Rare disease

R542X mutation in SMPD1 gene: genetically novel mutation with phenotypic features intermediate between type A and type B Niemann-Pick disease

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Summary

Niemann-Pick disease (NPD) is a heterogeneous group of progressive neurovisceral disorder characterised by lysosomal accumulation of sphingomyelin. NPD types A and B are caused by mutations involving sphingomyelin-phosphodiesterase-1 (SMPD1) gene and are characterised by deficiency of acid sphingomyelinase activity. We present a case of a 9-month infant with clinical manifestations intermediate between types A and B NPD and genetically illustrating a novel R542X mutation in the exon 6 of SMPD1.

BACKGROUND

Niemann-Pick disease (NPD) is an autosomal recessive disorder with lysosomal accumulation of sphingomyelin and clinically manifesting with splenomegaly and variable neurological deficits.^{1 2} NPD types A and B are caused by mutations in sphingomyelin-phosphodiesterase-1 (SMPD1) gene and characterised by primary deficiency of acid sphingomyelinase (ASM) activity.¹ The data on SMPD1 gene mutations from Indian subcontinent are sparse. We report a 9-month infant with a novel SMPD1 gene mutation and phenotypic features intermediate between types A and B NPD.

CASE PRESENTATION

Nine-month female infant, first child of a non-consanguineous marriage was noted to have mild developmental delay at routine outpatient visit. The child was unable to sit with support, and had hypotonia of trunk and all four limbs. Her spleen was palpable 11 cm below the left costal margin, and liver was palpable 9 cm below the right costal margin. Fundal examination revealed small circular macular spot (figure 1A).

INVESTIGATIONS

On investigation, she had hypochromic microcytic anaemia (hemoglobin=9.7 g/dl), with normal white blood cell and platelet count. Lipid profile revealed a low high-density lipoproteins (15 mg/dl) and cholesterol (37 mg/dl), with raised triglycerides (270 mg/dl) and low-density lipoproteins (201 mg/dl). The chest radiograph and remaining metabolic parameters including liver function and renal function tests were normal. Histopathological examination of bone marrow demonstrated large periodic acid-Schiff (PAS)-negative histiocytes with abundant, foamy lipid laden cytoplasm (figure 1B).

Fluorimetric assay revealed decreased residual activity of ASM in peripheral blood leucocytes. The residual ASM activity in our patient was 2.11 nmol/17 h/mg against a control of 11.62 nmol/17 h/mg suggesting only 18% residual ASM activity. Sequencing of SMPD1 gene illustrated a R542X

mutation (arginine to stop codon at amino acid 542, figure 1C) by a homozygous C to T substitution at nucleotide c.1624 in the exon 6 of SMPD1. On the basis of the aforementioned features, she was diagnosed to have NPD. Currently the child is on supportive care.

DISCUSSION

NPD types A and B are caused by an inherited deficiency of ASM activity. ASM is produced from a single gene (SMPD1) located within the chromosomal region 11p15.4.³ This gene is located within an imprinted region of human genome, and is preferentially expressed from the maternal chromosome (ie, paternally imprinted).^{1 4} The mutations involving this gene result in decreased/absent activity of ASM, and manifest phenotypically as NPD. It has been suggested that small deletions and non-sense mutations, which render ASM non-catalytic, cause type A NPD, whereas missense mutations, which are associated with the production of a defective enzyme with some residual activity, cause type B phenotype. Detection and reporting of these mutations in specific populations (like Ashkenazi Jews) has facilitated large-scale screening for NPD and has aided physicians and genetic counsellors in predicting the phenotypic consequence.¹

ASM is principally found in lysosomes, and it participates in degradation of sphingomyelin, which is a structural component of most cell membranes.⁵ ASM deficiency results in intracellular lysosomal accumulation of these lipids. Pathologically this is characterised by the presence of large lipid laden foam cells in reticulo-endothelial system of spleen, bone marrow, lymph nodes, blood vessels, Schwann cells in peripheral nerves, central nervous system and retinal cells.²

Phenotypically, type A NPD patients typically present in infancy with hepatosplenomegaly, failure to thrive, cherry red spot on fundal examination and abnormal neurodevelopment. Among these patients neuro-degeneration proceeds rapidly and leads to death within 3 years.^{1 2} In

Figure 1 (A) Fundus photograph demonstrating a small circular macular spot; (B) Bone marrow demonstrated large PAS-negative histiocytes with abundant, foamy lipid laden cytoplasm; (C) R542X mutation (arginine to stop codon at aminoacid 542) by a homozygous C to T substitution at nucleotide c.1624 in the exon 6 of SMPD1.

contrast patients with type B NPD usually present with hepatosplenomegaly, bleeding diathesis, highly atherogenic lipid profile, interstitial lung disease and little or no neurodegeneration. Type B NPD usually has a later onset with a good prognosis for survival into adulthood.^{1 2 6}

Currently, there is no treatment for NPD that modifies the onset or neurologic progression or prolongs the lifespan. Haematopoietic stem cell transplantation, retroviral mediated transfer using ASM cDNA, direct intracerebral transplant of neural progenitor cells are experimental approaches being evaluated.

There were two distinctive features in our case. First, phenotypically the child was intermediate between types A and B NPD. He had neurological delay with developmental age of around 6 months, along with atherogenic lipid profile. ASM activity was around 20% of control. Thus based on these features, he was intermediate between types A and B NPD and probably, represents a continuum between the types A and B NPD caused by inheriting different mutations in the ASM gene with variable ASM activity. Second, genetic sequencing revealed a novel R542X mutation in the exon 6 of SMPD1. This

involved a homozygous C to T substitution at nucleotide position c.1624. There is a paucity of genetic information of NPD in the Indian subcontinent. This mutation information can be used for prenatal diagnosis in this family and if reported in other NPD patients from this region can be useful for region specific carrier testing if clinically indicated.

To conclude, NPD is fatal lysosomal storage disorder caused due to decreased ASM activity. Although more than 100 mutation involving the SMPD1 gene have been reported, but the data from Indian subcontinent has been sparse. We report a novel mutation of SMPD1 gene manifesting phenotypically with features intermediate between types A and B NPD.

Learning points

- ▶ Niemann-Pick disease (NPD) should be considered in infants presenting with massive splenomegaly and hepatomegaly.
- ▶ Clinically, the patient may have features of both NPD types A and B representing a continuum between the types A and B NPD caused by inheriting different mutations in the acid sphingomyelinase (ASM) gene with variable ASM activity.
- ▶ Every child considered to have NPD should undergo genetic testing to facilitate future prenatal testing as well to characterise the mutations in the respective population.

Competing interests None.

Patient consent Obtained.

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