International Journal of Surgery 36 (2016) 590–595

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Genetic defects underlying renal stone disease

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HIGHLIGHTS

- The molecular basis of 4 inherited renal stone disorders is described.
- The underlying cause of renal stone formation is different for each disorder presented.
- The importance of detection of these disorders is emphasised for renal health and that of other family members.

ARTICLE INFO

Article history:
Received 10 October 2016
Received in revised form
6 November 2016
Accepted 7 November 2016
Available online 10 November 2016

Keywords:
Genetics
Stones
Hyperoxaluria
Cystinuria
Distal renal tubular acidosis
APRT deficiency

ABSTRACT

Renal stones are common and are usually secondary to risk factors affecting the solubility of substances in the urinary tract. Primary, that is genetic, causes are rare but nevertheless are important to recognise so that appropriate treatments can be instigated and the risks to other family members acknowledged.

A brief overview of the investigation of renal stones from a biochemical point of view is presented with emphasis on the problems that can arise.

The genetic basis of renal stone disease caused by (i) derangement of a metabolic pathway, (ii) diversion to an insoluble product, (iii) failure of transport and (iv) renal tubular acidosis is described by reference to the disorders of adenine phosphoribosyl transferase (APRT) deficiency, primary hyperoxaluria, cystinuria and autosomal dominant distal renal tubular acidosis.

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Renal stones (nephrolithiasis) are common, with various estimates that they affect from 6 to 15% of the population in the western world [1]. In the majority of cases these relate to environmental risk factors including occupation, diet, low fluid intake, lack of stone inhibitors, administration of insoluble drugs, e.g. antiretrovirals; or to acquired disease such as hyperparathyroidism or anatomical factors, e.g. horseshoe kidney. Nephrocalcinosis is a related disorder that may also indicate precipitation of calcium in the kidney. In a small but significant proportion nephrocalcinosis and nephrolithiasis are the result of inherited disease, autosomal dominant, recessive or X-linked disorders, and their detection has implications for disease prognosis, treatment and risks to other family members. This review will focus on the inherited disorders of renal stone disease. It is not intended to be fully inclusive as this would be impossible with an ever expanding list of disorders, but will focus on some reasonably well defined metabolic causes that are examples of (i) derangement of a metabolic pathway, (ii) diversion to an insoluble product, (iii) failure of transport and (iv) renal tubular acidosis.

Suspicion of an inherited cause of renal stone disease should be raised by any of the following factors: early age of onset, recurrent stones, bilateral stone disease, family history or history of consanguinity. The support for initial investigations (Table 1) can be provided by most clinical biochemistry laboratories either in-house (for the majority of tests) or by referral to specialist centres (oxalate, citrate, cystine, primary hyperoxaluria metabolites). Analysis of the kidney stone, if available, can be helpful [2] although data from an external quality assurance scheme run by my laboratory suggests that not all laboratories provide a reliable service in this regard, in some cases regularly misidentifying stone types, failing to identify other rare stone types and giving no indication of the relative contribution of the different components. Tests that use physical analysis, e.g infra-red, are more likely to give reliable results. Radiographic analysis will identify whether stones *insitu* are calcium containing (radio-opaque) or radiolucent, the latter pointing to uric acid or other purine material or only faintly radio-dense as seen with cystine-containing stones. Stone disease in children is

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http://dx.doi.org/10.1016/j.ijsu.2016.11.015
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Table 1
Investigations for renal stone disease.

Initial investigations	24 h urine (plain)	24 h urine (acid collection)
	Volume	Volume
	creatinine	creatinine
	urate	calcium
	protein	magnesium
	pH	citrate
	Cystine (spot test)	oxalate
Secondary investigations	Cystine (quantitation) if spot test positive	Primary hyperoxaluria metabolites (glycolate, glycerate, HOG and DHG)

more likely to be investigated by a metabolic profile but sadly the same is often not done in the adult where stones may simply be physically treated without concurrent biochemical investigations. Even in children it can take a significant amount of time for a diagnosis to be made, with delays contributing to long term renal damage.There is an old adage 'once a stone former always a stone former' and thus recurrent stone formers may simply be regarded as typical for patients with stone disease and not deserving of closer inspection.

Renal stones may be a direct effect of loss of an enzyme or a transporter leading to accumulation of an insoluble substance, while in others the gene defect may predispose the individual to renal stones, as for example in renal tubular acidosis. The total number of genes involved is as yet unknown but a recent study targeted 30 known 'stone' genes in consecutive patients in a renal stone clinic (excluding primary systemic disease and drug-related stones) and identified mutations in 15% of the families studied, just under 21% of paediatric cases and 11% of adults [3]. Cystinuria, caused by mutations in *SLC7A9* was the most common disorder.

1. Derangement of a metabolic pathway

Disorders of purine metabolism leading to deficiency of the enzymes adenine phosphoribosyl transferase (APRT) and xanthine dehydrogenase (XDH) are illustrative of this type of metabolic disorder. In both cases they lead to an accumulation of precursors immediately prior to the enzyme block. In the case of APRT deficiency, adenine accumulates and is metabolised to 2,8-dihydroxyadenine (DHA) by XDH; while lack of XDH leads to an accumulation of xanthine. DHA and xanthine are both highly insoluble and form almost pure, radiolucent stones. The non-specific wet chemical method that uses the reduction of Folin's reagent (phosphotungstate/phosphomolybdate) for detection of uric acid also gives a positive result with DHA and xanthine and therefore kidney stone analysis may give an incorrect result unless a physical method is used (Fig. 1). A more reliable result is obtained by infra-red spectrometry (Fig. 1) but even here, it requires an experienced operator to be able to confirm the stone type. XDH may also be suspected by very low serum uric acid assuming the patient is not receiving uricase inhibitors. Confirmation of both disorders can be made by measurement of relevant urine purine metabolites and for APRT, the measurement of enzyme activity in red cells [4].

Both diseases are autosomal recessive. The APRT enzyme is encoded by *APRT*, a gene on the long arm of chromosome 16 (16q24) [5]. More than 40 mutations have been described to date with some common to particular populations, e.g.p.Met136Thr with less than 10% of normal activity [6] has been found in over 79% of Japanese patients [7]. The most common mutation (40%) in a French cohort was c.400+2dup that leads to incorrect splicing [8] whereas c.194A > T (p.Asp65Val) is the next most common in Caucasians and is particularly common in Iceland [9]. Heterozygosity for the disorder, as estimated from enzyme studies, is thought to be 1/100 [10] suggesting that the defect may not be as rare as previously thought. This suggestion is supported by the finding of the c.400+2dup mutation in 1% of healthy newborns [8] and may in fact either present later in life or be incorrectly diagnosed as uric acid lithiasis as a result of inaccurate stone analysis. End stage renal failure is a consequence of this disorder that is not corrected by renal transplantation.

2. Diversion to an insoluble product

The primary hyperoxalurias (PH) are a perfect illustration of this particular type of stone formation. There are three known types of PH, all of which lead to metabolism of precursors to insoluble calcium oxalate that precipitates in the kidney as nephrocalcinosis or renal stones. The stone type is typically 100% calcium oxalate, often monohydrate indicating rapid formation and in cases of PH1 have an unusual morphology [11] but can also be mixed with calcium phosphate. The three types, PH1, PH2 and PH3, are all autosomal recessive disorders and are caused by deficiency of alanine:glyoxylate aminotransferase, glyoxylate/hydroxypyruvate reductase and hydroxyoxoglutarate aldolase enzymes (Fig. 2) encoded by *AGXT*, *GRHPR* and *HOGA1* genes respectively.

Urine oxalate excretion is similar in the three disorders and can be quite variable [12]. Concentrations greater than 0.7 mmol urine oxalate/day [13] have been suggested as a reasonable level at which to consider a primary cause (in children, the result should be expressed/1.73 m^2) but this does not necessarily exclude secondary causes, such as bariatric surgery [14]or chronic pancreatitis, neither does a concentration below this exclude PH so if still strong clinical suspicion additional tests need to be performed. The finding of increased 4-hydroxy-2-oxoglutarate (HOG) and dihydroxyglutarate in urine from patients with PH3 [15, 16] led us to set up a primary hyperoxaluria metabolites screen (OCM) as a next step for the investigation of this disease (Table 1). This analysis can provide additional support for the different primary hyperoxalurias: elevated glycolate (found in 70% of PH1), glycerate (found in >95% cases PH2) and dihydroxyglutarate (in all cases of PH3 to date) and therefore focus genetic testing. HOG is a less reliable marker as it is unstable unless collected into acidified urine and may therefore yield a false negative result [17]. PH1 is the more common of the three diseases accounting for approximately 80% of cases in our experience [18], PH2 and PH3 accounting for around 10% each. The age of presentation for the three disorders is similar with most presenting in early childhood, around 5y of age [19].

AGXT occurs in two allelic forms, the major and minor alleles, the latter encoding a protein with an amino acid change, p.Pro11Leu that has approximately 60% activity of the major [20]and introduces a weak mitochondrial targeting sequence [21,22]. The minor allele occurs at a frequency of approximately 20% in Europeans but is much less common in African Americans [23].Mutations occurring on the background of the minor allele tend to have lower activity and stability [24,25] at least *in vitro*. More than 170 mutations have been described (see www.uclh.nhs.uk/phmd), in most cases leading to considerable reduction or complete loss of enzyme activity [20]. The majority are single nucleotide changes

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