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KEY WORDS: Niemann Pick disease type B, hepatosplenomegaly, neuroregression. acid sphingomyelinase (ASM) gene

NIEMANN-PICK DISEASE TYPE B IN A CHILD – A CASE PRESENTATION

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ABSTRACT

Case report -7 year old female child of Indian origin presented with neuroregression since 3 years of age, episodes of generalized seizures, multiple falls with increasing abdominal distention and failure to thrive.
Examination - She had coarse facial features, swollen lips, gaps present between all teeth. She had cognition impairment, truncal ataxia with hepatomegaly and gross splenomegaly. Decreased ocular movements were noted with increased tone in all four limbs, brisk reflexes and extensor plantars. Her cerebellar signs were positive.
Investigations- She had anemia with thrombocytopenia. IQ was suggestive of mild intellectual disability. Abdominal scan showed hepatomegaly with massive splenomegaly. EEG and MRI brain was normal. Sphingomyelinase activity was deficient and Plasma Chitotriosidase was high.
Result- She was diagnosed clinically and enzymatically with Niemann Pick disease type B and was advised to continue with physiotherapy and occupational therapy.
Discussion- Niemann-Pick disease is inherited autosomal recessive metabolic disorder which is a form of lipidosis results from allelic mutations within the acid sphingomyelinase gene. These patients have a deficient activity of acid sphingomyelinase which results in the pathologic accumulation of sphingomyelin and other lipids in the monocyte-macrophage system, the primary site of pathology.
Conclusion-So far there is no specific treatment for this disorder. Prenatal diagnosis is routinely accomplished by sphingomyelinase assay. It is important to raise the awareness of this debilitating condition and the need of a multidisciplinary management of such patients. As there is no recognized effective treatment for this disorder, the possibility for prenatal diagnosis through amniocentesis or chorionic villous sampling especially in familial cases is of great importance.
Further studies in this area can help to lighten the treatment of this condition.

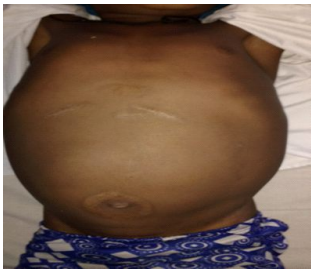
Objective - 7 year old female child of Indian origin presented with neuroregression, multiple falls, generalized tonic clonic seizures, failure to thrive and increasing abdominal distention. Sphingomyelinase activity was deficient and Plasma Chitotriosidase was high. She was diagnosed with Niemann-Pick disease type B disease.

Case report -7year old Female child of Indian origin presented with neuroregression since 3 years of age, 4-5 episodes of generalized seizures prior to admission one year with multiple falls while walking. She also had increasing abdominal distention since 3 yrs of age and increasing in size since then. There was no history of Tuberculosis, contact with tuberculosis, haemetemesis, malena or trauma.

Anthropometry

	Observed	Expected	Z-Score
Weight	15kg	22kg	< -3 SD
Height	118cm	120cm	0 to -3 SD
HC	48cm	52 cm	Less than 2 SD

On examination she had coarse facial features, swollen lips with gaps present between all teeth. She had cognition impairment with truncal ataxia. Decreased ocular movements noted with increased tone in all four limbs with brisk reflexes with extensor plantars. Her cerebellar signs were positive in the form of intention tremor and dysdiadochokinesis. She was found to be ataxic. Her Pain, touch, temperature was normal but vibration sense joint position and two point discrimination could not be assessed. Abdomen was grossly distended. Liver was firm in consistency and was palpable 2 cm below the right costal margin. Spleen was firm and was palpable 20 cm below the left costal margin.



Investigations – Complete blood count revealed Haemoglobin of 7.4 with WBC of 6300 and Platelet count of 90000 suggestive of anemia with thrombocytopenia. Renal and liver profile was normal.

Workup for TB, dengue, malaria and HIV was negative.

USG abdomen was suggestive of massive splenomegaly of 20cm with mildly enlarged liver. Portal vein was normal

Fundus revealed disc pallor. Haemoglobin electrophoresis was negative for sickle cell and thalassemia. IQ was 68 suggestive of mild intellectual disability .EEG and MRI brain was normal.

Bone marrow biopsy showed hypo cellular bone marrow with suppressed erythroid series showing micronormoblastic maturation

Liver biopsy suggested storage disorder.

Lysosomal enzymes Study from Leukocytes-

Enzymes	Result	Normal Range
Glycolipids and lipids		
Sphingomyelinase : nmol/17hr/mg protein (Niemann Pick Disease A & B)	0.8	1.8 - 8.5
b-glucosidase : protein (Gaucher's Disease)	6.3	4.0 - 32.0 nmol/hr/mg

Result- In a view of neuroregression, seizures, failure to thrive, massive hepatosplenomegaly, deficient Sphingomyelinase activity and high Chitotriosidase level she was clinically and enzymatically diagnosed with Niemann-Pick disease type B disease (Storage form)

She was advised to continue with physiotherapy and occupational therapy.

Discussion-
Niemann-Pick disease (NPD) is a rare autosomal recessive lysosomal lipid storage disorder which result from allelic mutations within the acid sphingomyelinase (ASM) gene products which are involved in the metabolism of sphingolipids. Their dysfunction

causes sphingomyelin to accumulate in different organs which leads to progressive multisystemic disorder.

ASM activity is also reduced in isolated leukocytes or cultured cells and two mutations within the ASM gene may be identified. Many ASM mutations have been identified in unrelated type A and B patients. **(1,2)**

These patients have a deficient activity of ASM, a lysosomal enzyme that hydrolyzes sphingomyelin (SPM) to phosphorylcholine and ceramid and results in the pathologic accumulation of SPM and other lipids in the monocyte-macrophage system, the primary site of pathology**(3,4)**

Over the time, this excessive storage of fat can cause permanent cellular and tissue damage, particularly in the brain, peripheral nervous system, liver, spleen, and bone marrow.

Type A and type B NPD are caused by mutations in sphingomyelin phosphodiesterase-1 gene with deficiency of acid sphingomyelinase (ASM).

Type C and type D NPD have normal or reduced sphingomyelinase activity but differ pathogenetically from type A and B.

The various types share common clinical features and the severity of the disease varies depending on the gene mutation, enzyme deficiency and the system involved.

The estimated incidence of type A and B NPD is 1:250000 and of type C is 1:150 000 live births **(5)**.

Type A NPD, with Ashkenazi Jewish predilection, is a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, cherry red maculae, and rapidly progressive neurodegenerative course, presents as psychomotor and neurodevelopmental regression, loss of motor function and intellectual capabilities, spasticity, and rigidity that leads to death by 2 – 4 years of age **(4).**

Except for type B, other types of NPD also have a variable neurodegenerative course. Type B disease is panethnic which is characterized by hepatosplenomegaly, hyperlipidemia, and variable survival to adulthood. Cherry red spot or haloes are rarely seen in the maculae of type B patients**. (6)**

Conclusion – So far, the treatment is supportive as there is no specific treatment for this disorder.

Prenatal diagnosis of NPD type A and B is routinely accomplished by sphingomyelinase assay **(7)**. The only effective method for prevention of disease appears to be the identification of heterozygotic individuals and the prevention of marriage of such individuals with each other.

It is important to raise the awareness of this debilitating condition and the need of a multidisciplinary management of such patients. As there is no recognized effective treatment for this disorder the possibility for prenatal diagnosis through amniocentesis or chorionic villous sampling especially in familial cases is of great importance.

Further studies in this area can help to lighten the treatment of this condition.

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