REVIEW ARTICLE

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Primary hyperoxaluria type 1: A literature review upon three clinical cases

Hiperoxaluria primária tipo 1: Uma revisão da literatura a propósito de três casos clínicos

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ABSTRACT

Primary hyperoxaluria type 1 is a rare metabolic disorder of the hepatic peroxisomes characterised by excessive oxalate production, kidney deposition and subsequent systemic oxalosis. The diagnosis is often delayed and about 30% of the patients have end-stage renal disease at the time of diagnosis. The recommended treatment when there is end-stage renal disease is combined liver and kidney transplantation, bridging the hepatic enzyme defect and renal dysfunction. We report three cases of young women with primary hyperoxaluria type 1 and end-stage renal disease, making a subsequent systematic review of this topic. The timing of diagnosis and, consequently, the start of therapy were different for the three patients and may have an impact on prognosis. Since it is such a rare disease, the diagnosis is dependent on a strong clinical suspicion. In patients with a history of nephrocalcinosis and/or recurrent nephrolithiasis with progression to chronic kidney disease, this diagnosis should be excluded, especially before considering an isolated kidney transplant.

Key-words: Alanine:glyoxylate aminotransferase; chronic kidney disease; combined liver-kidney transplantation; nephrolithiasis; oxalate; primary hyperoxaluria type 1.

RESUMO

A hiperoxalúria primária tipo 1 é uma doença metabólica rara dos peroxissomas hepáticos que se caracteriza pela produção excessiva de oxalato com deposição renal e subsequente oxalose sistémica. O diagnóstico é frequentemente tardio e cerca de 30% dos doentes apresentam doença renal crónica avançada com necessidade de terapêutica de substituição da função renal à data do diagnóstico. O tratamento

preconizado, quando já existe doença renal crónica, é o transplante duplo fígado-rim já que colmata o defeito enzimático hepático e a função renal deteriorada. Reportamos três casos de hiperoxalúria primária tipo 1 em mulheres jovens com falência da função renal, procedendo a uma posterior revisão sistemática deste tema. O *timing* de diagnóstico e consequentemente de início de terapêutica foi diferente para as três doentes e poderá ter tido repercussões no prognóstico. Tratando-se de uma doença tão rara, o diagnóstico depende de uma forte suspeita clínica. Em doentes com história de nefrocalcinose e/ou litíase recorrente com progressão para doença renal crónica, o diagnóstico de hiperoxalúria primária deve ser excluído, principalmente antes de se colocar a hipótese de transplantação renal isolada.

Palavras-chave: Alanina:glioxilato aminotransferase; doença renal crónica; hiperoxalúria primária tipo 1; nefrolitíase; oxalato; transplante duplo fígado-rim.

INTRODUCTION

Primary hyperoxaluria type 1 (PH-1) is a rare autosomal recessive metabolic disorder caused by a defect of the liver-specific peroxisome enzyme alanine-glyoxalate aminotransferase (AGT), which converts glyoxylate to glycine[1]. The absence of AGT activity leads to excessive oxalate production and subsequent deposition of calcium oxalate (CaOx) in several organs. Since the main source of oxalate removal is urinary excretion, the deposition of CaOx, which is very poorly soluble, occurs primarily in the kidney causing urolithiasis or/and nephrocalcinosis[2]. As a result of kidney injury, glomerular filtration rate (GFR) declines leading to chronic kidney disease (CKD), subsequent end-stage renal disease (ESRD) and ultimately systemic disease with oxalosis

The clinical manifestations of PH-1 are very heterogeneous and there are several described presentations: a rare infantile form with early ESRD; a childhood presentation with recurrent urolithiasis and rapid decline in renal function; and thirdly, occasional stone formation in adulthood with better renal outcome[3].

One of the main characteristics of PH-1 is its challenging diagnosis. Usually there is a few years delay after the onset of the symptoms and about 30% of the patients have end-stage disease at the time of diagnosis[4]. There are several conditions that contribute to the difficulty of diagnosis, such as the rarity of the disease, insufficient knowledge of inherited urolithiasis, non-specific, often undervalued, initial symptoms and, finally, obstacles to metabolic and genetic screening[5,6]. As such, in most cases, when the definitive diagnosis is finally attained, patients present with systemic oxalate deposits, which, without proper and timely treatment, inevitably lead to death

In patients with ESRD, dialysis does not remove CaOx efficiently and isolated kidney transplantation is always followed by recurrence of nephrocalcinosis due to the unremitting overproduction of oxalate by the liver, leading to a high rate of graft loss[7,8]. The only treatment performed successfully in these patients is combined liver-kidney transplantation, since the liver provides the missing enzyme, lowering oxalate production, and the kidney restores renal function[9,10].

We report three cases of primary hyperoxaluria type 1 in young women with ESRD, demonstrating the challenging diagnostic approach and how it can influence the prognosis.

CASE REPORTS

Case 1

A 32-year-old Caucasian female without relevant antecedents was referred to our institution´s Urology Department presenting a two-year medical history of recurrent renal colic. Her physical examination was unremarkable and initial laboratory tests revealed serum creatinine (sCr) 0.9mg/dL. Abdominal X-ray showed a staghorn stone (Fig. 1) on the right kidney

Figure 1

Patient 1 abdominal X-ray with staghorn stone and double J stent.

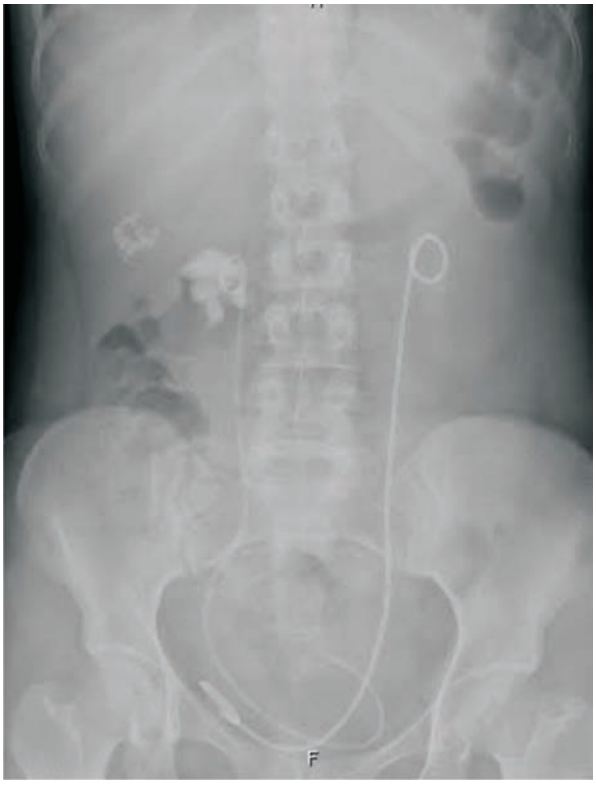
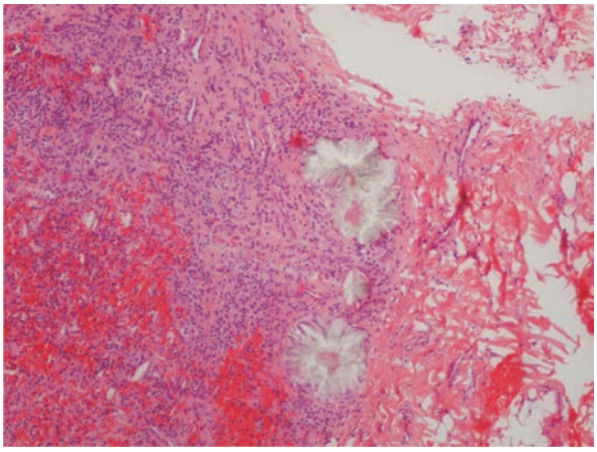


Figure 2

Synovial biopsy (H&E,x100).



and renal scintigraphy revealed kidney asymmetry with GFR 65 mL/min/1.73m² on the left and 17 mL/min/1.73m² on the right.

The patient underwent urological treatment with monthly extra corporeal shock wave lithotripsy (ESWL), bilateral double J stents and prophylactic antibiotherapy with nitrofurantoin. Six months later, she came to the Emergency Room presenting nausea, vomiting and asthenia and blood tests revealed sCr 17.3mg/dL, blood urea nitrogen (BUN) 157mg/dL and haemoglobin (Hb) 6.6 g/dL. Emergency haemodialysis (HD) was instituted and she was admitted to the Nephrology Department for subsequent workup. Further blood tests revealed PTH 359 pg/mL, calcium 6.8mg/dL, phosphorus 9.7mg/dL; negative viral serology and immunological tests and 24-hour urine sample with oxalate 4 mg (0.44mmol), proteins 508mg and microscopic haematuria. Renal ultrasound showed bilateral nephrocalcinosis and loss of sinus parenchymal differentiation. ESRD secondary to lithiasic chronic pyelonephritis and tissue damage by lithotripsy was presumed, so the patient was kept first on peritoneal dialysis, three years later on regular HD and enlisted for a kidney transplant. While on HD, the patient developed chronic hip synovitis with deposition of crystalloid material (Fig.2), left ventricular infiltrative process with maintained ejection fraction, erythropoietin-resistant anaemia and multiple vascular access failure.

She underwent a cadaveric kidney transplant six years after beginning renal replacement therapy with immediate diuresis but had renal graft dysfunction in the first 48 hours. A biopsy performed three weeks post-transplant showed focal lesions of chronic interstitial nephritis and diffuse ischaemic tubulopathy with intratubular deposition of a crystalline material, with no signs of acute rejection (Fig.3). PH was suspected and genetic screening was performed for the most frequent mutations on the exons one, four and seven, which were not found. The patient showed primary allograft dysfunction, was kept on maintenance HD but rapidly developed deterioration of her overall health with cachexia and muscular atrophy, vascular calcification, distal end ischaemia, hypothyroidism and skin lesions with *livedo reticularis*, calcinosis and algic hypersensitivity. A skin biopsy was made and was compatible with oxalosis (Figs. 4 and 5), which lead to a new complete genetic screening revealing a homozygous mutation g.12261G>T (IVS8+1G>T) confirming the diagnosis of PH-1.

Figure 3

Renal graft biopsy (H&E,x 200).

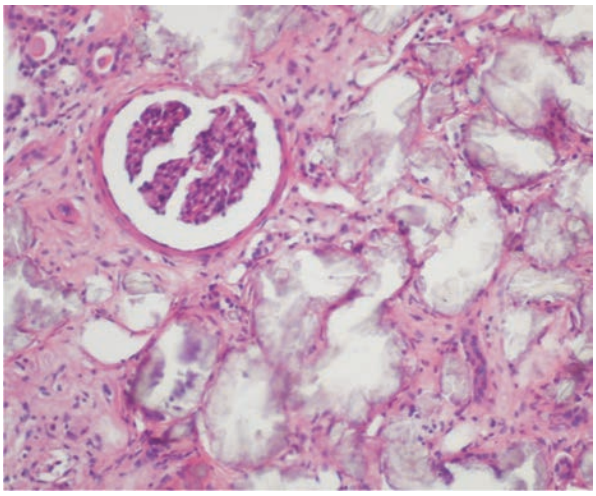
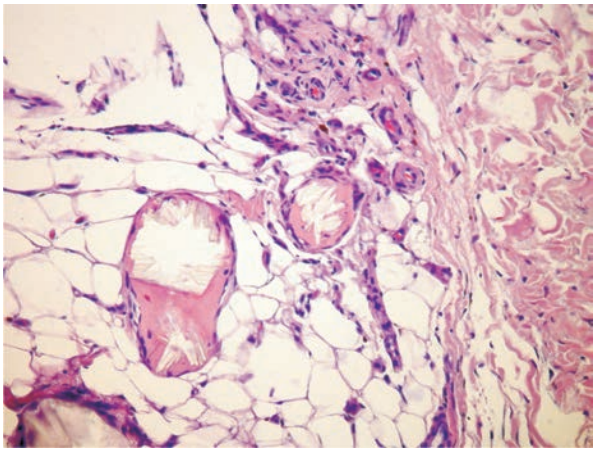


Figure 4

Skin biopsy, (H&E,x 100).



One month after diagnosis the patient died of cardiogenic shock at the age of 36 years.

Case 2

A 32-year-old Caucasian woman with a history of CKD secondary to nephrocalcinosis resorted to the Emergency Room of our hospital with complaints of abdominal pain and vomiting. She had a past medical history of bilateral nephrolithiasis and recurrent urinary tract infections since the age of 4 years. She had undergone surgical removal of a CaOx kidney stone and hyperoxaluria was confirmed with oxalate levels in 24-hour urine sample of 129 mg at the age of twelve. She was already on high dose pyridoxine, large fluid intake and urologic follow-up in her local hospital.

Figure 5

Skin biopsy (H&E,x 200).

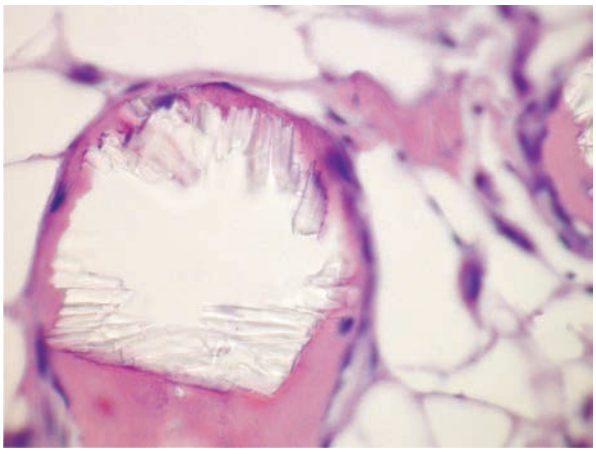
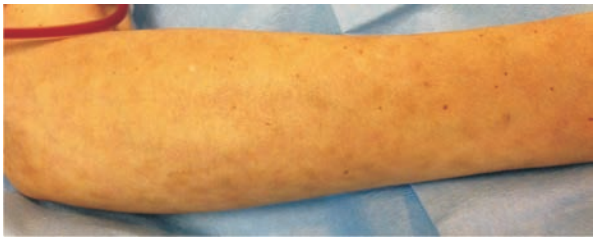


Figure 6

Patient 2: *livedo reticularis*; systemic oxalosis.



At the Emergency Room, her physical examination showed bilateral malleoli oedema and polypnea and initial laboratory tests revealed sCr 15.8mg/dL, metabolic acidosis and normocytic normochromic anaemia (Hb 10.4g/dL). On the kidney computerised tomography (CT) scan, there was medullary nephrocalcinosis and parenchymal scarring and renal scintigraphy

revealed severely impaired function bilaterally. The latest diagnostic procedures we could access, from the previous year, reported sCr 1.9mg/d, BUN 59mg/dL and kidney CT scan already showing small kidneys and calcifications throughout the parenchyma.

The PH was suspected, therefore, oxalate levels in urine and blood were measured, respectively 25mg/24h and 160 µmol/L, and genetic screening for the most common mutations was negative. The patient was started on regular HD and enlisted for a kidney transplant. Two years later, after having suffered the experience with the patient in Case 1, our Department decided to perform the complete genetic test, which confirmed PH-1 (homozygous mutation g.12261G>T (IVS8+1G>T). With this additional information, the patient was subsequently enlisted for a combined kidney-liver transplantation list. Meanwhile, she was kept on intensive daily HD, however she still developed systemic oxalosis with refractory anaemia, vascular calcification, bone disease, algic hypersensitivity, skin oxalosis (Fig. 5) and vena cava thrombosis.

The patient underwent a combined liver-kidney transplant from a deceased donor one year later and her immunosuppressive regimen consisted of induction therapy with basiliximab, and maintenance glucocorticoids, mycophenolate mofetil and tacrolimus. She had continuous venovenous haemodiafiltration prior to and during the surgical procedure and for the first 72 hours, later continuing daily HD for two weeks followed by four times a week of intermittent HD.

The post-operative period was uneventful and she had excellent hepatic and renal graft function. Plasma oxalate levels decreased progressively and urinary oxalate levels increased as from the beginning of an intermittent HD regimen (Table 1). Three weeks after the double transplant a renal graft biopsy was performed that showed no signs of acute rejection or oxalate crystal-deposition.

Table 1

Evolution of 24-hour urinary and plasma oxalate (uOx24h; pOx), serum creatinine (sCr) and dialysis treatment.

	Pre Tx	48h	10 d	1 M	2 M
sCr (mg/dL)	6.03	2.56	0.71	0.84	0.9
uOx24h (mg)	25	8.4	47.7	48.4	166
pOx (µmol/L)	160			55	32
Dialysis	HD pre surg.	Continuous HDF	Intermittent HD 4/week		

HDF = haemodiafiltration; Tx = transplant; HD = haemodialysis; d = day; h = hour; M = month

Presently, 5 months after the combined transplant, the patient is doing well, with normal hepatic and renal graft functions and no evidence of recurrence of oxalosis, Her current medication is prednisolone, mycophenolate, tacrolimus, statins, bicarbonate therapy and angiotensin converting enzyme inhibitors. Due to a high level of plasma oxalates (35 µmol/L), she is still on HD three times weekly and high fluid intake with the goal of urinary output superior to 3000mL.

Case 3

A 26-year-old Caucasian female with ESRD on maintenance HD three times a week was referred to our Hospital pre-kidney transplant evaluation. She suffered gross haematuria, nephrocalcinosis and recurrent urinary infections since the age of three. She had CaOx stones, high urinary oxalate levels and was medicated with pyridoxine, low oxalate diet and high fluid intake. She did not show good compliance with either medication or medical appointments.

Until she was 19 years old, her sCr was stable at 1.0mg/dL, but progressively worsened to renal failure with the need to start HD at the age of 26. The routine work-up showed no immunological or viral serology abnormalities and PH was suspected. She had high serum oxalate levels (111 µmol/L), although no marked systemic oxalosis. The complete genetic testing revealed a homozygous mutation p.I244T (c.731 T>C) that confirmed the diagnosis.

She is currently awaiting a combined liver-kidney transplant, complying daily HD and high dose pyridoxine (300mg three times a day). Her general condition is much beter then the other two patients at the time of diagnosis.

DISCUSSION

Primary hyperoxalurias are rare inborn errors of glyoxylate metabolism characterized by the overproduction

of oxalate, which is deposited as CaOx in various organs. There are three known types of PH (1, 2 and 3) and the most common, representing 80% of all PH, is type 1[11].

The PH-1 is an autosomal recessive condition caused by mutations in the AGXT gene on chromosome 2, which lead to dysfunction of the vitamin B6-dependent liver-specific peroxisomal enzyme AGT[1,12]. The absence of AGT activity results in conversion of glyoxylate to oxalate, which is not capable of being degraded (Fig.6). Since the main source of oxalate removal from the body is urinary excretion, the deposition of the poorly soluble CaOx occurs primarily in the kidney, either as urolithiasis or as interstitial deposition leading to nephrocalcinosis[13]. Progressive renal parenchyma inflammation and interstitial fibrosis due to nephrocalcinosis and recurrent lithiasis, cause renal impairment with evolution to ESRD. Once the GFR falls below 30mL/min/1.73m^2, reduced renal excretion and continued overproduction of oxalate by the liver leads to plasma CaOx super saturation (plasma oxalate › 30 µmol/L) and, consequently, systemic deposition of CaOx in organs such as bone, skin, soft tissues, heart, vessels and central nervous system[13,14]. Systemic oxalosis relates to high morbidity and poor quality of life and, if treated late or left untreated, progresses to early death.

An accurate and early diagnosis is essential in these patients, in order to begin appropriate therapy as soon as possible, thereby avoiding the development of systemic oxalosis. Unfortunately, the diagnosis of PH-1 is very challenging, usually delayed and only 30% of cases are diagnosed early[15]. There are several reasons for the difficulties in reaching PH-1 diagnosis. First, the rarity of the disease, which annual incidence is 0.11-0.26/100000 births and prevalence is 1-3/1000000 inhabitants[16]. Actually, in our Nephrology centre, which is integrated in a central public hospital with about 1500 beds and attending a population of 2 million people, there are only 5 cases described in the past 40 years, although it is an adult centre and the disease is more prevalent in children. Secondly, PH-1 has variable presentation with different forms of presentation depending on age, such as infantile oxalosis; childhood with recurrent urolithiasis and rapid decline in renal function; stone formation in adulthood; diagnosis only after failed isolated renal transplantation and diagnosis after family screening[17,18]. Also, the initial symptoms are very unspecific with findings of renal colic or urinary tract infections and there must be a strong clinical suspicion in order to proceed with more diagnostic tools.

The first patient reported, presented with the adulthood form, which is not very frequent, and although it is thought to have a better prognosis, the diagnosis is more difficult, since the symptoms are non-specific and there is less experience with PH in adults. The two other patients had their first symptoms during childhood and the progression to ESRD was slower, however, the diagnosis was still tardy even though hyperoxaluria was documented in an early phase of the disease.

Another issue regarding the diagnosis is the interpretation of the metabolic screening. On the one hand, renal calculi are very common and most adult patients do not undergo metabolic screening to determine the type of stone. On the other, even when metabolic screening is done and oxalate measurements are made, these are often misinterpreted. The normal value of 24h urinary oxalate is ‹ 45mg and if it is › 90mg the diagnosis of PH is highly probable. However, there are false positives to consider, such as enteric hyperoxaluria or high oxalate intake. False negatives are common in patients with ESRD, in whom urinary oxalate excretion decreases and urinary levels normalise. In such patients, plasma oxalate values superior to 30 µmol/L or 50 µmol/L pre-HD are very suggestive of PH[19,20].

After the clinical suspicion of PH-1, exclusion of secondary causes of hyperoxaluria (enteric or dietary) and concordant metabolic and biochemical screening, a molecular based diagnosis is feasible to confirm the diagnosis. Several common AGXT mutations have been identified and 70% of the mutations responsible for PH1 are located on exons 1, 4 and 7. It is recommended that a complete genetic analysis be performed for the entire AGXT gene in order to be able to confirm or reject PH-1 with certainty[21,22]. This was one of the biggest issues we had with our cases, not only because the genetic testing is not routinely done at our hospital, but also because the first attempt at AGXT gene screening was incomplete and represented a 3-year delay of the diagnosis.

For those patients where a molecular diagnosis cannot be established, a liver biopsy for enzyme

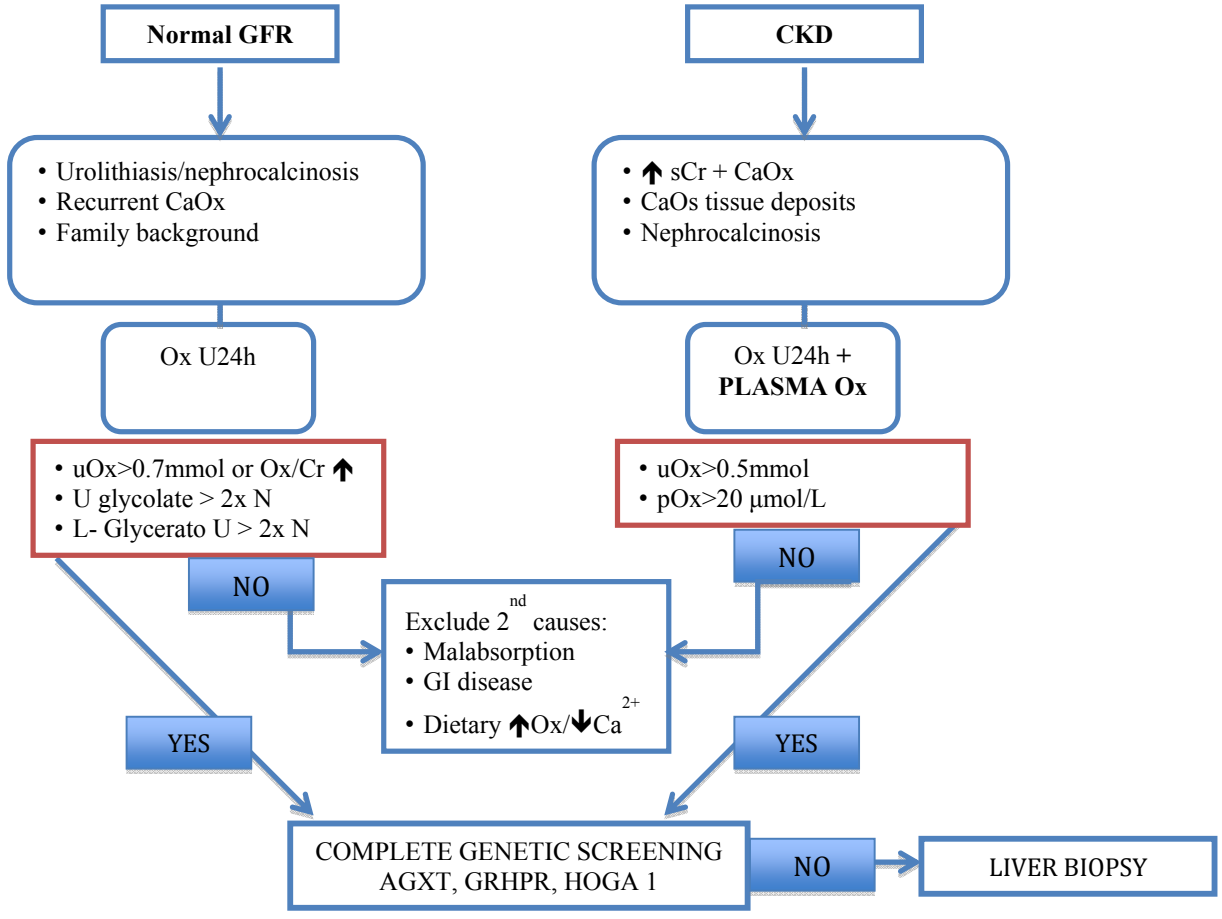
measurement may be necessary to provide a definitive diagnosis, but is not done routinely since it is an invasive procedure and was replaced by genetic screening[6]. Due to the difficulties in identifying PH, a consensus algorithm was developed as a product of the Oxalosis and Hyperoxaluria Meeting, in 2013 (Fig.7).

Regarding PH-1 treatment, there are still many doubts about the best procedure. As soon as the diagnosis of PH-1 has been suggested, conservative therapy should be started. Recommendations encompass high fluid intake, high dose pyridoxine and CaOx crystallization inhibition through urine alkalinisation[23]. Pyridoxine is a cofactor for AGT and can decrease urinary oxalate in approximately 30% of the patients with PH[24]. Some genetic mutations are more likely to respond to pharmacological doses of pyridoxine, such as p.Gly170Arg or p.Phe152Ile, and some patients are non-responsive. Only patients 2 and 3 did treatment with pyridoxine, but we did not evaluate the response to the therapy, which is defined by a 30% decrease in urinary oxalate excretion after a test period of a minimum of 3 months at maximum dose.

Intraluminal urological treatment is also challenging and the management of stones is complicated by potential concomitant nephrocalcinosis. Surgical interventions are only recommended when there is obstruction, infection or multiple urolithiasis and the preferential strategy is endoscopic procedure[25].

Figure 7

Diagnostic algorithm for hyperoxaluria – Adapted from "Primary Hyperoxaluria and Oxalosis: New Methods for Diagnosis", 2013[32]



Once patients develop ESRD and require HD, the prognosis is poor. In fact, HD should be avoided unless absolutely necessary and patients with progressive CKD should be referred for pre-emptive transplantation[23]. Although the molecular mass of oxalic acid is small (90Da), conventional HD is unable to remove sufficient quantities of oxalate proportionate to the continuous daily production[26]. Indeed, the difference between oxalate generation, 4-7mmol/day, and conventional HD removal, 1-2mmol/day, shows that tissue accretion rate is uncontrolled. Pre-dialysis plasma oxalate is reduced by ~60% after HD, but returns to 80% of the pre-HD levels within 24 hours. High efficacy dialysis, such as daily HD, nocturnal dialysis, high-flux dialysers and, possibly, a combination of overnight peritoneal dialysis and intermittent daily HD is recommended[6]. It is also recommended to perform haemodialysis/filtration for clearance of oxalate during and after organ transplantation in patients with systemic involvement and/or insufficient urine outflow in the early post-transplant period[27]. This was particularly important for the second patient reported as she had severe systemic oxalosis (plasma oxalate = 160 µmol/L) and CaOx deposits in the skin, bone and other tissues. Despite already having passed 5 months after transplantation, the patient maintains plasma oxalate levels very high (› 30 µmol/L) and so we are keeping the HD until plasma oxalate levels are less than 15 µmol/L, to avoid recurrence on the kidney graft. Urinary oxalate levels are still high but it is expected that oxaluria remains elevated for as long as several years[6].

Optimally, recognition for the need and planning for organ transplantation should occur prior to the onset of systemic oxalosis and ESRD and it is recommended at CKD stage 3b. Although combined liver and kidney transplantation has been advocated in many centres as the main approach to patients with PH-1 and ESRD, the experience with organ transplantation has been variable and transplantation strategies are also challenging.

There are different options for organ transplantation, such as isolated kidney transplantation, isolated liver transplantation and combined liver-kidney transplantation, which can be simultaneous or sequential.

There is no scientific rationale for isolated kidney transplantation and it is not recommended[13]. Pre-emptive isolated liver transplantation may be an option in selected patients, but such strategies raise ethical controversies since the transplant procedure is invasive and the decision to remove the native liver can be particularly difficult when the course of the disease is hard to predict[28]. Combined liver-kidney transplant has been accepted as a valuable treatment option providing good long-term results with patient survival rates of 80% at 5 years, although patients with a history of prolonged dialysis or systemic oxalosis have worse outcomes[8,29].

Regarding simultaneous or sequential combined liver-kidney transplantation, there are still doubts about the best approach. Sequential combined transplant, with liver transplantation first, has the advantage of decreasing the risk of recurrence and is to be considered for PH-1 patients who have ESRD and very high oxalate load. Simultaneous liver kidney transplantation has an immunologic advantage because the liver graft apparently has the potential to protect a simultaneously transplanted kidney from rejection and is done in one surgical time, decreasing the risk of septic and haemodynamic complications[30]. The second patient described was very ill and clinically unstable at the time she was transplanted and the procedure was considered life-saving, which was why simultaneous LKT was the procedure of choice. Also, given the shortage of organs, simultaneous liver kidney transplantation was our choice. Unfortunately the patient must be on HD in order to decrease the oxalate pool and to avoid recurrence on the kidney graft, but her general health status was significantly improved.

There are some new therapeutics being tested, such as oxalate degrading bacteria to prevent oxalate absorption in the gut[31] and novel approaches using hepatocyte cell transplantation or enzyme replacement by recombinant gene therapy may emerge in the future as the treatment of choice[7].

CONCLUSION

Despite recent improvement in the knowledge about the spectrum of this disease approach to its diagnosis and treatment strategies, PH-1 still represents a challenging issue for both adult and paediatric nephrologists worldwide. A timely diagnosis followed

by appropriate treatment is essential to improve the prognosis of patients, which is why it is of utmost importance to be alert and more aware of this rare disease.

Conflict of interest statement: None declared.

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