Hyperoxaluria in Tripoli children's hospital

Rowida MF Khashebi, Awatef El Bouaeshi and Mohammed Dekna

Tripoli Children's Hospital, Faculty of Medicine, University of Tripoli, Tripoli, Libya
Correspondence to: drdekna@yahoo.com

Abstract: Primary hyperoxaluria (PH) is a rare autosomal recessive inherited metabolic problem. It is a heterogeneous disease with variable age of onset and variable prognosis. The clinical presentations range from renal failure during infancy to asymptomatic cases during adulthood. To determine the pattern of PH in a group of Libyan children at Tripoli children's hospital. We reviewed the medical records of all children diagnosed as PH from 1994 up to 2007 in nephrology unit at Tripoli children's hospital. 36 patients (17 male and 19 female) diagnosed as primary hyperoxaluria during the study period. Their age of presentation was 3.9 ± 3.7 years with an equal sex distribution. 25 of 36 patients have family history of renal problems, 21 of 36 patients were production of consanguineous marriage. 17 of 36 patients were originally came from Al-Jabel gharbi. The patients presented commonly with recurrent urinary tract infections (UTI), renal stone and hematuria. 33 of the 36 patients had abnormal songraphic pattern, which include renal stone, and medullary nephrocalcinosis. Renal failure found in 3 of 36 patients at presentation while 4 patients developed renal failure later on during fellow up after mean interval of 7 years. Primary hyperoxaluria is not uncommon disease in our society and it causes chronic renal failure in children.

Keywords: primary hyperoxaluria, renal stone, renal failure, nephrocalcinosis, Libya.

Introduction

Hyperoxaluria is group of rare metabolic disorders characterized by excessive urinary execration of calcium oxalate with recurrent nephrolithiasis and chronic renal failure. It is classified into two main groups: primary and secondary hyperoxaluria (1). Primary hyperoxaluria is an autosomal recessive inherited disorder subdivided into two types according causative enzymes: primary hyperoxaluria type I (PH I). It is disorder of glyoxylate caused by deficiency of the hepatic peroxisomal enzyme alanine - glyoxylate aminotransferase (AGT). It is encoded by single gene located in chromosome 2 at locus q 37.3 and requires pyridoxine (vitamin B_6) as its cofactor (2).

Primary hyperoxaluria type II (PH II) is a rare disorder caused by deficiency of peroxismal enzyme (D-glycerate dehydrogenase) (1). Secondary hyperox-aluria is a non-genetic problem, it is due to several causes such as ingestion of oxalate precursor likes as vitamin C or ethylene glycol, pyridoxine deficiency, methoxy flurane anesthesia and enteric hyperoxaluria due to hyper-absorption of oxalate which occurred in short gut syndrome (1). The metabolic defect in PH I leads to extremely high oxalate concentrations within the proximal tubular cells. This leads to direct damage followed by foreign-body reactions (3). Presentation of PH I as the classic presentation characterized by recurrent calcium oxalate

nephrolithiasis and nephrocalcinosis in childhood, leading to renal failure during early adulthood or the infantile presentation characterized by nephro-calcinosis only leading to chronic renal failure in infancy or early childhood (4). Systemic oxalosis occurs when glomerular filtration rate (GFR) declines below 25 ml\min\ 1.73 m² (5). Age of presentation of PH I is variable and it depends on the severity of the disease. Symptoms can occur at any age and 50% of cases occur during age less than 5 years. Besides, 16% of cases at age less than one year (7). The prediction of outcomes for individual patients is very difficult. Patients with PHI with GFR of > 50 ml/min/1.73 m^2 may remain in a stable condition for many years but may rapidly and irreversibly loose residual function during episodes of dehydration, urinary obstruction, or noncompliance. Nevertheless, the patient prognosis with PH I tends to be considerably better, if the disease is properly treated. Over 80% will require renal replacement therapy by the end of their third decade (8). The hyperoxaluria is rare but yet important disorder and needs more studies especially in our society where consanguinity is still common and the renal medical problems are increasing. The aim of study is to explore some of the features of the PH in western part of Libya, specially the socio-demographic charac-teristic and the pattern of presentation.

Patients and methods

Study design: retrospective case series study setting: the nephrology unit of Tripoli children's hospital. Study period: review of all cases 12/2007. Study population: children were diagnosed as primary hyperoxaluria previously and are followed up at nephrology unit during (1994-2007).

Statistical analysis: the study carried out in on children were diagnosed as primary hyperoxaluria previously and are followed up at nephrology unit during 1994-2007. Data abstracted from the medical records and filed in a work sheet, which include: through history (age, sex, geographic distribution, history of consanguinity, presenting symptoms, family history of renal disease). Weight, height and blood pressure at presentation using WHO centile charts (9). Laboratory investigations: CBC, ABG, renal function tests and glomerular filtration rate (GFR) was estimated from Schwartz formula (10). GFR stages classified according to the kidney disease outcomes quality initiative (K/DOQI) of CKD (chronic kidney disease) (11). 24-Hours collection of urine for oxalate: urinary oxalate excretion more than 45 mg\24hr\1.73 m² or 0.5 mmol\day\1.73 m² will be considered high (12). Blood for oxalic acid: more than 7.4 mmol\l will be consider high (12). Ultra-sound of renal system (songraphic pattern).

Results

We have 67 patients on regular follow up in the nephrology unit and they received supportive treatment of PH. 25 patients were suspected to be PH but not confirmed; therefore, they were not included in our study. 36 patients (17 male and 19 female) with confirmed diagnosis of PH. The distribution of patients along the study period is shown in figure 1.

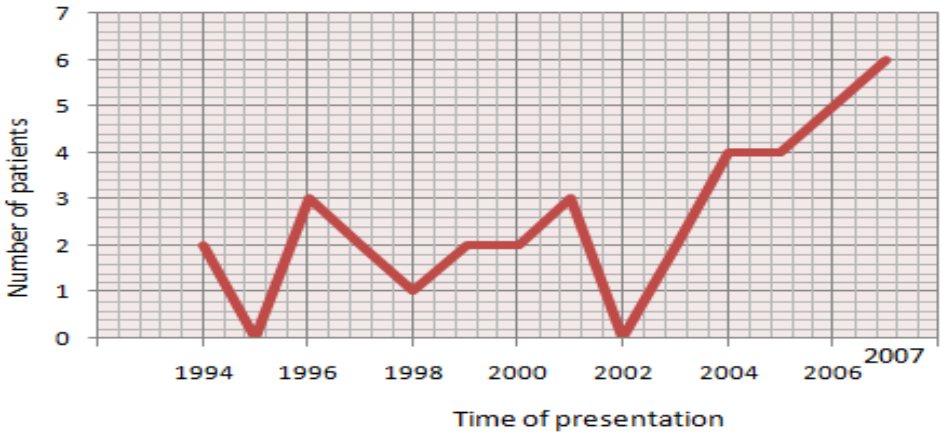

Figure 1: Distribution of our patients along the period of the study.

The patient's age at presentation ranged from 3 months to 12 years. The mean age is 3.9 ± 3.7 years, 33.3% of them presented during infancy, 33.3% of the cases presented at age between 1-5 years and 33.3% of the cases presented at age between 6-12 years. As shown in Figure 2, the geographic distribution of our patients, we found that (47.2%) patients are originally from Jabel gharbi, the remaining are originated from other cities. 14 of 17 patients are originally from Jabel gharbi also have history of consanguinity (82.3%). When we studied patients about family history of renal diseases, we found that 69.4% of them have family history of renal problems, on the other hand, 8.3% of them have no family history of any renal problems, the difference is statistically significant ($p < 0.00$). By studying the relationship between the family history of renal problems and presence of consanguinity between the patient's parents, we found that 72% of the patients with positive family history of renal problems, their parents are first or second cousins too.

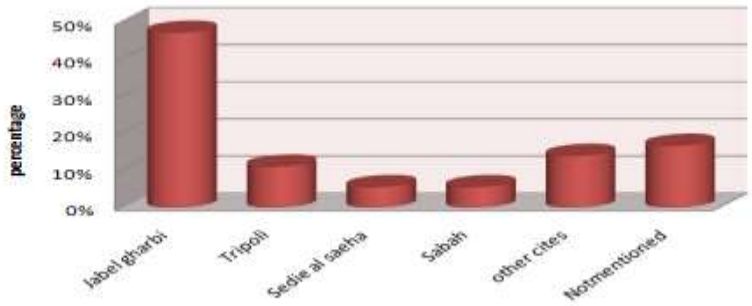

Figure 2: Geographic distribution of our patients.

When we studied the relation between patient patterns presentation as regarding their presentation age. We found renal stone, hematuria and polyurea and polydipsia found only in older patients (> 1 year). However, metabolic acidosis, FTT, convulsion, vomiting and diarrhea are more common in infants. While UTI was equal in both groups. As shown in table 1. In clinical examination, we revealed that 25% of patients weighed below or at third centiles for age and sex and 22.3% of patients their heights were below or at third centiles for age and sex. 11.1% of patients their weights and heights are below third centiles for age and sex. We found 11.1% of them had both diastolic and systolic blood pressure above 99th centiles for age and sex.

Table1: Pattern of presentation of patients to nephrology OPD in relation with age.

Presentation	Percentage from total, n=36	Age ≤ a year, n=12	Age > a year, n=24	P value
UTI	61.1%	58.3%	62.5%	1
Renal stone	**30.6%**	**0%**	**33.3%**	**0.03**
Hematuria	**25%**	**0%**	**37.5%**	**0.03**
Metabolic acidosis	8.3%	16.7%	4.2%	0.25
Poly urea & dipsia	5.6%	0%	8.3%	0.54
Renal failure	2.8%	0%	4.2%	1
FTT	11.1 %	16.7%	8.3%	0. 58
Convulsion	11.1%	16.7%	8.3%	0.25

The GFR at presentation of our patients, as shown in Figure 3. It is found that 44.4% of the patients their GFR is stage 1, 8.3% their GFR is stage 5 and 19.4% of the patients their GFR cannot be calculated because their height not measured.

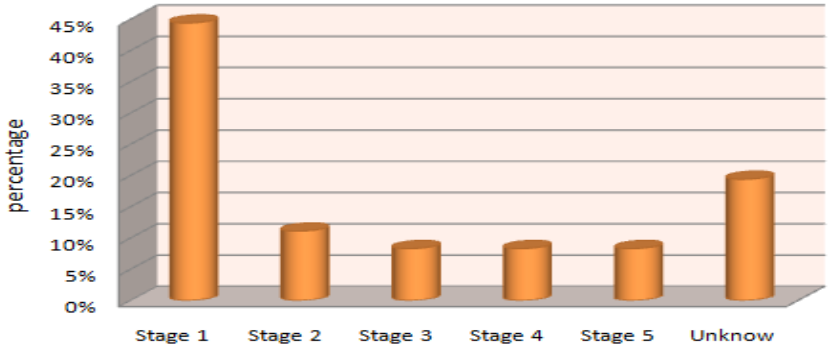

Figure 3: GFR at presentation of our patients**.**

When we studied the relationship between GFR as regarding their age at presentation, we found that 9.5% of the patients older than one year their GFR is stage 5. And, 12.5% of the infants their GFR is stage 5, which statistically is not significant (p = 0. 7). About the results of diagnostic investigation of patients and basic investigation of our patient as shown in tables 2 and 3, respectively.

Table 2: Diagnostic investigation

Diagnostic investigations	Frequency	%
24 hr urine for oxalate	29	80.6%
Renal stone analysis	8	22.2%
Plasma oxalate level	7	19.4%
Liver biopsy	2	5.6%

Table 3: Basic investigation

Basic investigations	Frequency	%
High urea	5	13.9%
high level creatinine	9	25%
anemia	15	41.7%
Metabolic acidosis	12	33.3%

The songraphic pattern at time of presentation, we revealed that 91.7% of the patients had abnormal songraphic pattern and 8.3% of them had normal songraphic pattern. Which is statistically significant (p < 0.001). When we studied the relation between songraphic pattern and age at presentation, we found renal stone exists in patients older than 1year only. Besides, nephrocalcinosis and hyper-echogenicity found in both age groups, but nephro-calcinosis is more common in infants (Table 4).

Table 4: Songraphic pattern of the patients in relation to age.

Songraphic pattern	Age ≤ one year NO = 12	Age > one year NO=24	P value
Renal stone	0%	75%	0.00
hyperechogenicity	8.3%	25%	0.40
Nephrocalcinosis	75%	29.1%	0.004
hydronephrosis	0%	25%	0.19
dilated ureter	0%	4.2%	0.19

Discussion

As shown in figure 1, the patients presented during the study period by ratio 2.5 patients per year. There is an increasing number of patients during the period from 2003 to 2007, which may be due to the increasing awareness of pediatricians to this disease, and availability of some diagnostic investigations. It is well known fact that autosomal recessive disorders are common in ethnic groups, in which consanguineous marriage is more common (13). In this study, consanguinity rate was 58.3% among parents of these patients which agrees with Cachet study (14), who reported consanguinity rate was 76% among the studied patients. The geographic distribution of these patients showed that 47.2% the patients originated from Jabel gharbi. 82.3% of these patients were product of consanguineous marriage, which explains the high percentage of patients who came from that region. Family history of renal diseases was found in 69.4% of patients supporting that this disease is genetic one. Patients with PH typically present early during childhood with the first signs of disease being presented in 50% of children under the age of 5 years (7). In the present study, 63% of patients presented before the age of 5 years. In our patients the age of presentation in patients ranged from 3 months to 12 years (3.9 ± 3.7). These findings agree with Tunisian (15), French (7) and Saudi (16) studies. Our figure differs from German study (17) in which the median age at presentation was 2.6 yrs, this difference probably caused by the method of their study, which is done by national survey at 1994 and up dated it during 2000 and 2004, while this method of study is hospital based data.

Regarding the pattern of presentation, (As shown in table 1) most of the patients presented with UTI, renal stone and hematuria. This result is in agreement with a German (17), Dutch (18) and Saudi (16) studies.Our patients did not receive an adequate diagnostic workup as showed in table 2. And, only two (5%) patients had liver biopsy revealed PHI. Our result is in agreement with other studies from developing countries , for instances Tunisian (15) and Saudi (16) studies .Where no patient was diagnosed by liver biopsy. On the other hand, studies from developed countries such as Japanese (19), American (20), French (7) and German (17) , we notice a high percentage of their

patients had liver biopsy, which give them the definitive diagnosis. Regarding the Son graphic findings at time of presentation (Table 4), these results agree with an American study (20). However, patients in a Saudi (16) and Tunisian (15) studies who had almost the same percentages of renal stone. They differ in nephrocalcinosis percentage. As shown in Figure 4, this difference is probably related to the small number of cases in their studies, and the high percentage of ESRF of their patients compared to our patients. We know that the destruction of the renal parenchyma in PH is caused by the diffuse deposition of calcium oxalate in the kidneys, which appears as nephrocalcinosis on ultrasound (21). In addition, the progression of renal insufficiency was statistically associated with the presence of nephrocalcinosis (18).

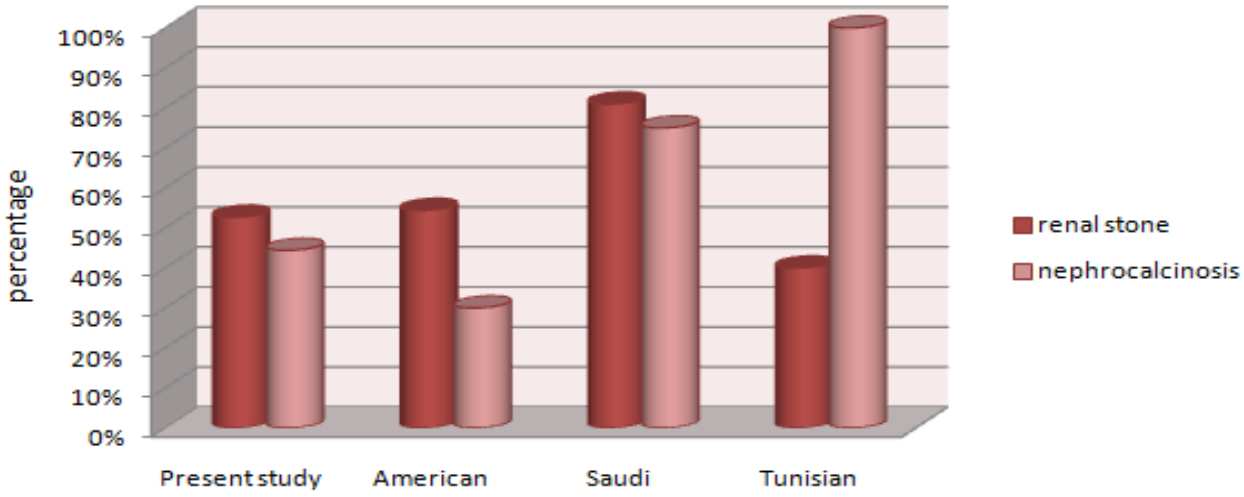

Figure 4: The sonagraphy pattern in different studies.

Because of lack of previous studies about the infantile presentation of PH in Libyan society, we studied our infant patients more deeply to explore pattern of presentation, it is found that 33.3% of the patients presented during infancy. The results is in agreement with the Tunisian study (15). Whereas, it differs from Dutch (18) and French (7) studies, in which only 22.5% and 16% of their cases presented during infancy, respectively. This difference may be caused by that adult patients were included in their studies. The infants with PHI demonstrate diffuse nephrocalcinosis without urolithiasis, which affects their clinical presentation. Hematuria as symptoms is attributed to renal stone. While, polyurea and polydipsia is attributed to reduced renal concentrating ability in ESRF (22).The present studied the relationship between patterns of presentation and their ages. As shown in table 1 , where we found renal stone, hematuria, and polyurea and polydipsia are present only in older patients (> 1 year). While, metabolic acidosis, FTT, convulsion, vomiting and diarrhea are more common in infants. The present results differ from Cachet study (14), in certain points as shown in table 5. This difference can be due to high percentage (33.3%) of the infant patients present with normal kidney functions (their GFR is stage one) and 8.3% of them presented with CRF versus 50% of patients in Cachet (14) study.

Table 5: The clinical presentation in infants in different study.

Clinical presentation	**Present study**	Cachet study (14)
UTI	58.3%	21%
FTT	16.7 %	22%
Renal failure	8.3%	14%

The classic presentation of PH is characterized by recurrent nephrolithiasis more than nephrocalcinosis and the infantile presentation, which is characterized by nephrocalcinosis without calculi (22). Ultrasound shows renal stone exists in patients older than 1year only. Besides, nephrocalcinosis and hyper-echogenicity found in both groups, but nephrocalcinosis is more common in infants (Table 4). We found, 8.3% of our patients their GFR were stage 5. In German study (17) in which 11% of patients presented with renal failure, which agrees with our results. And disagree with Saudi (16), Dutch (18), American (20), Japanese (19), and Tunisian (15) studies where they found 25%, 23%, 42%, 43% and 86% of their patients presented with chronic renal failure , respectively. The present results revealed low percentage of patients with renal failure. Combined liver kidney transplantation (CLKT) is treatment of choice for PHI, it is expensive and it needs highly specialized center. In this study, all patients (97.2%) received supportive treatment and only one patient (2.8%) underwent CLKT. Whereas in Tunisian study (15) no patient underwent CLKT. And, other studies revealed that more percentage of patients under went CLKT. As, Saudi (16), French (7), American (20), and German (17) studies in which 36%, 37%, 50%, and 63%, of their patients receive CLKT, respectively. We highlighted on the time of development of CRF in our patients, and found 8.3% of them presented with renal failure. In addition, 11.1% of them developed renal failure during fallow up. In addition, the mean interval from presentation to developing CRF is 7years with range (2-12 years) and were on supportive treatment. This result agrees with Saudi (16) study, in which the mean interval from diagnosis until develops CRF is 6 ± 1.5 years. Thus, more efforts are needed for earlier transplantation. Curative treatment of these patients must be applied early to prevent further loss of renal function. In conclusion, primary hyperoxaluria is not uncommon metabolic disease in western part of Libya, it is underestimated cause of renal failure in our society where consanguinity is still common and the renal medical problems are increasing.

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