Primary hyperoxaluria type 1 in Tunisian children

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Hyperoxalurie primaire de type 1 chez l'enfant Tunisien

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RÉSUMÉ

Prérequis : L'hyperoxalurie primaire de type 1 est une maladie métabolique rare, de transmission autosomique récessive. Elle est liée à un déficit en alanine glyoxylate amino-transférase et caractérisée par l'accumulation de l'oxalate de calcium dans les différents tissus particulièrement le parenchyme rénal et le tissu osseux. C'est une étiologie importante de l'insuffisance rénale terminale en Tunisie.

Buts : Etudier les caractéristiques épidémiologiques, cliniques, biologiques et radiologiques de cette affection chez l'enfant Tunisien et établir une corrélation entre ces différents aspects et l'évolution vers l'insuffisance rénale terminale.

Méthodes : Nous avons mené une étude rétrospective à propos de 44 enfants, suivis et traités pour hyperoxalurie primaire de type 1 durant une période de 15 ans allant de 1995 à 2009. Le diagnostic a été établi par le dosage de l'oxaliurie des 24 heures ou le rapport urinaire oxalate/créatinine, quand la fonction rénale est conservée. Chez les enfants en insuffisance rénale avancée, le diagnostic a été établi soit par l'étude de la biopsie rénale soit par l'analyse spectrophotométrique des calculs rénaux.

Résultats : Les patients se répartissent en 20 filles et 24 garçons. L'âge moyen est de 5, 75 ans. Environ 43% des enfants sont âgés de moins de 5 ans. Les circonstances de découverte sont dominées par l'insuffisance rénale chronique. Quatre patients étaient asymptomatiques, dépistés par l'enquête familiale. La néphrocalcinose était présente chez tous les patients. Elle était corticale dans 34% des cas, médullaire dans 32% et globale dans 34%. Au moment du diagnostic, douze enfants étaient au stade terminal de l'insuffisance rénale chronique. Le taux de réponse à la vitamine B6 était de 27%.

Conclusion : L'hyperoxalurie primaire de type 1 est caractérisée, dans la majorité des cas, par une néphrocalcinose, des néphrolithiases et une évolution plus ou moins rapide vers l'insuffisance rénale chronique. La réponse à la vitamine B6 est associée à un meilleur pronostic

Mots-clés

Enfant; hyperoxalurie, néphrocalcinose, pyridoxine, insuffisance rénale terminale

SUMMARY

Background: Primary hyperoxaliuria type 1 is an autosomal-recessive disorder characterized by increasing urinary excretion of calcium oxalate, recurrent urolithiasis, nephrocalcinosis, and accumulation of insoluble oxalate throughout the body. This inborn error of metabolism appears to be a common cause of end stage renal disease in Tunisia.

Aims: To review the clinical, biological and radiological futures of primary hyperoxaluria type 1 and to correlate these aspects with the development of end-stage renal disease.

Methods: we retrospectively reviewed 44 children with Primary hyperoxaliuria type I who were treated in our department during a period of 15 years between 1995 and 2009. The diagnosis was established by quantitative urinary oxalate excretion. In patient with renal impairment, the diagnosis was made by infrared spectroscopy of stone or by renal biopsy.

Results: Male to female ratio was 1.2. The median age at diagnosis was 5.75 years. About 43 % of those were diagnosed before the age of 5 years. Initial symptoms were dominated by uraemia. Four patients were asymptomatic and diagnosed by sibling screening of known patients. Nephrocalcinosis was present in all patients. It is cortical in 34%, medullary in 32% and global in 34%. At diagnosis, twelve children were in end-stage renal disease (27%). Pyridoxine response, which is defined by a reduction in urine oxalate excretion of 60% or more, was found in 27%.

Conclusion: In the majority of patients, the clinical expression of Primary hyperoxaliuria type 1 is characterized by nephrocalcinosis, urolithiasis and renal failure. Pyridoxine sensitivity is associated with better outcome.

Key-words

Child; hyperoxaluria, nephrocalcinosis, pyridoxine responsiveness, end-stage renal disease

Primary hyperoxaluria type 1(PH1) is a rare autosomal-recessive inherited disorder caused by mutations in the alanine: glyoxylate aminotransferase (AGT) gene which is an important enzyme in the detoxification of glyoxylate [1]. The insufficient AGT activity in peroxisomes leads to increased conversion of glyoxylate to oxalate, a toxic compound normally cleared by the kidney [2]. The excess oxalate combines with calcium to form an insoluble calcium oxalate. Kidney which is the sole route of excretion of calcium oxalate is the primary target organ of the disease process. So, the deposition of this substance in the kidney parenchyma and urinary tract results in renal failure, which in turn leads to accumulation of oxalate of soft tissues and bone [3, 4].

In Tunisia, PH1 appears to be a common cause of nephrocalcinosis and may be an important cause of end stage renal disease in our population [5,6]. We report in this study, our experience of 44 patients with PHI over the past 15 years to emphasize the role of early diagnosis, aggressive medical management, pyridoxine therapy and organ transplantation in the prevention and treatment of affected patients.

The aims of this study was to review the clinical, biological and radiological futures of primary hyperoxaluria type 1 and to correlate these aspects with the development of end-stage renal disease.

METHODS

A retrospective review of patients with PH1 identified 44 children who were assessed by our department between 1995 and 2009. An information sheet has been prepared containing the following data: clinical presentation (family history, consanguinity, initial symptoms, presence of nephrocalcinosis and/or urolithiasis), initial diagnostic procedure, treatment and outcome. Estimated glomerular filtration rate (GFR) was calculated using the previously validated Schwartz formula [7]. The classification of the stage of chronic kidney disease is as follows:

Stage 1: mild reduction in GFR (70-80 ml/min/1,73m^2)
Stage 2: moderate reduction in GFR (30-70 ml/min/1,73m^2)
Stage 3: severe reduction in GFR (15-30 ml/min/1,73m^2)
Stage 4: advanced kidney failure (10-15 ml/min/1,73m^2)
Stage 5: kidney failure (GFR< 10ml/min/1,73 m^2).

In the presence of a normal GFR the diagnosis of PH1 was made by either measuring urinary oxalate excretion in 24-hour urine collections, or by spot urine oxalate/creatinine. Normal reference values were summarized in table 1.

Table 1 : Normal reference values

Hyperoxaluria (urine oxalate>0.5 mmol/1.73 m2 per 24 hours) and	**Spot oxalate:** Creatinine ratio (mmol/mmol) 0.2 at birth 0.14 at 5 years of age 0.085 at 10 years of age 0.06 at 15 years of age
Hyperglycoluria (urine glycolate>0.5 mmol/1.73 m2 per 24 hours)	

Urine oxalate was determined by a kit method quantitative enzymatic assay of oxalate by oxalate oxidase. Urine glycolate was detected qualitatively by gas chromatography.

In the presence of chronic renal failure, the diagnosis was established either by infrared spectroscopy of stone or by renal biopsy or when clinico-radiological presentation was typical.

All patients were evaluated by renal ultrasound for diagnosis of nephrocalcinosis and / or nephrolithiasis. Nephrocalcinosis has been classified according to the Dick's method [8].

Medical management consisted of pyridoxine 10 to 20 mg/kg/day in two divided doses in all patients. Testing of the clinical vitamin B6 response was evaluated by measuring urine oxalate excretion before and 3 months after treatment in patient with GFR more than 50ml/min/1.73 m^2. This test was unreliable in patients with moderate to advanced renal insufficiency. A response was considered as favourable when the excretion rate decreased by two thirds compared to the initial rate.

Patients with normal GFR were instructed to receive a high fluid intake. Magnesium sulphate was administered in patients with GFR more than 50 ml/min/1.73 m^2.

Statistical analysis

Four different parameters in relation to outcome were investigated: age, nephrocalcinosis at diagnosis, GFR at diagnosis, level of urinary oxalate, and pyridoxine responsiveness. The statistical analysis was made using the Stat View software 5.0. Categorical variables were compared using the unpaired student's T-test. Nominal variables were compared using chi square. The level of statistical significance was at 5%.

RESULTS

Forty-four children were recruited into the study. Twenty-four of children (54.5%) were boys and twenty (45.5%) were girls. Thirty patients belonged to twenty different families. For 40 patients (90%), there was a family history of consanguinity. The most cases occur in central and southern Tunisia. The median age at diagnosis was 5.75 years (range 3 months-14years). About 43% of the total of 44 patients has being diagnosed as PH1 before the age of 5 years. It is noteworthy that 8 patients (18%) were older less than 12 months. Initial symptoms and signs were summarized in table 2. Four patients were asymptomatic and diagnosed by sibling screening of known patients with HPI. The sonographic examinations revealed 15 patients (34%) with cortical nephrocalcinosis and 14 patients (32%) with medullary nephrocalcinosis. Nephrocalcinosis in both cortex and medulla (fig. 1) was observed in 15 patients (34%). In 5 patients, ultrasound was not helpful in the diagnosis of nephrocalcinosis and showed an aspect of global cortical hyperechogenicity without urolithiasis. CT scan confirmed the existence of cortical nephrocalcinosis in all these cases (fig. 2). Urolithiasis was already present at diagnosis in one 22 patients (50%). It is associated with cortical nephrocalcinosis in 5 patients, with the medullary nephrocalcinosis in 10 patients and mixed nephrocalcinosis in 7 patients. No statistically significant correlation was found between the presence of nephrolithiasis and topography of nephrocalcinosis.

Table 2 : Initial symptoms (sometimes associated) of PH1

Initial symptoms	Percentage
Uremia	44
Urinary tract infection	26
Abdominal and/or flank pain	20
Passage of stone	15
Gross hematuria	10
Familial screening	9
Accidental discovery	5
Others*	5

*: Anorexia, fever, failure to thrive, polyuria, vomiting

Figure 1 : Kidney Sonography : Global nephrocalcinosis

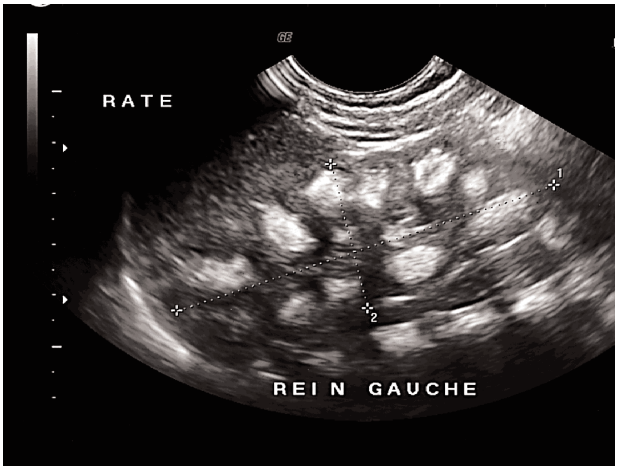
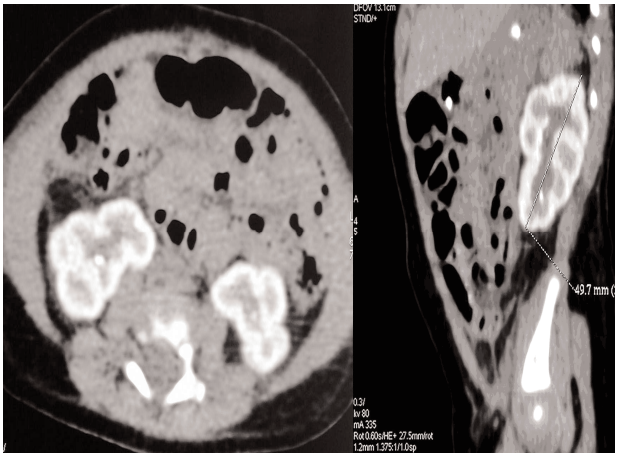


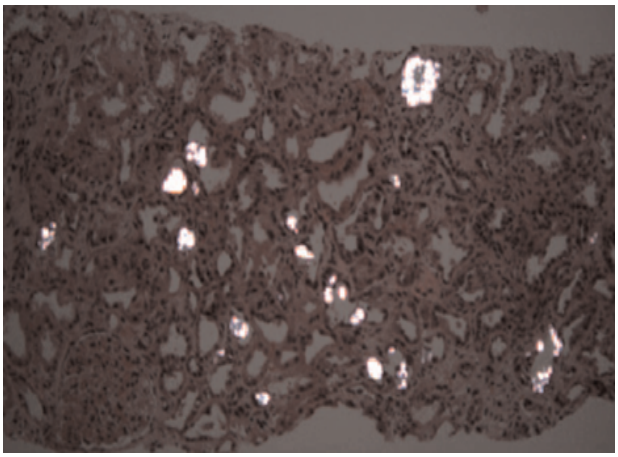
Figure 2 : Unenhanced CT scan showing a spontaneous hyperdensity of cortex



The diagnosis of PHI was made by quantitative urinary oxalate excretion in 19 patients, where the mean excretion rate was 1.13 ± 0.28 mmol/1.73 m2/24 hr. In 3 patients, the diagnosis was made by spot urine oxalate/creatinine mmol ratios, with a frankly pathological ratio.

Glycolic aciduria was present in all 12 patients tested. In 12 patients with ESRD, the diagnosis was established by kidney biopsy in 9 (in one case it was post-mortem) among them (fig.3). In 3 patients, the diagnosis was made through the family history of PH1, clinico-radiological presentation and by infrared spectroscopy of stone.

Figure 3 : Kidney biopsy: view under polarized light: the deposits are strongly birefringent



At diagnosis, twelve children were in ESRD (27%). Nine among them died due to complication of systemic oxalosis. Three patients are currently undergoing haemodialysis. Two ,children in severe reduction in GFR had ESRD after average delay of 13 months. Among three children with moderate renal impairment, two have progressed to ESRD. Twenty-two patients with normal GFR and 5 with had mild chronic renal failure were treated with the medical regimen described have maintained normal or mildly impaired renal function during treatment of up to 5 years in 52% of cases. There is a statistically significant correlation between progression to ESRD and cortical ($p<0.0001$).

Response to pyridoxine was evaluated in 22 patients; only 6 patients were pyridoxine-sensitive (27 %) and have maintained normal renal function.

DISCUSSION

PH1 is caused by a functional deficiency of the liver-specific, peroxisomal, pyridoxal phosphate dependent enzyme alanine: AGT. Numerous mutations and polymorphisms in the gene encoding AGT have been identified, but in only a few cases has the causal relationship between genotype and phenotype actually been demonstrated [9]. The prevalence of the disease has been well documented in developed countries like France and Switzerland, where the prevalence of 2.5 / 106 and 3.9 / 106 was found respectively [2, 10]. In our country, it is difficult to estimate the prevalence. We believe that the observed prevalence rate is still an underestimation of the true prevalence, since the difficulty of achieving systematic family screening and the vague initial symptoms can easily results in a delay of screening for PH1 or no screening at all.

The clinical symptoms of PH1 are the consequences of

excessive urinary excretion of the insoluble calcium oxalate crystals, which lead to nephrolithiasis and/or nephrocalcinosis. Uraemia, gross hematuria and urinary tract infection are the most frequent signs reported in our patients. They are comparable to those described in literature [3]. However, many patients remain asymptomatic for a long time or present with aspecific symptoms such as failure to thrive, anemia or dehydration. These symptoms were often not adequately understood and that therefore the opportunity for timely diagnosis was missed. So, ESRD may occur as the first presenting sign of PHI. In the study of Woerden et al., it was present in 40 % of pediatric patients [10]. In our study, ESRD was present in 27%. Some patients reach end stage renal failure within the first year of life, while others maintain satisfactory kidney function until well into middle age. This variability has not been satisfactorily explained and is only partially influenced by genotype or other factors such as degree of hyperoxaluria [11].

Early diagnosis of PH1 is of vital importance so that treatment can be initiated as soon as possible. The combination of both clinical and sonographic signs is a strong argument for PH1: the association of renal calculi, nephrocalcinosis and renal impairment; in addition, family history may bring additional information. In patient with normal renal function, the diagnosis can be approached by analysis of plasma oxalate, urinary excretion of oxalate and urinary glycolate [12]. In patients with impaired renal function, definitive diagnosis may sometimes require the measurement of AGT activity in liver tissue [13]. This enzymatic study is unavailable in our country; we have made in its place a renal biopsy in 9 patients. This diagnostic procedure has been used elsewhere by several authors in patients with ESRD. The typical appearance is an extensive oxalate crystal deposition viewed under Polaroid filter as we have observed in our patients [14].

The antenatal diagnosis of PH1 is possible. Various strategies have been adopted, including analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling at approximately ten to 12 weeks' gestation [3]. Independent of diagnostic value, mutation analysis may bring information on pyridoxine responsiveness, on complex enzyme phenotype, and, sometimes, on clinical prognosis [15].

The natural out come of the PH1 is ESRD [10,16]. The percentage of this disease as a cause of ESRD varies according to geographic region. In Tunisia, PHI is more common than other countries. It represents the cause of ESRD in 13% of pediatric patients as compared to only 0.3% in Europe [3]. The poor prognosis is mainly related to the marked hyperechogenicity of renal parenchyma which is directly related to the amount of oxalate of calcium deposit. The ESRD is more frequently associated with cortical nephrocalcinosis than with medullary nephrocalcinosis. In our study, the correlation between ESRD and cortical nephrocalcinosis has been well demonstrated ($p<0,001$). Otherwise, urinary lithiasis develops more frequently when medullary nephrocalcinosis is observed. These findings were also approved by the study of Diallo et al. [17].

The radical treatment for PH1 is liver transplantation to replace the functional defect of hepatic AGT. However, doing so requires complete removal of the patient's otherwise normal liver, exposing the patient to the risks of the transplant procedure, as well as the risks of life-long immune suppression [18].

In 30-50% of PH1 patients, reduction in urine oxalate excretion can be achieved by treatment with pharmacologic doses of pyridoxine, suggesting enhancement of AGT enzyme activity [19]. In our patients, the response to pyridoxine is low around 25%. This response rate is much lower than that reported in the literature probably because of genetic factors and poor adherence to treatment. Other treatment measures, directed to reduction in crystal and stone formation, include high fluid intake to reduce urine oxalate concentration, and oral medications that inhibit calcium oxalate crystal formation, specifically citrate and phosphate [20]. All of these modalities have been in use for more than 30 years. Though long term outcomes have improved with earlier diagnosis and currently available treatment, renal failure nonetheless still develops in 70% of patients. More effective treatments are urgently needed. Promising new directions using molecular chaperones, oxalate degrading bacteria, and exploitation of oxalate transport physiology are in various stages of investigation [3].

In conclusion, PHI is a heterogeneous disease with high variations of age of first symptom, of progression into renal failure and subsequent systemic oxalosis. Early diagnosis is imperative but is often delayed or overlooked and therefore it appears, as if PH1 is easily underestimated.

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