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ORIGINAL PAPER

Melamine-induced infant urinary calculi: a report on 24 cases and a 1-year follow-up

Xiangbo Zhang · Jinliang Bai · Pengcheng Ma · Jianhua Ma · Jianghou Wan · Bin Jiang

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Abstract Melamine has been the main factor leading to infant urinary calculi occurring on a rather wide scale in China in 2008, which were the results of a rapid aggradation of metabolites such as cyanuric acid diamide, cyanuric acid, etc., causing uric acid stone to accumulate. Here, we present a report on 24 infants who were admitted to our department, their ages ranging from 3 to 10 months. All of these infants had a confirmed history of having been fed with the "Sanlu" brand milk powder, which contained excessive levels of melamine, with the highest being 2,563 mg/kg. The diagnosis, medical treatment and follow-up by ultrasonography at 1, 3, 6, 12 months were reported. 22 cases of these infants were rehabilitated after medical treatment and 1 infant underwent pyelolithotomy for relieving an obvious ureter obstruction. No recurrence was found in these babies thereafter. Another infant died from rapidly worsening renal failure. Therefore, this series of cases have demonstrated that melamine contained in the "Sanlu" milk powder was the main cause of these urinary stones. Urine alkalinization and stone liberalization were the most effective treatments. Fast diagnosis and treatment of acute obstructive urolithiasis may prevent the development of acute renal failure, which is associated with high morbidity and mortality rates.

X. Zhang (✉) · J. Bai (✉) · P. Ma · J. Ma · J. Wan · B. Jiang
Department of Urology,
The First Hospital of LanZhou University,
West DongGang Road, ChengGuan District,
Lanzhou City 730000, Gansu, China
e-mail: zhangxb2006@yahoo.com.cn

J. Bai
e-mail: baijl2008@163.com

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Introduction

To our knowledge, urolithiasis caused by melamine-tainted milk is rare, and infant urinary stone induced by melamine has been even less reported. Here, we report on 24 cases admitted to our department, the ages of the infants ranging from 3 to 10 months. All of these infants had a confirmed Sanlu milk powder feeding history. The diagnosis, medical treatment and follow-up by ultrasonography at 1, 3, 6 and 12 months were reported. We hope that the advantages and disadvantages of our experience could benefit subsequent diagnosis, treatment and follow-up of melamine induced urinary stone patients.

Patients and methods

Patients

From April 30, 2008 to October 31, 2008, 24 infants with urinary stones caused by melamine-tainted Sanlu baby formula were admitted, then the clinical data of 23 babies at 1, 3, 6 and 12 months' follow-up by ultrasonography were retrospectively reviewed. These infants, 15 males and 9 females, were aged from 5 to 10 months (their mean age is 7.6 months) and their clinical experience lasted from 10 to 40 days (the mean being 18.5 days). There were six cases with left kidney stone, eight with bilateral kidney stones, four with right kidney or upper ureteral calculi, six with bladder stones and one with bilateral ureteral calculi, which

ultimately led to serious renal failure. All of these infants had confirmed Sanlu milk powder feeding history from 5 to 9 months (mean 7.6 months), and this brand milk powder contained excessive levels of melamine, the highest level being 2,563 mg per kg milk powder.

Management

The evaluation of each baby included anamnesis, clinical examination, laboratory tests (serum creatinine, BUN, uric acid level, serum electrolytes and routine blood test), plain X-rays of the abdomen. The empiric diagnosis of urate stones was based upon biochemical parameters associated with finding stones by ultrasound and absence of radiopaque calculi on plain film radiography.

Initial resuscitation consisted of respiratory control, vascular access, intravenous fluid, monitoring of vital signs and urinary catheter insertion, if necessary. After initial resuscitation, medical treatment was administered to eliminate stones spontaneously, as soon as a percutaneous nephrostomy was performed, if possible. The medical treatment consisted of fluid loading with loop diuretic to force diuresis (0.9% saline solution 20 ml/kg and furosemide 1 mg/kg, IV). 8.4% sodium bicarbonate (1 mEq/kg) was administered IV to alkalinize urine (desired urine pH > 7) and to inhibit uric acid production in all the infants. Ampicillin (100 mg/kg/day) was routinely added to medical treatment for prophylaxis. Following the relief of melamine stone, to accurately diagnose and evaluate stone disease, urine cultures, stone analysis and additional tests were performed using 24 h urine collections and IVU. Following these treatment, an ultrasound scan of the kidney and ureter at 1, 3, 6 and 12 months were performed, in order to evaluate possible recurrence.

Results

Diuresis started in 22 infants in the next 8 h (mean 6 h) after the beginning of therapy, following medical treatment. No serious side effects were observed in them. The conditions of these infants improved gradually and, about 4 days later, stones 2–3 mm in diameter started to pass spontaneously. All stone analyses revealed pure uric acid. Subsequent USG and IVU studies indicated no anatomical abnormalities or residual stones. The timing of follow-up imaging was based on renal function. The time interval for dissolution or spontaneous passing of all uric acid calculi in patients was 6 days (ranging 3–15 days). The urine cultures were sterile. First urine analysis displayed a low-pH level but subsequent 24 h urine collections showed normal urine. Pyelolithotomy was performed on one male infant to relieve an obvious ureter obstruction and he was discharged 1 week later. No urinary stone occurrence was found by ultrasound scan at 1, 3, 6 and 12 months' follow-up. Another infant (a boy, 5 months old), with acute anuria and postrenal azotemia, died 4 h after he was admitted and there was no time to perform any renal replacement therapy in the form of peritoneal or hemodialysis on him. The clinical experiences of these two infants were presented as follows.

Case report

Case 1

A 10-month boy with an 8-day history of vomiting, watery diarrhea and low-grade fever was initially admitted to a local hospital because of dehydration. He was healthy before and had not been given any medical treatment. No history of kidney problem, including urolithiasis, was found in his family members. When he was admitted to our place, physical examination revealed mild body edema, with a pulse of 120 beats per min, a respiratory rate of 56 per min and a temperature of 37.8°C. His body weight was 7.6 kg, average for his age.

Laboratory testing results were white blood cell count 11.1×10^9/L, hemoglobin 104 g/L, hematocrit 30.2%, platelets 12.5×10^9/L, blood plasma urea nitrogen level 4.2 mmol/L, serum creatinine 88.6 μmol/L, uric acid 212 μmol/L, sodium 129 mmol/L, potassium 5.3 mmol/L, chloride 97 mmol/L, calcium 2.12 mmol/L, phosphate 1.31 mmol/L and C-reactive protein 2.04 μg/ml (normal < 0.05). Urinalysis by dipstick showed hematuria (occult blood 3+), proteinuria (1+), and leukocyturia (2+). Urine pH and specific gravity were 4.21 and 1.014, respectively. Ultrasound scan of the kidney showed a strong echo of about 13 mm in the right ureter, with sound shadow following it. No positive discovery was made by plain X-ray examination. So a diagnosis of urinary tract obstruction by uric acid stone was made and ureterolithotomy was performed on him to relieve acute obstruction. A stone 12 mm in diameter was found in the lower ureter and stone analyse showed the main composition is uric acid.

Case 2

A 5-month boy with a 10-day history of oliguria was initially admitted to a local hospital because of anorexia. He was born in Caifu, a small village in Gangu County, Gansu Province. He was fed with goat's milk and powder milk since his mother lacked breast milk from his birth. At the local hospital, he was diagnosed with dyspepsia, and was given some digestants for 3 days. But his condition worsened progressively, so he was brought to local town hospital, where the doctor thought the baby was having urethritis and treated him with "oral drug" for another 3 days, the

detail of which was not clear. However, the symptomatic anuria continued to deteriorate. Finally, he was brought to the Hospital of Gangu County, where an ultrasound scan of the kidney was performed, showing bilateral hydronephrosis, although no obstructive lesion could be identified. At 10 p.m. of April 30, 2008, he was transferred to our hospital when he demonstrated prolonged oliguria despite sufficient fluid replacement therapy. Another ultrasound scan of the kidney performed in the emergency room showed bilateral hydronephrosis, a strong echo of about 5 mm in the right upper ureter, with sound shadow following it. The diameter of upper right ureter is about 8 mm, with a shown paragraph about 28 mm long. Renal sinus area can be seen as having an about 10 mm liquid separation, and a strong echo of about 8 mm with rear acoustic shadow was found. The diameter of the upper left ureter is about 6 mm, with a shown paragraph about 20 mm long. CT scan showed that the volumes of bilateral renal sinus area had increased, upper hydroureter was detected. Laboratory testing results were: white blood cell 18.5×10^9/L, red blood cell 3.15×10^{12}/L, hemoglobin 107 g/L, hematocrit 30.2%, platelets 135×10^9/L, blood urea nitrogen 46.8 mmol/L, serum creatinine 1062.2 μmol/L, uric acid 302 mmol/L, sodium 133.6 mmol/L, potassium 7.56 mmol/L, chloride 97 mmol/l, calcium 2.1 mmol/L, phosphate 5.6 mg/dl and C-reactive protein 4.04 μg/L (normal < 0.05). Urinalysis by dipstick showed hematuria (occult blood 3+), proteinuria (1+) and leukocyturia (2+). Urine pH and specific gravity were 5.0 and 1.017, respectively.

Based on these findings, a presumptive diagnosis of acute renal failure (ARF) resulting from bilateral ureter obstruction was made. We were to perform kidney drainage for him on May 1, 2008, 1:00 a.m., but the oxygen saturation in him suddenly decreased when he was administered with anesthesia intubation. So, we transferred him to an ICU ward where he was aided with ventilator-assisted breathing. Unfortunately, no treatment could save his life and he died after 4 h after admission despite fluid resuscitation, antibiotic treatment and continuous haemodiafiltration.

Discussion

Because of rare inborn errors of uric acid metabolism, i.e., complete or partial deficiencies in hypoxanthine–guanine phosphor-ribosyltransferase (HPRT) enzyme activity, named Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome, respectively [1, 2], or in conditions associated with excessive production of uric acid, such as tumor lysis syndrome, or lymphoproliferative/myeloproliferative disorders [1, 3], uric acid stones in infants rarely occur. The major factors precipitating uric acid crystals are a high excretion of urate, a small urine volume and a low urinary pH [4]. But all of our cases were induced by melamine, an organic industrial material. No metabolic abnormality or previously undiagnosed disease was found in the cases presented.

Melamine is a raw organic chemical, referred to as triamine, whose molecular formula is $C_3N_3(NH_2)_3$. Melamine is hydrolyzed in strong acid environment in the stomach, generating cyanuric acid diamide and cyanuric acid, which are absorbed into the blood from intestines and have an impact on the body when accumulating to a certain concentration, mainly resulting in cystitis and urinary tract stones, the main ingredients of the latter being uric acid and its salts. The tolerable daily intake is 0.63 mg/kg body weight and a baby's maximum tolerated dose is 15 mg/kg milk. However, the highest level of melamine in "Sanlu" milk powder was as much as 2,563 mg per kg. It has been rarely reported that prematurity and exposure to melamine-contaminated formula were associated with urinary stones, and no severe adverse renal outcomes, such as ARF or urinary tract obstruction, were detected in children after their exposure to low dose melamine [5]. But all of these infants had confirmed "Sanlu" milk powder feeding history, and this milk powder contained excessive melamine that was significantly above the normal level. Therefore, there is strong evidence that "Sanlu" milk powder is the main culprit for the stone cases in these infants.

The clinical manifestation caused by melamine stones depends on their sizes, locations and other factors. They may only present themselves as turbid urine or sand-like urine. Hematuria may appear when the stones do injury to urinary tract mucosa. When stones pass through the ureter, increasing urinary peristalsis and pressure of the collection system can lead to ureteral spasm and the affected children may cry due to intermittent abdominal pain, which is often synchronized with urinary peristaltic cycle. As our second case demonstrated, stones plugging in the bilateral ureter cause anuria; the baby would cry incessantly but nobody, not even the doctors, could know the reason. Then the baby lost appetite and caught cold, with fever, frequent urination, vomiting, anemia and malnutrition. No special symptoms suggested that he was stricken with urolithiasis until an ultrasonographic examination was performed on him. However, by then, severe ARF had developed and no treatment could save his life. Consistent with what was reported [6], the actual condition of a child might be more severe than that of an adult and thus may easily give rise to misdiagnosis and erroneous treatment.

The main component of a melamine stone is uric acid and its metabolites, which are not easily detected by X-ray, although abdominal X-ray plain film can visualize some of larger calculi [7]. Ultrasound screening can be used as a diagnostic method of first choice and it is also an accurate and reliable method for diagnosing melamine stones. It can

fully display the size and location of the calculus and indicate whether it has led to an urinary obstruction, etc., thus providing adequate information for clinical diagnosis or treatment options. For an individual infant with a complex calculus, CT examination could show the number or size of the stones, and also other relevant circumstances and information on the urinary tract. Another feature of stones caused by melamine is that the majority of them are small stones, which are loose, sand-like and easy to be excreted through the urinary tract.

Small calculi in few children will pass through the urethra spontaneously without proper treatment. Babies with uric acid lithiasis and normal renal function are typical candidates for medical treatment. For smaller stones, unilateral or incidental stones, it is appropriate to allow time for the stone to pass through with medical treatment such as ESWL and/or minimal invasive techniques. According to the literature, 4–5% of adult patients with obstructive renal failure have minimal or no dilatation of the renal pelvis [8, 9]. Causes for non-dilatation of the pelvicaliceal system remain uncertain. Kulkarni et al. [10] have explained that there could be either decompression of the pelvicaliceal system by extravasation of the urine from the fornices or modification in the physical properties of the urinary tract wall. Emergency treatment of that is based on urinary diversion, ideally by percutaneous nephrostomy under ultrasonographic control [11]. In our second case, there were bilateral pelvicaliceal dilatations caused by ureter obstruction, but the other cases showed minimal or no pelvicaliceal dilatation, so a urinary diversion was not preferred for initial management. These stones can also cause obstructive ARF in infants [12], as we reported in case 2.

Dissolving uric acid stones with medical therapy is clearly established [13–15], and a selective medical therapy provides almost complete dissolution of some non-obstructive renal stones, especially for uric acid stones. But the main component of melamine-stone is uric acid, which responds well to conservative therapy [16]. Alkalization of urine with citrate can prevent the formation of uric acid stones and can also dissolve them. The mean diameter of the stones that passed decreased to 2–3 mm, suggesting that medical treatment can be successful in these infants. At this point, we would like to stress the importance of water intake, since a large amount of fluid intake can increase urine output, thus reducing the formation of urinary calculi and the concentration of stone forming ingredients, and eventually reducing the stone formation or recurrence. Furthermore, the increase of urine flow in the urinary tract is also conducive to shortening the discharge time of stone patients. At night attention should also be paid to fluid intake. If the urethra were clogged with calculi, the catheter must be plugged into drain the urine from the bladder while, in the process, the stone can also turn into a loose form and will be easily discharged. Very few bilateral ureteral blockages of the urinary bladder in children can be maintained under bilateral ureteral catheter drainage, and the renal function can quickly return to its normal state in 1–2 days.

Fast diagnosis and treatment of acute obstructive urolithiasis may prevent the development of ARF, which is associated with high morbidity and mortality rates [17]. Feeding history may play an important role in the diagnosis of infant urinary calculi. As shown in our second case, urinary stone was rare in an infant and melamine stones had been even less reported, thus adequate attention had not been paid to the history of Sanlu milk feeding. Fortunately, because we noticed in case 1 that he had a long-term feeding history of Sanlu milk powder, a correct diagnosis with melamine stones was quickly made and proper treatment was administered to him as soon as he was admitted, thus avoiding more serious conditions.

In conclusion, renal damage caused by melamine stones may lead to severe conditions in an infant and usually no specific symptom is detected in such a case. Fast diagnosis and treatment of acute obstructive urolithiasis may prevent the development of ARF. As the feeding history plays an important role in the occurrence and development of infant melamine stones, careful inquiry into the feeding history, adequate attention to clinical clues and necessary examination of a questionable infant are effective ways in detecting a stone case. The cases in our care demonstrated that uric acid stones can be relieved with medical treatment. There are also reasons to think that the passage of other stones may be aided by some specific therapies, but they are less efficacious.

References

1. Ankem M, Glazier DB, Barone JG (2000) Lesch-Nyhan syndrome presenting as acute renal failure secondary to obstructive uropathy. Urology 56(6):1056
2. Hikita M et al (1998) Partial deficiency of hypoxanthine-guanine phosphoribosyltransferase manifesting as acute renal damage. Intern Med 37(11):945–949
3. Fujinaga S et al (2005) Acute renal failure due to obstructive uric acid stones associated with rotavirus gastroenteritis. Pediatr Nephrol 20(2):239–240
4. Tiselius HG (2003) Epidemiology and medical management of stone disease. BJU Int 91(8):758–767
5. Lam HS et al (2008) Renal screening in children after exposure to low dose melamine in Hong Kong: cross sectional study. BMJ 337:a2991
6. Guan N et al (2009) Melamine-contaminated powdered formula and urolithiasis in young children. N Engl J Med 360(11):1067–1074
7. Jia LQ et al (2009) Ultrasonographic diagnosis of urinary calculus caused by melamine in children. Chin Med J (Engl) 122(3):252–256
8. Naidich JB et al (1986) Nondilated obstructive uropathy: percutaneous nephrostomy performed to reverse renal failure. Radiology 160(3):653–657

9. Goldfarb R et al (1989) Nondilated obstructive uropathy. Urology 33(3):257
10. Kulkarni S et al (2005) Non-dilated obstructed pelvicalyceal system. Int J Clin Pract 59(8):992–994
11. Ansari ER, Kazim E, Husain I (1982) Management of the choked ureter in obstructive renal failure due to uric acid lithiasis. J Urol 128(2):257–261
12. Shen Y et al (2009) Blood purification therapy in treatment of acute renal failure in infants with melamine-induced stones. Chin Med J (Engl) 122(3):257–261
13. Sharma SK, Indudhara R (1992) Chemodissolution of urinary uric acid stones by alkali therapy. Urol Int 48(1):81–86
14. Shekarriz B, Stoller ML (2002) Uric acid nephrolithiasis: current concepts and controversies. J Urol 168(4 Pt 1):1307–1314
15. Low RK, Stoller ML (1997) Uric acid-related nephrolithiasis. Urol Clin North Am 24(1):135–148
16. Zhang L et al (2009) Melamine-contaminated milk products induced urinary tract calculi in children. World J Pediatr 5(1):31–35
17. Shokeir AA et al (2002) Recoverability of renal function after relief of acute complete ureteral obstruction: clinical prospective study of the role of renal resistive index. Urology 59(4):506–510