Unique pattern of urinary tract calculi in Australian Aboriginal children

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Abstract: Young Australian children in remote regions of tropical and desert Australia are at risk of developing urate stones in their upper urinary tract from an early age. These radiolucent calculi were only recognized with the availability of ultrasound diagnosis and are not associated with anatomic anomalies or abnormal uric acid production/metabolism. Although these stones appear to resolve spontaneously after the weaning period, some result in ureteric obstruction and infection which may lead to renal damage. This pattern of urolithiasis differs from the usual global urolithiasis pattern of either endemic bladder stones in young children in developing countries or predominantly calcium-based stones in upper tracts of older children and adults in affluent industrialized countries, where upper tract urate stones account for only a minority of childhood urinary tract stones. Risk factors for urate stones are low urine output and acidic urine. An association between urolithiasis and carbohydrate intolerance leading to chronic acidosis has been suggested for Aboriginal children, but existing limited evidence does not support this as a major aetiological factor. Although further studies on the epidemiology, natural history and management of these urate stones are needed, we believe the focus should be on improving the known social and environmental risk factors of remote Aboriginal children during the weaning period which contribute to the unacceptably high prevalence of failure to thrive, diarrhoeal disease, environmental enteropathy, iron deficiency and urolithiasis.

Key words: Australian Aboriginal; epidemiology; tropics; urinary calculi.

The two dominant global patterns of renal stones are endemic bladder stones in young children in the developing world and upper renal tract stones in adults in affluent industrialized countries. Although renal stones are uncommon in children in the developed world, those that occur tend to be in the upper urinary tract of older children and are associated with underlying anatomical or biochemical abnormalities in 50–75% of cases.1–7 These stones are predominantly calcium oxalate, often mixed with calcium phosphate, with only 4–10% consisting of uric acid. Conversely, children in rural areas of the developing world, with normal anatomy and biochemistry, are prone to forming urinary tract stones in early childhood, which are more common in boys, occur predominantly in the bladder and are usually composed of ammonium acid urate or calcium oxalate.3–7 This pattern also occurred in Europe and North America a century ago, but the pattern of stones changed with urbanization and affluence. Thus, excluding children with anatomic or biochemical predisposition, poor nutrition in rural settings appears to predispose to bladder stones in young children, whereas over-nutrition leads to an increased prevalence of upper tract stones in adults.8

A recent large hospital-based study of urolithiasis in Pakistani children has documented a male predominance (3:1), and a peak age of 6–10 years for upper tract renal stones compared to a peak of 1–5 years for bladder stones. This study noted a transition from predominantly bladder stones, which accounted for 60% of calculi from 1987 to 1995, to upper tract stones in 85% of cases since 1996.9 With regard to aetiology, the largest group (55%) was idiopathic in which, on further investigation with 24 h urinary analysis in hospital, the children tended to have hyperoxaluria, hyperuricosuria and hypocitruria. This transitional pattern also occurs in children from the Middle-East who tend to present in later childhood with calcium-containing stones in anatomically normal upper urinary tracts.10–12

AUSTRALIAN INDIGENOUS CHILDREN

Indigenous children living in remote areas of tropical and desert Australia have a unique pattern of renal stones. In many respects, their pattern of stones is similar to children in poor developing countries (idiopathic stones of predominantly urate composition with a male predominance) except that their stones are mainly in the upper urinary tract.13–15 This pattern of stone disease in indigenous children has been documented in the desert areas of Central Australia, the southern arid zone, and the hot tropical north in both inland and coastal communities. There are a few reports from temperate coastal locations, but no published or anecdotal reports from north Queensland in spite of its large indigenous population. In these same climatic zones, urolithiasis is rare amongst urban dwelling indigenous children, which is consistent with environmental risk factors rather than a genetic basis.

The urinary tract stones in Aboriginal children tend to be radiolucent, urate-based and form early in life.15 The median age of presentation in Darwin is 24 months with some stones recognized as early as 8 months of age. Although some present
with specific urinary symptoms and signs, many stones are diagnosed on diagnostic ultrasound while investigating children for urinary tract infection or failure to thrive (FTT), often with a history of diarrhoeal disease, although all these associations suffer from ascertainment bias.

Some stones appear to resolve spontaneously, with or without deliberate urinary alkalinisation, while others persist or grow during observation and may go on to obstruct and damage kidneys. This pattern of urolithiasis appears to be a relatively recent phenomenon with few reports more than 20 years old. A possible explanation for this recent emergence is the widespread availability of diagnostic ultrasound which is documenting a previously unrecognized relatively benign, self-limiting phenomenon. However, we believe that this disease is truly emergent and related to changing environmental and lifestyle factors. In support of this explanation is the lack of published or anecdotal reports of symptomatic and obstructive disease in earlier times. The natural history of these stones is incompletely described and their contribution to the high incidence of renal failure in adult indigenous Australians is also unclear, except for the small minority with renal loss from prolonged obstruction.

URIC ACID STONES

The proportion of urate stones varies from 5 to 40% of all urinary calculi in reported studies, with about 5% in children in developed countries and the higher proportion in poor developing countries. Uric acid stones in children are strongly associated with low urine output and acidic urine. Oral alkalinisation therapy with potassium citrate or sodium bicarbonate, keeping the urine pH >6.5, leads to high rates of stone dissolution and prevents recurrences but compliance with therapy is often poor. In idiopathic uric acid urolithiasis, urinary pH and fractional excretion of urate are significantly lower than in control subjects. A urinary pH <5.8 promotes uric acid crystal precipitation because urates are poorly soluble in acidic urine. An Indian study of childhood urolithiasis documented low citrate excretion in young children, particularly in the presence of calcium oxalate and phosphate stones, but also in 40% of those with uric acid stones.

Well recognized risk factors for uric acid stones are hyperuricosuria, rapid turnover of purine (myeloproliferative diseases) and rare metabolic disorders (Lesch–Nyhan syndrome). These are unlikely to be significant in indigenous children. Other factors associated with diet and environmental factors are likely to be more relevant. Low carbohydrate and high protein diets are associated with stone-forming propensity due to formation of acid urine, low citrate excretion and increased urinary saturation of undissociated uric acid. Hot summer temperatures with increased sweating is characterized by increased tendency for crystallisation of uric acid but not calcium oxalate or phosphate. Potassium and magnesium depletion in skeletal muscle was documented in stone-formers in Thailand, and was related to low potassium intake and high sweat loss. The rapid tissue turnover in children also increases uric acid concentrations, whereas magnesium is a known inhibitor of urinary stone formation. Thus, the likely risk factors for stones in Aboriginal children in the weaning period are decreased fluid intake, high ambient temperatures, the known high prevalence of diarrhoeal disease with dehydration and low potassium and magnesium levels (both low dietary intake and excessive losses with acute diarrhoeal acidosis).

CARBOHYDRATE INTOLERANCE HYPOTHESIS

Baldwin et al. in this issue of the Journal argue that chronic metabolic acidosis secondary to lactose intolerance is a major aetiological factor in urolithiasis in Aboriginal children. Only anecdotal, case-based evidence is provided in this report, but it was impractical for the authors to review a large series of cases because of Ethics Committee insistence upon individual written informed consent before accessing hospital notes. In our view, this is an over zealous interpretation of privacy principles and places at risk much of the vital quality assurance and audit activities of clinical practice.

Against this carbohydrate intolerance hypothesis is the lack of evidence that acute diarrhoeal disease causes either chronic acidosis or prolonged lactose intolerance. At the Royal Darwin Hospital, our studies have shown that acute metabolic acidosis with diarrhoeal disease in Aboriginal children is strongly associated with rotavirus infection and moderate to severe degrees of dehydration, but is much less common with bacterial or parasitic causes of diarrhoea. We have found neither chronic metabolic acidosis nor prolonged lactose intolerance (measured as stool reducing substances, rather than by breath testing) to be features of Aboriginal diarrhoeal disease, so we doubt the statement by Baldwin et al. that ‘chronic metabolic acidosis is a common effect of disaccharide intolerance. We have measured urine pH in 199 Aboriginal children on admission with acute gastroenteritis and 36 Aboriginal controls without diarrhoea. The mean (95% confidence intervals) urine pH with diarrhoea was 5.86 (5.76–5.96) compared to 5.75 (5.53–5.97) for controls (P = 0.35), so diarrhoeal disease alone did not appear to be a risk factor for more acid urine. Carbohydrate intolerance (stool reducing substances) was documented in 62 children, who had a mean urine pH of 5.81 (5.64–5.97). Although urine acidity did correlate directly with metabolic acidosis (P < 0.03, adjusted for age), it did not correlate with reducing substances in stool (P = 0.41), breastfeeding (P = 0.90) or blood lactose (P = 0.37). We did find that hypokalaemic children had an unexpected trend to higher urine pH (5.89 vs 5.77), despite more acidosis and dehydration, which may reflect hypokalaemic nephropathy or an inability to excrete an acid load (and also fully concentrate the urine) with potassium depletion. It seems unlikely that this would predispose to stone formation other than via dehydration.

However, the underlying tropical-environmental enteropathy in Aboriginal children can cause reduced mucosal lactase levels, which would lead to increased colonic lactose substrate in breastfed infants with increased production of short chain fatty acids (e.g. acetate, propionate, and butyrate) from fermentation. Theoretically, increased acetate absorption could lead to decreased urine pH and contribute to urate stone formation. Perhaps a more important contributor to acid urine formation is ketonuria from fasting and anorexia of infection. In any case, studies have clearly documented that low urine volume with high ambient temperatures is the greatest risk factor for uric acid stones.

Proof of an association between carbohydrate intolerance and urolithiasis might require a large scale prospective epidemiological study, since lactose intolerance is common with diarrhoeal disease, and diarrhoeal disease is highly prevalent, whereas stones are relatively uncommon. This would be an inappropriate use of research funding, in our view, since the importance of underlying intestinal mucosal damage in carbohydrate intolerance has already been documented in Aboriginal children. There have been a disproportionate number of descriptive studies in Aboriginal children, and too few interventional studies. What is needed is a preventive intervention.
with documented improved outcomes by rigorous research methods. From the perspective of environmental enteropathy, diarrhoeal morbidity and FTT, this intervention should involve improved hygiene, reduced overcrowding in houses, a better weaning diet and prevention of iron and micronutrient deficiencies.

MANAGEMENT

With regard to the management of children with established stones, there is much to learn. Current evidence suggests that many small non-calcified stones will resolve with or without specific medical therapy. Others however, persist and grow and lead to or are associated with renal damage. There seems to be a low incidence of recurrent stones if the kidney is completely cleared, which lends support to the hypothesis that these stones form in response to environmental conditions surrounding infancy and are not due to persistent inherited metabolic or anatomical factors. Thus, it seems reasonable to treat non-obstructing stones less than 1 cm in diameter conservatively. That is, eliminate and monitor infection, encourage high oral water intake, maintain alkaline urine through the use of oral supplements if necessary and monitor regularly by ultrasound examination. Operative intervention should be considered for large stones, for those that persist or enlarge on conservative treatment, for when the urine cannot be cleared of infection, and for any degree of obstruction. The creation of prospective regional databases would facilitate essential follow up and allow the evaluation of the effectiveness and safety of such a management policy. National cooperation, using such prospectively collected data, would allow the expeditious and safe introduction of prospective controlled trials of standardized management regimes and give long term robust information about the natural history of this disease and its sequelae.

To date, most operative treatment of these very young patients has been by open surgery. A concern regarding the long-term effect of extra corporeal shock wave lithotripsy (ESWL) on the ongoing development of these immature kidneys has led to this conservative approach. Most reports of the application of ESWL refer to experience in older children and while some urge caution regarding long-term effects, there is no strong evidence of harm in the medium term.5,31-36 Similarly, most reports of percutaneous endoscopic surgery for paediatric renal stones involve older children but continuing development of operative technology will allow this to be applied to younger patients.

PREVENTION

Given the imperfect clinical evidence available, what is likely to be the most effective strategy to prevent urinary stone formation? We believe that low urine output from a combination of hot environmental conditions and inadequate fluid intake are the key risk factors. There are undoubtedly other predisposing factors, including diarrhoeal disease with dehydration and underlying tropical-environmental enteropathy. Specific dietary factors may be less important, and include weaning foods low in potassium and magnesium. High protein and urate diets are unlikely risk factors in this setting. The association with urinary tract infection and even FTT may be spurious since they increase the opportunity for detection of asymptomatic stones by ultrasound investigation. Thus, prevention should involve promotion of increased fluid intake in children during the weaning period, especially during hot weather. Water with potassium citrate would be an ideal fluid supplement to both increase urine output and alkalise the urine when breast milk intake could not be increased.

CONCLUSIONS

In conclusion, uric acid stones occur in the renal tract of some young Aboriginal children in tropical and desert regions of Australia. It has been proposed that chronic metabolic acidosis from carbohydrate intolerance is an aetiological factor in the development of renal stones. There is only limited anecdotal evidence for this association, no evidence of the occurrence of chronic metabolic acidosis (only acute metabolic acidosis) with diarrhoea and some evidence that acute lactose intolerance does not decrease urine pH. There is a need for ongoing research into the aetiology, natural history and optimal treatment of this unique pattern of stone disease in young indigenous children. However, we believe that the major effort should be to apply existing knowledge to improve the profound social and environmental factors which underlie the poor health of Aboriginal children in remote regions of Australia.

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