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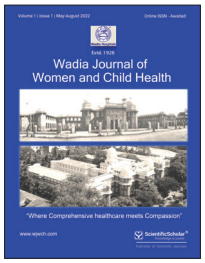

Case Report

An uncommon diagnosis of a common clinical presentation – Visceral Niemann–Pick disease

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ABSTRACT

Niemann–Pick (NP) disease is a diverse spectrum of disorders, autosomal recessive in nature, characterized by failure to thrive, visceral involvement in the form of hepatosplenomegaly and neurodegenerative changes. It is caused by an inherited deficiency of acid sphingomyelinase enzyme, leading to deposition of sphingomyelin and cholesterol within the lysosome of reticuloendothelial cells of various organs. We present a 16-month-old developmentally normal, well-grown girl with progressive, insidious onset abdominal distension, and no other symptoms. She was initially misdiagnosed as sepsis, but, on further evaluation was found to be genetically proven NP disease with autosomal recessive inheritance with sphingomyelin phosphodiesterase-1 gene positivity.

Keywords: Niemann–Pick disease, Sphingomyelinase, SMPD1 gene, Enzyme replacement therapy, Miglustat

INTRODUCTION

Niemann–Pick (NP) disease is an autosomal recessive disorder, predominantly characterized by hepatosplenomegaly, failure to thrive, and neurodegenerative changes. It is caused by an inherited deficiency of the enzyme Acid Sphingomyelinase (ASM). This leads to the deposition of sphingomyelin and cholesterol within the lysosome of reticuloendothelial cells of various organs.[1,2] Type A and B NP are characterized by the progressive accumulation of sphingomyelin and other lipids in the lysosomes of various tissues. Type C is due to defective cholesterol transport and involves NPC 1C and NPC 2C Gene. Diagnosis of Types A and B NP disease is confirmed by molecular genetic testing which is positive for Sphingomyelin Phosphodiesterase-1 (SMPD1) gene. NP type C is detected on biomarker screening for oxysterols. There is no definitive cure for NP disease.

CASE REPORT

A 16-month-old female, first by birth order, born of non-consanguineous marriage, presented with painless, progressive abdominal distension over the past four months, not associated with bowel or bladder complaints, jaundice, or bleeding manifestations. The child had received antibiotics before being referred to us, but without relief. She was born small for gestational age at full term with a birth weight of 1.75 kg with no significant antenatal or neonatal history.

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Developmental parameters were normal and she was partially immunized till 9 months of age. Anthropometric parameters showed a height for age at −3 standard deviation (SD), weight for age between −2 and −1 SD, and head circumference between −2 and −1 SD, while weight for height was between −1 and median. On examination, she had frontal bossing with multiple Mongolian spots over the back. There was no facial dysmorphism. There was evident splenohepatomegaly with no other systemic findings.

Laboratory investigations revealed significantly elevated hepatic transaminases with serum glutamic-oxaloacetic transaminase of 581 U/L and serum glutamic-pyruvic transaminase of 468 U/L, while serum bilirubin, serum albumin and coagulation profile were normal. Hepatitis screen and toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV profile were also negative. Other metabolic parameters that included serum lactate and serum ammonia were normal. The complete blood count was normal with Hemoglobin of 11.3g% and the peripheral smear revealed microcytic hypochromic anemia.

An abdominal ultrasonography showed gross splenohepatomegaly with early changes of portal hypertension.

Her ophthalmic examination and cardiac evaluation (by 2D-echocardiography) were normal.

Suspecting a storage disorder, a bone marrow aspiration and biopsy was performed that revealed foamy macrophages [Figure 1]. The dried blood spot revealed low level of enzyme sphingomyelinase, by fluorometry method (0.6 nmol/17 h/ml against a normal reference range of 1.0–3.9 nmol/17 h/ml).

Whole-exome sequencing confirmed an autosomal recessive inheritance, likely pathogenic mutation of SMPD1 gene on exon 1 of homozygous nature, suggestive of NP disease type B.

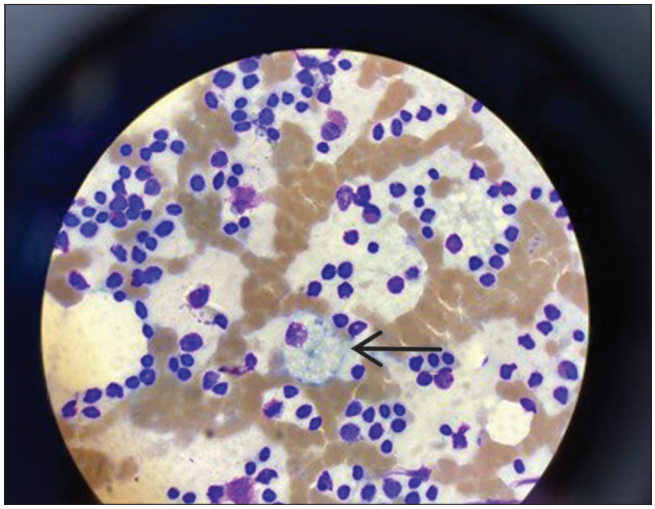

Figure 1: Bone marrow aspiration slide showing foamy macrophage (Arrow).

The child was subsequently referred to an ongoing trial for an enzyme replacement therapy at Gangaram Hospital in Delhi. Prenatal counselling was advised to the parents.

DISCUSSION

NP disease is a rare group of autosomal recessive disorders without gender predilection, with an estimated frequency of 0.4–1 per 100,000 live newborns[3] associated with splenomegaly, variable neurologic deficits.[1] Types A and B NP, resulting from deficiency of ASM activity, are characterized by progressive accumulation of sphingomyelin and other lipids in the lysosomes of various tissues, with the reticuloendothelial system being affected the most. Type C is due to defective cholesterol transport and involves NPC 1C and NPC 2C Gene. In an Indian study done in 2021, in 40 pediatric patients with ASM deficiency, variations in the SMPD1 gene were studied using Sanger sequencing. It revealed 18 previously unreported variants and 21 known variants including missense, non-sense, deletions, duplications, and splice site variations with potential to cause disease.[4]

NP Type A is characterized by a rapidly progressing neurodegenerative course. Type B has more non-neuronal manifestations with visceral involvement in the form of hepatosplenomegaly. Type C is characterized by developmental delay. Some of the cases have vertical gaze paralysis and hypotonia. Cherry red spots are occasionally seen in cases of NP. In an Indian study of 26 cases of NP disease, 21 presented in infancy. Hepatomegaly was a feature in all the cases while cherry red spots was detected in only three cases.[5,6] The diagnosed number of NP disease cases is minuscule compared to the actual burden due to lack of availability of diagnostic and treatment facilities for rare diseases.[7-9]

Bone marrow aspiration shows macrophages. Diagnosis of Types A and B NP disease is confirmed by molecular genetic testing which is positive for SMPD1gene mutations. NP type C is detected on biomarker screening for oxysterols.

The SMPD1 gene on chromosome 11p15.4 consists of six exons. The largest exon is the second exon which encodes 258 amino acids and comprises about 44 percent of the mature ASM polypeptide.[3,4] About 185 mutations have been reported in the SMPD1 gene in patients with ASM-deficient NP worldwide.[4,10] The mutational spectrum of the SMPD1 gene that has been reported in certain populations around the world has shown significant allelic heterogeneity.[4,10-12]

There is no cure for NP. Orthotopic liver transplant and bone marrow transplant have been attempted in a few cases of Types A and B with little success.[13] Clinical trials of enzyme replacement therapy with recombinant human ASM are ongoing worldwide including India (for which this child has been referred to).

Clinical trials of Miglustat, a glucosylceramide synthase inhibitor, which delays the progression of neurological manifestation in NP C – are ongoing in Europe.[14]

CONCLUSION

Hepatosplenomegaly is a very common presentation for a myriad of disorders involving reticuloendothelial system disorders. Hence, a thorough workup needs to be carried out with a high index of suspicion of rarer diseases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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