Original Article

A Survey of Urolithiasis in Young Children Fed Infant Formula Contaminated with Melamine in Two Townships of Gansu, China

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Abstract

Objective To determine the prevalence of urolithiasis in young children fed infant formula (IF) contaminated with melamine, and the association between IF consumption and urolithiasis.

Design A total of 2 733 children ≤3 years of age on September 1, 2008 in two townships of Gansu Province, China were studied. Cases of urolithiasis were diagnosed by ultrasonography. Milk product consumption was determined by their caregivers. Remaining IF samples were tested for melamine and cyanuric acid.

Results Of 2 733 eligible children in the two townships, 2 186 (80%) were enrolled in our study. Overall, 16.6% (362) of 2 186 children had urolithiasis. The prevalence was 24.6% in children exclusively fed Sanlu brand IF, 9.7% in those fed other IF, and 8.5% in those fed exclusively on other milk products. For children exclusively breast-fed, no urolithiasis was found (P<0.05). The prevalence of urolithiasis was 11.4% in children fed 400 g of Sanlu IF, rising to 37.5% in children fed over 25 600 g. Of 48 Sanlu IF samples, 91.7% contained melamine (median=1 800 ppm; range=45-4 700) and 66.7% contained cyanuric acid (median=1.2 ppm; range=0.4-6.3). Melamine was also detected in 22.2% of 36 other brand IF (median=27.5 ppm, range=4-50).

Conclusions Urolithiasis was associated with melamine-contaminated IF. Although one product caused most morbidity, other milk products may have also contributed to the outbreak.

Key words: Urolithiasis; Melamine; Infant formula; Contamination

Biomed Environ Sci, 2012; 25(2):149-155 doi: 10.3967/0895-3988.2012.02.004 ISSN:0895-3988

www.besjournal.com (full text) CN: 11-2816/Q

INTRODUCTION

Melamine is an industrially synthesized chemical used in a wide variety of products, such as laminates, coatings and plastics. Because of its high nitrogen content (66.6% by weight), and the inability of commonly used methods for protein analysis to distinguish between nitrogen from protein and non-protein sources, producers added it to animal foodstuffs for financial gain, but this resulted in an outbreak of urolithiasis and renal failure in dogs and cats from

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Received: October 23, 2011; Accepted: January 18, 2012

Asia and North America in 2004 and 2007[1].

On September 11, 2008, China announced the occurrence of widespread urolithiasis among children. Many of the initial patients had consumed the Sanlu brand of infant formula (IF)[2]. Melamine was detected in Sanlu IF and identified as the cause of the outbreak[3-4]. On September 13, 2008, the Chinese government began offering nationwide free screening of Infants and young children using ultrasonography[5]. By the end of November 2008, screening had identified 294000 infants and children with urolithiasis linked to melamine-contaminated IF. More than 50000 infants and children were hospitalized and six deaths were attributed to melamine-associated urolithiasis[6]. Few studies have been published about this outbreak to date, and none have provided a population-based estimate of the prevalence of urolithiasis in relation to various levels of exposure to IF. Within days of the initial announcement of this crisis in China, we conducted a population-based survey to determine the prevalence of urolithiasis in young children bottle-fed IF contaminated with melamine, in order to determine more clearly the relationship between melamine-contaminated milk and urolithiasis.

METHODS

Target Population and Subject Enrollment

We conducted a survey from September 15 to 27, 2008 in two townships of Wuwei City, Gansu Province, where the urolithiasis outbreak was first recognized. We identified 2733 children from the local immunization registry, who were born after September 1, 2005, as the study population.

The local government and village doctors requested parents or guardians of eligible children to take their children to the county hospital or to the two township hospitals to receive urolithiasis screening. As a result, 1904 children were screened in the township hospitals and 181 in the county hospital. We also selected a random sample of 101 children from the 547 eligible children who did not participate in the initial screening and screened them in their respective villages. Therefore, 2186 eligible children participated in the study giving a response rate of 80%.

Case Definition, Exposure Information, and Urine Specimen Collection

We defined a case as urolithiasis on ultrasonographic visualization of calculi ⩾2 mm in diameter in the kidney, ureter or bladder of an eligible child. The questionnaire was initially tested on parents or guardians of 43 hospitalized children with urolithiasis in two provincial hospitals. Twelve investigators from national, provincial and local Centers for Disease Control and Prevention (CDC) were trained to administer the final questionnaire to parents or guardians of the eligible children. The data included socio-demographic information, observations about urinary tract signs and symptoms, and a detailed feeding history from birth. The feeding history included IF, pasteurized milk, packaged liquid milk, other milk products, and breastfeeding.

For children who were fed with IF, we collected information about the brand of IF; for children, who were exclusively fed with Sanlu IF, we collected information about the number of bags or cans of IF consumed and different net content (g) for every type of bags or cans to estimate the accumulated Sanlu IF consumption. Following oral consent from parent or guardian, we collected urine specimens from each participant. Urinalyses included assessment for protein, occult blood, leukocytes, red blood cells, white blood cells, crystals, and casts.

Melamine and Cyanuric Acid Testing

Eighty four samples from remaining IF were collected from the families to test the melamine and cyanuric acid content. Melamine and cyanuric acid were extracted from the samples using a solvent mixture of diethylamine, water and acetonitrile (10/40/50, v/v/v,). The extracts were evaporated to dryness by a gentle nitrogen stream, and the target compounds were derivatized by a silylating reagent. Melamine and its analogues were detected by gas chromatography/tandem mass spectrometry, with 2,6-diamino-4-chloropyrimidine (DACP) as an internal standard[7]. Analyses were performed at the Institute for Nutrition and Food Safety, China CDC.

Statistical Analysis

EpiData 3.0, SPSS 13.0, and EPIINFO 3.5.1 were used for data management and analysis. Chi-square tests and Fisher's exact test were used to compare categorical data. All reported *P* values are two-sided with values <0.05 indicating statistical significance.

RESULTS

The prevalence of urolithiasis among children who were taken for screening in hospitals was 16.7% (348/2085), compared with 13.9% (14/101) among the random sample of 101 children who screened in their villages (P=0.46; Chi-squared test). The 101 children who screened in their villages did not differ in their age or sex distribution from the children who were taken for screening in hospitals. With the small differences between these groups, we combined all the data for further analysis.

Of the 2 186 children, 16.6% (362/2 186) had urolithiasis with similar prevalence in both sexes (16.7% in girls and 16.3% in boys, P=0.82). Overall, 99.7% (361/362) of calculi were in the renal pelvis. Only 4.8% (104/2 168) were found to have hydronephrosis on ultrasound examination. Boys were significantly more likely to have hydronephrosis (5.6%) than girls (3.5%) (Table 1).

Table 1. Urolithiasis and Hydronephrosis Among 2 186 Children ≤3 Years Old

Ultrasound Result	All (2 186)		Male (1 329)		Female (857)	
	n	%	*n*	%	*n*	%
Urolithiasis	362	16.6	222	16.7	140	16.3
Kidney Stone	361	16.5	221	16.6	140	16.3
Unilateral	244	11.2	143	10.8	101	11.8
Bilateral	117	5.4	78	5.9	39	4.6
Ureteral Stone	2*	0.1	2	0.2	0	0
Unilateral	2	0.1	2	0.2	0	0
Bilateral	0	0	0	0	0	0
Bladder Stone	2†	0.1	2	0.2	0	0
Hydronephrosis	104	4.8	74	5.6‡	30	3.5
Unilateral	86	3.9	61	4.6	25	2.9
Bilateral	18	0.8	13	1	5	0.6

Note. *Both accompanied by kidney stones. †One accompanied by a kidney stone. ‡The prevalence in boys and girls was significantly different (χ^2=4.92, P=0.026).

The prevalence of urolithiasis increased from 5.9% among children aged 0-5 months to a peak of 20% in children aged 12-17 months, and then decreased gradually as age increased (Figure 1).

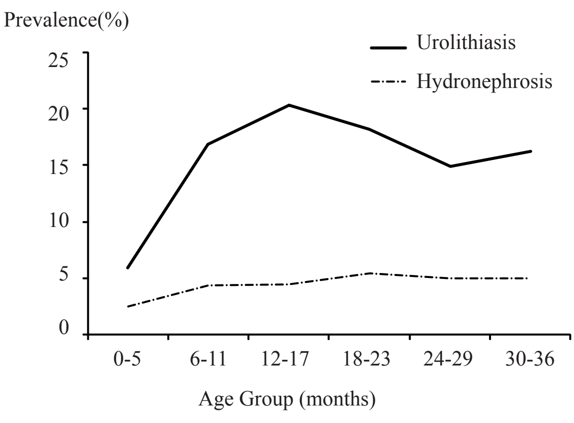

Figure 1. Urolithiasis and hydronephrosis prevalence among 2 186 children ≤3 years old in two townships, Wuwei prefecture, Gansu province, China, 2008.

Of the children identified with urolithiasis in ultrasound screening, 23.8% had one or more urinary symptoms or signs and were more likely than children without urolithiasis to have oliguria, cry on urination, have difficulty urinating, or had anuria. The risk of these features ranged from 6.4% to 10.9%. Urinalysis revealed that <8% of cases had hematuria, proteinuria, or leucocyturia. Crystals or casts were not found in either group of children (Table 2).

The prevalence of urolithiasis was 24.6% [95% confidence interval (CI): 20.1-29.1] among 350 children exclusively fed Sanlu IF, 17.8% (95% CI: 15.7-19.9) in children fed Sanlu IF plus other IF, 17.3% (95% CI: 15.7-18.9) in children fed any IF, 9.7% (95% CI: 6.9-13) in children fed any IF excluding Sanlu IF, and 8.5% (95% CI: 1.4-15.6) in children fed other milk products excluding IF. The 64 children (age range=1-35 months) who were exclusively breast-fed had neither urolithiasis nor hydronephrosis. These children were weaned on a typical local diet of vegetables, rice, and small amounts of meat that did not contain any milk or milk products. Children whose milk consumption had been exclusively breast milk had a median age of 9 months (range=1-35 months) while the other children had a median age of 21 months (range=0-35 months). In comparison to breast-fed children, the prevalence of urolithiasis in children fed with milk products was significantly higher (P<0.05). However, the prevalence of hydronephrosis was significantly higher only in children fed exclusively with Sanlu IF (P<0.05) (Table 3).

Table 2. Signs, Symptoms and Clinical Laboratory Findings among 2 186 Children Screened for Urolithiasis

Symptoms and Signs	Urolithiasis Children (*n*=362)		Other Children(*n*=1 824)		Difference% (95% CI)
	n	%	*n*	%	
Any urinary symptoms or signs	86	23.8	129	7.1	16.7 (12-21)
passing of stones	46	12.7	32	1.8	10.9 (7.3-14.6)
Oliguria	46	12.7	42	2.3	10.4 (6.7-14.1)
crying on urination	48	13.3	53	2.9	10.4 (6.6-14.1)
Urinary difficulty	46	12.7	54	3	9.7 (6.1-13.4)
Anuria	24	6.6	3	0.2	6.4 (3.7-9.2)
macro hematuria	4	1.1	4	0.2	0.9 (-0.38-2.1)
Edema	4	1.1	4	0.2	0.9 (-0.38-2.1)
Other symptoms and signs	57	15.7	121	6.6	9.1 (5.0-13.2)
Vomiting	32	8.8	42	2.3	6.5 (3.4-9.7)
Fever	42	11.6	75	4.1	7.5 (3.9-11.1)
Cough	22	6.1	61	3.3	2.8 (-0.03-5.5)
Urine microscopic exam*					
Red blood cell	9	2.6 (9/349)	12	0.7 (12/1737)	1.9 (0.008-3.8)
White blood cell	8	2.3 (8/349)	25	1.4 (25/1737)	0.9 (-0.99-2.7)
Urine analysis*					
Hematuria	26	7.7 (26/336)	78	4.7 (78/1654)	3 (-0.19-6.2)
Proteinuria	13	4.2 (13/306)	83	5.0 (83/1653)	-0.8 (-3.5-1.9)
Leucocyturia	2	0.7 (2/306)	26	1.6 (26/1653)	-0.9 (-2.2-0.36)

Note. *The different numbers of specimens for urine testing items are due to insufficient volume of urine.

Table 3. Prevalence of Urolithiasis or Hydronephrosis, by Milk Consumption Among Children ≤3 Years Old

Children's Feeding History	*n*	Exposed%	Urolithiasis			Hydronephrosis		
			n	Prevalence % (95% CI)	*P*	*n*	Prevalence % (95% CI)	*P*
Exclusively breast-fed	64	2.9	0	0	Ref.	0	0	Ref.
Milk products	2 122	97.1	362	17.1 (15.5-18.7)	<0.001	104	4.9 (3.9-5.7)	>0.05
Any infant formula (IF)	2 063	94.4	357	17.3 (15.7-18.9)	<0.001	100	4.8 (3.9-5.7)	>0.05
Sanlu IF	1 639	75	316	19.3 (17.4-21.2)	<0.001	88	5.4 (4.3-6.5)	>0.05
Exclusively Sanlu IF	350	16	86	24.6 (20.1-29.1)	<0.001	22	6.3 (3.8-8.8)	<0.05
Sanlu IF plus other IF	1 289	59	230	17.8 (15.7-19.9)	<0.001	66	5.1 (3.9-6.3)	>0.05
Other IF except Sanlu IF	424	19.4	41†	9.7 (6.9-12.5)	<0.01	12	2.8 (1.2-4.4)	>0.05
Only other milk products*	59	2.7	5‡	8.5 (1.4-15.6)	<0.05	4	6.8 (0.4-13.2)	>0.05
All children	2 186	100	362	16.6 (15.0-18.2)	-	104	4.8 (3.9-5.7)	-

Note. *Including pasteurized milk, packaged liquid milk, raw milk, rice soup, and soy milk. †Six children consumed only one other IF, and 35 consumed multiple other IF except Sanlu IF. ‡Four consumed only pasteurized milk, and one pasteurized and packaged liquid milk.

Melamine was found in 91.7% (44) of the 48 Sanlu IF samples with a median level of 1800 ppm (range=45-4700 ppm), while 22.2% (8) of 36 other IF samples had a median level 27.5 ppm (range=4-50 ppm). Cyanuric acid was found in 67% (32) of Sanlu IF with a median of 1.2 ppm (range=0.4-6.3), and in 64% (23) of 36 other IF samples with a median of 1.0 ppm (range=0.3-5.0 ppm). Both melamine and cyanuric acid were found in 60% (29) of Sanlu IF samples and in 17% (6) of the other IF samples (P<0.05).

The production dates for 36 Sanlu IF samples were examined. The highest contamination levels of melamine were from Sanlu IF produced in December, 2007 (4 700 ppm) and in July, 2008 (4 000 ppm). The highest contamination levels (6.3 ppm) of cyanuric acid found in the Sanlu IF specimens were produced in April, 2008.

Of 350 children exposed only to Sanlu IF, 344 caregivers were able to remember the number of bags of IF that were consumed. From these data we identified 19 children whose estimated consumption of Sanlu IF was <400 g. They had no urolithiasis. Above that consumption level, the prevalence of urolithiasis rose from 11.4% in the 400-3200 g level to 37.5% in the 25600-76000 g level (P<0.001, Chi-squared for linear trend) (Table 4).

Table 4. Prevalence of Urolithiasis According to Estimatedtotal Sanlu Infant Formula Consumption among 344 Children ≤3 Years Old Who Drank Exclusively Sanlu Infant Formula

Estimated total consumption (g) of Sanlu infant formula	No. Children	Urolithiasis	Prevalence (%)
20+	19	0	0.0
400+	70	8	11.4
3200+	44	7	15.9
6400+	51	12	23.5
12800+	96	34	35.4
25600-76000	64	24	37.5
Total	344	85	24.7

DISCUSSION

This population-based study showed that 16.6% of children ≤3 years old had urolithiasis. This estimate is much higher than children screened throughout China (1.3%)[6]. Among other studies during this crisis, there was a high variability in the estimated prevalence of melamine-related urolithiasis among young children, ranging from 10% in a hospital-based study in Beijing[8] to 0.05% in Hong Kong[9]. The high prevalence of urolithiasis in our survey may result from four factors. First, the consumption of IF in children in this area was high (94.4%), including 75% consuming Sanlu IF, which was the most heavily contaminated IF. Second, in our study, we found melamine in 92% of Sanlu IF samples, and the melamine contamination level was higher in Sanlu IF than in brands used in other parts of China (0.1 to 2563 ppm in 22 brands of IF)[10]. Third, we used a more sensitive screening criterion, ≥2 mm, for urolithiasis. Fourth, both the national screening and local studies had important selection biases related to the population. For example, children included in the national screening had a wider age range. Parents of some children whose initial ultrasound results showed no urolithiasis may have taken their children to different hospitals for repeat tests, thus reducing the prevalence with repeat negative tests.

An unexpected finding was the urolithiasis prevalence of 8.5% among children who were fed exclusively milk products other than IF. Of the five cases in this group, four used only milk from local township dairies. This figure greatly exceeds the population-based estimates of annual urolithiasis from other countries, including 6.9/100 000 (0-14 years old) in Kuwait[11], 6.3/100 000 (0-16 years old) in Iceland[12], and 1.2/100 000 (0-4 years old) in the United Kingdom and Ireland[13].

Hypothetically, contamination of fresh milk could occur through several mechanisms. First, the producer may have adulterated fresh milk with melamine or supplemented their production of fresh milk with milk reconstituted from contaminated milk powder. Second, melamine from food packaging materials and containers may migrate into milk. However, one study conducted in 2008 did not find melamine in various types of polypropylene and polycarbonate packaging materials[14]. Third, melamine had been used as a source of non-protein nitrogen supplement in cattle feed from 1958 to 1978 in China for ruminants[15]. However, this practice was generally discontinued when studies revealed that it was inefficient and led to urolithiasis in these livestock. Fourth, environmental contamination with melamine may have contaminated the pastures. Indeed, in the past, melamine was also used as a fertilizer until it was found that it released nitrogen too slowly. In any event, about 20% of any melamine in a cow's diet will be present in the milk[16]. This suggests the need for scrutiny of animal feed and environmental contamination.

Our study showed that urolithiasis associated with melamine was most often asymptomatic, and that kidney stones were the main clinical manifestation. About a quarter of children with urolithiasis had urinary symptoms or signs. Hematuria, a hallmark of urolithiasis, was also rare as was proteinuria and leucocyturia. Chemical analysis of the calculi from patients during this crisis revealed melamine and uric acid without cyanuric acid[17-18]. Very low concentrations of cyanuric acid in IF samples found in our study and in another survey[19] possibly represent residues from melamine synthesis or environmental contamination. Previous experience with urolithiasis from cyanuric acid and melamine involved much higher concentrations of cyanuric acid[1,20-22]. Since infants have higher uric acid excretion than adults, the precipitation of melamine–uric acid complexes may also be expected to be greater in infants. This probably accounted for the observation of melamine-uric acid calculi and urolithiasis formation without cyanuric acid.

There are at least three main limitations in our study. First, prevalence was estimated from a single screening. An unknown number of children who developed urolithiasis during the period of melamine contamination would have excreted all calculi before the screening. Thus, the point prevalence determination from this study would underestimate the total prevalence and cumulative incidence. Moreover, a proportion of the children with urinary tract symptoms and signs may also have had calculi at times other than the screening day. As a result, the true prevalence and cumulative incidence of symptomatic urolithiasis may be substantially higher than estimated from the screening. Second, we did not collect samples of other milk products to test for melamine since we did not expect to find an elevated prevalence of urolithiasis in children who were only fed other milk. Third, the feeding histories covered many months and were derived from recall of parents or guardians. This recall bias would tend to diminish the differences in prevalence estimates between the different types of IF and milk.

In conclusion, the outbreak of urolithiasis was caused by melamine-contaminated IF and, in particular, by the contaminated Sanlu brand. Other IF brands and even other milk products may also have contributed to the total prevalence. Generally, calculi were small and the urolithiasis was asymptomatic. Although a limited number of follow-up studies have shown that these exposures and morbidity have no effect on childhood growth and development of affected children 20 months after hospital discharge[23-24], health authorities and healthcare providers should evaluate and investigate children with melamine-related urolithiasis for long-term consequences when they visit the hospital in the future with related symptoms.

ACKNOWLEDGEMENTS

We warmly thank the local Centers for Disease Control and Prevention and Health Bureau of Wuwei City and Liangzhou district, Wuwei City Cancer Hospital, and Gaoba and Jinyang township hospitals for their assistance in coordinating, and participating in, the investigations, and for the logistical support. We especially appreciate the assistance of Dr. Robert E. Fontaine, Dr. ZHU Bao Ping and Michael Engelgau, resident advisors from the US CDC for helping us review the manuscript.

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