

# Melamine Related Bilateral Renal Calculi in 50 Children: Single Center Experience in Clinical Diagnosis and Treatment

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**Purpose:** We investigated the clinical diagnosis and treatment features of bilateral renal calculi in young children who ingested melamine tainted infant milk formula.

**Materials and Methods:** We retrospectively analyzed clinical data on 50 children (mean  $\pm$  SE age  $23.4 \pm 3.1$  months) with a history of ingesting melamine tainted infant milk formula and suffering from bilateral renal calculi. All patients underwent ultrasound and renal function evaluation. Treatment included cessation of melamine tainted formula consumption, hydration, urine basification and hemodialysis if necessary.

**Results:** Bilateral renal calculi peaked in 6 to 18-month-olds (58% of cases). The male-to-female ratio was 3.1:1.0. Calculi ranged in diameter from 4 to 10 mm in 33 patients (66%) and 2.5 to 4 mm in 17 (34%). Of the 11 patients with renal failure 8 underwent 1 to 4 sessions of hemodialysis. Of the 9 bilateral obstruction cases with renal failure 8 did not require surgical intervention but 1 required ureteral catheterization to drain the renal pelvis. All children experienced a good outcome and were discharged home after a mean  $\pm$  SE hospitalization of  $8.1 \pm 0.7$  days.

**Conclusions:** Melamine related urinary calculi were most often seen in patients 6 to 18 months old. Conservative management has been sufficient in most cases. However, these children need to be monitored for long-term effects of melamine tainted milk formula consumption.

**Key Words:** infant formula, kidney, melamine, pediatrics, urolithiasis

UROLITHIASIS is a common disease affecting approximately 10% of the population worldwide.<sup>1</sup> The incidence of urolithiasis in Chinese children is approximately 2% to 3%, and the condition generally manifests between ages 2 and 6 years.<sup>2</sup> Bilateral renal calculi are extremely rare in the absence of an underlying diagnosis. Since the first media reports in September 2008 linking an outbreak of renal diseases among children in mainland China with consumption of milk products contaminated with melamine, more than 50,000 chil-

dren are estimated to have been exposed to the tainted products.<sup>3,4</sup> All infants and children who consumed melamine tainted milk have received free screening and hospital treatment. At the same time the incidence of bilateral renal calculi in Chinese children has increased, although cases are infrequently reported.

Melamine is a chemical compound used in industrial manufacturing.<sup>5</sup> Little is known about the adverse effects of melamine consumption in humans, especially young children. In

## Abbreviations and Acronyms

BUN = blood urea nitrogen

Cr = creatinine

CT = computerized tomography

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China before October 2008 melamine was added illegally at milk collecting stations to increase apparent protein concentration readings so as to meet the national standard on the protein content of milk. It has been reported that the outbreak of urinary stones in young children is associated with consumption of melamine tainted formula.<sup>6</sup> After October 2008 the testing of new batches of formula by the Chinese government did not reveal the presence of melamine. Thereafter, no new melamine related urinary stones have been diagnosed. Accordingly a close tie may exist between the consumption of melamine tainted powdered milk and the outbreak of pediatric urinary stones.

We previously observed that bilateral renal calculi were observed in a third of all patients diagnosed with stones from September to October 2008. However, the clinical manifestation and treatment response were not reported. We investigated clinical features and treatment response of children with melamine related bilateral renal calculi.

## PATIENTS AND METHODS

### Patients

More than 3,000 children with a history of ingesting melamine tainted infant formulas from the areas of Zhengzhou received a free medical evaluation in September and October 2008. According to World Health Organization guidelines,<sup>7</sup> melamine related urinary stones were diagnosed in 165 patients, of whom 50 (mean  $\pm$  SE  $23.4 \pm 3.1$  months old, range 50 days to 7 years) had bilateral stones and 115 had a unilateral stone. Evidence of consumption of melamine tainted infant milk formula, including bags of powdered milk with batch number matched by data promulgated by Chinese authorities, was required at diagnosis. Duration of consumption was recorded at evaluation. Clinical presentation, blood urea nitrogen, serum creatinine and urinalysis were recorded at hospitalization.

### Imaging Evaluation

All patients were assessed by color Doppler ultrasound (Static Suppression Doppler, ProSound Alpha 10, Aloka, Wallingford, Connecticut) at a probe frequency of 3.5 MHz. Hydronephrosis, ureterectasia, and calculi size and location were recorded. Calculi diameters were measured at the longest axis. Only in indeterminate cases was there a need for other urinary tract imaging. Data for physical examination, and kidney and bladder ultrasound in 200 age matched breastfeeding infants and children (mean  $\pm$  SE  $22.3 \pm 5.5$  months old, range 60 days to 7 years) were collected as controls.

### Diagnosis

Melamine related urinary stone was diagnosed based on guidelines of the World Health Organization and the Ministry of Health of China. Diagnostic criteria were 1) consumption of melamine tainted infant milk formula; 2) presence of 1 or more clinical manifestations such as

unexplained crying (especially when urinating), vomiting and macroscopic or microscopic hematuria (urinary red blood normal on morphological evaluation), oliguria or anuria; 3) results of parathyroid hormone test (usually normal); and 4) ultrasound examination of urinary tract indicating stone.<sup>7</sup>

Renal failure was diagnosed when plasma BUN was greater than 15 mmol/l, or plasma Cr was greater than 355  $\mu$ mol/l or increased more than 44  $\mu$ mol/l per 24 hours.<sup>8</sup> Normal values of plasma BUN and Cr for our hospital laboratory are 7 mmol/l or less and 115  $\mu$ mol/l or less, respectively.

### Treatment

All cases were managed according to guidelines issued by the Chinese Ministry of Health. All patients/parents were immediately asked to stop consumption of melamine tainted infant milk formula. Then conservative treatment was administered, consisting of intravenous hydration or greater water intake to increase urine output, alkalization of the urine with 5% sodium bicarbonate (2 ml/kg daily diluted in 1.4% solution with 5% glucose) intravenously and an antispasmodic drug such as anisodamine (0.1 to 0.3 mg/kg) or atropine (0.1 to 0.2 mg/kg) to facilitate calculus passage. Urine pH was assessed 2 to 3 times daily and maintained at 6 to 6.54, with alkalization adjusted accordingly. After discharge home parents/patients were asked to maintain oral medication with tablets of sodium bicarbonate and antispasmodics until the next followup appointment.

Hemodialysis was considered if renal failure did not improve after 1 to 2 days of conservative management in cases with BUN greater than 15 mmol/l, Cr greater than 355  $\mu$ mol/l and/or serum potassium greater than 5.5 mmol/l, which indicated severe metabolic acidosis. Treatment response was categorized as successful (clinical symptoms and stone resolved, laboratory examination and urinary analysis normal) or partially successful (clinical symptoms resolved and stone size decreased). Stone analysis from 6 cases was performed using combined liquid chromatography/mass spectrometry (Esquire-LC, Bruker Daltonics, Billerica, Massachusetts).

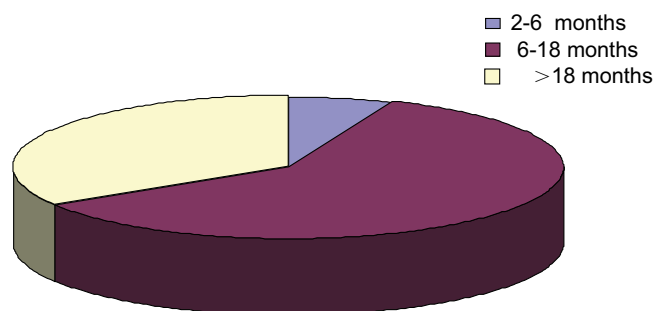
### Statistical Analysis

Statistical analyses were performed with SPSS®, version 1 for Windows. Values were expressed as mean  $\pm$  SE, and t test was used to evaluate differences. Values were considered statistically significant at  $p < 0.05$ .

## RESULTS

### Incidence, Age and Gender Distribution

Melamine related bilateral renal calculi occurred most often in children younger than 1.5 years (32 of 50 patients). The incidence peaked in individuals 6 to 18 months old, who accounted for 58% of the cases (fig. 1). There was no significant difference in male-to-female ratio of melamine related bilateral renal calculi in study cases vs controls (3.1:1.0 vs 2.8:1.0).



**Fig. 1.** Age distribution of patients with bilateral renal calculi following ingestion of melamine tainted infant formula.

### Clinical Features

Length of melamine tainted infant milk formula consumption ranged from 47 days to 42 months (mean  $\pm$  SE  $12.4 \pm 1.5$  months). Clinical presentation varied from no symptoms to renal failure. Various clinical symptoms were present in 31 patients (62%), including reduced or increased frequency of urination, crying at urination (23 patients, 46%), unexplained crying (8 patients, 16%) and oliguria or anuria (11 patients, 22%). Two or more symptoms were observed simultaneously in 13 patients (26%).

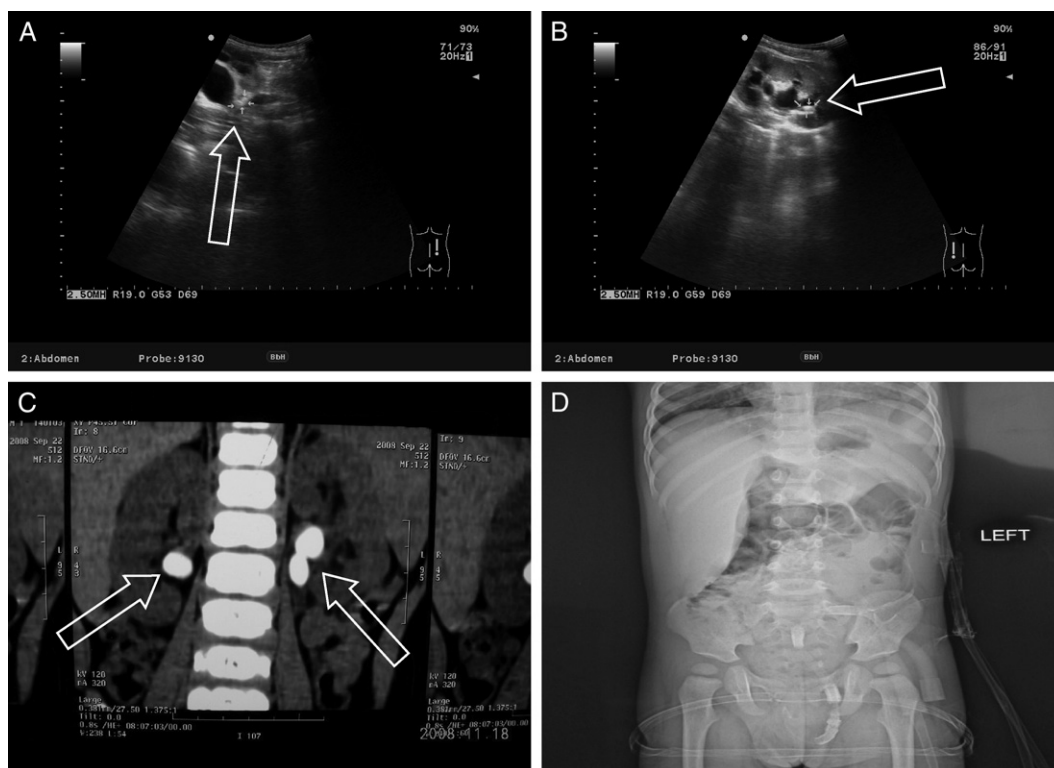
### Laboratory Examination

Urinary pH ranged from 5.0 to 7.5. A total of 28 patients (56%) had mildly acidic urine (pH 6 or less). Renal failure was diagnosed in 11 patients according to the previously mentioned criteria, of whom 10 had hyperkalemia at presentation. Stone analysis showed the main content was uric acid and melamine. Molar ratio of uric acid to melamine was approximately 2:1.

### Ultrasound Results

Bilateral renal calculi alone were found in 36 patients (72%), with unilateral ureteral calculi in 8 (16%), with bilateral ureteral calculi in 4 (8%) and with bladder calculi in 2 (4%). Calculus diameter was 4 to 10 mm in 33 patients (66%) and less than 4 mm in 17 (34%). Bilateral hydronephrosis was observed in 11 children, of whom 9 presented with renal failure. Ureterectasis was detected in 12 cases, of which 8 were unilateral and 4 were bilateral.

In 10 patients plain x-ray of the kidneys, ureters and bladder confirmed that the stones were radiolucent. Stones were clearly visible on CT (fig. 2). Only 1 kidney stone was found in 200 age matched controls, which was radiopaque.



**Fig. 2.** Ultrasound and CT in 16-month-old boy with bilateral calculi. A, ultrasound shows 1 calculus in pelviureteral junction of right kidney. B, ultrasound reveals 2 calculi in left kidney with mild dilatation of pelvis. C, CT demonstrates 1 calculus in pelviureteral junction of right kidney and 2 calculi in left kidney with mild dilatation of pelvis. D, plain x-ray of kidneys, ureters and bladder shows no kidney calculi.

## Treatment Response

After treatment at the hospital (mean  $\pm$  SE stay  $8.1 \pm 0.7$  days) clinical symptoms resolved in all patients and no patient died. Most cases exhibited a good response to conservative management. A total of 21 patients (42%) had the stones pass and 29 (58%) had the stones partly dissolve. One month later 12 additional children (including 2 with renal failure) became stone-free (all calculi expelled), while in the remaining 17 patients (including 6 with renal failure) the calculi decreased in size. No patient had new stones during followup.

Hemodialysis was performed in 8 patients with renal failure who had failed to exhibit improvement with conservative treatment. All of these patients gradually recovered after 1 to 4 sessions of hemodialysis. Of the 9 patients with bilateral obstruction and renal failure 8 did not require surgical intervention. The remaining patient required ureteral catheterization for 1 week to drain the renal pelvis due to lack of improvement following 4 hemodialysis sessions. In this patient the stone size decreased and the stone was finally expelled.

## DISCUSSION

Urinary stones, especially bilateral renal calculi, are rarely seen in children without metabolic disorders.<sup>9</sup> The outbreak of urinary calculi following melamine tainted infant milk formula consumption in China has increased the number of observed bilateral renal calculi. Although melamine tainted formula is no longer on the market, a large number of infants with urinary calculi are still being monitored and treated. A positive relationship between urinary stone formation and consumption of melamine tainted powdered milk has been reported in the media and the medical literature.<sup>6</sup> All patients in the present study had a similar history of melamine tainted powdered milk consumption.

In October 2008 tests of different batches of infant milk formula by the Chinese State Administration of Quality Supervision, Inspection and Quarantine revealed that San Lu products had the highest content of melamine, at 2,563 mg/kg, and that the formula produced by that company had been contaminated since January 2008.<sup>10</sup> In the present study 6 stone analyses demonstrated that the main component was uric acid and melamine, supporting a clear relationship between urinary calculi formation and consumption of melamine tainted powdered milk.

It is difficult to diagnose calculi in children because the presentation in this population is often atypical.<sup>11,12</sup> In the present study clinical symptoms

varied from none to anuric renal failure. The main clinical manifestations of melamine related bilateral renal calculi were changes in voiding pattern, including frequency/urgency and oliguria/anuria, and in some cases unexplained crying. All 11 patients with renal failure presented with oliguria/anuria, with bilateral obstruction/hydronephrosis noted in 9 (presumably due to renal toxicity caused by the tainted milk) and no hydronephrosis in 2. Other classic causes of renal failure, including dehydration, malnutrition and severe infection, were excluded by physical and laboratory examinations.

In the present study calculus diameter in children with renal failure was significantly greater than in those with normal renal function, indicating that renal failure may more likely occur in the presence of larger stones. We also found that bilateral renal calculi may develop in infants of any age but are more likely associated with the amount and length of consumption of melamine tainted infant milk formula without supplemental food. Additionally our study shows that males had more renal calculi than females, a predominance that is also confirmed in other causes of urinary calculi in children in other countries.<sup>13</sup>

Coward et al reported that most urinary calculi in children are composed of calcium oxalate or calcium phosphate.<sup>14</sup> The most striking difference that we observed was the apparent increase in uric acid concentration. Melamine, when associated with cyanuric acid, can cause renal failure due to formation of insoluble melamine cyanurate crystals in the renal tubules and/or calculi in the kidneys, ureters, bladder or urethra.<sup>15</sup> Routine urinalysis demonstrated low urinary pH in almost all patients. Strategies for decreasing serum uric acid levels are recommended to prevent the progression of renal failure.<sup>16</sup>

Analysis in this study showed that the main content of stones was uric acid and melamine. This composition differs significantly from the most common stones (calcium oxalate, calcium carbonate). In a study of F344/DuCrj male rats receiving 3% or 1% melamine in their diets stones consisted of 61.1% to 81.2% melamine and uric acid (contained in equal molar ratio).<sup>17</sup> The ratio of melamine to uric acid is different in rats from that in children, the reason for which is unclear.

In the present study all clinical symptoms resolved following conservative treatment, and the calculi elimination rate was 42% (21 of 50 patients) at discharge from the hospital. Since melamine related urinary stones are amenable to conservative treatment, we used hemodialysis, which maintained stable renal function and allowed the majority of



patients to recover without intervention. The exception was 1 patient in whom retrograde ureteral stenting was required to drain the renal pelvis. Even patients with melamine related bilateral renal stones rarely required open surgery to relieve the obstruction. Increased diuresis and urine alkalization appear to be sufficient, with hemodialysis applied when indicated.

Clinical signs and symptoms that may indicate renal failure include oliguria/anuria, nausea, vomiting, loss of appetite and renal function examination revealing abnormal plasma BUN, Cr or serum potassium. Recovery in our patients was characterized by a gradual decrease in plasma BUN, Cr and uric acid, increased urine output and passage of the calculus or a decrease in size. Despite the fact that infants who ingested melamine had a significant stone burden, more data are needed to determine the cause and effect relationship between consumption of melamine tainted powdered milk and urinary stone formation.<sup>6,7</sup>

## CONCLUSIONS

Bilateral renal calculi occurred more frequently in children exposed to melamine tainted milk compared to the general pediatric population. Calculus occurrence peaked in children 6 to 18 months old and was easily diagnosed. Ultrasound was useful in diagnosis, and only in indeterminate cases was there a need for other urinary tract imaging. Most melamine related bilateral renal calculi demonstrated a good response to conservative treatment. A few patients with renal failure required hemodialysis.

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## EDITORIAL COMMENT

This article is a retrospective account of the experience of 1 center in treating bilateral stone disease in patients exposed to melamine tainted formula. The take home messages are that stones occurring in these infants are radiolucent (made primarily of uric acid), and can be treated conservatively with hydration and urine alkalization. A debate would probably emerge regarding the group that presented with renal failure and apparent bilateral obstruction. Eight of 9 patients were treated with

hemodialysis instead of ureteral stenting, which the authors imply is an advantage. Many institutions, including ours, would have opted for stenting to relieve the obstruction, followed by conservative treatment until the stones resolved. Hemodialysis would have been reserved for those patients whose renal insufficiency persisted despite relief of the obstruction. Prompt diagnosis, medical support and conservative management work most of the time but sometimes surgical intervention is warranted.

This article is timely in that there has been much dramatic and zealous speculation in the news media regarding the urinary consequences of melamine exposure in children. Unfortunately the report does little to tie the occurrence of stone disease to melamine exposure in any other than a circumstantial way. The study is an observational account of 50 patients, and while there certainly appears to be a link, there are still few scientific epidemiological

data or mechanistic explanations that infant ingestion of melamine tainted formula results in kidney stones. As a result, the findings must be interpreted with some caution.

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## REPLY BY AUTHORS

We agree with stenting to relieve obstruction in the common stone case. However, hemodialysis was performed according to the regimen issued by the Ministry of Health, China. A good treatment effect was achieved for the patients with melamine stones and acute renal failure. In addition, not all patients with renal failure had significant ureteral obstruction and for those patients hemodialysis is appropriate. Furthermore, the patients at our center chose hemodialysis for renal insufficiency rather than stenting after knowing that these 2 methods

have a similar treatment effect. Finally although we agree that more proof is needed, many facts have been provided that demonstrated a close association between the consumption of melamine tainted powdered milk and urinary stones. A series of articles have been published on this topic (reference 6 in article).<sup>1,2</sup> Recently Guan et al reported significant evidence demonstrating that the outbreak of urinary stones in young children in late 2008 in China was related to the consumption of melamine tainted formula.

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