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Ultrasonographic Findings of Children Screened after Exposure to Melamine-Tainted Milk Products in a Local Centre

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Abstract To evaluate renal ultrasound findings related to melamine-tainted milk products. Between 26th September 2008 to 28th November 2008, 1,872 children aged 12 years or younger who had consumed melamine tainted milk products (MTMP) for more than one month were referred to our special assessment centre for renal ultrasound and urinalysis. Five children were found to have MTMP associated stones, which fulfilled the criteria: strong echogenic lesion ≥4 mm lying inside the collecting system or an ultrasonographic abnormality not completely fulfilling the aforementioned criteria with dilatation of either renal pelvis or renal calyx. Four children were found to have MTMP associated deposits, these were renal hyperechoic foci that did fulfill the stone criteria but were persistent on follow-up scans. Two children found to have MTMP suspected renal deposits, which were defined as renal hyperechoic foci that were not detectable on follow-up scan. Incidence rates of renal stones, renal deposits and suspected renal deposits are 0.27%, 0.21% and 0.11%, respectively. A similar study performed by Peking University of children up to three years of age who were exposed to MTMP showed a higher incidence of renal stones/deposits, which could be due to consumption of higher concentration of melamine tainted milk products and the large quantity of milk consumed in this younger age group. Melamine coalesces with other milk related products to form crystals that block tubules of the kidney. Little is known about the effects of melamine in humans. This study evaluates the spectrum and short term changes of ultrasound findings related to MTMP. Further evaluation and follow-up of these children shown to be affected by melamine may be useful in assessing the long term sequelae.

Key words Kidneys; Paediatrics; Ultrasound; Urogenitial

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Introduction

Chemical contamination of foods has long been reported in history amongst various communities. A recent example of note is the epidemic of melamine tainted milk products in Mainland China that came to light in 2008. Over 300,000 children were reported to be affected, resulting in 13,000 hospitalisations and 6 deaths.[1-3] It was initially discovered in powdered infant formula in Mainland China, and is now increasingly detected in other foods world-wide.

Melamine, an organic chemical compound developed in the 1830s, has had various uses. China, in fact, is not the only country to produce the chemical. It is also widely used in the United States and other western developed countries. It is commonly used, in combination with other chemicals or in isolation, in plastics, glues, cements, colorants, cleansers and many others. A matter of concern would be that melamine is also added to fertilisers, which will be ultimately absorbed by agricultural crops. Its concentration in food if it was only exposed to fertilisers with melamine, however, has so far been negligible. Therefore it remains to be seen what potential impact this could have in the long run.

So why would one intentionally add melamine to milk products? Nitrogen content has been used as a surrogate measurement of protein content of foods, and melamine has a substantial amount of nitrogen – 66% by mass. Prior to this incident, powdered infant formula in Mainland China was found to be low in protein content resulting in malnutrition in infants. This prompted the Chinese government to mandate that preparations increase their protein content, which was achieved by some producers by adding melamine. Another possible reason is that adding melamine produces a more "milky" appearance of powdered infant formula.

The toxic effects of melamine and its compounds have been known for decades. In 2007, it was found that pet food was tainted with melamine which resulted in the many deaths of cats and dogs.[4-8] This has led to the many studies of melamine and its effect on animals, and hence the deduction that melamine may be harmful to humans.

The amount of melamine that food must contain to have a harmful effect on humans remains largely unknown due to the lack of data. In particular, the level of melamine that is 'safe' for young children remains unclear, as they ingest a higher proportion of food for their size compared with adults, so their susceptibility to a potential toxin is higher. Initial clinical presentations are also variable and often subtle.

It is now known that melamine forms stones in the urinary system, causing obstructive uropathy, or even acute renal failure in more severe cases. The six children that died were a result that acute renal failure was only diagnosed much later. Preliminary data suggests that melamine stones are not fully radio-opaque. Most of the stones dissolved with standard treatment for stones, which included hydration or lithotripsy, and if needed dialysis can be used as supportive care. However, acute renal failure and its long term complications in children are often ominous, including hypertension and chronic renal failure. The long term consequences of melamine-induced acute renal failure still remain unknown.

In view of the wide range of melamine tainted milk products in Hong Kong given the proximity of Hong Kong to Mainland China, this prompted the Hong Kong government to initiate a territory-wide screening programme for children 12 years old or less who had consumed melamine tainted milk products.

In order to gain further understanding of the radiologico-pathoglogical correlation of melamine tainted milk products related renal disease, we retrospectively reviewed the sonographic features of renal stones or renal deposits related to melamine tainted milk products in a local centre. Comparison is also made between the data collected from our local centre and other centres in the region.

Materials and Methods

From 26th September to 28th November 2008, a total of 1,872 children were referred to our special assessment centre (SAC) in Kwong Wah Hospital, Hong Kong, and underwent screening assessment of the urinary system.

This is a territory-wide screening programme initiated by the Hong Kong government. Patients are screened at general out-patient clinics throughout Hong Kong on a voluntary basis. Children aged 12 years old or under and had daily exposure to melamine tainted milk products for one month or more were referred to SAC for further assessment. Melamine tainted milk products (MTMP) were defined according to tests results posted by the Hong Kong government.[8] The duration for screening for all screening centres in Hong Kong were similar.

All the children at our special assessment centre were arranged to have renal ultrasongraphy and urinalysis. Ultrasound examinations were performed by two dedicated ultrasonographers and radiologists to reduce the inter-observer variability. Positive findings were cross checked by our paediatric radiologist before being reported.

MTMP renal stones were defined as echogenic foci larger than 4 mm inside the urinary system or an abnormality smaller than 4 mm but associated with dilatation of the urinary system. MTMP renal deposits were defined as echogenic foci not fulfilling the criteria for stones and persistent on follow-up examinations. MTMP suspected renal deposits were defined as echogenic foci not fulfilling the criteria for stones and were not seen on follow-up examinations.

Prior to determining renal stones or renal deposits are related MTMP, a thorough clinical history and metabolic screening would be performed to exclude other causes. The estimated melamine milk intake was quantified using pack months, based on the calculation of number of packs per day (each pack measuring 250 ml) multiplied by duration in months. Informed Consent was received and study was approved by the Hospital Authority Kowloon West Cluster Ethics Committee.

Results

A total of 1,872 children were referred from general out-patient clinics to our SAC in Kwong Wah Hospital, and were arranged to have urinalysis and ultrasonography of the urinary system. The demographics profile was summarised in Table 1.

Using the defined ultrasonographic criteria, five children were found to have renal stones (prevalence = 0.27%), with a mean age of 6.7. The average melamine exposure was 26 pack months. The mean number of stones per patient was 1.2 (Tables 1 & 2). The average size of renal stone was 4.1 mm (Table 3). In three cases, there was associated posterior acoustic shadowing on ultrasonography (Figure 1), while another one showed comet tail artifact. One of the patients with renal stones showed associated dilatation of the urinary tract.

Four children were found to have renal deposits (prevalence = 0.21%), with a mean age of 9.5. The average melamine exposure was 47 pack months. The mean number of stones was 1. The average lesion size was 2.8 mm. In three cases, there was associated comet tail artifact on ultrasonography (Figure 2), and none of them showed posterior acoustic shadowing. There was no associated dilatation of the urinary tract.

Two children were found to have suspected renal deposits (prevalence = 0.11%), with a mean age of 7. The average melamine exposure was 24 pack months (Tables 1 & 2). The mean number of stones was 1. The average lesion size was 2.75 mm (Table 3). In one case, there was associated

Table 1 Demographics profile

Abnormality	Number	Male	Female	Average age (Years)	Melamine exposure duration (pack months)
Renal stones	5	5	0	6.7	26
Renal deposits	4	2	2	9.5	47
Suspected renal stones/deposits	2	1	1	7	24

Table 2 Prevalence of renal ultrasonography abnormalities

Abnormality	Number of children	Prevalence (%)
Renal stones	5	5/1872 (0.27)
Renal deposits	4	4/1872 (0.21)
Suspected renal stones/deposits	2	2/1872 (0.11)

Table 3 Results and imaging features of renal ultrasonography

Abnormality	Average size	Posterior acoustic shadowing	Comet tail artifact	Average number of stones per patient	Dilatation of urinary tract	Location		
						U	M	L
Renal stones	4.1 mm	3	1	1.2	1	4	0	2
Renal deposits	2.8 mm	0	3	1	0	1	2	1
Suspected renal stones/deposits	2.75 mm	1	1	1	0	0	2	0

U: upper; M: middle; L: lower

posterior acoustic shadowing on ultrasonography, while another case showed comet tail artifact (Figure 3). There was no associated abnormal dilatation of the urinary tract.

None of the 10 cases were associated with abnormalities of either haemautria, leuckocyturia or proteinuria on urinalysis.

Discussion

Comparison with Other Centres

In our centre, there were five cases of renal stones (0.35%), four cases of renal deposits (0.28%) and two cases of suspected renal deposits (0.14%). Compared with other centres in the region as published by Lam et al, Department of Paediatrics, Chinese University of Hong Kong (CUHK), in 2008 (Table 4),[5] the prevalence of renal stones associated with MTMP is higher than that in CUHK (0.03%). The prevalence of renal deposits in both centres are comparable (0.21%, 0.22%).

On a national level, we compared our data with that of Peking University, Third Hospital, Beijing (Table 5).[6] A significantly higher prevalence of renal stones (8.49%) and renal deposits (19.02%) was seen in the Beijing University study. This could be because the Beijing study included only children less than three years old, which could lead to a higher prevalence of melamine related deposits as younger children tend to have a higher proportion of milk in their diet. Also, a higher concentration of melamine contaminated milk products is also observed in Mainland

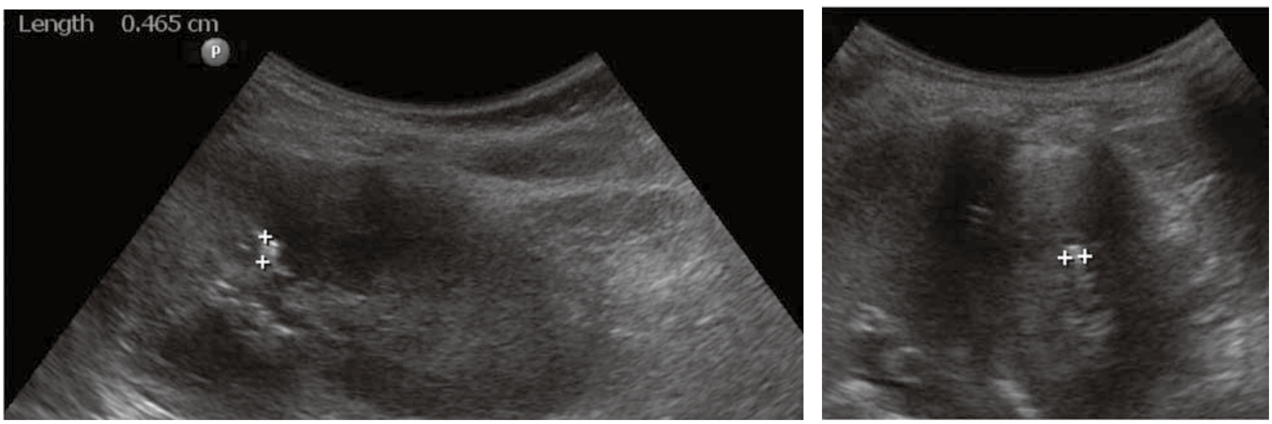

Figure 1 Ultrasonographic image showing a case of renal stone associated with MTMP. Note the echogenic focus (4.7 mm) casting a posterior acoustic shadow.

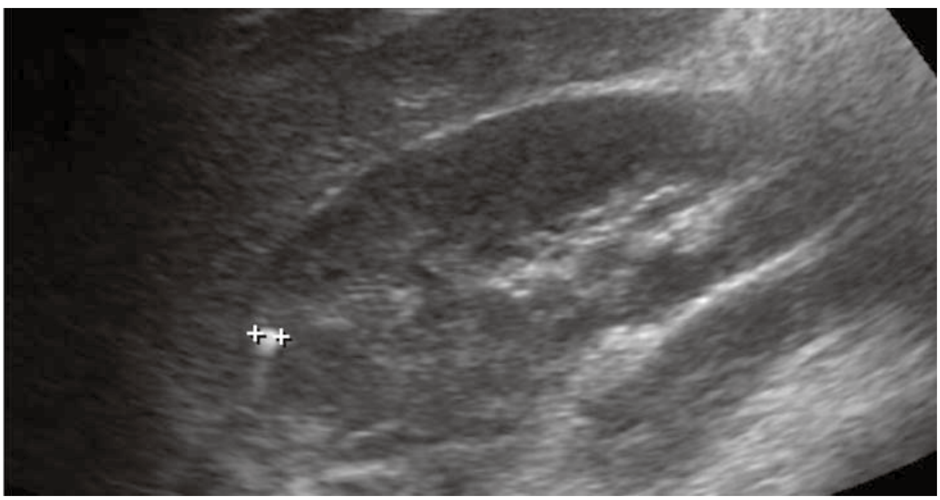

Figure 2 Ultrasonographic image showing a case of renal deposit associated with MTMP. Note the small echogenic focus with comet tail artifact.

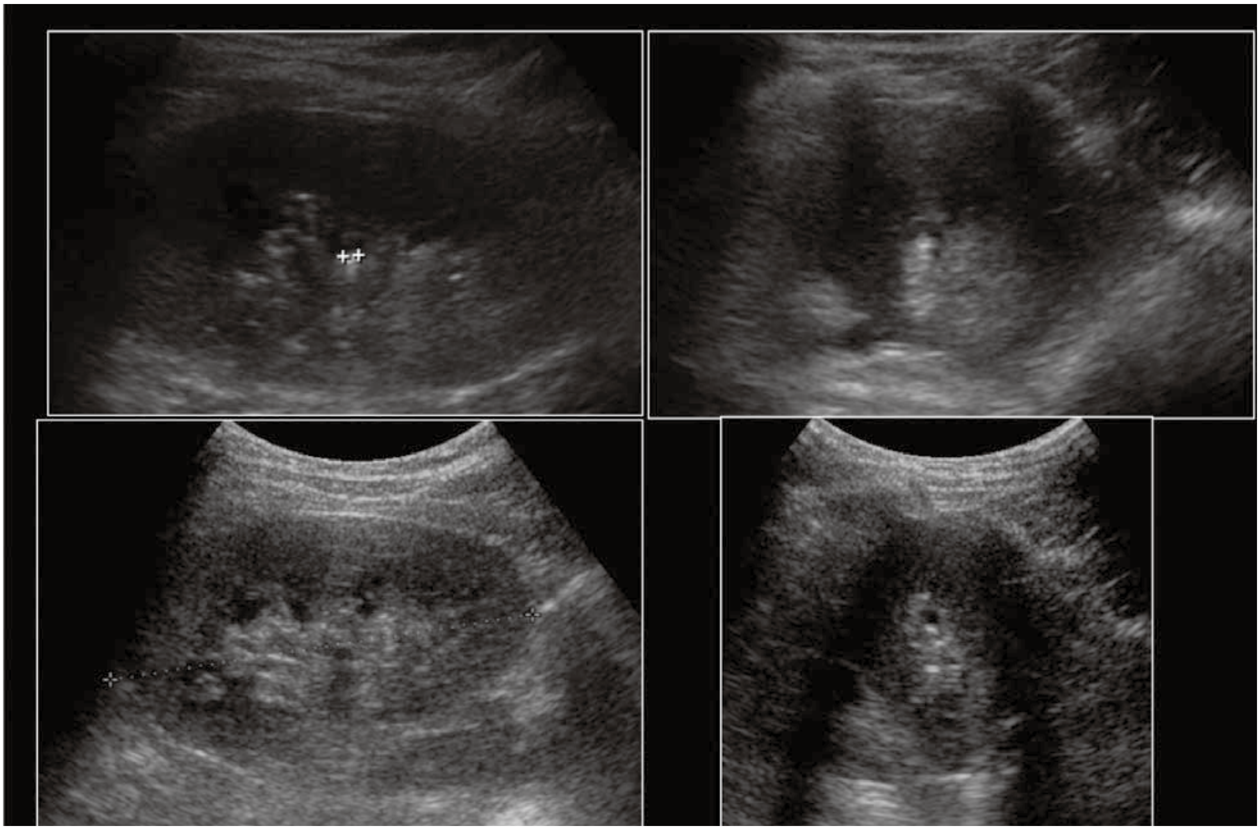

Figure 3 Ultrasonographic images showing a case of suspected renal deposit associated with MTMP. Note the small echogenic focus with comet tail artifact. Images on the top were from the initial examination with the follow-up images below.

Table 4 Comparison of results with regional data

Abnormality	Kwong Wah Hospital, Hong Kong (Prevalence, %)	Chinese University of Hong Kong, Hong Kong (Prevalence, %)
Renal stones	0.27	0.03
Renal deposits	0.21	0.22
Suspected renal stones/deposits	0.11	–

Table 5 Comparison of results with national data

Abnormality	Kwong Wah Hospital, Hong Kong (Prevalence, %)	Peking University Third Hospital, Beijing (Prevalence, %)
Renal stones	0.27	8.49
Renal deposits	0.21	19.02
Suspected renal stones/deposits	0.11	–

China. The highest level of melamine in tainted milk products was found to be 2563 mg/kg in Mainland China, contrasting with the highest level of melamine in tainted milk products in Hong Kong which was 68 mg/kg. The higher melamine concentration in Mainland China probably contributed to the higher rate of melamine related complications.

Acoustic Shadowing

The MTMP stones larger than or equal to 4 mm in our study were shown to be more likely to cast posterior acoustic shadowing. Posterior acoustic shadowing is an ultrasound feature that is dependent on the attenuation coefficient of the reflector, difference of the acoustic impedances encountered and ultrasound beam width.

The chemical composition of renal stones seems to have no effect on shadowing, as similar features are seen in calcium oxalate, magnesium ammonium phosphate hexahydrate and uric acid stones. The minimum size of a stone to cast a shadow appears to be largely limited by the beam width.[9, 10]

In vitro studies have shown that the minimum size of renal stone that would cast posterior acoustic shadowing is 3.5 mm to 4 mm, which is comparable to results on our study.

Comet Tail Artifact

Comet tail artifact is a reverberation artifact that is caused by multiple reflections of the ultrasound beam within two closely spaced reflectors.[7] It is an ultrasound feature that is specific not only to renal stones, but also seen in colloid crystals in thyroid nodules, cholesterol crystals deposits in gallbladder wall, and milk of calcium in calyceal cysts.[11-14]

Jia et al described the comet tail artifact to be associated with renal calculi between 0.1 cm to 0.3 cm in children exposed to melamine-tainted products.[15] Similar findings are observed in other studies in Hong Kong, as described by Ho et al.[16] This is concordant with our results, as comet tail artifact is mostly observed in renal deposits that are smaller than 4 mm.

The presence of comet-tail artifacts in melamine-related renal deposits is not unique to only melamine stone or crystal as it is also seen in oxalate-related stones.

Conclusion

Melamine, a synthetic nitrogen compound, is used in many industrial goods and even in fertilisers used for growing crops. It was found recently to be added to infant formula in Mainland China to increase their measured, but not biologically available, protein content. It is largely not degraded in humans, and the main route of excretion after absorption is through urine.

Most of the melamine related stones or crystals detected on ultrasound appear to be relatively small with renal stones larger than 4 mm showing posterior acoustic shadowing and stones less than 4 mm showing comet tail artifacts, which is comparable to conventional renal stones. The melamine related stones or crystals detected were only screened out in patients exposed to melamine ingestion, but are not necessarily MTMP-related stones/deposits, and other causes of stones need to be excluded as per Hospital Authority protocol. In fact even after exclusion, whether they are really caused by MTMP is doubtful, and should only be considered suspected cases. The clinical significance of such lesions remains unknown at this stage and requires long term follow-up to ascertain its effects.

One of the limitations of this study that is the sample size of the affected patients is small. It can therefore be argued that sample is not a complete and true representation. Another limitation is that we made an approximate estimation of the melamine concentration with calculating it as pack months. It would be most ideal if we could work out the exact concentration of melamine. However, this was practically not feasible with our clinical colleagues given the large amount of workload of the sudden increase in number of patients that needed to be seen.

There is a significant difference in prevalence and magnitude of renal complications between children in Hong Kong and Mainland China. This can be attributed to the difference in levels of exposure to melamine. So far, the severe acute complications appear to be only observed in Mainland China.

Each week more food is reported world-wide to contain melamine, with no one knowing the true extent of the present epidemic and its potential threats. No more deaths have been reported since the Chinese government and international authorities have become aware of the situation. Yet its long term effects remain unknown.

In modern world today, it is imperative that we understand and deal with global implications of food related diseases such as the melamine epidemic. It is hoped that in the future, should such outbreaks occur again, related substances can be studied more rapidly and with causative agent identified, reported and eliminated.

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