

## Brief Report

## Liver Involvement in Melamine-associated Nephrolithiasis

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It is currently believed that melamine ingestion can lead to insoluble crystals in an animal's urinary system with subsequent physical obstruction or bladder carcinoma. However, whether melamine can cause injury of other tissues and organs in humans is yet unknown. In this study, we encountered 3 affected children with liver lesions, 2 males and 1 female, and detailed their clinical characterizations. Their ages were respectively 2, 6, and 10 months. Among the 3 patients with liver lesions, only 1 exhibited symptoms of gradual progressive jaundice, abdominal distention, hepatic intumescence, and bilirubin abnormality; the other 2 were asymptomatic. The mechanism associated with liver lesion may, at least in part, be due to physical deposition and blockage of the biliary tract system. Disturbance of the acid-base equilibrium may be another reason that accelerates stone formation in human tissues.

**Keywords:** Alanine aminotransferase, child, liver lesion, melamine, nephrolithiasis, ultrasonography

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**Introduction**

Since the outbreak of the “Melamine Milk Crisis” in September 2008, many clinical and experimental investigations have revealed some common aspects of childhood urinary stones induced by melamine tainted formula.<sup>1</sup> We have previously described the correlation between stone formation and exposure history in 49 children with melamine-associated nephrolithiasis, and found that the size of melamine-induced stones was dependent on the melamine content of the formula ingested, but not on the duration of exposure.<sup>2</sup> However, whether melamine can cause injury of other tissues and organs in humans is yet unknown.<sup>3</sup> Here, we retrospectively review the clinical data of these patients and encounter 3 affected children with liver lesions.

**Materials and Methods**

A total of 49 children who suffered from melamine-associated nephrolithiasis were recruited into our study from September to December 2008. All patients ranged in age from 1 to 96 months, with a mean of 25 months. There were 32 males and 17 females. History of exposure to contaminated formula (formula brand, melamine content, duration of consumption, use of formula alone, or in combination with breast milk) was documented. The content of melamine was estimated according to the report by the General Administration of Quality Supervision, Inspection, and Quarantine of China (GAQSIQC).<sup>4</sup> Urinalysis, renal function [blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UA)], liver status [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), and  $\gamma$ -glutamyltransferase (GGT)], and serum

electrolytes ( $K^+$ ,  $Na^+$ ,  $Cl^-$ , and  $HCO_3^-$ ) were determined. Anion gap (AG) was calculated as  $AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$ . Urinary and hepatic ultrasonography was performed in all 3 children. Since most melamine-associated nephrolithiasis were small or sand-like, and none of our patients were in serious condition, simple conservative managements were adopted, that included fluid infusion, urine alkalization, increased water intake, and increased urination.

**Results**

There were 3 children, 2 males and 1 female, diagnosed with liver lesions (ALT > 40U/L, and/or AST > 40U/L, and/or GGT > 50U/L). Their ages were 2, 6, and 10 months. None suffered from any of the following infections: TORCH, HAV, HBV, HCV, EBV, HIV, and SY. In addition, other common or uncommon diseases, such as biliary atresia, progressive familial intrahepatic cholestasis, metabolic liver disease, and idiopathic neonatal hepatitis were ruled out. The other 46 patients who had no liver involvement ranged in age from 1 to 96 months, with a mean of  $23 \pm 7.8$  months. There were 30 males and 16 females. The median age at diagnosis was significantly earlier in children with liver lesions ( $P < 0.05$ ), while the male/female ratio was identical in the two groups ( $P > 0.05$ ).

Most affected children were asymptomatic (15 cases; 30.6%). Three main clinical presentations, including unexplained crying when urinating (9 cases) was seen in 18.4%, oliguria (8 cases) in 16.3%, and abdominal pain (6 cases) was noted in 12.2% of melamine-associated nephrolithiasis. Among 3 patients with liver lesions, only 1 exhibited gradual progressive jaundice, abdominal distention, hepatic intumescence, and bilirubin abnormality; the other 2 were asymptomatic.

The clinical data of the 2 groups in this study are shown in Table 1. Higher ALT, AST, TBIL, DBIL, IBIL, and GGT were present in patients with liver lesions when compared to those without liver involvement ( $P < 0.05$ ), whereas for the duration of consumption and the diameter of nephrolithiasis, the opposite was found ( $P < 0.05$ ).

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**Table 1.** The clinical data of patients.

Parameter	Patients with liver lesions (n = 3)	Patients without liver involvement (n = 46)	P-value
Melamine content (mg/kg)	1331.3 ± 1207.3	1295.3 ± 967.1	NS
Duration of consumption (m)	5.7 ± 4.5	19.5 ± 6.3	<0.0001
Urine pH	5.8 ± 0.3	6.3 ± 0.6	NS
BUN (μmol/L)	3.3 ± 0.6	4.7 ± 1.2	NS
Cr (μmol/L)	14.3 ± 3.8	12.7 ± 8.9	NS
UA (μmol/L)	221.0 ± 82.3	254.9 ± 74.8	NS
ALT (U/L)	119.3 ± 72.5	25.2 ± 8.7	<0.0001
AST (U/L)	107.3 ± 50.2	35.6 ± 9.5	<0.0001
TBIL (μmol/L)	57.3 ± 90.6	4.7 ± 1.7	<0.0001
DBIL (μmol/L)	39.0 ± 63.2	2.9 ± 1.1	<0.0001
IBIL (μmol/L)	18.0 ± 27.5	1.3 ± 0.2	<0.0001
GGT (U/L)	58.7 ± 68.7	15.7 ± 2.3	<0.0001
K <sup>+</sup> (mmol/L)	5.0 ± 0	4.5 ± 0.4	NS
Na <sup>+</sup> (mmol/L)	141.3 ± 4.9	139.5 ± 2.3	NS
Cl <sup>-</sup> (mmol/L)	105.0 ± 5.2	103.4 ± 2.4	NS
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	18.7 ± 0.6	19.4 ± 2.4	NS
AG (mmol/L)	22.7 ± 0.6	21.2 ± 2.4	NS
Diameter of nephrolithiasis (mm)	2.7 ± 2.2	6.5 ± 3.9	<0.0001

NS = not significant.

## Discussion

Former research has mentioned liver involvement in melamine-associated nephrolithiasis. In a report by Guan et al.,<sup>3</sup> serum ALT levels were normal in all but 2 children, similar to our results, both of who were also under 1 year of age. In addition, according to a report by Zhang et al.,<sup>5</sup> 5 children with urinary stones induced by melamine-tainted formula had liver abnormalities, which included hepatomegaly, elevated AST, and gallstones. These findings were compatible with the observations from animal model studies. In Chinese feeding studies where Roman laying hens were administrated melamine at 8.6~140.9 mg/kg for 34 days, concentrations of melamine in the kidney were 1.3~21.7 mg/kg and in the liver concentrations reached 0.5~6.9 mg/kg.<sup>6</sup> In our study, the concentrations of ALT and AST in all 3 patients were elevated to some extent. However, only 1 patient exhibited the significant manifestations of liver lesions, with gradually progressive jaundice, abdominal distention, hepatic intumescence, and bilirubin abnormality. The mechanism associated with liver lesions is unclear, but may, at least in part, be due to physical deposition and blockage of the biliary tract system. Significantly elevated levels of DBIL and GGT indicate the existence of obstruction. Disturbance of the acid-base equilibrium, such as higher AG and lower urine pH, may be another reason that accelerates stone formation in human tissues.<sup>7</sup>

Because many children with identified stones were asymptomatic, and liver status was not a part of routine screening, it was likely that there were many more cases with liver lesions not brought to the attention of medical authorities. Also, many children had small biliary tract stones undetectable by standard methods, which could have led to a possible underreporting of affected children.<sup>8</sup> Therefore, liver involvement in melamine-associated nephrolithiasis should be noted in future studies.

## Conflict of interest statement

The authors declare that they have no conflict of interest related to the contents of this manuscript.

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