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# THE ASSOCIATION OF NEPHROTIC SYNDROME AND RENAL VEIN THROMBOSIS: A CLINICOPATHOLOGICAL ANALYSIS OF EIGHT PEDIATRIC PATIENTS*

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*Key words: nephrotic syndrome, renal vein thrombosis, amyloidosis, childhood, membranoproliferative glomerulonephritis, congenital nephrotic syndrome*

Renal vein thrombosis (RVT) occurs in two forms in childhood: one, the most common life-threatening condition seen in infancy which often presents as acute renal failure usually causing hemorrhagic infarctions of the kidney, and the other, seen in association with the nephrotic syndrome (NS) mainly in older children and rarely in congenital NS cases that are not necessarily associated with infarction of the kidney[1,2]. There has been continual controversy regarding the etiology of the relationship of the nephrotic state to renal venous thrombosis that is, as to whether RVT is a cause or complication of it[3-5].

The incidence of the association of RVT in adult nephrotics is higher in membranous glomerulonephritis (MGN) or membranoproliferative glomerulonephritis (MPGN), ranging from 38 to 50 percent, and is lower in lipoid nephrosis (minimal lesion disease), focal glomerulosclerosis, rapidly progressive glomerulonephritis, amyloidosis, and lupus nephritis[3-7]. The overall incidence of thromboembolism (excluding RVT) is approximately 20 percent in adults and includes the pulmonary embolism, the most common severe type which accounts for eight percent of the cases[6].

When compared to adults, the occurrence of RVT in nephrotic children is rare. The present study evaluates eight pediatric nephrotic cases associated with tissue-diagnosed renal venous thrombosis. Clinical and laboratory findings suggestive of RVT in nephrotic patients are emphasized, and in addition, the association of various types of glomerulonephritis in nephrotic children with RVT and the pathogenesis of this association is discussed.

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## Material and Methods

Cases with a pathological diagnosis of RVT associated with NS were studied retrospectively for clinicopathological evaluation. There was a total 23 RVT cases in two thousand complete and/or partial consecutive pediatric necropsies including two cases of unilateral surgical nephrectomies, eight of which were nephrotic patients. All of the material had been investigated at Hacettepe University Children's Hospital over a nineteen-year period, from 1966 to 1985.

The renal tissues were fixed both in formalin and Dubosque Brasil solution. The sections were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), trichrome and Jone's silver reagent. Phosphotungstic acid hematoxylin (PTAH) stain for fibrin was applied when indicated. Gross and microscopical findings of some of the cases are shown in Figs. 1-7. Clinical and pathological findings of the eight cases are briefly summarized as follows.

## Cases Reports

*Case 1*

A four-day-old female baby was admitted to the hospital because of generalized body swelling since birth. She was the product of a 24-year-old, gravida-4 mother, following a spontaneous vaginal delivery. The placenta was enlarged and had a foul odor. A past history revealed a first-degree consanguineous marriage, and two siblings who had died with generalized edema before the age of two months.

Some of the pertinent clinical and laboratory findings revealed a weight of 3000 g; blood pressure of 85/50 mmHg; the liver three cm and the spleen one cm palpable below the costal margin. Bilateral pretibial pitting edema was present. Urinalysis showed (+++) proteinuria and microscopic hematuria. The hemoglobin level was 19.9 g/dl and white blood cell count 9400/$mm^3$; blood biochemistry revealed total protein 4.3 g/dl, albumin 2 g/dl, total lipids 1500 mg/dl, cholesterol 370 mg/dl, calcium 6 mg/dl; $Na^+$ 165 mEq/lt, $K^+$ 5 mEq/lt, $Cl^-$ 114 mEq/lt and BUN 20 mg/dl. IVP was within normal limits except for double ureters and double renal pelvises.

During the clinical course twitching of the upper extremities developed. On the tenth day of admission bronchopneumonia, and on the twenty-sixth day, diarrhea and sepsis developed. In spite of the administration of appropriate antibiotics and fresh plasma, the baby died on the forty-fifth day of admission.

*Case 2*

A 21-day-old female baby was admitted to the hospital with complaints of diarrhea, failure-to-thrive, and body swelling since birth. The baby's and the family's past histories were unremarkable including pregnancies and deliveries.

There was no parental consanguinity. The pertinent clinical and laboratory findings revealed a weight of 3400 g, blood pressure of 80/60 mmHg, and generalized edema with marked ascites. Urinalysis revealed (+++) proteinuria and hematuria. The hemoglobin level was 7.8 g/dl, white blood cell count 12,800/$mm^3$, peripheral blood smear showed 58% neutrophils with toxic granulation and the disappearance of platelets once during the clinical course; blood biochemistry revealed total protein 3.2 g/dl, albumin 1.6 g/dl, total lipids 21800 mg/dl, cholesterol 1355 mg/dl, creatinine 8 gm/dl, BUN 16 mg/dl, VDRL and dye-test both were negative, and IVP was within normal limits.

During the clinical course in addition to nephrotic state, sepsis complicated by disseminated intravascular coagulation (DIC) had developed. The patient was administered human albumin, antibiotics and dexamethasone. She expired on the eighteenth day of admission, at the age of 39 days.

*Case 3*

A three-month-old male baby was admitted to the hospital with complaints of fever and cough. He was born after an unremarkable pregnancy and there was neither a history of parental consanguinity nor familial disease. He had a healthy one-and-a-half year-old sister.

Physical examination revealed a weight of 4000 g and blood pressure of 90/70 mmHg. He was unconscious, dehydrated, febrile and had tachycardia and tachypnea. There were prominent intercostal retractions and crepitant rales. Only the liver was palpable 1.5 cm below the costal margin. Some of the pathological findings were trace proteinuria and microscopic hematuria; hemoglobin level of 11.79 g/dl decreasing to 8.30 g/dl in two days during which time the white blood cells rose from 8600/$mm^3$ to 15,600/$mm^3$, blood biochemistry revealed BUN 82 mg/dl, $CO_2$ content 8.25 mEq/lt, $Na^+$ 150 mEq/lt, $K^+$ 3.8-8.8 mEq/lt, and $Cl^-$ 116-102 mEq/lt.

During the clinical course septicemia associated with bronchopneumonia, gastroenteritis and dehydration developed. Parenteral fluid, intravenous antibiotics and a transfusion of fresh blood were administered. The patient expired on the fourth day of admission.

*Case 4*

A two-and-a-half-year-old boy was admitted to the hospital with generalized edema and fever of one month's duration. Physical examination revealed a height of 82 cm and weight 13.5 kg. He had edema of the eyelids and lower extremities. Urinalysis showed (+++) proteinuria and microscopic hematuria along with clusters of neutrophils. The hemoglobin level was 13.26 g/dl and white blood cell count 11,600/$mm^3$; blood biochemistry revealed BUN 12 mg/dl, serum total protein

4.1 g/dl, albumin 2.5 g/dl, total lipids 1480 mg/dl, cholesterol 560 mg/dl. IVP was within normal limits. While in the hospital in addition to the nephrotic syndrome tonsillitis, bronchopneumonia and urinary tract infection were diagnosed for which diuretics and appropriate antibiotic therapy were administered. A renal biopsy was performed and the diagnosis was that of membranoproliferative glomerulonephritis for which prednisolone 2 mg/kg/day and cyclophosphamide 5 mg/kg/day were started. On the twenty-first day of admission abdominal pain, vomiting, diarrhea, hypotension, dyspnea, and 5 cm hepatomegaly developed which resulted in his death on the thirty-eighth day of admission.

A stool culture taken prior to his death, and a postmortem blood culture taken after his death yielded *Salmonella paratyphi-B.*

*Case 5*

A 10-year-old-girl was admitted to the hospital with edema, abdominal distention and frequent but diminished urination for the last 15 days. Physical examination revealed a weight of 34 kg, blood pressure of 130/90 mmHg, marked pitting edema of the lower extremities, ascites and hydrothorax.

The relevant laboratory findings were microscopic hematuria; a daily urinary loss of protein of 1.2 g/$m^2$; hemoglobin level of 15 g/dl; white blood cell count 5800/$mm^3$. Blood biochemistry showed BUN 15 mg/dl; creatinine 0.6 mg/dl, total protein 4.4 g/dl, albumin 1.6 g/dl, total lipids 2300 mg/dl, cholesterol 640 mg/dl, $Na^+$ 115 mEq/lt, $K^+$ 4 mEq/lt, $Cl^-$ 95 mEq/lt, and IVP was normal except for duplication of the collecting system of the right side.

Prednisolone in a dose of 2 mg/kg/day along with diuretics and salt-free human albumin infusion were given. No clinical response was observed and the patient died on the thirty-eighth day of admission.

*Case 6*

An 11-year-old girl was admitted to the hospital with edema of the eyelids of 18-months' duration along with generalized edema for two months. There was marked swelling of the right leg for one week and anuria for two days. Physical examination revealed a blood pressure of 100/60 mmHg and pitting edema of the lower extremities.

Laboratory investigations revealed (+++) proteinuria, the presence of pyuria and bacteriuria; hemoglobin level of 8.55 g/dl, and white blood cell count 12.000/$mm^3$. Blood chemistry showed $Na^+$ 125 mEq/lt, $K^+$ 2-9 mEq/lt, $Cl^-$ 106 mEq/lt, $CO_2$ content 9.32 mEq/lt; BUN 53 mg/dl, creatinine 6.5 mg/dl, total lipids 530 mg/dl, cholesterol 112 mg/dl, calcium 7.2 mg/dl, phosphate 7 mg/dl, creatinine clearance 0.8 ml/min/1.73 $m^3$. Urine culture grew $10^5$ *coloni E. coli.* Plane X-ray examination of the abdomen showed enlarged kidneys. During the clinical course, inspite of

appropriate fluid, plasma, and electrolyte therapy, diuresis did not occur so that peritoneal dialysis was performed.

Due to hypotension, and hematochezia, salt-free human albumin was given. No clinical response was observed, and the patient expired on the sixteenth day of admission.

*Case 7*

A 13-year-old girl had a nine-year history of back pain, swelling of the lower extremities which began six months ago, diarrhea, vomiting and tachypnea of one month's duration for which she was hospitalized. Her mother and father were first cousins, and two of their four previous children had died; one at age five months and the other at age one. The other two remaining children were healthy as were the parents.

Clinical and laboratory findings revealed a blood pressure of 90/40 mmHg and pulse rate of 110/min. The patient's general condition was poor; she was dehydrated and had flank pain. Urinalysis showed (+++) proteinuria, pyuria and leukocyte casts. The daily urinary protein loss was 4-5 g/$m^2$; blood biochemistry showed $Na^+$ 126 mEq/lt, $K^+$ 2-3 mEq/lt; $Cl^-$ 110 mEq/lt, $CO_2$ content 9 mEq/lt, BUN 100 mg/dl, creatinine 7.1 mg/dl, total protein 3.5 g/dl, albumin 1.2 g/dl, total lipids 920 mg/dl, cholesterol 213 mg/dl, uric acid 10.6 mg/dl, calcium 8.2 mg/dl, phosphate 6.7 mg/dl, and creatinine clearance 2.4 ml/min/1.73 $m^2$. The chest X-ray was normal; but abdominal ultrasonography revealed bilaterally enlarged kidneys.

During the clinical course the general condition of the patient was poor. Appropriate fluid and electrolyte therapy was administered. She was given a blood transfusion because hematemesis and melena had developed. Peritoneal dialysis was performed because of uremic pericarditis. Her general condition worsened and she died on the tenth day of admission.

*Case 8*

A 10-year-old girl presented with swelling and pain in her joints of a three-year duration along with generalized edema of six months and anuria lasting for four days for which she was hospitalized. Peritoneal dialysis was performed because of chronic renal failure for the last two months. Physical examination revealed a blood pressure of 90/75 mmHg and a pulse rate of 80/min. She had generalized edema. The patient's general condition was very poor. Laboratory findings revealed a hemoglobin level of 3.48 g/dl, white blood cell count 11,000/$mm^3$; blood biochemistry showed $Na^+$ 137 mEq/lt, $K^+$ 5.5 mEq/lt, $Cl^-$ 95 mEq/lt, $CO_2$ content 11.7 mEq/lt, BUN 120 mg/dl, creatinine 3.8 mg/dl, calcium 5.5 mg/dl, phosphate 13.6 mg/dl, total protein 5.2 g/dl, and albumin 2.6 g/dl. No urine sample could be obtained.

Immediately following admission peritoneal dialysis was performed because of a high BUN level and hematemesis. A blood transfusion, appropriate fluid and electrolyte therapy and antibiotics were administered. The patient died on the fourth day of admission.

## Results

In our pathological material consisting of 2000 consecutive pediatric necropsies approximately 1 percent were RVT cases while 0.4 percent were nephrotic patients associated with RVT. In other words, 34 percent of all RVT cases were nephrotic.

The glomerulopathies of these RVT plus NS patients consisted of three cases of Finnish-type congenital NS (FCNS), three cases of renal amyloidosis, and two cases of MPGN. In all the nephrotic patients, a diagnosis of RVT was not made prior to postmortem examination. Four cases in our RVT plus NS series (Case Nos. 1, 2, 3 and 5) showed no distinctive clinical features when compared to the RVT cases without NS (Tables I and II). In Case No. 4, the rapid deterioration of the clinical course could have been related to either complicated salmonellosis or RVT. The common findings during the clinical course of the three renal amyloidosis cases (Case Nos. 6, 7 and 8) were that of rapid deterioration of renal function with the presence of anuria, azotemia and acidosis, and the development of hypotension. Additionally, one of these three cases (Case No. 7) revealed flank pain (Table III).

## Discussion

The association of the nephrotic syndrome and renal vein thrombosis was first recognized in 1840[8]. Before 1956, most cases were diagnosed at postmortem examination. Since then, with the development and application of more advanced radiographic techniques and selective catheterization, intravitam diagnosis of more cases of RVT has been made[7].

The significance of RVT in NS has been a subject of controversy for many years. It was thought that RVT was a cause of NS in 17.7 percent of adult patients[9]. Recent evidence, however, shows that RVT is a complication of NS rather than its cause.

In a prospective study of patients with NS who underwent venography, the incidence of renal vein thrombosis was reported to be 30 percent[1].

There have been many studies showing the hypercoagulable state in nephrotic patients[6,10-12]. It has been shown that patients with NS have an increase in the platelet count and platelet aggregation, fibrinogen, and factors,V, VII, IX and X[2,5,6,11]. Some evidence suggests that fibrinolytic activity is impaired in these

TABLE I: Some of the Clinical and Pathological Findings of Three Cases of Congenital NS Associated with RVT

| Case No. | Age Sex | Clinical diagnosis | Type of pathological study | Final pathological diagnosis | Location of thrombus: Main renal artery | Location of thrombus: Other | Infarct | Extrarenal thrombus |
|---|---|---|---|---|---|---|---|---|
| 1 | 45 days F | Congenital NS Septicemia | Necropsy | – Finnish-type congenital NS (FCNS)<br>– Septicemia<br>– DIC<br>– RVT<br>– Double renal pelvis and ureter | – | Interlobar vein | Microscopic | – Pulmonary vein |
| 2 | 39 days F | Congenital NS Septicemia | Necropsy | – FCNS<br>– Septicemia<br>– DIC<br>– CMV<br>– RVT (UL) (gross) | – | Interlobar Interlobular and arcuate veins | Microscopic | – Inferior vena cava (gross)<br>– Portal vein (gross)<br>– Pulmonary vein (gross, mic)<br>– Intrahepatic vein (mic)<br>– Adrenal vein |
| 3 | 3 months M | Septicemia | Necropsy | – FCNS<br>– Septicemia<br>– RVT (gross) (UL) | + | – | Microscopic | – absent |

DIC : Disseminated intravascular coagulation
RVT : Renal venous thrombosis
FCNS : Finnish-type congenital nephrotic syndrome
mic Microscopic
CMV cytomegalovirus infection

TABLE II: Some of the Clinical and Pathological Findings of Two Cases of MPGN Associated with RVT

| Case No. | Age Sex | Clinical diagnosis | Type of pathological study | Final pathological diagnosis | Location of thrombus: Main renal artery | Location of thrombus: Other | Infarct | Extrarenal thrombus |
|---|---|---|---|---|---|---|---|---|
| 4 | 2.5 years M | – NS<br>– Bronchopneumonia<br>Urinary tract infection | – Necropsy | – MPGN<br>– Septicemia<br>– RVT (mic) | – | – Interlobular veins | – | lung<br>heart<br>spleen |
| 5 | 10 years F | – NS<br>– MPGN<br>– % Amyloidosis | Necropsy (partial) | – MPGN<br>– RVT (gross) (UL) | – | – Arcuate and interlobar veins | – | not investigated |

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MPGN : membranoproli ferative glomerulonephritis
RVT : Renal venous thrombosis
NS : Nephrotic syndrome
UL : Unilateral
mic : Microscopic

TABLE III: Some of the Clinical and Pathological Findings of Three Cases of Amyloidosis Associated with RVT

| Case No. | Age Sex | Clinical diagnosis | Type of pathological study | Final pathological diagnosis | Location of thrombus: Main renal artery | Location of thrombus: Other | Infarct |
|---|---|---|---|---|---|---|---|
| 4 | 11 years F | – NS<br>– Amyloidosis<br>– Acute renal failure | Needle Necropsy Maternal | – Renal amyloidosis<br>– RVT (mic) | – | – Interlobular vein | Microscopic |
| 7 | 13 years F | – NS<br>– Amyloidosis<br>– Gastroenteritis<br>– Acute renal failure<br>– flank pain | Necropsy (partial) | – Renal amyloidosis<br>– RVT<br>– Amyloidosis in liver | + | – Interlobar and arcuate veins (gross) | none |
| 8 | 10 years F | – Amyloidosis<br>– Chronic renal failure<br>– Chronic pyelonephritis | Postmortem Nephrectomy | – Renal Amyloidosis<br>– RVT (mic)<br>– Renal scarring (gross and mic) (pyelonephritic type) | – | – Interlobular and arcuate veins (gross) | none |

RVT Renal venous thrombosis
NS Nephrotic syndrome
mic Microscopic

patients; inhibitors of fibrinolysis and impaired production of plasminogen activator have been observed[11]. Activated clotting factors are inhibited by naturally occurring coagulation inhibitors. Antithrombin III (AT III) is the most important of these coagulation inhibitors. It has been demonstrated that the serum AT III level in nephrotic patients is decreased and that there is a significant negative correlation between serum AT III concentration and urine protein excretion[6,11,12].

These alterations in the coagulation mechanism in nephrotic patients are reflected clinically in a widespread tendency towards intravascular coagulation, RVT formation or the occurrence of other extrarenal thromboembolic phenomena. It has been reported that in nephrotic patients, the incidence of RVT is about 35 percent while the incidence of extrarenal thromboembolic phenomena is about 20 percent[6]. Spontaneous thrombosis of femoral, mesenteric and pulmonary arteries and axillary, subclavian and leg veins have been observed[1,2]. The most common severe type of thromboembolic phenomena is the pulmonary embolism[2,6].

It has been observed that spontaneous RVT occurred in approximately 20 percent of rats with Heymann nephritis which was an experimental model of MGN[13]. This observation also supports the fact that RVT is a consequence of NS.

It has been argued that RVT causes NS by inducing an alteration in the permeability of the glomerular capillary wall which could result from two possible mechanisms[1,2]. The first is an elevation in venous pressure following thrombosis of the renal vein, causing alterations in glomerular permeability[1,2]. However unilateral renal vein ligation in a dog (rabbit or cat) does not cause nephrotic range proteinuria unless the contralateral kidney is removed[14]. Increased renal vein pressure due to thrombosis of the renal vein, constrictive pericarditis, occlusion of the vena cava above the renal veins, extreme obesity, and tricupsid valve disease may lead to disturbance of glomerular-capillary wall function in NS[1,2]. However, in many of the reported cases of NS, association of congestive failure or constrictive pericarditis, and injections of mercurial diuretics, are known causes of NS. In addition, there have been many cases reported of RVT with venal caval obstruction that were not associated with NS[1,2]. Thus, the relationship between increased renal venous pressure and the development of NS in man is debatable.

The second mechanism is that RVT may cause an immune-complex mediated type of glomurulonephritis by releasing renal tubular antigens which may induce glomerulopathy and associated NS. However, there is little evidence available supporting this theory[15-17]. The multiple factors leading to a hypercoagulable state and RVT are shown in Fig. 8.

There have been no reports in the literature concerning the incidence of RVT associated with NS in childhood in which a large group of patients have been

studied[1-4,7]. Our study, even though not large enough, also showed that RVT in childhood, when compared to its incidence in adults, is rare. But despite this fact, an incidence of nearly 34 percent of RVT was found to be associated with nephrotic children in the presented small series. This suggests the importance of thromboembolic events in children having glomerulopathy as has been shown in adults. Contrary to our findings, none of the 115 children with RVT which have been reported by the European Society of Pediatric Nephrology[1] nor the 50 children with RVT studied by Arneil et al[18] in Glasgow had associated NS. In our postmortem studies concerning RVT, a total of eight cases of nephrotic patients plus RVT were found: three cases with FCNS, three cases with amyloidosis, and two with MPGN.

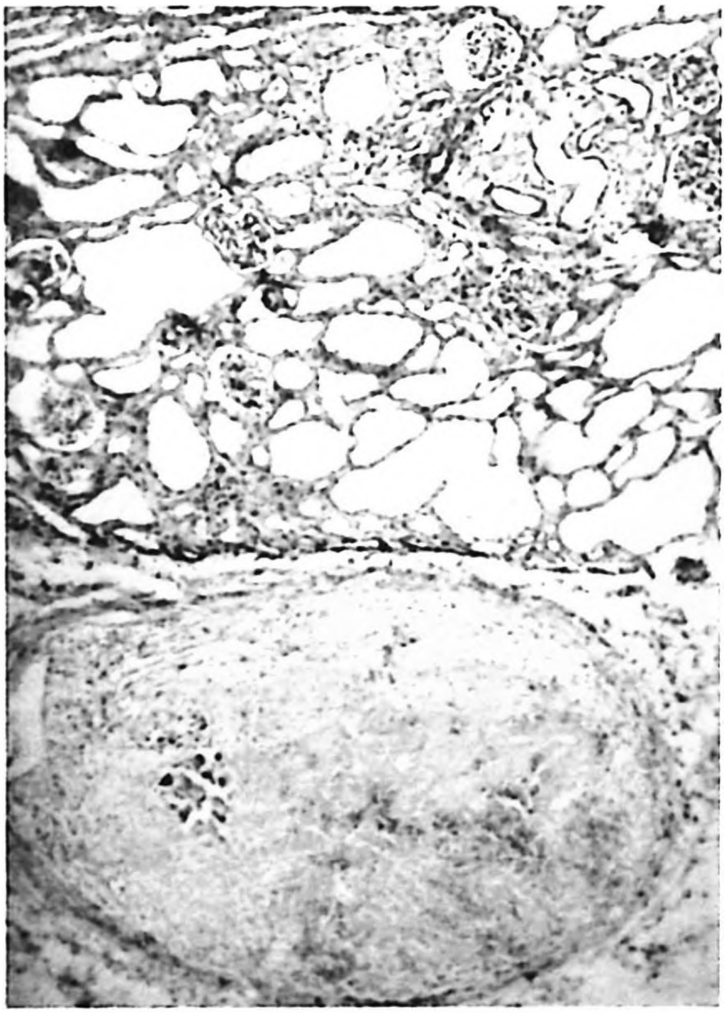

Fig. 1: Microscopical section of Finnish-type congenital NS showing a large, almost completely thrombosed vein (interlobar renal vein). The thrombus reveals areas of calcification (black dots), and cleft-like spaces (recanalization), fibrin depositions and fibrosis. Renal parenchyma reveals a rather characteristic appearance of microcystic dilatation of the convoluted tubules of FCNS (H.E stain X 75).

Renal venous thrombosis may occur in congenital NS but it is more likely a consequence rather than its cause. In the Finnish-type congenital NS, which is an autosomal recessive disorder, proteinuria is usually present at birth and or shortly after birth. This is one of the evidences which indicates that proteinuria can start in intrauterine life. Thromboembolic events can be seen in some congenital NS cases[19]. In addition to the coagulation abnormalities seen in nephrotic patients, infections and DIC observed frequently in these cases may lead to thrombosis[19-21]. Thus RVT occurs as a consequence of congenital NS.

In our series the three Finnish-type congenital NS cases revealed associated sepsis and/or DIC as was demonstrated histopathologically, in addition to RVT (Table I). The demonstration of the extrarenal venous thrombi in two of the congenital NS cases by macroscopic and microscopic examination supports the fact that sepsis and DIC lead to thromboembolic phenomena although specific studies were not performed. In addition, the hypercoagulable state occurring in

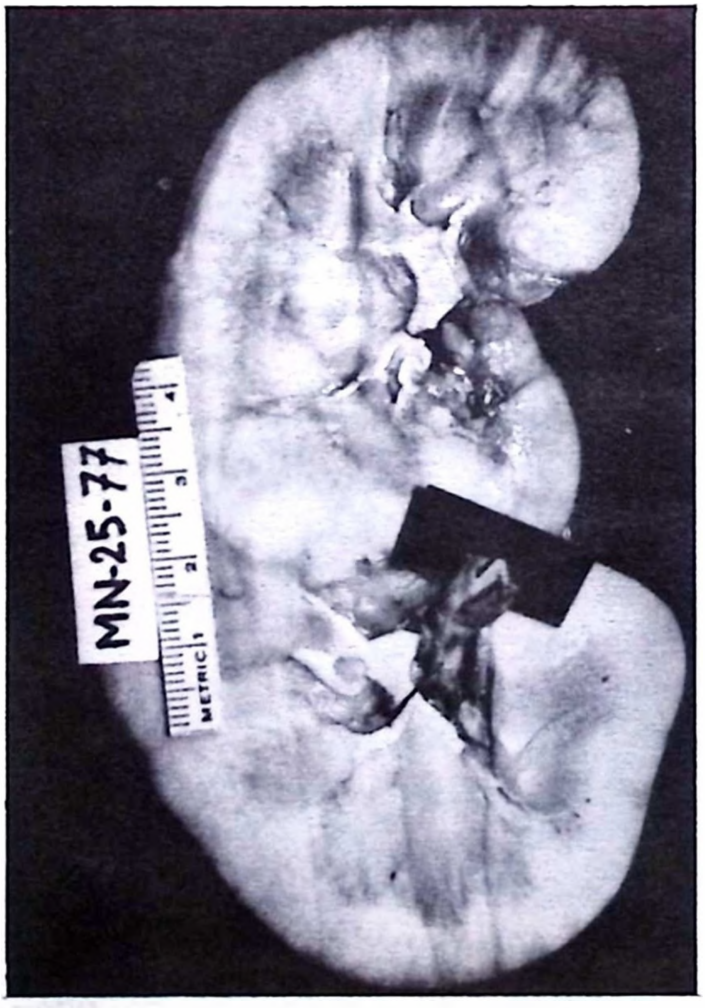


Fig. 2: Hemisected kidney of a case of MPGN shows a large bulging thrombosed branch of the main renal vein approximately 2 cm in length extending into the lower pole of the kidney (above the black rectangle).

nephrotic patients may play a role in the formation of RVT, as mentioned in the literature.

The ages of these patients ranged between 45 days and three months. The clinical signs and symptoms of NS had been present since their birth. Furthermore, microscopically and macroscopically the venous thrombi revealed organization, recanalization, and calcification (Figs. 2, 3). The findings in these cases suggest that the thrombi were two or three weeks old. It is concluded, therefore, that RVT occurred after the onset of NS. According to the data, it was agreed that the thrombosis in these three congenital NS cases occurred as a complication of the nephrotic state.

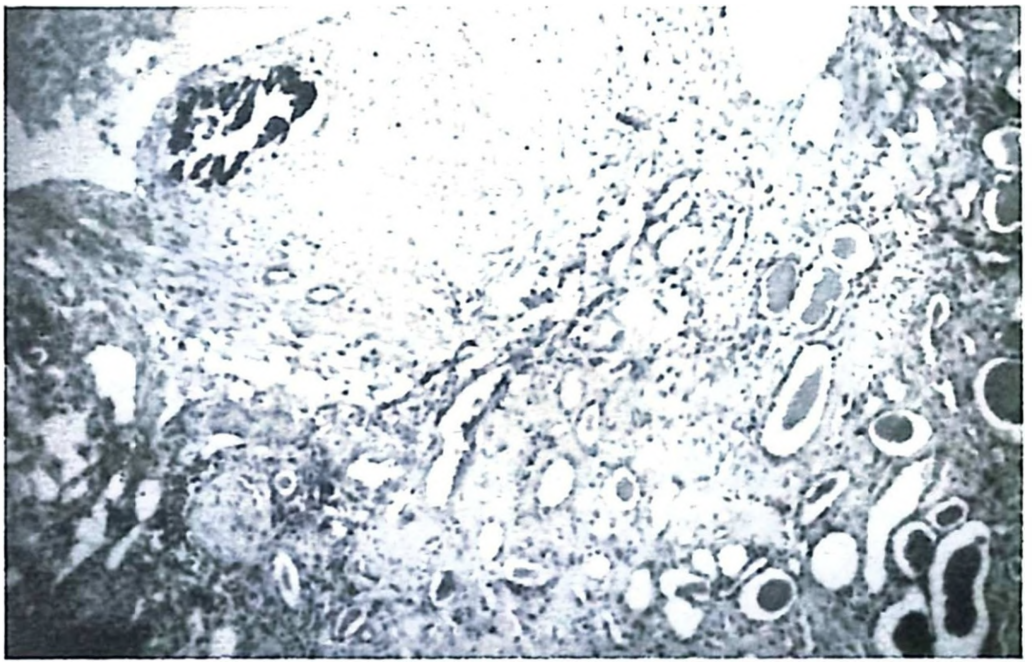

Fig. 3: Microscopical section of one of the renal amyloidosis cases showing a large vein near one corner of the picture which is completely thrombosed. The thrombus contains rather large areas of calcification (black dots) with clefts. Renal parenchyma shows an easily recognizable glomerulus which is completely obliterated due to amyloid deposition. There are homogenous tubular casts, varying in size, and the increased interstitial tissue is rather less cellular (amyloid deposition) (H.E. stain × 75).

The incidence of RVT in adult patients with MPGN or MGN has been reported to be between 38-41 percent[3,4,6,22]. In our study, only two of eight cases had MPGN, and sepsis was demonstrated in one of them (Fig. 4; Table II). After NS was diagnosed in these cases, cortisone, endoxan, diuretic and antibiotic therapy was given for approximately 35 days. It is known that cortisone, diuretics and also sepsis may precipitate thromboembolic events[2,6]. We believe that the hypercoagulable state in nephrotic patients, as reported in the literature, the therapy administered and the sepsis which was demonstrated in one case, may have led

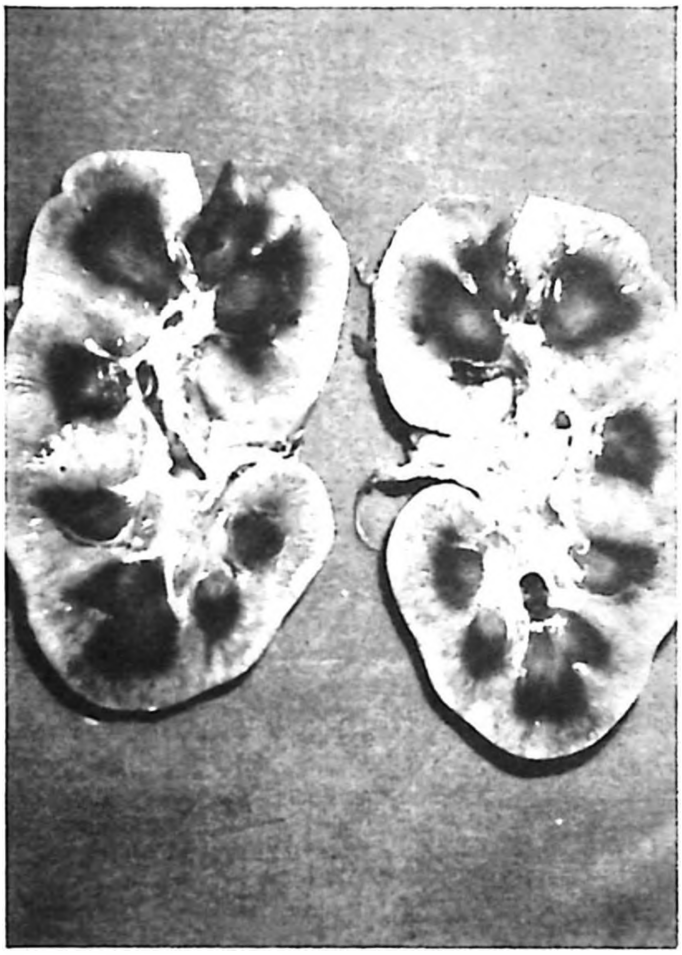

Fig. 4: Cut surfaces of a kidney of another case of renal amyloidosis showing dark areas corresponding to the infarct mainly located in the medullary of the pyramids. On the right side, close to the hilus, there appeared to be the presence of a lobar and/or arcuate vein. Dark discoloration of the renal pelvis is evidence of macroscopic hematuria.

to thrombosis in our patients. Due to fresh thrombi in the MPGN cases, it is presumed that the thrombi had occurred after the onset of MPGN (Fig. 2).

The last three cases in our study had RVT associated with amyloidosis (Figs. 5-7). The edema present in these patients lasted for six months (Case Nos. 6 and 7) and 18 months (Case No. 8). Acute deterioration in renal function supports the fact that RVT occurred after the development of the nephrotic state (Table III).

It should be stressed that in order to make an antemortem diagnosis of RVT, a good physical examination must be performed to detect the possible existence of RVT in nephrotic patients. If acute flank pain, marked costa-vertebral angle tenderness, macroscopic or microscopic hematuria, an increase in proteinuria, acute deterioration of renal function, an intravenous pyelogram revealing abnormalities with unilateral kidney enlargement and pelvocalyceal irregularities

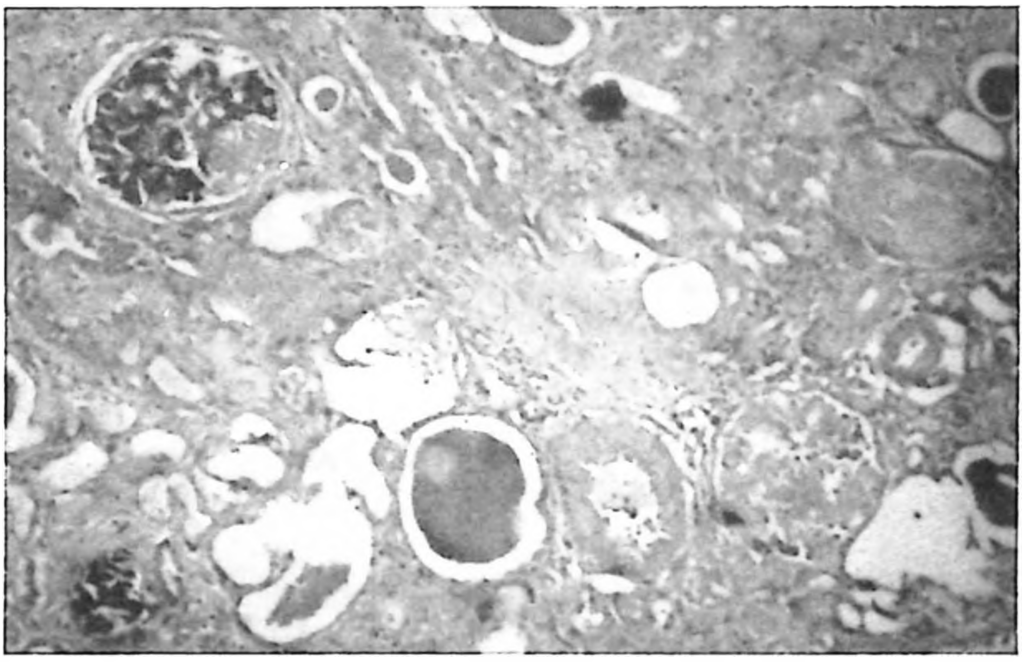

Fig. 5: Microscopical appearance of another case of renal amyloidosis showing amyloid deposition in the glomeruli. Additionally, there are calcifications in the glomeruli (dark-stained areas), tubular atrophy, tubular casts and widening of the interstitial tissue (H.E stain X 125); (This case shows renal venous thrombosis with calcification in the arcuate and lobar veins without renal infarction but these changes are not represented in this figure).

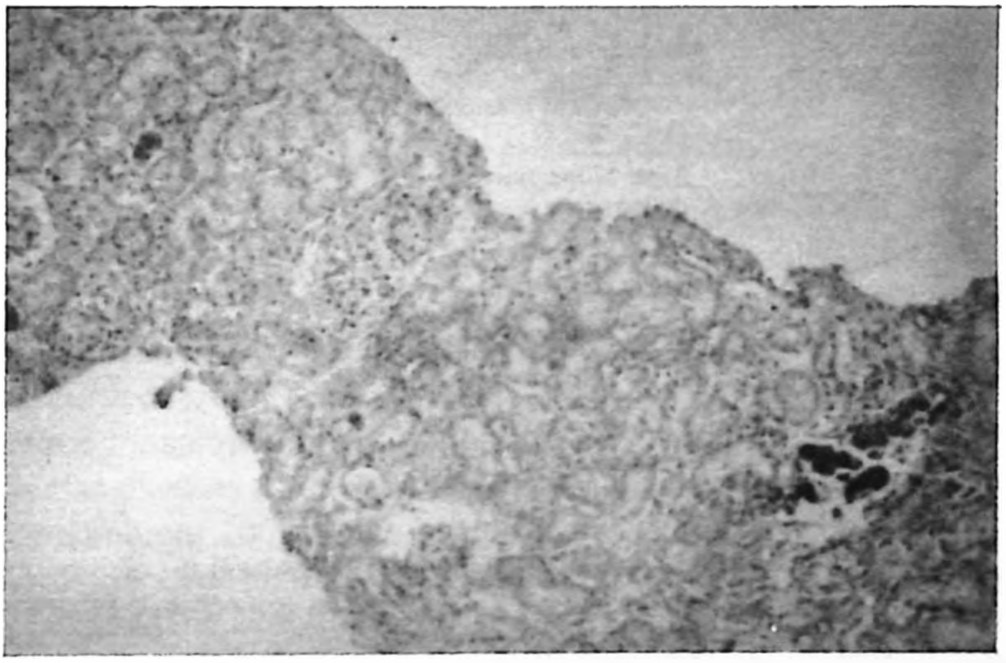

Fig. 6: Microscopic appearance of a needle renal biopsy (case in addendum) under medium power magnification in a case of mesangioproliferative glomerulonephritis. Note the dark-stained areas representing early thrombi in the arcuate and interlobular veins (H.E. stain X 75).

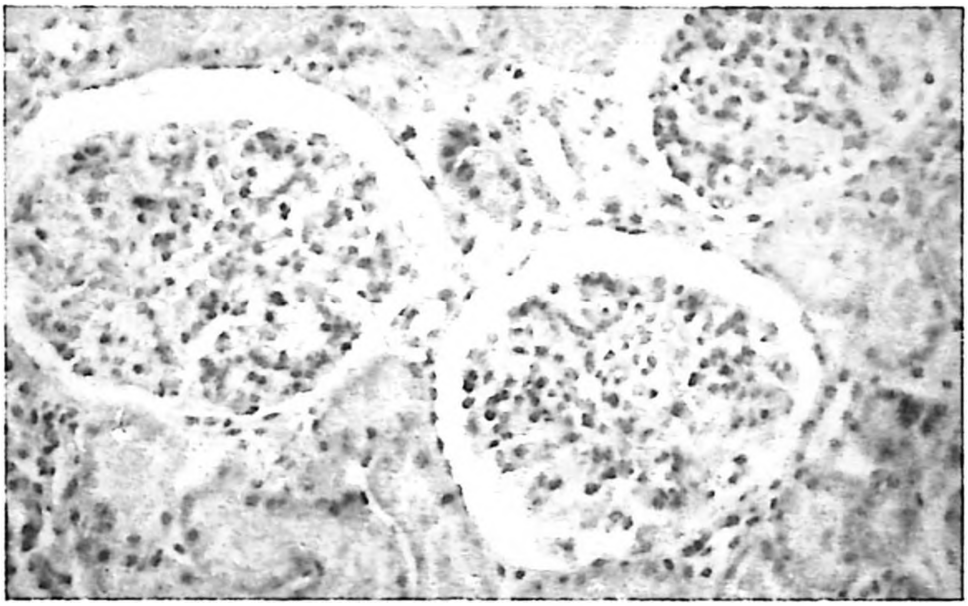

Fig. 7: Appearance of the glomeruli under higher magnification of case represented in Fig. 6 (H.E stain).

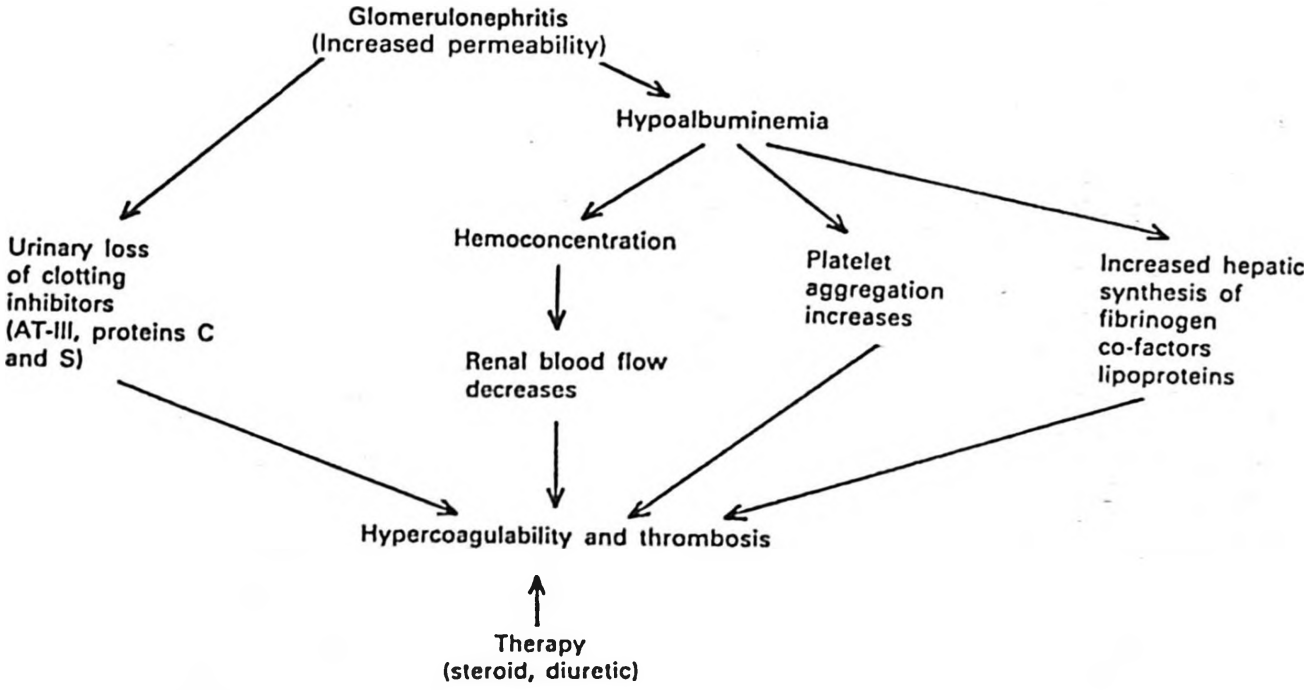


Fig. 8: A simple schema of etiopathogenic factors causing hypercoagulability, thromboembolic events and renal vein thrombosis in nephrotic syndrome.

are present, then RVT should be considered and the necessary investigations for a definite diagnosis should be made. After a diagnosis of RVT is made, a good prognosis depends largely on whether anticoagulant therapy is given to the patient to prevent hypercoagulability and thromboembolic events, along with specific therapy used to treat NS and a successful follow-up[1,2-4,17].

## Summary

Cases with a pathological diagnosis of renal venous thrombosis (RVT) associated with nephrotic syndrome (NS) were studied retrospectively for clinicopathological evaluation. The material consisted of 21 RVT cases which were diagnosed in 2000 consecutive pediatric necropsies, with an overall incidence of about one percent. Eight of the 21 RVT cases were associated with nephrotic syndrome (34%), and this group formed 0.4 percent of the total necropsies in our pediatric center. The glomerulopathies of these nephrotic patients consisted of three cases of Finnish-type congenital NS (FCNS), three cases of renal amyloidosis secondary to familial Mediterranean fever, and two cases of membranoproliferative glomerulonephritis (MPGN). The presence of sepsis associated with disseminated intravascular coagulation, and the morphological age of the thrombi suggested that the RVT was secondary to sepsis in the FCNS cases.

In the MPGN and secondary renal amyloidosis cases, the long duration of both the nephrotic state and the administration of diuretics along with glucocorticoid treatment and also the newly formed thrombi without infarction are strong evidences, although not definite, that the RVT developed as a complication of the glomerulopathy.

Even though there were no definite clinical criteria for the diagnosis of most of the RVT cases, we would like to emphasize the importance of flank pain, the rapid deterioration of renal functions in a stable nephrotic patient, as well as the hypercoagulable state in the consideration of the development of RVT which indicate the need for approriate radiological studies for confirmation of this condition during life.


## Addendum

After completing this manuscript, we encountered RVT involving arcuate and interlobular veins without infarction in a needle renal biopsy of a nine-year-old boy having corticosteriod resistant nephrotic syndrome. The glomerulopathy was that of diffuse mesangial proliferation with negative immunohistological findings which was classified as a variant of the idiopathic type of NS. This is the only case in our approximately 700 needle renal biopsy material, in a twelve-year period, which we diagnosed histologically during life. Even though hematuria could associate in cases of idiopathic NS, the presence of it in this particular patient might be a clue for the consideration of the development of RVT along with the other afore-mentioned findings.

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# LONG-TERM PROGNOSIS OF POSTSTREPTOCOCCAL ACUTE GLOMERULONEPHRITIS*

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*Emin Ünüvar MD****

*Key words: long-term prognosis, poststreptococcal acute glomerulonephritis*

The long-term prognosis of poststreptococcal acute glomerulonephritis (PSAGN) has been subject to controversy[1-3]. Some authors report an excellent prognosis without evidence of chronicity while others report progressive renal disease with variable incidence following PSAGN. Some of these discrepancies may be due to: differences in patient material under study (children versus adults, sporadic versus epidemic), severity of the acute episode, diagnostic procedures used (pathological versus clinical), and frequency and length of the follow-up period. Additionally, subclinical cases and cases of questionable diagnosis are not very rare and therefore also contribute to the mistakes made in determining the prognosis of PSAGN.

PSAGN is a disease frequently encountered in Turkey. The present study aims at determining the long-term prognosis of PSAGN patients. The subjects of our study, diagnosed as having PSAGN, were treated in the Pediatric Nephrology Department of Istanbul University Faculty of Medicine during the years 1973-1983 and were investigated with respect to a long-term prognosis.

## Material and Methods

Five-hundred and eighty-eight PSAGN patients who had been treated and followed up in the Pediatric Nephrology Department of Istanbul University Faculty of Medicine between 1973-1983 were recalled for a follow-up study between March-April, 1988. Only the patients diagnosed by exact criteria at the beginning of the disease were allowed to participate in the study. Patients diagnosed elsewhere, those with insufficient serological tests, or those seen after the acute phase were not included. In our practice, PSAGN patients are either hospitalized

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or treated as outpatients, being seen in the acute phase as frequently as the patient's condition requires. During the first six-month period patients are followed up frequently, thereafter they are seen at the end of the first year and then followed up annually for a five-year period. Follow-up after the five-year period may continue if the patient so desires. All patients included in this study were followed up for at least five years. Those responding to the follow-up calls were given thorough physical examinations. Blood pressure, serum creatinine, blood urea and $\beta_1$ C globulin levels were measured and a complete urinalysis was done.

## Results

Fifty-nine patients responded by coming in for a follow-up after receiving letters but 68 letters did not reach the patients due to a change in address. There were no responses from the remaining 461 patients. However, we believe that some of them were not reached due to a change in address.

The mean age of the patients was 8.2 years (range 3-15 years) at the time of the acute episode and 15.6 years (range 8-26 years) in 1988. The follow-up period was 5-14 years (Fig. 1). During the follow-ups between March-April, 1988, all the patients had normal physical findings, including blood pressure, and normal urinalysis. Serum creatinine, blood urea and $\beta_1$ C globulin levels were within normal limits (Table I). Some of the patients had reached adulthood and two of them were pregnant at the time of the follow-up.

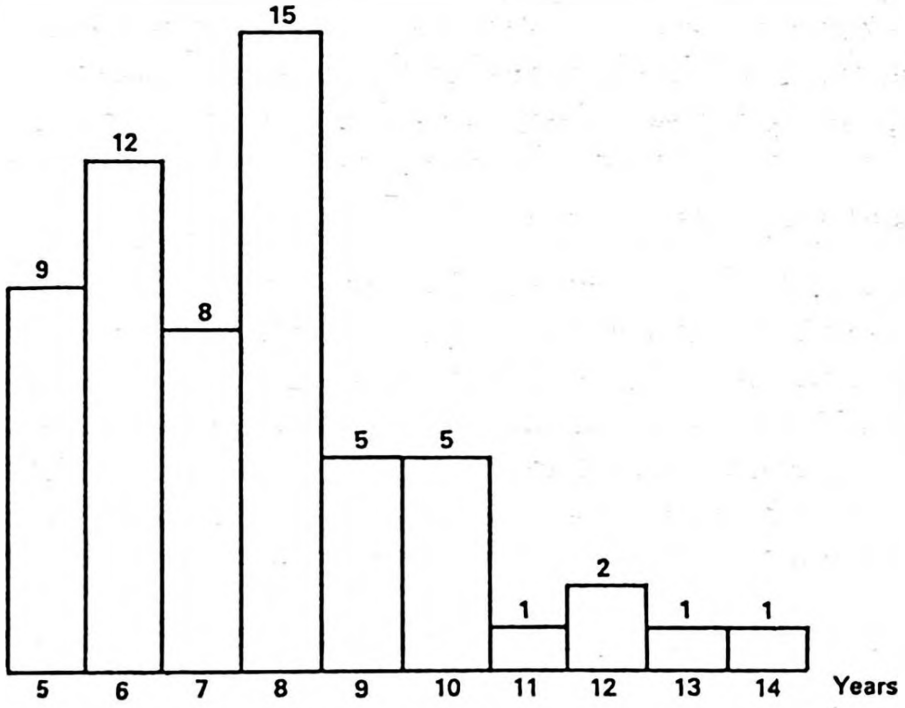


Fig. 1: Follow-up period (figures indicate number of patients in each follow-up period)

TABLE I: Results of Reevaluation of the Patients between March-April, 1988

| | |
|---|---|
| n: | 59 |
| Mean age: | 15.6 years (range 8-16 years) |
| Proteinuria: | absent |
| Hematuria: | absent |
| Physical findings: | Normal in all |
| Blood pressure: | Normal in all |
| Mean serum urea: | 17.6 mg/dl (range 10-34 mg/dl) |
| Mean serum creatinine: | 0.75 mg/dl (0.5-1.0 mg/dl) |
| $C_3$: | Mean 138.5 mg/dl (63-174 mg/dl) |

## Discussion

These results led to the conclusion that the long-term prognosis was favorable in our PSAGN patients since chronic renal failure had not been encountered. The patients not responding to the follow-up calls led us to be concerned but since their follow-up records prior to the end of the five-year period revealed no problems, it was concluded that the probable reason for their not responding was lack of any problems.

Although reports on the long-term prognosis of PSAGN are controversial, it is almost unanimously agreed that the outcome is always more favorable in children than in adults. Studies performed ten years after the Red-Lake PSAGN epidemic revealed no difference in the frequency of hematuria and in biopsy changes between the patients and the control group; none of the patients involved developed renal failure[2] Travis et al[3] have reported an eventual recovery rate exceeding 95% in PSAGN but they were uncertain of the outcome of acute glomerulonephritis (AGN) from other causes. Baldwin et al[4] have reported that more than half of the patients with PSAGN in New York showed evidence of renal damage in subsequent follow-ups in the absence of urinary and renal function abnormalities, however, the ultimate prognosis is unclear. Chronic renal failure developed in six of their 176 patients. Data from Trinidad indicate good long-term prognosis for most patients with epidemic PSAGN, with chronic renal failure resulting in only one patient[5,6].

Patients reevaluated five years after the Maracaibo epidemics displayed an excellent prognosis, with none developing chronic renal failure. Seventy-one of these patients were evaluated again 11-12 years after the epidemic. At that time one patient had developed chronic renal failure and required chronic dialysis.

Creatinine clearances were depressed in 12.6% of the patients, 11.2% had proteinuria and 4.2% had microscopic hematuria while two were hypertensive. These persisting abnormalities were present mostly in patients who were above the age of 12 at the onset of the disease[1,7].

Lewy[8] has reported chronic renal disease as a continuum of AGN in less than 5% of cases and emphasized that both age and renal functional status at onset are related to the rate of healing. Prognosis is excellent in preschool children while it is closely related to morphologic severity in school-age children. Hinglais et al[9] have performed biopsies early in the course of AGN and have reported on the predictive value with regard to the early histopathological features.

In our patient group, the cure rate was 100% during the follow-up period extending from 5-14 years. Contrary to reports of a low rate of chronicity in other series, chronic renal disease was not encountered at all in our series. Thus, from our experience, PSAGN appeared as a frequent disease having a benign course and a long-term prognosis.

**Summary**

Five hundred and eighty-eight patients diagnosed as having PSAGN were treated at our University Hospital and called in for a reevaluation study in 1988 to determine the long-term prognosis of the disease. Fifty-nine patients responded to the follow-up call, all of them being in good physical health. The blood pressure, urinalysis, serum creatinine, blood urea and $\beta_1$C globulin levels were within normal limits. These results led us to the conclusion that the long-term prognosis was favorable in our PSAGN patients since chronic renal failure had not been encountered.

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# DILUTED YOGURT (AYRAN) VERSUS WATER IN DISSOLVING ORAL REHYDRATION SALTS*

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*Key words: yoğurt, ayran, oral rehydration salts, diarrhea*

Oral rehydration salts of the World Health Organization (WHO) are still the first choice in the treatment of acute diarrhea, despite the fact that different formulae[1-4] and routes of administration[5] have been proposed. However, in practice the refusal of WHO's oral rehydration solution by some children has been a matter of concern. Once this solution is refused by a patient, either a change in the route of administration (e.g., gavage or I.V. line), replacement using another formula or a change in palatability is essential. Ayran is a traditional Turkish beverage which is prepared by diluting yogurt in varying amounts of water. In rural Turkey, salty ayran has been used extensively in the treatment of diarrhea. Keeping the electrolyte composition of the final solution at optimum (90 mEq/lt), an oral rehydration solution prepared in ayran (ORSA) was found more acceptable than an oral rehydration solution prepared in water (ORSW). In addition, ayran may be used as an "early food" for dehydrated children because it contains protein and a minimal amount of fat.

## Material and Methods

This study was carried out on 156 children with diarrhea at Tepecik Social Security Hospital, İzmir, between March, 1986 and January, 1987. Patients between three and 12 months of age were put into group A while those between 12 and 48 months of age were assigned to group B. Each group was subsequently subgrouped with regard to the solution offered (ORSA or ORSW). The degree of dehydration was assessed as: mild, moderate or severe according to physical signs[6]. In this study, we included only cases which were of a mild to moderate degree of dehydration.

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Routine laboratory tests (complete blood count, stool microscopy and culture, blood urea nitrogen, serum creatinine and electrolytes) were performed on all patients at admission and 24 hours after therapy.

Low-fat cow's yogurt was diluted in five parts water to obtain ayran. The electrolyte, carbohydrate, protein and fat content of ayran is shown in Table I. The electrolyte composition of the final ayran-based oral rehydration solution was about 85 to 92 mEq/lt.

Of the 76 patients who constituted group A, 36 were administered ORSA while 40 were given ORSW. In group B, of the 80 patients, 40 were given ORSA while the remaining 40 were adiministered ORSW. Throughout the course of treatment, solutions were given on demand and children who refused one solution were given the other.

TABLE I: Electrolyte, Protein and Fat Content of Ayran

| | |
|---|---|
| Sodium | 8-10 mEq/lt |
| Potassium | 9-11 mEq/lt |
| Protein | 1.5-2.2 g/dl |
| Fat | 0.5-0.6 g/dl |
| Carbohydrate | 1.1-1.5 g/dl |

**Results**

In group A, 34 out of 40 infants on ORSW (85%) and 32 out of 36 infants on ORSA (89%) accepted and tolerated the solutions well (Table II). Infants refusing one solution also refused the other, with one exception. In group B, 28 out of 40 children on ORSW (70%) accepted the solution whereas 37 out of 40 children (92.5%) on ORSA accepted the ayran-based solution. The difference between the two subgroups was significant ($p < 0.05$). In this group, 11 out of 12 patients who

TABLE II: Distribution of Patients in Groups

| Age | 3 - 12 Months | | 12 - 48 Months | |
|---|---|---|---|---|
| Solution | ORSW** (n: 40) | ORSA* (n: 36) | ORSW (n: 40) | ORSA (n: 36) |
| Accepted | 34 | 32 | 28 | 37 |
| Refused | 6 | 4 | 12 | 3 |

* ORSA : oral rehydration salt dissolved in ayran
** ORSW: oral rehydration salt dissolved in water

refused ORSW and one out of three patients who refused ORSA accepted the alternative solution.

At the beginning of the therapy sodium and potassium serum levels were slightly decreased in patients with gastroenteritis. If either solution was used, recovery was complete and within twenty-four hours there was a gain in weight.

## Discussion

Refusal of WHO's oral electrolyte solution by some dehydrated children has been a matter of concern in combatting diarrhea. We used ayran instead of water to dissolve the oral rehydration salts and from the acceptability point of view, ORSA was found to be superior to ORSW. However, both treatments, when accepted, provided satisfactory clinical and biochemical healing.

Early feeding is one of the important steps in the treatment of children with gastroenteritis. Ayran is a valuable early food for children with diarrhea because it contains protein, carbohydrates and a minimal amount of fat.

## Summary

Seventy-six children with gastroenteritis were treated with oral rehydration salts dissolved in ayran (diluted yogurt), and eighty patients were treated with oral rehydration salts dissolved in water. The patients whose ages ranged between three and twelve months accepted both solutions equally. However, the acceptance of the ayran-based solution was significantly greater than WHO's salt solution in the patients whose ages ranged between one and four years. It is proposed that ayran be used to dissolve oral rehydration salts in the treatment of diarrhea since it is more palatable and easily acceptable by children.

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# CONGENITAL INSENSITIVITY TO PAIN WITH ANYHYDROSIS: MORPHOLOGICAL STUDIES OF SKIN AND PERIPHERAL NERVES*

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*Key words: anyhydrosis, sensory neuropathy, insensitivity to pain*

Congenital insensivity to pain with anhydrosis is one of a group of diseases termed hereditary sensory neuropathies (HSN), which is characterized by the absence of pain, heat sensation, and perspiration[1]. The principal findings are episodes of fever, inability to perspire despite the presence of normal functioning sweat glands, lack of response to fainful stimuli, self-injury, painless fractures, and mental retardation. Since first reported by Gillespie and Preccua[2] in 1960, nineteen additional cases have entered the literature. This report deals with two male siblings in whom skin and sural nerve biopsies were investigated by light and electron microscopy.

## Case Reports

### *Case 1*

Two male siblings, aged five and two years, were the first and second products of consanguineous parents. The family history was non-contributory and the pregnancies were uneventful and full-term. Both subjects had frequent unexplained episodes of fever beginning in the neonatal period. After the age of one self-mutilations were noticed. The mother also became aware that the children did not experience pain on accidental injury and on being burned. It was also reported that they were unable to sweat, but lacrimation was present when the subjects were extremely upset. Developmental milestones were delayed.

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Physical examination revealed their height and weight to be between the 3rd and 25th percentiles. Both had dry skin and hair and some tissue loss was observed in the lower labium and tongue due to self-multilation (Fig. 1). The subjects did not have front teeth. There were many scars and ulcers on the extensor surfaces of the extremities which could be subject to trauma. The ends of almost all fingers and big toes were calloused and ulcerated with partial resorption of the terminal phalanges. All the nails were deformed (Fig. 2). The respective blood pressures were normal and did not change with posture. The examination of the other systems were within normal limits.

Neurological examination revealed subjects with mild retardation who were sociable but emotionally labile. Neuro-muscular development appeared to be retarded. Deep tendon and corneal reflexes were normal. The children reacted normally to strong olfactory, auditory and visual stimuli. Taste and tactile sensations were present. No pain response was observed from pinpricks, or from hot or cold stimuli to the skin of all major regions of the body. Pinching of the Achilles tendon and testicular compression provoked no protest. The subjects could not distinguish sharp and blunt objects.

Laboratory studies revealed normal biochemical and immunological findings along with a normal hemogram. Spinal fluids, electromyographies, electroencephalographies and computerized tomographies were within normal limits. Intradermal injection of 0.1 ml 1/1000 pilocarpine solution produced no sweating.

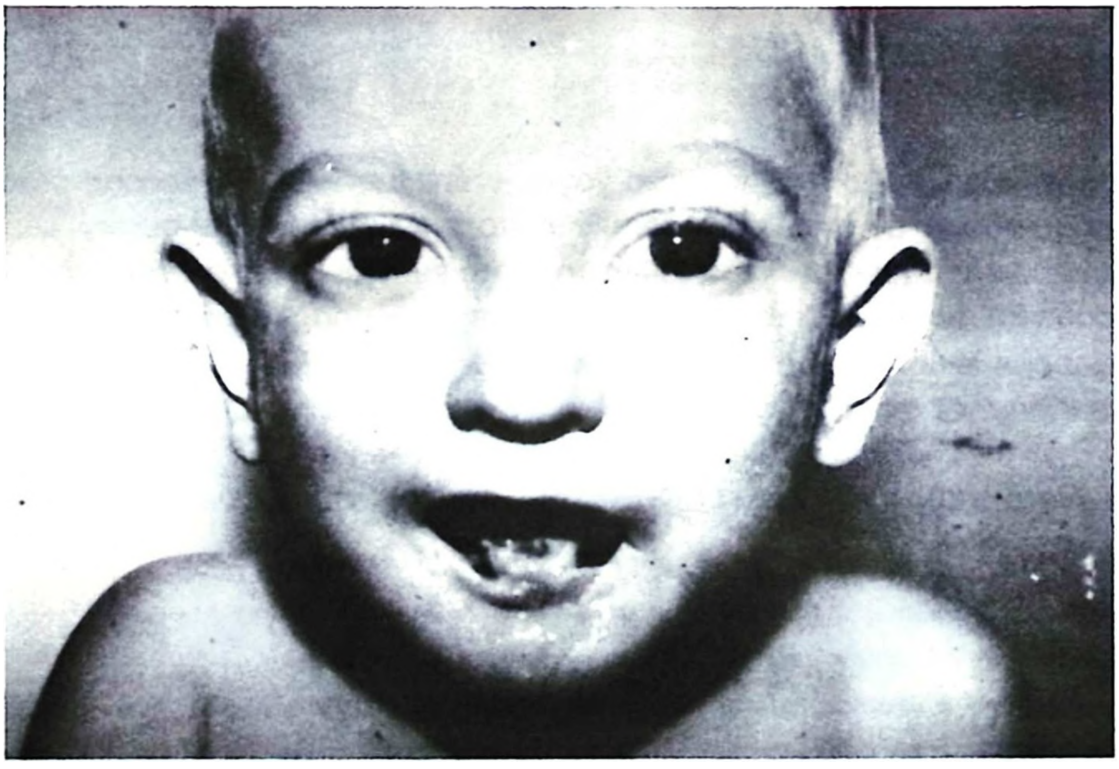

Fig. 1: Tissue loss in the lower labium and tongue due to self-mutilation.

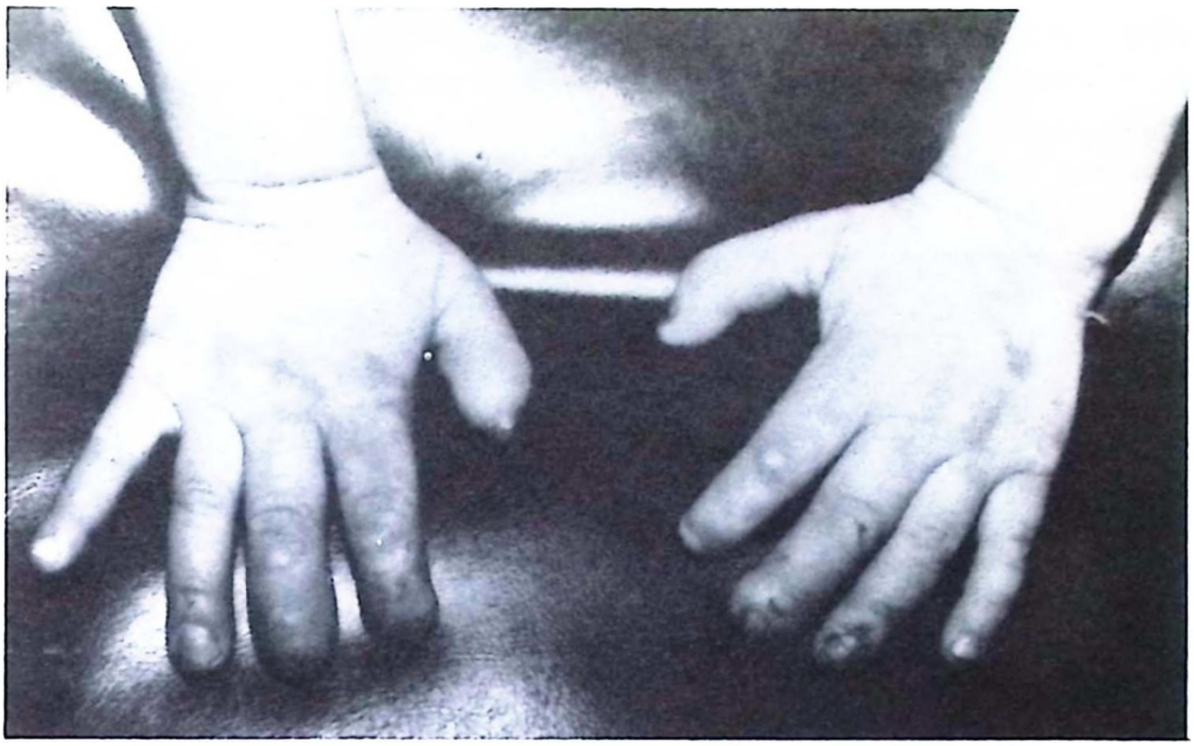

Fig. 2: Calloused and ulcerated fingers, partial resorption of terminal phalanges, deformed nails.

Roentgenograms of the hands revealed partial resorption of both thumbs, index and middle fingers (Fig. 3). The chromosomes were found to be normal with Giemsa-Trypsin-Giemsa (GTG) banding.

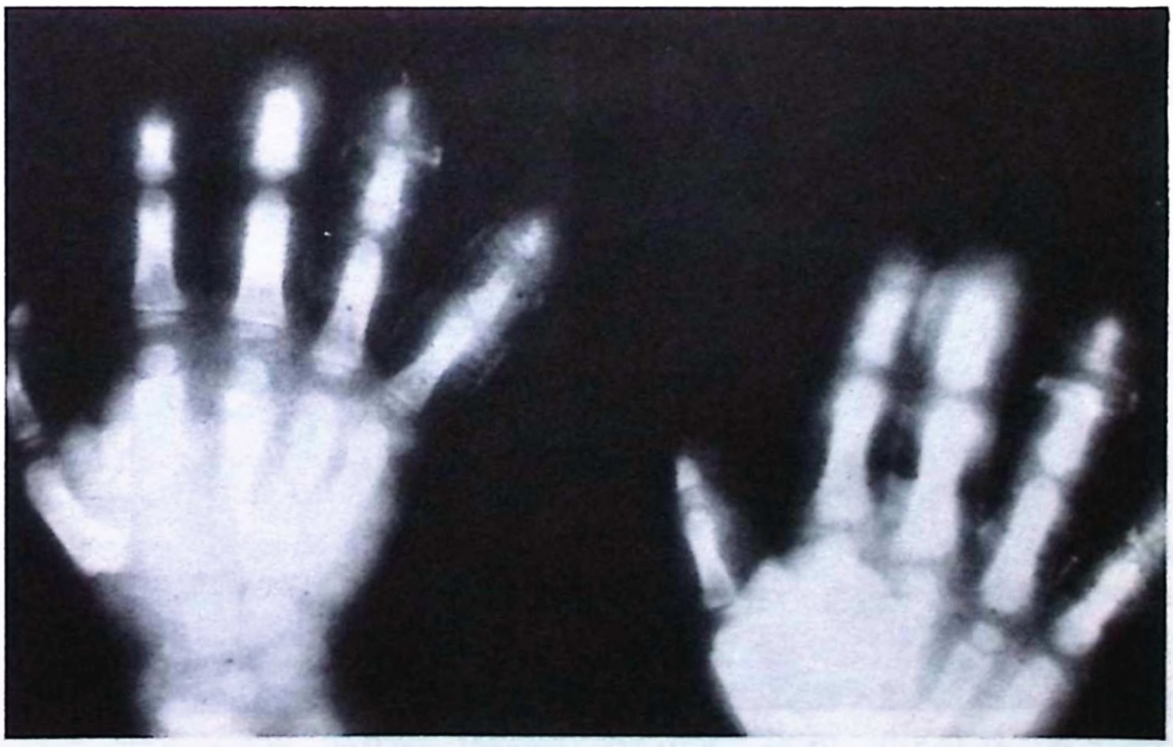

Fig. 3: X-ray examination of the hands.

Skin biopsies by light and electron microscopy demonstrated free dermal nerve networks and normal sweat glands (Fig. 4). Electron microscopy of the sural nerves revealed extreme paucity of unmyelinated fibers. Separation between axons and myelin shells were also noted (Fig. 5). An increase in collagen tissue between the fibers was an additional pathological finding (Fig. 6).

Fig. 4: All normal epidermal layers and excretion channels of sweat glands.

Fig. 5: Electron micrograph of the patients' sural nerve showing an almost complete absence of unmyelinated fibers.

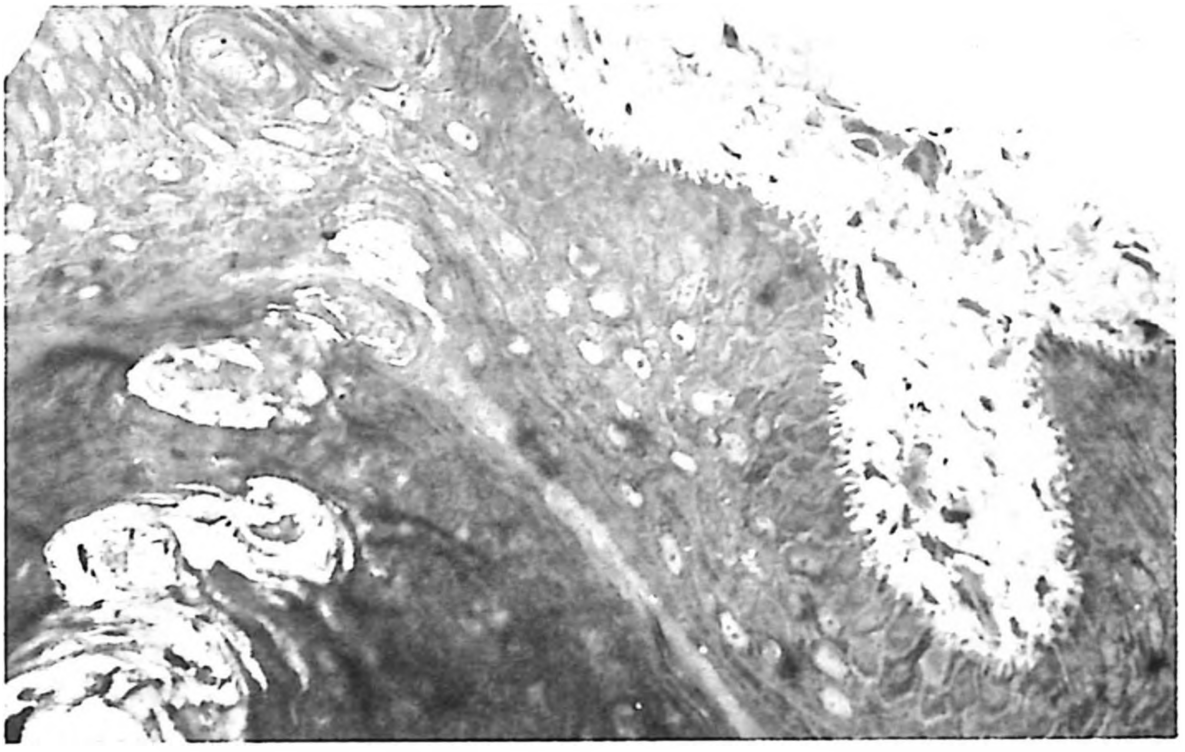

Fig. 6: An increase in collagen tissue.

## Discussion

The main findings of the two brothers presented were congenital insensitivity to pain, self-mutilation, inability to sweat in spite of various stimulation, episodes of fever of unknown origin and mild mental retardation. Congenital absence of pain is the most important finding in hereditary sensory neuropathies of which there are at least four separate entities[3]. The genetic, clinical and morphological findings of these have been summarized in Table I, and have been compared to our cases. The genetic and clinical characteristics of our cases correspond mostly to HSN type IV or congenital insensitivity to pain with anhydrosis. This disorder is seen quite rarely, and 16 cases have been reported so far[1,2,4-13]. Morphological examination of the skin by light and electron microscopy was found to be normal in most cases, as in ours[1,4-7,9,11,12]. Peripheral nerves were found to be normal in all cases using light microscopy[1,5-9]. Swanson, et al[14], in a case in which necropsy had been performed, showed that there was an absence of small neurons in the dorsal ganglia, a lack of small fibers in the dorsal roots and the absence of Lissauer's tract. Based on the afore-mentioned observations, he suggested that the primary event regarding congenital insensitivity to pain with anhydrosis could be a migration defect in the neuron precursors and an interruption in maturation.

In all cases of HSN type IV in which the peripheral nerves could be examined by electron microscopy, similiar pathologies have been reported[1,10-13]. In 1980, Goebel et al[10] examined sural nerve biopsies by electron microscopy and

observed an almost complete absence of unmyelinated fibers and a slight decrease in small myelinated fibers. In the same year, Rafel et al[11] showed that both small myelinated and ummyelinated fibers were absent in morphometrical investigations. In 1981 Matsuo et al[12] reported an essential decrease in unmyelinated fibers and a slight decrease in small myelinated fibers in a two-month-old boy. In 1982, Verity et al[13] also observed the lack of unmyelinated fibers. Finally, in 1986, Itoh et al[1] noticed extreme paucity of unmyelinated fibers and a reduction in myelinated fibers, especially of small caliber. They also reported that the endoneurium consisted of abundant collagen fibers. None of the workers mentioned regeneration and degeneration in the axon and myelin shells, as had been reported in other HSN types.

In our cases, similar to the above-mentioned findings, the unmyelinated fibers had almost disappeared, while the collagen fibers had increased. Based on the fact that the unmyelinated fibers had almost disappeared and the small myelinated fibers had decreased in the peripheral nerves of all the cases reported, it is suggested that the insensitivity to pain and heat in HSN type IV might be due to a congenital defect in the formation of neurons.

## Summary

Two male siblings born to consanguineous parents, with the diagnosis of congenital insensitivity to pain with anhydrosis are evaluated. The patients presented with unexplained bouts of fever, self-mutilation, repeated trauma and inability to sweat. Physical examination revealed both siblings to be insensitive to pain and temperature. The electron microscopic study of the skin was unremarkable whereas sural nerve biopsies yielded an essential lack of unmyelinated fibers.

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# PERIPHERAL VEIN CONTRAST ECHOCARDIOGRAPHY IN ATRIAL SEPTAL DEFECT*

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*Key words: echocardiography, atrial septal defect, contrast echocardiography*

Indirect findings of atrial septal defect are obtained by means of M-mode echocardiography[1,2]. Direct visualization of atrial septal defect is possible by two-dimensional echocardiography[3]. However, false-positive defects may be a diagnostic problem[3]. Although, peripheral venous contrast echocardiography has been used to detect intracardiac shunts[3-8], this method has not as yet been well established. This study was undertaken to further evaluate the diagnostic capability of peripheral venous contrast echocardiography in patients with isolated atrial septal defect.

## Material and Methods

233 children suspected clinically of having isolated atrial septal defect evaluated by physical examination, electrocardiography, and telecardiography were studied.The age range was between one and 17 years (mean age: nine years).

Two-dimensional echo studies were performed using either a mechanical sector scanner (Honeywell, Ultra-Imager) equipped with a 2.5 megahertz transducer or a Toshiba SSH-60A echocardiograph equipped with 3.75 and 5 megahertz transducers. The images were recorded on video-tape for further evaluation.

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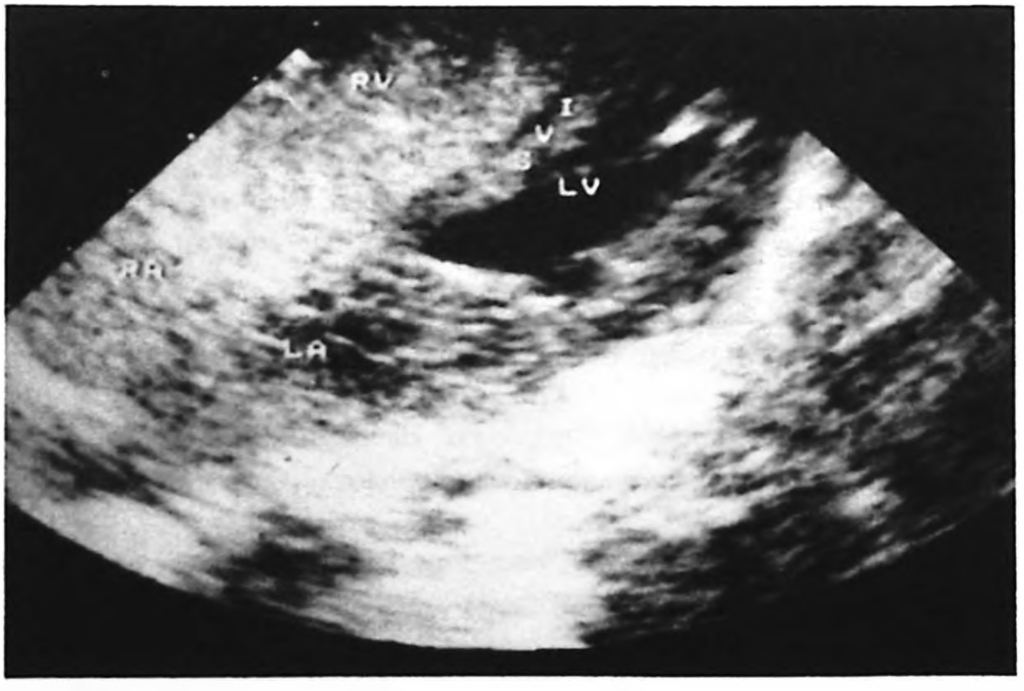
Three percent saline or 5 percent dextrose was used as contrast material. In patients revealing an unsatisfactory contrast image. $CO_2$ in the amount of 0.1 cc/kg was added to the saline or dextrose. Peripheral vein contrast material injections were administered in the arm, using a pediatric scalp vein set (gauge 21). A variety of transducer positions were used to visualize the interatrial septum and both atria. These included apical four-chamber, subcostal and modified parasternal short axis projections. This study was conducted on patients who were either in the supine or in the 30-degree left lateral position.

In the first few cases different amounts of echo contrast materials were injected with syringes of different sizes and at varying speeds. The best contrast image was obtained by a rapid injection of 10 cc of echo contrast material, especially 3 percent saline. The study was repeated 3-6 times in each case. If heart failure was present, 5 percent dextrose was preferred. In some cases, intravenous furosemide was given after the study was completed to prevent sodium accumulation if saline was used as the contrast material. Some patients were sedated in order that a comfortable study be performed.

The transfer of contrast material from the right atrium into the left atrium was evaluated as "positive contrast" (Fig. 1). Non-contrast blood, passing from the left to the right atrium was termed, "negative contrast" (Fig. 2). Positive contrasts were semiquantitively graded according to the following criteria: massive shunting 4+; strong shunting 3+; little shunting 2+; very little or questionable shunting 1+. A significant negative contrast effect was graded as 3− or 4−, and 2− contrasts were considered to be questionable. Three positive, 4+ and/or 3−,



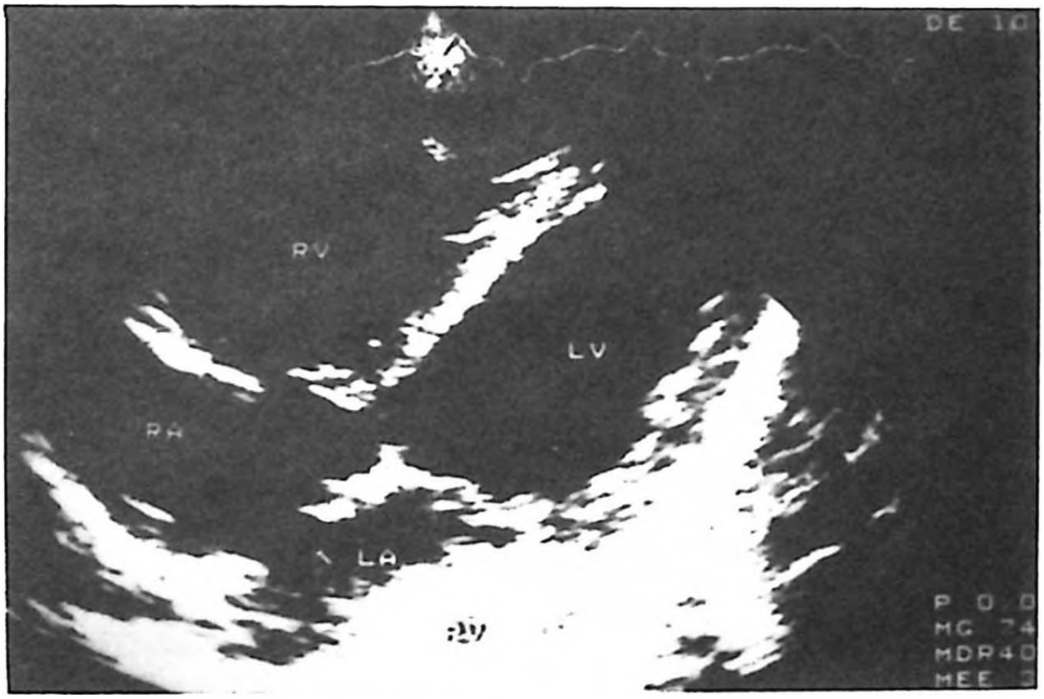
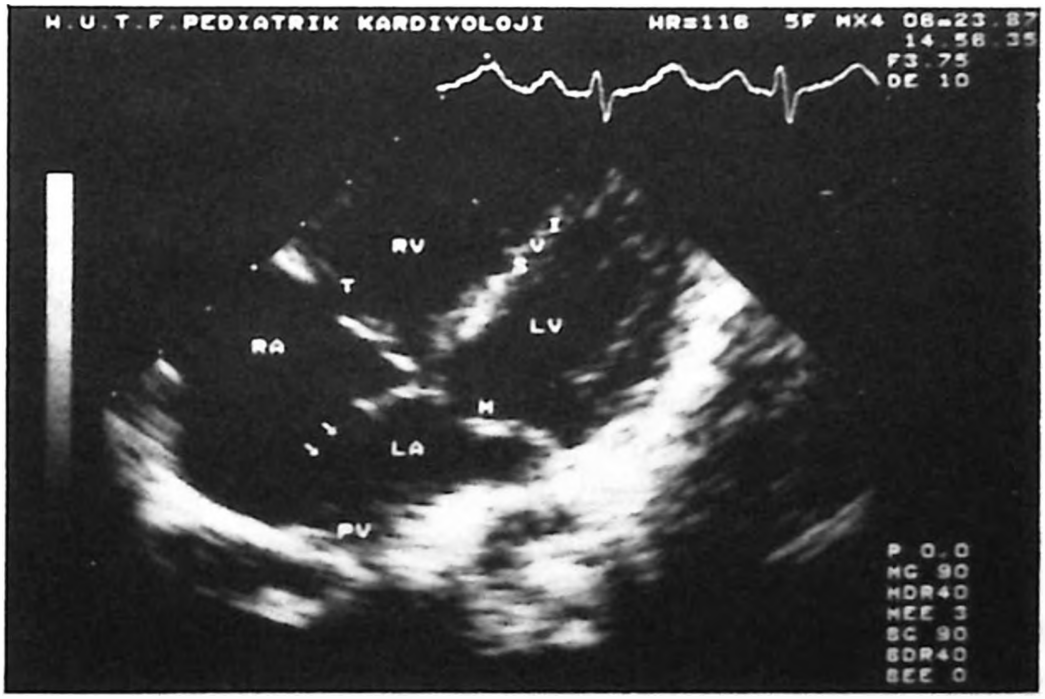



Fig. 1: Four chamber view echocardiograms. (a) Two-dimensional echocardiogram before injection of contrast material illustrates atrial septal defect (arrows). (b) Following peripheral vein contrast injection, right atrium and right ventricle filled with contrast material. Passage of 4+ contrast material from the right atrium to the left atrium through the atrial septal defect is seen. (RA, right atrium; RV, right ventricle; IVS, interventricular septum; T, tricuspid valve; M, mitral valve; PV, pulmonary vein).



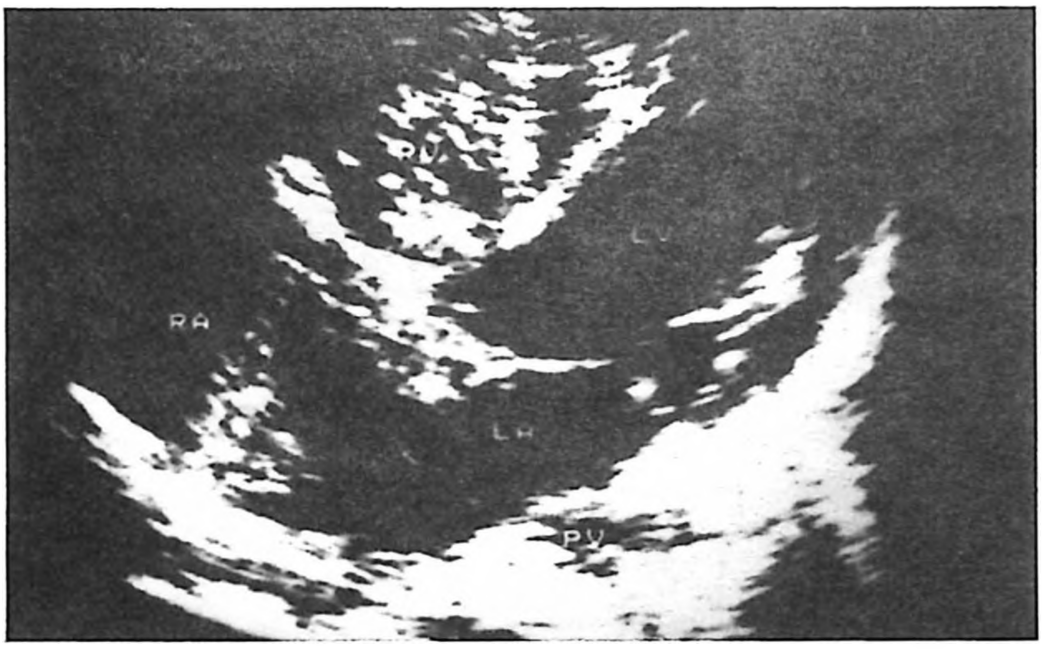



Fig. 2: Four chamber view echocardiograms. (a) Two-dimensional echocardiogram before injection of contrast material illustrates atrial septal defect (arrow). (b) Following peripheral vein contrast injection right atrium and right ventricle filled with contrast material. Arrow indicates 4– contrast effect resulted in the passage of non-contrast blood from the left atrium to the right atrium through the atrial septal defect. (RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PV, pulmonary vein).

4– contrast shuntings were considered to be definite evidence of an interatrial leak. It was decided that these patients were candidates for atrial septal defect closure. In the first few cases we were very cautious, and the surgery was performed as soon as possible in order to obtain a prompt surgical diagnosis. The patients with an insignificant contrast effect were evaluated as candidates for cardiac catheterization and angiocardiography.

## Results

154 patients showed a grade 3 or 4 positive and/or negative contrast effect. Among these patients 123 had only positive, nine negative, and 22 both positive and negative shunting. Of those 154 cases, 92 underwent atrial septal defect closure. The procedure was successful in all patients operated, the size of the defect being 2 × 2 cm or larger. Of the 31 patients with 1+ or 2+ shunting, 14 patients were catheterized. Thirteen of them were diagnosed as having atrial septal defect while one patient showed no evidence of atrial septal defect. Forty-eight cases did not reveal any contrast effect. Ten of them were catheterized. Six were diagnosed as atrial septal defect. Among the remaining four patients, one showed no cardiac pathology. However, two demonstrated mild pulmonary stenosis. One case showed evidence of partial anomalous pulmonary venous return with one of the left pulmonary veins draining into the left

innominate vein by way of the vertical vein. The other pulmonary veins were normally connected to the atrium. Angiography and catheter manipulation revealed no evidence of atrial septal defect.

## Discussion

Among the cases with a 3+, 4+ and/or 3−, 4− contrast effect, 92 underwent surgical treatment. In all, a surgical diagnosis of large atrial septal defect was obtained and the defects were closed. This result shows that the method presented is a safe and reliable one. Stark et al[9] operated on four cases with atrial septal defect diagnosed by two-dimensional echocardiography and suggested that further experience be gained regarding the subject. Bourdillon et al[5] studied ten patients with atrial septal defect using two-dimensional contrast echocardiography. They stated that the method was a potentially valuable one in identifying atrial septal defect.

In 31 cases with a 1+ or 2+ contrast effect, the diagnosis was accepted as not definite, although among those cases 14 were catheterized and atrial septal defect was diagnosed in 13. In the remaining one patient with a 1+ contrast effect no intracardiac shunt was detected by cardiac catheterization and angiocardiography. These findings are compatible with our description of 1+ contrast defined as a "very little or questionable contrast effect".

In 48 of our 233 cases, a contrast effect could not be seen. Of these 48 cases, ten were catheterized and the presence of atrial septal defect was detected in six. Among 14 cases diagnosed by cardiac catheterization Ginzton et al[6] were not able to detect atrial septal defect in one patient using two-dimensional contrast echocardiography. These results demonstrate that two-dimensional contrast echocardiography may fail to detect atrial septal defects in some cases. This occurs probably because of technical difficulties. We recommend cardiac catheterization and angiocardiography in the evaluation of such cases.

On the other hand, in our five patients among the catheterized 24 cases suspected clinically of having atrial septal defect, there were no septal defects; one of these cases had a partial anomalous pulmonary venous return without an atrial septal defect. Ginzton et al[6] found no intracardiac shunt in cardiac catheterization in their six patients among the 20 cases with clinical atrial septal defects. These findings, as traditionally accepted, show that just a clinical diagnosis alone is not sufficient for a definite diagnosis of atrial septal defect.

Weyman et al[4,8] found that non-contrast containing areas characteristically occurred immediately to the right of the atrial defect. They observed that a similar area of negative contrast had never been seen in patients with intact interatrial septae. This was explained by the flow of non-contrast containing blood from the

left atrium to the right atrium through the atrial septal defect. This finding (3– or 4– contrast effect) was present in our nine patients, and was shown to be definite evidence of a large atrial septal defect. However, a negative contrast effect is relatively difficult to evaluate. An echocardiographer should be aware of misinterpreting negative contrast images resulting from other sources, since in normal cases, continuous inflow from the inferior vena cava and coronary sinus is non-contrast containing.

Twenty-two patients showed both a negative and positive contrast effect. This occurs in atrial septal defect with the change of pressures in the right and left atria throughout the cardiac cycle[7]. The dominant shunt is left-to-right during the major part of the cardiac cycle. A right-to-left shunt of blood is present at the onset of ventricular contraction or during early ventricular diastole[7]. Appearance of a significant contrast effect (3+ or 4+) in a high percentage of our patients is a result of the latter hemodynamic event.

During the application of the technique, contrast injections were repeated using different transducer positions. The best evaluations were made using a modified transducer position between the parasternal short axis and the apical four chamber views. In this projection, four chambers were seen and care was taken on both sides of the atrial septum and left atrial cavity for positive and negative contrast effects.

We conclude that our method is not sensitive for a definite detection of atrial septal defect. However, the results discussed above obtained from 3+, 4+ and/or 3–, 4– contrast effects indicate that this method is a specific one.

We strongly recommend the application of peripheral contrast echocardiography in cases with a clinical suspicion of atrial septal defect.

## Summary

This study was carried out on 233 children suspected clinically of having atrial septal defect with the aim of investigating the diagnostic capability of peripheral venous contrast echocardiography. The transfer of contrast material from the right atrium into the left atrium was evaluated as "positive contrast", while noncontrast blood, passing from the left atrium into the right atrium was termed "negative contrast". Positive contrasts were quantitated in four grades. A significant negative contrast effect was graded 3– or 4–. Three positive, 4+ and/or 3–, 4– contrast effects were considered definite evidence of an atrial septal defect. Among the cases with the above findings 92 underwent surgical closure of atrial septal defect. The procedure was successful in all patients operated; the size of the defect was large. This result demonstrates that the method applied is a safe and reliable one. However, in a group of cases without the above

echocardiographic findings the presence of an atrial septal defect was detected by cardiac catheterization and angiocardiography. Therefore, we can conclude that the method applied is not a sensitive, but a specific one, for definite detection of atrial septal defect.

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# PHYSICAL GROWTH MEASUREMENTS OF 18,719 PRIMARY SCHOOL CHILDREN LIVING IN ADANA, TURKEY*

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*Key words: height and weight measurements, growth standards, Turkey*

Height and weight measurements are considered basic criteria in monitoring the growth of children. For this reason, growth standards or nomograms which yield mean optimal values have been constructed for children in many developed countries[1]. But, similar standards have not yet been established for children in most developing countries including, Turkey. Several studies have been carried out to evaluate the development of Turkish children[2-7]. They reveal varied measurements since they reflect the social and environmental differences existing in various parts of Turkey.

The aim of this study is to establish local urban standards for Turkish children living in Adana whose ages range between six and fifteen years and to compare these results with the data gathered from studies carried out in other parts of Turkey and the USA, a developed country.

## Material and Methods

This cross-sectional study was carried out in 1982 on 18,719 healthy children at 14 primary schools located in different parts of the city of Adana in order to establish the growth standards of children. Our study was part of a general concurrent study used to determine the frequency of congenital malformations. Since only healthy children were considered for our study, those with chronic diseases,

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neurological disorders, congenital malformations and poor nourishment along with children whose ages were doubtful, were excluded.

Measurements were taken under the supervision of a consulting pediatric surgeon and several senior residents. There were 9,135 girls and 9,584 boys whose ages ranged between six and fifteen years. Height and weight measurements were taken using standard portable equipment. The children wore only their underclothing when being weighed, and their height was determined while standing barefoot.

The mean and standard deviations were calculated for boys and girls. For each age and sex group, the $3^{rd}$, $10^{th}$, $25^{th}$, $50^{th}$, $75^{th}$, $90^{th}$ and $97^{th}$ percentiles were calculated. The boys were divided into the 6-13 and 13-15 year-old age-groups while the girls were divided into the 6-12 and 12-15 year-old age-groups. The subjects were put into their respective age-groups because of the acceleration in weight and height after puberty. A third-degree regression analysis was used to obtain continuous curves for the two groups of boys and the two groups of girls for each percentile.

## Results

The age and sex distributions of the children are shown in Table I. The mean and standard deviations of height and weight measurements of boys and girls for each age-group are shown in Tables II and III. Percentiles for boys and girls which are the result of third degree regression analysis are presented in Tables IV and V.

TABLE I: Age and Sex Distribution of Children

| Age (yrs) | Boys | Girls |
|---|---|---|
| 6 | 253 | 256 |
| 7 | 1372 | 1488 |
| 8 | 1807 | 1617 |
| 9 | 1500 | 1591 |
| 10 | 1654 | 1478 |
| 11 | 1393 | 1377 |
| 12 | 882 | 656 |
| 13 | 252 | 236 |
| 14 | 258 | 228 |
| 15 | 213 | 208 |
| Total | 9584 | 9135 |

TABLE II: Mean and Standard Deviation of Weight (kg) for Boys and Girls

| Age (yrs) | Boys | Girls |
|---|---|---|
| 6 | 21.00 ± 2.10 | 20.44 ± 2.40 |
| 7 | 22.61 ± 2.51 | 22.01 ± 2.51 |
| 8 | 25.31 ± 2.81 | 24.20 ± 2.70 |
| 9 | 27.29 ± 2.89 | 26.81 ± 3.11 |
| 10 | 30.21 ± 3.41 | 29.19 ± 3.79 |
| 11 | 33.11 ± 3.71 | 32.30 ± 4.20 |
| 12 | 35.51 ± 4.01 | 34.70 ± 4.80 |
| 13 | 38.20 ± 4.50 | 39.91 ± 5.51 |
| 14 | 44.39 ± 5.59 | 45.39 ± 5.59 |
| 15 | 50.71 ± 7.74 | 51.81 ± 5.81 |

TABLE III: Mean and Standard Deviation of Height (cm) for Boys and Girls

| Age (yrs) | Boys | Girls |
|---|---|---|
| 6 | 115.93 ± 4.64 | 115.16 ± 4.23 |
| 7 | 119.86 ± 4.04 | 119.46 ± 3.72 |
| 8 | 124.84 ± 4.31 | 124.10 ± 3.78 |
| 9 | 129.98 ± 4.17 | 129.35 ± 4.05 |
| 10 | 134.69 ± 4.52 | 133.84 ± 4.61 |
| 11 | 139.93 ± 4.69 | 139.59 ± 4.94 |
| 12 | 144.53 ± 4.55 | 144.87 ± 5.27 |
| 13 | 148.56 ± 4.91 | 151.19 ± 5.27 |
| 14 | 156.70 ± 6.14 | 157.55 ± 5.30 |
| 15 | 164.86 ± 6.32 | 163.91 ± 5.36 |

TABLE IV: Weight Percentiles of Boys and Girls

| Boys | | | | | | | Age (yrs) | Girls | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3rd | 10th | 25th | 50th | 75th | 90th | 97th | | 3rd | 10th | 25th | 50th | 75th | 90th | 97th |
| 16.72 | 18.14 | 19.59 | 21.00 | 22.40 | 23.82 | 25.73 | 6 | 15.56 | 17.18 | 18.79 | 20.68 | 22.51 | 24.78 | 25.71 |
| 17.84 | 19.48 | 21.15 | 22.76 | 24.39 | 26.03 | 27.67 | 7 | 17.21 | 18.84 | 20.46 | 22.04 | 23.67 | 25.52 | 27.50 |
| 19.48 | 21.32 | 23.19 | 24.99 | 26.87 | 28.66 | 30.44 | 8 | 18.75 | 20.57 | 22.38 | 23.98 | 25.98 | 27.82 | 29.81 |
| 21.45 | 23.48 | 25.54 | 27.54 | 29.57 | 31.60 | 33.63 | 9 | 20.29 | 22.41 | 24.53 | 26.43 | 28.76 | 30.89 | 33.75 |
| 23.56 | 25.79 | 28.05 | 30.24 | 32.48 | 34.70 | 36.93 | 10 | 21.94 | 24.42 | 26.88 | 29.30 | 31.82 | 34.33 | 36.77 |
| 25.64 | 28.08 | 30.56 | 32.97 | 35.41 | 37.86 | 40.30 | 11 | 23.80 | 26.62 | 29.43 | 32.02 | 35.06 | 37.94 | 40.71 |
| 27.50 | 30.18 | 32.90 | 35.56 | 38.25 | 40.93 | 43.62 | 12 | 25.10 | 28.30 | 31.50 | 34.70 | 37.90 | 41.10 | 44.65 |
| 29.20 | 32.29 | 35.20 | 38.20 | 41.35 | 44.35 | 47.35 | 13 | 28.90 | 32.57 | 36.24 | 39.91 | 43.58 | 47.25 | 50.94 |
| 33.20 | 36.93 | 40.66 | 44.39 | 48.32 | 52.03 | 56.21 | 14 | 34.20 | 37.93 | 41.66 | 45.39 | 49.12 | 52.85 | 56.57 |
| 42.10 | 42.97 | 46.84 | 50.71 | 54.58 | 60.54 | 66.15 | 15 | 40.20 | 44.07 | 47.94 | 51.81 | 55.68 | 59.55 | 63.36 |

TABLE V: Height Percentiles of Boys and Girls

| Boys | | | | | | | Age (yrs) | Girls | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3rd | 10th | 25th | 50th | 75th | 90th | 97th | | 3rd | 10th | 25th | 50th | 75th | 90th | 97th |
| 106.7 | 109.6 | 112.8 | 115.9 | 118.9 | 122.0 | 125.1 | 6 | 106.3 | 109.2 | 112.2 | 115.1 | 118.1 | 121.0 | 124 |
| 111.7 | 114.5 | 117.3 | 120.1 | 122.8 | 125.6 | 128.4 | 7 | 112.1 | 114.6 | 117.1 | 119.6 | 122.1 | 124.6 | 127.1 |
| 116.2 | 119.4 | 122.0 | 124.8 | 127.5 | 130.2 | 133.0 | 8 | 116.7 | 119.2 | 121.7 | 124.2 | 126.7 | 129.2 | 121.6 |
| 121.2 | 124.2 | 126.9 | 129.8 | 132.6 | 135.5 | 138.4 | 9 | 120.8 | 123.6 | 126.3 | 129.1 | 131.8 | 134.5 | 137.2 |
| 125.9 | 128.9 | 131.9 | 134.9 | 137.9 | 140.9 | 143.9 | 10 | 125.0 | 128.0 | 131.1 | 134.2 | 137.2 | 140.3 | 143.3 |
| 130.6 | 133.7 | 136.8 | 139.9 | 143.0 | 146.1 | 149.2 | 11 | 129.6 | 132.9 | 136.2 | 139.6 | 142.8 | 146.1 | 149.4 |
| 135.4 | 138.3 | 141.5 | 144.5 | 147.6 | 150.6 | 153.6 | 12 | 134.5 | 137.9 | 141.4 | 144.9 | 148.9 | 151.9 | 155.4 |
| 138.8 | 142.0 | 145.3 | 148.7 | 151.8 | 155.1 | 158.4 | 13 | 140.8 | 144.2 | 147.8 | 151.2 | 154.7 | 158.2 | 161.7 |
| 144.5 | 148.5 | 152.6 | 156.9 | 160.8 | 164.9 | 169.0 | 14 | 147.1 | 150.6 | 154.1 | 157.5 | 161.1 | 164.6 | 168.1 |
| 152.2 | 156.4 | 160.7 | 164.9 | 169.1 | 173.3 | 177.5 | 15 | 153.4 | 156.9 | 160.5 | 163.9 | 167.5 | 171.1 | 174.6 |

Weight and height percentiles for each sex are represented as curves in Figs. 1 and 2. Figures 3 and 4 illustrate comparisons of the 50$^{th}$ percentile with regard to weight and height of children living in Adana, İstanbul, Trabzon, Gemlik and the USA. There is also a comparison of the results obtained by Koksal[8] from Turkey. A statistical comparison could not be made because the numbers of children in the various surveys were not indicated.

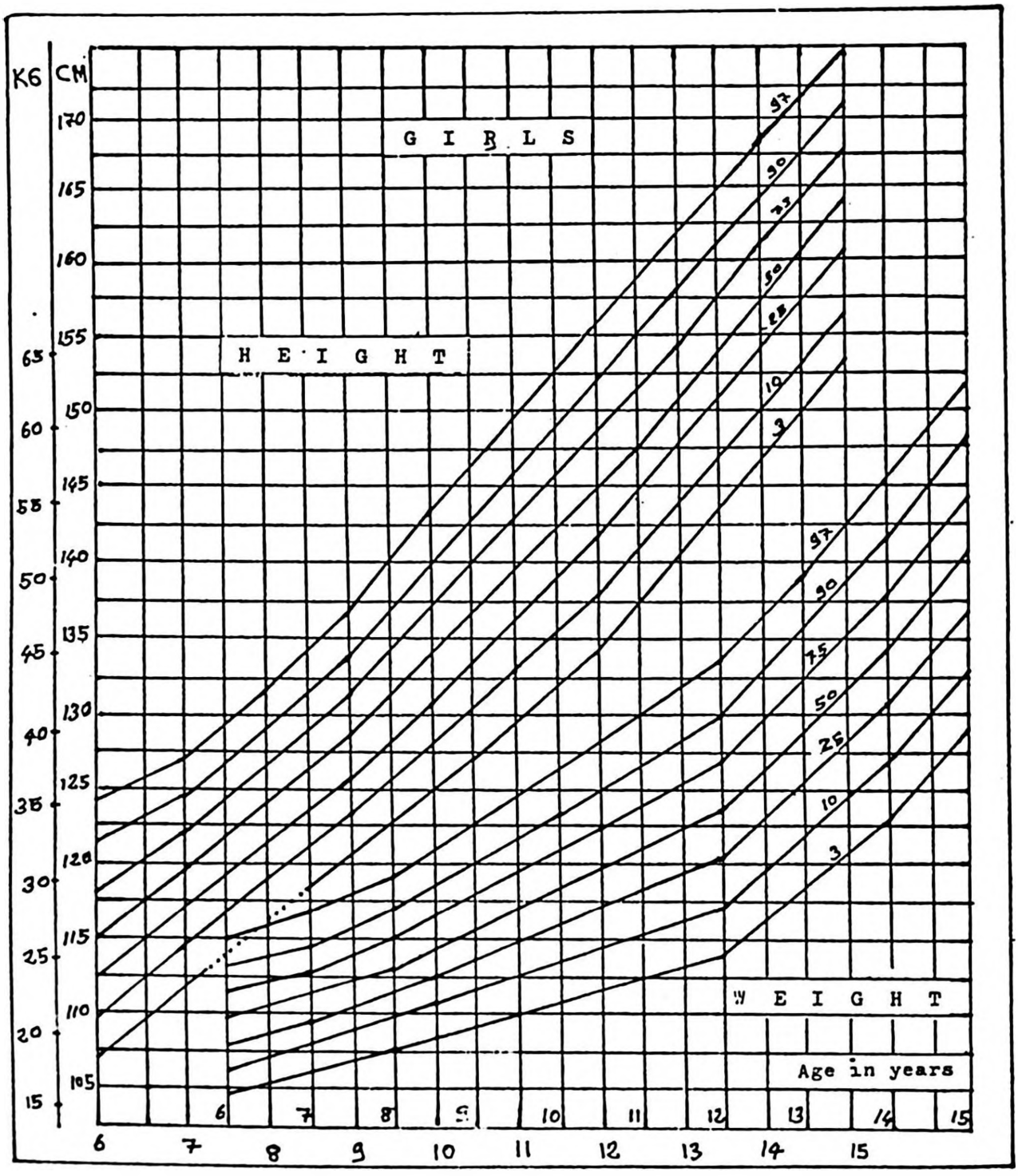


Fig. 1: Height and weight percentiles of boys.

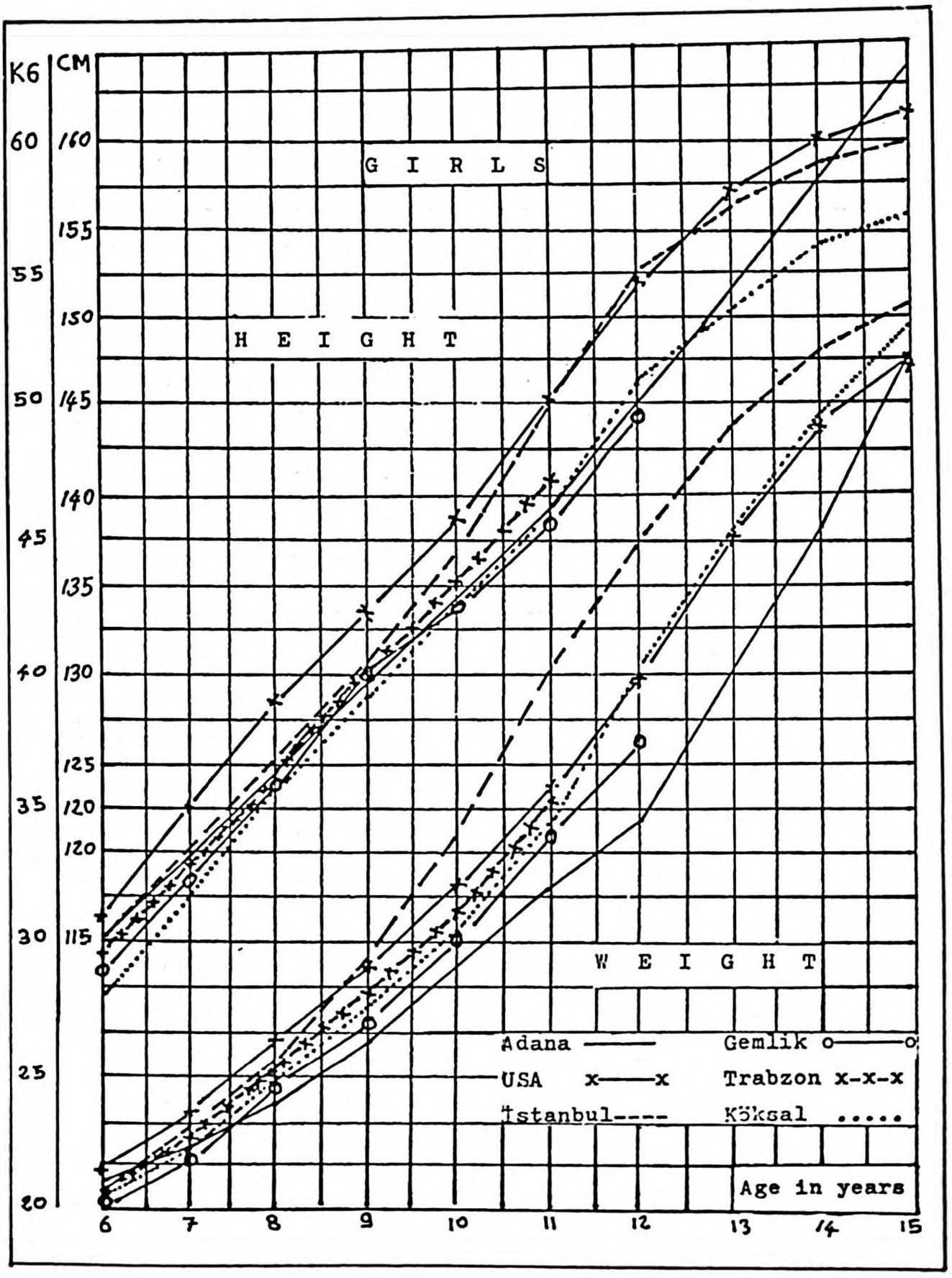


Fig. 2: Height and weight percentiles of girls.

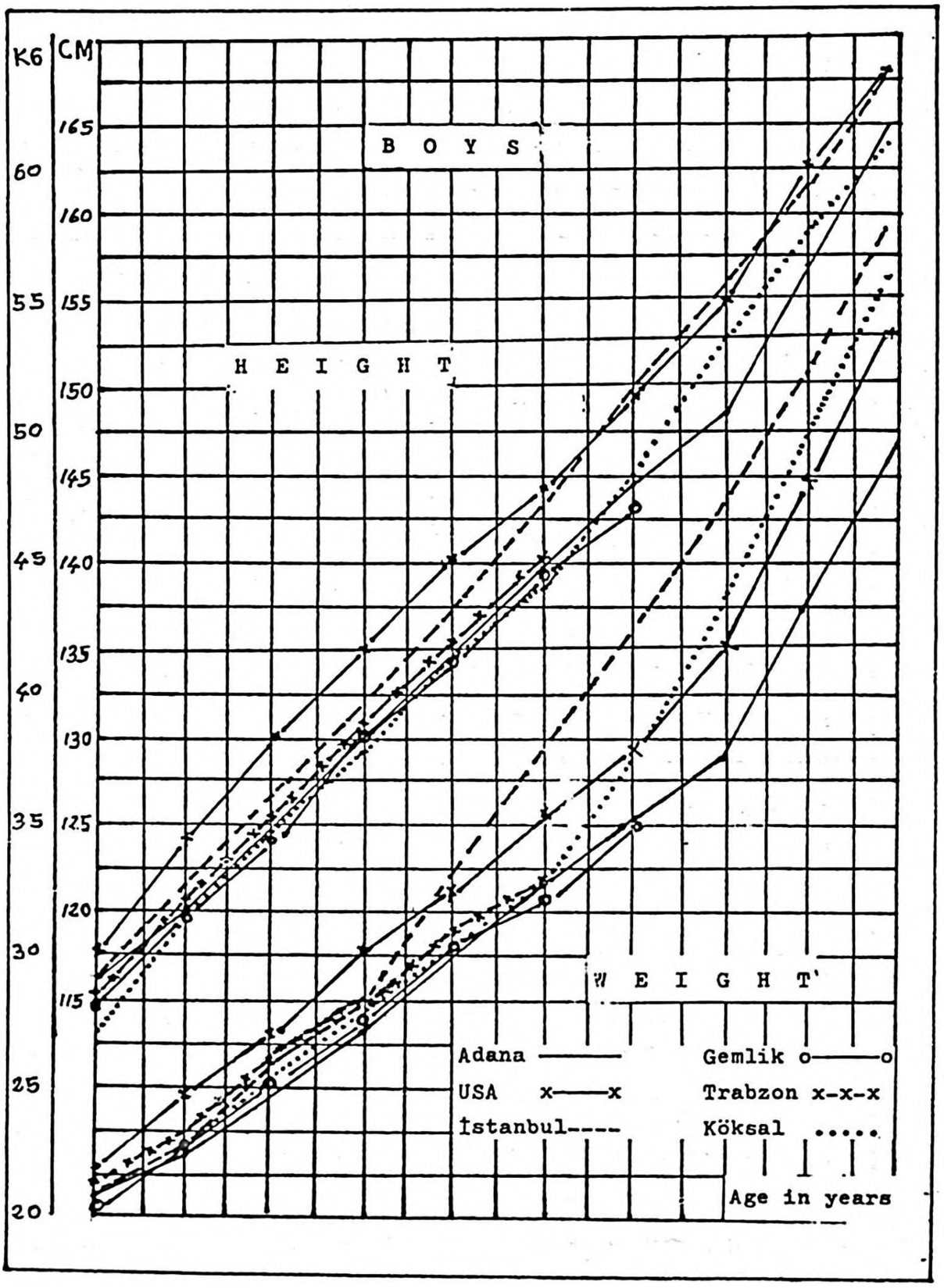


Fig. 3: Comparison of the 50th percentile with regard to weight and height of boys living in Adana with those living in the USA, Istanbul, Gemlik, Trabzon, and Köksal's[8] results.

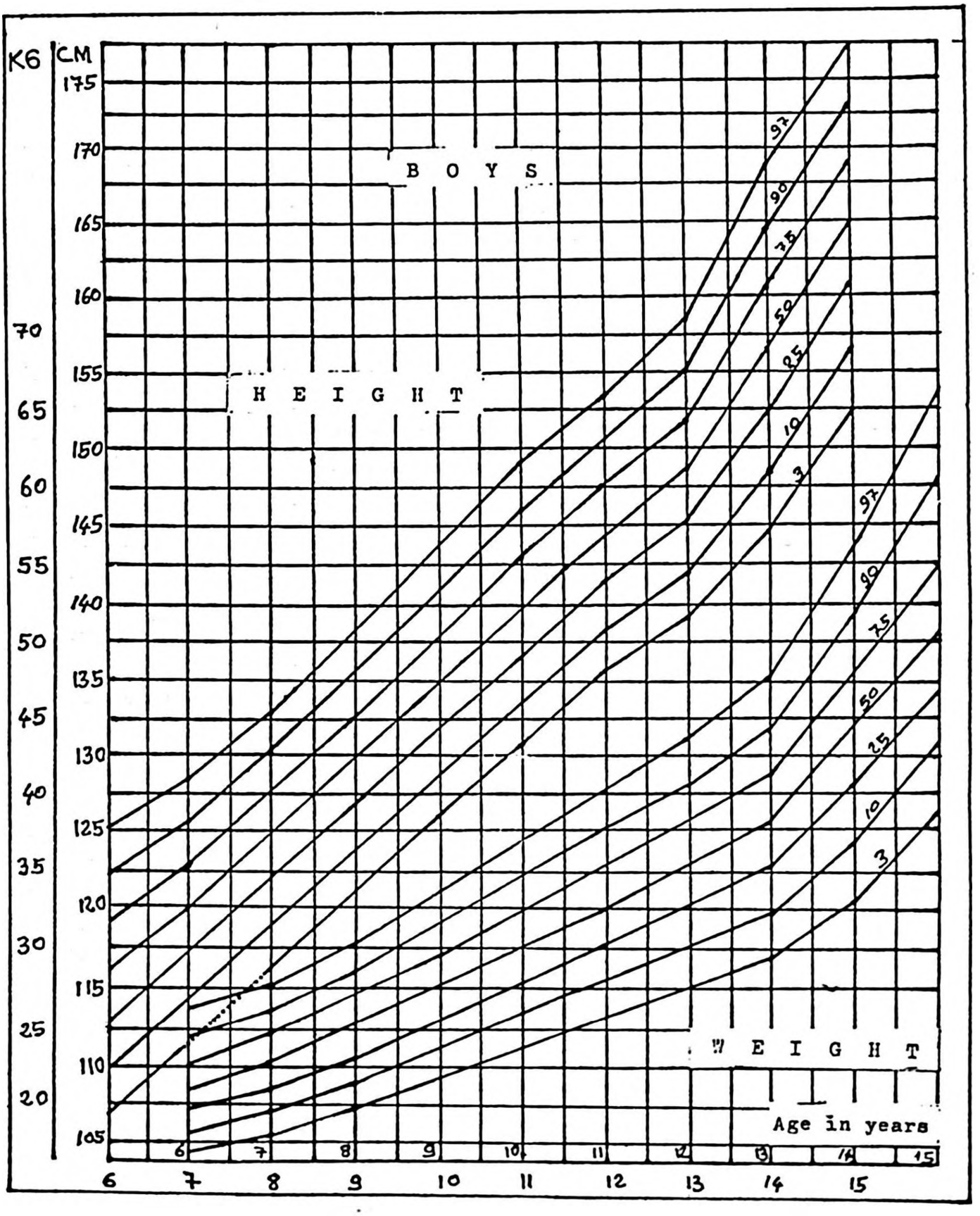


Fig. 4: Comparison of the 50th percentile with regard to height and weight of girls living in Adana with those living in the USA, Istanbul, Gemlik, Trabzon, and Koksal's[8] results.

## Discussion

In pediatrics the practice of measuring developmental growth and comparing the measurements with appropriate standards is very valuable[6]. Measurements of physical growth are used in child health care in order to detect abnormalities, reassure parents concerning normality, assess suspected abnormalities of growth and evaluate treatment[9,10]. They also provide concrete and definite criteria regarding the normal growth pattern which is influenced by the interaction of genetic and external factors[11] such as: nutrition, infection, intoxication and other deleterious external influences which are primarily seen in developing countries and can prevent the growth potential of children[11]. Therefore, the use of standards based on measurements taken from children in highly industrialized countries can result in misleading conclusions[1]. In taking into consideration these differences resulting from genetics and external influences, the World Health Organization (WHO) has recommended that every country use its own standards[11,12].

The first important survey of body measurements in the world was carried out by Quatelet in 1835, and several studies followed this[6]. The first significant study in Turkey was conducted by Doğramacı[13], between 1949-1954. This study showed that sex differences along with socioeconomic levels of parents influence the birth weight and height of children. Tanner et al[14,15] studied the effects of socioeconomic levels on growth measurements of children living in urban and rural regions in various European countries and showed that the socioeconomic level of the parents clearly influenced the growth index. Subsequently, several significant studies have been reported which clarify the issue[6,12]. Recently, in order to standardize the studies and obtain reliable values, WHO suggested that the following criteria be used[4,11]: The subjects selected should be well-nourished urban children; for each sex and age-group the sample should consist of at least 200 children; measurements should be taken by experienced personnel using standard equipment; a study should preferably be a cross-sectional survey since it will be used in this manner, and thus, the results obtained will represent the real growth potential of the population and can then be compared to data from other countries.

Our study carried out on a sampling of children and the measurement techniques and equipment used were in compliance with WHO's recommendations. The subjects that we chose were generally well-nourished and their families were of a high socioeconomic level. It has been suggested that universal growth standards be based on measurements of healthy children of a certain locality[7,11]. If this is not accomplished, the values obtained will be lower than the real values and might not represent the real growth potential of that population[1]. Therefore, WHO and the International Committee of Nutrition also recommended that the study

groups be members of families of higher socioeconomic levels living in urban areas[4,11,16]. Our study is in accordance with the afore-mentioned suggestions and it can be considered a reliable standard for the Çukurova Region.

In the comparison of the 50$^{th}$ percentile with regard to weight, the results obtained from the children living in Adana were significantly lower than the children living in İstanbul, Trabzon, and the USA. This relationship is illustrated in Figs. 3 and 4. Similar results were arrived at regarding children living in Gemlik and Adana. Koksal's[8] results represent the average of seven regions in Turkey and when our results were compared with his work, apparent differences were observed which might have been due to regional changes.

When the children's heights were compared, similar results were obtained. The differences in height and weight measurements of the children living in Adana, Istanbul, and the USA were greater in the older age-groups (Figs. 3 and 4). A comparison of the results showed that the growth standards of the children living in the evaluated regions of Turkey were apparently different; there also were differences in the height and weight measurements of the children living in Turkey and the USA.

Considering these results, we can conclude that local growth standards based on local measurements be utilised in evaluating the growth of children in certain regions of Turkey. Therefore, separate growth standards specific to a certain area should be determined and used in the evaluation of the growth of children living in different regions of Turkey. The measurements presented represent only the growth standards of children living in Adana, aged 6-15 years. We hope that our study will contribute to the establishment of standard norms for Turkish children throughout the country as a whole.

## Summary

Height and weight measurements of 18,719 healthy children were obtained and the results were compared with those obtained from children living in several regions of Turkey and the USA. The results of these measurements differed significantly. This study demonstrates that local growth standards should be established and used in the evaluation of children.

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# MULTIPLE PRIMARY HYDATID CYSTS OF THE BRAIN*

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*Key words: hydatid cyst, brain cyst, multiple cysts, echinococcus*

All reported cases of multiple hydatid cysts of the brain have resulted from spontaneous, traumatic or surgical rupture of a primary solitary cyst[1-6]. As far as we know, only one case of multiple primary cerebral hydatid cysts had been previously described[7]. We also present such a case. An extremely rapid growth of cerebral hydatid cysts in children is suggested.

## Case Report

A 15-year-old boy was admitted to Erciyes University Hospital with a two-month history of severe headache and intellectual deterioration. Ten days prior to admission he developed progressive dysphasia.

Neurological examination revealed bilateral papilledema, expressive dysphasia, and obtundation. Skull films demonstrated evidence of raised intracranial pressure. Computerized tomography (CT) showed four spherical, well-defined cystic lesions occupying the left supratentorial hemisphere. Of these, three were located in the frontoparietal region, and one measuring one cm in diameter, in the occipital region. The cerebral hemisphere was markedly compressed and the ventricular system was displaced to the opposite side. The lesions contained a fluid with a Hounsfield unit value similar to that of cerebrospinal fluid, and enhancement of a peripheral rim of the compressed brain was noted (Fig. 1). The CT appearance was diagnosed as multiple hydatid cysts. Laboratory studies were normal and there was no evidence of hydatid disease elsewhere.

During the operative procedure a large, frontoparietal bone flap was turned, the dura and arachnoid were opened, and a cortical incision was made over the most surperficial part of the cysts. The cysts were encountered at a depth of two mm.

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Saline was injected into the cyst-brain interface and a cyst measuring six cm across was delivered intact. After the removal of this superficial and largest cyst, four other cysts were exposed underneath. Of these, two were four cm, and two were two and half cm in diameter. All of the four cysts were removed intact using saline irrigation assisted by changing the position of the patient's head. A deep-seated cyst measuring one cm was tightly surrounded and could not be delivered by irrigation. The entire contents of this cyst were aspirated, and the collapsed cyst was lifted away. Large cotton tampons soaked in 3% NaCl were applied to the large cavity and left in place a couple of minutes. Then, the cavity was thoroughly and repeatedly washed with saline. No attempt was made to remove the small single occipital cyst. It was thought that deferring the surgical intervention and waiting for the evolution of the cyst would be the best choice. Microscopic examination of the pearly white cysts showed the characteristic ectocyst and scolices.

The postoperative course was uneventful. The patient's neurological condition markedly improved, and he was free of symptoms when discharged on the fifteenth day after admission. Seven months later, a new CT performed because

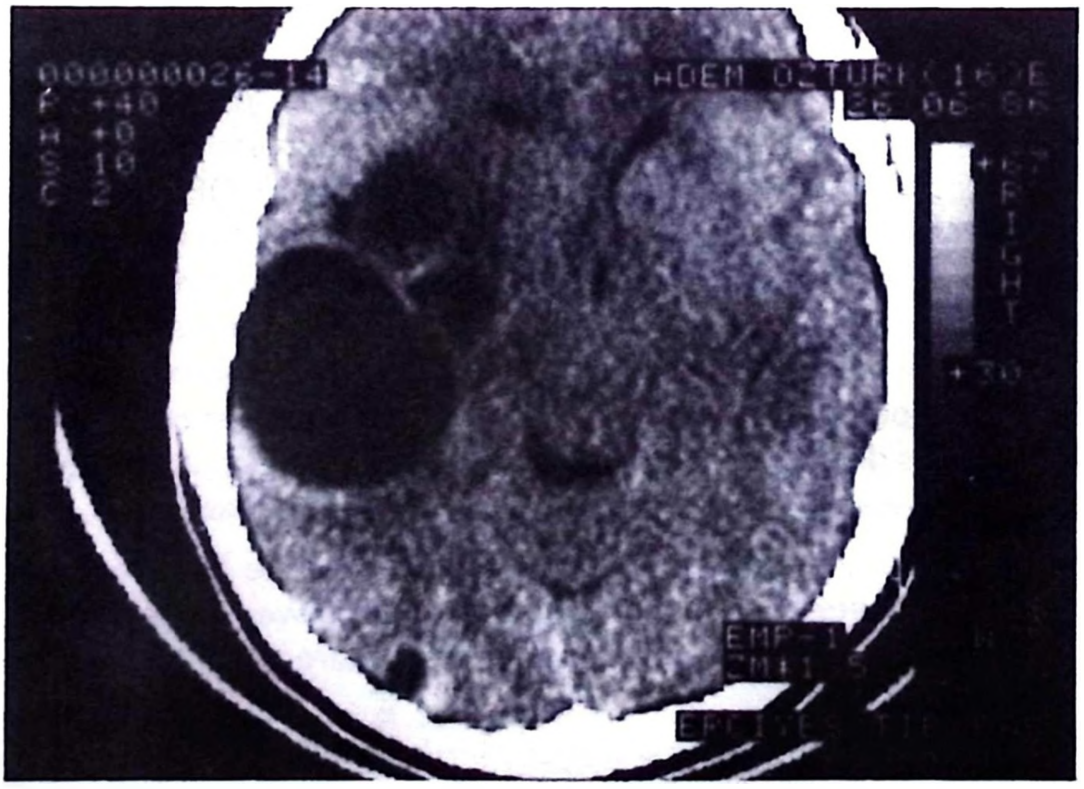

Fig. 1: CT scan showing multiple hydatid cysts occupying the left supratentorial region. Note the peripheral rim enhancement following intravenous contrast injection, and the small occipital hydatid cyst.

of dysphasia, revealed a large recurrent cyst in the sylvius. The small occipital cyst detected in the first CT was found to be seven cm in diameter (Fig. 2). These two cysts were removed intact using the same operative technique. The patient recovered rapidly after the second operation. He has had no symptoms since then and no cyst recurrence during a year follow-up period.

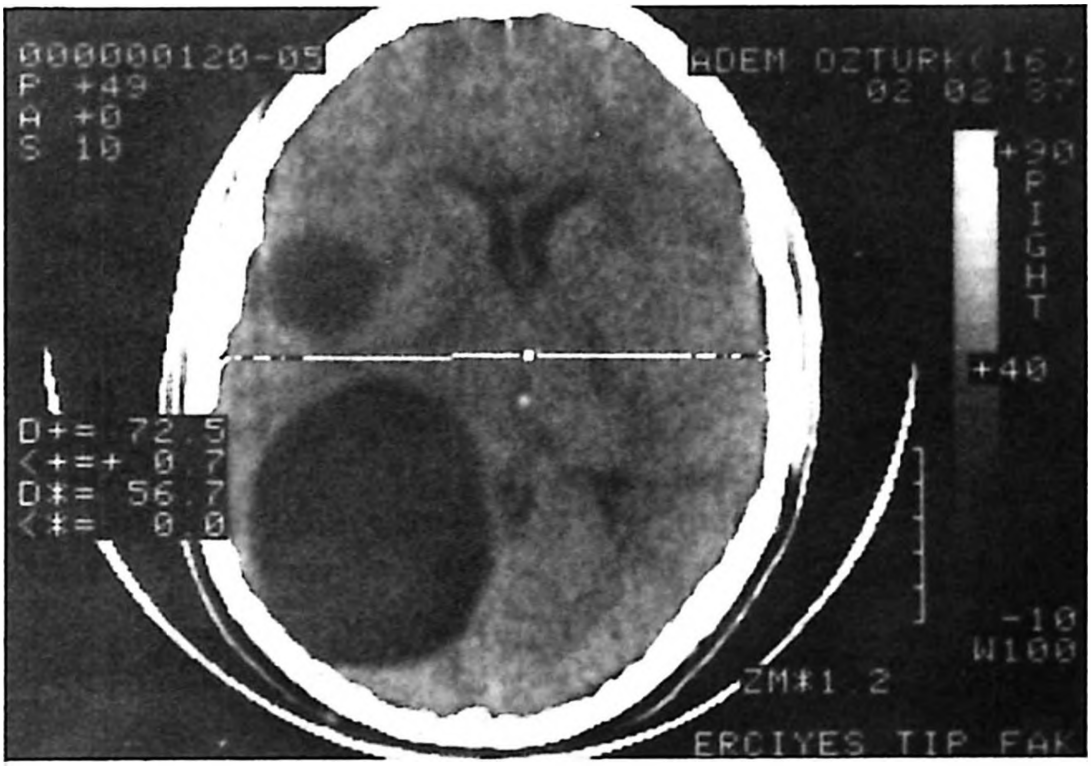


Fig. 2: Follow-up CT scan seven months later showing a large recurrent cyst in the operated area and extremely rapid growth of the small cyst seen in the first scan.

## Discussion

The incidence of hydatid cysts among intracranial space-occupying lesions varies between 1.6 and 5.2 percent[3] in different countries. In Turkey, this rate was found to vary between 3.4 and 2.4 percent[4,8]. Hydatid cysts of the brain are more common in children than in adults[1,2,5], and the cysts are always solitary when the primary localization is in the brain[3,4,9]. Multiple cerebral hydatid cysts are rather rare[2,3], and result from spontaneous, traumatic or surgical rupture of a primary solitary cerebral cyst or as a consequence of a cyst rupture elsewhere and embolization of hydatids to the brain[1-6,10-12]. These secondary cysts which are acephaloceles and infertile lack a broad capsule[3,5].

Although Gordillo et al[13] recently described a case of multiple cerebral hydatid cysts with no previous history of trauma or rupture of cysts elsewhere, there was no detailed information confirming that all were primary cysts. The only case of multiple primary hydatid cysts of the brain has been reported by Sharma and

Abraham[7]. In our case, the second case of multiple primary hydatid cysts of the brain, all the cysts contained broad capsules and scolices, and repeated postoperative follow-ups showed no evidence of hydatid disease elsewhere in the body.

Cerebral hydatid cysts are often very large, especially in children. They are tolerated for a long period, and are usually huge when diagnosed[2,3,5]. An average growth of one cm per year for intracranial hydatid cysts in the adult has been suggested[6,12,14]. This rate can be much faster in children, as in the case reported by Gordillo et al[13], and as in our case. The growth rate in our case was more than ten cm per year. We think that such extreme rapid growth of hydatid cysts must be considered in children and this aspect of the disease deserves detailed studies.

CT scanning can be relied on in the differential diagnosis of cerebral hydatid cysts. There is a spherical well-defined intracerebral cystic lesion containing fluid with a density value similar to that of CSF, with no ring enhancement[15,16]. Though multiple hydatid cysts can also be differentiated from other cystic lesions by these characteristic features, it should be remembered that contrast enhancement of the periphery of the cyst, probably due to compression of the surrounding parenchyma may be found[17], as was seen in our case.

The only treatment for hydatid cysts is surgery, with removal of the cysts intact and avoidance of spillage of the hydatid fluid. Nevertheless, deep-seated and tightly surrounded small cysts may not be able to be delivered intact and a ruptured cyst always carries a high risk of recurrence. Research into therapy with benzimidazole carbamates is in progress. The clinical trials of mebendazole and flubendazole have not been well-coordinated, and the results which mostly concern patients with liver, peritoneal, bone, lung, and spinal or paraspinal cysts, are inconclusive[18-22]. At present, there is not sufficient evidence to justify the routine pre-and postoperative use of these agents in patients with hydatid cysts of the brain.

We believe that surgical intervention should be considered in every case, even in the event of recurrence.

**Summary**

A rare case of multiple primary hydatid cysts of the brain is presented in a 15-year-old boy. The largest of the seven cysts located on the right hemisphere measured six cm across, while the smallest one was one cm in diameter. Detailed studies revealed no evidence of hydatid disease elsewhere in the body. The growth rate of an untreated cyst was about ten cm per year determined by follow-up computerized tomography. Since the only treatment of cerebral hydatid cysts is surgery, with removal of the cysts intact, surgical intervention should be considered in every case, even in the event of multiple recurrences.

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# HEMOBILIA FROM A RUPTURED HEPATIC ARTERY ANEURYSM IN A 16-YEAR-OLD GIRL*

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*Key words: hemobilia, hepatic artery, aneurysm*

The hepatic artery is the second most common site of visceral artery aneurysm, accounting for about one-fifth of reported cases[1]. Even though selective celiac arteriography is the most useful diagnostic procedure, most hepatic artery aneurysms are not discovered until a laparotomy has been performed. The diagnosis may be suggested by the triad of biliary colic, jaundice and gastrointestinal bleeding. The majority of patients are over fifty years of age, but some cases have been described at both age extremes[2].

Of the cases reported, infectious diseases, and atheromatous and fibromuscular changes have been responsible for the pathogenesis of hepatic artery aneurysm.

In this article, we present a case of hemobilia from a ruptured hepatic artery aneurysm due to fibromuscular dysplasia which occurred in a patient who was only sixteen years of age.

## Case Report

A sixteen-year-old female was admitted to Karadeniz University Hospital with a one-week history of right upper quadrant pain, nausea, vomiting and melena which occurred twice a day. There was also a history of dark urine and icteric sclera of several days' duration. There had been no recent history of systemic infection or trauma. On admission the blood pressure was 110/80 mm Hg, pulse rate 140/min, hemoglobin level 6.4 g/dl, serum total bilirubin 3.5 mg/dl, indirect bilirubin 3 mg/dl, alkaline phosphatase 40 Smogy units, and SGOT 100 mU/ml. The only positive sign was a thrill on the right upper quadrant of the abdomen. She was given 2000 cc of blood during the night to maintain her vital signs within normal limits. Gastroscopy revealed no abnormality. During this course of time hematemesis commenced and the cramping discomfort in the right upper quadrant and epigastrium continued. An emergency laparotomy was performed.

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The stomach, the entire small bowel and colon contained blood. During surgery, a pulsating mass was found in the region of the hepatoduodenal ligament. The mass was presumed to be an aneurysm of the hepatic artery. A choledochotomy was then performed and active arterial bleeding was encountered coming through a 1-2 cm communication of the aneurysm and the posterior wall of the common hepatic duct, which had small multiple perforations. The common hepatic artery was ligated and bleeding in the common bile duct instantly ceased. At surgery the gallbladder was edematous and grossly distended with blood; a cholecystectomy was performed. The gallbladder contained no calculi and the specimen revealed acute hemorrhagic cholecystitis. A T-tube was placed in the common bile duct and a penrose drain was placed in Winslow's foramen; the abdominal wound was closed in layers. During the operation four units of whole blood were administered to maintain the patient's vital signs within normal limits. T-tube drainage was clear postoperatively and a T-tube cholangiography was taken on the fifth day which illustrated the aneurysmal sac being filled from the common duct (Fig. 1).

Fig 1: T-tube cholangiography demonstrating the aneurysmal sac being filled from the common bile duct.

On the ninth postoperative-day the subject again experienced crampy right upper quadrant pain, nausea and arterial bleeding through the T-tube. Physical examination revealed nothing abnormal. The hematocrit reading was 34 percent, SGOT 120 mU/ml and serum biluribin 2.5 mg/dl. A laparotomy was performed again. When the T-tube was removed, arterial bleeding was encountered coming through the communication between the aneurysm and the common hepatic duct. The aneurysmal sac was seen and an erosion into the common hepatic duct was identified. The aneurysm was presumed to be an aneurysm of the right hepatic artery taking a retrograde blood supply from the gastroduodenal artery. The gastroduodenal artery was ligated. The bleeding stopped immediately. A biopsy specimen was taken from the communication between the aneurysmal sac and the common hepatic duct. The defect in the duct was then closed by using continuous 5-0 arterial sutures and a T-tube was inserted in the common bile duct without obstructing the flow of bile through the duct; the abdominal incision was closed in layers. Histological examination of the specimen revealed an aneurysm of the hepatic artery due to fibromuscular dysplasia (Fig.2). During

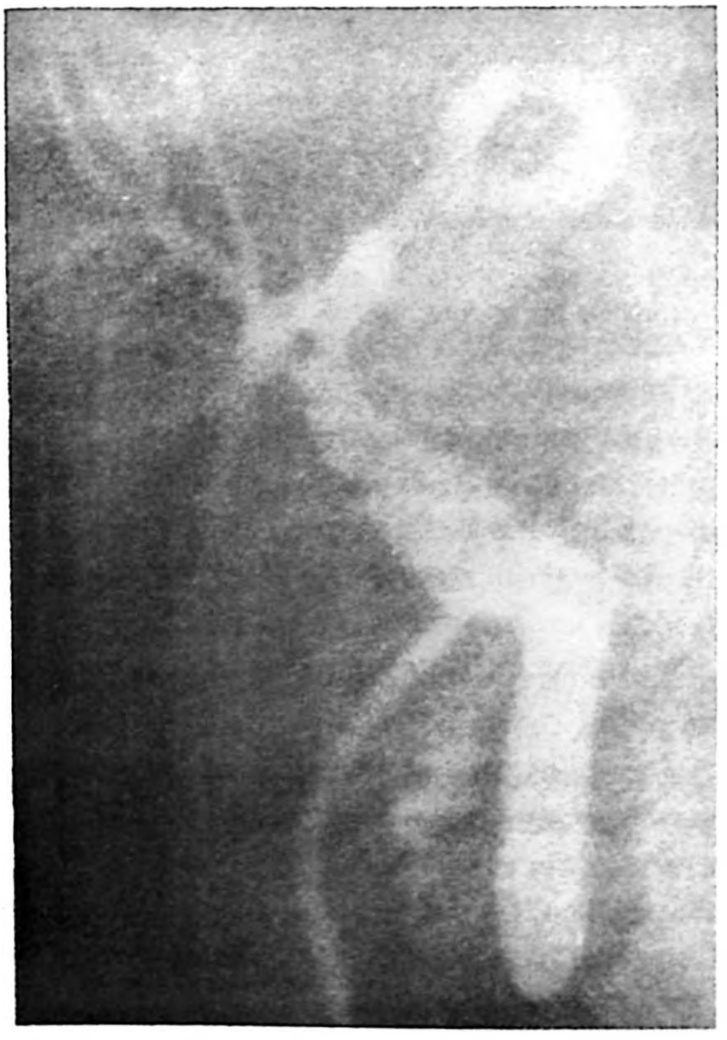

Fig 2: Spaces not having endothelial linings and areas containing fibrinoid necrosis infiltrated by mononuclear cells (HE × 12.5).

the postoperative course, slight hemorrhagic T-tube drainage was observed during the first two weeks and two units of whole blood were administered during this period. Three days following the second laparotomy, a T-tube cholangiography demonstrated no intraductal filling defects (Fig. 3), and therefore the T-tube was removed. The patient was discharged two days later.

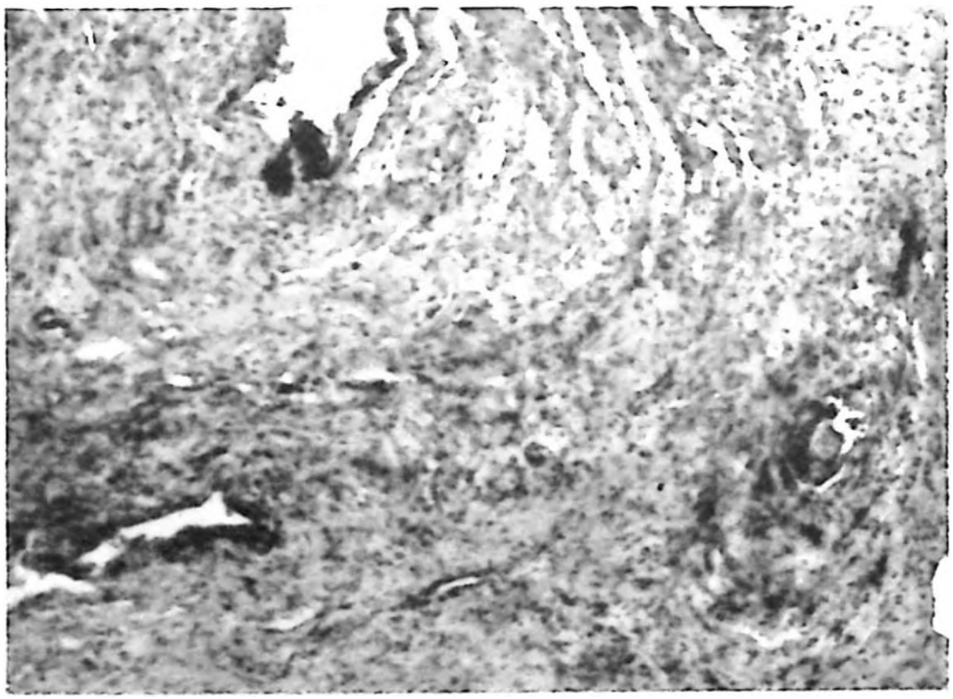

Fig 3: T-tube cholangiography after the fistulous opening was closed showing no aneurysmal sac or filling defects.

The patient did well until three months after the operation when she was readmitted to the hospital because of a two-day history of melena which occurred twice a day. On admission, her vital signs were within normal limits. The hemoglobin level was 10.5 g/dl, serum bilirubin 0.8 mg/dl, SGOT 40 mU/ml. Melena was found on rectal examination. Digital subtraction angiography showed good backflow to the liver (Fig. 4). The patient was discharged fifteen days after admission.

Three months after her last discharge from the hospital, the patient was again readmitted because of hematemesis and melena. Physical examination was normal. The hematocrit reading was 33%, hemoglobin level 8.8 g/dl, SGOT 100 mU/ml, and serum bilirubin 0.8 mg/dl. She was given two units of whole blood and was discharged a week after her admission. The patient was followed up biannually for three years postoperatively and there were no symptoms referable to either the gastrointestinal or biliary systems; her liver function tests were completely normal.

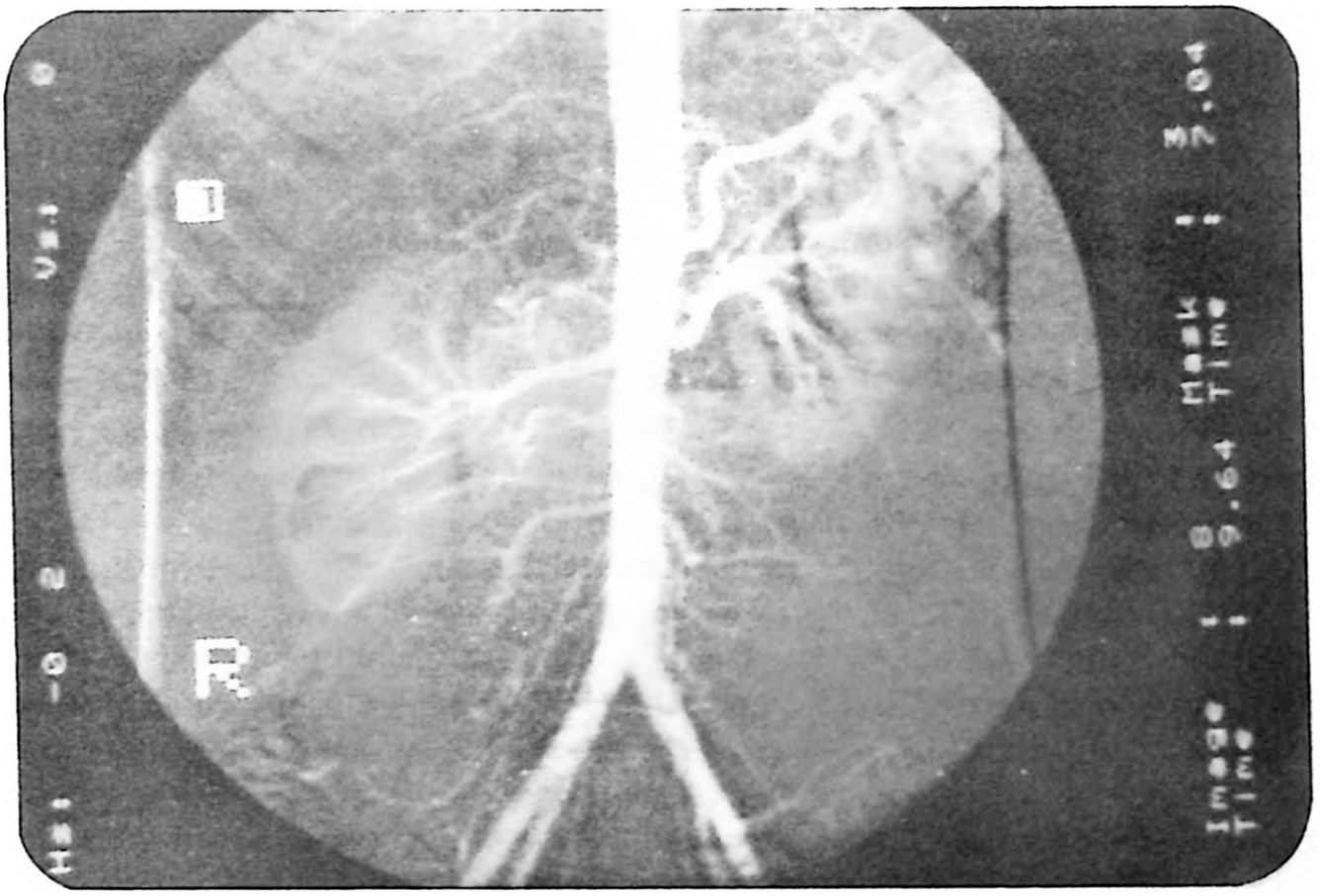

Fig 4: Digital subtraction angiography taken three years after surgery, demonstrating good backflow to the liver.

## Discussion

The most common cause of hemobilia is vascular disease and accounts for 55 percent of the 355 fully documented cases reviewed by Sandblom[3]. The most common vascular lesion causing hemobilia is an aneurysm of the hepatic artery. Hemorrhage from the rupture of an aneurysm of the hepatic artery into the common bile duct was first reported by Jackson[4]. Two-thirds of hepatic artery aneurysms are located in the common hepatic artery, with most of the remaining ones being located in the right hepatic artery[5].

In a review of reported cases only 16 percent of hepatic artery aneurysms had an infectious etiology[2]. Atheromatous changes are found in one-half of the hepatic artery aneurysms[6]. Fibrodysplastic changes are found in about one-fourth of the cases[1]. Fibromuscular dysplasia may involve a wide variety of arteries, sometimes in a multicentric fashion[7]. This condition normally becomes manifest during the third or fourth decade of life, although it can also be seen in children[8]. In our case, the microscopic examination of the specimen being taken from the communication between the hepatic artery aneurysm and the common hepatic duct could support a diagnosis of fibromuscular dysplasia. Figure 3 shows some areas which did not exhibit endothelial linings but contained a few erythrocytes in

their lumens and were surrounded by some groups of cells arranged in a concentric manner being parallel to each other, which probably were smooth muscle tissue. These areas were probably related to the defect between the aneurysmal sac and the common hepatic duct. Around these areas, the connective tissue was infiltrated by scattered mononuclear cells and a small focus of fibrinoid necrosis could be seen. Additionally, there were some ductal structures covered by prismatic epithelial cells which probably resembled the mucosal invagination of the biliary tract.

The classic triad of hemobilia is gastrointestinal bleeding, right upper quadrant or epigastric pain and jaundice[9]. The bleeding into the biliary tree secondary to a ruptured aneurysm may be slow, leading to melena and secondary anemia, or rapid, resulting in hematemesis and shock. In our case, it was granted that at her first presentation, the patient was suffering from shock, but at her second and third admittance, the patient exhibited no signs of shock, however, she was suffering from melena. When the hemorrhage flows from the gallbladder through the biliary tract, and if clotting prevents emptying, the distended gallbladder may be palpated[5]. Jaundice is caused by obstruction of the biliary tree resulting from blood clots or from compression by the aneurysm[10].

Generally, physical examination is not helpful in the diagnosis of hepatic artery aneurysm because of the small size of an expansive mass and the fact that bruit or thrill does not commonly accompany such lesions. However, in our case the patient's thrill was located on the upper quadrant of the abdomen. Although we did not palpate the gallbladder on physical examination, at surgery, the gallbladder was edematous and grossly distended with blood.

At present, the most useful diagnostic test is selective arteriography of the celiac axis, the hepatic artery or the superior mesenteric artery. Other methods include barium studies of the upper gastrointestinal tract, intravenous cholangiography, duodenoscopy with retrograde cholangiography, percutaneous splenoportography and scintigraphy of the liver[4,11]. Despite the advisability of preoperative arteriography most hepatic artery aneurysms have been discovered at the time of laparotomy. The aneurysm may be identified by palpation of hepatic vessels for dilation and thrills.

The first successful surgical treatment of a hepatic artery aneurysm which ruptured into the biliary tract was performed by Kehr[12], who treated such a patient by ligation of the hepatic artery in 1903. Since then, additional methods have been employed. Today, the surgical methods that have been used in cases of hemobilia secondary to hepatic artery aneurysm are ligation of the hepatic artery or one of its branches, excision of the aneurysm with or without anastomosis, obliterative or reconstrictive endoaneurysmorrhaphy and hepatic resection which have been used chiefly in cases of intrahepatic aneurysm.

The selection of any one method depends on the findings at the time of surgery. Despite concern about potential hepatic necrosis, hepatic arterial ligation on both sides of the aneurysm may be the safest treatment in certain individuals such as critically ill patients with either massive bleeding from the aneurysm or severe intraabdominal sepsis[13,14]. In our case, the patient was critically ill during the first operation, and we chose ligation of the common hepatic artery. After ligating the common hepatic artery the bleeding stopped instantly and considering the potential necrosis of the liver, we did not want to ligate the hepatic artery distal to the gastroduodenal artery. The feasibility of this approach under such adverse circumstances is supported by recent studies of hepatic artery ligation for liver tumor[15]. Hepatic artery ligation is usually well-tolerated[11] and under certain circumstances may be the safest method in treating hepatic artery aneurysms. Extensive collateral arteries to the liver were documented by the studies of Michels[16], and Redman and Reuter[17]. In our case, despite our ligating the common hepatic and the gastroduodenal artery, the patient was readmitted twice to the hospital because of melena and secondary anemia. We were of the opinion that the aneurysm still had enough flow from collateral vessels. But since in the later period, there were no signs or symptoms of hemobilia, it was considered to have been obliterated.

Aneurysmal rupture into adjacent structures necessitates their repair after managing the aneurysm. Erosion into the common bile duct may be treated by repair of the common duct along with T-tube drainage[18] by Roux-en-Y choledochojejunostomy or by choledochoduodenostomy[19]. We sutured the fistulous opening between the choledoch and aneurysmal sac with continuous 5-0 arterial sutures and performed T-tube drainage.

Digital subtraction angiography demonstrated that our patient's liver had a good backflow from the distal segment of the hepatic artery (Fig. 4). She was totally asymptomatic and her liver function tests including the studies of enzyme and coagulation factors were completely within normal limits.

**Summary**

A 16-year-old girl with hepatic artery aneurysm due to fibromuscular dysplasia which caused hemobilia is presented. This most unusual and life-threatening type of gastrointestinal bleeding was successfully treated by ligation of the common hepatic and gastroduodenal arteries. The clinical aspects and operative procedures of hepatic artery aneurysm are discussed.

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# RENAL LYMPHOMA*
## An Unusual Presentation in a Child

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*Key words: non-Hodgkin's lymphoma, kidney, primary renal, childhood*

Renal involvement is commonly seen in lymphoproliferative diseases, especially in non-Hodgkin's lymphoma. This involvement is usually associated with other findings such as lymphadenopathies, hepatosplenomegalia, bone marrow infiltration, and an abdominal or mediastinal mass. In other words, kidney infiltration in non-Hodgkin's lymphoma is a part of the disease[1-6]. Although lymphomatous renal parenchymal infiltration is frequently found at autopsy, it is rarely the cause of renal failure[7-9]. In this report a child with non-Hodgkin's lymphoma presented at the hospital with bilateral renal involvement as a primary localization.

### Case Report

A four-year-old boy was admitted to Hacettepe University Children's Hospital with a two-month history of abdominal enlargement. Physical examination of the abdomen revealed a fixed, firm mass in the left lumbar region which was thought to be the left kidney. The liver was enlarged one and a half cm below the right costal margin. Other findings of the physical examination were normal.

Laboratory findings revealed a hemoglobin of 14 g/dl, and white blood cell count of 4600/mm$^3$ with a distribution of 68% neutrophils and 32% lymphocytes. An intravenous pyelogram showed bilateral enlargement of the kidneys and elongated renal infundibula (Fig. 1). Abdominal ultrasonography revealed bilateral, enlarged, lobulated kidneys with increased echogenicity and parenchymal thickness (right kidney 11.5 cm; left kidney 12 cm on the longitudinal axis). In addition to diffuse parenchymal infiltration there were several hypoechoic nodules representing nodular involvement (Fig. 2).

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Fig. 1: Intravenous pyelogram showing bilateral enlarged kidneys and infundibular elongation at diagnosis.

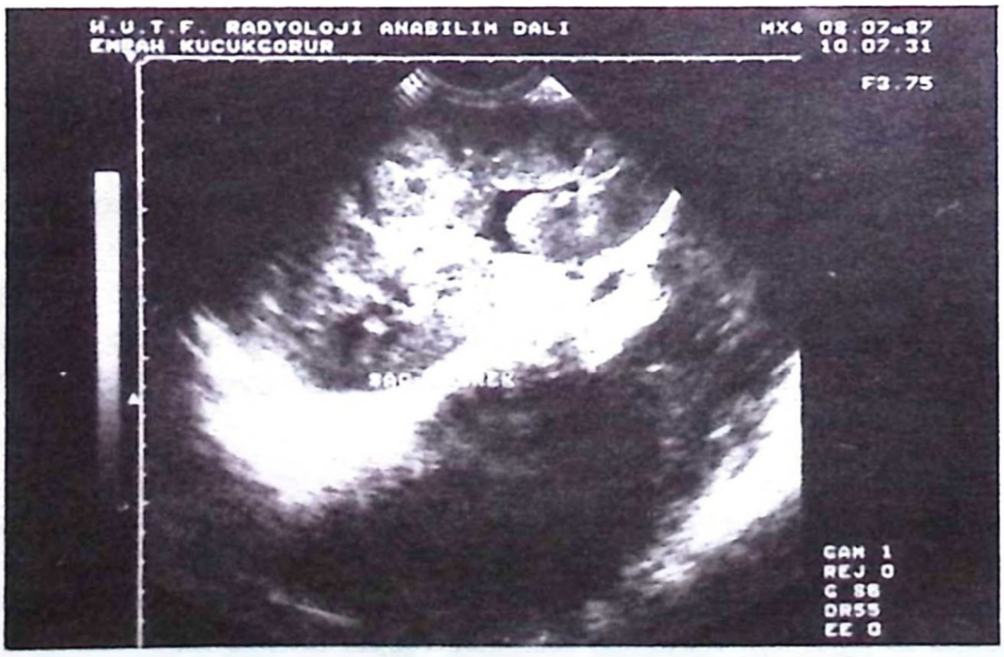


Fig. 2: Ultrasonography showing an enlarged kidney with parenchymal thickening on the right side. There are several hypoechoic nodules and diffuse infiltration.

BUN was 11 mg/dl, serum uric acid 6.9 mg/dl, and creatinine 0.5 mg/dl. Serum calcium, phosphorus, alkaline phosphatase, electrolyte and protein levels were within normal limits. Two-dimensional chest X-rays and the bone marrow smear were normal.

On the basis of clinical and laboratory findings, a malignant, infiltrative process non-Hodgkin's lymphoma was suspected. Due to the rare presentation and bilateral nature of the case, an exploratory laparotomy was performed which revealed a normal liver, spleen, and intraperitoneal and retroperitoneal organs; there was no lymphadenopathy. Both kidneys were enlarged and hard on palpation. A bilateral kidney biopsy was performed. The histological diagnosis was lymphoblastic non-Hodgkin's lymphoma involving both kidneys (Fig. 3).

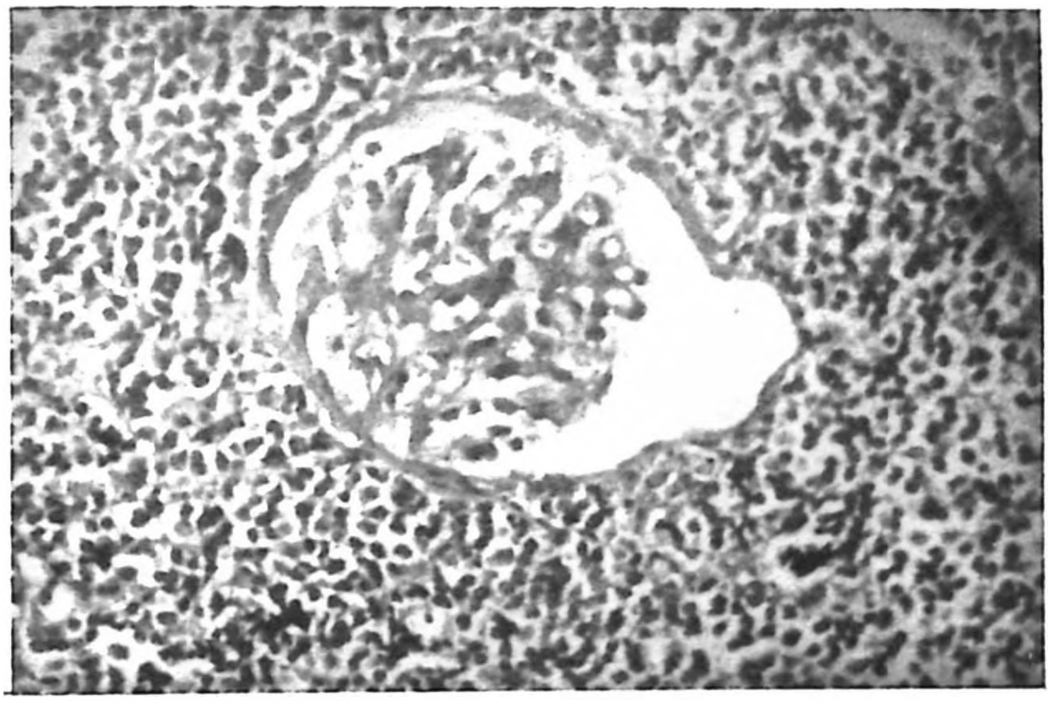

Fig. 3: Diffuse lymphoblastic infiltration in the left kidney (HE × 400).

Treatment with a modified $LSA_2$-$L_2$ chemotherapy regimen[10] was intiated and the patient was in complete remission after the induction phase of therapy. He has been in continuous complete remission for 14 months. His latest abdominal ultrasonography revealed normal size kidneys and also other organs which were normal (Fig. 4). An intravenous pyelography done four months later was interpreted as normal (Fig. 5).

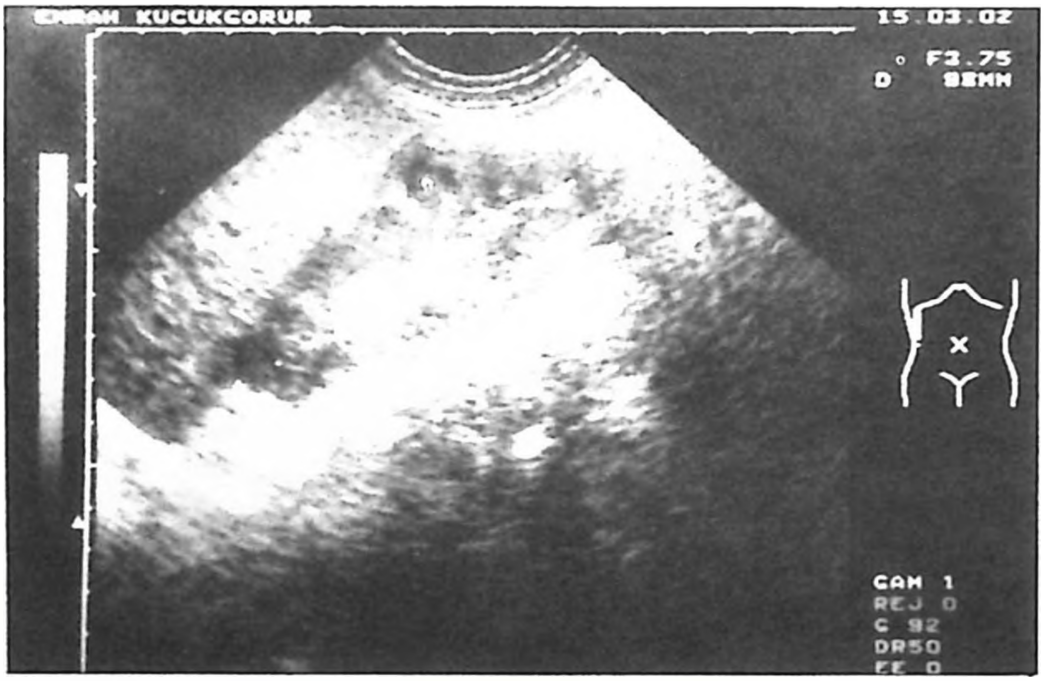


Fig. 4: Ultrasonography showing normal kidney after therapy.

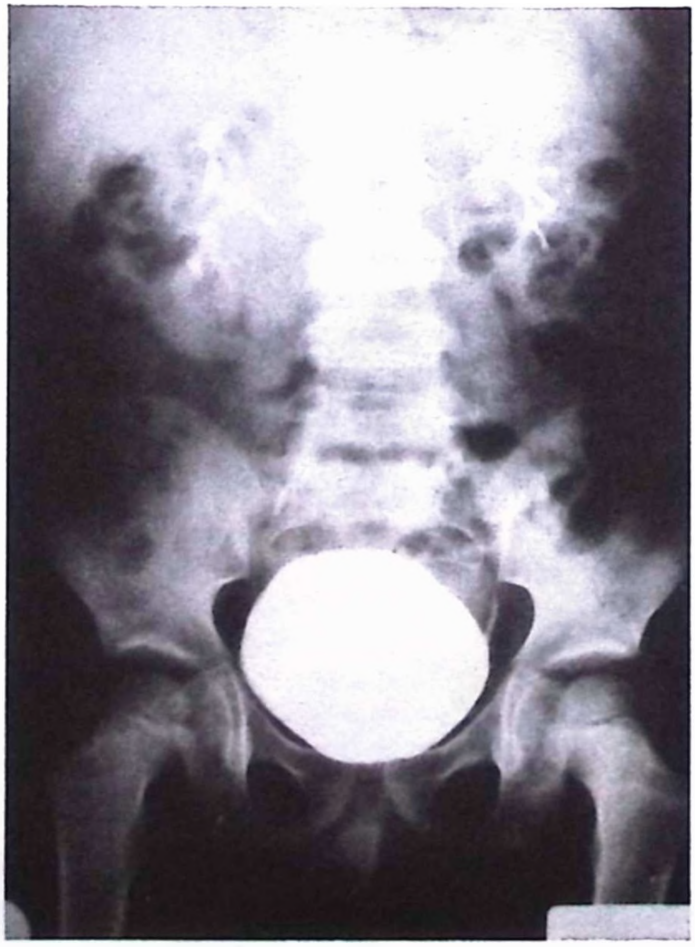

Fig. 5: Normal appearance of the kidneys seen on the intravenous pyelogram after therapy.

## Discussion

Lymphomas rank third after lung and breast cancer in frequency of metastasis to the kidney[2]. Richmond et al[3] have reported that kidneys are infiltrated more frequently than any other organ or tissue. In his autopsy series of 696 patients with lymphoma, the incidence of renal parenchymal involvement was 34 percent. In the same study only 14 percent of 142 patients whose antemortem clinical data was available had renal involvement recognized prior to death. In only 0.5 percent of these 696 patients could the cause of death be attributed to lymphomatous infiltration of the kidneys.

Ehrlich and Kuhn[11] reported 41 percent of renal involvement in 32 non-Hodgkin's lymphoma cases and recommended that abdominal CT be done in all children with non-Hodgkin's lymphoma. They also emphasized that renal involvement was more common than previously reported.

Although secondary renal involvement in non-Hodgkin's lymphomas is not uncommon, primary renal lymphoma is rarely reported in children[1-7]. The clinical manifestations are not overt when the disease is limited to the kidneys in the early period of the illness. Most of the reported cases have shown secondary involvement of the kidney as a part of the disease[3,4,7,8].

Our patient was an unusual case in that he exhibited bilateral renal involvement without any other findings of lymphomatous involvement. Jaffe and Tefft[2] reported a case which was first diagnosed radiologically as bilateral Wilms' tumor but whose tonsillectomy material and biochemistry showed lymphosarcoma and renal failure.

Glicklich et al[7] reported three cases and found 14 similar cases after a review of the literature. Four of them were pediatric patients. Only one had no primary involvement other than kidney. This patient also displayed renal failure. Recently Falconieri and Melato[9] reported a case of a 47-year-old woman with malignant lymphoma that presented as an isolated renal mass.

Occult lymphomas can be encountered clinically by manifestation of renal failure at the inital presentation. Diagnosis must be established by renal biopsy[8]. The combination of sonographic and computer tomographic findings will support the diagnosis of lymphoma which can be proven by renal biopsy. These noninvasive techniques should be considered prior to renal biopsy[11-14].

In spite of the high percentage of renal involvement in non-Hodgkin's lymphoma, urinary findings are uncommon and death attributed only to renal involvement is rare. Randolph et al[8] reported a case with lymphomatous infiltration of the kidneys presenting as uremia of unknown cause. Interstitial lymphomatous infiltration of the kidneys by tumor cells can cause atrophy in nephron units. In uremic patients the other causes of uremia i.e., hypercalcemia, hyperuricemia, ureteral obstruc-

tion, amyloidosis, and immunologically mediated necrosis should be considered and then ruled out[7,8]. Renal functions were normal in our case. Many patients with normal renal function have been reported[8]; this is true especially for early disease, but most of the advanced cases show a disturbance in renal function.

Systemic chemotherapy or limited radiotherapy is effective in controlling renal involvement. Treatment sensitivity of the disease confirms the diagnosis[7,8].

In our case there were no findings of renal failure, and systemic chemotherapy was administered promptly. The patient responded to the treatment and the enlarged kidneys regressed in size within two months. The findings of an exploratory laparotomy and an extensive staging procedure showed no other primary site. Although the renal involvement was bilateral, we believe that our patient was an interesting case of primary renal lymphoma.

**Summary**

An unusual case of non-Hodgkin's lymphoma with primary renal involvement in a four-year-old boy is presented. The diagnosis was established by renal biopsy. The findings of an exploratory laparotomy and an extensive staging procedure showed no other primary site. The patient has been followed up for 14 months and no evidence of recurrence has been observed.

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# MECKEL SYNDROME IN TWINS*

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*Key words: encephalocele, polycystic kidneys*

Meckel syndrome was first described in two siblings by Meckel in 1822[1]. In 1934, Gruber coined the term "dysencephalia splanchnocystica" to describe the malformations associated with this syndrome[1]. In 1969, Opitz and Howe reported the first case in the English literature and suggested the term Meckel syndrome[2]. In 1980, Tunçbilek et al[3] reported five cases of Meckel syndrome in Turkey.

The main defect in this syndrome, which is inherited as an autosomal recessive trait, is not known. The basic characteristics of this syndrome are encephalocele, polycystic kidneys and polydactyly, and in order for a diagnosis of Meckel syndrome to be made, two of the afore-mentioned features are required.

In this paper, we present Meckel syndrome in twins in order to emphasize the importance of genetic counselling, since prenatal diagnosis is possible.

## Case Report

A 33-day-old male infant, who was operated on for encephalocele and had hydrocephalus, was transferred to our clinic. He and his twin sister were born with encephaloceles and were operated on when they were three-days-old. The materials which were extirpated were examined in the Pathology Department of our University Hospital. The twin sister died postoperatively.

The mother, aged 28 years, and father aged 40 years, were second degree relatives. There was also an 11-year-old sister and a nine-year-old brother, who were healthy.

Physical examination revealed a hypoactive, hypothermic infant. Sucking was absent. His weight was 3150 g, length 52.5 cm, head circumference 39.5 cm,

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pulse 96 per min and body temperature 35.6°C. All the cranial sutures were separated and the anterior fontanelle was 4 × 6 cm. The eyes appeared to be deviated downward (setting-sun sign), leukoma was present in the left eye and micrognathia was evident (Fig. 1). The liver was enlarged two cm. Abdominal masses, possibly of the kidney, were palpated. One was 7 × 7 cm and localized in the right lower quadrant, and the other 7 × 5 cm and localized in the left lower quadrant.

Laboratory studies revealed that the hemoglobin level was 9.1 g/dl, white blood cell count 9,100/$mm^2$, with a distribution of 70% neutrophils and 30% lymphocytes. The morphology of the RBCs were normal and platelets were adequate. Urinalysis yielded an acid reaction, density 1004, protein and glucose were not present. The blood chemistry showed blood glucose 73 mg/dl, blood urea nitrogen 19 mg/dl, $Na^+$137 mEq/lt, $K^+$3.8 mEq/lt, and serum calcium 11 mg/dl. Serological tests for cytomegalovirus, toxoplasmosis and rubella were all negative. Amino acids in the blood and urine were normal. Chromosome analysis was also normal.

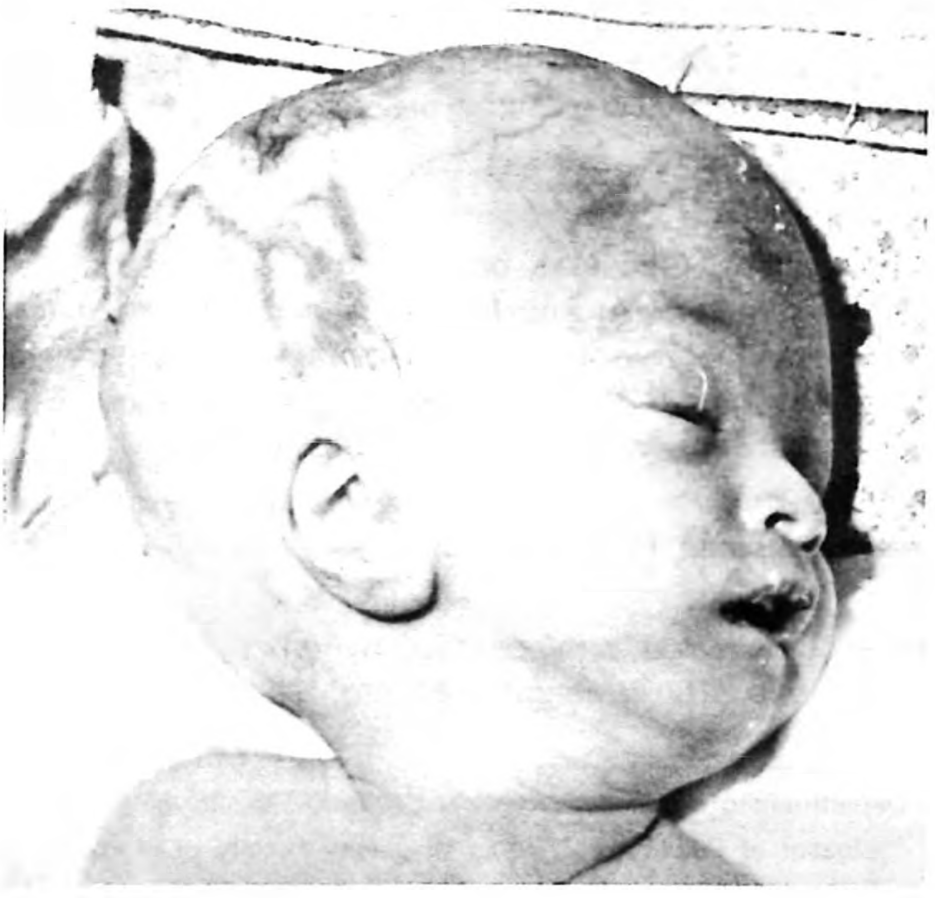

Fig. 1: The appearance of the face, hydrocephalus and micrognathia.

Computerized tomography of the brain revealed thin cortical tissue and abnormal enlargement of the ventricular structures while computerized tomography of the abdomen showed polycystic kidneys (Fig. 2). The encephalocele sac was covered with hairy skin. Microscopically meningeal and brain tissues were reported among the epithelial structures. Postmortem examination revealed polycystic kidneys.

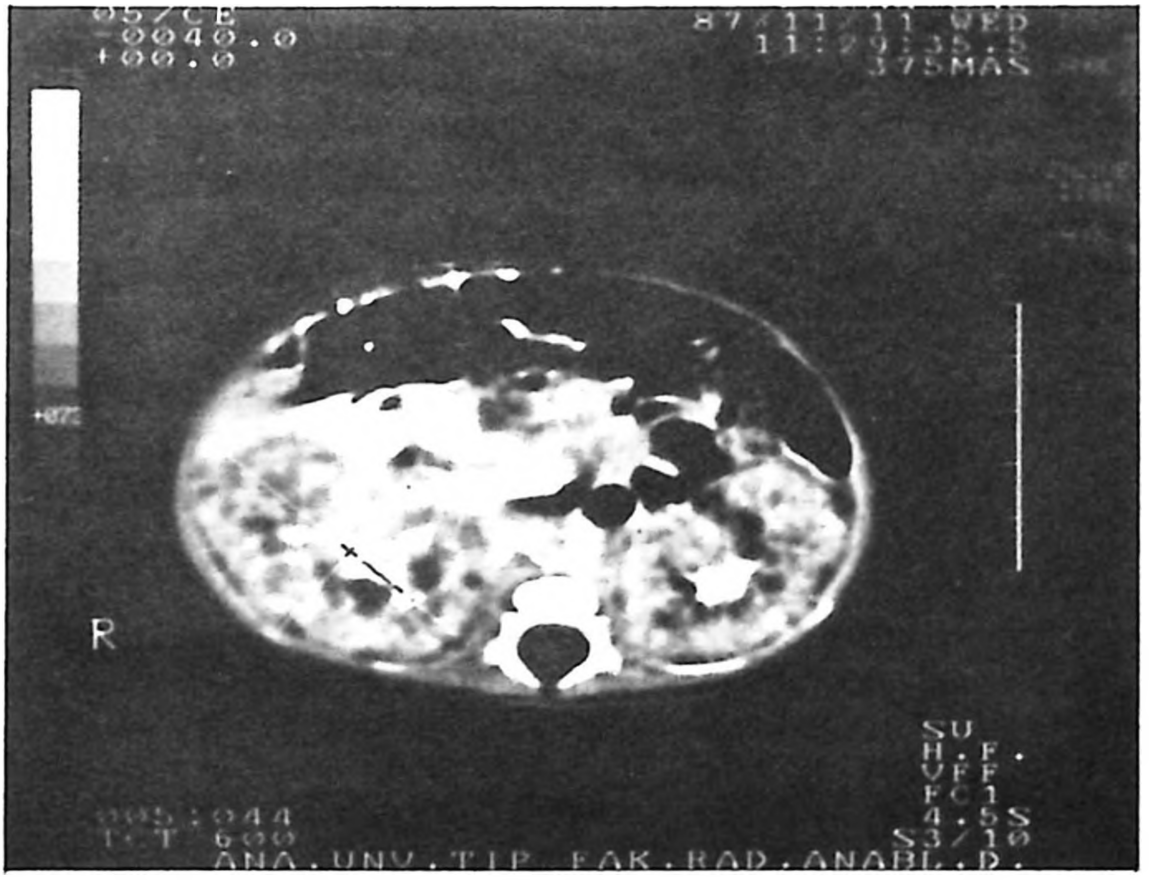


Fig. 2: Abdominal computerized tomogram; polycystic kidneys.

## Discussion

The most striking findings in our case were encephalocele, which was operated on, hydrocephalus and polycystic kidneys presenting as abdominal masses which were confirmed by computerized tomography. In the literature, many cases of polycystic kidneys associated with anomalies of the central nervous system (CNS) have been reported[4]. Our case was diagnosed as Meckel syndrome because two of the three defining characteristics of the syndrome were present.

Although this disorder characteristically involves the CNS, the kidneys, and skeletal system, malformations of the other organ systems have also been reported. The most common anomaly involves the kidneys, however, it is possible to detect microscopic and macroscopic cysts. Associated anomalies are horseshoe kidney, renal hypoplasia and a double-collecting system. Occipital encepholocele and microcephaly are the most common anomalies of the CNS. Hypoplasia of the cerebrum and cerebellum, hydrocephalus, absence of the olfactory lobes and

pituitary gland, defects in the hypothalmic region and anencephaly are minor findings of the CNS[2]. The most common skeletal anomaly seen in this syndrome is polydactyly. Short extremities, syndactyly, simian line and clinodactyly have also been reported[3]. Anomalies which involve the face, genital organs, heart and lungs are rarely reported[2]. Meckel syndrome is inherited as an autosomal recessive trait[5]. A high incidence has been reported in some kindreds. The histories of both the subject and his twin sister (deceased) revealed encephaloceles but an unquestionable diagnosis of this disorder could not be made because of a lack of sufficient data. However, if there is a definite diagnosis made of Meckel syndrome in one sibling, then one major and some minor features of this anomaly are adequate in order to confirm this disorder in the other sibling. Since our case was definitely diagnosed as having Meckel syndrome, his sibling was also accepted as having had this disorder. As far as we know, no instance of twins having this syndrome has been reported.

The probability of Meckel syndrome occurring in a subsequent pregnancy in a family already having a member with this anomaly is 25 percent. As in other neural tube defects, such pregnancies can be terminated following prenatal tests. Determinations of alpha-fetoprotein (AFP) levels in a mother's serum in the early stages of pregnancy and in amniotic fluid cells obtained at 14-16 weeks gestation along with measurements of acetylcholinesterase in amniotic fluid to confirm the presence of a neural tube defect to eliminate false positive elevations of AFP, can be helpful[6]. Genetic counselling should be offered to couples when prenatal diagnosis is possible, as in this case.

**Summary**

Meckel syndrome in twins is presented. Although several families have been reported as having this syndrome in more than one member, this is the first instance that twins having this disorder have been reported. We wish to emphasize the importance of genetic counselling in such a case in which prenatal diagnosis is possible.

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# ACUTE HEMOLYTIC ANEMIA CAUSED BY IRREGULAR RIFAMPICIN THERAPY*

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*Key words: acute hemolytic anemia, irregular rifampicin therapy*

Acute hemolysis as an adverse reaction to rifampicin is a rarely encountered complication[1-6]. The number of cases that have been reported in the literature to date is about fifteen[7]. The adverse reaction has been seen only in patients taking the drug intermittently or irregularly.

Acute hemolysis is sometimes observed in association with acute renal failure. All patients with acute hemolysis and most with acute renal failure have rifampicin-dependent antibodies in their sera[8-19]. In this article, a patient with acute hemolysis due to irregular and high-dose rifampicin administration for pulmonary tuberculosis is presented.

## Case Report

A thirteen-year-old girl was admitted to Cumhuriyet University Hospital in December, 1986 with complaints of fever, chills, nausea, vomiting, bilateral flank pain, diarrhea, pallor, and fainting. Two months prior to admission, the patient was diagnosed in another hospital as having tuberculosis and given rifampicin in a dose of 600 mg/daily and isoniazid in a dose of 400 mg/daily on an irregular basis. The patient discontinued the rifampicin treatment after 50 days. Following a six-day rifampicin-free interval, another doctor was consulted and recommended drug therapy. Twenty minutes after receiving a dose of rifampicin, the patient suffered nausea, vomiting, vertigo, bilateral flank pain and pallor. On the same day, the patient presented with these symptoms at Cumhuriyet University Hospital.

Physical examination revealed a temperature of 38°C, pulse rate of 132 per minute and a blood pressure reading of 90/40 mmHg. Her height was 142 cm and weight 30 kg. Her general condition was poor, and she had pallor. Diffuse rhonchal rales were auscultated. The liver was palpable three cm below the right costal margin and the spleen palpable two cm below the left costal margin. Both costavertebral regions displayed tenderness. Other findings were not contributory.

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Laboratory findings revealed the hemoglobin concentration to be 4.8 g/dl and white blood cell count 13,400/$mm^3$. Blood film showed evidence of hemolysis. Platelets were normal. The erythrocyte sedimentation rate was 45 mm/hour, urine color was dark and hemoglobinuria was observed. Other laboratory data revealed the BUN to be 18 mg/dl, serum creatinine 0.7 mg/dl, serum sodium 138 mEq/lt, chloride 98 mEq/lt, total serum bilirubin 7.2 mg/dl, direct bilirubin 0.4 mg/dl, SGOT 77 U, SGPT 35 U, and the PPD test 20 mm positive. The patient's blood group was A, Rh positive. The Paul-Bunnel test, HBsAg, sickling and direct Coombs tests were all negative. A bone marrow examination showed myeloid hyperplasia. Chest roentgenogram revealed mild bilateral infiltration.

During the tests carried out to determine the presence of anemia due to rifampicin-dependent antibodies in the patient, Cromatest Antiglobulin (Coombs) serum, Gama Biological Inc., anti $C_3$ and Gödecke anti $C_4$ sera and Biotest serum institute panel cells, a stock solution of rifampicin (100 mg in 100 ml saline), the patient's serum, compatible serum from a normal donor, fresh serum from a

TABLE I: Results of Antiglobulin Tests

| | Anti IgG | Anti $C_3$ | Anti $C_4$ |
|---|---|---|---|
| 1. Patient's serum<br>Rifampicin solution<br>Normal red cells<br>Complement | – | +++ | +++ |
| 2. Patient's serum<br>Normal red cells<br>Complement | – | – | – |
| 3. Patient's serum<br>(inactivated)<br>Rifampicin solution<br>Normal red cells | – | – | – |
| 4. Normal serum<br>Rifampicin solution<br>Normal red cells<br>Complement | – | – | – |
| 5. Inhibition test<br>(after incubation)<br>Patient's serum<br>Rifampicin solution<br>Normal red cells<br>Complement | – | – | – |

group AB donor as a source of complement and group 0 human red cells in 5% suspension in saline were used in equal volumes. All the mixtures for the different reactions were incubated at 37°C for two hours and, after washing the red cells, the necessary antiglobin and anticomplement tests were carried out. Cold agglutinin tests performed by cord erythrocytes, and enzyme (Ficin) treated or normal adult erythrocytes were also negative. The same test was repeated after the patient's serum had been inactivated at 56°C for 30 minutes, and found to be negative due to a history of discontinuation of the drug after a short period of time. Acute hemolysis was not noted during the tests. The positive results in the third mixture carried out without adding complement revealed that the complement level had increased. When complement was added to the patient's inactivated serum, the test was found to be (++). In order to determine the inhibitory effect of rifampicin, tests were repeated after equal volumes of the patient's serum and rifampicin solution were incubated for two hours at 37°C and again found to be negative. The results are shown in Table I.

The patient was transfused and her hemoglobin levels increased to 10 g/dl. She was then discharged. The patient was followed for one year after the withdrawal of rifampicin. During this period her general condition was satisfactory and no hemolytical crisis was encountered.

## Discussion

Since its introduction in the early 1960s, rifampicin has been widely used in the treatment of tuberculosis, nasopharyngeal carriage of *Neisseria meningitidis* and *Hemophilus influenzae,* and to a lesser degree, in various antibiotic combinations for bacterial and fungal infections[20].

When rifampicin is used regularly, adverse reactions are minimal and consist of hepatotoxic reactions and gastrointestinal symptoms[21]. These generally appear at the onset of treatment and immunological studies in these cases have shown no abnormality[22]. Adverse reactions occurring in the regimens of intermittent and high-dose rifampicin, flu-like syndrome characterized by fever, vomiting, diarrhea, muscle pain, thrombocytopenia, acute renal failure and hemolytic anemia have been reported[1,22-25]. Rifampicin-dependent antibodies have been found in patients with such reactions. An intermittent and irregular usage of drugs leads to an increase in rifampicin-dependent antibodies in the patient's serum.

Poole et al[22] have found rifampicin-dependent antibodies in 33 percent of 49 patients on bi-weekly and weekly doses of rifampicin. On the other hand, Girling[26] has encountered rifampicin-dependent antibodies in only one percent of 218 patients, and Rees[27] in one of 44 patients when rifampicin was administered three or more times per week.

It has been observed that the presence of rifampicin-dependent antibodies has no consistent correlation with clinically evident toxicity. While some patients on an intermittent regimen have had both symptoms and antibodies, others have not presented with the same picture[1,22,25].

Acute hemolysis due to rifampicin has been observed very rarely, and only in patients on intermittent or discontinuous therapy. In most reports, systemic symptoms developed two to three hours following a single discontinuous dose, and recovery was complete when rifampicin was withdawn[7]. Criel and Verwilghen[14] have reported a case with acute intravascular hemolysis and acute renal failure after a single dose of rifampicin following a six-month rifampicin-free interval. A strong relationship between reactions to rifampicin and the concentration of the drug in the blood has been considered to be possible[22]. This may likely be brought about by either dosage or rate of metabolism of the drug. Complications have been encountered more frequently in those receiving high doses of the drug[22,23].

The mechanism of rifampicin-induced hemolysis was noted to be similar to that described by Shulman and Rall[28] for quinidine. Both are relatively small molecules tightly bound to protein in the plasma, as haptens. These drugs can lead to the production of drug-specific antibodies in a given patient. In the presence of the drug in the serum, these antibodies fix and activate complement on the surfaces of the red cells which are eventually destroyed. The patient's serum fixes the complement to the surfaces of normal red cells only in the presence of this drug[9,27].

Diamond and Tahan[19] and Tahan et al[7] have reported intravascular hemolysis and non-oliguric renal failure after a single dose of rifampicin in a patient on an irregular regimen. They reported that their patients had rifampicin-dependent IgG antibodies with complement-fixing capability and concluded that the presence of rifampicin-dependent antibodies should be suspected in a patient with hemolysis and/or renal failure taking rifampicin.

In the case presented, acute hemolysis developed twenty minutes after the administration of a single dose of rifampicin following a six-day rifampicin-free interval. The presence of rifampicin-dependent antibodies was observed following special tests carried out on the patient's serum. Antibodies in the serum fixed the complement on the surface of normal red cells in the presence of the drug but failed to do so in its absence.

Although rifampicin-dependent acute hemolytic anemia is very rare and complete recovery may occur with its withdrawal, it causes very serious hemolytic anemia, displaying a reduced hemoglobin concentration of up to 4.8 g/dl, as observed in this case. In conclusion, we strongly recommend that this drug be not used irregularly and/or in high doses. Physicians should be advised to warn their patients regarding treatment with this drug.

## Summary

Acute hemolytic anemia characterized by vomiting, diarrhea, vertigo, lumbar pain pallor and high fever due to an irregular and high dose of rifampicin is described in a 13-year-old girl during her treatment for tuberculosis. The presence of rifampicin-dependent antibodies was identified by special tests.

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# DIASTEMATOMYELIA: A REPORT OF TWO CASES*

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*Key words: diastematomyelia, diplomyelia, intramedullary tumor, scoliosis, spinal dysraphism*

Diastematomyelia is a variety of spinal dysraphism in which there is a congenital splitting of a part of the spinal cord or, rarely, of more than one part[1]. The condition is sometimes called diplomyelia because the medial aspect of the gray matter of the two hemicords often displays small ventral and dorsal horns, suggesting duplication. However, there is no double innervation of the lower extremities[1]. It should be stressed that diastematomyelia refers to the split neural tissue and not to the septum[2].

In many cases the two spinal cords are contained within a single dural tube without an intervening septum. However, when each spinal cord has its own dural sheath there always is a septum of bone, cartilage or fibrous tissue that can prevent ascent within the vertebral canal as the vertebral column grows in length or it may be the cause of pressure laterally on one or the other spinal cord[3]. Therefore, in diastematomyelia a low conus medullaris or tethered cord is almost always present[1]. The results of septal pressure are, therefore, more likely to be seen in childhood, although adult cases have been reported rarely in the literature[3,4].

Diastematomyelia is usually accompanied by a number of other malformations including cutaneous changes, skeletal–especially vertebral-anomalies, hydromyelia, meningocele or myelomeningocele, the Klippel-Feil syndrome, hydrocephalus and the Arnold-Chiari malformation[1,5].

When diastematomyelia is associated with neurological deficits, treatment consists of surgical excision of the midline septum to release the tethering effect on the neural tissue. Even though excision is not followed by the anatomical restitution of normal structure, it brings about clinical improvement[5,6].

In this paper, we present two cases of a rather rare congenital anomaly, diastematomyelia, with hope that they will be of interest to pediatricians since they might encounter this type of case in their practice.

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## Case Reports

*Case 1*

A five-year-old girl presenting with right Sprengel's shoulder, mild congenital high thoracic scoliosis and diastematomyelia at the 4$^{th}$ lumbar vertebra (LV4) was referred to the Department of Surgical B Neurology from the Orthopedic Department of Edinburgh University. Neurological examination revealed that the patient's left leg was shorter than the right and the right foot smaller than the left. There was no abnormality of the cranial nerves or upper limbs. Systemic findings, power, tone, sensation, coordination and gait were all normal. Anal sphincter tone was also normal, as was sensation. Direct plain x-rays confirmed a right thoracic scoliosis which extended from LV4 into the sacrum with a possible diastematomyelic spur at LV4. Accordingly, the patient underwent a total myelography which illustrated an ovoid filling defect at the LV4 level with no other abnormality (Fig. 1).

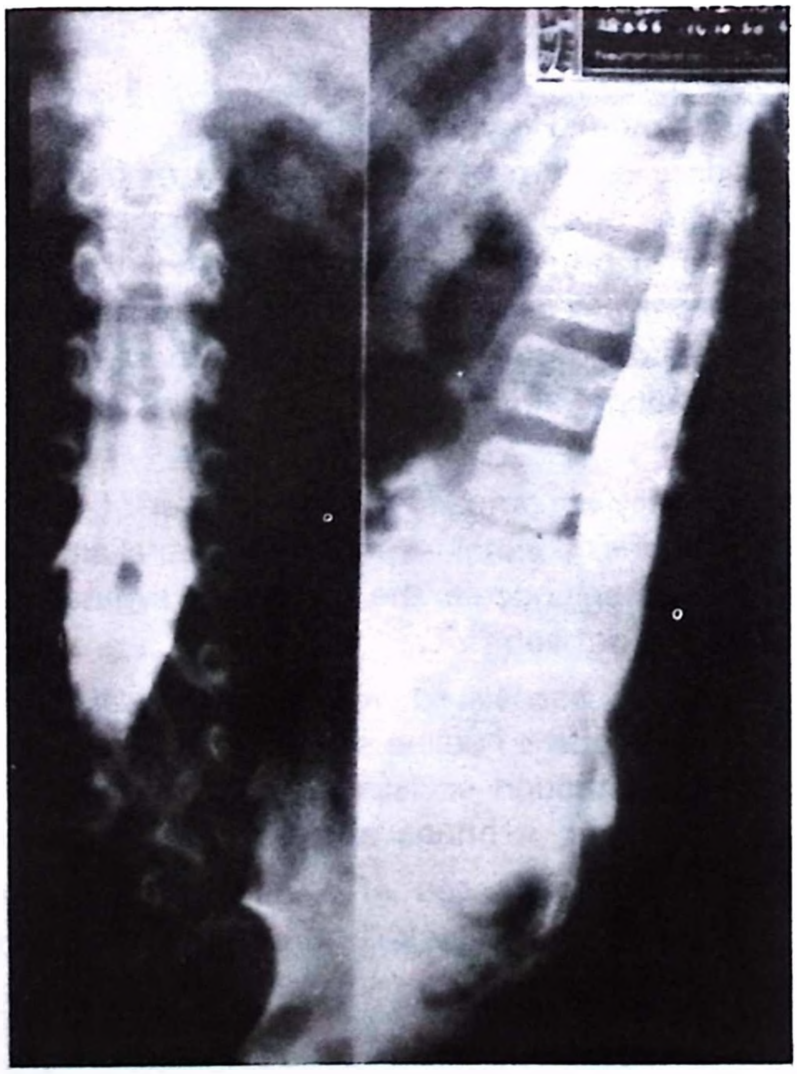

Fig. 1: Lumbar radiculography (Case 1) antero-posterior (AP) lateral views show an ovoid filling defect at the LV4 level.

Laminectomies were performed from LV3 to LV5. At the level of the 4th lumbar vertebra a bony spur was defined and two dural tubes surrounding it were exposed, which immediately divided above and reunited below the spur. After trimming away some of the posterior extremity of the spur, the dura mater was opened at the midline vertically above and below the spur. These midline incisions were then joined together. The bony spur was excised after which the dura mater was sutured posteriorly and anteriorly. The bony spur appeared to be keel-shaped and lightly adherent to the dorsal aspect of the vertebral body having a small rudimentary articular surface. During the operation it was also noticed that similar to the dura, a low cord had split just above the spur, encircled it and reunited immediately below, the left neural tube being the smaller of the two. Roots left the lateral aspect of these two halves of the cord. However, no roots left medially.

Fig. 2: Lumbar radiculography (Case 2). AP view shows an ovoid filling defect at the IV4 level.

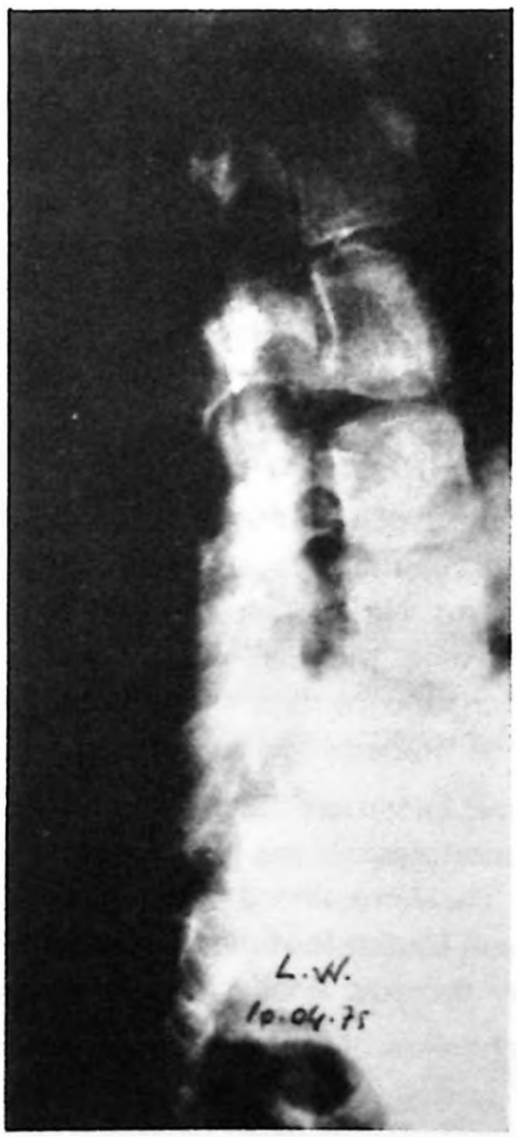


Fig. 3: Lateral view of lumbar radiculography (Case 2).

*Case 2*

A six-year-old girl was referred to the same neurosurgery department by an orthopedist because of congenital skeletal anomalies. Physical examination revealed that she had a limp and an elevated left shoulder (Sprengel's shoulder). Her thoracic spine was scoliotic and there was a hairy patch of skin over the apex of the scoliosis. Bilateral supinator jerks, ankle jerks, and a right knee jerk were all absent. Power, tone, sensation, and coordination in all limbs were normal.

Cervical spine x-rays showed a hypoplastic odontoid process and fusion of CV2-3 vertebrae. Thoracic spine x-rays revealed severe left thoracic scoliosis extending from CV7 to TV12, measured at 72°. Additionally, there were multiple congenital anomalies with a unilateral unsegmented bar on the concavity of the scoliosis extending from TV1 to TV9. Lumbosacral X-rays showed a possible diastematomyelic bony spur at the LV4 level. A total myelography confirmed that there was an ovoid central defect (Figs. 2, 3). The patient was operated on and laminectomies were performed from the LV4 to SV1 levels. As in the first case, the same surgical procedure was applied to excise the bony spur. In this case, however, there was additional pathology regarding the bony spur and low conus medullaris, that is, spina bifida from the LV4 to SV1. An epidermoid tumor was attached to the right halves of the conus medullaris. The bony spur and tumor were carefully removed. The patient's post-operative condition was satisfactory. At a later date, she underwent orthopedic intervention for the sciolosis.

## Discussion

Diastematomyelia is more common in females than in males. Although the average presentation age is 4.3 years, there have been reports of adult cases in the literature. No specific genetic disease was present in our two cases, which coincides with the data in the literature[1,2,4,7-9]. Since diastematomyelia was reported in two female sibships by Kapsalakis[7] in 1964, it is possible that his anomaly is transmitted in an autosomal recessive mode of inheritance.

James and Lassman[3] have reported that the most common presenting features of diastematomyelia are lumbrosacral hypertrichosis, foot deformities and a limp. Our first case presented with right Sprengel's shoulder, high thoracic scoliosis, and leg and foot deformities while our second case presented with left Sprengel's shoulder, thoracic scoliosis and hypertrichosis over the scoliosis.

The mechanism of neural damage whereby the septum and its dural attachments lead to damage within the split cord have been much discussed but poorly understood[2]. James and Lassman[3] found extrinsic bands in eight of eleven cases who were operated on for diastematomyelia. Microscopic examination of the bands revealed aberrant and atrophied nerve roots which were considered to be a

cause of neurological damage because of traction of the spinal cord, conus medullaris, filum terminale or cauda equina[2,3]. In Case 1 no extrinsic pathology was seen during the operation apart from a diastematomyelic bony spur, however, in Case 2, there was also an epidermoid tumor. It is not known how epidermoid tumors or teratomas are related to spinal cord malformations[5,10].

In one series the level of split was frequently seen at LV2 while in other reported series it occurred at LV4. This data is similar to the cases reported by us, although other levels of split have been reported rarely in the literature[2,8,9].

Both of our cases were operated on in order to remove the diastematomyelic bony spur, believed to have a considerable tethering effect on the neural system, thereby preventing the progression of neurological damage. The operation resulted in an entirely free and mobile segment of the low spinal cord, yielding a good result.

## Summary

Two cases of diastematomyelia are presented and the related literature is reviewed. Diastematomyelia, a complete or incomplete sagittal division of the neural axis into two halves, is usually accompanied by a number of other malformations. One of the cases in this paper appeared to have an epidermoid tumor which is rarely associated with this seldom seen congenital anomaly. Diastematomyelia, which becomes symptomatic in childhood, requires early surgical intervention to relieve the tethering effect on the cord by removal of the splitting pathology which is thought to be the main cause of neurological deterioration in the ensuing years.

## Acknowledgement

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# ANNOUNCEMENTS

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**THIRD INTERNATIONAL INTERDISCIPLINARY RESEARCH CONFERENCE ON FUNDAMENTALS OF BONE GROWTH: METHODOLOGY AND APPLICATIONS**

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