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FATAL OUTCOME OF INFANTILE OXALOSIS: CASE REPORTS FROM THREE FAMILIES AND A REVIEW OF LITERATURE*

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SUMMARY: Öner A, Demircin G, Tınaztepe K, Bülbül M, Teziç T. (Pediatric Nephrology Unit, Dr. Sami Ulus Children's Hospital and Nephropathology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Fatal outcome of infantile oxalosis: case reports from three families and a review of literature. Turk J Pediatr 1998; 40: 237-243.

Infantile oxalosis is a rare, autosomal recessive disorder. We present three unrelated cases of infantile oxalosis and their families, emphasizing its place as a cause of acute renal failure in infancy, and showing the clinical heterogeneity of the disease within the same family. The affected infants (two males, one female) were 2.5, 3.5, and five months old. Two families had first degree parental consanguinity; two revealed a history of nephrolithiasis; and one of these two had a member who received liver and kidney transplants because of primary hyperoxaluria type I. All the patients presented with the symptoms and findings of acute renal failure. Their hemoglobin levels were between 6.8-9.6 g/dl, urinalysis revealed (+) to (++++) proteinuria and microscopic hematuria. All had metabolic acidosis with BUN levels 67-113 mg/dl and creatinine 3.5-7.7 mg/dl. The abdominal ultrasonographies revealed normal sized hyperechogenic kidneys with the loss of corticomedullary junctions. Calcium oxalate crystals were demonstrated in retina and bone marrow of two patients, and in renal parenchyma of all the patients. The patients were treated with peritoneal dialysis. Renal functions continued to be abnormal (BUN: 47-168 mg/dl, creatinine: 2.8-11 mg/dl) after dialysis, and the outcome was fatal in all. In the presented families, because of the variation of the clinical presentation and the fatal outcome, presence of the multiple genetic loci appeared to be most likely. Further molecular studies will clerify the heterogeneity of this disorder.
Key words: infantile oxalosis, fatal outcome, renal failure, clinical heterogeneity.

Oxalosis in infancy is a rare condition, most frequently caused by a fulminant form of primary hyperoxaluria type I (PHI) resulting from a deficiency of the enzyme alanine-glyoxylate aminotransferase (AGAT)[1, 2]. There is considerable clinical variety within the disease, paralleled by enzymatic heterogeneity[3]. Although it is inherited most commonly as an autosomal recessive trait, other types of genetic inheritance, including an autosomal dominant pattern, have also been reported[4, 5].

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We present three unrelated cases of infantile oxalosis and their families to emphasize this disease as a potential cause of renal failure during infancy, to show the clinical heterogeneity of the disease within the family of the first case, and to present a review of the literature.

Case Reports

Case 1

A 2.5-month-old boy was admitted to the hospital with the complaint of vomiting since birth. He was the first child of unrelated parents, and his family history revealed some cousins with urolithiasis. One cousin (born from the marriage of his aunt and uncle) had received at the age of five combined renal and hepatic transplants because of PHI (Fig. 1). The patient's weight was 4600 g (below the 10^{th} percentile) and length 54 cm (3^{rd} percentile). He was pale, and retinal crystal deposition was detected on funduscopic examination. The laboratory tests showed: hemoglobin (Hb): 9.6 g/dl, (+) proteinuria, and microscopic hematuria. He was in renal failure with levels of blood urea nitrogen (BUN): 67 mg/dl, creatinine: 3.5 mg/dl, uric acid: 12.3 mg/dl, calcium: 5 mg/dl, phosphorus: 11 mg/dl, alkaline phosphatae (AP): 62 IU, Na: 140 mEq/L, K: 3.4 mEq/L, total protein: 5.4 g/dl, and albumin: 3.9 g/dl. The creatinine clearance was 7 ml/min/1.73 m^2; blood gases showed metabolic acidosis. Bilateral nephrocalcinosis was shown on plain abdominal radiography (Fig. 2). Abdominal ultrasonography revealed normal sized and diffusely hyperechogenic kidneys with a loss of corticomedullary differentiation (Fig. 3). Skeletal survey was normal. Urinary oxalate excretion rate was 60 µmol/day (N. 140-420 µmol/day). Peritoneal dialysis was done, and after the acute symptoms subsided, percutaneous renal needle biopsy was performed which showed calcium oxalate crystals located in the tubules, and tubular epithelial cells extending into the interstitial tissue (Figs. 4, 5). Calcium oxalate crystals were also detected in the examination of bone marrow aspiration. The patient was discharged with supportive therapy and his renal functions continued to deteriorate (BUN: 47 mg/dl, creatinine: 2.8 mg/dl) with metabolic acidosis. He died after 2.5 months of follow-up.

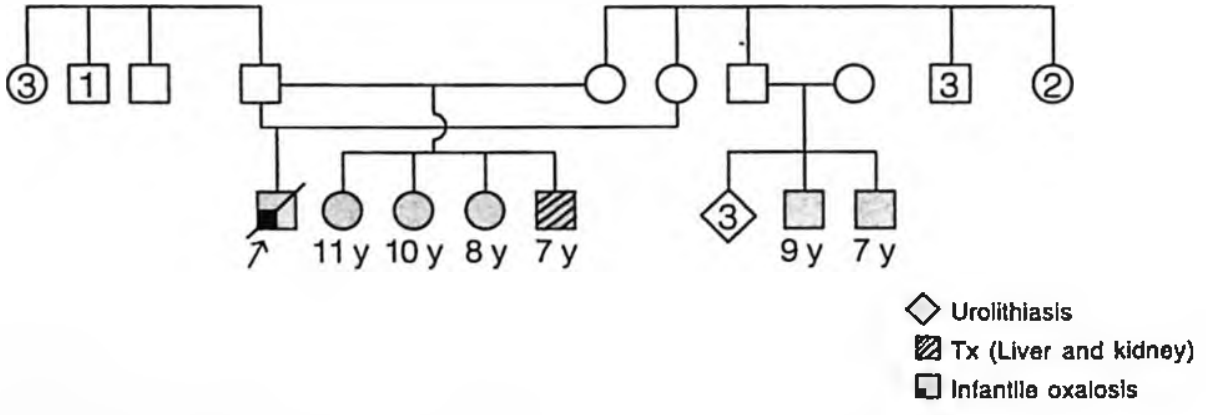

Fig. 1: Pedigree illustrating the family of Case 1 and the variable clinical expression of enzyme activity.

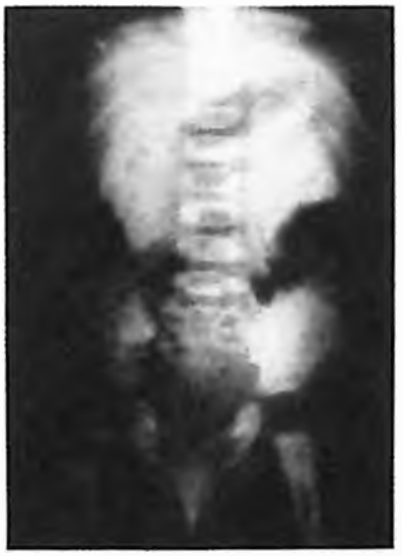

Fig. 2: Plain abdominal roentgenogram of Case 1 showing nephrocalcinosis.

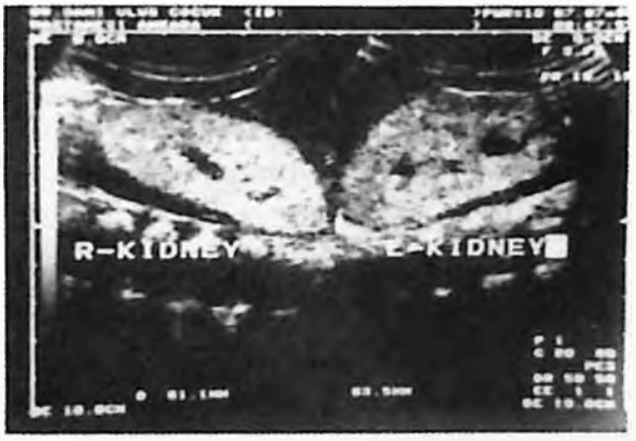

Fig. 3: Abdominal ultrasonography of Case 1 demonstrating normal sized kidneys with diffuse and intensive hyperechogenity and loss of corticomedullary differentiation.

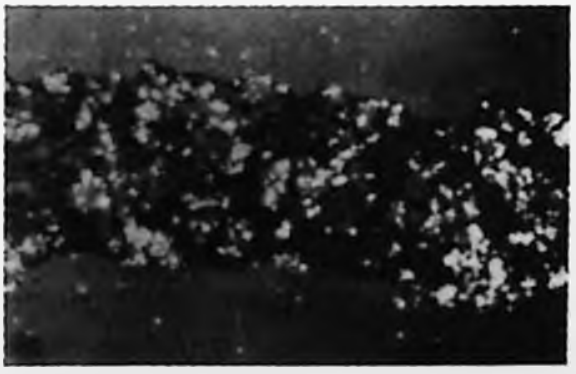

Fig. 4: Renal biopsy of Case 1 under lower magnification with half-polarized light showing masses of calcium oxalate crystals through the renal parenchyma (H+E stain).

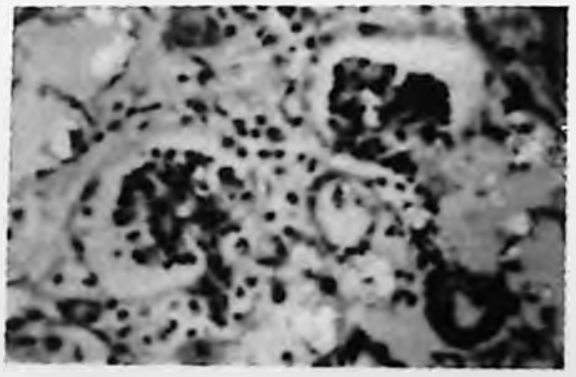

Fig. 5 Renal biopsy of Case 1 under the higher magnification with partially polarized light showing crystals located in the tubules, tubular epithelial cells extending into the interstitial tissue (H+E stain).

Case 2

A 3.5-month-old boy was admitted because of vomiting since birth and convulsions lasting for one week. His parents were first degree relatives and the family history revealed no significant disease. On physical examination he weighed 4800 g (below the 25th percentile) was 60 cm (below the 50th percentile) in length, and presented with hypertension and pretibial and periorbital edema. Funduscopic examination showed retinal crystal deposits. The laboratory examination revealed: Hb: 9.6 g/dl, (+) proteinuria and microscopic hematuria. He had renal failure with BUN: 113 mg/dl, creatinine: 7.7 mg/dl, uric acid: 16 mg/dl, calcium: 6.3 mg/dl, phosphorus: 11.1 mg/dl, A.P: 267 IU, Na: 138 mEq/L, K: 3.8 mEq/L, total protein: 5 g/dl, albumin: 3.7 g/dl. Creatinine clearance was 3.5 ml/min/1.73 m^2 and metabolic acidosis was detected. Urinary oxalate level could not be measured. Plain abdominal radiography showed bilateral nephrocalcinosis and bone roentgenograms were normal. Abdominal ultrasonography demonstrated normal sized kidneys that were diffusely and intensively hyperechogenic with the loss of corticomedullary differentiation. After therapy with peritoneal dialysis, percutaneous renal needle biopsy was performed and calcium oxalate crystals were shown through the renal parenchyma. After being discharged with supportive therapy, the patient was followed up for one month before his death, occurred with levels of BUN: 98.9 mg/dl, creatinine: 11 mg/dl, and metabolic acidosis.

Case 3

A five-month-old girl was admitted to the hospital because of vomiting and irritability since birth. Her parents were first degree relatives. Her 12-year-old sister had an operation for urolithiasis, and her grandmother had a nephrectomy, etiology unknown. Her weight was 5100 g (below 3rd percentile) and length 59 cm (below 10th percentile). On physical examination, she had pallor, a functional murmur, and hepatomegaly of 4 cm below the costal margin. On laboratory investigation Hb was 6.8 g/dl, (++++) proteinuria and microscopic hematuria were present, BUN: 77 mg/dl, creatinine: 6 mg/dl, uric acid: 2.8 mg/dl, Ca: 7.5 mg/dl, phosphorus: 18 mg/dl, A.P.: 113 IU, Na: 128 mEq/L, K: 8.2 mEq/L, total protein: 8.1 g/dl, and albumin: 4 g/dl. She had metabolic acidosis. Creatinine clearance was 5.5 ml/min/1.73 m^2. Urinary oxalate level measured 368 Umol/day (N: 140-420 Umol/day). The plain abdominal ultrasonography were similar to Cases 1 and 2, revealing bilateral nephrocalcinosis. Skeletal survey revealed no pathological finding. Peritoneal dialysis was performed. After dialysis, her BUN level was 168 mg/dl and creatinine 7.06 mg/dl. Calcium oxalate crystals were detected in a bone marrow aspiration. She died within 15 days. Postmortem renal necropsy showed calcium oxalate crystals in renal parenchyma.

Clinical data and laboratory findings of the patients are shown in Table I and II.

Table I: Clinical Data of the Patients

	Case 1	Case 2	Case 3
Age	2.5 months	3.5 months	5 months
Sex	Male	Male	Female
Complaints	Vomiting	Vomiting, convulsion	Vomiting, irritability
Parental Consanguinity	Absent	First degree	First degree
Family History	– Urolithiasis – Combined liver and kidney transplantation	– Urolithiasis —	– Nephrectomy
Physical Examination	– Pallor – Renal crystal deposition	– Hypertension – Edema – Retinal crystal deposition	– Pallor – Hepatomegaly – Functional murmur

Table II: Laboratory Findings of the Patients

	Case 1	Case 2	Case 3
Hemoglobin	9.6 g/dl	9.6 g/dl	6.8 g/dl
Biochemical Tests			
BUN	67 mg/dl	113 mg/dl	77 mg/dl
Creatinine	3.5 mg/dl	7.7 mg/dl	6 mg/dl
Uric acid	12.3 mg/dl	16 mg/dl	2.8 mg/dl
Calcium	5 mg/dl	6.3 mg/dl	7.5 mg/dl
Phosphorus	11 mg/dl	11.1 mg/dl	18 mg/dl
Blood gases	Metabolic acidosis	Metabolic acidosis	Metabolic acidosis
Creatinine Clearance (ml/min/1.73 m²)	7	3.5	5.5
Urinary Examination			
Protein	+	+	++++
Microscopy	Hematuria	Hematuria	Hematuria

Discussion

Infantile oxalosis is a very rare disorder[6]. In 1984 Zegher et al.[5] reported two infants with oxalosis, presented a literature review citing 20 other patients reported since 1951, and demonstrated clinical picture, diagnosis and treatment of all the cases. At that time, to our knowledge, only two other cases were reported in English literature[7,8].

Although other types of genetic inheritance have been reported, the disease is generally inherited in autosomal recessive pattern, and according to the enzymatic heterogeneity, different clinical presentations can occur[3,4]. One-third of the patients in the literature showed parental consanguinity[5]. Two of our patients were also born to consanguineous parents, and Case 3 had a family history

of urolithiasis and nephrectomy of unknown etiology, suggesting the probable presentation of primary hyperoxaluria with urolithiasis. Case 1 had the most striking family history. As shown in Fig. 1, the children born from the marriage of Case 1's aunt and uncle were also affected by the disease. Three of them had only urolithiasis, while the fourth one had liver and kidney transplants because of oxalosis at age five. Moreover, two other cousins also had a history of urolithiasis. The occurrence of variable degrees of severity of the clinical disease in the several affected members of this child's family may reflect the clinical variability of the disease due to heterogeneic enzyme activity[3]. Although the two families were unrelated, they were from the same region; autosomal recessive inheritance is the most probable pattern in this family. However, an autosomal dominant inheritance with different expressions in different generations cannot be excluded. Although the disease is inherited with the same gene in these families, the occurrence of such different clinical presentations, varying from the benign form of urolithiasis to the most severe infantile form, needs to be clarified by genetic and enzymologic studies.

In the literature, most of the patients with infantile oxalosis presented within the first six months of life with the complaints of anorexia, vomiting, convulsion, and signs and symptoms of renal failure. Abdominal roentgenograms of the patients usually revealed normal sized kidneys with homogenously increased radiopacity, while ultrasonographical analysis of kidneys showed diffuse and excessively enhanced echoes which are the characteristic findings of nephrocalcinosis. The diagnosis of oxalosis was based on the histological demonstration of calcium oxalate crystals in the kidneys of all cases. The diagnosis of PHI was confirmed in seven of 24 patients with infantile oxalosis in the literature, showing the increased excretion of oxalate, glycolate and glyoxylate in urine samples, and the others were concluded to have this disease after other causes of oxalosis were excluded (2-5, 7-9). In some cases calcium oxalate crystals could be demonstrated in the tissues (bone, bone marrow, heart, thymus, brain, eyes and vascular walls)[8, 10-12]. Our patients presented primarily with the complaint of vomiting, and in renal failure with metabolic acidosis in early infancy, like the patients in the literature. The diagnosis of PHI was made on the basis of the clinical picture, characteristic findings of nephrocalcinosis in radiological examinations, and the histological appearance of the kidney biopsy specimens. Urinary oxalate levels were measured as low in Case 1 and normal in Case 3, the latter probably because of renal failure[1]. Unfortunately, confirmatory laboratory tests to show increased urinary excretion of glycolate and glyoxylate could not be performed in any of these children.

The main objective of treatment of PHI is good hydration and dietary restriction of oxalate-rich foods[1]. In cases with residual enzyme activity, pyridoxine was shown to reduce the production and excretion of oxalate[6]. Chronic dialysis and eventual renal transplantation, usually combined with hepatic transplantation,

are the other therapeutic procedures in the patients that progressed to end-stage renal failure[13, 14]. However, in infantile oxalosis, rapid progression toward terminal renal failure appears to be the rule, and dialysis and renal transplantation are generally not recommended[5, 6]. Most of the patients in the literature died within three months after onset of symptoms[5]. Our patients also died within 2.5 months after first presentation, confirming the poor prognosis of the disease.

We presented these three infants with oxalosis to stress not omitting this rare disorder in the differential diagnosis of renal failure in infancy, especially in countries like Turkey where parental consanguinity is high[15]. We also presented a current review of the literature, to demonstrate the characteristic findings of the disease once more. We also wanted to demonstrate the probable presentation of different clinical expressions of the disease even in the same family, despite inheritance of the same gene.

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