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Authors

Sun, Qiang
Shen, Ying
Sun, Ning
[et al.](#)

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Diagnosis, treatment and follow-up of 25 patients with melamine-induced kidney stones complicated by acute obstructive renal failure in Beijing Children's Hospital

Qiang Sun · Ying Shen · Ning Sun · Gui Ju Zhang ·
Zhi Chen · Jian Feng Fan · Li Qun Jia ·
Hong Zhan Xiao · Xu Ran Li · Birgit Puschner

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Abstract A total of 25 Chinese patients aged 6 to 36 months hospitalised at Beijing Children's Hospital due to melamine-induced kidney stones complicated by acute obstructive renal failure in 2008 were included in a study in order to diagnose and treat these special cases more effectively. Feeding history, clinical presentation, ultrasound findings, treatments and effects were summarised. Twelve to seventeen months follow-up was reported also. Ultrasound examination showed that calculi were located at the kidney and ureters. Stones were composed of both uric acid and melamine in a molar ratio of 1.2:1 to 2.1:1. Treatments providing liquid plus alkalinisation of urine proved to be effective in helping the patients pass the

stones. Surgical intervention was needed in severe cases. Renal function returned to normal in all 25 patients after various durations of therapy. Sixty-eight percent of the patients expelled all of the calculi within 3 months, 90% in 6 months and 95% in 9 months, without sequelae till now. Melamine-contaminated milk formula can cause kidney stones in infants, which should be diagnosed by feeding history, clinical symptoms and ultrasound examination. Composition of the stones was not only of melamine but also uric acid. Providing liquid orally or intravenously plus alkalinisation of urine proved to promote the removal of the stones. Follow-up of 12 to 17 months after discharge showed no sequelae.

Q. Sun · Y. Shen (✉) · G. J. Zhang · Z. Chen · J. F. Fan
Department of Nephrology, Beijing Children's Hospital Affiliated
to Capital Medical University,
Beijing, China 100045
e-mail: ying_116sh@sohu.com

N. Sun · X. R. Li
Division of Urology, Department of Pediatric Surgery,
Beijing Children's Hospital Affiliated
to Capital Medical University,
Beijing, China 100045

L. Q. Jia
Department of Ultrasonography, Beijing Children's Hospital
Affiliated to Capital Medical University,
Beijing, China 100045

H. Z. Xiao
Beijing Institute of Microchemistry,
Beijing, China 100091

B. Puschner
Department of Molecular Biosciences,
School of Veterinary Medicine, University of California,
Davis, CA, USA

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Introduction

Urinary tract calculi with renal failure are rarely diagnosed in infants. Of all the patients admitted to Beijing Children's Hospital between 2003 and 2007, the incidence of urinary tract stones complicated by renal failure is only 0.05 to 0.45%. In 2008, a sharp increase of children diagnosed as urinary calculi complicated by acute obstructive renal failure was noticed in Beijing Children's Hospital, the biggest children's hospital in China. All of the admitted children were under the age of 3 years. Melamine contamination of infant formula was identified as the cause of the renal stones [1]. According to a report from the Chinese Ministry of Health in December of 2008, 22,384,000 examinations were conducted in infants in China with suspected melamine exposure. By the end of November, 294,000 infants were diagnosed as having

urinary tract stones and 51,900 infants were hospitalised [14]. In Beijing Children's Hospital, a total of 32,530 children were examined by ultrasound. Of all the screened children, 2.9% had urinary tract calculi, of which 4.2% were hospitalised, and 25 of the hospitalised children were subsequently diagnosed as urolithiasis with complication of acute obstructive renal failure. All of the 25 children had consumed the same brand of infant formula, Sanlu, which was contaminated with melamine. The aim of the current study was to describe the clinical and laboratory features, the composition of calculi, the treatment and outcome of the 25 inpatients with melamine-induced kidney stones complicated by acute obstructive renal failure.

Subjects and methods

From March 15th to November 17th in 2008, 25 inpatients diagnosed as urinary tract calculi and acute obstructive renal failure in Beijing Children's Hospital were enrolled in this study. They were aged 6 to 36 months. Seventeen patients were male and eight were female. The following data were collected: clinical signs, estimated consumption of contaminated formula, urinalysis, ultrasonography of the urinary tract, routine serum chemistry and haematology parameters, including serum urea nitrogen and creatinine, as well as treatment regimens, response to the treatments, duration of hospitalisation and outcome at 12 to 17 months follow-up. Removed calculi were qualitatively and quantitatively analysed by high-performance liquid chromatography coupled with mass spectrometry, gas chromatography coupled with mass spectrometry and Fourier transform infrared spectrometry. Three therapeutic regimens were assessed: cystoscopy and retrograde catheterisation, dialysis (peritoneal and haemodialysis), and fluid administration. Patients' renal function was assessed prior to and after the treatments. The main outcome measures were: cure (renal function returned to normal and all urinary tract calculi were removed), effective (renal function returned to normal and urinary tract calculi decreased in size) and ineffective (urinary tract calculi did not decrease in size). Urinalysis and ultrasound results were recorded every month and serum values of blood urea nitrogen (BUN), creatinine and uric acid were recorded every 3 months.

Results

Patient population and clinical and diagnostic findings

A total of 25 Chinese patients were included in this study (17 boys and eight girls). They were between 6 months and 3 years old, of whom 19 patients were under 1 year and six

patients were between 1 and 3 years old. The median duration of exposure to Sanlu infant formula was 9.5 months (range 15 days to 24 months). The median duration of hospitalisation after stone detection was 14 days (range 4 to 60 days). All of the 25 patients had oliguria, anuria or dysuria. Two patients had haematuria, eight had fever and 12 vomitted, plus diarrhoea or other gastrointestinal tract symptoms, e.g. bloating, abdominal pain, anorexia.

Urinary tract stones were identified by ultrasonography in all of the patients. Ultrasound examination showed that the calculi were usually present in the following two appearances: sand-like crystals, either solitary or in clusters, with no shadow or with a comet-tail-like shadow (Fig. 1); or as larger size, clump-like calculi with a light shadow (Fig. 2). Most of the calculi are located in the renal pelvis and calyces, and at the three stenosis sites of the ureter: the pyeloureteric junction, the site where the ureter spans the iliac blood vessels and the site where the ureter attaches to the bladder.

Renal functions were significantly impaired in all of the patients: BUN ranged from 14.7 to 49.0 mmol/l, creatinine ranged from 93.0 to 908.0 μ mol/l, serum potassium ranged from 2.94 to 7.91 mmol/l and serum uric acid ranged from 195.0 to 1,257.0 μ mol/l (Table 1).

Composition of the stones

Toxicologic analysis to determine the composition of seven of the expelled calculi was performed. Both melamine and uric acid (Fig. 3) were detected in all the calculi in a molar ratio of 1: 1.2 to 1: 2.1. None of the calculi contained cyanuric acid.

Treatment and response to treatment

Exposure to the contaminated milk formula was stopped immediately. Correcting electrolyte abnormalities became the first line of treatment. Children with acute obstructive renal failure and oliguria for at least 2 days or anuria for at least 1 day were dialysed until clinical their chemistry parameters returned to reference ranges. Surgical interventions to remove the stones were given to the patients with severe hydronephrosis and to the anuric patients in whom dialysis was ineffective or unsuitable. In our study, 11 patients (44%) underwent cystoscopy and retrograde catheterisation; seven (28%) patients were dialysed, of whom six received peritoneal dialysis and one was haemodialysed; and the remaining seven patients (28%) received only fluid administration for 4 to 20 days. The solutions of 1–1.4% sodium bicarbonate were administered intravenously once or twice daily at a dose of 2 ml/kg to these patients and they were encouraged to drink plain

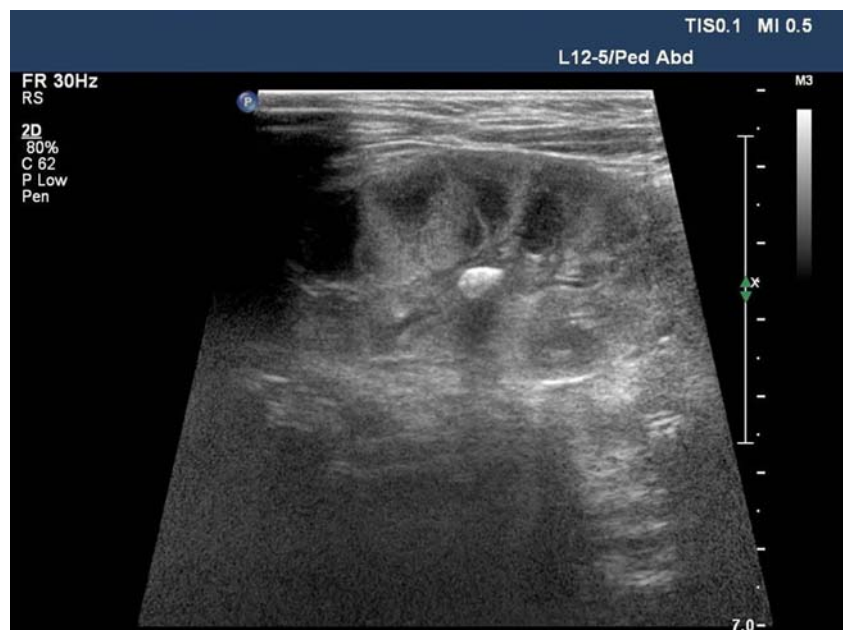
Fig. 1 Image of the kidney (ultrasonography): female, 8 months old, right kidney profile. A 0.15-cm² sand-like calculus (marked with +) at the renal calyx with a comet-like tail



water. Their urine pH values were continuously monitored for them to reach 6.5–7.0. Before fluid administration, the stone sizes ranged from 0.10 to 1.92 cm² (by ultrasound), but after alkalinisation, they reduced to 0 to 1.72 cm².

The renal functions returned to normal within 7 days (median 3 days) in all of the patients. Creatinine concentrations decreased to normal concentrations in 3.5 ± 1.89 days in the cystoscopy group, in 3.8 ± 2.26 days in the dialysis group and in 2.7 ± 1.60 days in the patients receiving fluids. According to the criteria we mentioned earlier in this article, six of the 25 patients were cured and 19 were effective by the time of discharging.

Fig. 2 Image of the kidney (ultrasonography): male, 10 months old, left kidney profile. The 0.6×0.4-cm² calculus at the renal calyx has a light shadow



Follow-up

Twenty-two patients were reviewed from May 1st 2008 to September 5th 2009; three patients failed the follow-up because of changes of address. At follow-up visits, all of the 22 patients had normal renal function and normal urine routine. The medium urine pH was 6.0. Serum uric acid values were normal. With ultrasonography study, 68% of the patients were found to have no urinary tract calculi at 3 months follow-up, 90% at 6 months and 95% at 9 months, respectively (Fig. 4). Hydronephrosis or other sequelae were not identified. To the two patients who still had calculi

Table 1 Specific data on each of the 25 infants hospitalised for melamine-induced kidney stones complicated by acute obstructive renal failure

Number	Gender	Age (months)	Duration of consuming the milk (months)	Main symptoms	Stone position	Size of stones (total, cm ²)	Serum potassium (mmol/l)	BUN (mmol/l)	Cr (μmol/l)	Serum uric acid (μmol/l)	Treatment	Effect
1	m	13	13	dysuria, fever	134	1.67	5.35	20.5	370.0	727	C	effective
2	f	7	5	anuria, fever	12	0.83	5.68	30.6	467.0	300	C	effective
3	m	20	20	abdominal pain, oliguria	23		4.60	18.8	305.9	546	C	effective
4	m	12	12	anuria, fever	134	1.43	7.91	30.7	355.0	537	C	effective
5	f	8	4	vomit, oliguria, fever	34		6.22	14.7	93.0	793	C	effective
6	f	8	4	vomit, diarrhoea, anuria	34	1.92	3.72	30.0	534.0	706	F	effective
7	m	8	8	vomit, oliguria, fever	134	2.69	5.96	23.7	420.0	815	PD	effective
8	m	7	7	anuria	24	1.61	8.12	49.0	908.0	635	PD	cure
9	m	6	6	anuria, fever	34	1.58	5.68	27.5	448.3	1,108	PD	effective
10	m	10	6	oliguria	2	0.99	5.67	16.1	164.8	833	C	effective
11	m	20	20	vomit, anuria, abdominal distention	12	1.79	5.73	39.7	711.0	647	C	effective
12	f	8	0.5	anuria	134	2.22	5.57	24.7	575.9	1257	PD	effective
13	m	7	7	oliguria, abdominal distention	234	0.34	5.78	21.0	248.8	820	F	cure
14	m	17	17	anuria	34	1.14	2.94	18.0	181.5	952	C	effective
15	m	7	7	diarrhoea, haematuria, oliguria	14	0.77	5.10	22.4	387.4	830	PD + C	effective
16	m	13	13	diarrhoea, vomit, anuria	12	1.12	5.42	23.5	381.0	1,247	F	effective
17	m	7	7	anuria	1234	1.78	6.48	25.6	375.0	614	PD	cure
18	f	8	8	diarrhoea, oliguria	124	2.58	6.34	30.5	854.0	993	PD + C	cure
19	m	22	12	anuria, fever	234	0.95	4.46	26.8	670.9	940	PD	effective
20	f	10	6	vomit, oliguria, fever	4		4.86	19.5	157.0	195	F	effective
21	m	12	7	anuria	14	1.21	5.59	21.0	290.0	709	F	effective
22	m	36	24	anorexia, oliguria	24	0.42	4.94	27.7	439.0	439	HD	cure
23	f	11	11	haematuria, oliguria	124	2.60	8.84	47.3	598.0	621	C	effective
24	f	11	11	dysuria	24	1.35	5.57	19.1	166.1	442	F	cure
25	m	8	2	anorexia, oliguria	1	0.10	4.53	21.3	194.3	769	F	cure

Stone position: 1. pyeloureteric junction; 2. ureter spanning iliac blood vessels; 3. ureter attaching to the bladder; 4. pelvis and calyces renales

Treatment: C cystoscopy and retrograde catheterisation; PD peritoneal dialysis; HD haemodialysis; F fluid administration

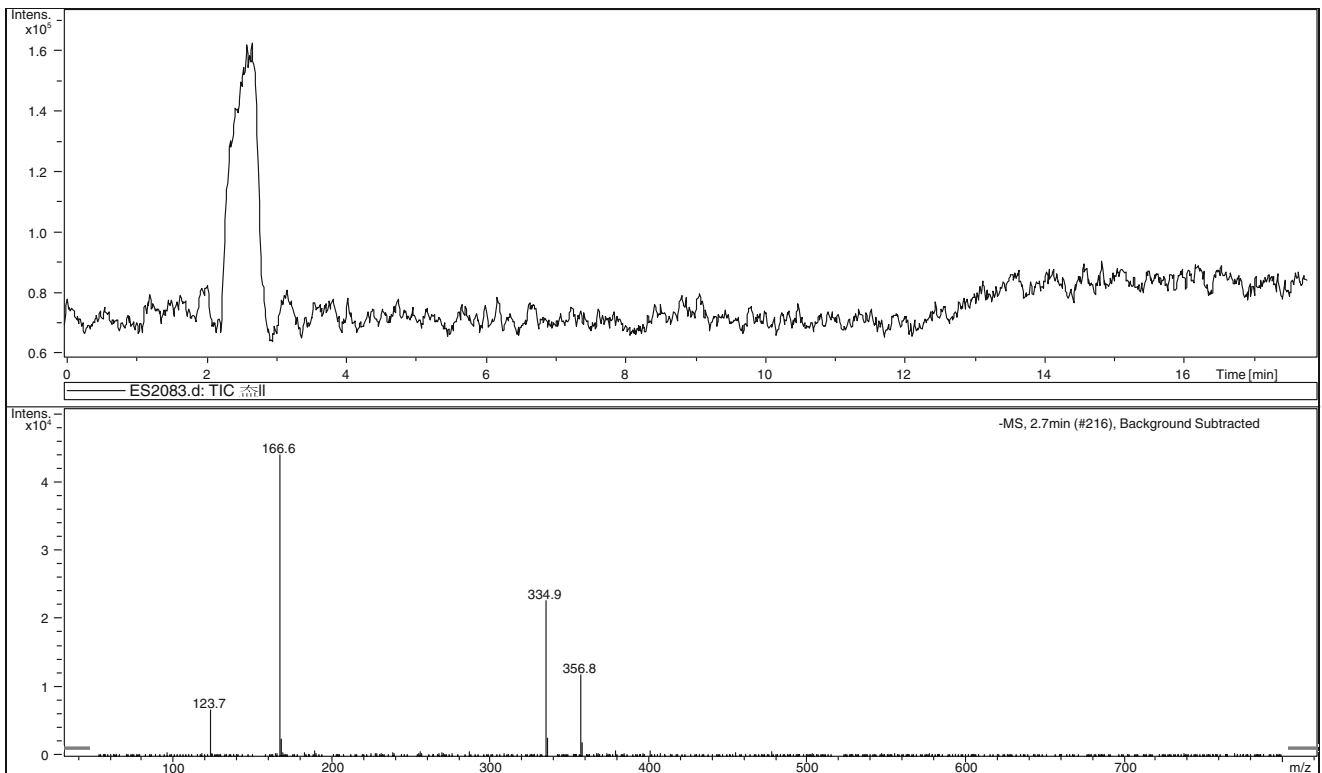


Fig. 3 Total ion chromatography of high-performance liquid chromatography–mass spectrometry (LCMS) and mass spectrogram of uric acid (detected in negative ion mode)

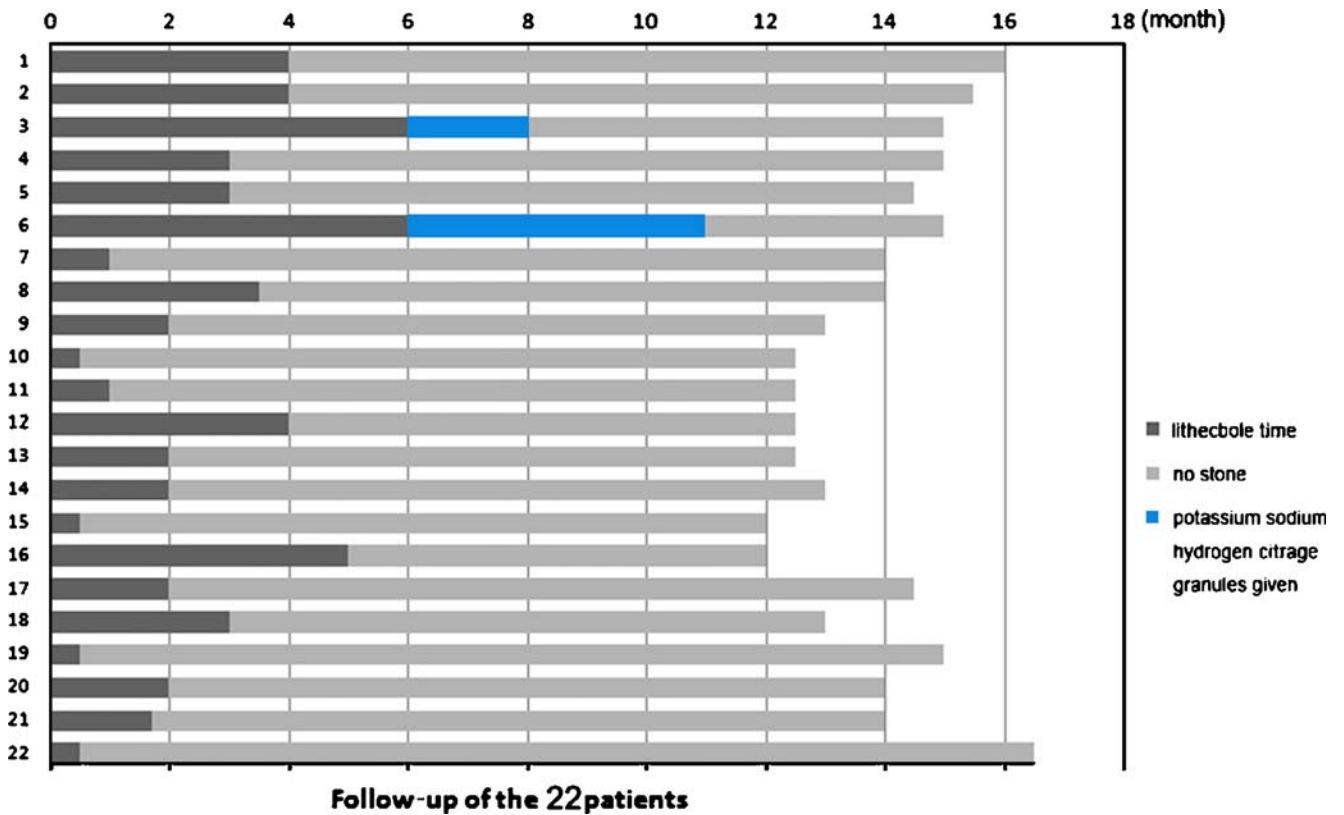


Fig. 4 Follow-up of 22 of the patients

after 6 months, potassium sodium hydrogen citrate granules (1 g/day, oral) was given. After that, one patient had no stones at 8 months and the other had his calculi decreased in size. The latter was an 8-month-old boy with the largest stone (2.69 cm²). Eleven months after discharge from our hospital, the size of the stone was still quite big (1.20 cm²), then, ultrasound-guided extracorporeal shockwave lithotripsy was given to this patient successfully. Till now (15 months follow-up), no stones were found by urinary tract ultrasonography, and the urinalysis and renal function of the patient remained normal.

Discussion

Physicians should take into consideration obstructive nephropathy when infants show clinical signs of pain, vomiting, haematuria and the presence of crystals during a urinalysis. The diagnostic approach for infants with suspected melamine-induced kidney stones relies heavily on ultrasonography of the urinary tract because melamine-uric acid calculi cannot be detected by radiography. Calculi or crystals have to be at least 1 mm in diameter in order to be detected by ultrasonography. Intravenous pyelography (IVP), in which calculi manifest as filling defects, may also be used to evaluate renal function, although this technique was not used in these 25 patients. Computerised tomography (CT) did not provide definite evidence for diagnosis, so is not recommended. Accurate diagnosis is the key to successful treatment and outcome, and must include detailed feeding history, clinical examination, imaging data and chemical analysis of urine and calculi [12].

The male:female ratio of the 25 patients was 2.1:1 in this study. This is in agreement with the ratio reported in a study assessing the influence of gender on the development of paediatric renal stones [3]. The anatomical features of the male urethra are different from females in terms of length, stenosis and arcuations; these differences may predispose male infants to urinary tract calculi because of the larger difficulty in passing stones.

This study demonstrates that no cyanuric acid contributed to the calculus formation in the affected infants and that the calculi consisted of both uric acid and melamine. We postulate that melamine is alkaline and some forms of melamine can turn into cyanuric acid while contacting strong acid in gastric juice, and cyanuric acid can then lower body fluid pH values. When pH values are lower than 5.5, uric acid tends to accumulate and form crystals that can block urine flow in the tubules [2, 4, 13]. The renal failure results from both intrarenal crystal-associated obstruction and an elevation in renal pressure that reduces renal blood flow and glomerular filtration. It is a

mechanical obstruction that results in renal damage, rather than a systemic toxic effect [5, 7–10].

As urinary pH played an important role in the development of melamine-uric acid calculus, urine alkalisation with potassium citrate or sodium bicarbonate in our treatment proved to be highly effective, resulting in dissolution of the existing stones [6, 11].

Twelve to seventeen months follow-up demonstrated that most of the patients passed all stones within 3 months. When it is difficult to expel stones after 6 months, surgical intervention should be considered to help the patient to get rid of the stones which are large in size (e.g. 1 cm²) or located at poor positions, e.g. renal pelvis and calyces renales. One of the 25 patients who did not expel all the stones after 11 months was given ultrasound-guided extracorporeal shockwave lithotripsy and the patient was cured without any complications. Currently, a further follow-up survey for the 25 patients is being carried out by our hospital.

In conclusion, melamine-contaminated formula can cause urinary system calculi and acute obstructive renal failure in infants. The stones are composed of uric acid and melamine at a molar ratio ranging from 1.2:1 to 2.1:1, without evidence of the presence of cyanuric acid or other melamine analogues. Therapeutic interventions have included oral fluid (plain water) administration, intravenous fluid administration and alkalisation of urine (to reach urine pH values of 6.5–7.0) with bicarbonate. Peritoneal dialysis, haemodialysis and surgical intervention for the removal of the stones were necessary in treating severe cases. The 12 to 17 months follow-up revealed no sequelae, while the long-term prognosis is still unclear and needs further observations.

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