When to suspect a genetic disorder in a patient with renal stones, and why

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ABSTRACT

Nephrolithiasis is a common disorder, with a rising prevalence in the general population. Its pathogenesis is still unclear, but a role for genetics has long been recognized, especially in cases of the more common calcium nephrolithiasis. Although relatively rare, monogenic causes of hypercalciuria and nephrolithiasis do exist and their timely recognition is important from a prognostic and therapeutic viewpoint. This article reviews the clinical and laboratory findings characterizing inherited causes of nephrolithiasis with a view to helping clinicians to recognize and manage these rare conditions.

INTRODUCTION

Nephrolithiasis is a common disorder, affecting ~10% of individuals in Western countries [1], with a recurrence rate of 50% at 5–10 years; it requires the related frequent need for urological treatments [2] and it is a significant cause of morbidity.

Although ‘common’ forms of calcium oxalate nephrolithiasis and idiopathic hypercalciuria are complex polygenic disorders, with several genes contributing to their pathogenesis in as high as 50% of cases [3, 4], there are also a few infrequent or even very rare Mendelian monogenic renal stone conditions that are worth identifying because they carry an unfavourable prognosis (renal failure) and risk receiving an incongruous treatment. It is also important to identify these conditions in order to avoid patients being identified only after the disease has recurred in a transplanted kidney [5] (Table 1).

The diagnosis of these hereditary diseases can be challenging due to their rarity, shortcomings in physicians’ knowledge of inherited nephrolithiasis and the variability of the clinical phenotype, and also because their manifestations may be shared by different disorders, including an overlap with the much more frequently encountered common forms of nephrolithiasis. This delays the diagnosis of even very severe inherited conditions; for instance, Type 1 primary hyperoxaluria (PH1) is diagnosed on average 5 years after the initial onset of symptoms [6]. It is self-evident that a delayed diagnosis of such a severe condition is likely to have dramatic effects on the patient.

The aim of the present article is to discuss the clinical and laboratory findings that should alert clinicians to the possibility of a renal stone former having an inherited disease responsible for their lithogenesis.

PREVALENCE OF INHERITED RENAL STONES

Data on the prevalence of these rare conditions in the general population or among stone formers are vague. There could...
<table>
<thead>
<tr>
<th>Orphanet number</th>
<th>Abnormal protein</th>
<th>Inheritance</th>
<th>Stone composition</th>
<th>Nephrocalcinosis or crystal-induced nephritis</th>
<th>Prevalence or number of reported cases</th>
<th>Risk of ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperoxaluria Type 1</td>
<td>ORPHA93598</td>
<td>Liver-specific peroxisomal alanine/glyoxylate aminotransferase</td>
<td>Autosomal recessive</td>
<td>Pure monohydrated calcium oxalate (whewellite)</td>
<td>Yes</td>
<td>1–9 pmp</td>
</tr>
<tr>
<td>Primary hyperoxaluria Type 2</td>
<td>ORPHA93599</td>
<td>Glyoxylate reductase/hydroxypyruvate reductase</td>
<td>Autosomal recessive</td>
<td>Pure monohydrated calcium oxalate (whewellite)</td>
<td>Yes</td>
<td>Fewer than 50 patients</td>
</tr>
<tr>
<td>Primary hyperoxaluria Type 3</td>
<td>Mitochondrial 4-hydroxy-2-oxoglutarate aldolase</td>
<td>Autosomal recessive</td>
<td>Pure monohydrated calcium oxalate (whewellite)</td>
<td>Yes</td>
<td>25 cases [59]</td>
<td>Yes</td>
</tr>
<tr>
<td>Dent’s disease Type 1 and 2</td>
<td>ORPHA93622-3</td>
<td>Cl⁻/H⁺ exchanger (ClC-5) or phosphatidyl inositol bisphosphate 5-phosphatase</td>
<td>X-linked recessive</td>
<td>Calcium salts</td>
<td>Yes</td>
<td>Type 1 &gt; 250 families, Type 2 &gt; 20 patients [60]</td>
</tr>
<tr>
<td>Hypophosphataemic rickets with hypercalciuria</td>
<td>ORPHA157215</td>
<td>Sodium-phosphate transporter 2c</td>
<td>Autosomal recessive</td>
<td>Calcium salts</td>
<td>Yes</td>
<td>&lt;1 pmp</td>
</tr>
<tr>
<td>Hypophosphataemic nephrolithiasis with osteoporosis</td>
<td>ORPHA244305</td>
<td>Sodium-phosphate transporter 2a</td>
<td>Autosomal dominant</td>
<td>Calcium salts</td>
<td>No</td>
<td>&lt;1 pmp</td>
</tr>
<tr>
<td>Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis</td>
<td>ORPHA31043</td>
<td>Claudin 16</td>
<td>Autosomal recessive</td>
<td>Calcium salts</td>
<td>Yes</td>
<td>Not known</td>
</tr>
<tr>
<td>Disorder</td>
<td>ORPHA Code</td>
<td>Gene/Pathway</td>
<td>Inheritance</td>
<td>Calcium Excess</td>
<td>Renal Stones</td>
<td>Refs</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td>Autosomal-dominant hypocalcaemic hypercalciuria</td>
<td>ORPHA428</td>
<td>Calcium-sensing receptor (CaSR)</td>
<td>Autosomal</td>
<td>Calcium salts</td>
<td>Yes</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Distal renal tubular acidosis</td>
<td>ORPHA93608-9</td>
<td>AE1 (anion exchange protein 1), or ATP6V1B1 or ATP6VOA4 subunits of the H+ ATPase ion pump</td>
<td>Autosomal dominant or recessive</td>
<td>Apatite</td>
<td>Yes</td>
<td>Unknown Yes</td>
</tr>
<tr>
<td>Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency</td>
<td>ORPHA510</td>
<td>HGPRT</td>
<td>X-linked recessive</td>
<td>Uric acid</td>
<td>Not described</td>
<td>1–9 pmp</td>
</tr>
<tr>
<td>Phosphoribosyl pyrophosphate synthase (PRPPS) hyperactivity</td>
<td>ORPHA3222</td>
<td>PRPPS</td>
<td>X-linked</td>
<td>Uric acid</td>
<td>Not described</td>
<td>1–9 pmp</td>
</tr>
<tr>
<td>Dihydroxyadeninuria</td>
<td>ORPHA976</td>
<td>Adenine phosphoribosyltransferase (APRT)</td>
<td>Autosomal</td>
<td>Dihydroxyadenine</td>
<td>Yes</td>
<td>10–90 pmp</td>
</tr>
<tr>
<td>Xanthine oxidase deficiency (xanthinuria)</td>
<td>ORPHA93601–2</td>
<td>Xanthine oxidase or molybdenum cofactor sulfurase</td>
<td>Autosomal</td>
<td>Xanthine</td>
<td>Not described</td>
<td>150 patients</td>
</tr>
<tr>
<td>Cystinuria</td>
<td>ORPHA214</td>
<td>rBAT or b&lt;sup&gt;0,+AT&lt;/sup&gt;</td>
<td>Autosomal dominant</td>
<td>Cystine</td>
<td>No</td>
<td>140 pmp</td>
</tr>
</tbody>
</table>

<sup>a</sup>Prevalence rates are from the Orphanet portal unless differently indicated.

<sup>b</sup>Renal stones and nephrocalcinosis are probably the consequence of the inadequate treatment of the condition with vitamin D.
also be a considerable variability among different populations and ethnic groups. To gain just a rough idea of their relative importance, it is helpful to look at the prevalence of particular stone compositions reported by one of the most important stone analysis laboratories worldwide, the Laboratoire Cristal at the Hôpital Necker in Paris [7]. Although the data from this case group are certainly biased for a number of reasons (e.g. because the laboratory is part of a hospital that is a referral centre for paediatric renal diseases, and because increasing use has been made in recent decades of extracorporeal or mini-invasive urological techniques that destroy or crumble the stone into loose fragments, hindering its analysis), they are very informative on the prevalence of the different types of stone. Among almost 44 000 stones investigated using infrared spectroscopy over a 25-year period, 1.9% were clearly associated with monogenic disorders. Cystinuria and primary hyperoxaluria (PH) were the most represented conditions: the former was more common in adult cases (84% of all inherited cases), while the latter was seen more in children (45% of all monogenic stone disorder patients). There were few cases (<5–8%) of overt distal renal tubular acidosis (dRTA), 2,8-dihydroxy adeninuria and other forms (Table 2).


<table>
<thead>
<tr>
<th></th>
<th>Children (&lt;15 years) (n = 1300) (%)</th>
<th>Adults (n = 42 500) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monogenic disorders (total)</td>
<td>132 (9.6)</td>
<td>714 (1.6)</td>
</tr>
<tr>
<td>Cystinuria</td>
<td>53 (40)</td>
<td>595 (84)</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>60 (45)</td>
<td>37 (5)</td>
</tr>
<tr>
<td>RTA Type 1 (distal)</td>
<td>6 (5)</td>
<td>54 (8)</td>
</tr>
<tr>
<td>2,8-dihydroxy adeninuria</td>
<td>6 (5)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>Others</td>
<td>7 (5)</td>
<td>10 (1)</td>
</tr>
</tbody>
</table>

Table 3. Pointers to inherited disease in renal stone patients

- Early onset
- Family cases
- Consanguineous parents
- Highly-active stone disease (bilateral, multiple stones, frequently recurrent)
- Associated nephrocalcinosis
- Renal hyperechogenicity
- Tubular dysfunction and related manifestations (statural growth deficit, polyuria, bone disorders)
- Renal failure
- Extrarenal manifestations (sensorineural hearing defects, ocular abnormalities, neurological disorders)
- Particular stone composition and crystalluria
  - Monohydrate calcium oxalate (whewellite)
  - Cystine
  - Dihydroxyadenine
  - Xanthine

**AGE AT ONSET**

Nephrolithiasis is unusual in children, with an incidence that has been estimated at ∼0.15% [8], much lower than among adults. It is worth noting, however, that as many as 40% of children with nephrolithiasis have a positive family history, suggesting a genetic disorder.

In the series of stones analysed at the Laboratoire Cristal [7], the proportion of stones associated with monogenic disorders differed between cases under or over 15 years old, being 9.6 and 1.6%, respectively (Table 2). Given that genetic causes of renal stones are so much more prevalent in children [7], a young age of onset of the disease should be considered a clue to the diagnosis of inherited causes.

The age of presentation may vary considerably, however, between patients with the same genetic stone disorder. In PH1, for instance, severe bilateral nephrocalcinosis and renal failure can occur as early as 2 years of age (infantile form), but adults with PH1 may develop only a single calculus and retain a normal renal function [9]. The same applies to cystinuria: more than 80% of patients develop their first stones before they are 20, but first stones may be passed at any age. In the small case series shown in Table 4, patients with childhood-onset cystine stones were in most cases correctly diagnosed as cystinuric straight away, while patients whose first stone episode occurred in adulthood waited, with one exception, from 3 to 13 years for a correct diagnosis. This
observation suggests that there is generally some reluctance to consider cystinuria as a cause of renal stones in adult cases, even—amazingly—in individuals known to have siblings with the condition (Table 4). Regrettably, patients may form multiple, and sometimes even severe stag-horn renal stones during such a long diagnostic delay and consequently need urological procedures, including nephrectomy (Table 4).

Table 4. Cystinuria: a real practice case series

<table>
<thead>
<tr>
<th>Subject (initials)</th>
<th>Familial cases</th>
<th>Age at 1st stone</th>
<th>Age at diagnosis (years)</th>
<th>Delay (years)</th>
<th>Mode of diagnosis</th>
<th>Stones ( qty during time to diagnosis)</th>
<th>Urol. treatments (during time to diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF</td>
<td>Yes</td>
<td>8</td>
<td>8 (1972)</td>
<td>0</td>
<td>Stone analysis</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>FMT</td>
<td>Yes</td>
<td>17</td>
<td>17 (1976)</td>
<td>0</td>
<td>Stone analysis</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>GA</td>
<td>No</td>
<td>27</td>
<td>31 (1983)</td>
<td>4</td>
<td>Stone analysis</td>
<td>2</td>
<td>Nephrectomy</td>
</tr>
<tr>
<td>TO</td>
<td>Yes</td>
<td>14</td>
<td>14 (1985)</td>
<td>0</td>
<td>Stone analysis</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>BG</td>
<td>No</td>
<td>9</td>
<td>9 (1986)</td>
<td>0</td>
<td>Aminoaciduria</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>FV</td>
<td>Yes</td>
<td>13</td>
<td>15 (1990)</td>
<td>2</td>
<td>Stone analysis</td>
<td>2</td>
<td>ESWL, PLT</td>
</tr>
<tr>
<td>ZP</td>
<td>No</td>
<td>27</td>
<td>27 (1994)</td>
<td>0</td>
<td>Stone analysis</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>PG</td>
<td>No</td>
<td>16</td>
<td>32 (1997)</td>
<td>16</td>
<td>Aminoaciduria</td>
<td>Many</td>
<td>/</td>
</tr>
<tr>
<td>SF</td>
<td>No</td>
<td>28</td>
<td>41 (2002)</td>
<td>13</td>
<td>Stone analysis</td>
<td>Many (1 stag-horn)</td>
<td>ESWL, PLT</td>
</tr>
<tr>
<td>PC</td>
<td>No</td>
<td>44</td>
<td>47 (2003)</td>
<td>3</td>
<td>Stone analysis</td>
<td>3</td>
<td>ESWL</td>
</tr>
<tr>
<td>TL</td>
<td>Yes</td>
<td>28</td>
<td>36 (2003)</td>
<td>8</td>
<td>Stone analysis</td>
<td>2 (1 stag-horn)</td>
<td>ESWL, PLT</td>
</tr>
</tbody>
</table>

Courtesy of Antonia Fabris, MD, Verona, Italy, unpublished. ESWL, extracorporeal shock wave lithotripsy; PLT, percutaneous lithotripsy.

In one of two sibling pairs (TO and TL), the diagnosis in TL was established 8 years after his first stone and 18 years after TO’s diagnosis. In the other pair (FF and FMT), although the correct diagnosis was established promptly after the first stone episode in FMT, it was still delayed by 4 years after the first episode in FF.

RENAL FAILURE

Among Mendelian stone conditions, one more or less common clinical trait is the possible onset of renal failure. Generally speaking, end-stage renal disease (ESRD) is rare in stone formers [10], although some reduction in glomerular filtration rate (GFR) and a risk of chronic kidney disease (CKD) have been associated with renal stones in epidemiological studies [11, 12]. In a survey conducted in north-east Italy, only 1.3% of ESRD patients had previously experienced stone episodes [13]. Struvite stones, hypertension, a history of severe obstructive episodes, recurrent pyelonephritis and invasive surgery often feature in the history of stone formers with a severely reduced renal function and ESRD [10, 14]. Other causes of renal failure in renal stone patients are the rare Mendelian disorders associated with stones, so an inherited condition should be strongly suspected when a stone patient develops renal failure. This situation is suspect whatever the patient’s age. In fact, although loss of kidney function and the need for renal replacement therapy frequently occur as early as in the second decade of life in ‘familial hypomagnesaemia with hypercalciuria and nephrocalcinosis’ [15] and PH1, patients with the latter develop ESRD at a mean age of 33 years, although this can happen as late as in the sixth decade of life [16]. Similar findings emerged in an Italian multicentre cohort of patients with Dent’s disease (A. D’Angelo and F. Anglani, University of Padova, personal communication). Thus, while an early onset of renal failure suggests an inherited cause of stone formation, renal failure occurring at an older age by no means rules out this possibility.

Renal failure is not invariably preceded by symptoms or episodes of stone formation in patients with a genetic stone disorder. Sometimes, these patients may have vague symptoms or none at all, with a silent progression to ESRD [5]. In a report from the Netherlands, in 59% of adult patients with PH1, the disease’s clinical presentation was so mild and misinterpreted that the diagnosis was only established when they developed chronic renal failure [17]. In patients with acute or chronic renal failure due to intratubular crystal precipitation or crystalline interstitial nephropathy, the diagnosis of 2,8 dihydroxyadeninuria (DHA) has reportedly been made by renal biopsy in the absence of any previous stone episodes [18]. Regrettably, this may be what happens after the disease has recurred in a transplanted kidney [19].

NEPHROCALCINOSIS AND RENAL HYPERECHOCOGENICITY

Many of the conditions listed in Table 1 cause nephrocalcinosis, i.e. the deposition of calcium concretions in the renal
parenchyma. Although this is usually the direct consequence of the genetic defect, nephrocalcinosis can also result from inappropriate treatments. This is the case, for instance, of vitamin D treatment in patients with ‘autosomal-dominant hypocalcaemic hypercalciuria’ [20].

Nephrocalcinosis can be diagnosed in a renal biopsy, but a biopsy is quite infrequently done in stone formers. In adults, the condition is generally recognized on plain abdomen radiography revealing typical radio-opaque images, generally with a medullary distribution, or hyperdense images with a similar distribution on computed tomography (CT) of the kidney, or papillary and medullary hyperechogenicity on kidney ultrasound (US). This last finding does not point unequivocally to nephrocalcinosis, however, since other causes of an increased renal echogenicity include the deposition of radiolucent concretions unrelated to calcium, like the 2,8-dihydroxyadenine crystals in the crystal nephropathy seen in patients with adenine phosphoribosyl-transferase (APRT) deficiency [21]. Although kidney US for nephrocalcinosis may have few pitfalls in neonates and preterm infants [22], and a comparison of US and CT in experimental nephrocalcinosis showed US to have higher sensitivity (96 versus 64%), but lower specificity (85 versus 96%) than CT [23], in infants and in children, kidney US is the most frequent and preferred tool for diagnosing nephrocalcinosis.

Nephrocalcinosis and other crystal-induced forms of nephritis are a potential mechanism behind irreversible and progressive renal damage leading to ESRD. They are associated with chronic interstitial nephritis, cellular infiltration, tubular atrophy and glomerular sclerosis [10]. On the other hand, medullary nephrocalcinosis usually occurs in Dent’s disease, but patients’ progression to ESRD is unrelated to the severity of their nephrocalcinosis (few Dent’s patients progress to ESRD in the absence of nephrocalcinosis, however) [24, 25]. Although dRTA generally coincides with a more severe nephrocalcinosis than in Dent’s disease, patients with the former have a better prognosis in terms of renal function: ESRD reportedly occurred in only 3% of patients during a follow-up of 12 years, [26] as opposed to more than 60% of patients with Dent’s disease [24].

### FAMILY HISTORY AND CONSANGUINITY OF PARENTS

Familial cases of renal stones are frequently observed in idiopathic calcium stone disease; in fact, a positive family history of nephrolithiasis is recorded in 15–20% of stone formers [27, 28]. This is because common calcium nephrolithiasis is a multifactorial disease with 50% of its pathogenesis relating to a number of genes [4]. Even so, family clusters of the same stone disease should alert physicians to the possible genetic origin of a patient’s condition.

Consanguinity (which may be quite widespread in some cultures) is also an issue because having a common ancestor raises the risk of developing recessive monogenic diseases. If parents are first cousins, the risk is twice as high as in the offspring of unrelated parents [29]. Consanguinity may not be obvious, but could nonetheless explain the higher prevalence of genetically inherited stone disease in families and communities that are genetically isolated. There are plenty of examples, such as the high prevalence of uric acid stones observed among a small, ancient founder population in Talana, a village in Sardinia [30], and the dRTA frequently encountered in Thai villages [31] is most likely another example. Finally, the finding that PH1 is responsible for <0.5% of the cases of ESRD in children in Europe, but for 10–13% in the Canary Islands [32], probably has to do with the greater frequency of PH1 due to consanguineous marriages [33].

It is also worth mentioning that apparently different renal disorders may be observed in family members of patients with renal stones. The familial clustering of renal disease is well known and probably relates to a generic predisposition to nephropathy and renal failure. We refer here to a different setting, however, i.e. the possible misdiagnosis of renal diseases in other members of the same family. To give an example, in a family with ‘familial hypomagnesaemia with hypercalciuria and nephrocalcinosis’ described by Praga et al. [34], two family members had medullary sponge kidneys (MSK). Rather than pointing to MSK as a potential manifestation of claudin 16 gene mutation, in our opinion, this implies that nephrocalcinosis is frequently misinterpreted by nephrologists and diagnosed as MSK because this is the most common and therefore best-known form of nephrocalcinosis observed in adult patients. Our own experience supports this interpretation: in a Dent’s disease family that we investigated, a maternal relative of the proband had ESRD and was said to suffer from MSK (which seldom causes ESRD in our experience, due to stone-related complications, such as obstruction, pyelonephritis, etc.); in actual fact, this diagnosis of MSK was based exclusively on the relative’s manifestation of nephrocalcinosis, whereas the coexistence of ESRD should have aroused the suspicion of other renal conditions.

Of course, the lack of other cases in a family does not rule out the possibility of a patient’s stone disease being caused by a genetic disorder. First-case mutations in autosomal-dominant forms or a recessive inheritance are the most obvious explanations for this, but there may also be other expressions of the disease (i.e. different clinical pictures within families), despite patients sharing the same gene mutations. This has been seen in families with PH1 in which some members presented with early, severe clinical signs and symptoms, while others remained asymptomatic for a long time [9]. This was also true of our experience in families with PH1, and in Dent’s disease and cystinuria too (Table 4); a teenager with PH1 underwent double liver–kidney transplantation [35], while the sister, who was 2 years older, was homozygous for the same mutation and hyperoxaluric, but had passed no stones, she disclosed no nephrocalcinosis, and her renal function was normal.

Screening for the same genetic defect in other (even asymptomatic) family members, and siblings in particular, is therefore mandatory when inherited stone disease is diagnosed because it could provide an important opportunity for the early identification of the condition in apparently symptom-free relatives, possibly sparing them episodes of severe renal disease (Table 4).
TUBULAR DYSFUNCTIONS AND THEIR CONSEQUENCES, AND OTHER EXTRARENAL MANIFESTATIONS

Finding that young renal stone formers have hypomagnesaemia (tetany, muscle spasms and weakness, paresthesias), magnesium and calcium wasting, or polyuria and hyposthenuria not secondary to an increase in water intake—i.e. potential signs of a Henle’s loop defect, as in familial hypomagnesaemia with hypercalciuria and nephrocalcinosis—should lead physicians to consider the diagnosis of this autosomal-recessive disorder caused by a defect in the claudin 16 gene [36]. The concurrence of ocular problems, such as severe myopia, horizontal nystagmus, or corneal calcifications, might also suggest such a diagnosis [34].

Systemic acidosis, failure to thrive, sensorineural hearing loss and osteoporosis or rickets in patients with renal stones should arouse a suspicion of dRTA [37–39].

Low serum phosphate levels, and/or low-grade proteinuria, or a rickets phenotype point to the cause of renal stones being Dent’s disease [40] or ‘hypophosphataemic rickets with hypercalciuria’ [41].

Low serum phosphate levels might also be associated with the rare ‘hypophosphataemic nephrolithiasis with osteoporosis’, a proximal tubular defect of the Type 2 sodium–phosphate transporter, which is encoded by the SLC34A1 gene [42]. Of course, primary hyperparathyroidism needs to be ruled out when low serum phosphate levels are observed. A mild drop in the levels of serum phosphate (which is not an infrequent finding in idiopathic calcium stone formers) may also be due to high or inappropriately normal circulating levels of fibroblast growth factor 23 [43].

The coexistence of non-renal manifestations, especially of neurological origin, in a stone patient should call to mind a possible genetic cause of the disorder. This is the case of generalized hypotonia at birth, failure to thrive and growth retardation in individuals with the ‘hypotonia–cystinuria syndrome’ [44], or of sensorineural deafness, hypotonia, motor delay, ataxia and autistic features in patients with ‘phosphoribosyl pyrophosphate synthetase hyperactivity’ [45], or of action dystonia, choreo-atetosis, ballismus, cognitive and attentional deficits and self-destructive behaviour as in full-blown Lesch–Nyhan syndrome, or also of the same symptoms, with a more limited and variable expression (depending on the disease’s severity), in cases of hypoxanthine-guanine phosphoribosyltransferase (HPGRT) deficiency.

Gouty arthritis and arthralgias in combination with uric acid or radiolucent nephrolithiasis in young adults could also be a hallmark of one of the various inherited purine metabolism disorders (HPGRT deficiency, phosphoribosyl pyrophosphate synthase hyperactivity, xanthine oxidase deficiency).

STONE COMPOSITION AND TYPE OF CRYSTALLURIA

The qualitative analysis of a stone is an important step in the diagnostic work-up on any stone former [46], but it becomes of the utmost importance in the diagnosis of inherited renal stone disorders [47], and of cystinuria, DHA and xanthinuria in particular. Infrared spectroscopy or X-ray diffraction should be the standard analytical methods used because chemical analyses are highly inaccurate in diagnosing most kinds of renal stones, and especially those produced in the inherited forms of the disease [46]. Cystinuria and DHA are often associated with the formation of typical urine crystals that—appropriately sought and identified—enable the correct diagnosis of these rare conditions. Unfortunately, laboratory technicians may not be familiar with these urine crystals and consequently often fail to appreciate their significance.

The first diagnosis of cystinuria is generally based on the findings of stone analyses or the discovery of characteristic hexagonal cystine crystals in the urine (Figure 1). Such cystine crystals are visible in 17–25% of urine samples from cystinuric patients [48]. Ideally, patients’ siblings should be screened by means of renal imaging and cystinuria assay, and assumed to suffer from cystinuria (even if they have no renal stones and/or urine crystals) if their urine cystine excretion exceeds 1300 mmol/g creatinine (150 mmol/mmol creatinine). An isolated finding of mildly increased cystinuria may be observed in some healthy carriers, but is not sufficient for a diagnosis of cystinuria [49]. Unfortunately, siblings are frequently not screened and their diagnosis is delayed until they have experienced a stone episode, and their stone has been analysed (Table 4).

DHA stones are generally diagnosed as uric acid stones due to their radiolucent appearance on radiographic studies. The composition of DHA stones is probably also often mis-diagnosed as uric acid because standard chemical analyses on renal stones fail to discriminate between the two types. Infrared spectroscopy and X-ray diffraction can identify the DHA composition of stones. Here again, a valuable clue to the diagnosis of this disease lies in the detection of spherical DHA crystals in the urine, which can be distinguished from other spherical crystals by the typical black cross visible inside them on polarized microscopy (Figure 2).

Although the erroneous diagnosis of uric acid stones in cases of DHA generally prompts treatment with allopurinol

![Figure 1](https://example.com/figure1.png)

**Figure 1:** Characteristic hexagonal cystine crystals in the urine sediment. (Courtesy of Michel Daudon, Hôpital Tenon, Paris.)
anyway, its standard dosage may be insufficient to prevent DHA stone recurrence and crystal nephropathy. Because DHA patients are likely to need higher doses of allopurinol than uric acid stone formers, a precise diagnosis of DHA is fundamental, particularly to prevent ESRD [19].

Xanthine stones are also invisible on X-ray and may be misdiagnosed as uric acid stones if the patient is not investigated by infrared spectrometry or X-ray diffraction. A clue to their differential diagnosis from uric acid stones lies in the patient’s markedly lower uric acid concentrations in plasma and urine.

Analyses on patients’ crystalluria and their stone’s morphology and composition may also be of major interest in the diagnosis of PH. Monohydrated calcium oxalate (whewellite) accounts for 4–5% of all renal stones occurring in children, and most of them are due to PH1 [32]. Daudon et al. [50] also noted that, by comparison with idiopathic calcium stones of similarly high whewellite content, PH1 and PH2 stones have specific morphological characteristics, i.e. a white or pale yellow surface and a loose, unorganized cross-section, very different from the dark brown surface and well-organized, radiating inner structure of common whewellite stones. In addition, whewellite crystals have an oval shape with a slight depression in the middle, and they form in urine only at very high oxalate concentrations observed in hyperoxaluria, unlike the dihydrated calcium oxalate (weddelite) crystallizing in hypercalciuric patients. The identification of whewellite crystals thus strongly supports the existence of a hyperoxaluric state [51]. The stone morphology seen in cases of intestinal hyperoxaluria is quite different from the one observed in PH, however [50].

FIGURE 2: Dihydroxyadenine crystals in the urine sediment. Typical black cross visible inside them on polarized microscopy. (Courtesy of Michel Daudon, Hôpital Tenon, Paris.)

CONFIRMING A DIAGNOSTIC SUSPICION OF GENETIC STONE DISEASE

Clinical findings and standard biochemical tests should orient a patient’s diagnosis. Knowing a stone’s composition is important in the diagnostic work-up of all renal stone formers, but especially so in suspected cases of genetically inherited disease. Although conducting chemical analyses on stones is not the best way to investigate their composition, it is still the most commonly used method. Chemical analyses are particularly inefficient in recognizing non-calcium stones, many of which are genetically determined, so stones should be analysed using infrared spectrometry or X-ray diffraction whenever a genetic condition is suspected.

If a stone is unavailable for analysis and a genetic condition is suspected, then careful observation of the urine sediment under optical and polarized microscopy is a mandatory step; a diagnosis can often be established from the relatively simple information obtained by these means.

More complex tests and genetic studies may sometimes be necessary to confirm a diagnosis.

We have already discussed the criteria for diagnosing cystinuria, and molecular genetics may be useful to confirm its diagnosis. In fact, an increase in urinary cystine and dibasic amino acid excretion may not enable a definitive diagnosis because of the difficulty of differentiating between homozygotes and heterozygotes [52].

The biochemical diagnosis of a genetic disorder may sometimes be necessary. For instance, a diagnosis of xanthinuria relies on estimating the uric acid levels in blood and urine. If hypouricaemia is confirmed, measuring xanthine and hypoxanthine in urine and plasma will confirm the diagnosis. To give another example, measuring APRT enzymatic activity in erythrocytes is useful in asymptomatic relatives of DHA stone patients if they do not carry any of the already known gene mutations [53, 54].

HGPRT deficiency, and its most severe form—the Lesch–Nyhan syndrome—can be diagnosed either by measuring HPRT enzyme activity in peripheral blood or intact cells (erythrocytes, fibroblasts) or by molecular genetic testing. The latter has almost completely replaced the use of biochemical diagnostic tests, however, and is indispensable for determining carrier status, which is usually asymptomatic and cannot be ascertained using biochemical and enzymatic methods [55].

PH1 is generally diagnosed in hyperoxaluric patients by means of biochemical tests revealing an increased urinary excretion of glycolate. It may be difficult to arrive at such a diagnosis in patients with severe chronic renal failure or ESRD, however, because their urinary oxalate and glycolate may appear normal as a result of their reduced GFR. Hence the need to measure plasma oxalate and glycolate levels in all patients with a history of renal stones and ESRD. Direct sequencing of the AGXT gene is a very effective tool for diagnosing PH1 in patients with a well-defined phenotype [56], but in atypical cases, a final diagnosis generally demands the measurement of AGT (alanine/glyoxylate aminotransferase) activity in liver tissue [57], especially in kidney–liver transplant candidates.

Molecular genetic studies are generally needed to confirm the diagnosis of other calcium stone conditions caused by inherited disorders. This is because none of these conditions has specific hallmarks, while having overlapping clinical manifestations. For instance, hypophosphataemia, which
would suggest a defective sodium–phosphate exchange, may be due to mutations of different sodium–phosphate transporters, Types 2a and 2c, encoded by different genes; but it is also a frequent finding in Dent’s disease which is due to a mutation of CL/H+ exchanger or phosphatidylinositol bisphosphate 5-phosphatase. Moreover, a number of genetic disorders that cannot be differentiated on a clinical basis may cause a rickets phenotype associated with calcium stones and/or nephrocalcinosis.

Very useful information on rare diseases (including those addressed in this review), and on the diagnostic tests and expert centres available in Europe, can be obtained from the Orphanet portal [58].

CONFLICT OF INTEREST STATEMENT

Contents of this article have not been published previously in whole or part.

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