CKJ REVIEW

Primary hyperoxaluria: the adult nephrologist's point of view

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ABSTRACT

In adults, primary hyperoxaluria (PH) does not always present as obviously as in children, leading to delayed or even missed diagnosis. When diagnosed in adulthood, PH usually progresses at a slower rate and the focus is on the prevention of recurrent kidney stones as much as it is on the preservation of renal function. The most tragic presentation is when the diagnosis is made after primary non-function of a renal graft for treating previously unknown renal disease. Recurrent stones, nephrocalcinosis and features of systemic oxalosis can all be presenting features. For these reasons, consideration should be given to screening for this rare condition, using biochemical and/or genetic means, but being careful to exclude common differential diagnoses. Such efforts should be synchronized with diagnostic methods for other rare kidney diseases.

Keywords: clinical presentation, diagnosis of rare diseases, kidney stones, primary non-function, screening for rare disease

Primary hyperoxaluria (PH) when diagnosed in children often gives rise to a severe phenotype, especially if diagnosed in very young children and often leads to end-stage renal disease (ESRD) [1]. Conversely, in most adult patients with PH, the focus is on prevention of recurrent stones at least as much as preserving renal function, especially in PH types 2 and 3 [2, 3]. The progression of the disease is slower in patients diagnosed in adulthood compared with the severe infantile form [26], but unfortunately this can lead to a reduced sense of urgency for treatment, as the condition is not perceived as 'life threatening.' Accordingly, a major focus in the adult population concerns how to diagnose patients with PH who would otherwise never have received a diagnosis.

SCREENING AND CLINICAL PRESENTATION IN ADULTS

Clinical clues in adults

The mode of presentation in adults is much more varied in terms of symptoms, timing and severity compared with children, so diagnostic strategies need to take this into account. It is important to note that PH can be diagnosed at any age, even in the elderly, but in many cases, a history of stones in earlier life (or even in childhood) may be retrospectively elicited. PH3, in particular, may be missed; e.g. PH3 was diagnosed in a 78-year-old man after a non-stone nephrectomy [4]. Here are some common modes of presentation in adults:

- Primary non-function of a renal transplant—unfortunately, this is still a common mode of diagnosis and there are numerous case reports [5, 6], all of which point out that a recipient without a diagnosis for ESRD but with a history of kidney stones and/or nephrocalcinosis should have a workup for primary hyperoxaluria before being listed for renal transplantation.
- Calcium oxalate stones with progressive chronic kidney disease (CKD)—this is one of the most suggestive presentations, especially in cases where there is bland urinary sediment. Apart from considering acute kidney injury due to an acute stone event, nephrologists may not immediately consider a connection between a history of the stone disease (sometimes in the distant past) and ongoing progressive non-proteinuric CKD. These patients should be referred to a specialist metabolic clinic (if available) or a specialist centre for workup, as Dent disease should also be considered. In many centres this may lead to a kidney biopsy to obtain a histological diagnosis and this might show features of oxalosis [7]. These include calcium oxalate crystals, often best appreciated in polarised light, and sometimes features of acute inflammation not expected in cases with bland urinary sediment. We would strongly encourage the consideration of kidney biopsy in these cases.
- Unexplained non-proteinuric CKD or nephrocalcinosis—sometimes the history of stones is in the distant past or not at all, or was never even noticed by the patient. Again, in many centres, this would prompt a kidney biopsy that should give a clue to the diagnosis [8]. Even the presence of a single calcium oxalate crystal in the renal tissue on light microscopy should be considered abnormal and should prompt further investigation. Very rarely, features of systemic oxalosis can be the presenting feature in adults, e.g. paraplegia [9] or cardiomyopathy (although this was in a case of PH2) [10].
- Family history—since primary hyperoxalurias are autosomal recessive, by itself a family history of kidney stones is less useful for diagnosis. Exceptions include cascade screening after a known case in the family or if there is consanguinity.
- Any patient with calcium oxalate stones (especially if pure calcium oxalate)—this is more controversial, as of course most kidney stones are made of calcium oxalate and the vast majority of these will not be due to primary hyperoxalurias. Stone analysis (even of a historic stone) may show calcium oxalate monohydrate without phosphate and relatively uniform mineral density in PH1, although variation is possible. Stereomicroscopic analysis of the surface and interior of calcium oxalate stones provides a powerful way of distinguishing between PH1 and non-genetic hyperoxaluria [25]. But such facilities and expertise are not available in many centres and biochemical/genetic tests are often quicker to arrange. The presence of nephrocalcinosis in a calcium oxalate stone former should raise the possibility of non-idiopathic stones, such as primary hyperoxalurias of any type [11–13]. Twenty-four-hour testing for oxalate excretion remains the mainstay of screening and should be performed in any patient with recurrent calcium oxalate stones [14].
- Hyperoxaluria detected on the routine workup of a patient with calcium oxalate stones—this is usually after screening with 24-h urine collection reveals the presence of hyperoxaluria. This is one of the most common reasons for requesting specific testing for primary hyperoxaluria and is explained in more detail below.

High-throughput screening

Is screening necessary to identify adults with PH? For a rare condition with varied presentation and often severe outcomes that may now be treatable, it makes sense to consider a wider screening programme in potentially affected patients. The requirements are high throughput, high sensitivity, a clear definition of the selected population and a cheap and easy-to-perform test. There is no single test that meets these criteria but options include spot urine tests and perhaps urine crystal assessment, although the latter is not widely used [15]. In addition, tests would need to include detection not just of PH1, but also of PH2 and PH3. Spot urine tests for glycolate, glycerate and 4-hydroxy-2-oxoglutarate have good sensitivity, particularly for PH2 and PH3 [16]. There would need to be a mechanism to deal with possible false positives and to offer genetic testing to those who screen positive. Also, screening for hyperoxaluric conditions should be combined with identification of other rare diseases, aiming to prevent long-term end-organ damage, e.g. as suggested in the UK Rare Disease Strategy [24]. Such screening is best placed within pathways to investigate unexplained CKD.

CONSIDERATIONS IN THE DIAGNOSIS OF HYPEROXALURIA IN ADULTS

If the presentation suggests that an adult patient may have an underlying hyperoxaluric condition, the next step would usually be a 24-h urine collection for oxalate (sometimes oxalate:creatinine ratio on a spot urine, although this would usually require a 24-h collection for confirmation). This may not be possible if a suspected patient is oliguric; in this case, plasma oxalate may be useful [17]. Even if hyperoxaluria is confirmed (approximately >400 µmol/24 h), the following need to be considered:

Enteric hyperoxaluria

In adults, this is comparatively more common than in children and is important to diagnose, as the management is completely different [18]. Although some causes such as bowel resection or bariatric surgery are obvious, other causes can be quite subtle, such as malabsorption associated with undiagnosed mild inflammatory bowel disease.

In the past, primary hyperoxaluria was a diagnosis of exclusion after considering the many causes of enteric hyperoxaluria, but with cheap genetic screens becoming available, it might soon be easier to exclude primary hyperoxaluria first.

Primary hyperoxaluria types 2 and 3

In adults, the severity of the phenotype of these types of PH can be greater than for PH1 in some cases [2]. Therefore, screening tests need to look for all these. One option is urine metabolite screening, which when performed in a specialist laboratory was efficient for the detection of glycerate (for PH2) and 4-hydroxy-2-oxoglutarate and 3-dihydroxyglutarate (for PH3) [19].

Limitations and consequences of genetic testing

Genetic testing is only useful if we know which genes to look at. There are many patients with so-called idiopathic hyperoxaluria who have high urine oxalate excretion (often into the range of values seen in PH syndromes) but do not have positive genetic tests and no convincing clinical evidence of en-

teric hyperoxaluria. Therefore a big role will remain for urine oxalate measurement.

The impact of genetic diagnoses on families, especially if there is consanguinity, also needs to be considered.

No role for liver biopsy in clinical practice

More mutations are being described, but it is difficult to predict responsiveness to pyridoxine from genetics alone [20]. Liver biopsy may help by providing information about AGXT enzyme activity and also help to confirm the pathogenicity of new mutations. However, obtaining liver tissue is highly invasive, with obvious risks. In addition, the histological samples must be obtained fresh and transported frozen to a laboratory capable of performing the assay, but there are very few laboratories capable of providing this service. As a result, liver biopsy is not recommended in clinical practice.

TREATMENT OPTIONS

Management of patients with persistent hyperoxaluria and risk of stone formation has relied on high fluid intake and the use of crystallization inhibitors such as potassium alkali, which may lower stone risk, although there are no trials in PH patients [17]. As the source of oxalate is mostly endogenous, a low oxalate diet is of little benefit. Avoidance of salt and volume depletion, or use of diuretics, is prudent to prevent calcium oxalate crystal formation in the nephron, which can cause deterioration of renal function [21]. Many patients diagnosed in adolescence continue into adulthood without the development of ESRD. Those with a good response to pyridoxine therapy may normalize urine oxalate excretion and maintain good kidney function. In others, oxalate excretion remains elevated, with risk for both stones/nephrocalcinosis and eventual progression to ESRD. Recurrent stone formation may lead to the need for stone removal procedures.

With the advent of effective oxalate-lowering drugs such as agents that inhibit hepatic oxalate-pathway enzymes such as glycolate oxidase and lactate dehydrogenase [22, 23], there may be an impact on long-term prognosis for renal function and stone recurrence, although data are still pending.

CONCLUSIONS

Screening strategies for adult patients suspected of PH currently rely on a high index of suspicion. Those with a history of kidney stones or nephrocalcinosis and progressive CKD, or established ESRD at presentation, are in need of evaluation for genetic forms of kidney disease, as these often increase the risk for CKD. This may include urine studies for oxalate or other metabolites in the endogenous oxalate pathway, with follow-up genetic testing in appropriate patients. Even though next-generation sequencing may make genetic testing the initial strategy of choice in the future, recognition of hyperoxaluria is likely to remain the mainstay as it will allow diagnosis of non-PH conditions and provide a means of monitoring treatment. Strategies for genetics should synchronize with efforts to diagnose other causes of rare kidney stone disease or CKD.

FUNDING

CONFLICT OF INTEREST STATEMENT

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