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Case Report

A novel mutation of Niemann-pick disease: a case report

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ABSTRACT

Niemann-Pick Disease (NPD) is a well-known entity among the rare causes of lysosomal storage disorders (LSD) and constitutes a significant public health burden globally. The incidence of NPD is 1 in 250,000 individuals with a high prevalence in Ashkenazi Jewish descent, affecting 1 in 40,000 individuals. We report a novel and hitherto unreported. Here we report a case of NPD in a 6 months old male child presented to our hospital with unexplained hepatosplenomegaly with cherry red spots on fundoscopy and with history of death of previous two siblings. The diagnosis of NPD was proven by whole exome sequencing (WES) with identification of novel mutation, homozygote missense variant c.500G>C in exon 2 of sphingomyelin phosphodiesterase 1 (SMPD1) gene that results in the amino acid substitution pCys167Ser. The patient was kept under management of multidisciplinary team. Age of presentation, hepatosplenomegaly, presence of cherry red spots was typical for NPD type A. We report a rare homozygote mutation in the SMPD1 gene.

Keywords: Niemann-pick disease, SMPD1 mutation, Whole exome sequencing

INTRODUCTION

NPD is a rare autosomal recessive disorder included in lysosomal storage disorders. It commonly affects the paediatric age group and only 6% of it occurs in adult population. The global prevalence is estimated between 4-6 case per 10,00,000 population and more frequent among ascendant Jewish population.[2] NPD presents with hepatosplenomegaly, jaundice and cytopenia. In severe form of the disease patients can present in early infancy with failure to thrive, hepatosplenomegaly or pulmonary manifestations. The clinical manifestations have been classified into type A, B and C presentations.

Type A and B have SMPD1 gene mutation while type C have NPC1 and NPC2 gene mutations. Type A and B result from deficient activity of sphingomyelinase and the SMPD1 gene located on bands 11p15.1-p15.4 and referred to as acid sphingomyelinase deficiency (ASM).[3] The enzymatic defect results in pathological accumulation of sphingomyelin, a ceramide phospholipid and other lipid in monocyte macrophage system. Type A is most severe form of the disorder, resulting in early death. Type B is later onset non-neurologic form characterized by hepatosplenomegaly which is often compatible with survival till adult age. Another intermediate variant, type A/B has also been reported wherein affected individuals manifest mild to moderate developmental delay with some level of neurological involvement, which is why it has been proposed that ASM deficient NPD and should be considered as a single disease entity with a spectrum of clinical manifestations.[4,5] In many cases the diagnosis rests on identification of cherry red spots in fundus on ophthalmic examination or presence of storage cells in the marrow.[6]

The enzyme analysis is available only in selected laboratories for sphingomyelinase and may not be accessible in all suspected cases. Type C NPD is characterised by neurological alteration. For this type, diagnosis traditionally required a liver biopsy and Filipin staining. Now-a-days, biomarker studies and molecular testing for genes have helped in better diagnosis. Earlier bony marrow biopsy was routinely done for diagnosis of storage disorder. Now-a-days with better expertise and availability of good laboratory facilities, sometimes

enzyme analysis is done upfront for diagnosis of storage disorder. In last few years trends have shifted toward molecular testing.

CASE REPORT

We present a case of 6 months old male child brought with complain of gradually progressive abdominal swelling for last two month noticed by mother. He was born out of non-consanguineous marriage, full term by caesarean section, birth weight was 3.9 kg, cried immediately after birth and there is no history of neonatal jaundice or neonatal ICU stay.

There was no significant past history and developmental history was as per age and immunization was as per universal immunization program (UIP) schedule. There is no family history of any storage disorder but mother had history of one spontaneous abortion at 8 weeks of age and first order baby passed away at 10 months of age with hepatosplenomegaly and acyanotic heart disease. In anthropometry child weighed 6.9 kg (on 75th centile), had length of 63 cm (on 75th centile), head circumference was 41 cm (on 3rd centile). Vitals were within normal limit with pulse rate of 110/min, respiratory rate of 28/min, blood pressure at 90th centile and temperature 98° F.

FINDINGS RELATED TO PHENOTYPE

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classifcation
SMPD1 NM_000543.5	c.500G>C p.Cys167Ser	Exon 2	Homozygote	CADD: 26.6 SIFT: Tolerated Polyphen2: N/A MT: Damaging	NIEMANN-PICK DISEASE, TYPE A:257200 NIEMANN-PICK DISEASE, TYPE B:607616	Autosomal Recessive	Uncertain Significance

Figure 1: Result of whole exome sequencing.

On examination child had mild pallor, no cyanosis, icterus, clubbing, neck glands or engorged neck veins. In gastro-intestinal system examination abdomen seemed distended with normal flanks and all quadrants moving equally with respiration, overlying skin was normal. On palpation, liver was 6 cm below right costal margin with 14 cm liver span, firm in consistency, sharp borders, smooth surface with no tenderness, pulsation or hepato-jugular reflex. Spleen was 8 cm below left costal margin in splenic axis with palpable anterior notch, firm in consistency, smooth surface and sharp borders and no tenderness.

There was no abdominal lymph nodes and no shifting dullness. Respiratory system revealed normal shape, movement of chest, respiratory rate of 28/minute with normal vesicular breath sounds in all areas. Cardio-vascular system examination was normal. Neurological examination showed higher functions, cranial nerve examinations, power, tone within normal limits. Fundoscopy was suggestive of cherry red spots.

Management and outcome

Complete blood count showed 8 gm/dl haemoglobin with peripheral smear suggestive of microcytic hypochromic RBCs with target and tear drop cells. Mild alteration in lipid profile was noted. Transaminase level was within normal limit with normal renal function test. Stool for fat globules was positive. Skeletal survey did not show any dysostosis. Keeping a clinical diagnosis of Gaucher and Niemann Pick disease, liver and bone marrow biopsy was planned. But parents refused for biopsy despite of informed counselling. Thus, WES was done which identified a homozygous missense mutation. It was a variant c.500G>C in exon 2 of SMPD1 gene (Figure 1). In our instance, a multidisciplinary team was needed to manage the patient.

DISCUSSION

We present a case of 6 months old male child with hepatosplenomegaly with death of two siblings. After ruling out common causes of hepatosplenomegaly, we started workup in line of storage disorders. All patients with NPD type A have a classical eye finding of cherry-red spot and about one-third of patients with type B NPD have the cherry-red spot and neurological symptoms.[7]

Presence of cherry red spots in fundoscopy was strongly indicative of NPD type A. Neurological manifestations is typical for NPD type A but its absence in our case does not rule out the probability as it may develop later.

Although enzyme assay has been considered to be gold standard method for diagnosis for LSD, but it has many limitations like enzyme being subject to degradation which can lead to false positive results. Bone marrow biopsy was planned but parents did not agree for the invasive procedure. Due to lot of drawbacks in enzyme assays and biopsy, the current trend is shifting towards WES as first line of investigation.

In our case WES was done suggestive of a homozygote missense variant c.500G>C in exon 2 of SMPD1 gene that results in the amino acid substitution p.Cys167Ser. This mutation was of an uncertain significance associated with NPD type A and B. The severity of impact of this variant on protein is medium, based on effect of protein and rare exome variant ensemble learner (REVEL) score.

To date around 185 mutations in patients with NPD have been described worldwide and the p. (Arg542*) (c.1624C>T) was the most commonly identified mutation. 8 Ranganath et al, reported 66.7% missense mutation, 8.9% nonsense mutation and 20% frame shift mutations in Indian context. Apart from it 68.8% were

novel mutations, implying the uniqueness of SMPD1 mutation spectrum in Indian population with p. (Arg542) being most common mutation.[8] We have identified a novel mutation, c.500G>C p.Cys167Ser, in our case. Although basing upon the REVEL score this variant has been classified as uncertain significance at present, with the widespread use of WES in suspected population more mutations can now be identified in our community. It can add to the existing spectrum of SMPD1 mutation in Indian population.

CONCLUSION

In conclusion, whenever a diagnosis of LSD in contemplated including NPD, WES should be done for the patient and the parents whenever possible and where cost is not a constraint. WES will help in providing definite diagnosis, before proceeding to any invasive procedure. Although the above described newly found mutation is described as of uncertain significance, more data in future may put more light on it.

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