Accepted Manuscript online: 2023-02-06 Article published online: 2023-03-16



# A Neonate with Mucopolysaccharidosis Type VII with Intractable Ascites

Kana Fukui, MD[1] Shoichiro Amari, MD, MHPE[1] Nobuyuki Yotani, MD, PhD[2] Rika Kosaki, MD, PhD[3] Kenichiro Hata, MD, PhD[4] Motomichi Kosuga, MD, PhD[3] Haruhiko Sago, MD, PhD[5] Tetsuya Isayama, MD, MSc, PhD[1] Yushi Ito, MD[1]

[1] Division of Neonatology, National Center for Child Health and Development, Tokyo, Japan
[2] Division of Palliative Medicine, National Center for Child Health and Development, Tokyo, Japan
[3] Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan
[4] Department of Maternal-Fetal Biology, National Center for Child Health and Development, Tokyo, Japan
[5] Center for Maternal-Fetal, Neonatal, and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan

**Address for correspondence** Kana Fukui, MD, Division of Neonatology, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo, 157-8535, Japan (e-mail: fukui.oka.kn58@gmail.com).

AJP Rep 2023;13:e25–e28.

## Abstract

We report a case of a patient with severe fetal hydrops and refractory ascites, diagnosed as mucopolysaccharidosis type VII (MPS VII) by whole-exome sequencing, and discharged at 5 months of age after long-term ventilatory management. A male neonate was born by emergency cesarean section due to fetal distress at $30^{1/7}$ weeks' gestation. Physical examination and X-rays revealed pleural effusion, ascites, and generalized edema, indicating severe fetal hydrops. He underwent tracheal intubation because of respiratory distress that was attributed to massive ascites, pulmonary hypoplasia, and pulmonary hypertension. He received mechanical ventilation and inhaled nitric oxide therapy. Prednisone, octreotide, and a factor XIII preparation were used as the treatment for ascites, and the ascites gradually decreased. He was extubated within 2 months of age. At 4 months of age, the results of whole-exome sequencing of the cord blood showed a compound heterozygous mutation in the *GUSB* gene, the gene responsible for MPS VII. Enzyme replacement therapy was initiated, and the ascites was resolved. Careful systemic management, including lung-protective respiratory management and the early establishment of nutrition, is important for the long-term survival of infants with fetal hydrops, and early aggressive workup, including whole-genome sequencing for the cause, should be performed in the case of refractory ascites.

**Keywords**
- MPS VII
- *GUSB* gene
- fetal hydrops
- refractory ascites

Mucopolysaccharidosis type VII (MPS VII) is an autosomal recessive, lysosomal storage disorder that is characterized by a deficiency in β-glucuronidase activity.[1] MPS VII is a rare disorder, and precise epidemiological data are scarce.[2] The frequency of this disease is estimated to be 1/300,000 to 1/2,000,000.[2]

**received**
September 23, 2022
**accepted after revision**
January 18, 2023
**accepted manuscript online**
February 6, 2023

**DOI** https://doi.org/10.1055/a-2028-7784.
**ISSN** 2157-6998.



Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

Patients with MPS VII have short stature, skeletal dysplasia, hepatosplenomegaly, inguinal hernias, cardiac diseases, pulmonary insufficiency, and cognitive impairment; this presentation resembles MPS I and MPS II. In MPS VII, a distinguishing clinical feature is a history of nonimmune fetal hydrops.[2–4]

Although MPS VII patients with improved fetal hydrops could survive,[5–7] there are few survival reports of patients with refractory fetal hydrops. We report a case of a patient with severe fetal hydrops and refractory ascites, diagnosed as MPS VII by whole-exome sequencing, and discharged at 5 months of age after long-term ventilatory management.

## Case

The mother was 29 years old, gravida one and para zero, with no medical history or family history. The fetus was noted to have subcutaneous edema, pleural effusions, and ascites at 18 weeks of gestation. A fetal thoracoamniotic shunt was placed at 22 and 23 weeks of gestation. The neonate with hydrops was born by emergency cesarean section due to fetal distress at $30^{1/7}$ weeks' gestation. A male neonate was born with a birth weight of 1,846 g (+2.4 SD), and the Apgar scores were 2 points at 1 minute and 5 points at 5 minutes.

He underwent tracheal intubation in the delivery room because of respiratory distress that was attributed to massive ascites, pulmonary hypoplasia, and pulmonary hypertension (PH) (►**Fig. 1**). Physical examination and X-rays demonstrated pleural effusion, ascites, and generalized edema, indicating severe fetal hydrops.

His blood test showed coagulation abnormalities. Because of massive ascites, an abdominal drain was placed, and the cell count in the ascites was 125/μL (all were mononuclear cells). After birth, the thoracoamniotic shunt was removed, and there was no further pleural effusion. In the neonatal intensive care unit, he received mechanical ventilation, inhaled nitric oxide (iNO) therapy, catecholamines, and hydrocortisone for circulatory failure and PH. As PH improved, iNO was discontinued at 5 days of age.

Until 3 days of age, drained ascites consisted of more than 100 mL/d. Prednisone, octreotide, and a factor XIII preparation were used as the treatment for ascites, and the ascites gradually decreased at 3 weeks of age. Enteral feeding was started with medium-chain triglyceride (MCT) milk at 28 days of age, and the abdominal drain was removed at 32 days of age. As the respiratory status improved, he was extubated at 53 days of age. Thereafter, he underwent high-flow nasal cannula therapy, which was changed to oxygen therapy with nasal cannula from 92 days of age.

Lymphatic scintigraphy was performed at 96 days of age because the patient had a reaccumulation of ascites (that did not require drain reinsertion), accompanied by massive scrotal edema (►**Fig. 2**). The scintigram revealed that there was an impaired lymphatic return to the central tract.

The following tests were performed to identify the underlying congenital diseases. Echographic examination revealed no cardiac, renal, or gastrointestinal malformations. Chromosome examination revealed a normal karyotype (46, XY).

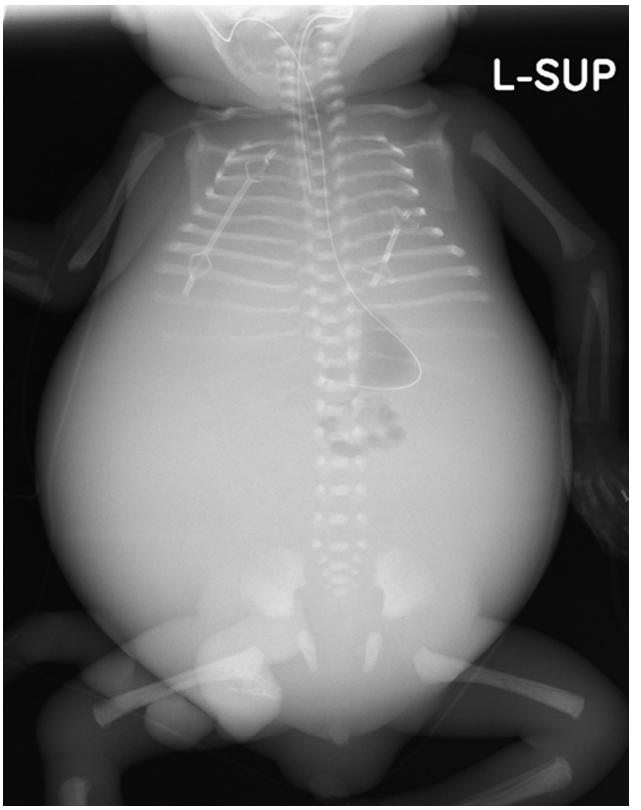


**Fig. 1** X-rays demonstrated pleural effusion, ascites, and generalized edema. Thoracoamniotic shunts were placed bilaterally in the chest.

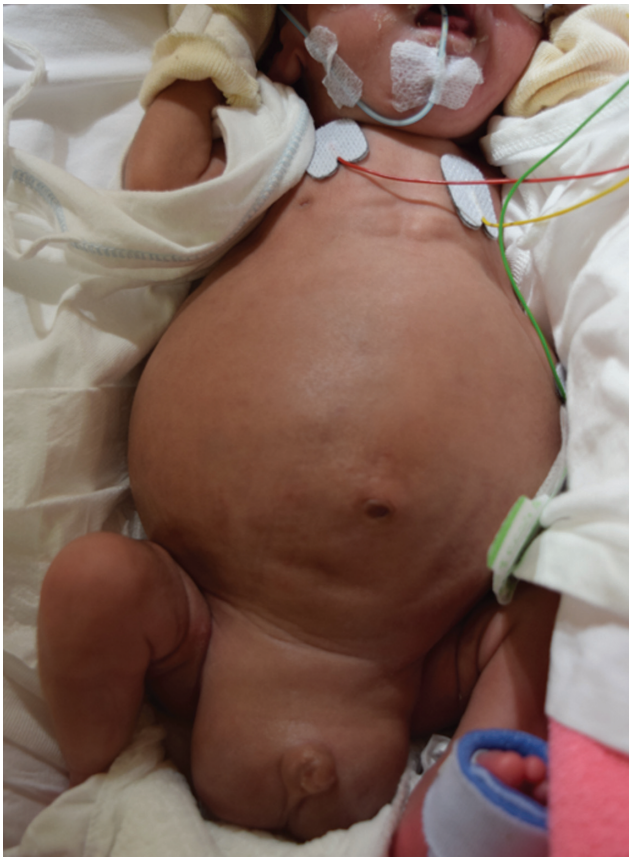

**Fig. 2** Significant ascites and scrotal edema at 90 days of age.

Ascites cytology showed no malignant cells. Maternal serological tests for infections, including toxoplasma, rubella, cytomegalovirus, and herpes simplex virus, revealed all negative results for first infection during pregnancy. Immunological fetal hydrops was also ruled out, as irregular antibodies were negative and fetal sonography showed no fetal anemia.

Other examinations showed no hepatomegaly and no ophthalmologic disease, but bilateral severe hearing loss was recognized. Whole-body bone X-ray, which was performed at 4 months of age, showed oar-shaped deformity of the ribs and punctate cartilage calcification.

At 4 months of age, the results of whole-exome sequencing of the cord blood showed a compound heterozygous mutation in the *GUSB* gene, the gene responsible for MPS VII. The whole-exome sequencing was approved by the Institutional Review Board (IRB) of the National Center for Child Health and Development, Japan (IRB number: 236,926). Genomic analysis was conducted with the informed consent of the patient's family. Beta-glucuronidase activity in leukocytes was low, and urinary uronic acid level was high, both of which were abnormal. Based on these results, we diagnosed his disease as MPS VII. He was discharged home with home oxygen therapy and gastric tube feeding when he was 5 months old. Enzyme replacement therapy was initiated at 7 months of age; the ascites was resolved, and the massive scrotal edema was also improved.

## Discussion

We identified a case of MPS VII who was discharged alive despite severe fetal hydrops and refractory ascites.

We found two important clinical issues. One is the importance of careful intensive care management for fetal hydrops, and the other is the importance of early and intensive workup for the cause of refractory ascites, including whole-exome sequencing.

The severity of MPS VII ranges from mild to severe and includes coarse facial features, corneal clouding, frequent upper respiratory infections, short stature, marked skeletal dysplasia, macrocephaly, gingival hypertrophy, hepatosplenomegaly, hernias, and cognitive impairment.[8,9] The most severe form of MPS VII is characterized by the presence of fetal hydrops.[10]

About half of the deaths occur before the age of 1 year, and the causes are fetal hydrops, respiratory failure, and renal failure.[2] In previous reports, MPS VII patients with pleural effusions and ascites that improved in a relatively short period of time were able to survive, whereas those with intractable effusions were likely to die. Montaño et al[2] showed that 10 MPS VII patients with severe fetal hydrops died of heart, renal, or respiratory failure. Saxonhouse et al[6] and Whybra et al[5] reported MPS VII patients with ascites that improved within a week, and both survived at least 27 months and 1 year, respectively. To our knowledge, our report is a very rare case of survival despite severe fetal hydrops and refractory ascites lasting more than 5 months. One of the reasons for the patient's survival may have been related to careful intensive care management after birth.

Respiratory, circulatory, and nutritional management for fetal hydrops is important for long-term survival. In our case, the lung-protective respiratory management and early establishment of nutrition were considered effective. During the acute phase, iNO was used for PH, and high-frequency oscillatory ventilation, which maintains constant intra-alveolar pressure and prevents lung damage caused by over-expansion, was used for lung-protective respiratory management. In addition, fluid management was performed to maintain adequate circulating blood volume while balancing edema and ascites. We were able to discontinue iNO at 5 days of age, and he was extubated within 2 months of age. These findings suggested that lung-protective respiratory management was effective, and the lungs had grown to some extent. It is difficult to establish enteral feeding in cases of fetal hydrops because nutrition is not often initiated smoothly, as pleural effusions and ascites may worsen, but in our case, we were able to start enteral feeding at around 1 month of age with MCT formula and establish nutrition at an early stage.

Early and intensive workup for the cause of refractory ascites is important. Although there are many symptoms of MPS VII, it is difficult to detect facial features, rib deformities, and corneal opacity at an early age. In our case, the rib deformity appeared at 4 months of age, and the corneal opacity appeared at 6 months of age.

MPS VII was diagnosed in 34% of patients below 1 year of age, as follows: 16% from 1 year to 3 years of age, 11% from 3 to 5 years of age, 20% from 5 to 10 years of age, and 12% older than 10 years of age.[2] Only about one-third of cases are diagnosed within 1 year of age, indicating that early diagnosis is difficult.

There are many causes of refractory ascites, including chromosomal abnormalities, lymphatic abnormalities, infections, and cardiac diseases. Metabolic diseases are also an important differential diagnosis, and MPS VII should be considered as one of the differential diagnoses of refractory ascites. Enzyme replacement therapy has been developed for MPS VII, and an early definitive diagnosis is important. Therefore, detailed assessment by genetic analysis, including whole-genome sequencing, in the early stages of infancy may be important for cases with hydrops and refractory chylous effusion.

## Conclusion

In conclusion, careful systemic management, such as lung-protective respiratory management and the early establishment of nutrition, are important for the long-term survival of infants with fetal hydrops. We reported a severe case of MPS VII who was discharged alive despite fetal hydrops and refractory ascites. For cases of nonimmunological fetal hydrops with refractory ascites, whole-genome sequencing should be considered after ruling out cardiac, renal, and gastrointestinal malformations, chromosomal abnormalities, tumors, and congenital infections.

**Conflict of Interest**
None declared.

Acknowledgment
We wish to thank the medical editor from the Center for Postgraduate Education and Training at NCCHD for editing this manuscript.

## References

1 Sly WS, Quinton BA, McAlister WH, Rimoin DL. Beta glucuronidase deficiency: report of clinical, radiologic, and biochemical features of a new mucopolysaccharidosis. J Pediatr 1973;82(02): 249–257
2 Montaño AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). J Med Genet 2016; 53(06):403–418
3 Poorthuis BJ, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999;105(1-2):151–156
4 Van Dorpe J, Moerman P, Pecceu A, Van den Steen P, Fryns JP. Non-immune hydrops fetalis caused by beta-glucuronidase deficiency (mucopolysaccharidosis VII). Study of a family with 3 affected siblings. Genet Couns 1996;7(02):105–112
5 Whybra C, Mengel E, Russo A, et al. Lysosomal storage disorder in non-immunological hydrops fetalis (NIHF): more common than assumed? Report of four cases with transient NIHF and a review of the literature. Orphanet J Rare Dis 2012;7:86
6 Saxonhouse MA, Behnke M, Williams JL, Richards D, Weiss MD. Mucopolysaccharidosis Type VII presenting with isolated neonatal ascites. J Perinatol 2003;23(01):73–75
7 Walter-Nicolet E, Rakza T, Storme L, et al. A new case of mucopolysaccharidosis VII presenting as non immune hydrops fetalis. Eur J Pediatr 2003;162(7-8):520–521
8 Hoyme HE, Jones KL, Higginbottom MC, O'Brien JS. Presentation of mucopolysaccharidosis VII (beta-glucuronidase deficiency) in infancy. J Med Genet 1981;18(03):237–239
9 Nelson J. Incidence of the mucopolysaccharidoses in Northern Ireland. Hum Genet 1997;101(03):355–358
10 Groener JE, de Graaf FL, Poorthuis BJ, Kanhai HH. Prenatal diagnosis of lysosomal storage diseases using fetal blood. Prenat Diagn 1999;19(10):930–933

 