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CASE REPORT

Prenatal-Onset Niemann—Pick Type C Disease with Nonimmune Hydrops Fetalis

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Niemann—Pick type C (NPC; OMIM 257219) disease is a neurodegenerative lysosomal storage disorder characterized by accumulation of unesterified cholesterol in the lysosomal/late endosomal system. This autosomal recessive disorder occurs in approximately 1/150,000 births. The broad clinical spectrum ranges from a prenatal severe presentation to an adult-onset chronic neurodegenerative disease. Data about prenatal presentation of NPC are limited. A female newborn was born at 34^2 weeks' gestation with a birth weight of 3070 g, and transferred to the Neonatal Intensive Care Unit because of nonimmune hydrops fetalis (NIHF) and respiratory distress. On admission, a physical examination revealed skin edema, mild respiratory distress, and abdominal distention due to massive ascites. Hepatosplenomegaly and cholestasis increased progressively and bleeding diathesis occurred. Results of an abdominal ultrasonography showed hepatosplenomegaly and segmental multicystic dysplastic left kidney. Foamy cells with a lysosomal phospholipid storage pattern compatible with NPC were found in the bone marrow smear. Cultured fibroblasts showed a strongly elevated filipin staining (classical NPC cellular phenotype), establishing the diagnosis of NPC. The infant died on the 52^{nd} day of life because of respiratory distress due to

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lung involvement of NPC, massive ascites, and progressive liver failure. Results of an autopsy showed multiorgan storage disease involving the liver, spleen, lymph nodes, thymus, lungs, and brain. Here, we present a preterm infant with NIHF as a sign of severe prenatal-onset NPC and review the literature.

1. Introduction

Niemann—Pick type C (NPC; OMIM 257219) disease is a neurodegenerative lysosomal storage disorder (LSD), which is characterized by the accumulation of unesterified cholesterol in the lysosomal/late endosomal system.[1,2] This autosomal recessive disorder occurs in approximately 1/150,000 births.[3] Mutations in the *NPC1* and *NPC2* genes are responsible for the anomaly of intracellular transport of low-density lipoprotein-cholesterol. Disrupted cellular Ca^{2+} signaling has been reported in the pathogenesis of LSD. A previous study has shown that defective lysosomal Ca^{2+} uptake and defective nicotinic acid adenine dinucleotide phosphate-mediated lysosomal Ca^{2+} release causes disruption in endocytosis and lipid storage.[4] The broad clinical spectrum ranges from a prenatal severe presentation to an adult-onset chronic neurodegenerative disease.[5,6] Neurological signs are useful for distinguishing several clinical forms: delay in developmental motor milestones in the early infantile form (2 months—2 years), gait problems, falls, clumsiness, cataplexy, school problems in the late infantile (2—6 years) and juvenile form (6—15 years) (classical form), and ataxia not infrequently following initial psychiatric disturbances in the adult form (>15 years). The most characteristic sign is vertical supranuclear gaze palsy. In 40% of cases, the disease occurs during the neonatal period. Neonates present with prolonged cholestatic jaundice, which usually disappears toward the age of 2—4 months, but this may also progress to fatal liver failure.[7] The prenatal presentation of NPC has been described previously in detail in only a few case reports.

First, Maconochie et al reported two cases with NPC initially presenting with fetal ascites at 18 and 33 weeks of gestation. These patients were born prematurely with pronounced hepatosplenomegaly and ascites.[8] Later, Manning et al reported a similar case of a patient with NPC who presented with polyhydramnios and fetal ascites at 26 weeks of gestation.[9] He was also a preterm infant with massive ascites and hepatosplenomegaly. Two of these three patients died within the 1st month of life due to rapidly progressive liver failure.

Here, we present a preterm infant presenting with nonimmune hydrops fetalis (NIHF) as a sign of prenatal-onset NPC and review the literature pertaining to this condition.

2. Case Report

A female newborn was born to a gravida 3, para 1 30-year-old mother by cesarean section at 34^{2} weeks' gestation with a birth weight of 3070 g and an Apgar score of 7/8/8 in the 1st, 5th, and 10th minute, respectively. The baby was transferred to the Neonatal Intensive Care Unit because of NIHF and respiratory distress. The parents were not consanguineous. A detailed obstetric ultrasonography at the 27th week of gestation showed hydrops fetalis, fetal ascites, and polyhydramnios. The blood group of the mother was an Rh positive. The results of further work-up, including fetal echocardiography and maternal serology for herpes, rubella, cytomegalovirus, toxoplasma, and parvoviruses were normal.

On admission, a physical examination of the newborn revealed skin edema, tachypnea, mild respiratory distress, and abdominal distention due to ascites. Initially, she had no dysmorphic features or organomegaly and her weight and height were at the 90th percentile. The results of the initial hematologic tests revealed thrombocytopenia (platelet count: 47 $\times$ 10^{9}/L) and diagnostic paracentesis revealed a transudate fluid.

Hepatosplenomegaly and cholestasis appeared gradually and the coagulation parameters worsened at the end of the 1st week. Ursodeoxycholic acid and spironolactone were administered in addition to fresh-frozen plasma transfusion and vitamin K. Results of an abdominal ultrasonography showed hepatosplenomegaly and a segmental multicystic left kidney. The blood and urinary levels of amino acids and organic acids were normal. Serum chitotriosidase activity and lysosomal enzyme screening were also normal. Foamy cells with a lysosomal phospholipid storage pattern compatible with NPC were found in the bone marrow smear (Figure 1). The results of filipin testing in cultivated fibroblasts were highly elevated, establishing the diagnosis of NPC. Molecular genetic analysis revealed that the infant was compound heterozygous for the deletion of p.D611_E612del (c.1831_1836delGATGAA) in exon 12 and for the deletion p.P1245fs (c.3734_3735delCT) in exon 24 of the *NPC1* gene. The infant died on her 52nd day of life because of respiratory distress due to lung involvement of NPC, together with massive ascites and progressive liver failure. Written informed consent was obtained from parents.

A pathologic examination of the placenta revealed placentomegaly [1100 g (*N*: 389 g)], villous edema, and focal infarct. In the liver, there were vacuolated hepatocytes with pseudoglandular transformation and rare multinucleated giant cells. Portal fibrosis and intralobular-perisinusoidal fibrosis were noticed. There were numerous foamy storage cells within the hepatic sinusoids, portal tracts, and splenic sinuses (Figure 2). In the lungs, the alveoli contained many foamy storage cells. The upper pole of the left kidney was multicystic and there was a double collecting system on that side. The upper ureter was

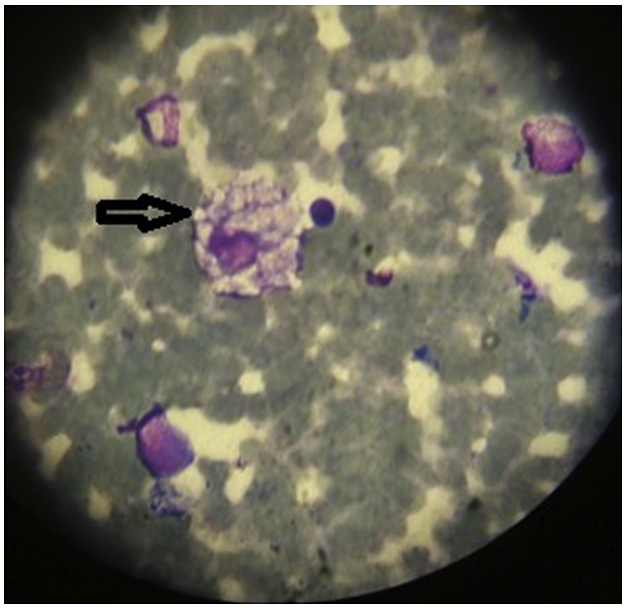

Figure 1 Bone marrow smear of the patient showing foamy cells (arrow) with a lysosomal phospholipid storage pattern compatible with Niemann—Pick type C.

thinner and the orifice to the bladder was obliterated. A microscopic examination was performed, which revealed segmental dysplasia of the upper pole of the left kidney. There were firm and pale-white areas in the periventricular white matter of the frontal and occipital lobes of the brain, where foamy storage cells and reactive astrocytosis were demonstrated. These findings were highly suggestive of NPC disease, which was confirmed by positive filipin staining in cultured skin fibroblasts and later with molecular study.

3. Discussion

NIHF results from a vast array of underlying pathologies including chromosomal anomalies, intrauterine infections, congenital heart disease, fetal arrhythmias, hereditary anemias, and lymphatic diseases. In large retrospective series, the relative frequency of the LSDs in the context of NIHF or ascites was 1.4%.[10] The LSDs related to NIHF consist of type 2 Gaucher disease, sialidosis type II, galactosialidosis, Salla disease, mucopolysaccharidosis types IV and VII, GM1 gangliosidosis, inclusion-cell disease, NPA and NPC, Wolman disease, and Farber disease.[11] The prenatal onset of NPC disease is exceptionally reported in association with NIHF.[8,12]

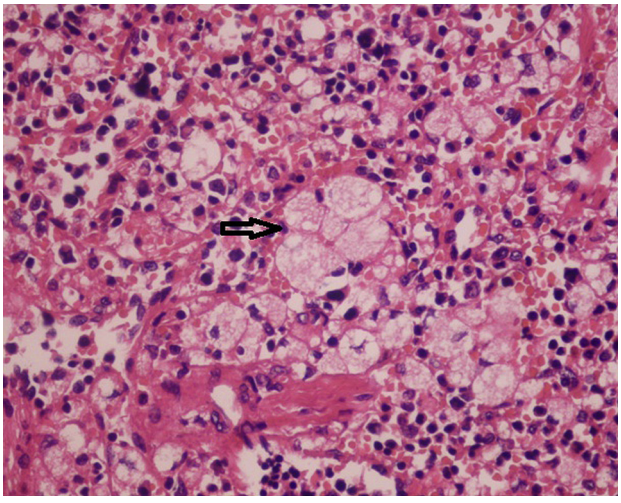

Figure 2 Clusters of foamy cells (arrow) and extramedullary hematopoiesis present in the patient's spleen.

Data on the prenatal onset of NPC disease are limited. Spiegel et al reported seven cases that were diagnosed as fetal-onset NPC. The fetal clinical findings of NPC consisted of *in utero* splenomegaly (6/7), hepatomegaly (5/7), ascites (4/7), intrauterine growth restriction (2/7), and oligohydramnios (2/7).[13] Three patients were delivered preterm. Postnatally, the most common clinical findings were congenital thrombocytopenia (4/4), anemia (2/4), and petechial rash (2/5). The authors noted a poor outcome in both prenatal and postnatal periods with deaths occurring within the first months of life due to rapidly progressing fatal liver failure. As found in these reported cases, our patient was born with fetal ascites after a preterm delivery and hepatosplenomegaly developed within the 1st week of life. Congenital thrombocytopenia was the accompanying comorbidity and progressive liver failure was the main cause of mortality. In addition, the infant had segmental multicystic dysplastic left kidney due to double collecting system, which had not previously been reported in association with NPC. There are no data about renal malformation seen together with NPC. In summary, the results of the molecular analyses together with a classical filipin signal and a typical clinical presentation confirmed the diagnosis of NPC disease in our patient. In addition, this is the first reported case in our country, the diagnosis of whom was confirmed with the collaboration of filipin staining, autopsy, and molecular genetic analysis. Neither of the deletions has previously been described, but both are very likely disease causing: the deletion p.P1245fs leads to a frameshift while the deletion of p.D611_E612del likely affects the protein structure.

Placental findings could be cautionary for the diagnosis of LSD, including placentomegaly and foamy cells in the villous stroma.[13] Similarly, the placental findings of our patient revealed placentomegaly but there were no histopathologic features for LSDs. In addition, the autopsy of our patient showed multiorgan storage disease involving the liver, spleen, lungs, and brain. Moreno et al reported two siblings with prenatal-onset NPC and the autopsy revealed multiorgan storage disease including the spleen, liver, lymph nodes, thymus, lungs, adrenals, and brain.[3]

In conclusion, our case, in common with the previous cases, showed that antenatal presentation of NPC disease is most often correlated with a severe and rapidly progressing fatal form of the disease that is histopathologically accompanied by multisystemic involvement. Despite promising treatments with *N*-butyl-deoxynojirimycin[14] and miglustat,[15] to date there has been no curative treatment for NPC. Therefore, identification of index case is essential for genetic counseling and antenatal diagnosis.

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