

*Country Data*

## The Clinical Pattern of Primary Hyperoxaluria in Pediatric Patient at Queen Rania Abdulla Children Hospital

Reham I. Almardini\*, Mahdi G. Alfarah, Ghazi M. Salaita

Pediatric Nephrology Unit, Queen Rania Abdulla Children Hospital, Jordan

### Abstract

**Introduction:** Hyperoxaluria is a metabolic disorder that can lead to end stage renal disease (ESRD). It can be either inherited or acquired. Primary hyperoxaluria (PHO) is more common and characterized by an excessive production of oxalate leading to recurrent urolithiasis and progressive nephrocalcinosis. Due to the high rate of consanguineous marriage in Jordan this disease is commonly diagnosed in pediatric nephrology clinics. We aimed to demonstrate the clinical pattern and progression to ESRD in pediatric patients with hyperoxaluria at Queen Rania Abdulla Children Hospital.

**Methods:** Medical records of all patients followed up in the pediatric nephrology clinic with the diagnosis of PHO during the period between September 2007 and March 2013 were reviewed.

**Results:** There were 70 patients with the diagnosis of PHO, 52.9% were males. The median age at presentation was 3 years  $\pm$  3 months with the youngest child being two months old. Diagnosis was made in the first year of life in 15.7% of patients. The most common presenting symptom was hematuria, while 14% of patients were asymptomatic and detected by family screening after the diagnosis of an index case. At the time of initial presentation, 15.7% of patients had ESRD and 25% had impaired renal function. Kidney stones were found in 57% of cases and nephrocalcinosis was found in 37%.

**Conclusion:** High index of suspicion is needed to diagnose PHO in children presenting with kidney stone or unexplained hematuria. Twenty-four hour urine collection for oxalate are required to make the proper diagnosis. Family screening, when appropriate, is indicated for early detection of PHO.

**Keywords:** End Stage Renal Disease; Primary Hyperoxaluria; Urinary Oxalate

*The authors declared no conflict of interest*

### Introduction

Hyperoxaluria can be either inherited or acquired. Primary Hyperoxaluria is more common and characterized by an excessive production of oxalate leading to recurrent urolithiasis and progressive nephrocalcinosis.

There are three types of primary hyperoxaluria (PH); the most common is PH type I which results from deficiency of a peroxisomal, liver specific, pyridoxal phosphate dependent enzyme; alanine glyoxylate amino transferase deficiency [1]. PH type 2 is caused by deficiency in the cytosolic enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR) [2]. The recently identified PH type 3 is linked to the gene DHDPSL, encoding a mitochondrial enzyme [3].

Oxalate is one of the end products of glycine metabolism [4], it can't be metabolized in the body and has to be eliminated by the kidney. Hyperoxaluria leads to nephrocalcinosis or recurrent urolithiasis resulting in kidney injury. When the glomerular filtration rate falls below 30-50 mL/min/1.73m<sup>2</sup>, plasma oxalate exceeds the supersaturation point for calcium oxalate (Pox >30  $\mu$ mol/L); leading to systemic deposition of oxalate in different tissues such as bone, retina, skin, soft tissues, heart, vessels, and central nervous system, hence it is called oxalosis [5]. The infantile form often presents as a life threatening condition and rapidly progresses to ESRD due to early oxalate load along with the immature GFR during the first year of life.

The measurement of oxalate in a timed 24-hour urine collection corrected for body surface area is the preferred method for the diagnosis of PH since it is easier to do and is widely available [6]. The limitation of 24 hour urine

\* Corresponding author; Pediatric Nephrology Unit, Queen Rania Abdulla Children Hospital, Jordan.

oxalate level determination as a method of diagnosis for PHO is the day to day variability of urine volume and inaccuracy in collection which can affect the result. In addition, this method cannot differentiate between primary and secondary hyperoxaluria, although in cases of secondary hyperoxaluria the oxalate level is usually 45-90 mg/1.73m<sup>2</sup>/day while in cases of PHO it is usually above 90 mg/1.73m<sup>2</sup>/day [7]. Urinary oxalate excretion may also be falsely low in patients with decreased GFR due to oxalate retention and systemic deposition.

Urinary glycolate excretion is elevated in most patients with PH type I, whereas urinary L- glyceric acid excretion is increased in nearly all patients with PH type II [8]. Liver biopsy for enzymatic analysis is needed for definitive diagnosis if liver transplantation is considered, unless the genotype is known or the diagnosis has been confirmed in a sibling. DNA analysis as a diagnostic procedure is not a standard technique except in populations with a high frequency of a specific mutation [7].

## Methods

Medical records for patients who were followed at the nephrology division with the diagnosis of primary hyperoxaluria over a 5 years period were reviewed; data including age, sex, age at first presentation, symptoms at diagnosis, diagnostic procedures, duration of follow-up, therapeutic strategies and outcome were analyzed.

All the patients were diagnosed to have hyperoxaluria by 24 hour collection of oxalate, a value of 45 mg/1.73 m<sup>2</sup>/day or more was considered abnormal [9, 10]. All patients with renal failure who had good urine output were diagnosed by the same method. One patient who didn't have good urine output with negative family history was excluded from the study. Two patients found to have secondary hyperoxaluria (secondary to malabsorption) were excluded from this study.

The oxalate concentration was determined using an oxalate kit (No: 591C; Trinity Biotech, St). Laboratory measurement of oxalate level was performed on 24-hour urine specimen which was preserved by adding 10 ml hydrochloric acid. Oxalate is oxidized to carbon dioxide and hydrogen peroxide by oxalate oxidase. The hydrogen peroxide reacts with 3-methyl-2-benzothiazolinone hydrazone (MBTH) and 3-(dimethylamino) benzoic acid (DMAB) in the presence of peroxidase to yield an indamine dye which is measured by using spectrophotometer. The intensity of the color produced is directly proportional to the concentration of oxalate in the sample.

Neither liver biopsy nor enzymatic assay were performed since no one of the patients were planned for liver transplantation. Genetic testing was not performed for diagnostic purposes. Few patients had genetic testing for research purposes (results not published). Renal ultrasound was done initially for all patients and repeated every six month or if patients developed renal colic. Patients were kept on high fluid intake, sodium bicarbonate, and pyridoxine with an average dose of 10 mg/kg/day in two divided doses (5- 0 mg/kg) [11].

## Results

A total of 70 patients were diagnosed to have PHO, from 50 different families. Thirty-seven (52.9%) were male and 33 (47.1%) were female. The mean follow up period was 3.2 years. The age at presentation ranged between 2 months to 13 year. The median age at the time of diagnosis was 3 years ± 3months.

The most common presentation was hematuria in 16 (22.8%), followed by urinary tract infection in 11 patients (15.7%), chronic kidney disease (CKD) in 11 patients (15.7%), screening after diagnosis of an index case in 10 patients, accidental ultrasound finding in six patients, abdominal pain in five patients, renal colic in three patients, passage of stones in three patients, polyuria and distal renal tubular acidosis in three patients and acute renal failure due to obstruction in two patients. Positive family history of stones or similar cases was present for 19 patients, while consanguinity was present in 21 cases.

Eighteen (25.7%) patient had impaired kidney function at the time presentation. Two patients had complete obstruction by stone, both were treated surgically and improved. One patient had urinary tract infection (UTI) and improved after antibiotic treatment. Eleven patients had ESRD while four patients had CKD and were managed conservatively. Among ESRD patients, seven were managed by hemodialysis, one was managed by peritoneal dialysis and three were managed conservatively after discussion with family. None of the patients detected by family screening was found to have CKD. During the study period, four (5.7%) patients who initially presented with normal kidney function developed mild deterioration of kidney function. Five patients progressed to ESRD during the study period, 80% of them presented initially with impaired kidney function.

Ultrasound done at the time of diagnosis was normal in only two patients. The majority of the patients (57%) had



kidney stones, 26 patients (37%) had nephrocalcinosis and three patients had gravel.

All patients who presented with ESRD had nephrocalcinosis at presentation as did patients whose kidney function deteriorated after diagnosis. Twenty three (32.9%) patients underwent surgical procedures related to nephrolithiasis. Ten patients had open procedures. Five patients had ESWL with double J stent (DJS) insertion. Three patients had nephrostomy with DJS insertion. Ten patients had DJS only.

All patients were advised to have high fluid intake and treated by sodium bicarbonate tablets since other urine alkalinizing agents such as potassium citrate were not available. Vitamin B6 was also prescribed. Unfortunately, none of patients with ESRD received liver or combined liver and kidney transplant so far.

## Discussion

Primary hyperoxaluria (PHO) is rare autosomal recessive disorder. PHO type 1 has a prevalence of 1-3 per million population with an incidence rate of 1:100 000 live birth in Europe [12, 13]. Due to lack of national registries, epidemiological information from developing countries come from major referral centers.

In North America, the prevalence of ESRD secondary to hyperoxaluria was reported to be three per million children. In comparison, PHO accounts for less than one percent of pediatric ESRD in USA, UK, and Japan [15-17]. In this center, hyperoxaluria was the cause of ESRD in 16.7% of the pediatric hemodialysis population in 2005 [14]. Data from the Arab world showed that 10.4% of ESRD cases in children in Kuwait and 13% in Tunisia were secondary to PHO [18]. High rate of consanguineous marriages in those countries contributes to higher incidence of this recessive disease in comparison to other countries.

According to Cochat, reviewing 78 patients from different developed and developing countries revealed that half the patients experienced ESRD at the time of diagnosis and 80% develop ESRD by the age of 3.2- 6.4 years [19]. In our series, 94.3% of children who developed ESRD presented initially with chronic kidney disease, 20% of them were below the age of one year. In this study, 25.7% of patient had impaired kidney function at the time of presentation, 16.6% of them had acute renal failure secondary to either obstruction or infection and they regained normal kidney function after treatment while 61.1% of them were actually ESRD patients and had

nephrocalcinosis. Similar observations were reported from Netherland [20].

In comparison, children detected by screening and treated before complications appeared did not develop nephrocalcinosis or renal abnormality. This emphasizes the importance of family screening when an index case is diagnosed and the initiation of measures that enhances the excretion of oxalate.

In our series, the median age at presentation was 3 year in comparison to 6 and 13 years in Netherland and Japan respectively [20, 22].

Treatment of Hyperoxaluria includes conservative measures of high fluid intake 2- 3 L/m<sup>2</sup>/day distributed through day and night [23]. Inhibition of calcium oxalate crystallization is achieved by alkalization of the urine using citrate or sodium bicarbonate. Pyridoxine, a cofactor of AGT, is associated with 10-30% reduction in urinary oxalate in some cases of PH type 1 with a starting dose of 5 mg/kg/day up to 10 mg/kg/day [25, 25]. In this study, all patients were treated by pyridoxine including patients with ESRD.

The urological treatment of stone is indicated in cases of obstruction, open and percutaneous surgery should be avoided if possible [26]. Most of our patients were treated conservatively and those who needed urological interventions were managed initially by ESWL. Some patients presented with large stones which needed open intervention.

No form of dialysis, is able to keep up with the endogenous production of oxalate, *let alone* to reduce the body oxalate burden [27, 28]. This results in continuing tissue deposition of oxalate and risk of organ damage. Better results may be obtained by combining daily high-flux hemodialysis and peritoneal dialysis or by long daily hemodialysis sessions [29]. In our centre, all patients were treated by conventional hemodialysis or peritoneal dialysis. Both methods do not adequately correct hyperoxaluria due to the huge load of oxalate [27, 30] or prevent the development of the disease complications such as corneal, brain and bone marrow involvement.

Isolated kidney transplantation is contraindicated unless the response to pyridoxine is documented. Isolated kidney transplantation is the treatment of choice for PH type 2. Combined or sequential liver and kidney transplantation are best recommended for PH type 1. Unfortunately none of our patients received a transplant, which reflects the

hesitancy to do liver transplantation for patients with normal liver function tests [31].

## Conclusion

Hyperoxaluria is a relatively common disease in Jordan. Although the actual prevalence is unknown, it contributes significantly to ESRF. High index of suspicion is mandatory in dealing with children with kidney stones and nephrocalcinosis. In patient presenting with hematuria of unexplained etiology, 24 hour urine collection for oxalate is mandatory. Family screening is a must when an index case is found so that early management may delay the progression to renal failure. Combined liver and kidney transplantation are still not used as a modality of treatment in Jordan.

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