# The study of the difference between the melamine stone induced hydronephrosis and congenital hydronephrosis in infants: clinical features and their 24-month follow-up

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**Abstract:** To study the difference of clinical features in hydronephrosis induced by urinary melamine stone (HNMS) with that due to congenital ureteropelvic junction obstruction (HNUPJO) in infants. Forty six infants (18.5±10.0 months) with HNMS and 85 infants (20.4±9.3 months) with HNUPJO were included. All HNMS and 30 HNUPJO infants with mild pelvic dilation similar to those of HNMS were followed up for 24 months. Renal ultrasonography, renal function and urinalysis were evaluated at admission and follow up. The clinical features of two groups were compared. At admission, unilateral hydronephrosis occurred in 35 (76%) HNMS and 77 (91%) HNUPJO. More bilateral hydronephrosis were found in HNMS than in HNUPJO (24% vs. 9%, $P < 0.05$). HNMS showed more symptomatic and less abdominal mass appeared comparing with those of HNUPJO. Five cases of acute renal failure were observed in HNMS and none in HNUPJO. The degree of hydronephrosis of HNMS was significantly smaller than those of HNUPJO ($P < 0.05$). At 24-month of follow-up hydronephrosis resolved in 93% HNMS whereas remained stable in 80% HNUPJO. While 5 cases with HNUPJO deteriorated and pyeloplasty had to be performed. Only one HNMS infant needs surgical treatment due to the radiolucent stone has changed to radio-opaque stone, which induced significant ureteral obstruction. Significant difference of clinical feature existed between HNMS and HNUPJO. HNMS appears to be relatively benign. Non-operative management with close follow-up is a reliable and efficacious method for these HNMS infants.
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## 1. Introduction

Pediatric hydronephrosis is a common disorder encountered by physicians in their daily practice. Nowadays, fetal hydronephrosis is more frequently detected due to popular used antenatal ultrasonography [1,2]. It is well known that one of the most common causes of congenital hydronephrosis is ureteropelvic junction obstruction (UPJO) which has been previously characterized in the literature [3].

In 2008, the outbreaks of melamine related urinary stone (MRUS) occurred in China[4] and thereafter, the ultrasound examination become the routine tool to evaluate the renal morphology as well as finding the urinary stone, the number of hydronephrosis in infants increased dramatically [5]. Actually, hydornephrosis is one of the main complications in infants with MRUS, approximately reached 1/3 of cases [6].Clinically, hydronephrosis induced by urinary melamine stone (HNMS) need to be distinguished with the hydronephrosis due to congenital ureteropelvic junction obstruction (HNUPJO) considering the different treatment and follow up strategy. However, the differential diagnosis is not always easy, especially in cases with mild degree of hydronephrosis and that induced by a small or occult MRUS.

Although early diagnosis of patients with hydronephrosis is not difficult due to the advances in ultrasonography during the last two decades, disagreement exists over the different diagnostic tests to define obstruction accurately or predict which kidney will benefit from surgical intervention. Furthermore, the indications for and timing of surgery or initial non-operative approach for severe hydronephrosis are still debated. Currently, no data are available regarding the different clinical features of HNMS from those of HNUPJO at admission and that for 2 years follow up. During the outbreaks of melamine related urinary stone at 3 year ago, more than 3000 infants and young children with a history of exposure to melamine contained milk powder came to our hospital for medical evaluation. According to the diagnostic criteria for MRUS established by World Health Organization (WHO) [7], 46 children suffered from HNMS.

The purposes of present study were to summarize the different clinical characteristics of HNMS from those of HNUPJO either at admission and the 24-months follow up.

## 2. Material and Methods

### Patients

The present study included 46 infants (18.5±10.0 months old, 34 boys and 12 girls) who suffered from HNMS and were treated in the First Affiliated Hospital of Zhengzhou University in China in 2008.

MRUS was diagnosed according to the diagnostic criteria established by the WHO [7] and we have reported previously [8]. In brief, key diagnostic criteria include the history of feeding melamine-contaminated infant formula; having one or more clinical manifestations such as unexplained crying and/or vomiting; macroscopic or microscopic hematuria (urinary red blood cell morphology shows normal morphology of red blood cells), acute obstructive renal failure: oliguria or anuria; parathyroid hormone test (normal); ultrasound B exam indicated urinary system stone imaging.

The hydronephrosis diagnosis is mainly depending on the ultrasonography, which was graded according to the Society for Fetal Urology (SFU) guidelines [9].

Evidence of consumption of melamine-contaminated infant formula, including powdered milk bags with batch number matched by data promulgated by Chinese authorities, was required at the time of diagnosis. Analysis of six discharged stones with a combined liquid- phase chromatography/mass spectrum method (Esquire-LC MS analyzer, produced by Bruker Co.) revealed that the main components of stone were uric acid and melamine. All cases in prenatal ultrasonography screening did not show urologic congenital anomalies.

Eighty five age- and gender-matched infants (20.4±9.3 months old, 68 boys and 17 girls) with prenatally diagnosed HNUPJO and confirmed after birth served as controls and these children did not have any history of consumption of toxic milk powder.

Radiographic, functional, and laboratory data of urinary system were recorded. The study was approved by the Medical Ethics Committee of Hospital and parents.

### Treatment at admission

All cases with HNMS received conservative, short-term hospital treatment, including cessation of melamine-contaminated infant formula consumption immediately, intravenous hydration, urine alkalinization and anti-spasmodic drugs after diagnosis. Five severe acute renal failure cases underwent hemodialysis. After discharging patients were asked to maintain oral medication with tablets of sodium bicarbonate and antispasmodics. The choice of conservative or surgical management to HNUPJO patients was based on the results of ultrasonography and IVU. Surgical intervention was necessarily performed if there was evidence of obstructive injury, defined as a reduction in renal function, persistent anuria and/or ultrasonographic progression of hydronephrosis

### Follow-up

Pyeloplasty was the initial therapeutic approach in 55 HNUPJO (65%) and conservative follow-up was undertaken in the remaining 30 HNUPJO (35%) and all HNMS for 24 months after discharging from the hospital. The follow up data collection form is consisting of two sections. The first section recorded background information such as age, sex, body height and weight, feeding mode (mixed/artificial), oral calcium supplementation and history of exposure to melamine-tainted milk formula with brand name and duration of exposure. Mixed feeding was defined as breastfeeding and artificial feeding. The second section contained detailed clinical data, including symptoms, urinary tract ultrasound, urinalysis, routine blood testing, and hepatic and renal function. Plain abdominal radiography was performed for differential diagnosis, MRUS were radiolucent.

### Statistical analysis

Statistical analyses were performed with SPSS, version 10.0 for Windows. All values were expressed as mean ±SD. *t* test, chi-square were used to evaluate the differences. A P value of less than 0.05 was considered to indicate statistical significance.

## 3. Results

### Clinical features at admission

There was no significant difference in male-to-female ratio of HNMS vs. HNUPJO (2.8:1 vs. 4.0:1); however, male preponderance in each group is obvious.

Hydronephrosis was unilateral in35 (76%) HNMS and 77 (91%) HNUPJO patients. More bilateral hydronephrosis were found in HNMS than in HNUPJO (24%, 11/46 vs. 9%, 8/85, $P < 0.05$) (Table 1). HNMS show more symptomatic (abdominal mass, dysuria, renal colic (unexplained crying, oliguria or anuria, macroscopic or microscopic haematuria and hypertension) than those of HNUPJO (67% vs. 41%, $p < 0.05$) (Table 2). Five cases of acute renal failure were observed in HNMS and none in HNUPJO. More than 2 kinds of

symptoms were found simultaneously in 4 of HNMS and in 11 of HNUPJO.

According to the Society for Fetal Urology (SFU) guidelines hydronephrosis graduation, there were 27 HNMS cases and 30 HNUPJO of a mild degree (SFU grade 0, 1), 19 HNMS cases and 44 HNUPJO cases of a moderate degree (SFU grade 2, 3) and 0 HNMS cases and 11 HNUPJO of a severe degree (SFU grade 4). Mean degree of hydronephrosis of HNMS was significantly lighter than HNUPJO ($p < 0.05$) (Table 1).

There was no significant difference of the BUN and Scr between in HNMS and HNUPJO ($p > 0.05$) (Table 3). The PH value of urine was significantly lower in HNMS children compared with HNUPJO ($p < 0.05$), whereas the SUA was significantly higher in HNMS children compared with HNUPJO ($p < 0.05$) (Table 3).

**Treatment and Fellow-up**

Conservative short-term treatments were used in all HNMS patients immediately after diagnosis. Hemodialysis was performed in 5 HNMS with severe renal failure, and all cases gradually recovered after 1 to 4 times of hemodialysis treatments. Extracorporeal shock wave lithotripsy (ESWL) was performed in 1 HNMS cases. Primary pyeloplasty was performed in 55 cases with HNUPJO, whereas follow up was carried out in the remaining 30 cases HNUPJO, in which the degree of hydronephrosis is similar to those of HNMS at discharging. During the follow up, 5 HNUPJO patients underwent pyeloplasty due to progressive hydronephrosis and/or reduction in renal function.

At 24-month of follow-up, no mortality was observed, and 98% (45/46) HNMS and 83% (25/30) HNUPJO showed asymptomatic (Table 2). Ultrasonogram follow-up showed that hydronephrosis decreased rapidly during the first 6 months and then more gradually with time. Hydronephrosis resolved spontaneously in 43(93%) HNMS and in none of HNUPJO, remained stable in 2(4%) HNMS and 24(80%) HNUPJO (Table 4). The dilation degree of hydronephrosis decreased significantly in HNMS compared to those of HNUPJO (6.5%, 3/46 vs. 97%, 29/30, $P < 0.05$). The renal function of all the patients were recovered to normal, and the urinary output of whom returned to normal levels.

**Table 1. Site location and Hydronephrosis graduation at admission and 24-month follow-up**

| | HNMS | | HNUPJO | |
|---|---|---|---|---|
| | Initial (46 pts.) | Follow-up (46 pts.) | Initial (85 pts.) | Follow-up (30 pts.) |
| Left Hydronephtosis | 27 | 3 | 59 | 22 |
| Right Hydronephtosis | 8 | 0 | 18 | 6 |
| Bilateral Hydronephtosis | 11 | 0 | 8 | 2 |
| **Hydronephrosis graduation** | | | | |
| Mild | 27 | 3 | 30 | 19 |
| Moderate | 19 | 0 | 44 | 6 |
| Severe | 0 | 0 | 11 | 5 |

**Table 2. Clinical presentation at admission and 24-month follow-up**

| | HNMS | | HNUPJO | |
|---|---|---|---|---|
| | Initial (46 pts.) | Follow-up (46 pts.) | Initial (85 pts.) | Follow-up (30 pts.) |
| Symptomatic | 31 (67%) | 1 (2%) | 35 (41%) | 5 (17%) |
| Asymptomatic | 15 (33%) | 45(98%) | 50 (59%) | 25 (83%) |

**Table 3. laboratory data at admission and 24-month follow-up**

| | HNMS | | HNUPJO | |
|---|---|---|---|---|
| | Initial (46 pts.) | Follow-up (46 pts.) | Initial (85 pts.) | Follow-up (30 pts.) |
| PH value of urine | 5.6±0.6 | 5.9±0.6 | 5.9±0.5 | 6.0±0.5 |
| BUN（mmol/L） | 6.2±4.8 | 5.0±1.8 | 5.5±4.0 | 4.8±1.5 |
| SUA（umol/L） | 452±304 | 338±182 | 312±119 | 307±107 |
| Scr（umol/L） | 108±72 | 90±22 | 94±48 | 84±28 |

**Table 4. Response at 24-month follow-up**

| | HNMS (46 pts.) | HNUPJO (30 pts.) |
|---|---|---|
| Resolve | 43 | 0 |
| Improve | 1 | 1 |
| Stable | 2 | 24 |
| Worsen | 0 | 5 |

## 4. Discussions

It is well known that most of HNUPJO cases can be identified and diagnosed in the perinatal period with prenatal ultrasonography screening and treated before renal function is reduced [10]. However, hydronephrosis caused by urolithiasis, especially in infants and young children is rare. Since the scandal of melamine-contaminated infant formula in 2008, many infants come to hospital for ultrasound examination even with no history of exposure of melamine containment milk powder just due to their parents worried them suffering from the MRUS. Consequently, many of infants was occasionally found exist renal pelvic dilatation during their ultrasound screening. Many HNUPJO case showed a similar degree of hydronephrosis to HNMS.

How to distinguish of them and what different clinical feature of them during the treatment and follow up is unclear. It is well known both hydronephrosis has different etiology and physiology, as well as the treatment method is also not same. Therefore, to compare their clinical features and follow up their development or cure course is valuable for clinical practice.

As previously demonstrated, there was male preponderance in the children with HNUPJO [11,12]. In present study, a male-to-female ratio of 2.8:1 from children who suffered HNMS was found. This is in agreement with the ratio reported in a study assessing the influence of gender on the development of pediatric renal stones [13]. Similar to HNUPJO, the hormonal and urinary saturation effects on hydronephrosis formation might be the major influence factors and further studies are required.

Our data show that HNMS showed more symptomatic and less abdominal mass comparing with those of HNUPJO, and degree of hydronephrosis of HNMS was significantly smaller than HNUPJO, suggesting that the different etiology and physiology exist between them. Five cases of acute renal failure were observed in HNMS and none in HNUPJO. The renal failure may result from both intrarenal crystal-associated obstruction and an elevation in renal pressure that reduces renal blood flow and glomerular filtration rather than a systemic toxic effect [14].

At admission, mean degree of hydronephrosis of HNMS was significantly smaller than HNUPJO, whereas, at 24-month follow-up, the dilation degree of hydronephrosis decreased significantly in HNMS compared to those of HNUPJO indicating that infants with HNMS can be managed nonoperatively safely. The finding confirmed that most of these hydronephrotic kidneys of HNMS will recovery with the disappeared of MRUS after conservative treatment..

Treatment options for prenatally diagnosed HNUPJO include conservative and surgical management, with the aim of preserving renal function and preventing complications such as pain or infection [15]. Present study show 17% of HNUPJO may need surgical treatment due to deterioration of kidney function. While 2% HNMS infants may need surgical treatment.

In conclusion, significant difference of clinical feature existed between HNMS and HNUPJO. HNMS appears to be relatively benign. Non-operative management with close follow-up is a reliable and efficacious method for these HNMS infants. Recently, melamine contained food has been reported in media again in China. It has been predicted that this will be a long term risk for human food [16]. Therefore, to continue our researches on the melamine related kidney stone is necessary.

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