Niemann–Pick Disease Type B – A Case Report

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Abstract

Introduction: Niemann–Pick Disease (NPD) is an autosomal recessive disorder, characterized mainly by the accumulation of lipids, mostly sphingomyelin and cholesterol, in different organs such as liver, spleen, bone marrow, lungs and brain. The Sphingomyelins accumulate in lysosomes, which are responsible for carrying substances in and out of the cell. NPD is classified in 4 types: Types A, B, C and D. In type A and B, there is deficiency of acid sphingomyelinase which helps to break down Sphingomyelins, whereas Type C and D are caused by a defect in the transport of intracellular cholesterol. Thus, the 4 disease types can be grouped into 2 main categories: Type (I) which includes type A and B; and Type (II) which includes type C and D. Each type affects different organs. Symptoms depend upon severity of the disease and organs involved. The diagnosis is done by measurement of enzyme activity in peripheral white blood cells or in cultured fibroblasts. The pathologic hallmark in Niemann-Pick disease (NPD) types A and B is the characteristic lipid-laden foam cell termed as Niemann-Pick cells on bone marrow examination. Mutation analysis for detection of SMPD1 mutations is a complex procedure but can be done if facilities are available. There is no specific treatment for Niemann-Pick Disease. Type A is a severe form of disease, with average life span of 18 months. In all other types, treatment is aimed at controlling levels of cholesterol. Newer drugs like Miglustat which is able to delay neurodegeneration, β-cyclodextrin- hydroxypropyl (HBP-CD) which is claimed to attenuate clinical symptoms are being investigated in trials. Genetic counseling and genetic testing are recommended for families who have history of Niemann–Pick disease.

Case Report: A 7 year old female child was brought with complains of abdominal distension which started at the age of 3 years. There was also history of intermittent fever, difficulty in walking in the form of repeated falls and multiple episodes of tonic clonic seizures since last 1 year. Development history was significant since the the patient had normal development till the age of 3 years following which she started lagging behind in all aspects of development. She also had a younger sibling having similar complaints of abdominal distension and developmental delay. On examination patient had global developmental delay with mild mental retardation (IQ= 68). There was significant abdominal distension with moderate hepatosplenomegaly. Bone marrow examination was done which showed characteristic lipid-laden foam cell termed as Niemann-Pick cells. Lysosomal enzyme studies confirmed the diagnosis of pieman pick disease type B. Anticonvulsants (Levipril) was started. Patient was discharged with an advice for regular follow up. Parents were referred for genetic counseling.

Conclusion: Sphingomyelinase deficiency or Niemann-pick disease should be suspected in pediatric patients presenting with hepatosplenomegaly and developmental delay. The diagnosis is usually done by bone marrow examination and lysosomal enzyme studies. Genetic counseling should be offered to parents having children with Niemann-pick disease.

Keywords: Niemann-pick disease, sphingomyelinase, Developmental delay, Genetic counseling.
Introduction
Lipid storage diseases, or lipidoses, are group of inherited metabolic disorders in which lipids accumulate in cells and tissues of the body. Individuals suffering from these disorders either do not produce enough of one of the enzymes needed to metabolize lipids, or they produce enzymes that do not work properly [1]. Over time, this excessive lipid deposits can cause permanent cellular and tissue damage, particularly in the central and peripheral nervous system, liver, spleen, and bone marrow. The common examples of lipid storage disorders are Niemann-Pick disease, Fabry disease, Krabbe disease, Gaucher disease, Tay-Sachs disease, Metachromatic leukodystrophy, multiple sulfatase deficiency and Farber disease [2].
Niemann pick disease (NPD) is a rare form of lipidoses which is divided into two distinct entities: (1) Acid sphingomyelinase-deficient Niemann–Pick disease (ASM-deficient NPD) which result from mutations in the SMPD1 gene and includes type A and type B and intermediate forms; (2) Niemann–Pick disease type C (NP-C) and type D which result from mutations in NPC1 or the NPC2 gene [3]. The inheritance pattern is autosomal recessive in both of these sets of NPDs. NPD type A usually proves fatal in infancy. Hepatosplenomegaly develops by age 6 months and development does not progress beyond age 12 months. A relentless neurodegenerative course with regression of milestones and seizures ensues and it usually results in death by age of 2 years [4]. NPD type B has a variable age of presentation and non-lethal course. The presentation is usually in early childhood with hepatosplenomegaly, mental retardation, regression of milestones and seizures. Pulmonary involvement may be prominent in NPD-B. The prognosis is definitely better than NPD-A and the affected children usually survive up to adulthood. Type C and D are milder form of the disease and the patients usually survive up to fifth and sixth decades [5].

We are reporting a case of 7 year female who presented with splenohapatomegaly, regression of milestones and seizures. She was diagnosed to be having NP-B on the basis of leukocyte lysosomal enzyme studies. We are reporting this case because NPD though common in Ashkenazi Jews is rare amongst people of south east asia. This case emphasizes the need to keep NPD in differential diagnosis of children presenting with hepatosplenomegaly, mental retardation and regression of milestones.

Case Report
A 7 year old female child, 2\textsuperscript{nd} Birth by order, born of non consanguineous marriage was brought with complaint of abdominal distention since 3 yrs of age. This abdominal distension was gradually increasing in size and was associated with low grade intermittent fever. There was history of 4-5 episodes of generalized tonic clonic convulsions in past 1 year. Milestones were appropriate for age up till 3 years of age. After that the child started lagging behind in development and eventually developed global developmental regression. There was history of repeated falling while walking. On general examination the patient was vitally stable. She was underweight and stunted. There were coarse facial features with swollen lips, mal-aligned teeth. Nystagmus was also present. Higher functions and Cranial nerves were normal. Motor System showed clasp knife Spasticity present in both upper and lower limbs. Deep tendon reflexes were brisk and clonus was present. Cerebellar signs like Intention tremors, past pointing, dysdiadochokinesis was present. On palpation, there was mild hepatomegaly with severe splenomegaly (Figure 1).

Other systemic examination was normal. Investigations showed Complete blood count was done which was suggestive of microcytic hypochromic anemia (Hb=7.4) and thrombocytopenia (platelet count= 90000).Ultrason of the abdomen showed gross splenomegaly (20cm), mildly enlarged liver with normal Portal vein.MRI brain and EEG was
normal. Fundus examination showed disc pallor. Hb electrophoresis was done which was normal. Mild mental retardation was present (IQ-68). Bone marrow biopsy showed hypo-cellular bone marrow with suppressed erythroid series showing micronormoblastic maturation. Liver biopsy showed maintained lobular architecture with normal hepatocytes. Based upon history of regression of milestones, coarse facial features and splenohepatomegaly lysosomal storage disorder was suspected. Lysosomal enzyme study from leukocytes was done the result were as following (Table 1).

**Figure 1**: Coarse facial features, swollen lips misaligned teeth and splenomegaly was evident on examination.

### Table 1: Results of leukocyte lysosomal enzyme studies suggestive of sphingomyelinase deficiency

<table>
<thead>
<tr>
<th>ENZYMES</th>
<th>RESULTS</th>
<th>NORMAL RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphingomyelinase (neimann pick disease a/b)</td>
<td>0.8</td>
<td>1.8 - 8.5 nmol/17hr/mg protein</td>
</tr>
<tr>
<td>B- glucosidase (gaucher disease)</td>
<td>6.3</td>
<td>4.0 - 32.0 nmol/hr/mg protein</td>
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Depending upon the results of lysosomal enzyme study and age of presentation diagnosis of Niemann-Pick disease type B was made. Patient was started on Livipril. She responded well to the treatment and there were no further episode of seizures. Later patient was discharged with an advice for regular follow up. Parents were advised to attend genetic counselling OPD.

**Discussion**

Niemann–Pick disease is a group of inherited, severe metabolic disorders in which there is accumulation of Sphingomyelins in lysosomes. Niemann-pick disease was first described by Albert Niemann in 1914. But it was only in 1927 that Ludwick Pick conclusively showed the tissues affected due to deposition of Sphingomyelins. Hence the name Niemann-Pick Disease. In 1961 Crocker categorized NPD into types A,B,C and D [6]. In 1980, the etiology of type A and type B was found to be different from type C and D. NPD affects all segments of the population with cases reported in North America, South America, Europe, Africa, Asia, and Australia. However, a higher incidence of NPD has been found in certain populations like Ashkenazi Jews, French Canadian population of Nova Scotia, Maghreb region (Tunisia, Morocco, and Algeria) and Spanish-American population of southern New Mexico and Colorado (NPC). The incidence of Niemann-Pick disease among Ashkenazi Jews is estimated to be about 1:40,000. The incidence of both Niemann–Pick disease types A and B in all other populations is estimated to be 1:2,50,000 [7]. It is inherited in autosomal recessive manner. Symptoms vary according to the type of disease, organs involved and also the age of presentation. In perinatal presentation it may present as hydrops fetalis, neonatal cholestatic jaundice, progressive hepatosplenomegaly, and respiratory distress due to pulmonary involvement. In early infantile period (3 months to <2 yrs) and late infantile period (2 to <6 yrs): Isolated splenomegaly and hepatosplenomegaly, Delayed milestone, loss of acquired motor skills, spasticity, intention tremor, and hearing loss. Brain imagery may show leukodystrophy, white matter signal hyperintensity in T2, or brain atrophy which is the characteristic finding. In Infantile and early childhood period it may present as hepatospleno-megaly, ataxia, clumsiness, and frequent falling. In some children it may present as deafness, dysarthria with delayed speech and impaired pronunciation, and dysphagia, focal or generalized...
In severe cases, mental impairment becomes more marked. NPD and NPC-D are usually present in late childhood or early adolescent period. It commonly presents with spino-oculomotor glaucoma, Detection of an isolated NPC-1 gene mutation is the most prominent feature of NPC-1, and NPC-1 should be carefully monitored. The diagnosis is based on clinical examination. Diagnostics is made by biopsy, MRI, and enzyme assays. The mainstay of treatment is a low cholesterol diet and hypolipidemic drugs. The patient is offered genetic counseling.

Miglustat is the only disease-specific oral therapy approved to treat progressive neurological manifestations. Miglustat is a small water-soluble iminosugar molecule which reversibly inhibits glycosphingolipid synthesis. It has beneficial effects on lipid trafficking defects and reduces the synthesis and activity of the GM3 in the brain and delays the progression of neurological symptoms of NPC. In order to effect on the systemic manifestations of NPC, it has no effect on the skin, blood phospholipids, and gangliosides GM1 and GM2 levels. Miglustat is taken three times a day and dosage in patients under 300 mg of patients 12 years and above is 200 mg daily. It is recommended dose of miglustat for the treatment of 12 years and above is 200 mg daily. It is also helpful to take with antiglaucoma medical products such as lopemidol. It is also helpful to take with antiglaucoma medical products such as lopemidol. It is also helpful to take with antiglaucoma medical products such as lopemidol.
Conclusion
Though uncommon in South East Asian countries including India NPD should be kept in differential diagnosis of children presenting with regression of milestone, hepatosplenomegaly, seizures and coarse facial features.

Conflict of interest: None

References