Compound Heterozygote Mutation in the SMPD1 Gene Leading to Nieman-Pick Disease Type A

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Patient: Male, 11-month-old
Final Diagnosis: Niemann-Pick disease type A
Symptoms: Hepatosplenomegaly • failure to thrive • neurodegenerative disorder
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Rare disease

Background: Niemann-Pick disease (NPD) type A is an autosomal recessive lipid storage disorder caused by acid sphingomyelinase deficiency due to a mutation in the SMPD1 gene. Type A is the most severe phenotype of NPD, with early onset in infancy and unfavorable outcome in early childhood.

Case Report: An 11-month-old boy with hepatosplenomegaly, elevated liver transaminases, and faltering growth was admitted to our hospital for further assessment of potential liver disease. He had severe generalized muscular hypotonia, muscular hypotrophy, reduced muscular strength, joint laxity, weak deep tendon reflexes, and severe motor developmental delay. Leukodystrophy was seen on the brain MRI, and brainstem auditory evoked potentials were characteristic for auditory neuropathy. A chest X-ray showed signs of interstitial lung disease, which was not further evaluated due to absence of respiratory distress. Liver biopsy histopathologic findings were indicative for lipid storage disease. Genetic analysis showed that the patient is a compound heterozygote in the SMPD1 gene – (NM_000543.5): c.573delT p.(Ser192Alafs*65), which was inherited from the mother and c.1267C>T p.(His423Tyr) was inherited from the father. Both variants were previously individually reported in NPD type A and B. The clinical phenotype in our patient was characteristic of NPD type A, with an early onset and a rapidly progressive neurodegeneration. The patient was included in multidisciplinary follow-up, providing him symptomatic treatment and support.

Conclusions: We present a case of NPD type A caused by a rare compound heterozygote mutation in the SMPD1 gene. Most clinical findings and the disease course were typical for NPD type A, except for bilateral auditory neuropathy, which seems to be an uncommon finding in this phenotype and could be underestimated due to infrequent testing for auditory dysfunction.

Keywords: Genetics • Neurodegenerative Diseases • Niemann-Pick Disease, Type A • Rare Diseases • SMPD1 Protein, Human

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Background

Niemann-Pick disease (NPD) type A is a lipid storage disorder caused by acid sphingomyelinase (ASM) deficiency [1]. The ASM lysosomal enzyme deficiency resulting from mutations in the SMPD1 gene leads to progressive accumulation of sphingomyelin and consequent damage of multiple organs [2,3]. Type A is the most severe phenotype of NPD (also called infantile neurovisceral form), which is clinically characterized by onset in infancy or early childhood, with failure to thrive, hepatosplenomegaly, and a rapidly progressive neurodegenerative disorder [2].

Case Report

An 11-month-old boy presented for gastrointestinal evaluation due to elevated liver transaminase levels. He was a second-born child. His older sibling had a history of vesicoureteral reflux but was otherwise healthy. Two members on the mother’s side of the family had idiopathic transient hyperbilirubinemia in childhood. The pregnancy was uneventful, prenatal ultrasound showed polyhydramnion, and the child was born at term with vaginal delivery (birth weight of 3810 g and length 53 cm). The Apgar score was 9/10. Due to mild respiratory distress, he needed transient oxygen therapy without ventilatory support. He had mild transient indirect hyperbilirubinemia, not meeting the criteria for phototherapy.

Faltering growth and motor delay with hypotonia and nystagmus were identified at 3 months of age. A brain MRI showed delayed myelination and the patient was followed by a pediatric neurologist. One month later, he had an acute gastroenteritis, and higher liver transaminase levels (AST 1.38 mcgkat/l, reference value <0.58 mcgkat/l, ALT 1.08 mcgkat/l, reference value <0.74 mcgkat/l) were noted. Gama-GT was normal (0.4 mcgkat/l). At the age of 10 months, he had significant hepatosplenomegaly and transaminase levels further increased (AST 3.77 mcgkat/l, ALT 4.40 mcgkat/l, gama-GT 0.85 mcgkat/l); therefore, he was admitted to our Pediatrics’ Gastroenterology Department. Liver transaminases were persistently elevated (AST 6.44 mcgkat/l, ALT 5.28 mcgkat/l, gama-GT 0.9 mcgkat/l) and bilirubin levels were normal. He had mild normocytic anemia (Hb 101 g/l), normal platelet count, and normal coagulation. Proteinogram and immunoglobulin levels were normal. He had increased alpha-fetoprotein level (up to 27.2 kU/l), increased total cholesterol (5.2 mmol/l, reference value <3.9 mmol/l), decreased HDL (0.6 mmol/l, reference value >1 mmol/l), increased LDL (4.9 mmol/l, reference value <2.6 mmol/l), and increased triglycerides (3.4 mmol/l, reference value <1.7 mmol/l). Celiac disease was excluded, with normal levels of t-TG IgA and IgA. Blood gas analysis, acylcarnitines, plasma amino acids, urine organic acids, and ammonia were normal. Diagnostic tests for liver diseases (alpha-1-antitripsin, ceruloplasmin, EBV and CMV antibodies, hepatitis viruses A, B and C, autoimmune hepatitis antibodies) were all negative. Abdominal ultrasound showed hepatosplenomegaly (liver size 109×104×82 mm, spleen longitudinal size 113 mm) without signs of portal hypertension. The beta-glucosidase level was normal and chitotriosidase was moderately increased (4620 nmol/ml/h, reference range 3-65 nmol/ml/h). Liver biopsy was performed. Histological evaluation showed numerous enlarged histiocytes with intracytoplasmic inclusions both in hepatic lobules and portal tracts (Figure 1A). Hepatocytes and biliary epithelia appeared swollen, with pale eosinophilic cytoplasm. Ultrastructural analysis showed accumulation of concentrically laminated myeloid structures in hepatocytes, Kupffer cells, endothelium, biliary epithelial cells, and fibroblasts (Figure 1B), which combined with histological findings suggested lipid storage disease. Due to liver biopsy results, we conducted targeted clinical and genetic tests.

Figure 1. (A) Liver biopsy showing clusters of enlarged histoyctes with foamy cytoplasm (Niemann-Pick cells) both in hepatic lobules and portal tracts. (B) Electron micrograph showing concentric myelin-like inclusions and laminated zebra bodies in Kupffer cells.
for NPD. Acid sphingomyelinase level was unmeasurably low (<0.4 mcg/mol/l) and lyso-SM-509 was increased (10.9 ng/ml, reference value <0.01 ng/ml).

For genetic analysis, next-generation sequencing (NGS) was performed. We reached 99.9% at least 10× coverage for a patient. The selected core panel for hepatopathy was used for filtering. Genetic analysis showed that patient was compound heterozygote in the SMPD1 gene; (NM_000543.5) – c.573delT p.(Ser192Alafs*65) was inherited from the mother and c.1267C>T p.(His423Tyr) was inherited from the father. Both variants are associated with NPD type A and B. The clinical phenotype was consistent with type A NPD. A blood sample for genetic analysis was collected from both parents to determine gene carriers for possible further genetic counseling.

During the hospitalization, we observed dysphagia and consequent inadequate caloric intake, which was improved with dietetic counseling. Neurologically, the boy had severe generalized muscular hypotonia, moderate muscular hypotrophy, and reduced muscular strength, joint laxity, weak deep tendon reflexes, and severe motor developmental delay (motor quotient 50). Continuous cardiac and respiratory function monitoring in sleep and EEG were normal. Brainstem auditory evoked potentials showed auditory neuropathy with bilaterally increased auditory thresholds. Cardiac ultrasound showed mild left ventricular hypertrophy, with normal systolic and diastolic function. Vision acuity and fundoscopy were normal. A chest X-ray showed signs of interstitial lung disease, which was not further investigated due to absence of respiratory distress. The patient was included in multidisciplinary team follow-up for symptomatic treatment and support.

Discussion

The primary organs affected in all ASM-deficient patients are the spleen and liver [3]. Hepatosplenomegaly was also the most prominent early clinical finding in our patient. Foam cells are found in various organs and bone marrow of patients with both type A and B NPD, and in our patient numerous foamy histiocytes (Niemann-Pick cells) were found on the liver biopsy. Quantifying the ASM activity in circulating leukocytes or cultured skin fibroblasts is the standard confirmatory diagnostic procedure [3]. ASM activity in our patient was undetectably low (<0.4 mcg/mol/l). ASM is produced from a single gene (SMPD1) located within the chromosomal region 11p15.4, which has a high potential for imprinting. Sequencing of the SMPD1 gene can be used for confirming the diagnosis. Over 200 mutations of the SMPD1 gene are currently known. Types A and B NPD are inherited as recessive traits, and the degree of clinical involvement depends on the type of SMPD1 mutations inherited and possibly due to inheritance of specific mutations on the maternal versus paternal alleles [4,5]. Our patient was found to be a compound heterozygote, and genetic analysis showed 2 genetic variants in SMPD1 gene, both already affiliated to ASM deficiency. This mechanism of inheritance is rarely described in the literature in type A NPD, with 2 Dutch cases reported by Sícora et al in 2003 [6].

The patient had normal neurodevelopment up to 3 months of age, which is consistent with other reports of NPD cases [7]. Bilateral pyramidal signs with increasing spasticity and loss of deep tendon reflexes are the most prominent neurologic signs described in the literature. Our patient had diminished deep tendon reflexes, but spasticity had not evolved by the age of 17 months. Brain imaging showed leukodystrophy, which is also typical for NPD type A according to previous studies [2,3]. Brainstem auditory evoked potentials were distinctive for auditory neuropathy. Hearing abnormalities were not yet described in NPD type A, but a study from King et al [8] reported a prevalent auditory dysfunction in patients with NPD type C1, with clinically significant high-frequency hearing peripheral hearing loss and a progressive course. Ophthalmological exam results in our patient were normal, although it is known that a cherry-red spot is present in the macula in approximately 50% of these infants [3].

A chest X-ray showed signs of interstitial lung disease, which is rare but reported in various types of NPD, most frequently in type B [9]. Niemann-Pick cells accumulate in the alveolar septa, bronchial walls, and pleura, leading to progressive restrictive lung disease with decreased diffusion capacity and potential oxygen dependence. Our patient had no signs of respiratory distress, and continuous monitoring of respiratory function in sleep was normal; therefore, this finding was not further investigated [10].

Laboratory results showed anemia, dyslipidemia, elevated liver transaminases, and moderately increased chitotriosidase. The platelet count was normal, although thrombocytopenia is the most common finding according to some studies [11]. All abnormal laboratory results in our patient were previously described in NPD type A [11,12].

Unfortunately, there is no treatment available for NPD type A; therefore, management is symptomatic [3]. Final stages of the disease include loss of spontaneous movement, chronic respiratory failure, and recurrent respiratory infections. Life expectancy is 1.5-3 years of age [7]. Assessment is complex due to the diverse spectrum of problems.

Conclusions

Our patient, diagnosed with NPD type A, was found to be a compound heterozygote with 2 genetic variants of the SMPD1
gene, each inherited from one of the parents. This type of genetic inheritance mechanism is rarely described in the literature. Our patient had a typical early disease onset with hepatosplenomegaly, failure to thrive, and progressive neurodegeneration. Additionally, brainstem auditory evoked potentials showed signs of bilateral auditory neuropathy, which seem to be an uncommon finding in this phenotype and could be underestimated due to infrequent testing for auditory dysfunction in these patients.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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