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%.1 The true incidence in childhood is not known, but a frequency of two children per million UK population per annum has been suggested.2 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.3 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.4 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 excreting 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).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Classification of renal stones in childhood</th>
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<tr>
<td>Struvite stones (radio-opaque)</td>
<td>Associated with urinary tract infections (often proteus)</td>
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<tr>
<td>Calcium stones (radio-opaque)</td>
<td>See fig 1</td>
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<tr>
<td>Oxalate stones (radio-opaque)</td>
<td>Primary hyperoxaluria type I</td>
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<td>Cystine stones (usually radio-opaque)</td>
<td>Primary hyperoxaluria type II</td>
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<td>Stones associated with hypocitraturia</td>
<td>Enteric hyperoxaluria</td>
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<tr>
<td>Uric acid stones (radiolucent)</td>
<td>Idiopathic</td>
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<tr>
<td>Chronic volume contraction associated with bicarbonate losses, e.g. chronic diarrhoea, short gut syndrome</td>
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Stones associated with hypocitraturia

Other metabolic disorders (radiolucent)

Cystinuria

Xanthinuria

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 chil-
dren 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 detect-
ing nephrocalcinosis and may detect radiolu-
cent 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 encour-
gaged 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 avail-
able for analysis as is the case with surgically
removed calculi.

There are no recent reports of the epidemi-
ology of urinary tract stones in children in the
UK, but North American data of analysed
stones identifies the frequency and composi-
tion 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 disor-
ders 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 re-
quested. Figure 1 presents a suggested proto-
col for investigations.

Twenty four hour urine collections are
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 excre-
tion 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 magne-
sium excretion and is fairly representative of a
24 hour calcium/creatinine concentration.5

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 estima-
tion is required to diagnose primary hyper-
oxaluria type II, but special handling of the
urine collection is not necessary as this forms
part of a urinary organic acid screen.

Figure 1 Diagnostic approach to childhood urolithiasis.
Table 2  Conditions associated with calcium stones

<table>
<thead>
<tr>
<th>Hypercalciuria with normocalcemia</th>
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<tr>
<td>Idiopathic</td>
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<tr>
<td>Distal renal tubular acidosis</td>
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<td>Frusemide treatment</td>
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<tr>
<td>Generalised renal tubulopathies</td>
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<tr>
<td>Hyperalimentation</td>
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<td>Hypophosphataemia</td>
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<td>Juvenile rheumatoid arthritis</td>
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<td>Medullary sponge kidney</td>
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<th>Hypercalciuria and low molecular weight proteinuria</th>
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<tr>
<td>Dent's disease</td>
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<tr>
<td>Hypercalciuria</td>
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<tr>
<td>Tubular proteinuria</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
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<tr>
<td>Rickets</td>
</tr>
<tr>
<td>Renal impairment</td>
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<tr>
<td>Chloride channel defect X linked Xp 11.22-3</td>
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Struvite stones
Infected stones are frequently diagnosed in male children under 5 years of age, over 90% of whom have infected urine at the time of diagnosis. Stone fragments are soft and easily passed in the urine, and are sometimes described by parents as a paste. The urine infection may be resistant to antibiotic treatment and a proteus infection should always alert the physician to the possibility of renal calculi. The stone is frequently located in the upper tract, usually renal pelvis, and is termed "staghorn" as a result of its shape.

Calcium stones
Calcium containing stones are often associated with underlying metabolic abnormalities, particularly if nephrocalcinosis is also present (see table 2). In childhood, the three most common causes of nephrocalcinosis are hypercalciuric states, distal renal tubular acidosis, and the hyperoxalurias. Idiopathic hypercalciuria is not well understood, but two forms are described:

- Absorptive hypercalciuria, in which there is increased intestinal absorption of calcium
- Renal hypercalciuria, in which there is reduced renal tubular calcium reabsorption as a primary abnormality.

These two forms can be differentiated by the response to a low calcium diet as well as to calcium loading. The distinction between these two forms may be considered relevant as the absorptive hypercalciuria can be controlled by moderate dietary calcium restriction, whereas the renal hypercalciuria is managed by a thiazide diuretic. The introduction of a high potassium but low sodium diet is of benefit to hypercalciuric children as the urinary calcium excretion can be reduced, as long as the diet can be maintained. Hyperparathyroidism is very rare in children and occasionally may cause renal calculi.

Frusemide use in low birth weight infants and cardiac patients is more frequently recognised nowadays as a cause of diffuse nephrocalcinosis. Frusemide inhibits the Na/K/2Cl channel in the thick ascending limb of the loop of Henle, which induces notable calciuria associated with the natriuresis. Nephrocalcinosis as a complication of the treatment of hypophosphataemic rickets, is much less frequently noted 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.

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 nephrocalcinosis, and is associated with inactivating mutations of the X linked chloride channel, CLC-5. The renal impairment is slowly progressive and rarely seen in childhood, although the other clinical features may be overlooked. An increase in the urinary excretion of low molecular weight proteins, beta 2-microglobulin, or retinol binding protein, is highly specific for renal tubular disease.

Familial renal magnesium wasting, hypercalciuria with nephrocalcinosis, and partial distal renal tubular acidosis has been identified as a course of renal failure in children.

Oxalate stones
The primary hyperoxalurias (PH) are rare autosomal recessive defects of oxalate metabolism that cause excessive endogenous oxalate production. The toxicity of oxalate in humans results from the extreme insolubility of its calcium salt, calcium oxalate, which may precipitate in the renal parenchyma or renal tract, causing either nephrocalcinosis or stones. There are two recognised forms of PH. Type I (PH I) is more common and is caused by a functional deficiency of the peroxisomal enzyme, alanine glyoxylate aminotransferase. Phenotypically PH I shows great heterogeneity, ranging from severe infantile oxalosis and death, to milder forms with renal stone disease in later life. Primary hyperoxaluria type II (PH II) is characterised by hyperoxaluria and L-glyceric aciduria, the underlying defects being the result of decreased glyoxylate reductase activity. Patients with PH II have a less severe clinical course than PH I and their predominant clinical feature is nephrolithiasis rather than nephrocalcinosis. With increased awareness of the appropriate tests indicated in patients presenting with hyperoxaluria, more patients with these disorders are currently being diagnosed.

Children with small bowel disorders, particularly those affecting the terminal ileum, may present with enteric hyperoxaluria related to increased dietary oxalate absorption. This results from the loss of the normal inhibitory
effect of calcium ions, as they are precipitated by the unabsorbed free fatty acids as calcium soaps.

The finding of calcium oxalate stones in older children and adults is often not associated with hyperoxaluria.20

Cystine stones
Cystinuria is an inherited error of defective transport of cystine, lysine, ornithine, and arginine across intestinal and renal tubular cell membranes. Cystine stones occur in children of all ages and have been identified in the newborn period.2 Twenty per cent of patients pass their first stone during childhood.2 In very young children bladder calculi may occur, but in later childhood renal calculi are more frequent. All cystine calculi are radio-opaque, although at times are not as dense as calcium containing stones, and may sometimes be missed on the plain abdominal film.

Uric acid stones
Uric acid is derived from endogenous sources, as well as from dietary ingestion of purines. Reduced urine volume with dehydration, hyperuricaemia, and a urinary pH that is consistently less than 6 are important factors that influence uric acid stone formation. Uric acid gravel in both kidneys may lead to acute renal failure in the absence of radiological evidence of calcification. This latter complication is less common with the adequate preparation of leukocytes during 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 glycosgen 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 of the laboratory staff. Dihydroxyadenine stones occur as a result of a deficiency of the enzyme adenosine phosphoribosyl transferase. The diagnosis of these cases is important because allopurinol has a satisfactory therapeutic effect and alkalinisation of the urine decreases solubility of the dihydroxyadenine.20

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

calcium, 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.21 25

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