The enzyme 4-hydroxy-2-oxoglutarate aldolase is deficient in primary hyperoxaluria type III

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Introduction

During the last years, the group of patients with the typical clinical signs of primary hyperoxaluria (PH), but negative diagnostic results for the two types of PH known up till then has grown increasingly larger [1, 2]. It was, however, always obvious that the dramatic clinical course of most of these patients with unclassified hyperoxaluria, e.g. recurrent calcium-oxalate (CaOx) kidney stones already during the first years of life, together with the severeness of hyperoxaluria (>0.8 mmol/1.73 m²/day), could not be based on a secondary origin. This was also proved by low intestinal oxalate absorption and hence, it was long speculated that another yet undefined defect of the glyoxylate metabolism could be a reason for at least a third type of autosomal recessive inherited PH [3].

In 2010, mutations in the HOAG1 gene (4-hydroxy-2-oxoglutarate aldolase, formerly known as DHDPSL, OMIM 613616) were then found to cause PH type III in a group of patients with up to then unclassified hyperoxaluria [4]. HOAG1, located on chromosome 10q24, consists of seven exons encoding a mitochondrial protein of 328 amino acids (35 kDa). The enzyme is expressed in the liver and kidney and catalyzes the final step of the mitochondrial hydroxyproline metabolism from 4-hydroxy-2-oxoglutarate to glyoxylate and pyruvate. Therefore, it was assumed that accumulation of the oxalate precursor glyoxylate results in subsequent increased oxalate generation and a gain-of-function mechanism was proposed, although demonstration of the predicted HOAG activity of the recombinant protein had failed [4].

Clinical appearance

Patients with PH III appear to be different compared with other PH populations: the range of urinary oxalate excretion overlaps, but seems to be lower than in type I or II hyperoxaluria. However, intermittent or even constant severe hypercalciuria is found in PH III in addition to a rather high amount of urinary uric acid excretion [5, 6]. These urinary abnormalities would normally suggest an even higher risk for recurrent CaOx kidney stones and/or progressive nephrocalcinosis, but the clinical picture is totally different: the patient population, including that of the current paper from Williams et al. [6] in this issue of Nephrology Dialysis and Transplantation, shows a decline of severe clinical symptoms over time. Recurrent stone passage or the necessity for minimally invasive stone removal procedures is seen during early childhood (Figure 1), or at the latest by adolescence or young adult age, followed by a more or less complete absence of PH-specific symptoms, at least in the currently known patients with PH III. Also and very interestingly, up until now no patient with end-stage renal failure and the need for renal replacement therapy has been reported.

Fig. 1. Eight-months-old boy with recurrent abdominal pain, recurrent stone passage, multiple stones in both kidneys (here right kidney) and intermittent pyelopelvic dilatation. Stones depicted typical for PH type III being mainly composed out of CaOx dihydrate with some CaOx monohydrate embedding. SEM picture shows typical disordered structure of a PH stone (SEM photos were provided by B. Grohe, PhD, CIHR Group in Skeletal Development and Remodeling, University of Western Ontario, London, Ontario, Canada). He was later diagnosed to have PH III by HOAG1 mutation analysis.
True mechanism of HOGA1 deficiency

Very soon it became a matter of debate, whether the gain of function as originally suggested, was truly a reason for the accumulation of glyoxylate and hence the overwhelming oxalate production [4]. However, activating mutations would be very unusual in an autosomal recessive disorder. With the identification of a frequent homozygous HOGA1 splice-site mutation c.700+5G>T, reported in the heterozygous state as c.701+4G>T in the initial paper in 2010, it was later demonstrated that loss of function is much more likely the underlying mechanism in PH III [5]. The current paper by Williams et al. describes the c.700+5G>T mutation as the most common (67%) in a central European setting, which is also the case in the population of PH III patients diagnosed in our centre. The paper by Williams et al. [6] also adds further proof of the loss-of-function theory by demonstrating the pathogenicity of the c.700+5G>T mutation in expression studies on hepatic mRNA. In addition, the detection of two novel missense mutations within exon 1 (c.117C>A and c.208C>T) of the HOGA1 gene expressed, showed that hyperoxaluria in PH III is based on a deficiency of the 4-hydroxy-2-oxoglutarate aldolase enzyme and is not due to gain of function [6].

As also reported by Williams et al. in the current paper, the precise molecular/biochemical mechanisms inducing hyperoxaluria based on the defective 4-hydroxyproline catabolism due to HOGA1 mutations remain unknown. It was recently demonstrated by Riedel et al. [7] that in contrast to the related bacterial enzymes termed dihydrodipicolinate synthases (DHDPS), the human HOGA1 favours forward cleavage of 4-hydroxy-2-oxo-glutarate to glyoxylate and pyruvate [8]. However, this reaction is fully reversible and hence, glyoxylate can be both a substrate and a product of the HOGA1 enzyme reaction. HOGA1 blockade and therefore the mitochondrial build-up of the relatively unstable 4-hydroxy-2-oxoglutarate with subsequent enzymatical or non-enzymatical formation of glyoxylate has been hypothesized to be the culprits for increased endogenous oxalate production [5, 6]. Here, glyoxylate as a highly reactive molecule is metabolized in a manner by either cytosolic/mitochondrial glyoxylate reductase (GR) to glycocolate, peroxisomal alamine-glyoxylate-aminotransferase (AGT) to glycine or by cytosolic lactate dehydrogenase to oxalate. However, as both the GR and AGT enzyme activity and/or localization are normal in PH III patients, production of excess oxalate should be limited by metabolism of glyoxylate by the mentioned enzymes.

Role of hypercalciuria

The pathogenesis and significance of the intermittent hypercalciuria are, even more, not yet explicable. In patients with PH I, significant hyperoxaluria leads to nearly complete binding of urinary calcium and low calcium excretion is determined in 24 h urine samples [5, 9]. Therefore, computed urinary CaOx saturation (βCaOx) levels are low in patients with PH I (βCaOx <12, most often <8 relative units) [10, 11], but are calculated to be extremely high in the patient with PH III based on hyperoxaluria and are elevated or at least have a high calcium excretion (our own calculations, βCaOx >12 relative units, not published). In contrast, the clinical follow up in PH I is clearly more dramatic with most of the patients experiencing end-stage renal failure in the long term [9]. Therefore, other yet unknown parameters must play a significant protective role in the long-term course of PH III.

Heterozygous HOGA1 mutations

Recently, heterozygous HOGA1 mutations were also found in idiopathic CaOx stone formers [5]. It was speculated that HOGA1 defects and therefore disturbances in the 4-hydroxy-2-oxoglutarate aldolase enzyme may predispose to CaOx urolithiasis. Taking this into account further metabolic studies to better delineate the pathophysiology for both PH III and idiopathic CaOx stone disease are definitively needed! This may also offer evidence for new treatment options.

Differences in kidney stones depending on type of PH

There is, however, a clear-cut difference in the appearance of PH III versus PH I, but also into idiopathic CaOx stone formers [12]. Stones of the latter group of patients are mostly composed of CaOx monohydrate (COM) and have a structured composition (core and mantel region). In contrast, the PH stones appear to have an unsorted structure (Figure 1). Whereas COM calculi are also predominant in PH III, the white yellow and more spongy-appearing PH III stones are mostly composed of CaOx-dihydrate with some COM embedding.

Conclusions

With the finding that HOGA1 mutations are the culprits in PH III, ∼30% of the so-called unclassified hyperoxaluria patients could now be diagnosed. Therefore, PH III emerges as the second-largest group of patients, with a prevalence supposedly higher than PH II. Still, a significant number of patients with undefined hyperoxaluria, but the clinical signs and symptoms of PH remain. Hence, unravelling of further molecular background(s) of PH can be anticipated.

Also, there seems to be a clear distinction at least between the PH I and III patients, with ‘some’ protective parameters in PH III, which help to slow down the clinical symptoms over time. Especially (early) end-stage renal failure is not a concern in PH III. Hence, a more profound unravelling of the molecular background of HOGA1, but also further (geophysical and proteomic) stone analyses may help to evaluate the protective mechanism. Clearly, this may also lead to new therapeutic options definitively needed in the most devastating form of primary hyperoxaluria, namely PH type I.
Conflict of interest statement. I declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

(See related article by Williams et al. The enzyme 4-hydroxy-2-oxoglutarate aldolase is deficient in primary hyperoxaluria type 3. Nephrol Dial Transplant 2012; 27: 3191–3195.)

References


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