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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 ie 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 splenohepatomegaly, 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.

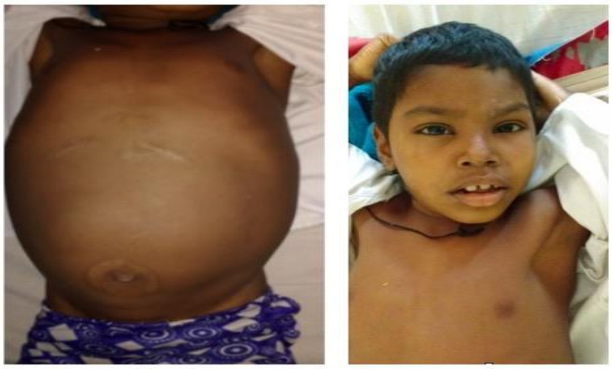
Case Report

A 7 year old female child, 2nd 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).Ultrasound 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 splenohepatomgaly was



evident on examination.

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

ENZYMES	RESULTS	NORMAL RANGE
Sphingomyelinase (neimann pick disease a/b)	0.8	1.8 - 8.5 nmol/17hr/mg protein
B- glucosidase (gaucher disease)	6.3	4.0 - 32.0 nmol/hr/mg protein

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 hepatosplenomegaly, 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

seizures. In severe cases mental impairment becomes more marked. NPD-C and NPD-D usually present in late childhood or in early adolescent period. It commonly presents with organomegaly. Detection of an isolated splenomegaly at this period is an initiatory sign of NPD-C and should be carefully monitored. The most prominent features of NPD-C are the neurological manifestations, characterized by learning disability and school failure with difficulties in writing and impaired attention and behavioral problems. Progressive ataxia in combination with dystonia of the hands and the face, dysarthria, dysphagia, and myoclonus can also be present. Majority of the children may get seizures in some stage of the disease. In adult life it may present with psychiatric manifestations, ataxia, dystonia, dysarthria with variable cognitive dysfunction, psychiatric symptoms and dementia, while epilepsy, vertical gaze and splenomegaly are rare in adult NP-C patients. NPD-D also have similar indolent course [8].

Diagnosis is based on clinical examination, biochemical markers studies and genetic testing. High degree of suspicion should be maintained in patients having progressive hepatosplenomegaly, regression of milestones, ataxia, dysarthria and seizures. Filipin test can be used for the diagnosis of NPD. It is the most sensitive and specific test and should be conducted in specialized expert centers. It is a fibroblast culture of living cells from a skin biopsy. The fibroblasts are cultured in a low density lipid (LDL) enriched medium, fixed and stained with Filipin. Using fluorescence microscopic examination, one can see numerous cholesterol-filled perinuclear vesicles, in about 85% of cases. Enzyme studies of lysozymes in leucocytes show acid sphingomyelinase deficiency associated with NPA and NPB. Genetic testing also helps in detection of mutant gene responsible for NPC and NPD. There is no cure for Niemann Pick Disease, especially type A. In other less severe forms, treatment is mainly supportive.

Miglustat is the only disease-specific oral therapy approved to treat progressive neurological manifestation of NP-C. It is a small water-soluble, iminosugar molecule which reversibly inhibits glycosphingolipid synthesis. It has beneficial effects on lipid trafficking defects and reduces the neurotoxic accumulation of glucosylceramide, lactosylceramide, and gangliosides GM2 and GM3 in the brain and delays the progression of neurological symptoms of NP-C but it has no effect on the systemic manifestations. In order to stabilize or slow neurological progression, miglustat should be started immediately at the earliest sign of neurological manifestation .The recommended dose of miglustat for the treatment of patients 12 years of age and above is 200 mg three times a day and dosing in patients under the age of 12 years should be adjusted based on body surface area. The most common adverse effects associated with miglustat treatment are gastrointestinal with mild to moderate diarrhea, vomiting, flatulence, and weight loss which tends to decrease over time. These can usually be managed with antipropulsive medical products such as loperamide. It is also helpful to take miglustat between meals, have a temporary dose reduction, and be on low lactose, sucrose, and maltose diet. Other reported side effects are tremors and mild reduction in platelet counts without associated bleeding tendency [9].

The other forms of treatment available are bone marrow transplantation or liver transplantation. Although following bone marrow transplantation there is a regression of hepatosplenomegaly and lung infiltration it is not effective in treating neurological symptoms in NPC1 patients. Encouraging results have been reported supporting early hematopoietic stem cell transplantation in NPC2 patients. Hypercholesterolemia seen in patients can be managed with a combination of low cholesterol diet and hypocholesterolemic drugs. The parents of the affected child should be offered genetic counseling [10].

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

1. Sarkar S, Carroll B, Buganim Y, et al. Impaired autophagy in the lipid storage disorder Niemann–Pick type C1 disease. Cell reports. 2013;5(5):1302-1315.
2. Schulze H, Sandhoff K. Lysosomal Lipid Storage Diseases. Cold Spring Harbor Perspectives in Biology. 2011;3(6):a 0048 04.
3. Madra M, Sturley SL. Niemann–Pick type C pathogenesis and treatment: from statins to sugars. Clinical lipidology. 2010;5(3): 387-395.
4. Santos-Lozano A, Villamandos García D, Sanchis-Gomar F, et al. Niemann-Pick disease treatment: a systematic review of clinical trials. Annals of Translational Medicine. 2015;3(22):360.
5. Mengel E, Klünemann H-H, Lourenço CM, et al. Niemann-Pick disease type C symptomatology: an expert-based clinical description. Orphanet Journal of Rare Diseases. 2013;8:166.
6. CROCKER AC, FARBER S Niemann-Pick disease: a review of eighteen patients. Medicine (Baltimore). 1958 Feb; 37(1):1-95.
7. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010 Jun 3;5:16.
8. Runz H, Dolle D, Schlitter AM, Zschocke J. NPC-db, a Niemann-Pick type C disease gene variation database. Hum Mutat. 2008 Mar;29 (3):345-50
9. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. Lancet Neurol. 2007 Sep;6(9):765-72.
10. Brock DJH. Prenatal diagnosis and genetic counselling. Journal of Clinical Pathology Supplement (Royal College of Pathologists). 1974;8:150-155.