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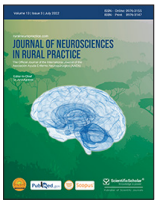

Letter to Editor

A rare case of intermediate phenotype Niemann-Pick disease with a rare pathogenic variant of 1624C>T in SMPD1 gene

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Dear Editor

A 12-month-old girl, first born to non-consanguineous parents, presented to the pediatric neurology clinic with delayed attainment of developmental milestones. The birth and perinatal period were uneventful. The family history was unremarkable. On examination, she had multiple Mongolian spots over the trunk. She had hepatomegaly of size 4 cm and splenomegaly of size 3 cm. She had central and peripheral hypotonia, could move all four limbs against gravity, and deep tendon reflexes were not elicitable. She had no abnormal startle reflex, nystagmus, or tremor. The rest of the systemic examination was unremarkable. Ophthalmology evaluation revealed the presence of bilateral cherry-red spots.

On investigation, the lipid profile showed high-density lipoprotein level of 23 mg/dl, serum triglyceride level of 198 mg/dl, low-density lipoprotein level of 135 mg/dl, and serum total cholesterol level of 168 mg/dl. A skeletal survey revealed metaphyseal widening of the humerus and femur. Fundus evaluation revealed the presence of bilateral cherry-red spots. Clinical exome sequencing revealed a homozygous, non-sense pathogenic variant c.1624C>T (p.Arg542Ter) in exon 6 of the sphingomyelin phosphodiesterase 1 gene (*SMPD1*) gene (chr11:g.6394335C >T; depth: 163 ×), resulting in the amino acid substitution of arginine to a premature STOP codon, leading to premature truncation of the protein at codon 542 suggestive of Niemann-Pick disease (NPD). Both parents were asymptomatic heterozygous carriers for the same pathogenic variant.

NPD, also known as sphingomyelin-cholesterol lipidosis, is a rare autosomal recessive lysosomal storage disorder. NPD type A and type B are due to absent or reduced activity of the acid sphingomyelinase enzyme, respectively, and the defect lies in the *SMPD1* on chromosome 11p15.4.[1,2] NPD type A (OMIM #257200) is an early onset, an acute neuronopathic form characterized by hepatomegaly, feeding difficulties, developmental delay, hypotonia, and absent deep tendon reflexes resulting from peripheral neuropathy. This is a rapidly progressive condition resulting in death at 2–3 years of age. NPD type B (OMIM #607616) is a later onset and less severe non-neuronopathic form characterized by hepatosplenomegaly, delayed skeletal maturation, short stature, ocular abnormality, and pulmonary involvement. They usually survive into late childhood or early adulthood.[1,2] An intermediate form between these two types has been described in only a few patients with mostly novel mutations.[3] An intermediate phenotype of "subacute neuronopathic form" represents a spectrum of NPD types A and B, where they present with the phenotype of NPD type B but with neurological involvement. The index case is a 12-month-old infant with an "Intermediate" phenotype of NPD with a rare pathogenic variant of c.1624C >T in the SMPD1 gene. This variant has been reported only once in the Indian population.[4] These children have better survival than NPD type A.[5] There is no cure currently available for both NPD type A and type B, and the cornerstone of treatment is supportive care.

An early and accurate genetic diagnosis is essential in managing by decelerating the disease progression and enhancing the quality of life by preventing complications. The multimodal management should include parental testing and counseling regarding future pregnancy.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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