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EDUCATIONAL REVIEW

Primary hyperoxaluria type 1: practical and ethical issues

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Abstract Primary hyperoxaluria type 1 (PH1) is a rare inborn error of glyoxylate metabolism of autosomal recessive inheritance, leading to progressive systemic oxalate storage (named 'oxalosis') with a high rate of morbidity and mortality, as well as an unacceptable quality of life for most patients. The adverse outcome, however, is partly due to issues that can be overcome. First, the diagnosis of PH is often delayed due to a general lack of knowledge of the disease among physicians. This accounts specifically for patients with pyridoxine sensitive PH, a group that is paradoxically most easy to treat. Second, lack of adherence to a strict conduction of conservative treatment and optimal urological management may enhance an adverse outcome of the disease. Third, specific techniques to establish PH1 and specific therapies are currently often not available in several low-resources countries with a high prevalence of PH. The management of patients with advanced disease is extremely difficult and warrants a tailor-made approach in most cases. Comprehensive programs for education of local physicians, installation of national centers of expertise, European support of low-resources countries for the management of PH patients and intensified international collaboration on the management of current patients, as well as on conduction of clinical studies, may further improve outcome of PH.

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Introduction

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disease of glyoxylate metabolism due to a defect of the specific liver peroxisomal enzyme alanine glyoxylate aminotransferase (AGT), leading to hyperoxaluria, progressive renal involvement, and subsequent systemic deposition of calcium oxalate [1].

At this stage, called oxalosis, organ involvement affects bone, joints, retina, skin, soft tissues, heart, vessels, and peripheral and central nervous system. This is associated with high morbidity, pain, disability, unacceptable quality of life, and if treated late or untreated, early death. In addition, physicians often delay the diagnosis (based on clinical and sonographic findings, urine oxalate assessment, and DNA analysis) due to insufficient knowledge of the disease. Early initiation of an aggressive conservative treatment (including high fluid intake, inhibitor of calcium oxalate crystallization, and pyridoxine in responsive cases) can help to maintain renal function in adherent subjects. In stage 4 and 5 chronic kidney disease (CKD) patients, the best outcomes have been achieved with combined liver-kidney transplantation (Tx) that corrects the enzyme defect and replaces damaged kidneys. This renal/metabolic disease is one of the most challenging for both patients and caregivers since hospital dependence, permanent discomfort, and life-threatening events may occur at any stage. Its management therefore requires specific facilities and financial resources, such that it cannot be universally offered.

PH1 may present at all ages and has an extensively heterogeneous clinical phenotype in terms of severity of disease, even within the same family. Its presentation may vary from infantile nephrocalcinosis and signs of renal

failure to recurrent or occasional stone formation. Yet, even patients with late presentations with occasional stones may develop end-stage renal disease (ESRD). Therefore, all children with a first kidney stone and all adults with recurrent or familial stone disease or nephrocalcinosis should undergo metabolic screening for PH1 [2]. The pathophysiology of PH1 is unique in humans and it is one of the most severe inherited inborn errors of metabolism that can be managed by nephrologists. Early initiation of an aggressive conservative treatment can significantly improve outcome and delay the need for combined liver and kidney Tx. In this paper, we will discuss some of the practical barriers and ethical dilemmas that directly affect the outcome of PH patients.

Delay in diagnosis

Diagnostic delay is one of the major problems in PH. According to several cohort studies, the median time interval between initial symptoms and diagnosis is more than 5 years.

Unfamiliarity with the disease among physicians and diagnostic pitfalls are the most important reasons for missing the diagnosis. Due to its rarity, PH is unknown to most medical students and young practitioners. As a result, specific investigation that is required in any patient with unusual presentation of nephrolithiasis is often not carried out on time. Secondly, establishing PH can be troublesome. Improperly conducted 24-h oxalate assessment can easily lead to undetected hyperoxaluria due to precipitation of oxalate in the urine bowl, and plasma oxalate assessment may be normal or subnormal in patients with preserved glomerular filtration rate (GFR). Ultrasound assessment of diffuse cortical nephrocalcinosis can be mistaken for other parenchymal renal impairment. Patients with a GFR below 60 ml/min per 1.73 m^2 are at risk for systemic oxalosis and should undergo fundoscopy and screening for bone abnormalities by X-ray. The retinal abnormalities are typical, yet unfortunately often not recognized. This is also true for bone abnormalities, which may mimic renal osteodystrophy. Since there is no reliable noninvasive marker of systemic oxalate burden to date, research should be encouraged in this field in order to use systemic storage assessment as a major criteria facing optimal timing for organ transplantation.

The direct consequence of the therapeutic delay is that many patients have unnecessarily developed CKD at the time of diagnosis. In patients who are diagnosed at adult age, over 50 % have developed ESRD and systemic oxalosis at the time of diagnosis [3, 4]. Typically, these patients have a history of recurrent stone disease and are mostly sensitive to B6 therapy and therefore relatively easy to treat. Yet, despite their ‘mild’ biochemical phenotype, they are often only diagnosed at the time of development of ESRD. In around 10 % of patients, the diagnosis is only established after recurrence of the disease in a renal graft (Cases 1 and 2) [5–7].

How should we deal with this problem? It is certainly not realistic to implement an extensive course on such a rare disease as PH in the basic medical training. What should be taught to all medical students is that stone disease in children and recurrent stone disease or nephrocalcinosis in adults always warrants further metabolic screening.

Secondly, more effort should be put into stimulation of clinical studies in PH, in order to provide more evidence for management guidelines and to optimize treatment. Like other very rare diseases, this can only be achieved by a collaborative effort to create an international, comprehensive database that gives more insight in the clinical phenotype and can serve as a basis for interventional studies. To date, due to its rarity, there is little interest for PH among drug fabricants as well as most national health institutes. Yet timely adequate management may prevent the development of a relatively mild disease into a devastating, but also very costly systemic oxalosis.

> Dilemma: Suboptimal care and consequently adverse outcome of patients with PH due a general lack of knowledge about PH among physicians (internists, general practitioners, pediatricians).
> Solution: National programs for easy accessible information on orphan disease and training programs.
> Stakeholders (depending on the local situation): Local government, societies for pediatrics, pediatric nephrology, nephrology, urology.

Inadequate conductance of conservative therapy

Conservative therapy may be very effective as long as it is strictly carried out, even in PH patients with a potentially detrimental mutation. Patients should take in at least three liters of water per 24 h. This hyperhydration should be vigorously assessed, especially in B6 unresponsive patients, which means that abundant fluid intake should become a way of life, including overnight intake [2]. Small infants may need fluid substitution by nasogastric tube or by gastrostomy. In case of diarrhea or vomiting, patients should be easily admitted to the local hospital in order to ensure fluid intake. Gastro-enteritis is a well-recognized moment of risk for exacerbation of the disease towards systemic oxalosis. Citrate has been shown to be effective in keeping calcium oxalate soluble and should be taken at a frequency of at least two times per day.

Unfortunately, these measures are often not correctly carried out (case 3). Hyperhydration is a burden for many

patients, especially small children. Citrate prescription can be troublesome. Blunt potassium citrate is very distasteful and many pharmacists are reluctant to prepare an adjusted, tastier solution for children that may overcome their reluctance to take it. In addition, these drugs may be lacking in many developing countries as health resources are limited.

Detailed and repeated information to patients, parents, family, local physicians, and local pharmacists by the use of repeated interviews, drawings, leaflets, and online explanations is therefore the cornerstone of the management of PH. The knowledge of overall prognosis may help in discussing prenatal diagnosis, which is not universally accepted for personal, cultural, or religious reasons. Indeed, some parents may be reluctant to undergo chorionic villi sampling procedures and pregnancy termination. In addition, prenatal diagnosis and pregnancy termination are often unavailable/illegal in those developing countries where there is a relatively high incidence of PH1. Screening relatives of index cases is better accepted, and must be performed as soon as any case of PH1 has been confirmed.

Local physicians are not always fully aware of the immediate threat for PH patients that a mild dehydration may cause. Therefore, all patients should carry a protocol for measures that have to be taken in case of immediate dehydration.

> Dilemma: Unnecessary development of adverse outcome by non-adherence to conservative measures as a result of inadequate information and education of patients, parents, and local care givers.
> Solution: Comprehensive information programs for patients as well as for local care givers.
> Stakeholders (depending on the local situation): Local government, societies for pediatrics, pediatric nephrology, nephrology, urology.

Sub-optimal urological care

The primary mechanism for CKD from kidney stones is usually attributed to repeated infection/obstruction episodes and to progressive nephrocalcinosis [8]. PH1 patients usually present with a combination of all risk factors, and any kind of parenchymal aggression may lead unabated towards ESRD. Non-endoscopic treatment (i.e., lithotripsy) holds the risk of misinterpretation, which means that shock waves are applied on nephrocalcinosis spots instead of stones, which may alter the renal tissue [9]. There is, however, another reason why lithotripsy should never be applied in PH: like cystine stones in cystinuria, calcium oxalate stones in PH are too abrasive to be approached successfully, so that it is sometimes better to leave in place non-infected, non-obstructed urolithiasis. In case of obstructive stones, different minimally invasive methods like semi-rigid or flexible ureterorenoscopy, percutaneous nephrolithotomy, and laparoscopic approaches are recommended for interventional stone treatment and should be the first option in PH1 patients [2]. However, these procedures require specific resources and training that are not available worldwide. Unfortunately, the diagnosis of PH1 still comes following immediate irreversible ESRD in undiagnosed PH1 patients who have been referred to urologists.

> Dilemma: Inadequate urological conductance in PH1 patients.
> Solution: Training programs. Collaboration with specialized urological teams. Stone analysis.
> Stakeholders: Local societies of urology, pediatric urology, nephrology, and pediatric nephrology.

Management of advanced disease

Following stage 3 CKD, kilograms of oxalate will accumulate throughout the body and mainly in the skeleton. Yet, diagnosis of systemic oxalosis is extremely difficult and oxalate-induced abnormalities can easily be mistaken for CKD-related diseases, such as renal osteodystrophy. Retinal oxalate depositions show a very typical brownish pattern, yet fundoscopy is often not performed. Myocardial and vascular disease are usually only recognized in a very advanced stage of the disease, including sudden death. Bone disease often causes major problems, especially in patients on dialysis, who may develop bone pain, deformities and fractures [10]. The management of these fractures is rather challenging and requires experienced orthopedic surgeons, since bone structure is highly abnormal and remodeling is always impaired. In addition to optimal control of hyperparathyroidism, oxalate bone disease may be prevented by aggressive dialysis strategy, often combining daily hemodialysis and nocturnal automated peritoneal dialysis, aiming at keeping plasma oxalate below 40 μmol/l. However, such dialysis ‘over adequacy’ leads to iatrogenic phosphate depletion that contributes to abnormal bone metabolism and further fractures. Ongoing bone disease in PH may lead to a state of continuous pain, disability, unacceptable quality of life, growing dependence, unemployment, depression, and sometimes suicide (case 4).

Is there a place for dialysis?

Oxalate is a small molecule and easy to clear, but its estimated generation by the liver is 4 to 8 mmol/1.73 m^2 per day and the clearance by conventional hemodialysis

approximates 1 to 2 mmol/1.73 m^2 per day. This means that sufficient oxalate removal can only be obtained by very intensive dialysis strategies consisting of high flux hemodialfiltration of more than 6 h per day or combined regimes of daily hemodialysis and nocturnal peritoneal dialysis. Even the most intensive dialysis regimes will not be able to remove already stored systemic oxalate from the body (case 5). For all these reasons, there are limited indications for dialysis: (1) if the diagnosis of PH1 has not been established, (2) in children with neonatal/infantile onset waiting for organ transplantation, (3) in preparation for kidney transplant, whether before or after liver transplantation, in order to deplete oxalate from the body, (4) following isolated kidney or combined liver-kidney transplantation with any delay in achieving optimal renal function, as a temporary adjunct in the case of high oxalate burden, or with transient loss of transplant function, (5) very exceptionally in older patients if the only alternative is no dialysis, (6) in developing countries, optimal dialysis may be indicated as only a preference to absolute withdrawal of all therapy [11]. In order to avoid any form of dialysis, organ Tx should be considered when CKD stage 3b has been reached.

Which strategy for organ transplantation?

Combined liver-kidney transplantation

In PH1 patients with CKD4 and CKD5, combined liver-kidney Tx seems to be the best option at this moment. Ideally, organ Tx should be planned prior to the onset of ESRD and systemic oxalosis, i.e., at CKD stage 3, in order to guarantee organ replacement therapy at stage 4 [1, 2]. Since the liver is the only organ responsible for glyoxylate detoxification by AGT, the excessive production of oxalate will continue as long as the native liver is left in place. Therefore, PH1 can be cured only when the deficient host liver has been removed, so that partial liver Tx cannot be applied.

In Europe, combined liver-kidney Tx has been the preferred approach over the past 25 years, and kidney graft survival in these patients has reached 82 and 79 % at 1 and 3 years, respectively [12], contrary to the situation in North America [13]. Registry data indicate that if low perioperative mortality can be provided, a combined liver-kidney Tx by far offers the best outcome in PH1 (cases 6 and 7) [2, 14]. Simultaneous liver and kidney Tx seems the most logical strategy for patients with CKD stage 4 and those patients with CKD stage 5 who have only been on dialysis for a very short time, i.e., with a limited systemic oxalate storage. A sequential procedure (first liver Tx, then dialysis until sufficient oxalate has been cleared from the body, followed by kidney Tx) could be an alternative for CKD stage 5 patients, mainly infants, with a long waiting time and subsequent major systemic oxalate storage. To date, due to limited experience, there is no evidence that supports this approach, but there is a strong biochemical rationale [11]. Therefore, even in developed countries, it is recommended to discuss Tx strategy with experts and to collect information in large databases.

Isolated kidney transplantation

We believe that isolated kidney Tx should generally be avoided in PH1 patients. Kidney Tx allows significant removal of soluble plasma oxalate but the biochemical defect is in the liver, so that overproduction of oxalate and subsequent deposition in tissues continues unabated. Isolated kidney Tx has lead to a poor graft survival and patient morbidity as a result of oxalate deposition in the graft: in Europe, the 5-year graft survival is 14 % compared to 85 % in non-PH1 recipients, and to 76 % in PH1 children who received a combined liver-kidney Tx [12]. Proven pyridoxine-responsive patients (usually associated with Gly170Arg and Phe152Ile genotypes) may theoretically benefit from isolated kidney Tx but the clinical evidence for this is still sparse (cases 6, 8, 9, and 10) [15]. Isolated kidney Tx is sometimes provided as a temporary solution in some developing countries before managing the patient in a specialized center for further combined liver-kidney procedure. However, since the chances for success are so extremely low, especially under sub-optimal conditions, we believe that this approach should be discouraged. An exception in this respect could possibly be made for selected adult patients with a pyridoxine-sensitive mutation.

Isolated orthotopic liver transplantation

If only CKD stage 3, but not yet CKD stage 4, is apparent at time of preparation for Tx, isolated orthotopic liver Tx could be considered [13, 16]. Indeed in the Hamburg experience, four pediatric recipients with a GFR between 27 and 98 ml/min per 1.73 m^2 received a preemptive liver transplant, and three of them still have significant residual renal function after a median follow-up of ~12 years [17]. Another group reported good results at 5 years in four PH1 children who received a preemptive liver Tx with a mean pretransplant GFR of 81 ml/min per 1.73 m^2 [18]. However, this strategy raises ethical controversies, especially when the GFR is superior to 40–60 ml/min per 1.73 m^2, since the progression of CKD cannot be anticipated (cases 11, 12, and 13). In addition, PH1 is the only peroxisomal disease without psychomotor delay

due to cerebral involvement, and the conservative management of such patients has significantly improved during the last 10 years [19]; this may influence the indication of preemptive liver Tx in such patients (case 12). Even with good results from case series [17, 20, 21], the risk of death associated with the liver Tx procedure shows that it cannot be regarded as a first-line option, so that the procedure should be postponed in those patients with well-preserved GFR until CKD stage 4 has been reached, leading to preemptive combined liver-kidney Tx.

Dilemma: PH management in patients with advanced CKD warrants a tailor-made approach in specialized centers. Especially patients with an estimated GFR between 30 and 60 ml/min need a personalized strategy. More data are needed to define an evidence-based strategy for all CKD stages.
Solution: Early referral to specialized centers for PH. International collaboration in patient care and international cohort studies in order to improve clinical knowledge of PH.
Stakeholders: National centers of expertise in PH. International societies for pediatric and adult transplantation, databases and registries.

Donor source

The choice of the donor source may rely either on immunological bases (i.e., using the same donor for both organs) or on biochemical rationale (i.e., using a two-step procedure according to oxalate body store) [14]. Indeed, most publications report on the use of one deceased donor, but PH1 patients should benefit from specific priority since patients who have reached ESRD suffer from progressive systemic involvement and subsequent cumulative problems (fractures, pain, disability) along with time duration on dialysis. Due to the small number of patients, priority should be given to PH1 recipients by national and international organ allocation networks. A living-related donor may be considered under certain conditions, such as young patients with aggressive forms of PH1 or patients coming from a developing country with their own donor. An option would be a first-step deceased donor for the liver and a second-step living donor for the kidney (case 14). However, in case of living-related donor, the use of heterozygous subjects may raise questions, as they may have subtle hyperoxaluria that may contraindicate such Tx. On the other hand, in some countries this may raise the possibility of using living-unrelated (sometimes paid) donors who may be exposed to an unacceptable risk in terms of both morbidity and mortality.

Dilemma: Need for deceased donors at short notice
Solution: Adjusted allocation rules with special priority of post-mortem donation for PH1 patients
Stake-holders: National transplantation societies

Inaccessibility to proper diagnostic tools and essential treatment in low-resource countries with high prevalence of PH

PH1 represents around 1 % of children with ESRD in Western Europe and North America, but this may reach more than 10 % in countries where there is a high rate of consanguinity, such as in North Africa and the Middle East. However, many of these countries currently have limited medical resources and patients have no access to adequate conservative measures (including water!) or to adequate organ replacement, so that many patients die [22]. In addition, the establishment of PH requires sophisticated diagnostic tools and, for example in France, the cost of urine oxalate measurement is ~140€ and DNA sequencing ~630€. Therefore, most patients coming from low-resource countries cannot be treated according to current recommendations [2]: diagnostic tends to be late, prenatal diagnosis is not available/accepted, conservative measures (high water intake, pyridoxine, citrate) are not available, so inadequate dialysis is often the only option, and organ Tx is either unavailable or limited to isolated renal Tx with a 100 % risk of recurrence (the cost of combined liver-kidney Tx in France is ~138,000€). Timely diagnosis in patients from those countries must be kept in mind, since conservative treatment is cheap, can be very effective and has no important side effects (case 15) [2, 19].

Infantile PH1 in a low-resource country is the worst imaginable situation. The only option for survival for these patients is combined liver-kidney Tx at the shortest possible notice, something that is most often not accessible. For these patients, treatment withdrawal/withholding seems to be an acceptable option from an ethical point of view (case 5) [23].

Dilemma: Access to the necessary specialized diagnosis and care is limited in low-resource countries that also have the highest prevalence of PH.
Solution: Aid programs from Western countries, development of local diagnostic tools, and access to conservative measures
Stakeholders: International societies for pediatric nephrology and nephrology, European Community, US governmental institutions.

Prospects and next steps

In order to provide an early diagnosis, neonatal screening may be considered but (i) urine oxalate can be excreted in highly variable amounts in neonates, and (ii) national

screening programs are currently limited to blood sample assessment (case 16).

There are exciting basic research projects, including development of chemical chaperones that can stabilize mutant AGT, hepatocyte transplantation using cells either from a normal liver or the patient's own liver cells virally transduced ex vivo to express AGT.

These therapeutic approaches are currently being developed in humanized transgenic KO mice or in transformed mammalian cell lines, but not yet accessible to humans [24, 25].

In the absence of new developments, all patients cannot be managed in reference centers, but any physician is asked to adapt available guidelines to each individual, and to optimize patient care quality by participating with international databases and contacting expert centers.

Independent of improving knowledge on PH1, current research focuses on alternative organ-orientated approaches, a challenge that mainly depends on the remaining population of liver cells still producing oxalate.

Conclusions

Although it has improved over time, the outcomes of PH remain poorer than of other diseases leading to ESRD. Yet, part of the deleterious issues of PH1 is caused by underdetection and sub-optimal management as a result of a general lack of knowledge among physicians.

Programs to improve knowledge of PH1 among pediatricians, nephrologists, and urologists should therefore be top priority, especially in those countries where the incidence of PH1 is high. Such an education of physicians may help shorten the delay between initial symptoms, diagnostic confirmation and starting adequate therapy by specialists. In addition, information to patients will help them understand the pathophysiology of their disease that is the main tool for complete adherence to the treatment.

Resources is the second priority, since the management of PH1 requires specific biological investigations, access to combined organ transplantation, access to combined dialysis procedures and access to research and international collaborations.

Ethical issues are present at all stages of the disease, from preimplantation genetic diagnosis to final treatment withdrawal, but some practical solutions arise from basic and clinical research, experience from databases and cohort studies, medical and patient education, guidelines and recommendations, and media and governments when PH1 stands as a "public health" issue.

Learning points

- Education of physicians for early recognition of nephrolithiasis is mandatory, mainly when it is suggestive of a metabolic cause, i.e., young age at onset, associated nephrocalcinosis, bilateral presentation, stone recurrence, etc.
- Early adequate management of primary hyperoxaluria type 1 is based on aggressive conservative measures in the absence of advance chronic kidney disease that may bring major benefits to prognosis.
- The best treatment options for patients who require organ transplantation should be adapted to local resources, current knowledge of the most recent treatment options, and individual characteristics, including both phenotype and genotype.

Research points

- In order to improve knowledge on the disease and results of treatments, the use of large international databases is required.
- Future developments are aimed at correcting the underlying metabolic defect without exposure to life-long risks associated with organ transplantation, i.e., the use of chaperone molecules, and prospects for cell or gene therapy.
- The management of primary hyperoxaluria type 1 raises a lot of critical issues and is therefore a major example for developing more evidence to be used for solving ethical problems.

Case 1

Diagnosis of CKD of unknown origin in a 17-year-old French female student in 2002. Preemptive kidney Tx at 20 years of age from her 23-year-old brother. Early graft dysfunction and graft loss after 6 months leading to a diagnosis of PH1. Combined liver-kidney transplantation at 22 years of age. Good outcome.

Case 2

Twenty-five-year-old Indian male with ESRD associated with nephrolithiasis. Bilateral nephrectomy, followed by living-related kidney Tx. Progressive worsening of kidney function 2 weeks post Tx. Pathological review of nephrectomy and Tx kidney biopsy: abundant calcium oxalate crystals. Further workup revealed PH1. Later he developed fever, breathlessness, and hemiparesis, and died 10 weeks post Tx. Autopsy revealed multiorgan deposits of oxalate crystals as well as widespread zygomycosis [6].

Case 3

Female newborn infant with consanguineous parents of Tunisian origin. Index brother case with complete enzyme deficiency (AGT activity measurement from a liver biopsy) and I244T homozygous mutation. Aggressive conservative measures from birth. GFR=122 ml/min per 1.73 m^2 at 21 years of age, stone free. Treatment discontinuation due to nonadherence lead to renal colics and progressive CKD with a GFR of 70 ml/min per 1.73 m^2 at 23 years of age.

Case 4

Male Slovak patient with ESRD of unknown origin at 5 years of age. Treatment with peritoneal dialysis followed by early failure of a first kidney Tx from a deceased donor. Four-year period on conventional hemodialysis before isolated kidney re-Tx from the mother. Graft loss 6 months later, leading to a diagnosis of PH1 at 10 years of age. Treatment by conventional hemodialysis for 7 years until severe disability requiring wheelchair assistance. Organization of a charity funding process by the family in order to plan a combined liver-kidney Tx in another country. Combined liver-kidney Tx at 17 years of age: dramatic skeletal and systemic improvement despite early recurrence of oxalate deposits in the renal graft and initial GFR of 60 ml/min per 1.73 m^2. Progressive deterioration of GFR; return to dialysis at 21 years of age. Still on daily hemodialysis with poor general condition, unacceptable quality of life and complete disability.

Case 5

Male Egyptian twins with a diagnosis of PH1 at 6 months of age in the presence of ESRD. Treatment with intensive peritoneal dialysis strategy. Very low family and medical resources. Prompt progression of oxalosis together with malnutrition. Death at 11 and 13 months of age, respectively.

Case 6

French male patient with no medical history until 55 years of age. Late occurrence of stones leading to a diagnosis of PH1, as GFR was 50 ml/min per 1.73 m^2. Progression to ESRD over one year. Isolated kidney Tx from a deceased donor on the basis of a very late onset of the disease and the presence of heterozygous Gly170Arg mutation [15]. Immediate recurrence post-Tx leading to graft loss. Return to short-daily hemodialysis.

Case 7

Thirty-eight-year-old Dutch female (A) with recurrent stone disease. Diagnosis of pyridoxine-responsive PH1 in 1991. Treatment with pyridoxine and hydration: favorable long-term outcome. No contact with other family members, screening refused.

Fifty-year-old sister (B) with nephrocalcinosis and advanced CKD (serum creatinine of 200 μmol/l) in 1998; no work up, no diagnosis; ESRD after 6 months.

A and B had the same homozygous Gly170Arg mutation.

Case 8

Young Pakistani female with a history of multiple stone passages and nephrocalcinosis, on regular hemodialysis from age 10, with further progressive systemic involvement and disabling bone disease. Investigations funded by family at large in another country for diagnosis and treatment. Diagnosis of PH1 at age 13, but no access to combined liver-kidney Tx for financial reasons. Isolated kidney Tx at 14 years of age from a living-unrelated (paid) donor in India. Graft loss to recurrence 6 months later. Return to conventional hemodialysis. Lost to follow-up.

Case 9

Thirty-year-old French male with a late diagnosis of PH1 in 1991. After 4 years on conventional hemodialysis, the patient accepted a combined liver-kidney Tx strategy but refused native liver hepatectomy. A partial heterotopic auxiliary liver Tx combined with a kidney Tx from the same deceased donor was performed. He presented with early recurrence of nephrocalcinosis and lost his renal graft 3 weeks post-Tx. In addition, the liver graft had to be removed due to repeated local bleeding and failure of the Tx procedure. He returned to dialysis and died 3 months later.

Case 10

Forty-year-old Dutch female with a late diagnosis of PH1 in 2007. Combined liver-kidney Tx after 3 years on regular three times per week hemodialysis scheme. Immediate kidney failure due to oxalosis. Successful isolated kidney re-Tx after 2 years on short daily hemodialysis strategy.

Case 11

Four-year-old Rom female with an early diagnosis of PH1 because of a cousin index case. Pre-emptive combined liver-kidney Tx as GFR was 20 ml/min per 1.73 m^2. Immediate kidney graft failure due to arterial graft thrombosis. Normal

liver tests. Ongoing improvement of GFR: 40 ml/min per 1.73 m^2 after 2 years despite nephrocalcinosis.

Case 12 [4]

Four-year-old Tunisian boy with fortuitous diagnosis of PH1. Pre-emptive isolated liver Tx at 5 years of age (GFR 60 ml/min per 1.73 m^2). Transient improvement of both nephrocalcinosis and GFR of the native kidneys. Further progressive decrease of GFR due to pre-existing tubulointerstitial lesions and anti-calcineurin nephrotoxicity. Deceased donor kidney Tx at 20 years of age. Ongoing chronic kidney allograft nephropathy.

Case 13

Canadian girl, 2 years of age at the time of diagnosis of PH1. Perfect education and adherence to conservative measures. GFR of 30 ml/min per 1.73 m^2 at 10 years of age: discussion of pre-emptive combined liver-kidney Tx. Unexpected stable GFR at 17 years of age despite repeated stone passages. Waiting for further significant GFR deterioration.

Case 14 [21]

Diagnosis of PH1 as causing ESRD in a 3-year-old Belgian female. First step liver Tx from a deceased donor followed 4 months later by a kidney Tx from a living-related donor, after normalization of plasma oxalate concentration and improvement of urine oxalate excretion. Excellent short-term result with normal GFR and maintained plasma and urine oxalate concentrations.

Case 15

A 3-month-old Dutch boy died of infantile oxalosis. Two younger sisters screened at birth: both have the same mutation and B6-responsive hyperoxaluria of whom one still has an optimal renal function after 32 years and another an eGFR of 50 ml/min per 1.73 m^2 after 26 years due to vigorous overnight hydration and citrate from birth.

Case 16

Four-month-old Dutch child (C), presenting with ESRD due to PH1. Severe course, nearly blind, 25 fractures. One liver Tx and two kidney Tx.

Four-year-old brother (D) with hematuria and nephrocalcinosis at 6 months of age, diagnosis missed. Severe nephrocalcinosis at 4 years of age, both children same mutation. Excellent result of conservative measures in D: disappearance of nephrocalcinosis at 18 years of age, normal renal function.

Would renal function have been preserved in patient C if a diagnosis had been established earlier in D or if diagnosis in both was established by perinatal screening?

Multiple-choice questions (answers are provided following the reference list)

1. Primary hyperoxaluria may lead to severe systemic involvement but it is the only peroxisomal disease without:
   a. Neurodevelopmental delay
   b. Bone disease
   c. Ocular involvement
   d. Cardiovascular involvement
   e. Dermatological involvement

2. Treatment withdrawal can be acceptable
   a. In a 30-year-old European female who experienced kidney graft failure to recurrence prior to diagnosing PH1, with 100 % anti-HLA sensitization and a long history on dialysis complicated by fractures
   b. In a 3-month-old male infant with severe infantile PH1 requiring immediate dialysis and living in sub-Saharan Africa
   c. In a European male neonate with an older sister who died from complications of proven PH1 at 8 years of age, presenting at 2 weeks of age with significant hyperoxaluria and normal serum creatinine
   d. In a 50-year-old male with proven PH1 and first symptoms at 20 years of age, having experienced two failing isolated kidney transplantations, refusing liver transplantation
   e. In a 4-year-old girl living in Central America with proven PH1, starting PD at 2 years of age and suffering from multiple bone fractures, with a possibility of combined transplantation abroad from a living-related donor

3. A diagnosis of PH1 must be investigated in the presence of:
   a. Repeated spontaneous abortion in the mother
   b. Low-citrate urolithiasis in adults
   c. History of nephrolithiasis and impaired GFR
   d. Dihydrated calcium oxalate crystals in the urine
   e. Corneal crystal deposits at slit-lamp examination

4. Conventional hemodialysis (i.e., 3×4 to 5 h per week) is indicated
   a. In PH1 children waiting for a combined liver-kidney transplantation
   b. During the first weeks following any transplantation procedure in PH1 patients

c. In order to clear oxalate in selected PH1 patients with a normal GFR
d. In PH1 patients when peritoneal dialysis is not available
e. If the diagnosis of PH1 has not yet been established

5. The first option for organ transplantation in adult pyridoxine nonresponsive PH1 patients with CKD stage 5 in Europe usually relies on

a. Combined liver-kidney transplantation
b. Isolated kidney transplantation with intensive pyridoxine treatment post-transplantation
c. Partial auxiliary liver transplantation combined with kidney transplantation
d. Isolated liver transplantation
e. Combined hemodialysis and peritoneal dialysis for 1–2 years prior to transplantation

References

1. Harambat J, Fargue S, Bacchetta J, Acquaviva C, Cochat P (2011) Primary hyperoxaluria. Int J Nephrol. doi:10.4061/2011/864580
2. Cochat P, Hulton SA, Acquaviva C, Danpure CJ, Daudon M, De Marchi M, Fargue S, Groothoff JW, Harambat J, Hoppe B, Jamieson N, Kemper MJ, Mandrile G, Marangella M, Picca S, Rumsby G, Salido E, Straub M, van Woerden CS, on behalf of OxalEurope (2012) Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant 27:1729–1736
3. van der Hoeven SM, van Woerden CS, Groothoff JW (2012) Primary hyperoxaluria Type 1, a too often missed diagnosis and potentially treatable cause of end-stage renal disease in adults: results of the Dutch cohort. Nephrol Dial Transplant 27:3855–3862
4. van Woerden CS, Groothoff JW, Wijburg SA, Waterham HR, Wanders RJ, Janssen MJ, Duran M (2007) Primary hyperoxaluria remains undiagnosed in patients with hyperoxaluria and recurrent urolithiasis. Clin Chem 53:1553–1555
5. Harambat J, Fargue S, Acquaviva C, Gagnadoux MF, Janssen F, Liutkus A, Mourani C, Macher MA, Abramowicz D, Legendre C, Durrbach A, Tsimaratos M, Nivet H, Girardin E, Schott AM, Rolland MO, Cochat P (2010) Genotype-phenotype correlations in primary hyperoxaluria type 1: the p.Gly170Arg *AGXT* mutation is associated with better outcome. Kidney Int 77:443–449
6. Madiwale C, Murlidharan P, Hase NK (2008) Recurrence of primary hyperoxaluria: an avoidable catastrophe following kidney transplant. J Postgrad Med 54:206–208
7. Spasovski G, Beck BB, Blau N, Hoppe B, Tasic V (2010) Late diagnosis of primary hyperoxaluria after failed kidney transplantation. Int Urol Nephrol 42:825–829
8. Rule AD, Krambeck AE, Lieske JC (2011) Chronic kidney disease in kidney stone formers. Clin J Am Soc Nephrol 6:2069–2075
9. Gambaro G, Favaro S, D'Angelo A (2001) Risk of renal failure in nephrolithiasis. Am J Kidney Dis 37:233–243
10. Day DL, Scheinman JI, Mahan J (1986) Radiological aspects of primary hyperoxaluria. AJR Am J Roentgenol 146:395–401
11. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO (2006) Primary hyperoxaluria type 1: still challenging! Pediatr Nephrol 21:1075–1081
12. Harambat J, van Stralen K, Espinosa L, Groothoff JW, Hulton SA, Cerkauskiene R, Schaefer F, Verrina E, Jager KJ, Cochat P, on behalf of the European Society for Padiatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry (2012) Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. Clin Am J Soc Nephrol 7:458–465
13. Jamieson NV, Jamieson KA (2009) Primary hyperoxaluria type 1: Gene therapy by k-liver transplantation. Transplantation 87:1273–1274
14. Darwish AA, McKiernan P, Chardot C (2011) Pediatric liver transplantation for metabolic disorders: Part 1: Liver-based metabolic disorders without liver lesions. Clin Res Hepatol Gastroenterol 35:194–203
15. van Woerden CS, Groothoff JW, Wijburg FA, Annink C, Wander RJ, Waterham HR (2004) Clinical implications of mutation analysis in primary hyperoxaluria type 1. Kidney Int 66:746–752
16. Cochat P, Faure JL, Divry P, Danpure CJ, Descos B, Wright C, Takvorian P, Floret D (1989) Liver transplantation in primary hyperoxaluria type 1. Lancet 1:1142–1143
17. Brinkert F, Ganschow R, Helmke K, Harps E, Fischer L, Nashan B, Hoppe B, Kulke S, Müller-Wiefel DE, Kemper MJ (2009) Transplantation procedures in children with primary hyperoxaluria type 1: outcome and longitudinal growth. Transplantation 87:1415–1421
18. Perera MTPR, Sharif K, Lloyd C, Foster K, Hulton SA, Mirza DF, McKiernan PJ (2011) Pre-emptive liver transplantation for primary hyperoxaluria arrests long-term renal function deterioration. Nephrol Dial Transplant 26:354–359
19. Fargue S, Harambat J, Gagnadoux MF, Tsimaratos M, Janssen F, Llanas B, Berthélémé JP, Boudaillez B, Champion G, Guyot C, Macher MA, Nivet H, Ranchin B, Salomon R, Taque S, Rolland MO, Cochat P (2009) Effect of conservative treatment on the renal outcome of children with primary hyperoxaluria type 1. Kidney Int 76:767–773
20. Herden U, Kemper M, Ganschow R, Klaassen I, Grabhorn E, Brinkert F, Nashan B, Fischer L (2011) Surgical aspects and outcome of combine liver and kidney transplantation. Transpl Int 24:805–811
21. Malla I, Lysy PA, Godefroid N, Smets F, Malaise J, Reding R, Sokal EM (2007) Two-step transplantation for primary hyperoxaluria: cadaver liver followed by living donor related kidney transplantation. Pediatr Transplant 13:782–784
22. Cochat P (2007) Primary hyperoxaluria: diagnosis and treatment in the third world. Urol Res 35:258–259
23. Cochat P, Koch Nogueira PC, Mahmoud AM, Jamieson NV, Scheinman JI, Rolland MO (1999) Primary hyperoxaluria in infants: medical, ethical and economic issues. J Pediatr 135:746–750
24. Beck BB, Habbig S, Dittrich K, Stippel D, Kaul I, Koerber F, Goebel H, Salido EC, Kemper M, Meyburg J, Hoppe B (2012) Liver cell transplantation in severe infantile oxalosis – a potential bridging procedure to orthotopic liver transplantation? Nephrol Dial Transplant 27:2984–2989
25. Jiang J, Salido EC, Guha C, Wang X, Moitra R, Liu L, Roy-Chowdhury J, Roy-Chowdury N (2008) Correction of hyperoxaluria by liver repopulation with hepatocytes in a mouse model of primary hyperoxaluria type 1. Transplantation 85:1253–1260

Answers

1: a
2: b
3: c
4: e
5: a