Evaluation of urinary tract calculi in children

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Renal stone disease remains a significant health problem in the adult population, with the incidence of urolithiasis estimated to be as high as 12%. The true incidence in childhood is not known, but a frequency of two children per million UK population per annum has been suggested. Understanding the factors involved in urinary stone formation and the appropriate investigations for a child presenting with signs and symptoms of renal stone disease, will allow for earlier recognition of the problem and may assist in the prevention of recurrent stone formation.

The term “nephrocalcinosis” implies an increase in calcium content in the kidney, and is distinct from urolithiasis (stone in the urinary tract), although the two conditions may coexist. Nephrocalcinosis occurs less frequently than urolithiasis and may be focal, occurring in an area of previously damaged parenchyma, or generalised, usually as a result of an underlying metabolic disorder.

The incidence and composition of renal stones differs significantly with regard to geographic region. In European children infection related stones predominate. These stones are often located in the upper urinary tract, are composed of struvite (magnesium ammonium calcium phosphate), and are frequently related to proteus urinary tract infection. Hypercalciuria is the most common metabolic cause of stones in Western children. No diagnosis is determined in a quarter of cases. If more detailed investigations are undertaken it is possible that the number of “idiopathic” cases will decrease. The aim of this paper is to increase awareness of the importance of urolithiasis in children and to suggest an outline of investigations that will assist the physician in elucidating any underlying disorder.

**Pathophysiology of stone formation**

The formation of renal calculi is a complex process and depends on the interaction of several factors, including:
- Urinary concentration of stone forming ions
- Urinary pH
- Urinary flow rate
- The balance between promoter and inhibitory factors of crystallisation, for example, citrate, magnesium, pyrophosphate
- Anatomic factors that encourage urinary stasis, for example, developmental anomalies, foreign bodies.

Attention given to the above factors forms the basis of therapy aimed at prevention of the recurrence of renal stones.

**Presentation**

Abdominal or flank pain occurs in approximately half of the children presenting with urolithiasis, but the classical description of excruciating loin pain associated with the passage of the stone is uncommon. In infants stone symptoms may often be confused with colicky abdominal pain. Microscopic haematuria is present in over 90% of children with stones, and the possibility of urolithiasis should always be considered in children with non-glomerular haematuria. Urinary tract infections are often associated with renal calculi and pyuria may be seen. Table 1 shows the clinical disorders most frequently associated with paediatric renal stone formation.

**Investigations**

The evaluation of a child presenting with a renal stone should proceed in an ordered manner. The initial consideration is whether urinary obstruction is present which must be relieved promptly. Further evaluation can usually be performed on an outpatient basis. Special dietary precautions should be avoided as these may obscure some diagnoses (for example, hypercalciuria).

**Urinalysis**

Urinalysis and microscopy will identify haematuria, pyuria, and bacteria which may be present. Urine microscopy of fresh urine may

<table>
<thead>
<tr>
<th>Table 1 Classification of renal stones in childhood</th>
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<tbody>
<tr>
<td><em>Struvite stones (radio-opaque)</em></td>
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<td><em>Calcium stones (radio-opaque)</em></td>
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<td><em>Uric acid stones (radiolucent)</em></td>
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<td><em>Enteric hyperoxaluria</em></td>
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<td><em>Orotic aciduria</em></td>
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</table>

**Oxalate stones (radio-opaque)**

Primary hyperoxaluria type I
Primary hyperoxaluria type II
Enteric hyperoxaluria
Idiopathic

**Idiopathic**

**Other metabolic disorders (radiolucent)**

Xanthinuria

**Cystine stones (usually radio-opaque)**

**Cystinuria**

**Cystinuria**

**Orotic aciduria**

**Idiopathic**

**Idiopathic**

**Oxalate stones (radio-opaque)**

Primary hyperoxaluria type I
Primary hyperoxaluria type II
Enteric hyperoxaluria
Idiopathic

**Uric acid stones (radiolucent)**

Familial

Over production

Hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency
Glucose-6-phosphatase (G-6-P) deficiency
Phosphoribosyl pyrophosphate synthetase (PRPs) superactivity
Adenine phosphoribosyl transferase (APRT) deficiency
Hyperuricosuria
Related to high purine diet
Tumourlysis
Chronic volume contraction associated with bicarbonate losses, e.g. chronic diarrhoea, short gut syndrome

**Stones associated with hypocitraturia**

**Cystinuria**

**Cystine stones (usually radio-opaque)**

**Cystinuria**

**Orotic aciduria**
also identify crystalline elements that point to a diagnosis, for example, cystine crystals. The urine should be sent for culture and sensitivity to identify bacterial infection, which is not uncommonly noted at the presentation of children who are subsequently found to have an underlying metabolic cause for the renal stone.

**RADIOLOGICAL IMAGING**

All children presenting with a urinary tract infection or haematuria should undergo renal ultrasound examination to exclude urolithiasis. Small stones may not be detected by this method and plain abdominal radiography should be performed if the suspicion of stones is high. Ultrasound is more sensitive in detecting nephrocalcinosis and may detect radiolucent stones.

**STONE ANALYSIS**

Chemical analysis of a calculus passed in the urine or removed surgically is very helpful in elucidating the underlying cause and should not be overlooked. Parents should be encouraged to retain for analysis any granular material passed in their child's urine. One of the problems with lithotripsy is that renal stones are fragmented, and a whole stone is not available for analysis as is the case with surgically removed calculi.

There are no recent reports of the epidemiology of urinary tract stones in children in the UK, but North American data of analysed stones identifies the frequency and composition of urinary tract stones as:

- Calcium oxalate: 70–80%
- Calcium phosphate: 5–10%
- Uric acid: 5–10%
- Struvite: 5–10%
- Cystine: 1–5%

If infection related stones are not sent for analysis the frequency of struvite stones may be underestimated.

**METABOLIC REVIEW**

Inherited metabolic diseases are identified more frequently in children than in adults and therefore investigations to identify such disorders are indicated. The yield from a metabolic screen in a child with Proteus urine infection and a stone is often small, but any child with recurrent stones, a family history, or sterile urine requires adequate assessment.

All children with urolithiasis must be screened for cystinuria as medical therapy improves long term outcome. Conditions such as hyperoxaluria, which have hitherto been considered very rare, may be identified more frequently if the appropriate tests are requested. Figure 1 presents a suggested protocol for investigations.

Twenty four hour urine collections are extremely difficult to arrange in young children and are not necessary in the evaluation of a child presenting with renal stones. A spot urine collection can be used to determine the excretion of a substance in the urine by comparing it to the concentration of creatinine in the urine. Traditionally the second morning urine sample is used to determine the calcium and magnesium excretion and is fairly representative of a 24 hour calcium/creatinine concentration.

Particular attention must be paid to the method of urine collection for oxalate analysis. The patient must not be receiving vitamin C supplements, as the latter falsely elevate oxalate values. A fresh sample must be collected and sent immediately to the laboratory for analysis unless the urine is collected in a container acidified with hydrochloric acid. Delays will cause false elevation of oxalate concentration by oxidation. Urinary L-glyceric acid estimation is required to diagnose primary hyperoxaluria type II, but special handling of the urine collection is not necessary as this forms part of a urinary organic acid screen.

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**Figure 1** Diagnostic approach to childhood urolithiasis.
of Henle, which induces notable calciuria associated with the natriuresis.\textsuperscript{10} Nephrocalcinosis as a complication of the treatment of hypophosphataemic rickets, is much less frequently seen now, as a result of the use of 1,25-dihydroxycholecalciferol. It is suggested that this form of nephrocalcinosis is compounded by the hypercalciuria complicating oral phosphate supplementation.\textsuperscript{11}

In distal renal tubular acidosis the finding of an alkaline urine and hypercalciuria with a low urinary citrate excretion, favours the precipitation of calcium salts with resultant stone formation. Therapy consists of sufficient alkali to neutralise endogenous acid production, but unfortunately stone formation sometimes continues despite adequate alkali supplementation.

Dent’s disease is a renal tubular disorder characterised by low molecular weight proteinuria and hypercalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciuria with nephrocalciur
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allopurinol has a satisfactory therapeutic efficacy of these cases is important because they occur as a result of a deficiency of the enzyme xanthine oxidase. In these patients undergoing therapy. The inborn errors of purine metabolism are rare, for example, Lesch–Nyhan syndrome (a disorder characterised by self mutilation, hyperuricaemia with uric acid calculi, and choreoathetosis). Uric acid stones have been reported in patients with type I glycogen storage disease, but the mechanism is unclear. Some children, particularly males of Mediterranean background, may present with uric acid stones without hyperuricaemia or uricosuria. It is possible that these children have dihydroxyadenine stones which are not routinely distinguished from uric acid stones, unless specifically requested by the laboratory staff. Dihydroxyadenine stones occur as a result of a deficiency of the enzyme xanthine oxidase. The diagnosis of these cases is important because allopurinol has a satisfactory therapeutic effect and alkalinisation of the urine decreases solubility of the dihydroxyadenine.

Xanthinuria is a rare condition caused by a deficiency of xanthine oxidase with a resultant failure to convert xanthine to uric acid. The plasma uric acid concentration is therefore very low, but because xanthine is insoluble in acid urine, radiolucent calculi develop. Xanthine calculi should be considered if the parents report an orange/brown sediment in the urine or similar coloured staining of the nappy.

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