HK J Paediatr (new series) 2014;**19**:15-21

Growth of Children with Urolithiasis Associated with Melamine-contaminated Milk Powder: A Follow-up Study

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Abstract

Objective: To study the impact of melamine-contaminated milk powder on children's growth and development and the elimination of urinary tract stones. ***Patients and Methods:*** Seventy-three patients aged ≤4 years with ultrasonographically diagnosed urolithiasis after intake of contaminated milk powder were compared with 79 healthy controls. Assessment included indicators of growth and development based on reference data from World Health Organisation (WHO) standards, Brightness mode (B-mode) ultrasonography as well as urine and blood lab analysis. ***Results:*** According to WHO standards, whether at time of diagnosis or 18 months after follow-up, urolithiasis patients all showed generally lower z-scores, compared with control. At time of diagnosis, the differences were statistically significant for weight-for-age, weight-for-length and head circumference in children age ≤2 years and for weight-for-age, length/height-for-age and head circumference in the age groups 2 to 3 years and 3 to 4 years (all $p<0.05$). Eighteen months after follow-up, urolithiasis patient, had significant smaller values for length-for-age in children age ≤2 years and for weight-for-age, length/height-for-age and head circumference in the age groups 2 to 3 years and 3 to 4 years (all $p<0.05$). While the patient group and the control showed no statistically difference between diagnosis and 18 months follow-up. On follow-up B-mode ultrasonography 18 months after the diagnosis, five (6.85%) children still showed intrarenal calculi, one (1.37%) child suffered from hydronephrosis. Serum levels of alanine aminotransferase, creatinine and uric acid were within normal range. Proteinuria was not observed. ***Conclusions:*** Consumption of melamine-contaminated milk power affects growth and development. Melamine-associated urolithiasis can persist for longer periods of time after cessation of melamine intake. A significant long-term effect of contaminated milk powder on liver and kidney function was not observed.

Key words Children; Growth and development; Melamine; Urolithiasis

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Received January 4, 2013

Introduction

In September 2008, the consumption of melamine-contaminated milk powder was first recognised as the underlying cause in a large number of infant and children diagnosed with urolithiasis in China. Meanwhile, a number of studies have confirmed the increased incidence of urinary tract calculi after intake of melamine-containing dairy products.[1-4] Short-term growth and development are adversely affected in children with urolithiasis.[5] To date, there is a paucity of data from follow-up studies investigating growth and development in such children. We evaluated general development and urinary tract pathologies in children with melamine-induced urolithiasis at 18 months after the diagnosis in comparison with healthy controls.

Patients and Methods

15577 children who had been exposed to melamine-tainted powdered formula were screened for urinary tract calculi in our hospital, 562 had urinary tract calculi on Brightness mode (B-mode) ultrasonograph. Among these children, 305 with detailed data were enrolled in our study. Inclusion criteria were: (i) age ≤4 years; (ii) a history of consuming melamine-contaminated milk powder for at least one month; (iii) without congenital abnormalities of the urinary tract or history of other renal disorders or other systemic disorder.

According to the above criteria, 105 children were excluded, including 84 age >4 years, 11 children had consumed the melamine contaminated milk powder for less than one month and 10 children could not be reached. Then we selected 100 children randomly for further study, 27 children's guardians refused. Finally 73 children were enrolled in the patient group including 29 girls and 44 boys with a gender ratio of 1:1.5. Patient age ranged from 19 to 48 months, mean age was 33 months. Thirteen patients were younger than 2 years, 35 patients were aged between 2 and 3 years and 25 patients were between 3 and 4 years. They were exposed to contaminated formula for 1 to 30 months, mean 10 months. Upon diagnosis, all patients stopped the intake of the tainted milk powder and received adjuvant treatment, including sufficient oral hydration. The weight, length/height and head circumference were recorded when diagnosis. In addition 61 patients (83.6%) were children of migrant workers from other provinces or came from rural areas in Zhejiang province, 12 patients lived in the Hangzhou municipal area.

The control group comprised 79 healthy age-matched and sex-matched children who had the medical examination at Changhe Street Health Care Center in Hangzhou Binjiang district, a rural area in Zhejiang province where the workers from other provinces gathered. Sixty-five children's parents (82.2%) were migrant workers from other provinces and 14 were native. They were without melamine-contaminated milk powder consumption or urolithiasis or other diseases. The group included 29 girls and 50 boys with a gender ratio 1:1.7. Age ranged from 18 to 47 months, mean age was 31 months. Seventeen controls were younger than 2 years, 42 controls were between 2 and 3 years and 20 controls were between 3 and 4 years.

All urolithiasis patients were administered a questionnaire containing general patient information on milk powder brands consumed, contact details and the growth parameters at time of diagnosis as well as questions on patient history, such as painful voiding, vomiting, haematuria, urinary frequency, dysuria and other urinary tract symptoms. During physical examination, we measured length (≤ age 3 years), height (> age 3 years), weight, head circumference and calculated weight-for-length/height. Follow-up ultrasonography was performed 18 months after the initial examination and the presence of urolithiasis was recorded. Lab analysis included routine urine analysis and blood analysis with parameters of liver and kidney function. In controls, questionnaire information on patient characteristics and general health condition was collected, accordingly. Data on length (≤age 3 years), height (>age 3 years), weight and head circumference was collected and weight for length/height was calculated.

For evaluation of physical growth and development, we chose 2006 World Health Organisation (WHO)[6] child growth standards as reference. We compared patients and controls to the reference z-scores, considering z-scores ±2.0 as normal range. The nutritional status was assessed as follows: underweight as a weight-for-age z-score ≤-2; growth retardation as length/height-for-age z-score ≤-2; wasting as weight-for-length/height z-score ≤-2; and overweight as length/height-for-age z-score ≥2.

Statistical Analysis

We used the WHO Anthro 2005 software (www.who.int/childgrowth) to calculate the z-scores of weight-for-age, length/height-for-age, age-adjusted head circumference and length/height-for-weight based on the 2006 WHO child growth standards as reference. Data analysis was performed with the SPSS 16.0 software package for Windows (SPSS Inc., Chicago, United States of America). Between-groups differences were tested for with the t test or non-parametric tests, as appropriate. Cross-table analysis was performed with the χ^2 test. P values <0.05 were considered as indicating statistical significance.

Results

All 73 children in the urolithiasis group had consumed melamine-contaminated milk powder. Among these, 63 children had been fed a single brand of contaminated milk powder, 7 children had two different brands and 3 children three different brands. The most commonly consumed brand was Sanlu (n=50, 58.8%), followed by Yashili (n=17, 20.0%), Shengyuan (n=10, 11.8%), Yili (n=6, 7.1%), Shi'en (n=2, 2.4%), Gucheng (n=1, 1.2%). Clinical symptoms included restlessness and crying in six children, pollakisuria in three children and urgency in one child.

Data comparing weight, length/height and head circumference of patients and controls at 18 months after follow-up are outlined in Table1. Measured values for weight, length/height and head circumference were generally lower in the urolithiasis group, compared with controls. The differences reached statistical significance in the age groups 2 to 3 years and 3 to 4 years (p<0.05), but not in the age group ≤2 years.

According to 2006 WHO growth standards, the z-scores for weight-for-age, length/height-for-age, weight-for-length/height and age-adjusted head circumference in patients and controls, at time of diagnosis, are outlined in Table 2.

Based on the 2006 WHO growth standards, the z-scores are generally lower in the patient group at time of diagnosis. Specifically, the z-scores of weight-for-age, weight-for-length and head circumference in the age group ≤2 years and of weight-for-age, length/height-for-age and head circumference in the age groups 2 to 3 years and 3 to 4 years were significantly lower for urolithiasis patients, compared with control (all p<0.05). In the patient group ≤ age 2 years, we found two underweight children (15.4%), two children with wasting (15.4%) and one growth retardation child (7.7%), while there was one overweight child (5.9%) among the age-matched controls. In the patient group aged 2 to 3 years, three children (8.6%) were diagnosed with underweight, two child (5.7%) with growth retardation, three children with wasting (8.6%) and three with overweight (8.6%), whereas the age-matched controls included one underweight child (2.4%), one child with growth retardation (2.4%) and one overweight child (2.4%). In the age group 3 to 4 years, there were one underweight (4.0%) and three growth-retarded (12.0%) patients as well as one (4.0%) patient with wasting. Among controls, we

Table 1 Comparison of growth parameters 18 months after follow-up

	Urolithiasis group	Controls	P value
Aged ≤2 years			
N	13	17	
Weight (kg)	11.72±2.15	12.70±1.58	0.160
Length (cm)	84.63±3.11	87.25±4.62	0.090
Head circumference (cm)	47.89±0.82	48.27±1.26	0.355
Aged 2-3 years			
N	35	42	
Weight (kg)	13.27±1.82	14.25±1.61	0.014
Length (cm)	91.15±3.88	93.94±3.34	0.001
Head circumference (cm)	48.40±1.76	49.45±1.27	0.003
Aged 3-4 years			
N	25	20	
Weight (kg)	14.79±1.93	16.43±2.70	0.022
Height (cm)	97.80±5.47	101.51±3.88	0.014
Head circumference (cm)	49.32±1.38	50.29±1.37	0.023

Table 2 Comparison of growth parameters z-scores based on 2006 WHO growth standards at time of diagnosis

	Urolithiasis group 1	Controls 1	P value
Aged ≤2 years			
N	13	17	
Weight-for-age	-0.34	0.75	0.008
Length-for-age	0.24	0.72	0.276
Weight-for-length	-0.52	0.56	0.009
Head circumference	-0.33	0.54	0.011
Aged 2-3 years			
N	35	42	
Weight-for-age	-0.07	0.49	0.041
Length-for-age	0.15	0.72	0.049
Weight-for-length	-0.13	0.24	0.242
Head circumference	0.13	0.61	0.006
Aged 3-4 years			
N	25	20	
Weight-for-age	-0.24	0.57	0.008
Height-for-age	-0.23	0.73	0.001
Weight-for-height	-0.20	0.22	0.193
Head circumference	-0.02	0.65	0.004

Urolithiasis group 1: patient group at time of diagnosis; controls 1: control group at time of diagnosis found one (5.0%) child with wasting and three overweight (15.0%) peers. Statistical analysis showed no difference between the proportions of patients and controls affected with underweight, wasting, growth retardation and overweight in the three age groups (all p>0.05).

The result of data analysis based on z-scores according to 2006 WHO growth standards at 18 months after follow-up are outlined in Table 3.

The z-score statistics based on WHO data show generally lower values for urolithiasis patients, as compared with healthy controls. Statistically significant differences were found for length-for-age in children below age 2 years and for weight-for-age, length/height-for-age and head circumference in the remaining two age groups (all p<0.05). With WHO standards applied, the patient group aged ≤2 years included one (7.7%) underweight, one (7.7%) child with wasting and one (7.7%) overweight child, while there was only one (5.9%) overweight child among the healthy peers. The patient group aged 2 to 3 years included one (2.9%) underweight and one (2.9%) growth-retarded child and three (8.6%) overweight individuals, whereas there were two (4.8%) overweight children in controls. In the patient group aged 3 to 4 years, we identified one (4.0%) underweight child, two (8.0%) children with growth retardation and one (4.0%) child with wasting. The age-matched control group included one (5.0%) child with wasting and three (15.0%) overweight children. The proportion of individuals deviating from the normal range did not show statistical significant differences between patients and controls in any of the age groups (all p>0.05).

All 73 patients showed single or multiple urinary calculi on B-mode ultrasonography at diagnosis, stone size from 1mm to 13 mm, average measured as 4.1 mm, including 56 children with multiple urinary calculi and 17 with single urinary calculi. Eight children had large calculi (>9 mm in diameter), 19 had medium sized calculi (4~9 mm in diameter) and 46 had small calculi (<4 mm in diameter) including 9 had sand-like calculi. All of them received follow-up B-mode ultrasonography of the kidneys and the urinary tract 18 months after the baseline examination. On follow-up, ultrasonographical findings were normal in 62 patients (84.93%) with regard to renal morphology and the absence of ureter dilatation, calculi and hydronephrosis. Small renal calculi were observed in five children (6.85%) as dotted hyperechogenicities in the renal parenchyma. Another five patients (6.85%) were diagnosed with renal calculi and one child (1.37%) with hydronephrosis (Table 4). Three children had undergone operative treatment for hydronephrosis. On follow-up, none had calculus. One of these children showed a postoperatively enlarged ipsilateral (left) kidney. In another child, a dilation of the upper portion of the ipsilateral ureter to a maximum diameter of 4.2 mm was observed after operative treatment of right kidney hydronephrosis. The third child had normal postoperative sonographical findings.

Urine samples were available for routine analysis in 72 of 73 urolithiasis patients. One child (1.39%) showed leukocyturia and three patients (4.16%) were positive for microhaematuria. No case of proteinuria was observed. Serum levels of alanine aminotransferase, creatinine, urea and uric acid were all within the normal reference range.

Table 3 Comparison of growth parameters z-scores based on 2006 WHO growth standards at 18 month after follow-up

	Urolithiasis group 2 (P*)	Controls 2 (P$^{\Delta}$)	P value
Aged ≤2 years			
N	13	17	
Weight-for-age	-0.01 (0.090)	0.77 (0.774)	0.053
Length-for-age	-0.37 (0.343)	0.56 (0.077)	0.028
Weight-for-length	0.21 (0.135)	0.65 (0.288)	0.363
Head circumference	0.15 (0.079)	0.45 (0.428)	0.229
Aged 2-3 years			
N	35	42	
Weight-for-age	0.03(0.154)	0.54(0.362)	0.016
Length-for-age	-0.33 (0.560)	0.51(0.132)	0.001
Weight-for-length	0.26(0.054)	0.37(0.181)	0.653
Head circumference	-0.08 (0.273)	0.58 (0.645)	0.002
Aged 3-4 years			
N	25	20	
Weight-for-age	-0.31 (0.536)	0.60(0.798)	0.016
Height-for-age	-0.47 (0.711)	0.67(0.549)	0.000
Weight-for-height	-0.06 (0.314)	0.29(0.383)	0.326
Head circumference	-0.14 (0.544)	0.60 (0.540)	0.009

P*: the comparison between diagnosis and 18 months follow-up in patient group; Urolithiasis group 2: patient group at 18 months after follow-up. P$^{\Delta}$: the comparison between diagnosis and 18 months follow-up in control group; controls 2: control group at 18 months after follow-up.

Discussion

Melamine is a nitrogen-containing heterocyclic toxic organic compound. Animal experiments show that melamine combines with cyanuric acid into nephrotoxic crystal structures and is thus not suitable as an additive to human or animal food.[7,8] The Kjeldahl method is an analytic approach commonly used for quantification of protein content in food which works by measuring total nitrogen in food stuff.[9] As melamine contains 66% nitrogen by mass, compared with an average of 16% nitrogen in food proteins, melamine as a contaminant can make diluted or low-protein containing food wrongly appear to be of higher protein content.[10] The scandal on contaminated pet food in the United States of America in 2007 and the 2008 Chinese milk scandal developed along these lines.[11,12]

In the 2008 Chinese milk scandal, melamine contamination was demonstrated in various dairy products, with the highest concentrations in Sanlu brand infant formula milk power amounting to 2563 mg/kg. Melamine concentrations in other brands of milk powder reached 150 mg/kg (Shengyuan), 53.4 mg/kg (Yashili), 17.0 mg/kg (Shi'en) and 12.0 mg/kg (Yili),[13] greatly exceeding the WHO recommended maximum tolerable daily intake of 0.2 mg/kg.[2] In our present follow-up study, we found that children suffering from melamine-associated urolithiasis had most frequently consumed milk powder of the Sanlu brand, followed by Yashili and Shengyuan brand. Melamine adulteration of milk powder wrongly suggests a high protein content,[10,14] where in fact the real nutritional value is low and inversely related to melamine concentrations. Melamine-associated urolithiasis affects infants and children under age 3 years in 99.2% of the cases.[15] These young children undergo a period of particularly fast growth and development and require large amounts of nutritional protein. A previous study demonstrated that children with urolithiasis secondary to the consumption of melamine-contaminated milk powder show delayed growth and development in the short term, as compared to peers without urolithiasis.[5]

Growth standards presently are the most commonly employed tool to assess nutritional status and physical development. Parameters, such as height/length, weight and head circumference, are readily measured and analysed and allow straightforwad assessment.[16] Body weight is a sensitive indicator of short-term nutritional status. Length/height reliably reflects infant long-term nutrition and growth rate. Weight-for-length/height allows the diagnosis of overweight and underweight. Head circumference is a measure of brain and skull development.[17] WHO growth standards is a new set of growth standards for children below 60 months of age published by WHO in April 2006 which should serve as a valid basis for assessment and international comparison of physical growth and development in children.[6] We used the 2006 WHO growth standards to evaluate children's growth and development in our study by comparing the four parameters weight-for-

Table 4 Ultrasonographical findings in 11 children with urolithiasis and/or hydronephrosis on follow-up

Patient number	Age (months)	Sex	Ultrasonography at baseline	Ultrasonography at follow-up
1	31	Male	Multiple calculi in both kidneys, largest diameter 2.6 mm	Dotted hyperechogenicities in left renal parenchyma
2	24	Male	Multiple calculi in both kidneys, largest diameter 12 mm	Dotted hyperechogenicities in left renal parenchyma
3	31	Female	Calculus in the right kidney, 5 mm in diameter	Dotted hyperechogenicities in right renal parenchyma
4	37	Female	Multiple calculi in left kidney, largest diameter 6.8 mm	Dotted hyperechogenicities in left renal parenchyma
5	26	Female	Multiple calculi in both kidneys, largest diameter 5 mm	Dotted hyperechogenicities in both renal parenchyma
6	42	Female	Nephrolithiasis, multiple calculi in the right kidney, largest diameter 10 mm	Single calculus in the right kidney, diameter 8 mm
7	40	Male	Multiple calculi in the proximal ureter bilaterally, largest diameter 7.7 mm	Sand-like calculi in both kidneys
8	36	Male	Sand-like calculi in both kidneys	Sand-like calculi in both kidneys
9	38	Female	Small calculus in the left kidney, 2.4 mm in diameter	Small calculus in the left kidney, 3 mm in diameter
10	38	Male	Calculus in the right kidney, 13 mm in diameter	Calculus in the right kidney, 13 mm in diameter, hydronephrosis of the right kidney
11	27	Male	Bilateral nephrolithiasis, maximum diameter 4 mm	Hydronephrosis of the left kidney

age, length/height-for-age, weight-for-length/height and age-adjusted head circumference. By means of our 18 months follow-up study, we showed that, according to WHO growth standards, growth and development in patients with melamine-associated urolithiasis aged below 4 lagged behind healthy peers whether at time of diagnosis or 18 months after follow-up. While the patients and the healthy peers, none of them showed difference between diagnosis and 18 months follow-up. We therefore conclude that consumption of melamine-contaminated milk power adversely affects growth and physical development in infancy and early childhood. Considering that significantly lower head circumference measured in the urolithiasis group, melamine may even interfere with brain and skull development. We also found that in children below age 2 years, the discrepancy in growth parameters between patients and controls was less pronounced, compared with older children. We assume that this finding reflects the shorter duration of melamine consumption in younger children and conclude that early discovery of milk powder adulteration and instant cessation of melamine intake can alleviate its detrimental effects on growth and development. Further follow-up studies are still necessary to prove this point.

Urinary tract calculi caused by melamine intake are compositions of melamine and uric acid,[18] they are characterised by a low degree of hardness and a loose, sediment-like composition.[19] These stones can form larger conglomerates. In our study, most of the patients with melamine-associated urolithiasis (63.0%) had small calculi (<4 mm diameter), similarly as the report of He et al.[19] In calculi measuring less than 4 mm in diameter, cessation of melamine exposure, oral hydration and frequent voiding often suffice as therapeutic measures and can effectively eliminate the stones. Larger calculi may require comprehensive interdisciplinary treatment of urolithiasis. In our study, the vast majority of patients responded well to conservative treatment. Of all the 73 patients, the calculi discharging rate at 18 months after diagnosis was 84.9% (62/73). However, ultrasonographical follow-up found persisting calculi or hydronephrosis in 15.1% of the patients after 18 months. These data compare well with a follow-up study by Liu et al, who found persisting urinary tract pathology in 12% of the patients after 6 months.[20] But higher than that (4.5%) reported by Shen et al 12 months after diagnosis.[21] and lower than that (28%) in Sichuan patient with melamine-associated urolithiasis at 12-month follow-up.[22] According to the analysis, we assumed that stone size was the most important factor for the stones discharging, children with smaller stones could pass all the stones more easily and quickly. Consumption of melamine-contaminated formula may therefore seem to result in prolonged urolithiasis and associated nephropathy in a number of patients.

The harmful effects of melamine on health in humans and animals are so far not fully recognised. Well-documented is the melamine-induced nephropathy after long-term and repeated melamine exposure.[23] In our study group, we did not encounter impaired kidney or liver function. The proportion of patients with haematuria (6.9%) and leukocyturia (1.4%) was relatively low and comparable to data presented by Guan et al. with 5.9% haematuria and 2.9% leukocyturia in children with melamine-associated urolithiasis,[4] who did not find a significant association between the pathological urine analysis and urolithiasis. On the basis of our data, we cannot exclude the possibility of a causal relationship between haematuria, leukocyturia and melamine-induced kidney damage. Further studies on the toxic effects of melamine are necessary to elucidate this issue.

Conclusions

Consumption of melamine-contaminated milk power affects growth and development. Melamine-associated urolithiasis can persist for longer periods of time after cessation of melamine intake. A significant long-term effect of contaminated milk powder on liver and kidney function was not observed. We suggest that further follow-up is required.

Acknowledgements

We thank all the doctors, nurses, and other staff members of the Departments of Children's Health Care, Children's Rehabilitation, Ultrasonic Medicine, and Laboratory Medicine of The Children's Hospital of Zhejiang University School of Medicine who kindly provided their cooperation in this study. And we would like to thank Chao-Chun Zou for help with the data analysis on an earlier version of the manuscript.

Conflict of Interest Statement

We declare that we have no conflict of interests.

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