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A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria

Received: 26 September 2002 / Revised: 2 May 2003 / Accepted: 13 May 2003 / Published online: 15 August 2003
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Abstract Primary hyperoxaluria (PH) is a heterogeneous disease with a variable age of onset and a variable progression into kidney failure. Early diagnosis is mandatory to avoid the damaging effects of systemic calcium oxalate deposition. In 1997, we initiated a nationwide survey of American nephrologists to ascertain epidemiological data and current practices. PH was reported in only 102 patients, with PH I in 79 and PH II in 9; 14 patients were not classified. Most patients were Caucasian (84%). Main symptoms at diagnosis were urolithiasis (54.4%) and nephrocalcinosis (30%). A significant delay of diagnosis was seen in 42% of patients and 30% of patients were diagnosed only at end-stage renal disease (ESRD). Diagnosis was usually based on history and urinary oxalate excretion. Glycolate and L-glyceric acid excretion were rarely determined. To determine the enzyme defect, a liver biopsy was performed in 40%. Even at ESRD, only 56% of patients received an adequate diagnostic work-up. Half of the patients showed 'good' or 'fair' pyridoxine sensitivity. In addition to B₆, most patients received either citrate or orthophosphate. Kidney transplantation (KTx) failed in 19 of 32 transplants (*n*=27 patients) and was due to recurrent oxalosis in 8 transplants. Liver Tx was performed after KTx in 5 patients (1 patient died). Combined liver-kidney Tx in 21 patients (in 9 patients after failure of KTx) achieved good organ function in 13 patients; 7 patients, however, died shortly after transplantation. In conclusion, the time between first symptom and diagnosis of PH must be minimized, and the diagnostic procedures have to be im-

proved. The cases of unclassified hyperoxaluria suggest the possibility of additional type(s) of PH. As isolated KTx failed in 59% of patients, combined liver-kidney Tx seems to be the better choice in place of isolated KTx as the primary transplant procedure.

Keywords Primary hyperoxaluria · Oxalosis · Diagnosis · Treatment · Transplantation

Introduction

The primary hyperoxalurias (PHs) are autosomal recessive, inherited diseases caused by defects in glyoxylate metabolism [1, 2, 3]. Although two forms are distinguished by genetic mutations of two enzymes in the glyoxylate pathway, other types of PH likely exist [4, 5]. PH type I (PH I, MIM 259900) is caused by low, absent, or mislocalized activity of liver-specific peroxisomal alanine:glyoxylate aminotransferase (AGT, *AGXT* gene on chromosome 2q37.3), which leads to elevated urinary excretion of both oxalate and glycolate [1]. PH type II (PH II, MIM 260000) is due to diminished activity of glyoxylate reductase (GR), an enzyme that also possesses both D-glycerate dehydrogenase and hydroxypyruvate reductase (HPR) activities, leading to elevated urinary excretion of both oxalate and L-glyceric acid (*GR/HPR* gene on chromosome 9p11, [1, 2]). Both primary forms of hyperoxaluria have a highly elevated urinary excretion of oxalate (>0.5 mmol/1.73 m² per day [6, 7, 8]) and concomitantly, a urine supersaturated with respect to calcium oxalate ($\beta_{\text{UCaOx}} >10$ relative units [9]). These urinary abnormalities produce urolithiasis, medullary nephrocalcinosis, or both [6, 8]. Recurrent renal stones and/or progressive medullary nephrocalcinosis lead to progressive kidney damage and declining glomerular filtration, and thereby produce an elevation above normal in plasma oxalate concentration and plasma calcium oxalate saturation (β_{PCaOx}) [10, 11]. The resultant supersaturation in β_{PCaOx} leads to crystal deposition in the parenchyma of most solid organs, as well as

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in bones, joints, and in the retina, defining the entity of systemic oxalosis [8, 10].

Although PH is a monogenic disease, its clinical expression and severity are only partly correlated with the degree of enzyme deficiency [6, 7, 8]. Better described in PH I than in PH II is a wide clinical, biochemical, and genetic heterogeneity, with some patients presenting in the first years of life with kidney failure due to nephrocalcinosis and others who only have occasional passage of stones in adult life with preserved kidney function [6, 7, 8]. Even siblings with the same disease genotype may manifest a completely different phenotype, which best expresses the large heterogeneity of the disease [12].

Given the clinical heterogeneity of the PHs, we sought to determine the spectrum of diagnostics and treatment practices, and provide a snapshot of patient outcomes by establishing a database of such patients in the United States.

Materials and methods

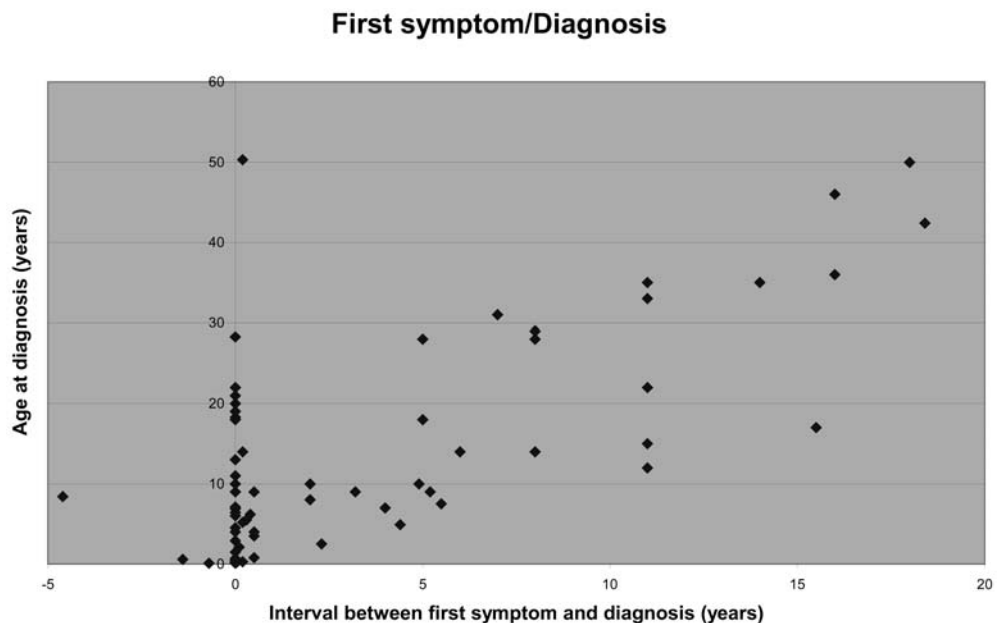
In 1997, we initiated a nationwide mail and internet-based survey of United States-based adult and pediatric nephrologists to ascertain epidemiological data and current practices in diagnosis, treatment, and follow-up of patients with primary and unclassified hyperoxalurias. An unclassified hyperoxaluria was defined as non-PH I or II, but having another primary form of hyperoxaluria with urinary excretion of oxalate being consistently $>1.0 \text{ mmol}/1.73\text{m}^2$ per 24 h [4, 5]. Therefore, secondary forms of hyperoxaluria (enteric, dietary, absorptive) were excluded a priori in such unclassified hyperoxaluric patients [8]. All (~5,500) members of the American Society of Nephrology (ASN) and the American Society for Pediatric Nephrology (ASPN) received the survey by mail to the address identified in these societies' databases. In addition, the survey was available on the web-site of the Oxalosis and Hyperoxaluria Foundation (OHF, www.ohf.org). After an introductory question to ascertain whether the physician ever saw a patient with or without suspected PH, the following questions were included:

1. General information and clinical presentation: age, gender, and ethnicity of the patient; family history; prenatal diagnosis; time of first symptom; time of diagnosis; suspected diagnosis (PH I or PH II, unclassified); symptoms leading to diagnosis (recurrent urolithiasis, nephrocalcinosis, hematuria, end-stage renal failure (ESRD), systemic oxalosis); current symptoms.
2. Diagnostic procedure at the time of diagnosis: urinary biochemical measurement (oxalate, glycolate, L-glyceric acid); plasma oxalate; liver biopsy (AGT activity, AGT immunoreactivity, AGT localization); molecular genetic analysis of *AGXT*.
3. Current therapy: daily fluid intake; vitamin B₆ (pyridoxine), B₆ dosage, sensitivity (good, fair, none); citrate (dosage); orthophosphate (dosage); magnesium (dosage); additional medications.
4. ESRD/transplantation: age at ESRD; start of dialysis; type of dialysis; kidney (KTx), liver-, liver-kidney transplantation; outcome; recurrence of disease.
5. Current patient status: patient alive; urinary biochemical levels of oxalate; serum creatinine; glomerular filtration rate; kidney ultrasound appearance; allograft function (kidney, liver, liver-kidney); signs of systemic oxalosis.
6. Validation of diagnosis: was a liver biopsy performed, were molecular studies performed?

Results

The first evaluation period began in April 1997 and stopped in December 1998. During that period, 202 physicians (3.67%) returned the survey by mail or facsimile, with most ($n=113$) indicating that they had not seen a patient with known or suspected PH. Since the initial mailings, and as the survey is still available on the Internet, we received 30 additional survey forms. In all, PH I was diagnosed in 79 patients (11 dead), PH II in 9 patients, and unclassified hyperoxaluria was found in 14 patients (1 dead). Thirty-eight patients were diagnosed after 1990, 21 patients between 1980 and 1990, 16 patients from 1970 to 1980, and 27 patients were diagnosed before 1970. The group of patients included 3 infants, 48 children, and 51 adults, with a slight preponderance of fe-

Fig. 1 Interval between age at first symptom and age at diagnosis



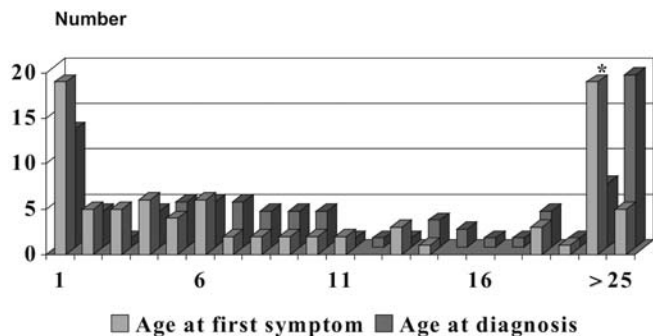


Fig. 2 Relationship between age at first symptom and established diagnosis. Two peaks appear during childhood: one in infancy and the other at age 3–7 years. *Patients aged 20–25 years and >25 years of age are shown as one bar. The numbers in these age groups were equally distributed over all ages until age 94 years

males (55 female, 47 male patients). Most patients were of Caucasian ethnicity ($n=87$), followed by Arabic (6), Hispanic (3); 6 were of African-American ethnicity. Nine physicians took care of more than 1 patient with PH.

In 42% of the patients who are alive, the diagnosis of a PH was made at 3.4 ± 5.4 years after the first symptoms occurred (Fig. 1). In 30% of the patients (27) in the survey the diagnosis of a PH was not made until ESRD, 25 of them with PH I as their diagnosis. Diagnostic procedures utilized by the 9 physicians who took care of more than 1 patient were greater than those of the other physicians.

Two peaks for both the onset of symptoms and established diagnosis were obvious during childhood, with one during infancy and one at age 3–7 years (Fig. 2).

Urolithiasis and nephrocalcinosis were most often stated as the reason for a diagnostic evaluation leading to a diagnosis of hyperoxaluria (Table 1). Twelve patients (3 infants) were found to have signs of systemic oxalosis at the time of diagnosis. All patients with systemic oxalosis had PH type I.

The diagnostic approach in the patients differed with respect to observed kidney function (normal, chronic kidney insufficiency versus ESRD, Table 2). Measurement of urinary oxalate excretion was not performed in 10% of the non-ESRD patients. Measurement of urinary glycolate and L-glyceric acid excretion, necessary to distinguish PH I from PH II in non-ESRD patients, was performed in a small minority of patients (Table 2). Liver biopsies, performed for measurement of AGT enzymatic activity, were obtained in 36 patients (25 children) with suspected PH I (40%). When liver biopsy was performed, it revealed PH I in all cases, with either a low or absent AGT activity, and/or peroxisomal to mitochondrial AGT mistargeting [5]. In 5 of those patients examined by liver biopsy the G₆₃₀A mutation in AGXT, the most common mutation worldwide, was found [5, 6]. In 7 of 27 patients diagnosed at ESRD, the classification of a PH was based on a plasma oxalate determination, since it appears that plasma oxalate is significantly higher in PH patients than non-PH patients with ESRD [10]. Liver biopsy was performed in 13 of the ESRD patients. More than 10% of the patients identified by this survey had no diagnostic test performed, except patient history, for assignment of a diagnosis of a PH (Table 2).

Reported therapy in non-ESRD patients consisted of a generous fluid intake in all patients (more than 3 l of fluid per day was recommended). Additional medical treat-

Table 1 Symptoms at diagnosis (other symptoms include acidosis, recurrent abdominal pain, hematuria), multiple entries were possible, 38 patients had more than one presenting symptom (UTI urinary tract infection, ESRD end-stage renal disease, PH primary hyperoxaluria)

Symptom	All patients ($n=90$)	%	PH I patients ($n=68$)	%	PH II patients ($n=9$)	%	Unclassified ($n=13$)	%
Urolithiasis	49	54.4	40	58.8	5	55.6	4	30.8
Nephrocalcinosis	27	30.0	23	33.8	3	33.3	1	7.7
UTI	1	1.1	1	1.5			1	7.7
ESRD	27	30.0	25	36.8	1	11.1	1	7.7
Systemic oxalosis	12	13.3	12	17.6				
No information	5	5.6	5	7.4				
Other symptoms	4	4.4					4	30.8
Asymptomatic/screening	11	12.2	6	8.8	3	33.3	2	15.4

Table 2 Diagnostic procedures

Patients/diagnostics	All patients alive ($n=90$)	Normal renal function/ mild insufficiency ($n=63$)	ESRD ($n=27$)
Urinary oxalate	61 (67.7%)	56 (89.7%)	5 (18.5%)
Urinary glycolate	22 (24.4%)	21 (33.3%)	1 (3.7%)
Urinary L-glyceric acid	8 (8.9%)	8 (12.7%)	
Plasma oxalate	19 (21.1%)	11 (17.5%)	8 (29.6%)
Liver biopsy	36 (40%)	23 (36.5%)	13 (48.1%)
Kidney biopsy	3 (3.3%)	3 (4.8%)	
No information	8 (8.9%)	1 (1.6%)	7 (25.9%)

Table 3 Medication and response to pyridoxine therapy

Medication	Response	Number of patients
Pyridoxine	Good	22
	Fair	23
	None	12
No-pyridoxine		28
Orthophosphate		30
Citrate		23
Others/magnesium		13

ment included pyridoxine in 57 of 90 cases (57.8%). The pyridoxine dosage varied from 5 to 30 mg/kg body weight per day. No side effects of B₆ therapy were reported. A 'good' reduction of urinary oxalate excretion was reported in 24% and a 'fair' decrease in urine oxalate excretion was seen in 25.5% of patients with pyridoxine medication (Table 3). Orthophosphate or citrate medications were added in 30 and 23 patients, respectively, in an effort to increase the urinary solubility of calcium oxalate [14, 15]. Six patients received both orthophosphate and citrate medications in addition to pyridoxine therapy. Magnesium supplementation was given in 13 of 90 patients.

Isolated KTx was performed in 27 patients with PH. Five patients received a second KTx after primary allograft failure. A 'good' transplant function at the time of the survey was reported for 8 and a 'fair' function for 5 patients. However, 15 primary and 4 secondary transplants failed or showed 'poor' function. In 8 of the transplants, kidney failure was due to disease recurrence, and 2 patients died after transplantation. Liver transplantation as a source of enzyme replacement therapy was performed in 5 patients after prior KTx, and was successful in 4 patients. One patient, however, died after transplantation due to severe infection. Simultaneous liver/kidney transplantation was performed in 21 patients, including 9 patients who received a combined graft after failure of the first, isolated KTx. Thirteen patients remained with 'good' (8) or 'fair' (5) combined graft function, but there was 1 failed procedure and death in 7 patients after simultaneous liver/kidney transplantation. Death was due to a non-functioning kidney, an intracranial hemorrhage, cardiac failure, or sudden death at home. One patient died because of acute liver rejection with multi-organ failure and septicemia. He also had developed a post-transplant lymphoproliferative disorder.

At the time of the survey, 90 of 102 patients reported to have either a primary or unclassified hyperoxaluria were still alive. Forty-nine patients did not have need for KTx or liver transplantation. Hemodialysis was being performed in 9 patients and 3 patients were on peritoneal dialysis. Nineteen patients were alive with either a liver or a liver/kidney transplant. In another 9 patients kidney transplant function was 'good'. Twelve patients had died, including 10 patients who died after organ transplantation.

Discussion

Only a minority of members of both the ASN and the ASPN participated in this first United States mail and internet-based survey on PHs. This low response rate might be due to the fact that the incidence of the disease classically described as PH I is very low, with 2 cases per million population reported [13, 14]. Alternatively, the small number of responding physicians may be because a diagnosis of PH is difficult to establish, since the disease is clinically heterogeneous [6, 8]. We favor the latter hypothesis, since these data reflect a long delay, often over 1 year, between first symptom and diagnosis. In addition, the reliability of the assignment of patients to the diagnosis of either PH I, II, or to an unclassified hyperoxaluria must be questioned, as the necessary diagnostic studies were only performed in a minority of patients, and were unrelated to the year of diagnosis.

Urolithiasis and nephrocalcinosis were the first manifestations of disease in most patients. Therefore, all patients with kidney stones or nephrocalcinosis should be carefully screened for (primary) hyperoxaluria [8]. However, we were interested to note that urinary oxalate was not determined necessarily in all non-ESRD patients thought by their physicians to have a form of PH. Urinary glycolate and L-glyceric acid, measurements that allow PH I to be distinguished from PH II, were determined only in a minority of patients. Therefore, how were the PHs then characterized? Plasma oxalate, which is elevated above normal even in PH patients with preserved renal function [10], was determined in 29.6% of patients (ESRD). Liver biopsy and subsequent biochemical study provide evidence for the specific enzyme defects, liver-specific peroxisomal AGT in PH I and glyoxylate reductase in PH II [1, 2, 3]. Biopsy was performed in only 40% of all patients and in only 13 of 27 patients at ESRD. Currently, there is no United States center for such analyses of liver biopsy specimens, although there is one North American site and several in Europe. Therefore, for a significant number of the patients reported as having PH, it remains unclear how the disease was characterized.

It is of concern that liver transplantation can be considered without prior enzyme analysis, since only PH I can be cured with successful enzyme replacement therapy afforded by the liver allograft [4, 5]. Not all patients identified in the survey undergoing the procedure had a prior liver biopsy.

Medical therapy for the PHs remains uncertain. It appears that all physicians recommended a generous fluid intake for non-ESRD patients. Thereafter, pyridoxine was used frequently despite data to support a reduction in endogenous oxalate production in but a minority [8, 16]. Medication to increase the urinary solubility of calcium oxalate was also administered (citrate, orthophosphate). Whether such medication does lead to a change in clinical stone formation, or in cessation of progression of nephrocalcinosis, cannot be answered on the basis of our data. However, a response to these medications

might yield evidence for decisions about the optimal organ transplant procedure. For example, it is counter-intuitive to recommend isolated KTx in a patient whose endogenous oxalate production is not reduced with pyridoxine therapy [17]. In addition, preemptive liver transplantation in PH I might only be advisable if kidney function is preserved adequately by early and proper medication. Kidney preservation, even in pyridoxine-unresponsive patients, was shown previously with the use of either orthophosphate or citrate medications [9, 18]. If a patient does not respond to any therapeutic regimen, early combined liver/kidney transplantation might be considered rather than an isolated KTx. Early transplantation is advisable, as no form of renal replacement therapy (dialysis) is capable of removing sufficient amounts of oxalate [11, 19].

Despite this algorithmic response to organ replacement therapy, 27 patients with PH I received 32 kidney transplants, with 19 transplant failures, including 8 recurrences of disease and 2 deaths due to sepsis following transplantation, each in combination with severe systemic oxalosis. Combined liver/kidney transplantation will cure the enzyme defect definitively in PH I, and is best expressed by the fact that transplant failure in liver/kidney transplantation was not due to disease recurrence in such patients. However, it was discouraging that 7 patients died after combined transplantation. This has been noted previously in the United States [17]. The European experience gave evidence that the success of such combined transplantation depends on when it is performed [20]. If severe systemic oxalosis was present, or time on dialysis was long (>2 years), liver/kidney transplant outcome was poor when compared with patients who received their transplants earlier in the disease course [20]. Our data may suggest lack of familiarity with the disease, but this remains untested by the survey. Preemptive liver transplantation was recently suggested as a method of choice in patients with preserved renal function [15]. But, when should transplantation be performed in such a heterogeneous disease, especially because an otherwise healthy liver is removed? Hence, it remains an unanswered question, both medically and ethically, as to whether and when to perform such a preemptive procedure [21].

For the PHs the time between first symptom and diagnosis has to be minimized to optimize patient outcome. This is especially the case in patients with PH I, as they tend to have the more severe and progressive form of hyperoxaluria, expressed by the numbers of patients only diagnosed in ESRD or having systemic oxalosis (Table 1, [8]). Diagnostic procedures should include not only the determination of urinary oxalate, but also the measurement of urinary glycolate and L-glyceric acid excretion to distinguish PH I from PH II. The patients with unclassified hyperoxaluria are likely underestimated, as recently suggested by others [4, 5]. However, specific diagnostic measures like a [$^{13}\text{C}_2$] oxalate absorption test and stool examinations to detect the absence of oxalate-degrading bacteria (e.g., *Oxalobacter formigenes*) might

need to be performed to rule out secondary reasons for hyperoxaluria in these patients [22, 23]. Before organ transplantation is considered, a liver biopsy should be performed to determine the diagnosis of PH type I or II. This was not performed in 6 patients receiving a liver or combined liver/kidney transplantation in this survey [24]. Until new therapeutic options arise, KTx might be an option in PH I patients who are B_6 responsive. Preemptive liver transplantation is a debatable option, but liver/kidney transplantation after a minimum period of renal replacement therapy is likely the best therapeutic choice.

We encourage our readers to participate in the survey now, since it remains available at www.ohf.org. Only when the entire spectrum of clinical and molecular heterogeneity is established will a true understanding of that disease be possible.

Acknowledgements We thank all participating physicians for providing data on patients with PH. We also thank the Oxalosis and Hyperoxaluria Foundation for the financial support to initiate the survey.

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