

CKJ REVIEW

Primary hyperoxaluria: the pediatric nephrologist's point of view

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ABSTRACT

The clinical presentation of primary hyperoxaluria in children ranges from mildly symptomatic nephrocalcinosis to very early onset end-stage kidney failure with systemic oxalosis, a devastating complication. We review the various manifestations of pediatric hyperoxaluria, treatment options for children with preserved kidney function and appropriate dialysis regimens. Liver or combined liver/kidney transplantation is currently the only definitive treatment for primary hyperoxaluria type 1, but novel RNA interference treatments offer hope for the future. Finally, we address the medical and ethical dilemmas facing pediatricians treating children with hyperoxaluria.

Keywords: dialysis, hyperoxaluria, kidney transplantation, liver transplantation, pediatrics, systemic oxalosis

INTRODUCTION

Primary hyperoxaluria (PH) is a rare condition, caused by three known autosomal recessive diseases termed PH1, 2 and 3. PH1 is the most common, accounting for approximately 80% of PH patients, and virtually all patients with infantile oxalosis [1]. PH2 can cause significant morbidity in children, but only rarely causes kidney failure in the first year of life [2, 3]. Patients with PH3 typically do not progress to kidney failure [4]. The extremely difficult management of infantile oxalosis and the adherence problem to the conservative management of children with PH are the typical challenges that pediatric nephrologists are faced with, as the following case reports may illustrate.

CASE REPORTS

A 5-month-old child, 'A', was referred because of increased vomiting and failure to thrive after a short period with diarrhea. On admission, his body weight was -2 SD, height was -2.3 SD, blood pressure was 150/90 mmHg and his serum creatinine was 1333 $\mu\text{mol/L}$ (15 mg/dL). Further investigations revealed

signs of systemic oxalate deposition including diffuse hyperdensity of both kidneys, consistent with cortical nephrocalcinosis, and brown-colored retinal spots, suspect of crystal deposition. Bone radiography demonstrated dense metaphyseal bands and submarginal metaphyseal lucency. Plasma oxalate levels were severely increased at 150 $\mu\text{mol/L}$ ($n < 6.8$). At that time, mutation analysis was not available. The diagnosis was established by liver biopsy (alanine-glyoxylate aminotransferase activity $<15\%$) in his 4-year-old brother, case 'B', who presented with hematuria and medullary nephrocalcinosis. Ten years later, DNA analysis showed that both boys were homozygous for a missense mutation p. (Gly170Arg) in combination with the so-called minor allele polymorphism, a common mutation associated with PH1. Due to local insurance problems, combined liver and kidney transplantation could not be performed up until 3 years later. The child had been on peritoneal dialysis (PD) since, and treated with pyridoxine. Despite treatments of chronic kidney disease-mineral bone disease (CKD-MBD) and growth hormone therapy, he had been suffering from persistent growth stunting and recurrent bone fractures. At that time, combined liver and kidney transplantation was performed. The kidney

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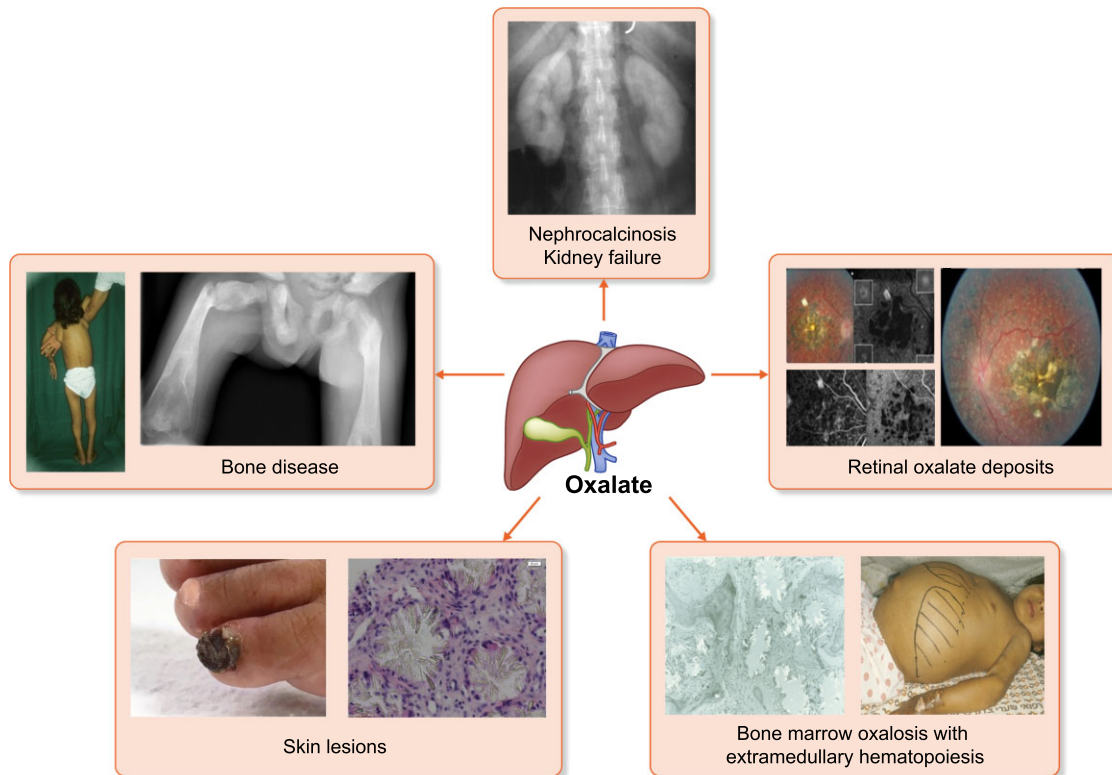


FIGURE 1: Manifestations of systemic oxalosis.

graft failed immediately, caused by massive calcium-oxalate depositions in the kidney graft, as revealed by histology. Two years later, he received a second kidney graft. Five years following the second kidney transplantation and more than 7 years after liver transplantation, his urinary oxalate excretion normalized. His last bone fracture occurred 3 years after the second kidney transplantation, which was the 26th in a row. At age 18 years, his final height was 155 cm (mother 176 cm, father 186 cm), and he suffered from sensory deafness, severely impaired vision and mild psychomotor retardation. At age 24 years, he had to start hemodialysis (HD) therapy as his second kidney graft failed, and 2 years later, he received his third kidney graft.

Meanwhile, his brother, case B, had preserved kidney function at the time of diagnosis when he was 4 years old. It turned out that he was known to have nephrocalcinosis ever since the age of 6 months. Although he was screened for hyperoxaluria at that time, the diagnosis was missed, most probably due to an incorrect handling of the 24-h urine collection. He responded to treatment with pyridoxine with normalization of oxalate and glycolate excretion, and at the age of 10 years, signs of nephrocalcinosis on ultrasound had disappeared. At age 17 years, he suffered from a kidney stone attack after a period of non-compliance. At age 27 years, his kidney function is still preserved, but he has several stones in both kidneys on renal ultrasound and mild hyperoxaluria with pyridoxine levels that were consistent with incomplete compliance.

CLINICAL APPEARANCE OF INFANTILE OXALOSIS

Infantile oxalosis is a term used to describe the appearance of diffuse nephrocalcinosis and advanced CKD in the first

weeks/months of life, with rapid progression to end-stage kidney disease (ESKD). Case A is a classical illustration of infantile oxalosis: failure to thrive for apparently unknown reason, increasing feeding problems, a history suspected of (mild) dehydration, diffuse white kidneys on ultrasound, which is apparent in over 90% of cases [5, 6], and signs of organ damage (eye and bone) that cannot be attributed to the ESKD status. Infantile oxalosis combines the burden of ESKD and multi-organ disease by systemic storage of oxalate.

Multi-organ failure by systemic oxalosis

Multi-organ disease by systemic oxalosis is a hallmark of infantile oxalosis. In a recent European registry study on infantile oxalosis, nearly 100% of the affected patients presented with signs of systemic oxalosis [6]. Although the exact threshold has not been established, it is believed that systemic storage of oxalate starts from the moment that the glomerular filtration rate has dropped below 20–30 mL/min/1.73 m² [7]. The severely impaired kidney filtration leads to an impaired oxalate removal and subsequent increase of plasma oxalate and oxalate deposition in various tissues, such as bone, retina, myocardium, arterial wall and nerves (Figure 1)

- (i) Eye involvement is typically found in infants with PH [8]. In a recent survey of 68 PH1 patients, severe retinal alterations were found in all 24 infantile PH1 patients, which included macular crystals and hyperpigmentation, with or without chronic retinal edema. The high incidence of eye involvement in PH with severe kidney injury typically occurs in infants. This might be explained by the fact that infant eyes are particularly sensitive to oxalate toxicity due to an

immature and therefore more susceptible choroid-Bruch's membrane retinal pigment epithelium (RPE) complex. Visual acuity may be compromised in children with severe involvement (e.g. optic disk atrophy, subretinal fibrosis).

- (ii) Bone disease accounts for most of the oxalosis-related morbidity and often manifests in infantile oxalosis. Oxalate deposition in bones, in addition to the mineral bone disease related to kidney failure, leads to multiple fractures and skeletal malformations. The first radiologic sign of bone oxalosis is the appearance of a sclerotic band in areas of rapid growth [9–11], thought to represent crystal deposition at Harris' lines of growth arrest. Over time, a lucent area, similar in consistency to the diaphysis, forms distal to the sclerotic band. Fractures begin to occur, on average, in the second half of the first dialysis year, usually concurrent with the child starting to walk and inevitably fall. Fractures are often caused by very mild trauma, such as twisting an ankle between the bars of a bed or falling from a standing height. Vertebral fractures causing worsening kyphosis, and severe bone pain requiring opioid treatment appears in later stages of dialysis treatment [10, 11]. Precipitation of oxalate crystals within the marrow space induces chronic granulomatous inflammation and fibrosis, replacing normal bone marrow tissue and causing extra-medullary hematopoiesis. The clinical presentation is erythropoietin-resistant anemia or pancytopenia and splenomegaly [12, 13].
- (iii) Cardiac deposition of calcium oxalate causing arrhythmias, specifically heart block and cardiomyopathy, are more typically found in adult patients, but subclinical features can be found in infantile oxalosis [14–17]. In a recent registry study, signs of oxalate deposits were most frequently found in the retina ($n = 43$), bones ($n = 34$) and heart ($n = 11$) [6].
- (iv) Other additional features of systemic oxalosis include neuropathy, hypothyroidism and skin lesions such as subcutaneous nodules, eschars and ulcers caused by vasculitis, but are less often apparent in infantile oxalosis [18–20].

MANAGEMENT OF INFANTILE OXALOSIS

Management of infantile oxalosis combines the challenge of ESKD management in a small child and prevention of (further) development of multi-organ disease by oxalate accumulation. The management of ESKD features is beyond the scope of this paper. Here, we will discuss the specific oxalosis management (Table 1).

- (i) Dialysis: Dialysis has been found to be an insufficient tool to cope with the endogenous oxalate production in PH. Studies in adults have shown that the net oxalate storage under conventional HD regimens may be more than 50 $\mu\text{mol/kg}$ body weight/day [21]. A recent study with stable isotope infusion of [$U\text{-}^{13}\text{C}_2$] oxalate showed that PH1 patients may have an endogenous oxalate production between 1.28 (pyridoxine sensitive) and 3.16 (pyridoxine insensitive) mmol/day [22]. This is in accordance with previous estimates based on daily urinary oxalate excretion rates in PH1 patients. Old studies have demonstrated that conventional HD regimens remove oxalate more efficiently than PD, but neither treatment can keep up with the oxalate accumulation rate [23]. Illies *et al.* showed that with intensive HD of six times per week for 4 h or combined HD and PD regimen, up to 24 mmol per week of oxalate could be removed, with PD only 4.5 mmol [24]. Therefore technically, intensive HD or combined HD and PD regimens should cover the

Table 1. Complications and challenges of pediatric hyperoxaluria: infantile oxalosis

Problem	Action
Stunted growth	<ul style="list-style-type: none"> • Sufficient calorie intake • Management of CKD-MBD • Management of systemic oxalosis
Prevention of multi-organ disease by oxalate storage	<ul style="list-style-type: none"> • Frequent HD, high flux membrane or combine with PD • Vitamin B6 (20% responsive)^a • Early liver transplantation, either directly combined with kidney transplantation or sequentially performed • RNAi (?)
Prevention of cardiovascular disease	<ul style="list-style-type: none"> • Strict fluid management and hypertension control • Early transplantation
Prevention of bone disease	<ul style="list-style-type: none"> • p-Oxalate control • Ca/phosphate/PTH/bicarbonate control
Prevention of kidney graft failure by oxalate	<ul style="list-style-type: none"> • p-Oxalate control by frequent dialysis • RNAi (?) • Assessment mutation: B6-sensitive?^a • Assessment of level of systemic storage; either sequential or simultaneous liver/kidney transplantation

^a Mutation analysis, assessment and monitoring p-glycolate response on B6 supplementation. PTH, parathyroid hormone.

endogenous production. However, even under intensive HD regimens with an adequate weekly clearance, oxalate levels may rise to levels at the dialysis interval moments that may lead to further systemic oxalate depositions. Children with PH1-associated kidney failure were found to have supersaturation levels of calcium oxalate even after aggressive HD [2]. A long period of dialysis in PH is associated with more clinical manifestations of systemic disease, such as bone fractures. Another problem is the recommended dialysis technique itself. Although (frequent) HD is superior and recommended over PD alone as a renal replacement therapy bridge to transplantation, it is a challenging treatment mode for small infants. The relatively high extra-corporal volume may induce episodes of hypotension, and the central lines with small volumes are especially susceptible to catheter infections and occlusions [25]. Combined PD and HD treatment, while feasible, requires two separate catheters, significantly raising infection risk, and places a very high burden on patients and their families.

- (ii) Liver/kidney transplantation: Either simultaneously or sequentially conducted liver and kidney transplantations are still the keystone therapies for infantile oxalosis. No evidence exists for the superiority of one of the approaches with respect to mortality or kidney graft survival [26, 27]. The technical challenge of the simultaneous approach is the opposite recommendation of fluid supply (liver graft: as restrictive as possible; prevention of oxalate nephropathy in kidney graft: as much as possible). Temporary

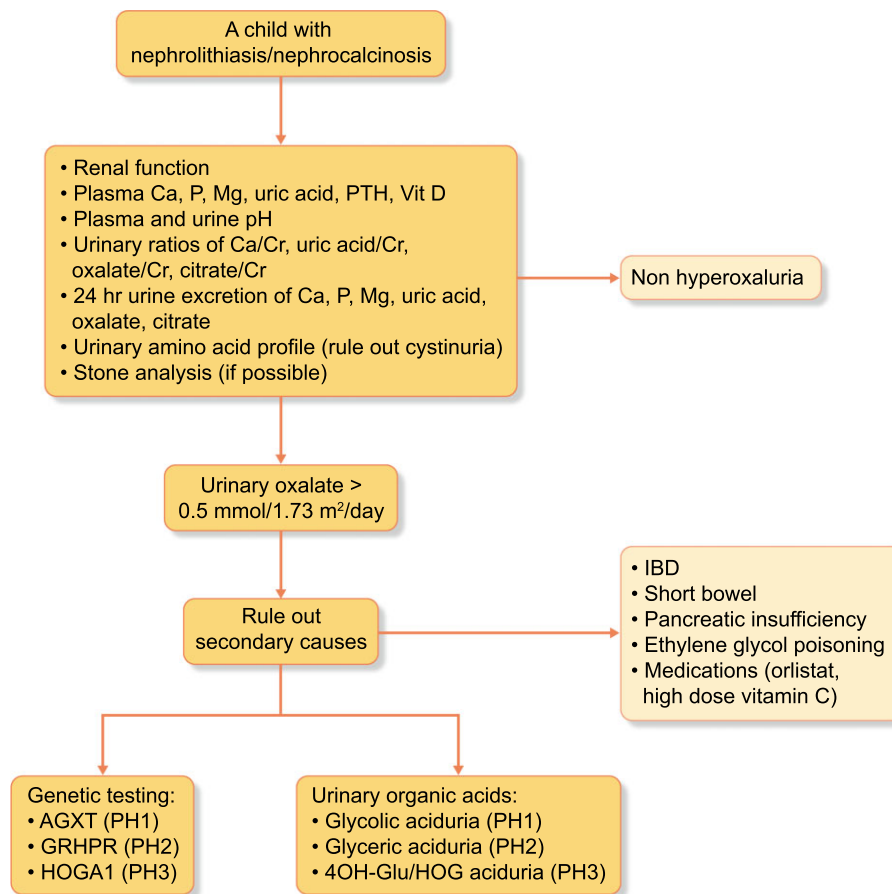


FIGURE 2: Diagnostic approach to a child suspected of having primary hyperoxaluria. PTH, parathyroid hormone; Cr, creatinine; IBD, inflammatory bowel disease.

continuous veno-venous hemodiafiltration after transplantation may be required to prevent a high oxalate burden for the kidney graft. Despite cessation of pathological oxalate production by the transplanted liver, clearance of the systemic calcium-oxalate load results in elevated urinary oxalate levels, which may persist for many years. The transplanted kidney should therefore be protected by adequate fluid intake and by the administration of crystallization inhibitors as long as oxalate excretion remains increased.

(iii) Monitoring and diagnostic procedures: Monitoring of the efficacy of therapy is hampered by the lack of urine output and the fact that plasma oxalate levels are often difficult to interpret. Non-PH patients with ESKD may have plasma oxalate levels up to 5–8× normal values of patients with normal kidney function. Moreover, lowering of plasma oxalate levels by therapeutic intervention such as intensified dialysis, vitamin B6 or RNA interference (RNAi) may be delayed in time due to systemic oxalate storage. A lowering of plasma glycolate under vitamin B6 therapy is indicative of B6-sensitivity. This occurs in a minority of children with infantile oxalosis [6, 28, 29]. Potential B6-sensitivity can be confirmed by mutation analysis, a reason why early mutation analysis not only is essential for the final diagnosis, but might also impact the management of these children.

(iv) RNAi: The new RNAi-based therapies, lumasiran and nedosiran are promising agents for these difficult patients [30, 31]. Lumasiran inhibits glyoxylate production by block-

ing glycolate oxidase (GO), acting as a substrate reducing agent. Treatment with lumasiran has been shown to lower the oxalate excretion on average by 65.4% in a randomized controlled trial among PH1 patients with preserved kidney function. Data in patients with severe kidney failure are about to appear [30]. Nedosiran, which inhibits lactate dehydrogenase-A, the final metabolic step from glyoxylate to oxalate, has shown a significant lowering effect on plasma oxalate levels in a compassionate-use PH1 patient on dialysis [31]. Trials with nedosiran are currently being conducted.

OUTCOME AND ETHICAL DILEMMAS OF INFANTILE OXALOSIS

In a recent European registry study on 95 patients with infantile oxalosis who were born between 1980 and 2018, 30% early mortality was found. At the same time, the authors noted a sharp decrease of mortality over time [6]. These figures are in line with an earlier study of Harambat et al. on data of the European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) registry, who found 26% 3-year mortality in PH children <2 years of age [27]. They found that patients with infantile oxalosis (defined here as <2 years of age with ESKD) had a 3.4 times higher risk of early death (adjusted hazard ratio, 3.44; 95% confidence interval, 1.15–10.28; $P = 0.02$) compared with PH patients

aged >2 years at the onset of renal replacement therapy [27]. Also, this study reported a significant decrease in mortality risk of infantile PH after 2000.

These figures, however, concern patients from Western countries. Pediatric urolithiasis is endemic in North-African and Middle Asian countries due to several factors, such as hot climate and dietary habits. The prevalence rates for urolithiasis are up to 15% of children aged <15 years in Middle Asian countries, as compared with 1–5% affected in Western countries [32]. Hyperoxaluria as a factor of pediatric kidney stones was found in 40% of cases in an Indian survey [32]. The incidence of PH itself is also much higher in these countries due to a high rate of consanguinity [33]. In Saudi Arabia, for instance, PH was reported as a primary cause of pediatric ESKD in 10.7% [34]; a dialysis center in Northern Israel reported that 38% of their dialysis patients were PH patients from Druze–Arab origin [35]. Hot climate, low resources, inadequate infrastructure and lack of diagnostic tools for PH monitoring may all limit the means to conduct the required complicated care for children with PH in some of these countries where even sufficient water supplementation may be unreachable. Infantile oxalosis therefore presents great difficulty for the responsible physician in places such as Middle East and Maghreb countries, especially if resources are lacking. Combined kidney and liver transplantation, currently the only option for survival, is often beyond reach.

Yet, even in highly developed countries, starting kidney replacement therapy in infants is under discussion. Although a combined ESPN/ERA-EDTA, Australian and New Zealand dialysis and transplant association (ANZDATA), International Pediatric Peritoneal Dialysis Network (IPPN) and Japanese registry study conducted in 2014 showed that the actual outcome of 264 patients who started kidney replacement therapy within the first month of life was remarkably good, with 81% 2-year survival [36], offering chronic dialysis to infants is still often considered as optional rather than obligatory [37]. Many doctors recommend starting dialysis in ESKD infants, but accept palliative care if this is requested by the parents. Key factors in this decision are the burden of the therapy that is imposed upon the family and the extent of comorbidity [37]. It is beyond dispute that the combination of six times per week HD or combined HD and PD, the possible necessity of combined liver and kidney transplantation, and the additional comorbidity due to systemic oxalosis put children with infantile oxalosis in the worst category when considering the best care.

For all these reasons, Cochat *et al.* in 1999 concluded that (infantile) oxalosis could be regarded as a rare condition for which ‘therapeutic withdrawal may be an acceptable option according to local necessity’ [5]. Introduction of the new RNAi drugs at a reasonable price, even for a period to overcome the first years, might dramatically change this situation and could therefore be a promise for the near future [30, 31].

HYPEROXALURIA IN OLDER CHILDREN

The diagnostic approach to a child with nephrocalcinosis or kidney stones is summarized in Figure 2. Of note, a 24-h urine collection in small children often requires a urinary catheter. Spot-urine oxalate to creatinine ratio provides a reasonable estimation of urinary oxalate excretion [38]. Case B showed the challenges of a so-called mild clinical appearance in children. Although cases A and B had the same mutation and both had their first clinical manifestations at infancy, B only presented with hematuria and signs of medullary calcification, whereas A had an ultrasound image consistent with cortical nephrocalcinosis and ESKD. Fortunately, B responded well

to B6 supplementation, with normalization of the oxalate excretion and disappearance of the nephrocalcinosis. This highlights the importance of early diagnosis and appropriate timely treatment [39, 40]. However, the therapy adherence was insufficient, and as a result of that, he developed several kidney stones over time. About 30–40% of Caucasian patients with PH1 respond with more than 30% reduction of oxalate excretion to vitamin B6 supplementation. High fluid intake, up to more than 3 L/m² body surface, and potassium-citrate are the other recommended conservative measures to prevent kidney failure and new stone events in PH of all types [7, 33]. Especially the recommended fluid intake in particular appears to be an extreme burden for children. For comparison, adherence to the less strict recommendation for adults with stone disease of at least 2.5 L/day was found to be less than 50% [41]; this situation is even more complicated in children, and the recommended fluid substitution is higher [7]. Small children may therefore require fluid substitution by gastrostomy or a nasogastric tube. Potassium-citrate intake can also be troublesome, as the delivered solution is often very distasteful.

Another threat that is especially related to children is dehydration, e.g. in the case of gastroenteritis or while fasting before medical procedures, which may induce a rapid decline in kidney function in PH patients with severe nephrocalcinosis. Many local physicians are not aware of the immediate threat that dehydration may pose in these patients [42]. Educating parents to request intravenous hydration in such cases may help prevent complications.

CONCLUSIONS

The care of pediatric PH patients can be extremely complicated and should be conducted by physicians specialized in this field, especially when it concerns children with infantile oxalosis. The new RNAi drugs are promising and could dramatically improve the outcome of these children, provided that the established efficacy of oxalate lowering indeed pays off in the protection of the kidney function, something that still needs to be established, and if the financial hurdles for access to these drugs can be overcome.

PATIENT CONSENT

The patients or their families gave informed consent to publish these cases.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format. The authors have no conflict of interest to declare.

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