Systemic Oxalosis in Infants:
Two Cases and Literature Review

İnfantlarda Sistemik Oksalozis:
İki Olgu ve Literatürün Gözden Geçirilmesi

ABSTRACT

The infantile form of primary hyperoxaluria is a very rare disease and often presents as a life-threatening condition because of rapid progression to end-stage renal disease and systemic oxalosis. We described two infants with primary hyperoxaluria type 1 (PH1). Persistent severe hyponatremia and hypoalbuminemia were noted in both patients and cerebral and pulmonary involvements of systemic oxalosis were suspected in one patient. Such a severe phenotype of infantile PH1 is an important finding that should be added to the list of manifestations of PH1.

KEY WORDS: Systemic oxalosis, Infant, Persistent hyponatremia and hypoalbuminemia, Pulmonary involvement

ÖZ

Primer hiperoksalürinin infantil formu çok nadir bir hastalık olmakla birlikte hızla son dönem böbrek yetmezliğine ilerlemesi ve sistemik oksalozis nedeniyle sıklıkla hayatı tehdit eden bir durumdur. Biz primer hiperoksalüri tip I (PH1) tanılı iki olgu sunduk. Her iki olgunun dirençli hiponatremi ve hipoalbuminemisi, bir olgunun ise sistemik oksalozisin çok nadir tutulumları olan serebral ve pulmoner tutulumları görüldü. İnfantil PH1 in bu şiddetli tutulumları PH1 in bulgular listesine eklenmelidir.

ANAHTAR SÖZCÜKLER: Sistemik oksalozis, İnfant, Dirençli hiponatremi, Dirençli hipoalbuminemi, Pulmoner tutulum

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INTRODUCTION

The primary hyperoxalurias (PH) are inborn errors of metabolism, which result in a marked increase in the synthesis of oxalate by the liver. Two distinct autosomal recessive inherited enzyme defects of glyoxylate metabolism have been related to type 1 and type 2 PH, i.e., alanine: glyoxylate aminotransferase (AGXT) and glyoxylatereductase/hydroxypyruvate reductase, respectively: in addition non-PH1 non-PH2 patients have been reported (1-3).

Primary hyperoxaluria type 1 the most common form of PH characterized by overproduction and accumulation of oxalate in the body (2). About 100 gene mutations have been identified and both sexes are equally affected (4,5). The main target organ is the kidney, as oxalate cannot be metabolized and is excreted in the urine, leading to nephrocalcinosis, recurrent urolithiasis, and subsequent renal impairment. The infantile form often presents as a life-threatening condition because of rapid progression to end-stage renal disease (ESRD), due to both early oxalate load and immature GFR: one-half of affected infants experience ESRD at the time of diagnosis and 80% develop ESRD by the age of 3 years (5-8). Calcium oxalate is deposited in all organs (kidneys, bone, joints and soft tissues, myocardium, vessels, and eyes) - a condition called "systemic oxalosis" (1-6).

In this case report, we present two infants with primary hyperoxaluria type 1 (PH1). Persistent severe hyponatremia and hypoalbuminemia were noted in both

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patients and cerebral and pulmonary involvements of systemic oxalosis were suspected in one patient.

CASE REPORTS

Case 1

A 4-month-old male was admitted to our hospital with vomiting, diarrhea, rapid breathing, restlessness and seizure. The baby was the first child of healthy non-consanguineous parents. We learned that he had suffered diarrhea, vomiting and restlessness for the past week, and one day prior to admission, oliguria and convulsion developed in the patient.

On admission, his body weight and length were between the 50th and 75th percentile for age. Physical examination revealed restlessness, agitation, cutis marmoratus and dyspnoea. Arterial blood pressure was 105/70 mmHg (>95th percentile for age), and his pulse rate was 165 beats/min.

At his initial examination, laboratory tests revealed haemoglobin 5.9 g/dl, blood urea nitrogen 98 mg/dl, creatinine 14.4 mg/dl, bicarbonate 10 mmol/L, sodium 122 mmol/L, potassium 4.9 mmol/L, chloride 87 mmol/L, total protein 5.2 g/dl, albumin 3.2 g/dl, phosphate 11.2 mg/dl and uric acid 11.5 mg/dl. Urinanalysis revealed 1+ protein on the dipstick and mild microscopic haematuria. Renal ultrasonograpy (US) showed homogeneously hyperechoic normal-sized kidneys, with no cortico-medullary differentiation, at the same time intense radio-opacity of the kidneys on radiographs indicated massive nephrocalcinosis (Figure 1). The patient was started on intravenous fluids with sodium bicarbonate and peritoneal dialysis. An ultrasound guided renal biopsy, was carried out seven days after admission. Striking features were seen in the tubules, many of which were filled wi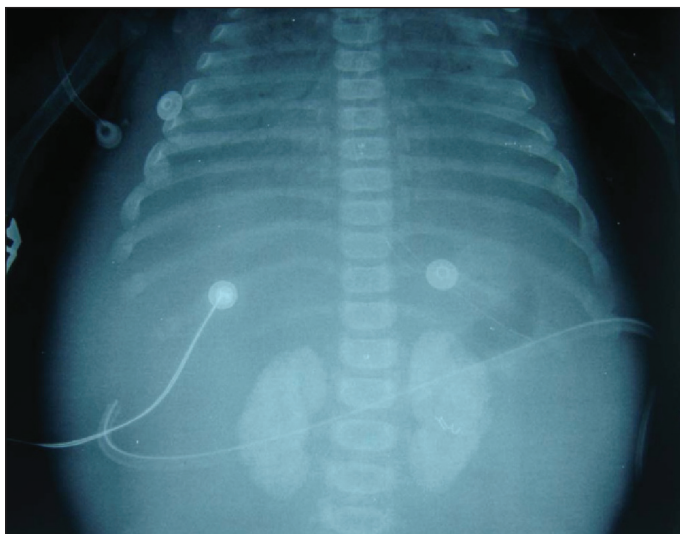th crystalline deposits, obstructing the lumina completely (Figure 2). After the renal biopsy a severe renal hemorrhage developed because of arteriovenous fistula then treated which was by stent application. Echocardiography showed hyperechogenity in myocardium and decreased left ventricle functions and hypertrophy of left vetricle. An eye examination revealed bilateral submacular yellowish deposits, compatible with oxalosis maculopathy. Transfontanel US showed the brain's hyperecogenic white matter, basal ganglia and globus pallidus. Plasma oxalate concentration was 45 µmol/L (normal <33 µmol/L) (5). An assessment of the AGXT gene showed mutations of A295T amino acids.

Our clinical conclusion was ESRD from hyperoxaluria. He was treated with sodium chloride for persistent hyponatremia and sodium bicarbonate supplements administered intravenously for acidosis. Peritoneal dialysis was carried out but failed. Persistent hyponatremia (119 mmol/L) and hypoalbuminemia (0.9 g/dl), anuria, intermittent convulsions and edema continued in the patient throughout his short life. Antihypertensive and anticonvulsant drugs, intermittent diuretics and albumin infusions were also administered. Episodes of peritonitis, pneumonia, sepsis and gradually increased respiratory distress developed during patient follow-up care. A chest X-ray revealed poor ventilation of both lungs, which may be a sign of pulmonary involvement of systemic oxalosis (Figure1). He died from respiratory distress due to sepsis and systemic oxalosis 6 months after admission. Autopsy was not performed in this patient.

Case 2

A 2-month-old boy presented with seizures after one-day history of oliguria and poor feeding. His parents, who were first cousins, were both in good health. There were no other siblings or significant family history. His physical examination was
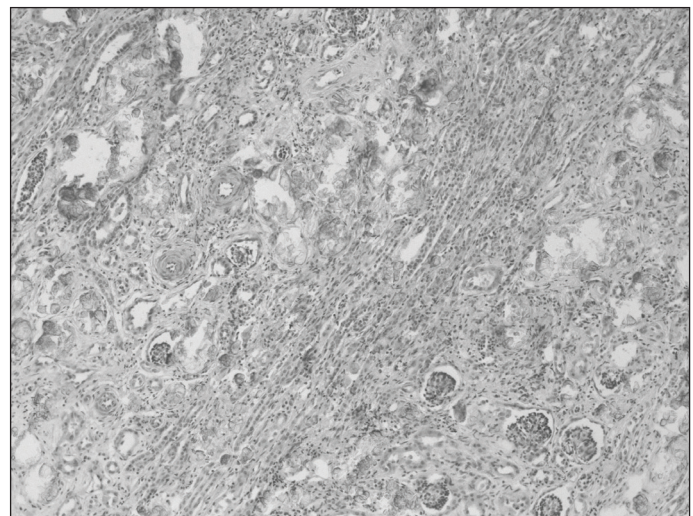

Figure 1: Intense radio-opacity of the kidneys on radiographs indicated massive nephrocalcinosis and chest X-ray revealed inadequate aeration of bilateral lungs indicated systemic oxalosis.

Figure 2: Intratubular obstruction with oxalate cyristals in renal biopsy.

Table I: Characteristics of patients with primary hyperoxaluria type 1.

Patients	Case1 (male)	Case 2 (male)
Age of diagnosis	4 months	2 months
Hb (g/dl)	5.9	5.3
Na (mmol/L)	122	104
K (mmol/L)	4.9	6
Cl (mmol/L)	87	78
BUN (mg/dl)	98	85
Cr (mg/dl)	14.2	8.5
Albumin(g/dl)	0.9	1.2
Plasma oxalate mmol/L	45 (normal <33)	21 (normal<33)
Urine oxalate mmol/1,73 m^2/24 h	0.7 (normal <0,5)	0.7 (normal<0,5)
Nephrocalcinosis	Yes	Yes
Genetic analysis	Mutations of A295T aminoacid on AGXT gene	
Treatment	Peritoneal dialysis, pyridoxine and supportive treatments	Peritoneal dialysis, pyridoxine and supportive treatments
Follow up	Died on 6 months after admission	Waiting matching donor for liver-kidney transplantation.

unremarkable except for restlessness and cutis marmoratus. His arterial blood pressure was 115/70 mmHg (>95th percentile for age), and his pulse rate was 156 beats/min.

Initial biochemical investigations showed the patient had renal impairment with blood urea nitrogen 85 mg/dl, creatinine 8.2 mg/dl, potassium 6 mmol/L and uric acid 13.5 mg/dl. There was no urine output in the patient at admission. His blood gases showed severe metabolic acidosis. Other laboratory features revealed hemoglobin 5.3 g/dl, sodium 104 mmol/L, chloride 78 mmol/L, total protein 4.3 g/dl, albumin 2.9 g/dl and phosphate 4.9 mg/dl. The patient was submitted to peritoneal dialysis after initial acute resuscitative measures. Renal US showed markedly increased echogenicity in normal-sized kidneys, with no cortico-medullary differentiation. An ultrasound guided renal biopsy was performed five days after admission. Renal biopsy showed extensive amounts of pale, irregularly shaped crystalloids in the interstitium and in the lumen of the tubules. After renal biopsy, severe renal haemorrhage occurred. Indirect fundoscopy showed widespread fleck-like deposits in both retinas, compatible with oxalate-induced retinopathy. Plasma oxalate concentration was 41 μmol/L (normal <33 μmol/L). 24-hr urine oxalate excretion was 5 mmol/1.73 m^2/24 hours (normal <0.5 mmol/1.73 m^2/24 hours) (5). Assessment of AGXT gene showed mutations of A295T aminoacids.

Our clinical conclusion was ESRD from hyperoxaluria. He was treated with sodium chloride for persistent hyponatremia and sodium bicarbonate supplements administered intravenously for acidosis. Antihypertensive drugs and 100 mg dose of oral pyridoxine daily. Intermittent diuretics and albumin were administered intravenously for persistent hypoalbuminemia. Peritoneal dialysis was carried out. Persistent hyponatremia (120 mmol/L) and hypoalbuminemia (1.2 g/dl), oliguria, and episodes of peritonitis developed in the patient during follow-up. The patient is still under our care as an out-patient. The patient is followed-up with peritoneal dialysis while waiting for a matching donor for liver-kidney transplantation. Characteristics of the two patients with PH 1 are listed in Table I.

DISCUSSION

The severe infantile form of PH1 is very rare (2,3,9). It is characterized by chronic renal insufficiency with massive parenchymal oxalosis; these patients did not develop renal calculi. Older children, on the other hand, present with symptoms of urolithiasis or, in some cases, complete obstruction with acute renal failure (9). Both patients were admitted exhibiting clinical picture of acute renal failure including elevated blood urea nitrogen and creatinine levels, hyperphosphatemia, hyperuricemia, hyponatremia, metabolic acidosis and hypertension, and they had severe anemia. On admission both
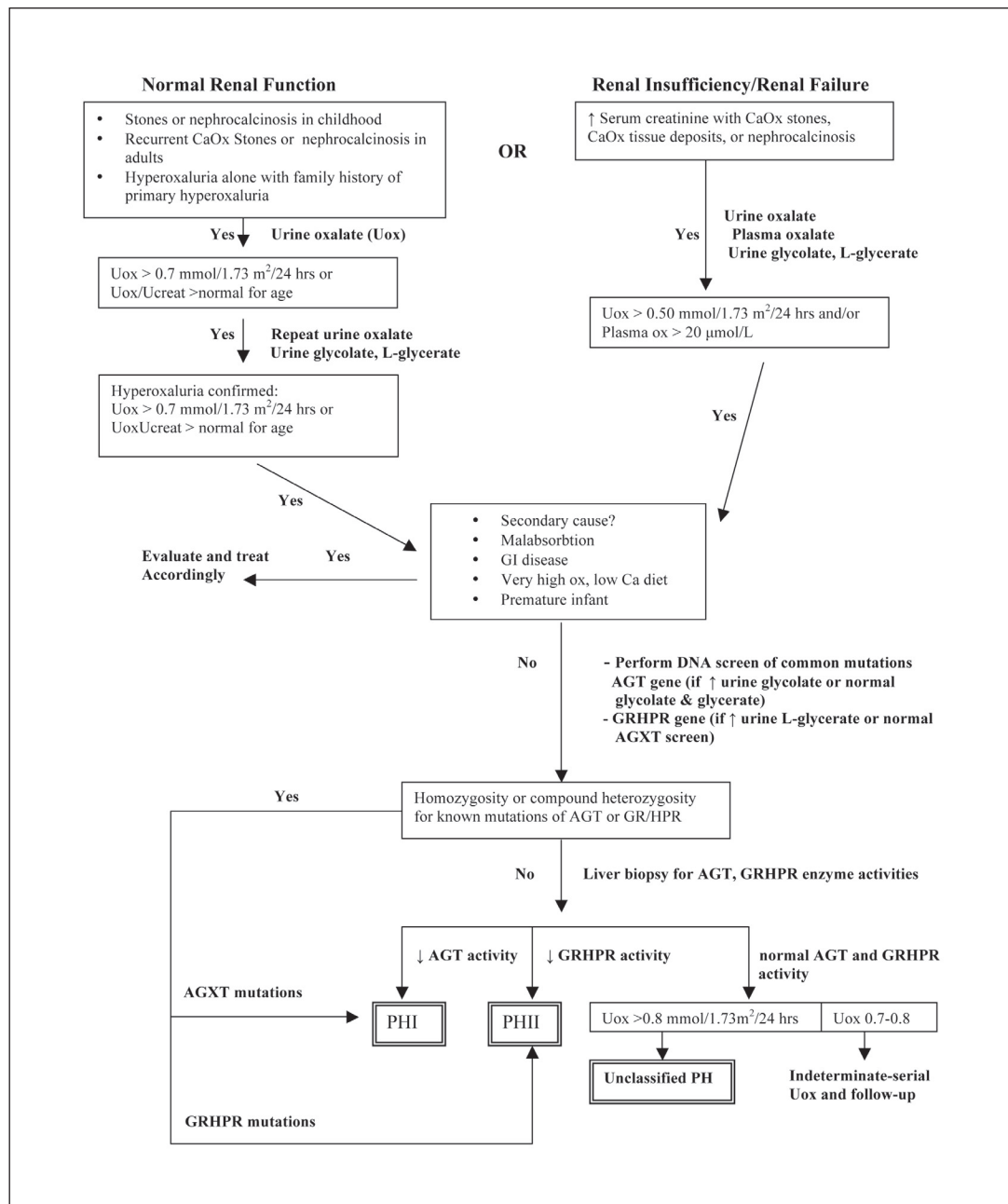
Figure 3: Algorithm for diagnosis of primary hyperoxaluria (Milliner DS. Am J Nephrol. 2005).

patients had a convulsion. We suggested that the convulsion resulted from hyponatremia in our patients. Tantbirojn et al.(10) reported an infant similar to our patients' clinical and laboratory features including hyponatremia. Presence of both persistent hyponatremia and hypoalbuminemia in both cases who had anuria was interesting.

Cause of hyponatremia may be due to sub-optimal free water clearance in the anuric cases with ESRD. In addition, persistent hypoalbuminemia developed in both cases during follow-up. The reasons for hypoalbuminemia may be related to inadequate

protein intake, infection and sepsis, peritoneal dialysis, or catabolism of uremia.

Kidneys, always involved with calcium oxalate crystal deposition, can present two sonographic patterns: either cortical or medullary nephrocalcinosis. The parenchyma is markedly hyperechoic, and there is acoustic shadowing and a lack of cortico-medullary differentiation (6). As is known, echogenic kidney in infants should be taken as a clue for early diagnosis (3,11). Renal US of our patients showed homogeneously hyperechoic normal-sized kidneys, with no cortico-medullary

differentiation, at the same time intense radio-opacity of the kidneys on radiographs indicated massive nephrocalcinosis (Figure 1).

Oxalosis should be considered in the differential diagnosis of intrinsic renal failure in infants especially when on clinical evaluation there are no signs or symptoms other than those, which can be explained by renal failure. An US must be performed in every child with renal failure (6). Documentation of cortical/global nephrocalcinosis in an infant warrants further careful evaluation. Thus ARF, when associated with cortical nephrocalcinosis, is a strong pointer for oxalosis especially when there is an insignificant past history.

With declining renal function, high oxalate blood levels result in the deposition of oxalate crystals in other tissues, such as bone, bone marrow, joints, soft tissues, myocardium, vessels and the retina. This massive deposition of oxalate is known as systemic oxalosis (1, 11, 12). Up to 10% of patients who are diagnosed with infantile oxalosis often die from renal failure during the first months of life (1). Both of our patients had involvement of the kidneys and eyes, evidence of systemic oxalosis. In addition, case 1 had myocardial, brain and pulmonary involvements, which occur only very rarely. Pulmonary involvement of PH has been identified in adult patients, but has not been identified in infants (13). Since autopsy was not performed on the patient, we were unable to obtain evidence of pulmonary involvement of oxalosis. Also, pulmonary edema due to overhydration or infection could be reason to the pulmonary findings of our patient, but he had gradually increased respiratory distress and while he did not have sepsis or hypervolemia, he suffered respiratory distress. Thus, we think respiratory distress have occurred, because of pulmonary involvement due to systemic oxalosis rather than pulmonary infection or congestion.

Primary hyperoxaluria type 1 can be diagnosed by measuring urine oxalate and glycocolate excretion and plasma oxalate measurement. More than 100 mutations have been identified. Some mutations are more frequent and play a clinical and biochemical phenotype role (2). Our patients had high levels of urine and plasma oxalate. Variation of A295T aminoacid on the AGXT gene was identified in case1 and case 2. This genetic variation isn't single nucleotide polymorphism. The same genetic variations in both unrelated cases are a unique and interesting result. Similar clinical and biochemical features in our patients can be explained by their experiencing the same genetic variations. Soylu et al (14) described two brothers with primary hyperoxaluria type 1. For this reason, siblings of patients with primary hyperoxaluria should be screened for hyperoxaluria.

There was bilateral nephrocalcinosis in the renal US of our patients who were admitted with picture of renal failure. We did not suspect primary hyperoxaluria. We performed renal biopsy in order to illuminate the etiology of renal failure, after the general condition of the patients improved by peritoneal dialysis. We suspected the diagnosis of hyperoxaluria when renal biopsy showed intratubular obstruction with crystalloids. After renal biopsy, severe renal hemorrhage occurred. We diagnosed primary hyperoxaluria cause of plasma and urine oxalate concentration was to high, macular changes suggestive of PH1 and mutation of the AGXT gene. Assesment of urine and plasma oxalate levels and fundoscopy in infants with nephrocalcinosis may be diagnostic for PH1. Renal biopsy may be unnecessary in this context and resulted in complications. Because renal biopsy could be very dangerous for infants on peritoneal dialysis and even unhelpful for diagnosis, it should be contraindicated.

Treatment of PH is aimed at reducing oxalate biosynthesis and calcium oxalate supersaturation, and preventing systemic oxalosis. Oxalosis is not preventable with current dialysis techniques. In the last few years, combined liver-kidney transplantation has become the elected procedure in the majority of patients and appears to give excellent results. However, the results are poor when transplantation is delayed and advanced systemic oxalosis has developed (15,16).

The diagnosis is delayed in some patients with PH. Milliner published an algorithm for diagnosis of PH (17). The algorithm shown in Figure 3.

Moreover, the management of infants presenting with severe oxalosis is still controversial, as a high mortality rate has been reported (18). Kavukçu et al. (19) described three cases with primary hyperoxaluria. These cases have been showed favorable clinical outcomes after combine liver-kidney transplantation. Early combined liver-kidney transplantation should therefore be strongly recommended to save life of infants with PH1.

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