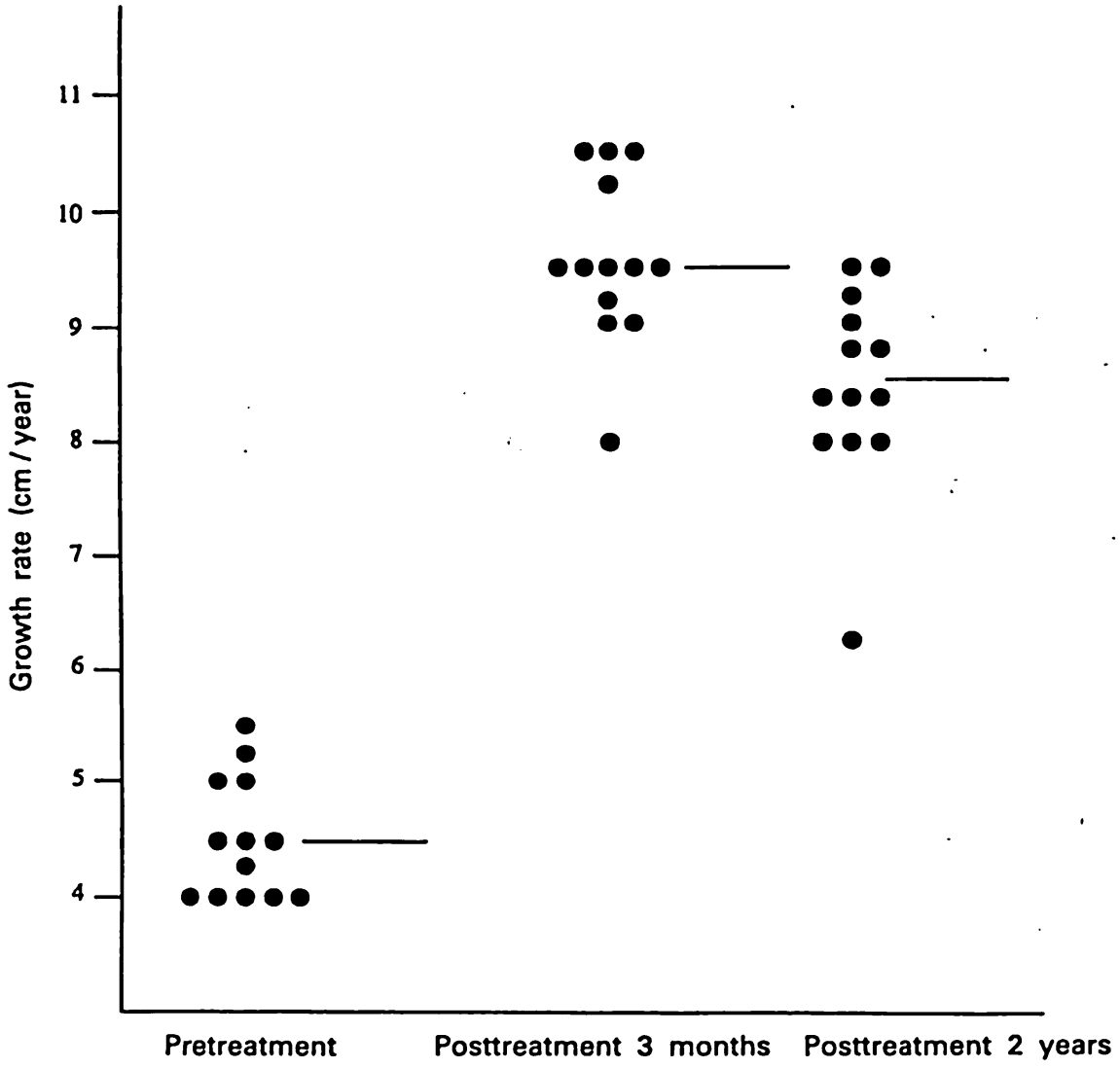

Fig.2: Effect of testosterone therapy on growth rate in CDP boys. Horizontal line represents the mean value.

Discussion

The child with CDP will spontaneously enter puberty between the ages of 14 and 18 years and will ultimately achieve a normal adult height. In this normal growth variant situation, an approach to the patient and his parents with reassurance and a policy of watchful waiting is necessary. There are some situations, however, in which the child is so upset by the combination of short stature and delayed appearance of secondary sexual characteristics that the possibility of intervention needs to be considered seriously[7].

The retardation of growth and delay in sexual maturation exhibited by adolescents has psychological and social consequences. These boys are under the pressure of being short and sexually immature. Some authors have reported that late-maturing boys show greater evidence of negative self-concepts, prolonged dependency needs, and feelings of rejection and rebellion[7,10]. The same authors

claim that after treatment of CDP, the same group of adolescents demonstrated an improvement in both school and extracurricular social activity, suggesting that normalization of growth and sexual maturation may well permit more effective involvement in normal adolescent behavior[7,10].

Although it is shown by several studies that a short course of long-acting testosterone esters promotes puberty in CDP patients without any decrease in predicted adult heights, this is dose-dependent and still a point of investigation.

In our CDP boys treated with a short course of a combination of short-and long-acting testosterone esters, all had entered puberty after the last treatment dose. There was no significant decrease in height for bone age SD scores and predicted heights after two years of follow-up, but growth rates increased significantly. We propose that a combination of testosterone esters (sustanon) at a dose of 200 mg four times at three week intervals is as effective as testosterone enanthate at the same dose and schedule used by several authors for CDP[3,5,7]. Although there was no significant difference in predicted adult heights, final adult height measurements should be determined in order to make the precise decision.

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THE USE OF IgM – ENRICHED INTRAVENOUS IMMUNOGLOBULIN FOR THE TREATMENT OF NEONATAL SEPSIS IN PRETERM INFANTS*

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SUMMARY: Erdem G, Yurdakök M, Tekinalp G, Ersoy F. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The use of IgM-enriched intravenous immunoglobulin for the treatment of neonatal sepsis in preterm infants. Turk J Pediatr 1993; 35: 277-281.

The value of IgM-enriched immunoglobulin therapy in 44 preterm infants with neonatal sepsis was evaluated in a prospective randomized study. All infants received antibiotic therapy and fresh plasma and / or whole blood transfusions. Twenty randomly-chosen infants were allocated to receive 5 ml / kg / d of IgM-enriched immunoglobulin intravenously for three days. Although the mortality rate in preterm infants whose gestational ages were 31-34 weeks in the immunotherapy group was slightly lower than in the control group, the general mortality rate from sepsis in the control group (9 / 24) and in the immunotherapy group (6 / 20) showed no statistically significant difference (37.5% vs 30.0%, $p < 0.05$). *Key words: intravenous immunoglobulin, neonatal sepsis, fresh plasma.*

The high mortality and morbidity rates of neonatal sepsis in preterm infants despite the development of new generation broad-spectrum antimicrobial drugs and improved perinatal care have led to the search for other treatment modalities[1]. It has been reported that intravenous immunoglobulin IVIg therapy in conjunction with antibiotic therapy significantly reduces mortality from neonatal sepsis[2]. We report the results of our study using IgM-enriched IVIg in the treatment of this condition.

Material and Methods

Fourty-four preterm infants between the gestational ages of 31 and 37 weeks who had sepsis but no severe congenital malformations, inborn error of metabolism, intrauterine infection or intracranial hemorrhage were enrolled in the study.

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The early diagnosis of neonatal sepsis was made by using Töllner's Sepsis Scoring System[3]. Prior to therapy, blood samples were drawn for culture, white blood cell count and peripheral blood smear. The cases having a positive blood culture were classified as "proved sepsis" and the others as "suspected sepsis".

All infants with neonatal sepsis received supportive therapy including daily fresh frozen plasma and / or blood transfusions, as well as antibiotic therapy. The initial antibiotics used in all infants were penicillin (100.000 U / kg / d) and amikacin (15 mg / kg / d) until culture results were available. Antibiotics were changed according to susceptibility-test results. Antibiotic therapy was continued for at least ten days regardless of the culture result.

Twenty infants with sepsis (immunotherapy group) randomly were chosen to receive 5 ml / kg / d IgM - enriched IVIg (Pentaglobin, Biotest Pharma, Frankfurt, Germany) consisting of IgM 6 mg, IgA 6 mg and IgG 38 mg per 1 ml. This therapy was administered for three successive days. For each infant the outcome of sepsis was recorded and the Student's *t* test was used to compare results.

Results

The two groups were comparable with regard to infants' gestational age, sex, birth weight, history of prolonged rupture of membranes and Apgar score at five minutes. The blood culture was positive in 15 infant (75.0%) in the immunotherapy group, and 15 (62.5%) in the control group (Table I).

Although the mortality rate in preterm infants with gestational ages of 31-34 weeks in the immunotherapy group was lower than that in the control group, this difference was not statistically significant. The outcomes of the infants in both groups were also similar; nine (37.5%) and six (30.0%) infants died in the control and immunotherapy groups, respectively (Table I).

Discussion

IVIg therapy has been recommended for prophylactic use in infants at high risk of developing sepsis (e.g. < 32 weeks or < 1500 g) or as a "rescue" therapy for infants who already have sepsis[2]. The results of prophylactic therapy are controversial[4-8], as two of the trials concluded that prophylaxis could not reduce septicemia in preterm infants[7,8].

The two reported "rescue" trials showed improved survival in septic neonates[9,10]. Sidiropoulos et al[9] completed a randomized open "rescue" trial with intravenous IgG (Sandoglobulin) in 22 preterm infants with confirmed sepsis. Four of the nine infants (44%) in the control group and one of the 13 infants (8%) in the group receiving IVIg died ($p < 0.04$). Haque et al[10] conducted a double-blind "rescue" trial with intravenous IgM-enriched immunoglobulin (Pentaglobin) in sixty preterm infants who had suspected sepsis which was confirmed bacteriolo-

Table I: Selected Clinical Findings and Outcomes of Preterm Infants with Neonatal Sepsis Who Had or Had Not Received Intravenous Immunoglobulin

	Control Group	Immunotherapy Group
No.	24	20
Male / Female	17 / 7	13 / 7
Gestational age (wk)	34.9 ± 1.7	34.4 ± 1.9
Birth weight (g)	2050 ± 369	2085 ± 352
No. of infants SGA	5 (20.8%)	3 (15.0%)
No. of infants with PROM	2 (8.3%)	6 (30.0%)
Apgar score below 7 at 5 min	6 (25.0%)	9 (45.0%)
Blood culture results		
Escherichia coli	6	7
Klebsiella pneumoniae	2	4
Pseudomonas aeruginosa	2	1
Staphylococcus aureus	4	2
Staphylococcus epidermidis	1	1
Mortality		
Gestational ages		
31-34 wk	5 / 10 (50.0%)	3 / 10 (30.0%)
35-37 wk	4 / 14 (28.6%)	3 / 10 (30.0%)
Proved sepsis	7 / 16 (43.8%)	5 / 15 (33.3%)
Suspected sepsis	2 / 8 (25.0%)	1 / 5 (20.0%)
Total	9 / 24 (37.5%)	6 / 20 (30.0%)

Abbrevations:
SGA : small for gestational age.
PROM : prolonged rupture of membranes (longer than 24 hours).

gically in 44. Mortality from sepsis was significantly higher: six of the 30 infants (20%) in the control group, and one of the 30 (3%) in the immunoglobulin-treated group ($p < 0.001$).

We used the same IgM-enriched immunoglobulin preparation (Pentaglobin) as did Haque et al[10] to treat preterm infants with sepsis in this study. Although Haque et al concluded that IgM-enriched immunoglobulin therapy in conjunction with antibiotic therapy significantly reduces mortality from neonatal sepsis in preterm infants, our findings do not support this conclusion.

Our findings may be explained by the use of fresh frozen plasma or whole blood in this study. There has been no prospective randomized controlled study using fresh frozen plasma or whole blood transfusions as adjuvant therapy in infected

newborn infants, but this modality is widely used in all countries. The rationale for the use of such therapy is to improve peripheral and pulmonary perfusion and to enhance humoral and cellular immunity and complement dependent opsonization in the infected newborn infant[11].

Although several investigators[9,10] have suggested that combining IVIg with antibiotics might be more effective than using antibiotics alone, the results of their studies should be cautiously interpreted because: 1) there is a lack of expanded trials from different parts of the world; 2) there is a lack of type-specific antibodies against microorganisms commonly seen in developing countries in IVIg preparations prepared from donors living in western countries[12]; 3) high doses of IVIg seem to block the reticuloendothelial system[13]; 4) in animal models, it has been shown that high doses of IVIg may cause blockage of neutrophils or bacterial receptors[14]; 5) high doses of IVIg may impair the therapeutic benefit of penicillin G against neonatal sepsis[15]; and 6) the risk of acquiring hepatitis C is higher in infants receiving IVIg manufactured from a few thousand donations than fresh plasma or whole blood transfusions from one or a few donors[16]. In addition, IVIg treatment is very expensive. So, we are waiting for the results of additional clinical trials before making a conclusion.

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MOYAMOYA DISEASE AND ALTERNATING HEMIPLEGIA
A REPORT OF TWO CASES*

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SUMMARY: Renda Y, Gücüyener K, Özen H, Topçu M. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Moyamoya disease and alternating hemiplegia. A report of two cases. Turk J Pediatr 1993; 35: 283-289.

Moyamoya disease is one of the cerebrovascular disorders and is characterized by bilateral stenosis or occlusion of the distal internal carotid arteries and their main branches. Repeated ischemic episodes in children and intracranial hemorrhage in adults with moyamoya disease is usually noted. In this report, we describe two children with moyamoya disease who presented with alternating hemiplegia. The final diagnosis was made by cerebral angiography and cranial computed tomography in these patients. Other neurological and radiological features of the patients were described. *Key words: moyamoya disease, alternating hemiplegia.*

Moyamoya disease is the angiographic diagnosis of one of the cerebrovascular disorders. It is characterized by bilateral stenosis or occlusion of the distal internal carotid arteries and their major branches, resulting in development of an abnormal vascular network[1-3]. The disorder has a worldwide distribution. In children, the initial symptoms consist of repeated ischemic episodes leading to various degrees of permanent neurological deficit, whereas adults usually present with intracranial hemorrhage. Although the underlying cause has not been identified, a generalized immunological arteritis, especially in those arteries innervated from the superior cervical sympathetic ganglia, is under speculation[4].

In this report we present two children found to have moyamoya disease and discuss the nature of the disease as seen in childhood.

Case Reports

Case 1

A 5-year-old boy had developed left hemiparesis and facial asymmetry when admitted to the hospital. Two similar attacks of alternating hemiplegia, the first one a year ago and the second 16 days ago, had occurred and resolved without

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any neurological sequelae. He was the first child born to healthy parents and had an unremarkable past history except a mild head trauma at two years of age. On admission he was alert and cooperative but had nonfluent speech and left central facial paralysis. Motor examination showed left-sided hemiparesis, hyporeflexia and left plantar extensor response.

Laboratory studies including complete blood count, blood and urine amino acids, electrocardiography, chest x-ray, tests for collagen vascular disease; blood urea nitrogen, creatinine, serum transaminase activities, tests for infectious diseases and coagulation disorders, were all in normal range. Electroencephalography (EEG) showed diffuse slow wave activity in the right hemisphere with slow sharp wave activity in the right frontotemporal region. Cranial computed tomography (cranial CT) revealed multiple low-density areas in the right temporal, parietal and left parietal regions consistent with cerebral infarctions.

^{99m} THMPAO single photon emission computed tomography (SPECT) study showed irregular hypoperfusion areas in the bilateral frontal, right temporal, parietal and right cerebellar regions. On digital substruction angiography (DSA) the patient had bilateral stenotic lesions in the syphon and dilated collaterals in basal levels. Bilateral middle and anterior cerebral arteries were filled via the posterior communicating artery from the vertebro-basillary system. The right internal carotid artery was filled with the transdural collaterals from the external carotid circulation. During the hospital stay the hemiparesis resolved and his speech returned to normal and the patient was discharged on acetyl salicylic acid and diphenylhydantoin.

Case 2

An 11-year-old boy came to the hospital with right-sided paralysis and aphasia. Two days before he had complained about not being well and had had slurred speech. His symptoms progressed rapidly, and finally he was unable to walk and talk. His past and family history were unremarkable.

On physical examination, he was alert, moderately cooperative and mildly hypotonic. His ability to name objects and repeat words was impaired, thus giving the impression of mild mental retardation. He had right central facial paralysis, right sided hemiplegia, hypoactive tendon reflexes and a bilateral positive Babinski sign. The rest of the examination was normal.

Laboratory examination: The routine work-up done for the first patient was also carried out for this patient and revealed no abnormality except bilateral maxillary sinusitis. EEG showed disturbed basal activity and voltage suppression and asymmetry of the two hemispheres. Cranial CT revealed an area of hemorrhagic infarct in the left frontal lobe.

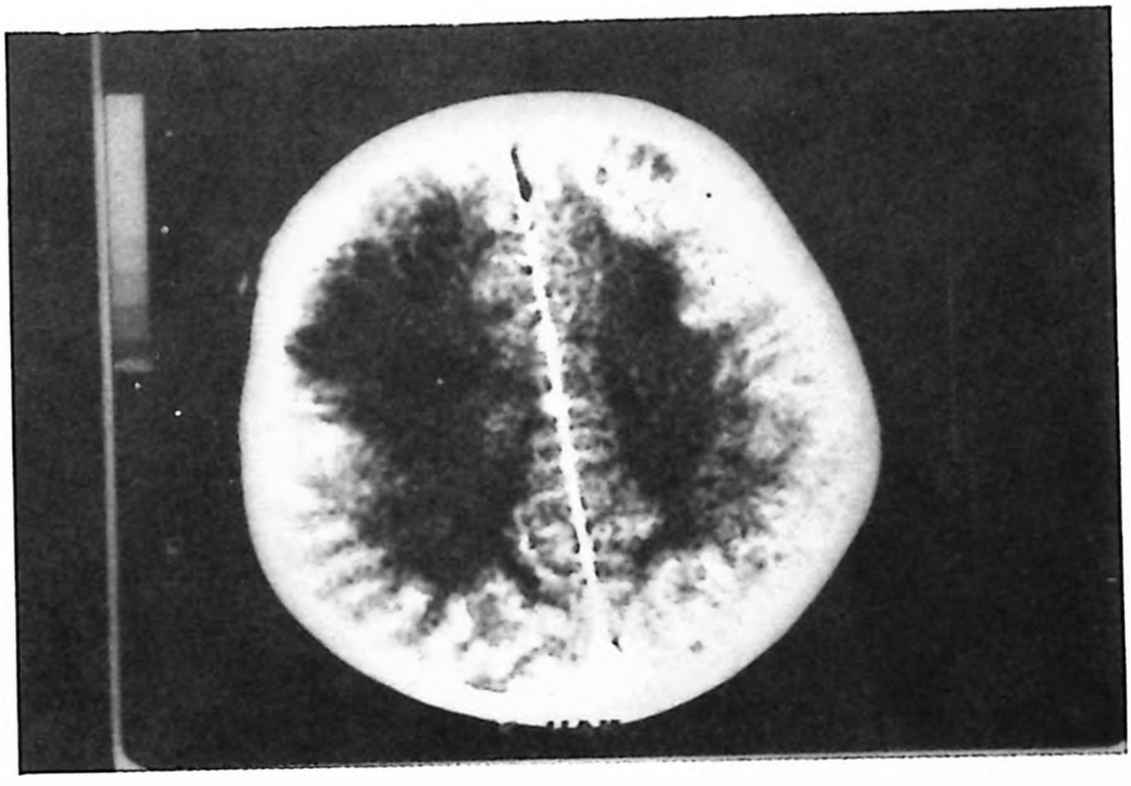

Fig. 1 a: CT of Case 1: Multiple low-density areas in the right temporal-parietal and left parietal regions.

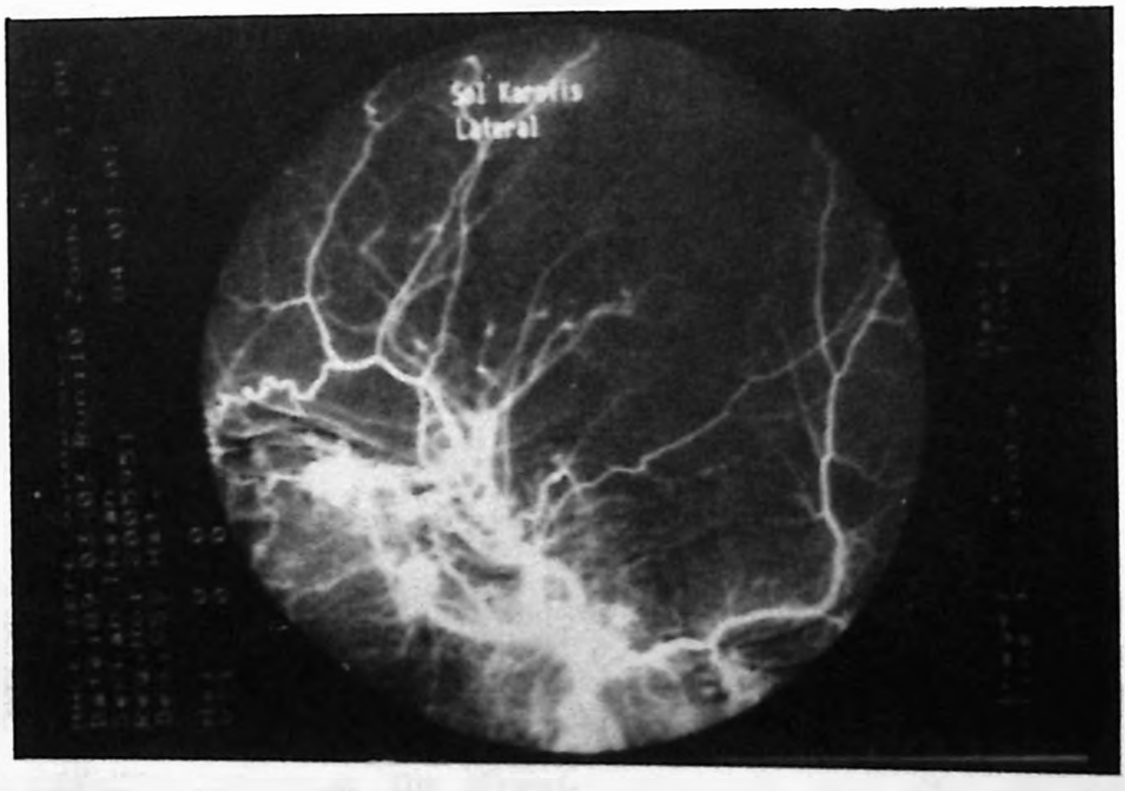

Fig. 1 b: Angiography of Case 1: Total occlusion at the cavernous portion of internal carotid artery.

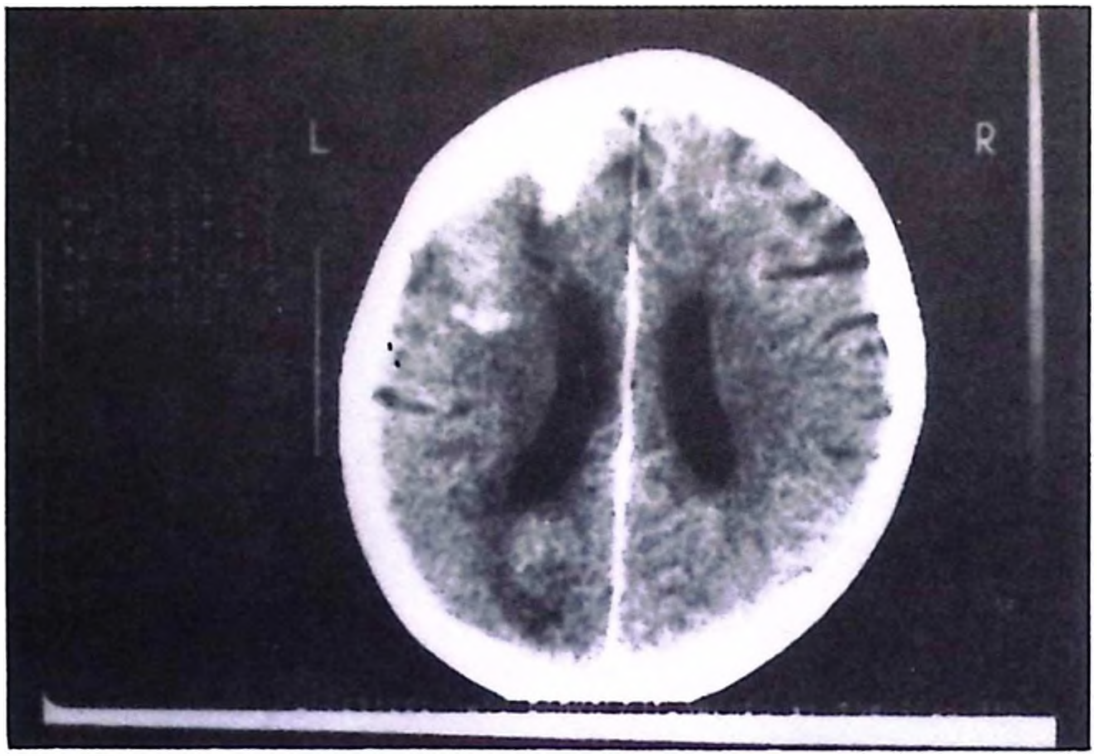

Fig. 1 c: CT of Case 2: Hemorrhagic infarct in the left frontal lobe.

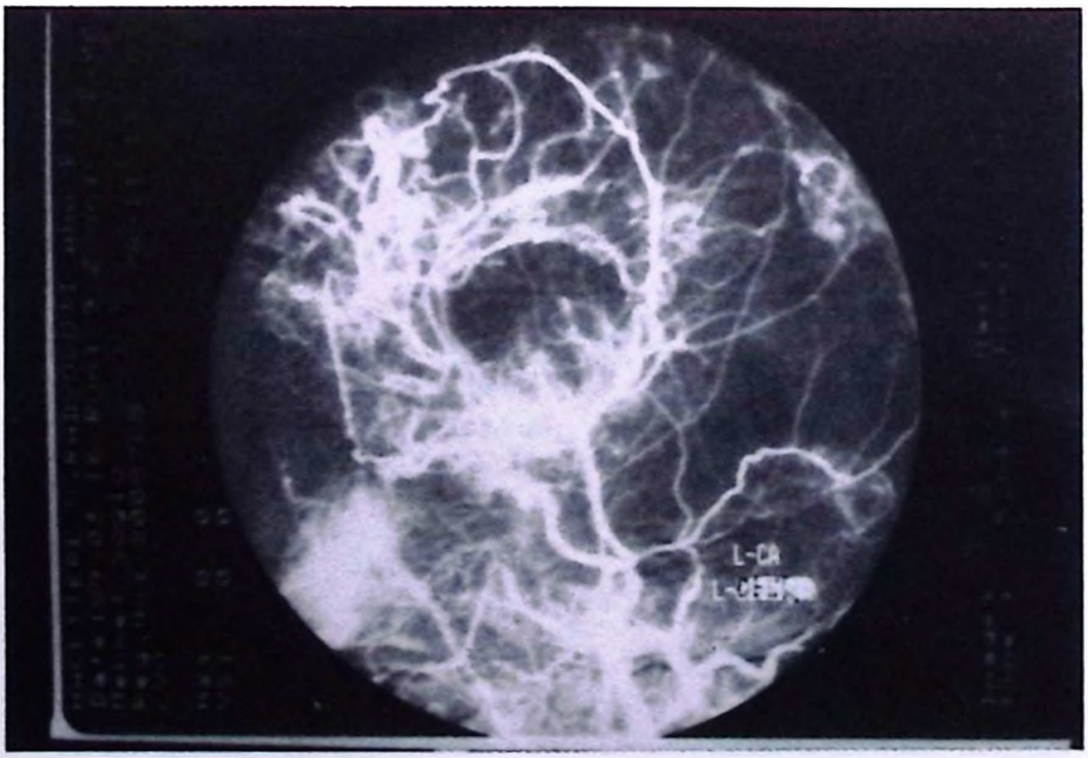

Fig. 1 d: Angiography of Case 2: Total occlusion at the bifurcation of internal carotid artery and basal collaterals.

On cerebral angiography, bilateral obliteration of the internal carotid arteries after the syphon and typical dilated collateral basal vessels were shown. Perfusion was maintained by the orbital and transdural collaterals from the external carotid circulation. In the vertebro-basillar system, the right middle cerebral artery was filled by the enlarged right posterior communicant artery, and the blood supply to the cerebellum was maintained by the collaterals developed from the posterior cerebral arteries. In the follow-up period, hemiparesis markedly improved.

Discussion

Moyamoya disease is a chronic occlusive cerebrovascular disorder characterized by the angiographic features of:

1. Stenosis primarily involving the region of the internal carotid artery bifurcation.
2. Presence of dilated basal collaterals.
3. Bilateral abnormalities[2,5].

If these features are found in association with any of the conditions listed in Table I a diagnosis of "moyamoya syndrome" is appropriate. When the angiographic pattern is limited to one side only without the above conditions a "probable moyamoya disease" should be considered[5]. This situation is known to be rare and is mainly caused by spontaneous occlusion of middle cerebral and internal carotid arteries.

Table I: Conditions Associated with Moyamoya Disease

Neurofibromatosis	Fanconi's anemia
Tuberosclerosis	Down's syndrome
Encephalotrigeminal angiomatosis	Cerebral glioma
Fibromuscular dysplasia	Congenital heart disease
Vasculitis	Hypertension
Tuberculous meningitis	Type I glycogenosis
Radiation - induced arteritis	Myopathy
Sickle cell anemia	

Although moyamoya disease has been described most often in the Japanese poulation, with an estimated incidence of 1:100.000[2], many sporadic cases have been reported in other parts of the world[6-9], with a female predominance. There is no definite evidence of genetic determination[10].

In the pediatric age-group, the disease commonly presents with repeated ischemic episodes and is one of the important causes of acute hemiplegia and focal neurological deficits[2,4,7]. The hemiplegia may alternate between the right

and left sides. Mental and sensory disturbances may occur. Headache and seizures are also described during and between the ischemic episodes. In children, by serial angiographic studies, the disease is shown to be progressive with respect to the extent of the occlusion[1,2,10]. When the occlusive process has stopped, the maximum number of collateral vessels have been developed and the clnical course is stabilized. In a study of 39 cases of pediatric patients, the fatality rate was 13% and 77% of the patients had developed significant neurological deficits. Only 23% of the living patients had remained neurologically intact despite repeated ischemic attacks[10]. If the onset is before the age of four, rapid deterioration and intellectual regression with irreversible neurological deficits develop[4,7,10]. In adults, intracranial hemorrhage is the prevailing presentation[6,10,11] but cerebral infarctions may also be seen[5,8].

A generalized immunological arteritis manifesting in the arteries which are innervated by the superior cervical sympathetic ganglia has been suggested as an etiologic factor. The high incidence of tonsillitis, otitis media and other infections above the neck supports the theory that there may be a connection between such infections and the arteritis[7]. One of our patients had bilateral maxillary sinusitis. The pathological studies have demonstrated endothelial hyperplasia and fibrosis with no associated inflammatory reaction while the tunica media and adventitia have remained intact[1,4,10]. The association of moyamoya disease with cerebral aneurysms has been defined[12] but the combination with arterio-venous malformations is rare and coincidental[13,14]. Cerebral angiography is needed to confirm the diagnosis of moyamoya disease and six stages in the angiographic course of the disease in children have been defined[1,2]. Our patients' angiographic appearances were consistent with the disease.

Cranial CT studies demonstrated multiple and bilateral infarctions in our patients as reported in the literature[5,7,15,14]. By SPECT, in one of our patients we noted frontal hypoperfusion which could be highly suggestive of moyamoya disease. As in our patients, EEG may show increased slow wave activity and focal abnormalities without any significance. Magnetic Resonance Imaging studies have shown evidence of large and small infarcts and can also detect slow blood flow within the middle cerebral artery in severe cases[16]. In a recent study, a significant correlation between the neurological deficit and abnormalities in evoked potentials was shown[17].

The medical treatment of moyamoya disease has been unsuccessful[7]. However, a number of surgical procedures such as by-pass of the stenotic arteries and cervical perivascular ganglionectomy in order to improve perfusion and prevent neurological deterioration have been recommended[7,10].

In any child presenting with a transient ischemic episode, moyamoya disease should be considered in the differential diagnosis.

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The Turkish Journal of Pediatrics 35: 291-297, 1993

COMPUTED TOMOGRAPHY AND ANGIOGRAPHIC FINDINGS OF CHILDHOOD MOYAMOYA DISEASE*

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SUMMARY: Cila A, Yüksel S, Balkancı F, Besim A. (Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Computed tomography and angiographic findings of childhood moyamoya disease. Turk J. Pediatr 1993; 35: 291-297.

Moyamoya disease is a rare entity consisting of bilateral stenosis or occlusion of internal carotid arteries with abnormal collateral vessels at the base of the brain. We present five Turkish children with this disease, which is more common in Japan.

Focal neurologic deficits and/or epilepsy were the common presenting symptoms in two girls and three boys between the ages of 1.5 and 11 years. Multiple cerebral infarcts were diagnosed in all of the cases by Computed Tomography (CT). Abnormal net-like vessels at the base of the brain were detected in three patients. Cerebral angiography, which is necessary to confirm the diagnosis, showed moyamoya vessels and bilateral stenosis or occlusion of the internal carotid arteries in all cases. Although the angiographic staging was advanced in three patients, neither clinical status nor parenchymal abnormalities detected with CT were different from the other two cases. *Key words: carotid arteries, brain, moyamoya disease.*

Moyamoya is the descriptive term used for angiographic picture consisting of abnormal net-like vessels (ANV) at the base of the brain[1]. Bilateral stenosis or occlusion of the terminal parts of the internal carotid arteries (ICA) along with ANV specific for moyamoya disease. Although the disease has been described in Western literature, the Japanese are most frequently affected, with estimated cases numbering more than 2000[2].

Angiography is needed to confirm the diagnosis[1,3-7]. But other imaging modalities such as Computed Tomography (CT)[3] and Magnetic Resonance Imaging (MRI)[4,5] may suggest moyamoya disease.

Material and Methods

Between the years 1988 and 1990, two girls and three boys between the ages of 1.5 and 11 years were referred for cerebral angiography and were diagnosed with

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moyamoya disease. The cases are summarized in Table I. In two of our cases, upper respiratory tract infections appeared first, followed by hemiplegia, which necessitated evaluation of the patients.

Table I: Clinical Data of Patients With Childhood Moyamoya Disease.

	Age (Years)	Sex	Symptoms
Case 1	1.5	F	Focal motor epilepsy, right hemiparesis
Case 2	4	M	Epilepsy
Case 3	5	M	Alternating right and left hemiplegia and recovery within 10 months
Case 4	8	F	Focal motor epilepsy, right hemiplegia
Case 5	11	M	Mental and motor retardation, right hemiplegia

All of the patients had at least one CT examination before angiography. CT examinations were done at different centers. They were taken in the axial plane and the slice thickness was either 9 or 10 mm.

Cerebral angiography was performed by Digital Subtraction Angiography (DSA) technique using Digital Vascular Imaging (Philips, the Netherlands). All examinations were performed under general anesthesia. A transfemoral approach with a 5.0 F straight or 45 degree-curved visceral catheter was used. Selective cathetherization of both carotid and vertebral arteries was successfully performed except on the youngest patient, and anteroposterior, oblique and lateral projections were obtained in every patient. Iohexol (300 mgI/ml) was diluted by the same amount of saline and manually injected. The total dose of the contrast medium did not exceed 2 ml/kg.

Results

CT and DSA findings are listed in Table II. Suzuki and Kodama[7] gave two classifications of moyamoya disease: ethmoidal moyamoya and vault moyamoya, depending on the location of ANV. Satoh et al[6] suggested a new staging system based on the progress of vessel stenosis, which seems more accurate for therapy planning and follow-up: Stage 1: Slight to moderate stenosis of ICA bifurcation; Stage 2: Severe stenosis of ICA bifurcation; Stage 3: Occlusion of anterior or middle cerebral arteries; Stage: 4: Occlusion of ICA or anterior and middle cerebral arteries with partial retention of peripheral artery's trunk (Fig. 1); and

Table II: CT and DSA Results

	CT	DSA	Stage
Case 1	Bilateral parietal infarcts	R-ICA stenosis, L-ICA occlusion, ANV	2
Case 2	Cerebral atrophy Bilateral cortical infarcts ANV	Bilateral ICA stenosis, MCA, ACA, PCA stenosis, ANV	3
Case 3	Multiple frontal infarcts	Bilateral ICA occlusion, partial retention of MCA and ACA trunks, ANV	4
Case 4	Multiple cortical infarcts in left cerebral hemisphere ANV	Bilateral ICA occlusion, Partial retention of MCA and ACA trunks, ANV	4
Case 5	Cerebral atrophy Left frontal infarct ANV	Bilateral ICA occlusion, Partial retention of MCA and ACA trunks, ANV	4

(ICA: Internal carotid artery, ANV: Abnormal net-like vessels, MCA: Middle cerebral artery, ACA: Anterior cerebral artery, PCA: Posterior cerebral artery).

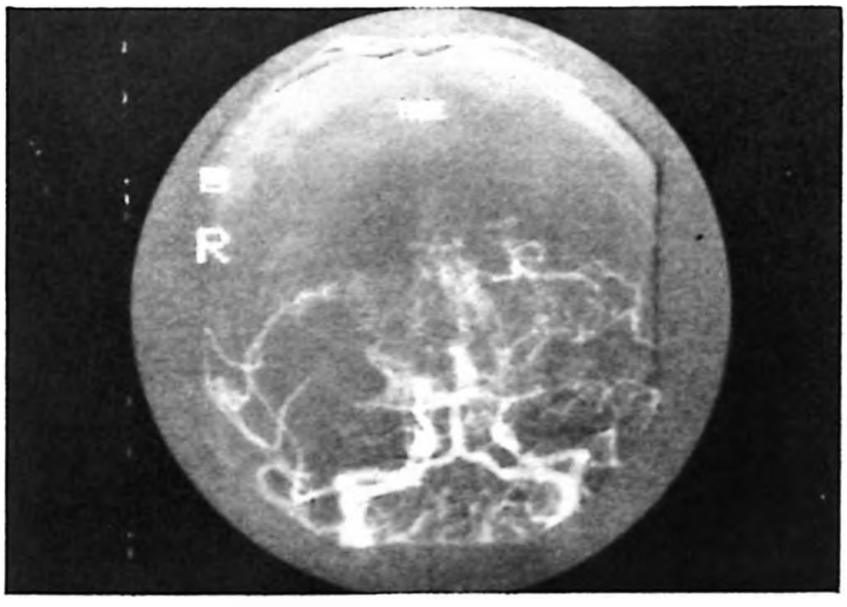

Fig. 1: Case 3, A-P cerebral DSA showing bilateral stenosis at ICA bifurcation, stenosis and occlusion of ACA and MCA along with abnormal net-like vessels at the base of the brain.

Stage 5: Occlusion of ICA or anterior and middle cerebral arteries with no main trunk. We used Satoh's staging system in our cases, as shown in Table II.

ANV were present in all our cases. ANV at the base of the brain fed by ICA and/or the posterior cerebral artery was the most common location (Fig. 2). Ethmoidal and ophthalmic collaterals and collaterals arising from the external carotid artery were less common in our patients.

Aneurysm and subarachnoid hemorrhage incidence is high in the adult form of moyamoya disease[2,7]. No aneurysm was found in our cases.

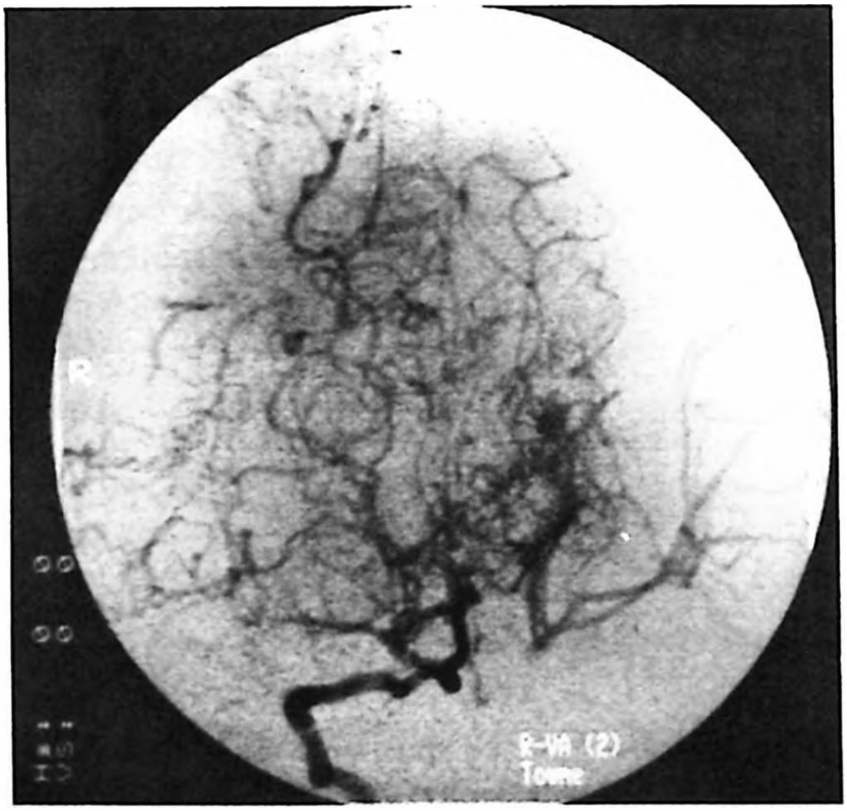

Fig. 2: Case 4, R-Vertebral artery arteriography showing abnormal net-like vessels fed by posterior cerebral arteries. On the right side, vault moyamoya vessels could also be seen.

Discussion

Moyamoya, a Japanese word meaning "something hazy like a puff of cigarette smoke drifting in the air" is the descriptive term applied to abnormal net-like collaterals seen in cerebral angiography[7]. In addition to ANV, stenosis or occlusion of the ICA at the level of its terminal bifurcation, with bilateral but asymmetric stenosis of anterior and middle cerebral arteries is a common finding. Its etiology is still unknown. Most authors consider the carotid stenosis to be the primary condition and ANV to be the result of it[7]. Basal meningitis, tumor, radiation therapy, neurofibromatosis, atherosclerosis, connective tissue abnormalities, sickle cell disease, Fanconi's anemia and congenital spherocytosis can cause ICA

stenosis and development of ANV[7,8]. But familial incidence (7%)[9], a report of monovular twins[10] and other infantile cases[10] suggest a genetic factor. Exclusion of the above-mentioned possible causes of "acquired" moyamoya disease is necessary for the final diagnosis.

Children with moyamoya disease usually present with repeated cerebral ischemic attacks (hemiplegia, paresthesia, convulsions). Hemiplegia may be reversible and alternating. If left untreated, cerebral atrophy and mental motor retardation develop, as in our oldest patient.

Usually CT is performed first when evaluating a child with cerebral ischemic symptoms. The major CT feature of moyamoya disease is cerebral atrophy and focal areas of low density in the basal ganglia or cerebral cortices representing infacrcts (Fig. 3). The curvilinear tortuous vascular densities correspond to the parenchymal, dural and leptomeningeal collaterals seen on cerebral angiography[3]. In three of our cases, these ANV could be seen around basal ganglia (Fig. 4). MRI has the great advantage of contrast medium[5]. Although MRI is expensive and not readily available, it must be used in patient follow-up because angiography has a high incidence of morbidity, especially in children[4].

Superficial temporal artery-middle cerebral artery by-pass, which was introduced by Yaşargil, has become an established mode of treatment for both childhood and adult moyamoya disease[11]. Although by-pass surgery helps to maintain cerebral blood flow, childhood moyamoya disease usually progresses, and the incidence of intracranial hemorrhage increases with age[6].

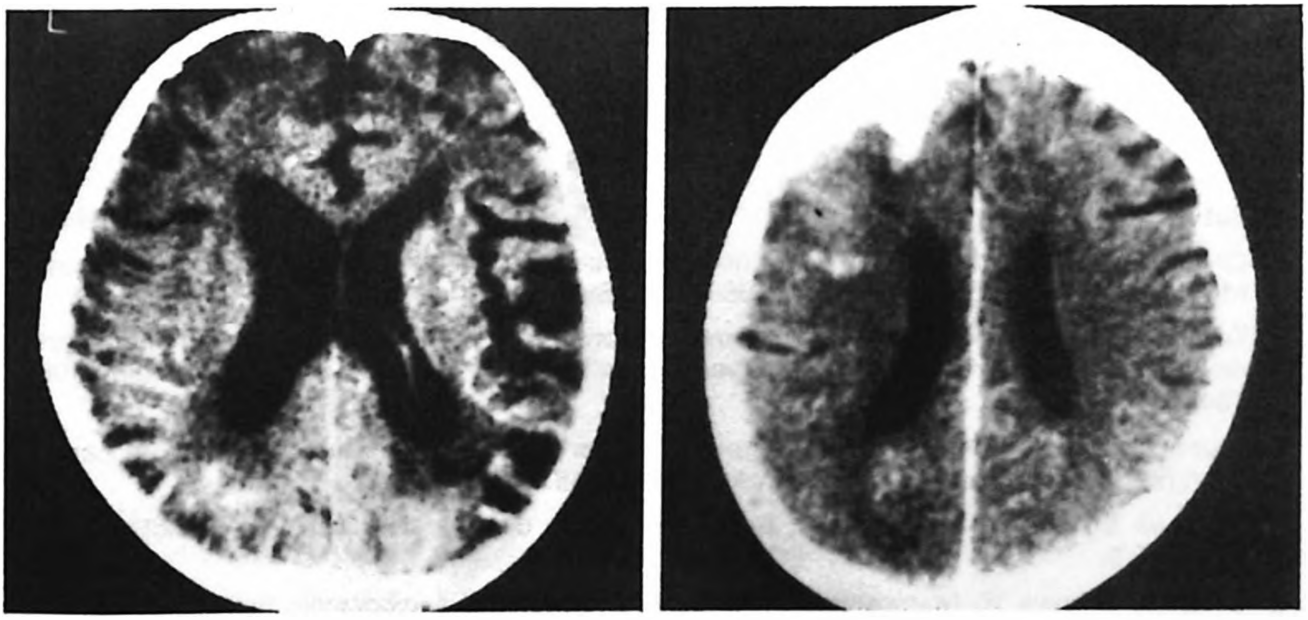

Fig. 3: a) CT of Case 2: Cerebral atrophy and multiple cortical infarcts. b) CT of Case 3: Right frontal sub-acute cortical infarcts enhanced with contrast medium.

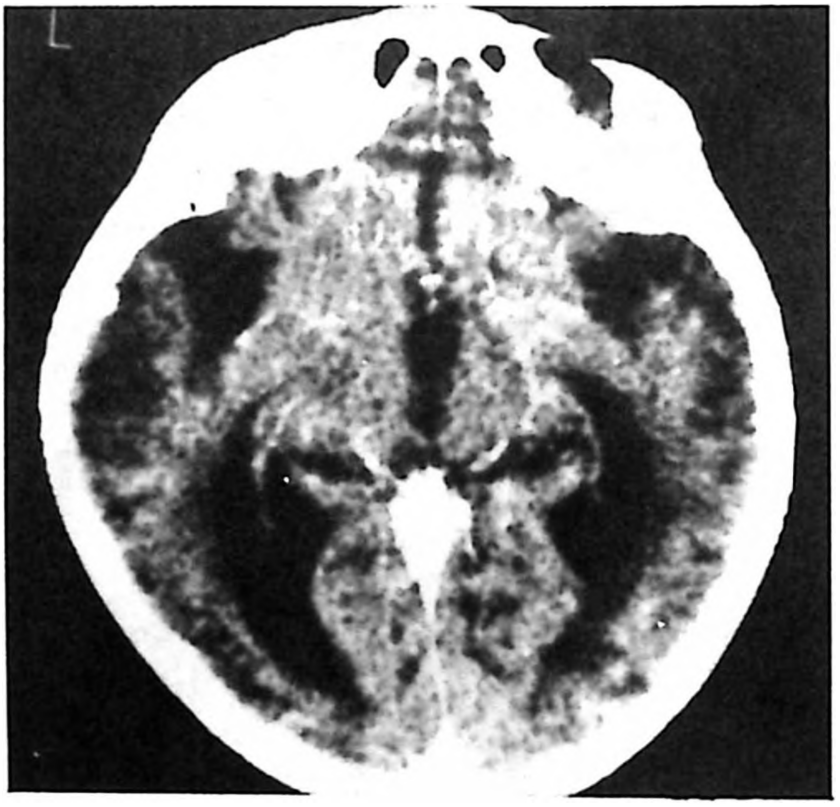

Fig. 4: Case 5: CT showed linear vessels in basal ganglia representing abnormal net-like vessels. Note dilated temporal horns and subarachnoid space secondary to cerebral atrophy.

Recurrent and alternating hemiplegia in a child must raise the suspicion of moyamoya disease. Cerebral atrophy, multiple infarcts and collateral vessels seen on CT are highly suggestive of the disease. Selective cerebral angiography is needed to confirm the diagnosis and planning for surgical intervention. Once the diagnosis is established, MRI is the best method for follow-up.

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CONGENITAL CYSTIC ADENOMATOID MALFORMATION*
A report of a case and review of the literature

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SUMMARY: Göçmen A, Kiper N, Tanyel C, Göğüş S, Özçelik U, Büyükpamukçu N. (From the Pediatric Chest Disease Unit, Department of Pediatrics, and the Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Congenital cystic adenomatoid malformation. Turk J Pediatr 1993; 35: 299-303.

A ten-month-old boy was admitted to our hospital with fever, cough and dyspnea. His history was remarkable for mild respiratory problems from the early neonatal period. Although medical treatment was administered several times in a local hospital, his symptoms recurred. Chest x-ray revealed multiple cystic lesions on the right side. The diagnosis of congenital cystic disease was considered preoperatively, to our knowledge for the first time in our hospital. The patient's postoperative course was uneventful, and no respiratory problems have recurred in 24 months of follow-up. *Key words: lung, cystic adenomatoid malformation, congenital.*

Congenital cystic disease of the lung is an uncommon malformation accounting for about 25% of lung anomalies. Lobar emphysema, bronchogenic cysts, pulmonary lymphangiectasia, and congenital cystic adenomatoid malformation of the lung (CCAM) are the four pathologic categories of congenital cystic disease of the lung[1,2]. CCAM was first described as a separate entity by Chin and Tang[3]. Most cases have been reported to occur in the neonatal period[2,3]. In this period, the respiratory symptoms result from the compression of normal lung and mediastinum by the cysts. Later in life, CCAM causes recurrent lower respiratory tract infections[3]. As in our case, CCAM should be considered when recurrent respiratory infections and cystic radiological findings are persistent.

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Case Report

A 10-month-old boy was admitted to our hospital with fever, cough and respiratory distress. The pregnancy and delivery were uncomplicated. The family history was unremarkable. In the early neonatal period, his mother noted that he was slow to feed. At six months of age, he was admitted to a local hospital with fever and cough, and his chest x-ray revealed multiple cystic lesions on the right side. Intravenous antibiotics were administered for 15 days for suspected but not confirmed staphylococcal pneumonia. Two weeks after treatment, his chest x-ray findings remained unchanged and his symptoms recurred, so he was referred to Hacettepe Children's Hospital. The patient did not have contact with individuals known to have tuberculosis.

On physical examination, the patient's body temperature was 38.8°C, pulse rate was 110/minute and respiratory rate was 56/minute. Blood pressure was 100/50 mmHg. His weight was 9 kg (50th percentile) and his height was 77 cm (90th percentile). The child appeared well. On chest examination, a mild pectus carinatum and diminished breath sounds were noted on the right side. The liver was palpable 5 cm below the right costal margin, and the spleen tip was palpable at the lower left costal margin. Physical examination was otherwise negative.

The results of laboratory studies included a hemoglobin of 10.25 g/dl, white blood cell count of 9600/mm^3 with 34% polymorphonuclear leukocytes, 2% stub and 64% lymphocytes. Urinalysis, serum proteins, blood urea and electrolytes were normal. Sweat chloride concentration was 22 mEq/L. Serum immunoglobulins were within normal levels. A chest x-ray displayed multiple cystic structures with areas of surrounding atelectasis on the right (Fig. 1a). A computed tomographic (CT) scan of the thorax disclosed a normal appearance of the left lung and a solid mass with surrounding multiple cystic structures on the right middle and lower lobes. Radionuclide scanning revealed a generalized perfusion defect on the right side and non-specific signs on the left.

Antimicrobial therapy was administered intravenously for secondary infection. On the 20th day of the patient's hospitalization, he was afebrile and his condition was stable. With his history and positive chest x-ray, our preoperative diagnosis was CCAM. A right posterolateral thoracotomy was performed and revealed multiple cystic structures in the lower lobe, which were removed. The child had an uneventful postoperative course. Gross and microscopic findings confirmed the diagnosis of type I CCAM of the lung (Fig. 2). Eighteen months later his physical examination and x-ray findings were normal (Fig. 1b).

Discussion

Congenital cystic adenomatoid malformation (CCAM) of the lung may result from an embryonic defect occurring within the first fifty days of gestation[1]. The lesion

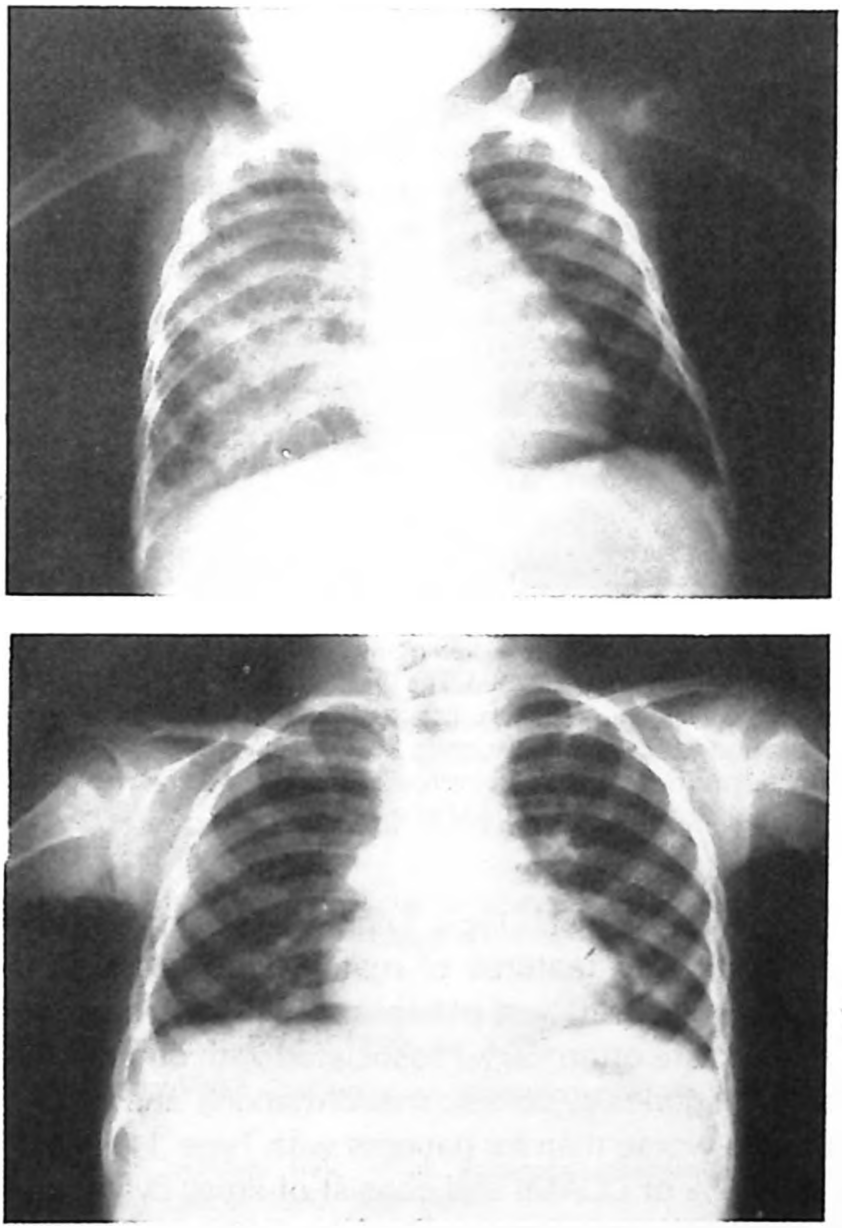

Fig. 1a: Chest radiography of an infant with CCAM of the right lung, showing multiple cysts of varying sizes and shapes; mediastinum is shifted to the left side. b: Postoperative chest-radiography.

is considered to be a "hamartoma" due to excessive growth of terminal bronchiolar structures. However, Buntain and colleagues[4] have suggested that it is "a focal pulmonary dysplasia" because in many cases there is skeletal muscle in the cyst walls. Microscopic examination reveals the following: 1-cysts of varying sizes, lined by cuboidal to ciliated pseudostratified columnar epithelium; 2-polypoid configuration of the mucosa of the cysts; 3-absence of cartilage plates except as components of "entrapped" normal bronchi; 4-presence of a group of mucogenic cells lining the cyst wall; and 5-absence of inflamation. These are the generally accepted histopathological criteria[4,5].

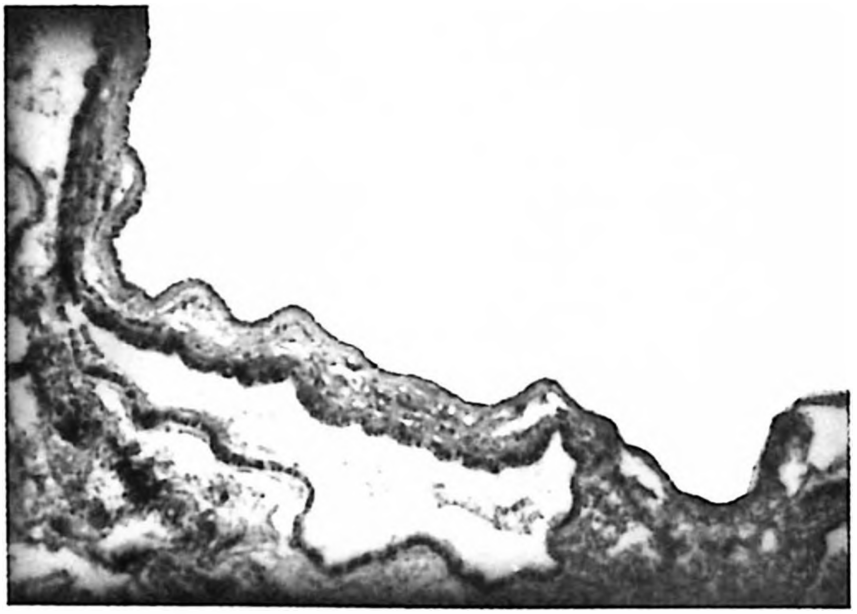

Fig. 2: Right lower lobectomy material revealed many cystic structures which measured 0.5-2.5 cm in diameter and occupied a portion of the lobe. The walls of the cysts were lined by pseudostratified columnar epithelium overlying fibromuscular tissue of variable thickness. Relatively normal alveoli were present between and adjacent to these cysts. A chronic inflammatory reaction was also noticed in the lobectomy material. These gross and microscopic findings confirmed the diagnosis of type I CCAM of the lung.

There are three types of CCAM[6]. Type I consists of single or multiple, large (1-5 cm in diameter) cysts with features of mature lung tissue between the cysts. Type II lesions, occurring in 20% of patients with CCAM, consist of multiple small (0.5-1.5 cm) cysts and are often (60%) associated with other anomalies, especially renal agenesis or dysgenesis, cardiac malformations and intestinal atresia. The survival rate (40%) is worse than for patients with Type I lesions. Type III lesions are the rarest (only 5% of CCAM) and consist of small cysts, less than 0.5 cm in diameter. The survival rate is reported to be 50%.

Type I is the most common, and 80 percent of cases present in the neonatal period with respiratory distress[2,5]. After the first year of life, cysts are very prone to secondary infection. In this period, chest x-ray differentiate staphylococcal pneumatoceles. In our case, the diagnosis of CCAM had been made with the help of the history and serial radiography, and was confirmed by histopathological examination. As a presenting symptom, recurrent respiratory infection is rare[2,5].

The radiological findings are usually sufficiently specific to distinguish CCAM from other forms of pulmonary disease. Approximately 75% of type I lesions are on the right side, and the most typical radiologic findings are sharply outlined radiolucent areas of irregular sizes and shapes and areas of surrounding atelectasis. Our patient had findings similar to those reported in the literature. Bronchoscopy, bronchography, and radionuclide scanning are of limited value for

diagnosis. Angiography and computed tomography of the chest are recommended[2,4]. This abnormality may also be diagnosed antenatally by ultrasound[7].

Definitive diagnosis is based on histological examination of the excised lobe, and definitive treatment of CCAM of the lung is by thoracotomy and excision of the affected lobe[1-3]. Long-term follow-up has not shown any restriction of pulmonary function, and radioisotopic scanning shows that the remaining lung grows normally and expands to fill the thoracic cavity[1].

As in our case, this uncommon malformation should be considered in the differential diagnosis of recurrent respiratory infection. Early diagnosis and treatment of this condition will permit the salvaging of an otherwise normal child.

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The Turkish Journal of Pediatrics 35: 305-312. 1993

THE AICARDI SYNDROME*
A Case report and review of the literature

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SUMMARY: Altınbaşak S, Baytok V, Yalaz M, Önenli N. (Departments of Pediatric Neurology and Ophthalmology, Çukurova University Faculty of Medicine, Adana, Turkey). The Aicardi Syndrome. A case report and review of literature. Turk J Pediatr 1993; 35: 305-312.

A case of Aicardi's syndrome is described. The main features described are infantile spasms, pathognomonic chorioretinal lacunar defects, agenesis of the corpus callosum, psychomotor retardation, female sex, characteristic EEG changes and costovertebral anomalies. This is the second reported case in Turkey. *Key words: Aicardi syndrome.*

The Aicardi syndrome was initially described by Aicardi et al[1] in 1965 as a syndrome characterized by infantile spasms, agenesis of the corpus callosum, specific chorioretinal lacunar defects and costovertebral anomalies. Since then, more than 100 cases have been reported. Many other congenital abnormalities have since been included in this syndrome such as Dandy-Walker malformation, hydrocephalus, papilloma of choroid plexus, cleft lip and palate, and absence of the pineal gland[2-5]. While this syndrome has so far been reported to occur only in females, there is one case with male phenotype and XXY karyotype in the literature[6].

This report presents a description of the second case in Turkey. The first was reported by Karagöl and Yalaz[7].

Case Report

A three-month-old girl with a history of seizures was admitted to our hospital. When she was 40 days old, myoclonic jerkings started five to six times per day. One month later, she began having seizures of the same frequency, beginning on

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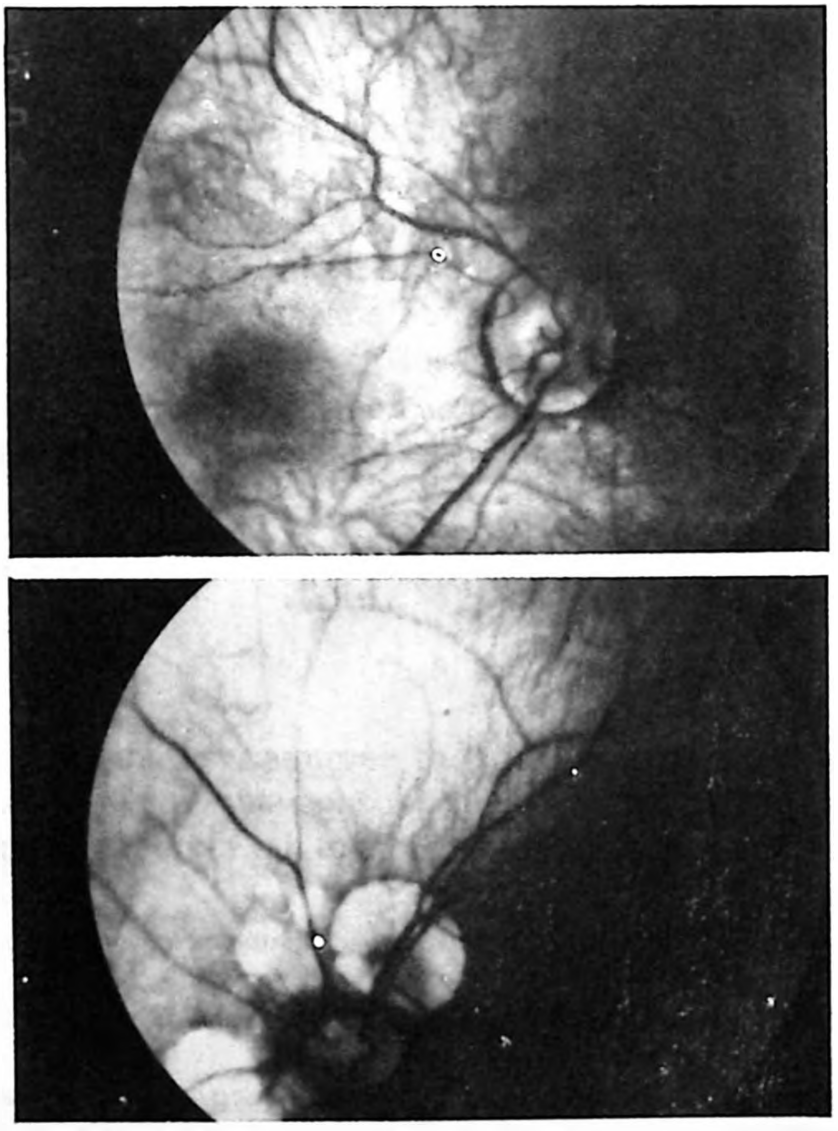
the right side of the body but sometimes becoming generalized. She was the first child of a 30-year-old, healthy mother and 32-year-old, healthy father. After an uncomplicated gestation, she was born at term by cesarean section, with a birth weight of 3200 g. No perinatal anoxia was described. There was no consanguinity.

On admission, the patient's weight was 5500 g (50th percentile), length was 60 cm (75th percentile), head circumference was 38 cm (20th percentile), and her vital signs were normal and stable. Circulatory and respiratory system and abdominal findings were normal. She had good sucking and Moro reflexes and good muscle tone. Deep muscle stretch reflexes were normal. She could not hold her head in an upright position. When she was in the prone position, she could not elevate her head. Her eyes did not follow light. An ophthalmological evaluation revealed ptosis and exotropia in the right eye; colobomatous optic discs which were smaller on the right, large and ovoid on the left; and chorioretinal lacunae and depigmented areas on the retinae (Figs. 1, 2).



Figs. 1, 2: Fundus photographs of the patient's right and left eyes showing colobomatous discs, irregularly shaped lacunae and hypopigmentation and hyperpigmentation areas near the discs.

Laboratory findings: complete blood count, serum glucose, urea, electrolytes, aminotransferase, calcium, phosphorus, ammonia, urine analysis, blood gas analysis, cerebrospinal fluid (CSF) examination, urine metabolic screening and amino acid chromatography of blood were normal. TORCH titers were negative. Chromosome analysis revealed 46, XX. Chest and spine radiographs were normal. Cranial computed tomography revealed cerebral atrophy and agenesis of the corpus callosum (Fig. 3). On her first electroencephalography (EEG), there was no abnormal discharge, and the background activity was relatively normal on the right side of the brain; on the left side, however, there were no sleep spindles and many high-amplitude sharp wave, poly spike and wave discharges which appeared in intervals of varying lengths and lasted 0.5-3 sec. along with irregular background activity (Fig. 4). These findings persisted despite intravenous infusion of 100 mg pyridoxine.

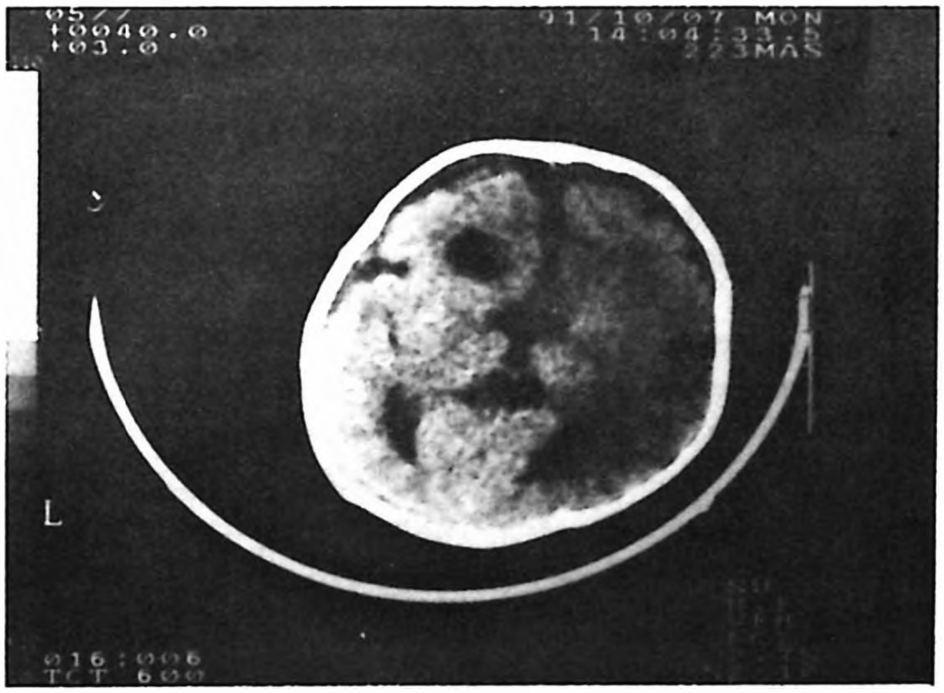


Fig. 3: Computerized tomographic scan of the patient showing cortical atrophy and agenesis of corpus callosum.

After admission to the hospital, the patient's secondary generalized seizures were controlled by oral phenobarbital at a dose of 5 mg/kg/day. Her myoclonic seizures were extensor in type (Fig. 5). For these myoclonic seizures, oral clonazepam was started at a dose of 0.05 mg/kg/day and gradually increased to 0.17 mg/kg/day. Clonazepam was then discontinued and valproic acid was given at an initial dose of 10 mg/kg/day, and gradually increased to 30 mg/kg/day. Administration of course of adrenocorticotropic hormone (ACTH) at a dose of 0.5 mg once per week intramuscularly was attempted twice. The first time was to be a 10

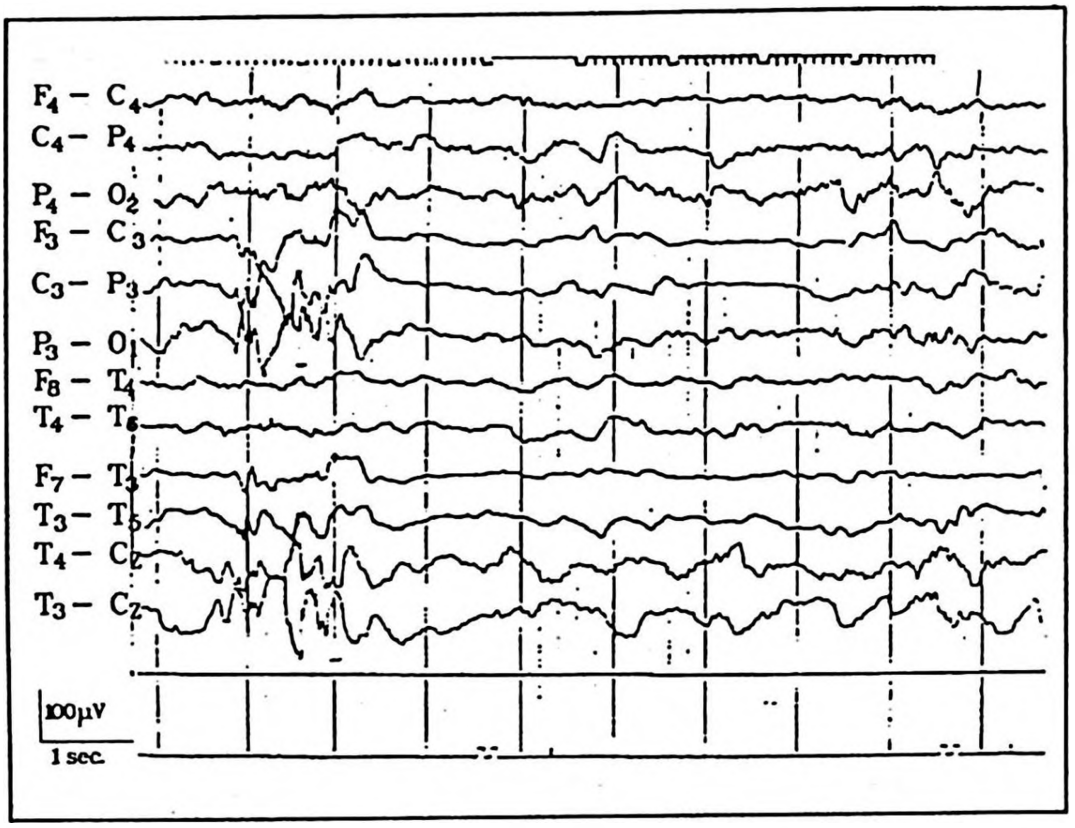


Fig. 4: The first EEG of the patient at 3 months of age showing normal right hemisphere, abnormal background activity and epileptiform discharges with irregular intervals and partial suppression periods on the left hemisphere.

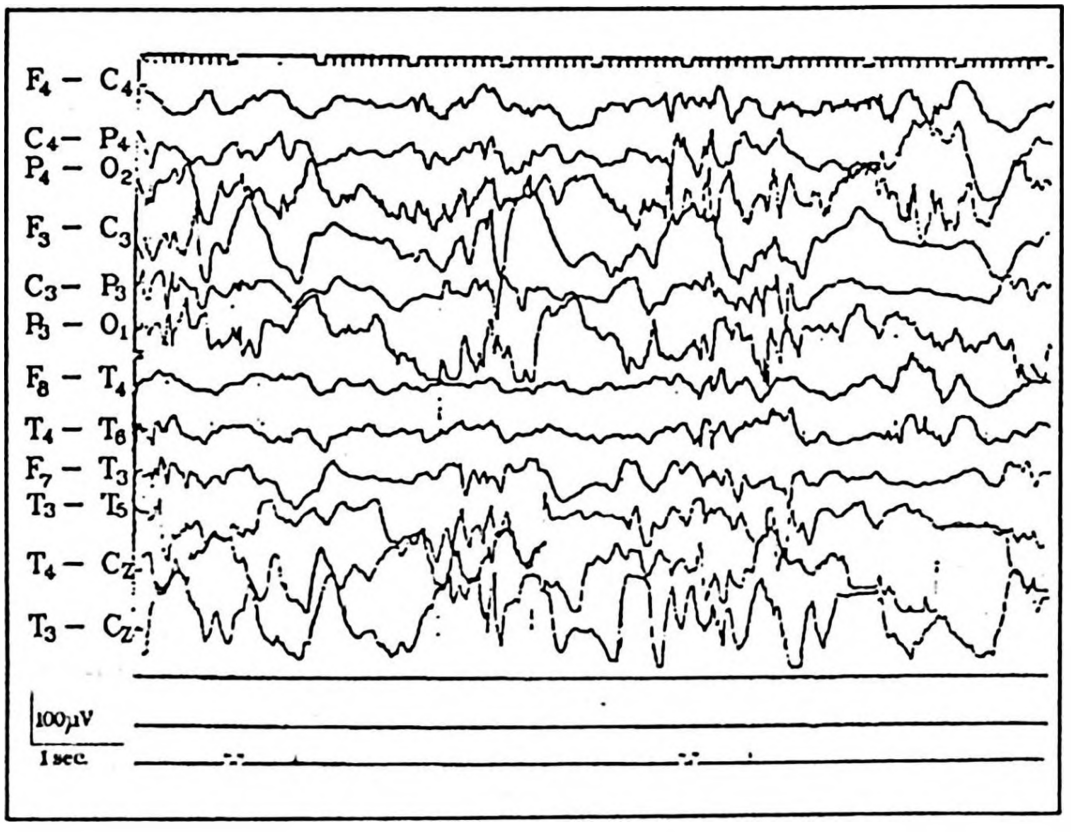


Fig. 5: An EEG obtained at 11th months showing abnormal discharges on the right hemisphere and increase of abnormal discharges and suppression periods on the left.

week course and the second a six week course, but both times it needed to be discontinued because of pulmonary infection. This medication provided only partial control of myoclonic seizures. Abnormal discharges on EEG, which were seen only on the left side at the beginning, appeared on the right side, though were less severe, when the patient was eight months old. The asymmetry of sleep spindles, irregularity of background activity, abnormal discharges and suppression periods were continuous. However, abnormal discharges increased, sleep spindles on the right decreased, background activity became more irregular and multiple spike activity appeared when the patient was 11 months old.

Discussion

Our patient had the characteristic features of this syndrome as described by Aicardi[1,8], such as female sex, infantile spasms, mental subnormality, specific EEG abnormalities, agenesis of the corpus callosum and chorioretinal lacunar defects, but did not have costovertebral anomalies. Aicardi et al[8] reported that chorioretinal defects were diagnostic for this syndrome.

The etiologic origin of the syndrome has been debated since the original description. The commisural plate, which develops from the commisura anterior, is formed in the fetus between the fourth and seventh weeks of gestation. The corpus callosum is formed by intussusception during the third month. The retinal pigment appears in the fourth week and the choroidal pigment in the fifth; the papilla also closes during the fifth week. The pathogenetic agent, either exogenous or endogenous, should work at this time or earlier[4]. Although early intrauterine insults by exogenous agents can lead to severe developmental anomalies, the tests for infective and toxic agents have been negative[9]. Aicardi et al[8] reported that this syndrome is most-likely inherited as an X-linked dominant trait with lethality in the male hemizygote. This is a rare mode of inheritance but has been described in several human diseases[10,11]. The occurrence of this syndrome exclusively in females, with exception of one male with 47, XXY karyotype, is very suggestive of an X-linked mutational event. Occurrence in a single dizygotic twin[12] confirms this concept. A balanced de novo X/3 translocation was detected in one patient, suggesting that the affected gene is located on the short arm of the X chromosome[11]. Until Moline et al[13] described two cases in sisters, not twins, the offspring of healthy parents, this syndrome was described in six sets of twins, five dizygous and one unspecified[14], and the occurrence of more than one case in the some family was not reported. This fact supported the concept of X-chromosome mutation. The occurrence of two cases in the same family with normal phenotypic mother[13] decreased the possibility of X-linked dominant inheritence of the disorder. A germinal mutation in one of the X-chromosomes of either the father or the mother may explain these two cases in the same family. In a study done to detect an X-chromosome inactivation pattern

in peripheral lymphocytes from seven patients with Aicardi syndrome, Neidich et al[15] reported the absence of a random X-inactivation pattern; however, some exhibited a skewed X-inactivation pattern, suggesting the occurrence of an X-linked locus. Again, in this study no deletion in X-chromosome was detected.

Aicardi et al[8] reported that the average age of onset of seizures was 1.8 months with range of one day to 4 months; the age of onset of flexor spasm ranged from one to five months. The onset of myoclonic jerking in our patient was at the age of 40 days, while focal seizures started at the age of two months. Myoclonic seizures, generally reported in the literature as flexor in type, were extensor in type in our patient. But there are several cases with extensor spasms reported in the literature[13]. Other than myoclonic, the seizure type was usually focal in the original series of Aicardi[8,16], as it was in our case. It was reported that the frequency of seizures and the severity of psychomotor retardion varied from case to case[15]. The seizures were usually refractory to therapy, as in our case. Intractibility of epileptic seizures, the type of EEG abnormalities, and severe mental retardation are related to cortical heterotopias, and they are never present in children with isolated agenesis of the corpus callosum[16]. The lacunae vary in size from 0.1 mm to several disc diameters and have a sharply demarcated "punched out" appearance (Fig. 1, 2). The other reported eye findings included microphthalmia, hypopigmented and hyperpigmented areas on the retina, persistent pupillary membrane, iris synechiae, staphyloma and glial tissue on the disc and retina[16-18]. Many other congenital anomalies have been described in numerous cases. These include ventricular dilatation, Dandy-Walker malformation, cerebral and cerebellar atrophy, papilloma of the choroid plexus, microgyria, lissencephaly, cleft lip and palate, costovertebral dysplasias, segmentation and fusion of vertebrae, absence of dorsal vertebrae and dorsal portion of ribs, hemivertebrae, scoliosis, plagiocephaly, syndactyly and other bone abnormalities[16,19].

Fariello et al[16] reviewed 32 EEGs from six cases of Aicardi syndrome and reported that there was a characteristic EEG pattern in all cases which included multifocal epileptiform anomaly, burst- suppressions, and asynchronous activity in the two hemispheres as if coming from different brains; after six months the EEG pattern included multifocal epileptiform discharges over a quite irregular background activity, no normal electrophysiologic sleep activity such as sleep spindle, vertex sharp wave and K-complex. They suggested that these characteristic EEG features are important clues in the diagnosis of Aicardi syndrome. When our patient was three-months old, there was irregular background activity without sleep spindle, abnormal discharges coming with irregular intervals consisting of sharp wave, spike and wave, and polyspike and wave which lasted 0.5-1 sec, after which partial suppression periods were seen in the left hemisphere; however, the

right hemisphere displayed normal background activity and sleep spindles and no abnormal discharge. On the EEGs in the 6th, 7th, 8th and 10th months, irregular background activity, independent activity of the two hemispheres and suppression periods persisted. During therapy with ACTH, abnormal discharges decreased. But after discontinuing this medication, abnormal discharges were also seen in the right hemisphere and increased in the left. Dennis and Bower[20] reported two important features of EEG in a case of Aicardi syndrome. One feature was independence of bioelectric activities of the two hemispheres, and the other was periodicity. We detected independence of bioelectric activities of the two hemispheres and the presence of abnormal discharges in both hemispheres, but did not see periodicity in five consecutive EEGs of our case.

Prognosis is poor in Aicardi syndrome. Although one case survived until at least 15 years of age, all other cases died within the first decade –most within the first several years– because of respiratory infections[2,5]. Psychomotor retardation is evident and seizures are intractable, as in our patient.

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The Turkish Journal of Pediatrics 35: 313-317, 1993

THE UROLOGICAL MANIFESTATIONS OF THE TETHERED SPINAL CORD*

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SUMMARY: Kavukçu S, Özaksoy D, Türkmen M, Kovanlıkaya İ, Köse G, Tavlı V. (Departments of Pediatrics and Radiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). The urological manifestations of the tethered spinal cord. Turk J Pediatr 1993; 35: 313-317.

The tethered cord is the fixation of the cord resulting in stretching as growth occurs. In this paper, three cases of tethered cord with symptoms related to the urinary tract were presented. In the first case, a 12-year-old girl presenting with abdominal pain and urinary incontinence had bilateral hydronephrosis and neurogenic bladder due to a tethered cord without having any other neuropathological manifestation. In the second case, an eight-year-old girl presented with enuresis and a mass in her back was found to have a lipomyomeningocele, hyperactive tendon reflexes in the lower limbs and pes cavus. Tethered cord associated with lipomyomeningocele caused a neurogenic bladder and bilateral hydronephrosis. In the third case, a seven-month-old girl presented with hydrocephalus as well as bilateral dilation of the renal pelvis, unilateral ureteral duplication and vesicoureteral reflux. A tethered cord was revealed in this patient, who had a meningomyelocele operation in the neonatal period. Renal function test in the first two cases were abnormal. *Key words: tethered spinal cord, bladder dysfunction.*

The tethered spinal cord is the fixation of the cord in a caudal location resulting in stretching and ischemia of the cord as growth occurs. Presenting symptoms and signs include motor and sensory deficit of the lower limbs, muscle atrophy, spastic gait, hypo- or hyperactive tendon reflexes, neurogenic bladder, urinary tract infections, stool soiling, scoliosis, pes cavus and talipes[1,2].

Three cases of tethered spinal cord were referred to our clinic with initial symptoms related to the urinary system.

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Case Reports

Case 1

A 12-year-old girl presenting with abdominal pain and urinary incontinence showed no abnormalities on her physical examination. Urine analysis revealed pyuria and bacteriuria. Urine density was 1005; BUN: 50 mg/dl; serum creatinine: 2 mg/dl; endogenous creatinine clearence: 65 ml/min/1.73 m^2. Bilateral hydronephrosis and neurogenic bladder were present. The diagnosis of tethered cord was made using magnetic resonance (MR) imaging. In the sagittal T_1 weighted images, the caudal spinal cord seemed thinner and the dural sac terminated at the S_1 level, fatty tissue filled the rest of the canal (Fig. 1).

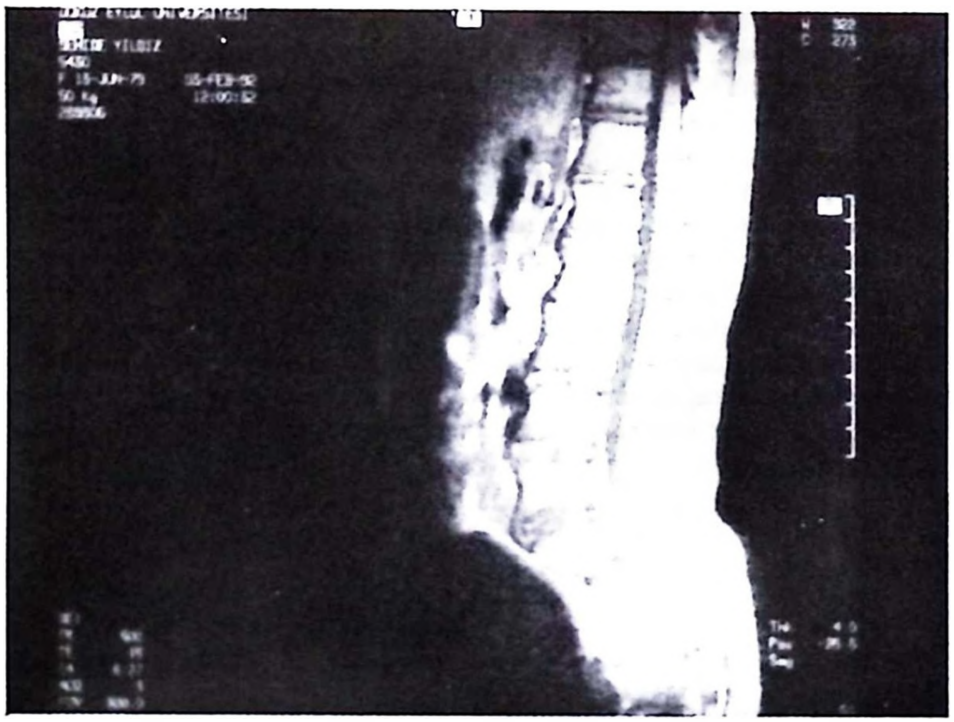

Fig. 1: In the sagittal T_1 weighted MR images, caudal spinal cord seemed thinner and dural sac terminated at S_1 level, fatty tissue filled the rest of the canal. (SE, TR 500, TE 15)

Case 2

An eight-year-old girl presented with fever, enuresis, malaise and masses in her back and abdomen. Physical examination revealed a cystic mass in the left lower abdominal region, a lipomyomeningocele in the lumbosacral region, hyperactive tendon reflexes in the lower limbs, hypotonic anal reflex and pes cavus. Urine analysis showed pyuria and bacteriuria. Urine density was 1010; BUN: 60 mg/dl; serum creatinine: 3.9 mg/dl; endogenous creatinine clearence: 50 ml/min/1.73 m^2. There was left-sided, fourth-degree vesicoureteral reflux with bilateral hydronephrosis and neurogenic bladder. Her sagittal T_1 weighted MR images showed lipomyomeningocele, which displaced the conus and its neural attachments downward (Fig. 2).

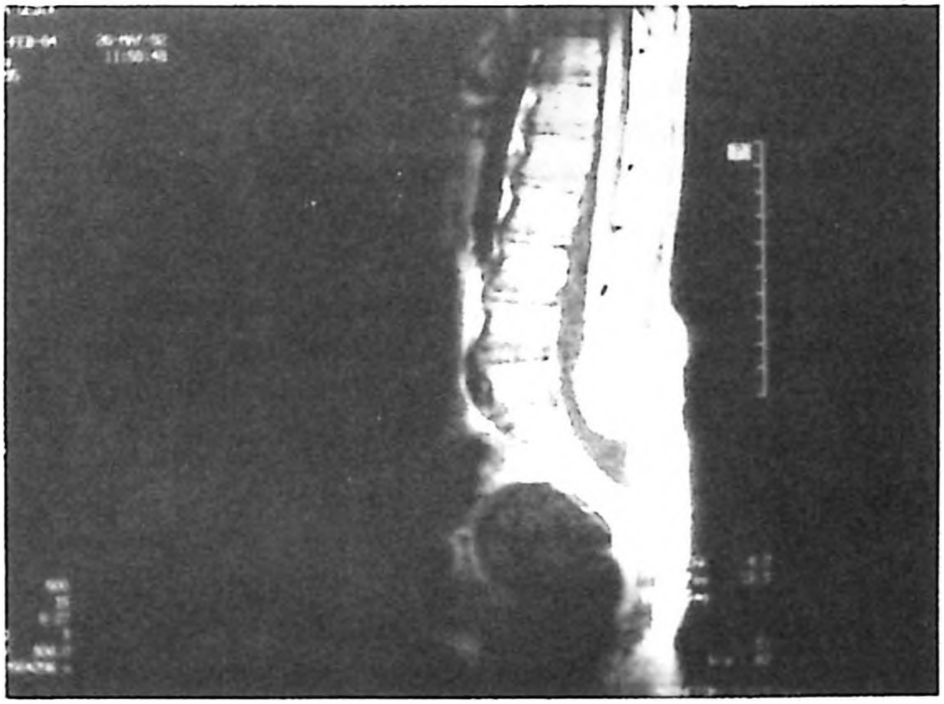

Fig. 2: Sagittal T_1 weighted MR imaging showed lipomyomeningocele which displaced the conus and its neural attachments downward. (SE, TR 500, TE 15)

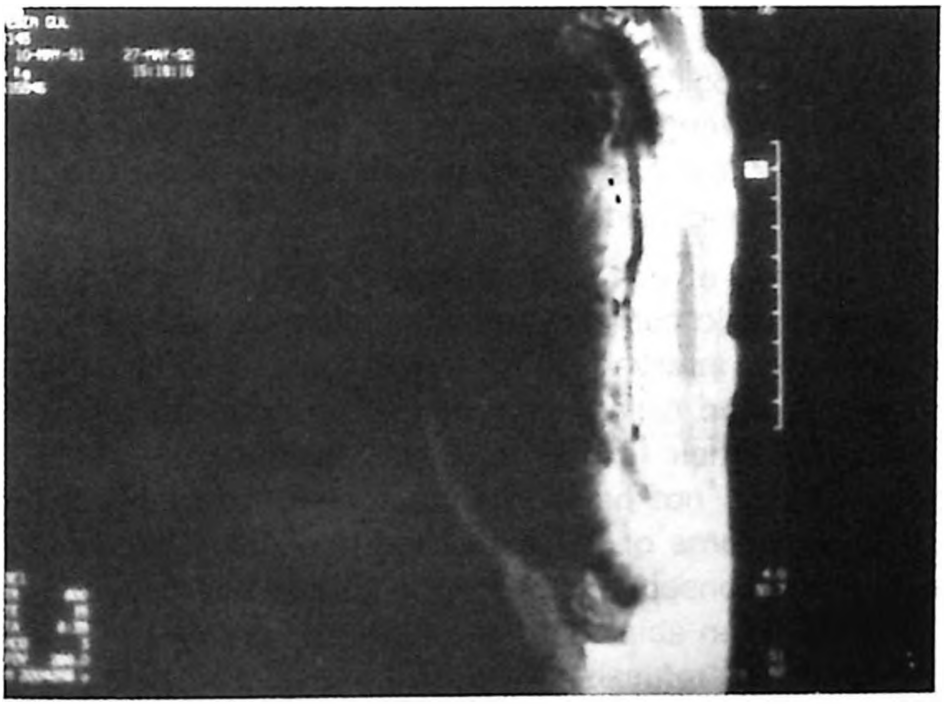

Fig. 3: Sagittal T_1 weighted MR imaging revealed a thin, elongated spinal cord terminating with a lipoma and cervical-thoracal syringomyelia. (SE, TR 500, TE 15)

Case 3

This seven-month-old girl presented with recurring fevers. In her history, the patient had a myelomeningocele and was operated on as a newborn. On her physical examination, she had hydrocephalus and her lower limbs were hypotonic with hypoactive tendon reflexes. Kidney function was within normal limits. She had bacteriuria and pyuria. There was unilateral ureter duplication, bilateral dilation of the renal pelvis, and unilateral ureter with vesicureteral reflux. Sagittal T_1 weighted MR imaging revealed a thin, elongated spinal cord terminating with a lipoma. The thickness of filum terminale at S_1 level was more than 2 mm in repeated sections. Moreover, cervical and thoracal syringomyelia was present (Fig. 3).

Discussion

Magnetic resonance imaging is proven to be safe and valuable in the diagnosis of intrinsic spinal cord disease[1]. Children with tethered spinal cord present in many different ways. About 20% of patients with cord tethering will have a neurogenic bladder and may present to the pediatrician or urologist with recurrent urinary infections, enuresis or an other disturbance of micturition; often neurological abnormalities or deformity in the legs suggest the diagnosis, but tethering can be responsible for a neurogenic bladder without any other manifestations[3]. The first case is an example of an initial presentation with only neurogenic bladder, and no accompanying neurological manifestations. The other two cases presented with both urinary and neurological symptoms. Neuropathic bladder was identified using ultrasonography, excretory pyelogram and cystourethrogram in the second and third cases. In the first case, a urodynamic study was used in the further assessment of neurogenic bladder.

In general, the outcome of early neurosurgical intervention is excellent for the resolution of nephropathic complications secondary to tethered spinal cord[4-6]. Therefore, neurosurgical intervention for the first case was considered to be too late. The first and second cases are receiving intermittent catheterization and systemic antibiotics in their follow-up. In the second case, the extirpation of lipomyomeningocele has not helped in the prevention of bladder dysfunction progression. The symptoms of the third case may either be due to congenital neuropathology or the consequence of neurosurgical extirpation in the neonatal period. We have not been able to do any further intervention on the third case because of her parents' refusal.

In our experience, as the patient grows older, obstructive nephropathy becomes more prominent. This fact emphasizes the importance of early diagnosis and intervention. In conclusion, tethered spinal cord should be considered in all patients presenting with only bladder dysfunction and no accompanying neurolo-

gical symptoms in order to facilitate early intervention so that the progression of obstructive uropathy or nephropathy can be minimized.

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LEPRECHAUNISM (DONOHUE'S SYNDROME): A CASE REPORT*

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SUMMARY: Tokatlı A, Özsoylu Ş, Özme Ş. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Leprechaunism (Donohue's Syndrome): A case report. Turk J Pediatr 1993; 35: 319-322.

Features of leprechaunism, including low-birth weight, a grotesque elfin face with clubbed nose, hirsutism, large low-set ears, enlarge external genitalia, distended abdomen with emaciated extremities, and growth and motor retardation were present in a 3-month-old girl. Because of parental consanguinity in this patient, a recessive mode of inheritence seems likely. *Key words: leprechaunism, female infant.*

In 1948, Donohue WL[1] described an infant with grotesque elfin facies, a flat nasal bridge, flaring nostrils, thick lips, hirsutism, large low-set ears, enlarged external genitalia and psychomotor retardation. Because of an associated endocrine disturbance, he called the syndrome "dysendocrinism". Since Donohue's original description, 37 additional cases have been described[2].

The name of dysendocrinism has been abandoned and the term "leprechaunism" is generally accepted.

We report here an additional patient who has the features of leprechaunism.

Case Report

A.K., a 3-month-old girl, was admitted to Hacettepe Children's Hospital with growth retardation. The patient was born to parents who were first cousins after a normal, full-term pregnancy. The birth weight was 2750 g. The mother noticed failure to thrive and delay in the motor developmental milestones of baby. One sibling had been similar in appearence to this child. The sibling had been admitted to the hospital when she was 4 months old with loose skin, elfin facies, hepatosplenomegaly and retarded bone age. Her liver biopsy revealed non-specific changes.

On admission, the general appearence of the patient was that of an emaciated, underdeveloped infant with an unusual face; her weight was 4100 g (<3rd

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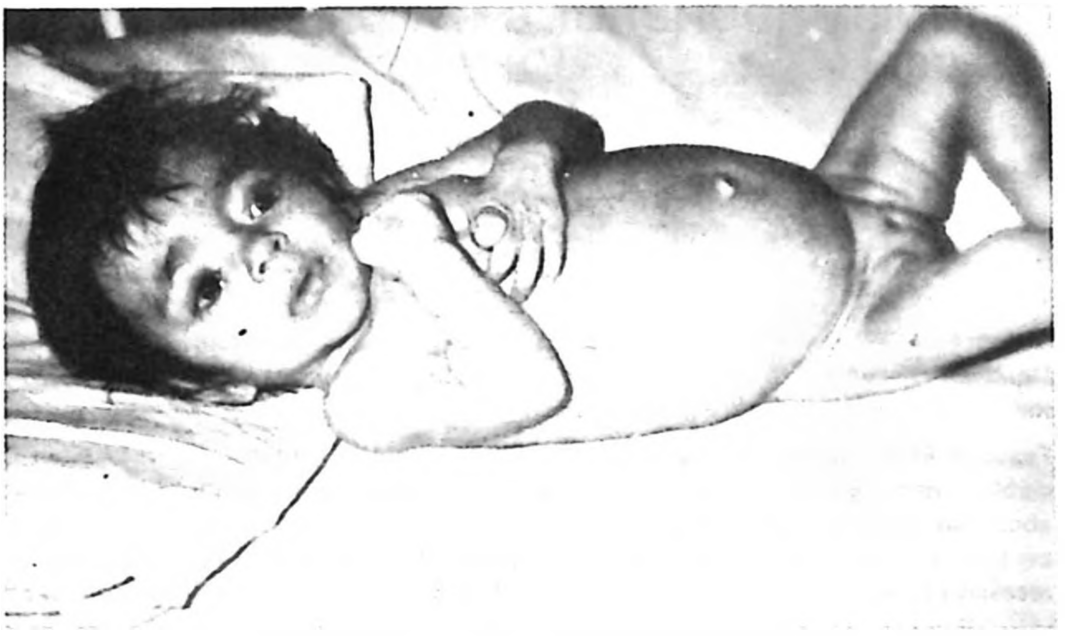

Fig. 1: General appearance of the patient.

percentile), height was 58 cm (25th percentile), head circumference was 39 cm (25th percentile) (Fig. 1). The skin was loose with minimal subcutaneous fat. There was generalized hirsutism, involving mainly the forehead, back and arms. The scalp hair was sparse but long and silky and extended down over the forehead. Examination of the eyes revealed long eyelashes, thick eyebrows and hypertelorism. The ears were large and low-set. The nasal bridge was flat, and clubbed nose was observed. The lips were thick, the palate was narrowly arched and micrognathia was present. The nipples were somewhat prominent and the abdomen was distended (Fig. 2). The liver and spleen edges were palpated 7 cm

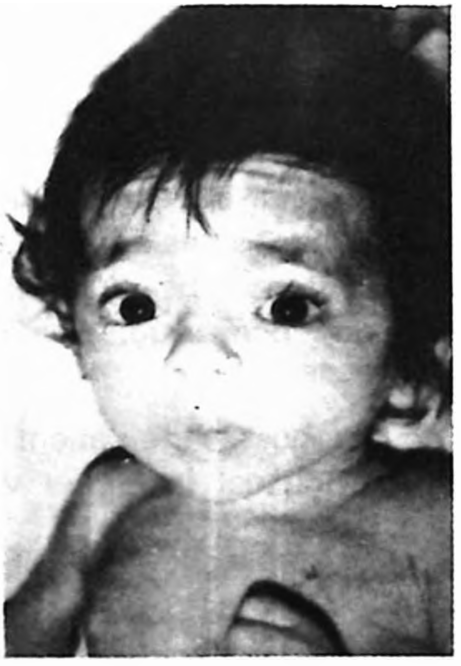

Fig. 2: Facial appearance of the patient.

below the respective costal margins. External female genitalia appeared to be normally formed but were markedly prominent. The extremities were normal but markedly thin. A generalized decrease in muscle mass and muscle tone was noted. The patient could not hold up her head, but she could follow objects with her eyes.

The complete blood count, urine analysis, blood urea nitrogen, levels of chloride, sodium, potassium, calcium, phosphorus, uric acid, creatinine, cholesterol and total lipids were all within normal limits. The blood glucose level was low (28 mg/dl). Serum GOT, GPT, alkaline phosphatase, bilirubin, PT and PTT were elevated, and PT and PTT did not return to normal after vitamin K administration. Serologic markers of viral hepatitis were negative. A mild non-specific generalized aminoaciduria was detected. Urine mucopolysaccharides were negative, and bone age was found to be somewhat retarded (bone age of one month with chronological age of three months). The bone marrow aspiration did not show any storage cells, and liver biopsy could not be obtained because of elevated PT and PTT.

Discussion

It has been emphasized that "the description of any patient as an example of Donohue's syndrome is based upon the clinical appearance, since no characteristic laboratory or histologic features are known"[3].

The diagnosis of our patient was based on clinical findings and comparison with Donohue's original cases and the previously reported cases. Some cases had enlarged liver and spleen[4,5], but none of the previous cases had massive hepatosplenomegaly, which was found in our case.

Recently, an inherited defect in a high-affinity insulin receptor was considered in the pathogenesis of this syndrome[6-8]. The biochemical evidence for this insulin resistance includes elevated plasma insulin levels, impaired glucose homeostasis, absence of anti-insulin-receptor antibodies and altered insulin-receptor binding. Although the plasma insulin level or anti-insulin receptor antibodies could not be studied, hypoglycemia was also documented in our case.

Because of parental consanguinity noted in several of the earlier cases, recessive inheritance is considered to be a possible factor[1,9,10]. In the present report, there was a history of a sibling who was similar in appearance, and the parents were first cousins These factors emphasize that the mode of inheritance is autosomal recessive.

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THE INFLUENCE OF PULMONARY INSUFFICIENCY ON VENTRICULAR FUNCTION FOLLOWING TOTAL CORRECTION OF FALLOT'S TETRALOGY: EVALUATION USING RADIONUCLIDE VENTRICULOGRAPHY AND CLINICAL FINDINGS*

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SUMMARY: Arsan S, Yorgancıoğlu C, Paşaoğlu İ, Erbaş B, Bozer YB. (Department of Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). The influence of pulmonary insufficiency on ventricular function following total correction of Fallot's tetralogy: evaluation using radionuclide ventriculography and clinical findings. Turk J Pediatr 1993; 35: 323-331.

Long-standing pulmonary insufficiency after repair of tetralogy of Fallot may adversely affect ventricular function. We evaluated 20 patients postoperatively by radionuclide ventriculography and clinical findings after total correction of tetralogy of Fallot. Patients were divided into two groups as follows: Group I patients (10) had no pulmonary insufficiency; Group II patients (10) had moderate or severe pulmonary insufficiency. Preoperatively, there was no difference between groups in terms of age, functional capacity according to the New York Heart Association criteria, hemoglobin and hematocrit level, cardiothoracic ratio, McGoon ratio, left and right ventricular ejection fraction, cardiac output or cardiac index. Postoperatively, right ventricular ejection fraction was 40.10 ± 2.28 in Group I and 29.5 ± 2.86 in Group II, $p < 0.01$. Left ventricular ejection fraction was 59.3 ± 2.90 in Group I and 50.9 ± 4.19 in Group II, $p < 0.01$. Radionuclide ventriculography is a useful means of identifying right ventricular dysfunction following repair of tetralogy of Fallot. The dysfunction appears significantly worse in patients with pulmonary insufficiency. *Key words: tetralogy of Fallot, pulmonary insufficiency, radionuclide ventriculography.*

Complete repair of tetralogy of Fallot (TOF) can be accomplished with low operative mortality and excellent long-term symptomatic benefits[1,2]. Current expectations following complete repair of TOF include low operative risk, abolition of arterial desaturation and polycythemia, prevention of secondary complications,

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the capability to engage in a physically unrestricted lifestyle, and a relatively normal life expectancy. The natural history of surgically repaired TOF still requires additional decades of observation before final conclusions can be formulated[3-6]; however, there is little doubt that surgical treatment has dramatically improved life expectancy.

The technique used to relieve the right ventricular outflow tract obstruction is an important determinant of early and late cardiac function[7,8]. Repair with a transannular patch resulted in pulmonary insufficiency and in some cases exercise intolerance. In particular, longstanding severe pulmonary insufficiency may result in significant right ventricular dysfunction and symptoms[9].

We studied a group of 20 patients after repair of TOF. This report correlates the presence or absence of postrepair pulmonary insufficiency with ventricular function as measured by radionuclide ventriculography.

Material and Methods

A total of 20 patients underwent complete preoperative and postoperative evaluation consisting of echocardiography and radionuclide ventriculography before and after repair of TOF. None of them had additional cardiac defects. The mean age of patients was 5.2 ± 2.1 years (range 2 to 11 years). The functional capacity was noted according to the New York Heart Association criteria. Cardiothoracic ratios were calculated from standard posteroanterior chest roentgenograms. The diameter of the main pulmonary artery, the left and right branches, and the aortic diameter at the level of the diaphragm were measured by M-mode echocardiography, and the McGoon ratio[1] was calculated. Radionuclide ventriculography was performed preoperatively and three days post-operatively by labeling red blood cells with ^{99m}Tc pertechnetate. Phase and amplitude analysis of scintigraphic images and multiharmonic Faurier analysis of time activity curve were generated. Systolic and diastolic functional parameters (right and left ventricular ejection fraction, cardiac output and index and regurgitant fraction) were also calculated. Intra-operatively, right and left ventricular peak systolic pressure, right ventricle end diastolic pressure, and pulmonary artery systolic and diastolic pressure were measured approximately 30 minutes after cardiopulmonary bypass. The post-repair ratio between peak pressure in the right ventricle and that in the left ventricle ($P_{RV/LV}$) was calculated.

Patient Groups: The 20 patients were divided into two groups on the basis of the presence or absence of pulmonary insufficiency. Group I (n = 10) consisted of patients with no pulmonary insufficiency on whom a transannular patch was not used and pulmonary valves were protected. Group II (n = 10) consisted of the remaining patients who had moderate or severe pulmonary insufficiency treated by placement of a transannular patch and excision of pulmonary valve tissue.

Surgical Techniques: All surgery was performed with moderate hypothermia. Aortic cross-clamping was done with topical hypothermia and cold crystalloid cardioplegia. Ventriculotomy was performed vertically in all patients, and the ventricular septal defects were patched by means of interrupted and continuous suture techniques. Infundibular muscle resection was carried out to variable degrees, and commisurotomy was performed when valvular stenosis was also present. In 10 patients, a transannular patch was placed and pulmonary valve tissue was excised.

Statistical analysis: Statistical significance at the 95% confidence level was determined by the two-tailed t test for the difference between two means. Chi square test was also used. Results are expressed as mean ± standard error.

Results

The preoperative features for the 20 patients are shown in Table I. There was no difference in the functional capacity, cardiothoracic ratio, McGoon ratio, right and left ventricular ejection fraction, cardiac output or index between groups. The operative and postoperative features are shown in Table II. The post-repair ratio between peak pressure in the right ventricle and that in the left ventricle, and right ventricular end diastolic pressure were higher in patients with pulmonary regurgitation. In contrast, the peak systolic gradients from the right ventricle to the pulmonary artery were lower in patients with pulmonary regurgitation.

Comparison of ventricular function between the two groups by means of radionuclide ventriculography showed better right and left ventricular function in patients without pulmonary insufficiency. Right ventricular ejection fraction was impaired in both groups, although it was 40.1 ± 2.28 in patients without pulmonary insufficiency (Group I) compared to 29.5 ± 2.86 in patients with pulmonary insufficiency (Group II), $p < 0.01$ (Figs. 1 and 2). Left ventricular ejection fraction as well as cardiac output and index were also better in those patients without residual pulmonary insufficiency (59.3 ± 2.90) than in those with pulmonary insufficiency (50.9 ± 4.19), $p < 0.01$.

There was an inverse correlation ($r = 0.8436$) between the regurgitant fraction and the RVEF (Fig. 3).

Cardiothoracic ratios (Tablo II) in those patients with pulmonary insufficiency in whom a transannular patch had been used (Group II) were significantly greater than those in Group I, $p < 0.01$.

Functional capacity according to New York Heart Association criteria were found to be better in those patients without pulmonary insufficiency than in those patients with pulmonary insufficiency (Fig. 3).

Table I: Preoperative Features

Pts.	FC	CTR	McG.	RVEF	LVEF	CO	CI
Group I.							
1	III	48	0.55	41	68	420	745
2	III	45	0.52	35	56	386	711
3	II	49	0.46	47	65	600	1150
4	II	51	0.35	53	68	558	1053
5	II	55	0.31	51	65	555	1150
6	II	51	0.30	52	82	495	912
7	IV	50	0.58	58	65	588	975
8	III	53	0.51	48	62	493	846
9	III	48	0.48	40	61	1280	1660
10	II	48	0.38	47		612	956
Group II.							
1	III	54	0.45	48	53	412	855
2	II	53	0.32	58	60	715	1360
3	II	50	0.33	44	78	366	844
4	II	48	0.40	48	68	450	812
5	II	46	0.38	52	67	480	952
6	III	45	0.48	43	55	512	945
7	III	48	0.51	51	71	432	915
8	III	51	0.55	59	58	392	769
9	III	55	0.49	47	64	612	1055
10	IV	52	0.55	58	62	512	931

FC : Functional Capacity (According to New York Heart Association).
CTR : Cardiothoracic Ratio (%).
McG : McGoon Ratio.
CO : Right Ventricle Ejection Fraction (%).
RVEF : Cardiac Output (ml/m).
CI : Cardiac Index (ml/m/mP^2).

$$\text{McGoon Ratio} = \frac{\text{Diameter of descending aorta}}{\text{Diameter of left and right pulmonary artery}}$$

Table II: Operative and Portoperative Features

Pts.	$P_{RV/LV}$	RVEDP	Grad.	RVEF	LVEF	CO	CI	CTR
Group I.								
1	0.45	6	12	40	67	430	707	47
2	0.44	10	18	33	60	355	657	46
3	0.30	5	20	50	63	700	1228	46
4	0.29	5	15	52	70	600	1132	45
5	0.36	9	18	45	62	502	1045	45
6	0.35	13	20	38	54	387	716	46
7	0.56	17	23	42	70	560	833	46
8	0.40	11	22	35	51	398	686	48
9	0.41	18	14	36	55	1112	1444	45
10	0.68	22	25	30	41	338	528	45
Group II.								
1	0.64	20	20	35	50	428	892	55
2	0.42	18	10	48	62	815	1538	48
3	0.38	12	8	38	83	405	988	50
4	0.62	21	11	22	40	215	390	55
5	0.36	23	15	28	43	245	490	56
6	0.70	20	13	25	42	270	500	62
7	0.43	18	22	34	53	305	649	55
8	0.56	22	15	24	52	179	351	58
9	0.56	25	17	20	43	302	621	59
10	0.56	20	21	21	41	360	654	57

FC : Functional Capacity (According to New York Heart Association).
CTR : Cardiothoracic Ratio (%).
McG : McGoon Ratio.
RVEF : Right Ventricle Ejection Fraction (%).
CO : Cardiac Output (ml/m).
CI : Cardiac Index (ml/m/mP^2).

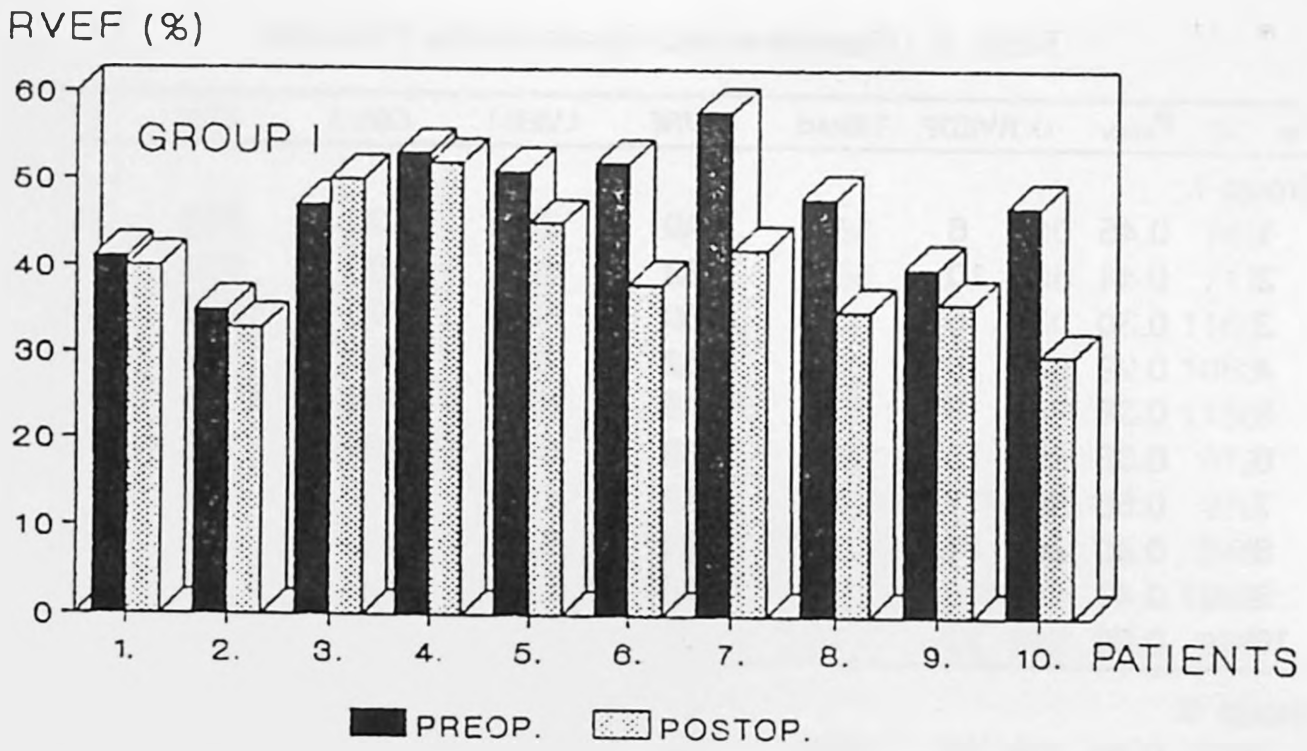

Fig. 1: Comparison of RVEF in Group II patients. RVEF: Right ventricle ejection fraction (%), Preop.: Preoperative, Postop.: Postoperative.

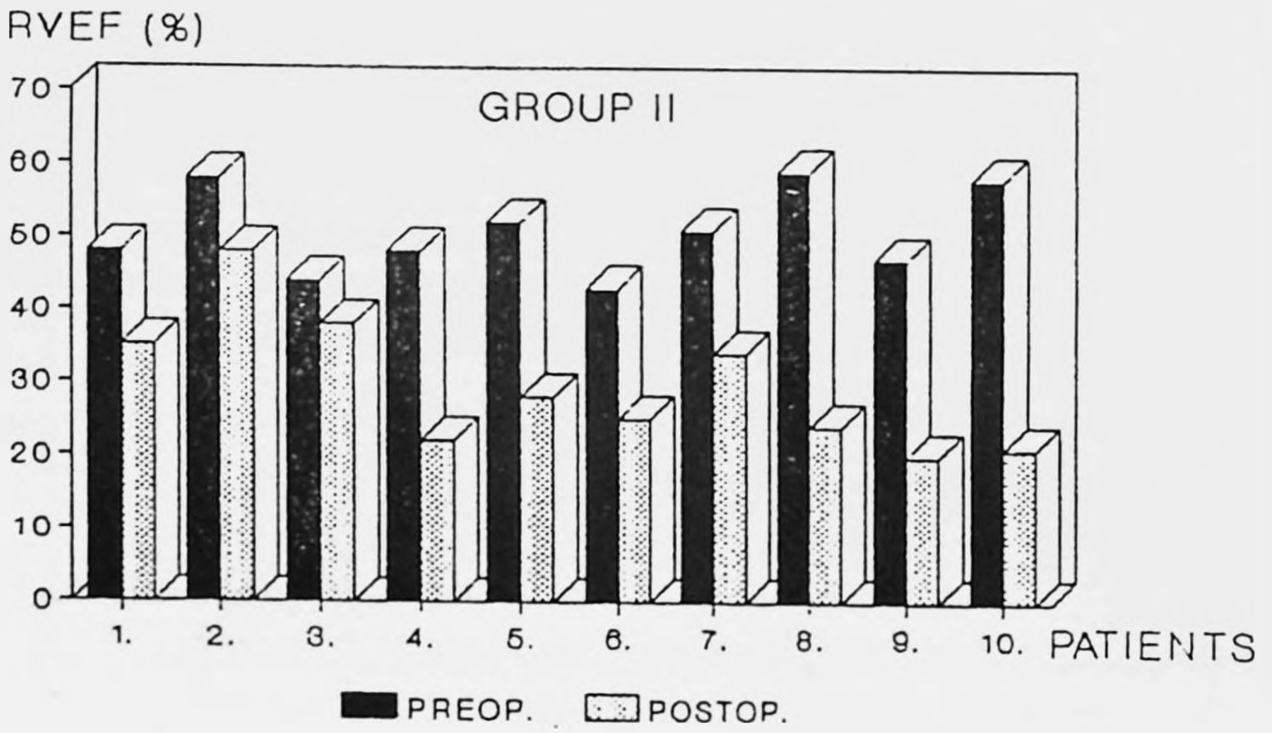

Fig. 2: Comparison of RVEF in Group II patients. RVEF: Right ventricle ejection fraction (%), Preop.: Preoperative, Postop.: Postoperative.

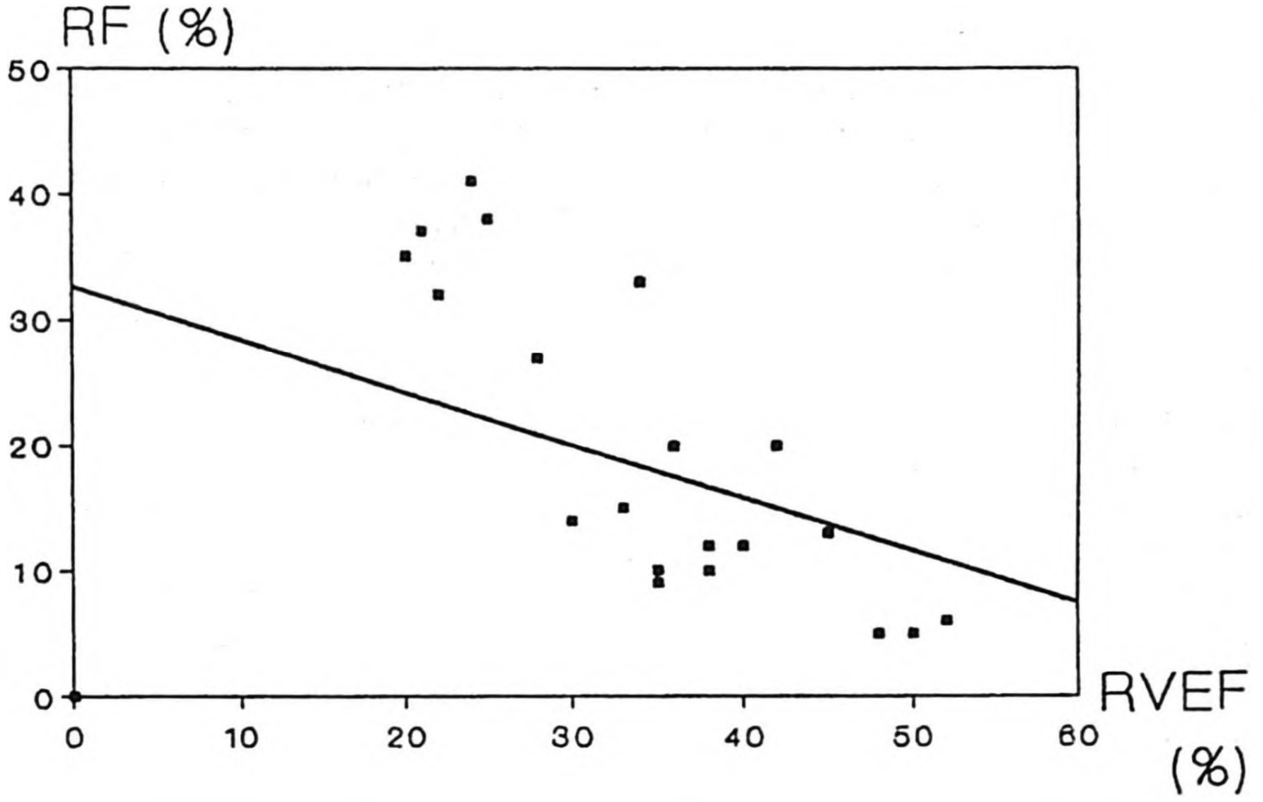

Fig. 3: Inverse correlation between RF and RVEF. RF: Regurgitant fraction (%), RVEF: Right ventricle ejection fraction (%).

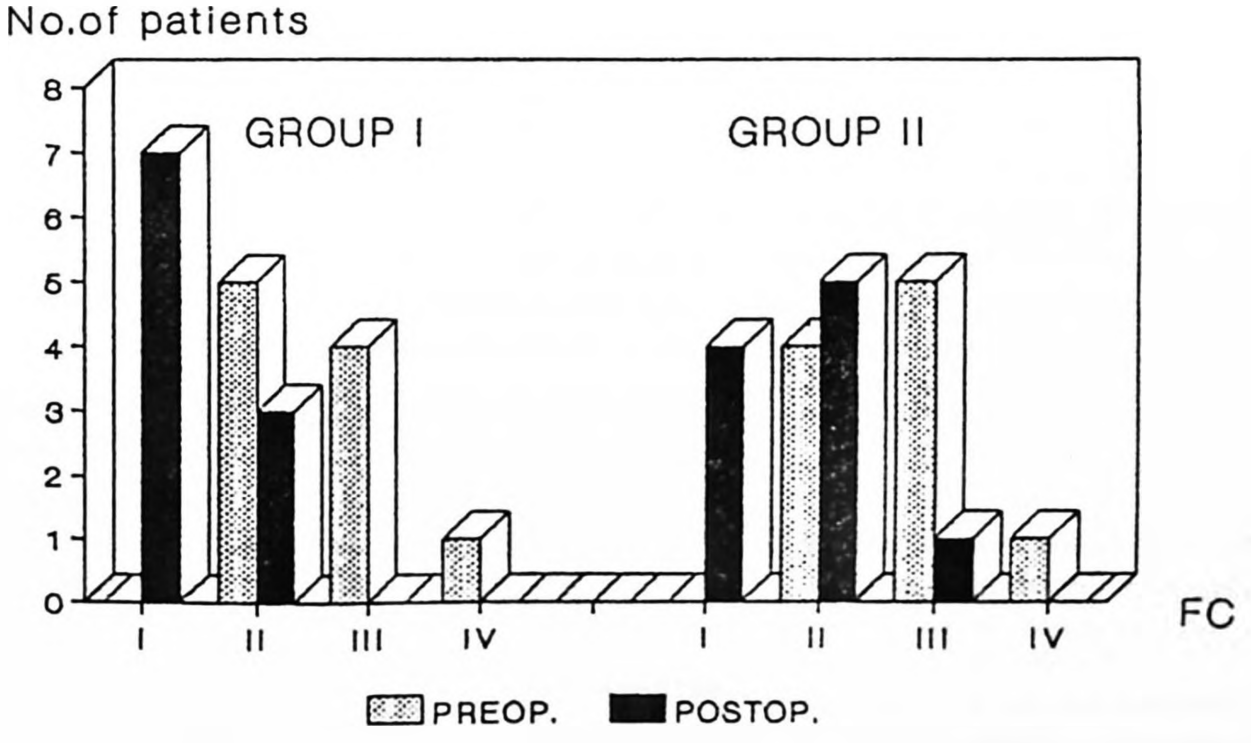

Fig. 4: Comparison of FC according to NYHA in Group I and II patients. FC: Functional capacity.

Discussion

The development of ventricular dysfunction is a widely recognized problem following repair of TOF[10]. The present study indicates that evaluation of symptoms alone is sufficient for detecting patients with impaired ventricular function in the early postoperative period. This study was designed to evaluate selectively the problem of pulmonary insufficiency after repair of TOF.

Radionuclide ventriculography is a proved method of evaluating left ventricular function[11]. Although less well established, its use in evaluating right ventricular function appears to be accepted. Because this technique is independent of the geometry of the ventricular chamber, it is particularly appropriate for use with the right ventricle. Our data indicate that patients with clinically moderate to marked pulmonary insufficiency following repair of TOF have diminished left and right ventricular function compared to patients with no or minimal regurgitation[12-14]. LVEF was normal in Group I patients and below normal in Group II patients. RVEF was impaired in both groups, although group I patients' levels (40.1 ± 2.28) fell not far below the accepted normal of 0.45.

In fact, asymptomatic pulmonary insufficiency after corrective surgery does not seem to guarantee that the patients remain asymptomatic for longer periods[2,5]. The question of surgery for pulmonary insufficiency remains controversial, but there are many good reasons for early repair[15]; one of great relevance is the protection of right ventricular function. If one waits for only the most severe symptoms of right ventricular dysfunction to develop, advanced and irreversible right ventricular damage can occur before the hemodynamic protection of a competent valve is provided. The last problem is perhaps the most intriguing: the alternatives available for creating outflow valve competence. Mechanical valves, heterografts, dacron or porcine conduits and monocusp patch are not suitable in this position[16-18]. Now, the improved characteristics of the viable allograft (aortic or pulmonary) make it the logical choice for all pulmonary ventricle outflow tract reconstructions in patients for whom a valve is indicated[19-22].

In conclusion, the method of radionuclide ventriculography is the most useful noninvasive assessment tool in evaluating postoperative pulmonary insufficiency in asymptomatic patients with an outflow patch across the pulmonary annulus. The deterioration of left and right ventricular function is also correlated with pulmonary insufficiency.

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The Turkish Journal of Pediatrics 35: 333-336, 1993

A CASE OF PRADER WILLI SYNDROME WITH DEL 15 (q11 → q13)*

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SUMMARY: Tunçman G, Tükün A, Yalaz K, Bökesoy I. (Department of Medical Biology, Ankara University Faculty of Medicine, Ankara, Turkey). A case of Prader Willi syndrome with del15 (q11 → q13). Turk J Pediatr 1993; 35: 333-336.

Prader Willi syndrome is a sporadically seen genetic disease with an incidence of 1:25.000. In 56% of cases there is an interstitial deletion (q11 → q13) on chromosome 15.

Cytogenetic analysis was performed on a four-year-old girl with obesity, mental retardation, recurrent febrile convulsions and a provisional diagnosis of Prader Willi syndrome. High-resolution banding was done to observe the subchromosomal deletion. An interstitial deletion (q11 → q13) on one of the 15th chromosomes was observed in all metaphases. *Key words: PWS, clinical manifestations, cytogenetic findings, chromosome 15.*

Prader-Willi Syndrome (PWS) was first defined by Prader and his colleagues in 1956[1], and hundreds of cases have been reported since then. It is generally seen sporadically with an incidence of 1:25,000. Major clinical features include: infantile hypotonia (94%), an early-childhood manifestation of obesity (94%), mental retardation with an IQ average of 65 (97%), short stature (76%), small hands and feet (83%), hypogenitalism (95%), and a typical facial expression[2].

In 1980, Ledbetter et al[3] were the first to assert that a deletion at 15q could be a cause of PWS. In 56% of cases there is an interstitial deletion (q11 → q13) on chromosome 15[2]. Cytogenetic translocations, inversions and duplications have been reported[2]. Since there is no karyotypical anomaly in 40% of cases, a mutation at the molecular level is also considered to be a possible cause of the PWS[2,4,5].

Variety in the clinical findings of PWS, as in some other autosomal dominant syndromes, has raised questions about the influence of more than one gene expression, and since 1988, it has been placed in a category of "contiguous gene syndrome"[6].

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The other fact that affects the clinical expression is the parental origin of the chromosome, and this encouraged scientists to define some models to explain the diversity of inheritance, including imprinting[2,5]. Since 1989 PWS has been considered to be a result of the phenomenon of imprinting[7].

Case Report

The patient is a four-year-old girl who was admitted to the Medical Faculty of Hacettepe University Pediatric Neurology Department because of her recurrent febrile convulsions. She was sent to our laboratory for cytogenetic analysis with a provisional diagnosis of PWS. She was born by vacuum extraction, with a birth weight of 2,500 g, and her gross motor development was as follows: she lifted her head at approximately the fifth or sixth month of age, she sat without support at the sixth month, she walked holding on to furniture at the age of fifteen months and walked well at the age of three. Despite being on a diet, she progressively gained weight.

The pedigree analysis revealed a parental age of 25 at her birth and no consanguinity. She had a healthy brother.

At the time of admission, the patient was 99 cm tall (10^{th}-20^{th} percentile), weighed 21 kg (90^{th} percentile), and had a head circumference of 47 cm ($< 5^{th}$ percentile). She was obese and hypotonic. On physical examination, she was found to have low-set ears, plain occiput, simian line at the right hand, pes equinus, small labia majora and hirsutism on the legs. T3, T4, lactic acid, and pyruvic acid levels were found to be within normal limits. Bilateral calcifications at the basal ganglia on cranial computed tomography (CT), dysrhythmia at the mid-portions of the left hemisphere on EEG, and myopathy on EMG were depicted, while the muscle biopsy was found to be normal. Because of the patient's age, hypogonadism could not be evaluated.

For cytogenetic analysis, high-resolution chromosomes of the cultured lymphocytes from the patient's peripheral blood were used with Methotrexate synchronisation at the 48^{th} hour and addition of Thymidine for the last five hours[8] (Fig. 1a). An interstitial deletion (q11 → q13) on one of the 15^{th} chromosomes was observed (Fig. 1b) in all metaphases. Parental cytogenetic analysis is planned for the near future.

Discussion

Early-onset obesity, hypotonia and hypogenitalism/hypogonadism are the major findings observed in nearly all cases of PWS[2,9,10]. Obesity and hypotonicity were remarkable in our patient. Investigations of hypopigmentation and small hands/feet have led researchers to name a "contiguous gene syndrome"[2,5,11-13]. Whether there is a correlation between the 15 (q11 → q13) deletion, hypopigmen-

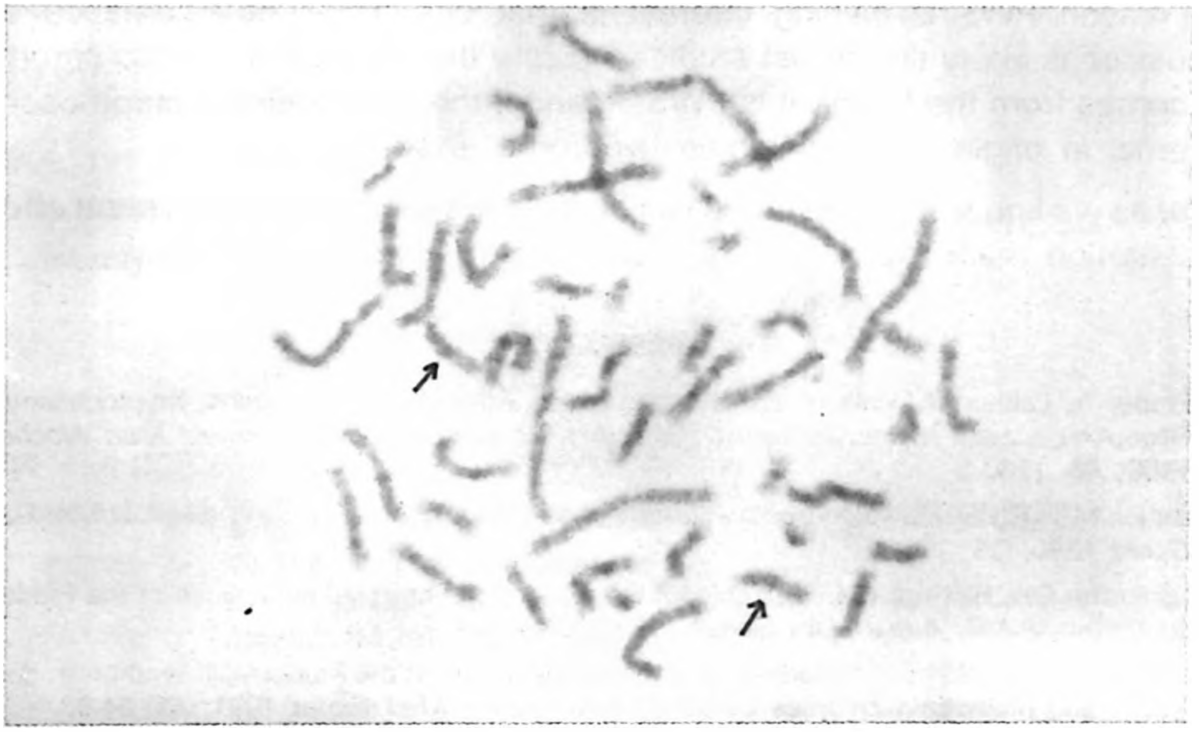

Fig. 1a: The metaphase of the patient.

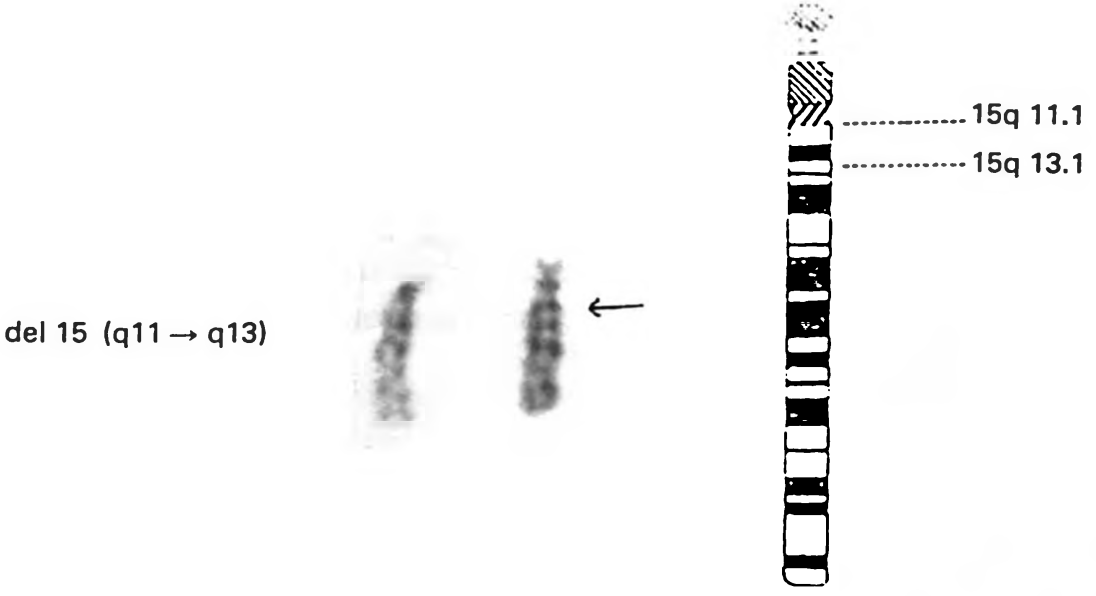

Fig. 1b: Del15 (q11 → q13) is shown at the left side with the ideogram of no 15 on which the deleted region is shown.

tation and small hands/feet is still a matter some controversy, at least at the cytogenetic level. Molecular research suggests that the genes responsible for these characteristics should be separate from the critical PWS locus. And our case supports this theory in that none of these findings was present except deletion.

The reason PWS is gaining interest is that one mode of inheritance under discussion is imprinting. Most studies indicate that when the deleted chromosome comes from the father, it is PWS[2,5], and if the same deleted chromosome is maternal in origin then Angelman syndrome is seen.

As far as we know, this presented case is the first published PWS patient after the presentation made by Kılıç et al[14] with typical deletion in Turkey.

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