SHORT COMMUNICATION

Niemann Pick Disease: A Case Report

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Abstract:

Niemann Pick disease is a rare lysosomal storage disease of infancy which occurs due to accumulation of sphingomyelin in various tissues of the body. This leads to characteristic features of failure to thrive, marked organomegaly and neurodegenerative regression. The disease is uncommon in South East Asia and here we present this case as it is rarely found in Bangladesh.

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Introduction:

Niemann Pick disease (NPD) is a fatal autosomal recessive lysosomal disorder of infancy characterized by failure to thrive, hepatosplenomegaly and a rapidly progressive neurodegenerative course.[1] It results from the deficiency of a lysosomal enzyme, acid sphingomyelinase(ASM). The enzymatic defect results in pathologic accumulation of sphingomyelin, a ceramide phospholipid, and other lipids in the monocyte-macrophage system including spleen, liver , lungs, eyes, bone marrow.[2,3] Additional progressive deposition of sphingomyelin in the CNS results in the neurodegenerative course observed in NPD.[1] The diagnosis of NPD is based on hepatosplenomegaly and failure to thrive within the first year of life. A cherry-red spot is present in the macula in ~50% of these infants. The disease is characterized by a rapidly progressive neurodegenerative course, with profound hypotonia and failure to attain milestones. Insufficient ASM activity is the hallmark of types A and B NPD, quantifying this enzyme activity in convenient cells such as circulating leukocytes or cultured skin fibroblasts is the standard confirmatory diagnostic procedure. The characteristic vacuolated 'sea blue cells' in bone marrow is also indicative of NPD but is not diagnostic in the absence of enzymatic and/or genetic confirmation.[4]The incidence of NPD is estimated to be about 1:40,000 among Ashkenazi Jews. The incidence of both NPD types A and B in all other populations is estimated to be 1 per 250000 populations.[5] Prevalence of the disease in Bangladesh is not known.[6] Here we are reporting this case as a rare incidence in Bangladesh.

The Case

A ten month old male child, only issue of nonconsanguineous parents presented with the

Fig.-1: *Coarse facies with thick eyebrows*

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complaints of gradual regression of development from 7 months of age and abdominal distension from 3 months of age. The baby was born by normal vaginal delivery at term at home without any complications. He was exclusively breast fed upto 6 months of age after which complimentary feeding was started. He achieved neck control at 3 month of age and could sit without support from 6 months. He had a good social interaction. Regression of milestone started from 7 months as manifested by loss of neck control and unable to sit even with support. There was also loss of social interaction and swallowing difficulty. He also developed gradual distension of the whole abdomen from 3 months of age. His bowel and bladder habits were normal. On examination, the child had a coarse face and thick eyebrows (Fig-1).He was moderately pale There was no lymphedenopathy. On skin survey there were multiple non blanching hyperpigmented areas of variable sizes present all over the body (Fig-2) but more prominent on the back, gluteal region and limbs. They were bluish black in colour and appeared since birth but gradually increased in numbers with age.His vital parameters were normal. He was moderately stunted and underweight. The patient had gross hypotonia with reduced muscle bulk and power. His reflexes were normal and cranial nerves were intact as per examined. His eye movement was normal.

He had global developmental delay. On abdominal examination, liver was palpable with liver span 8 cm and spleen palpable 6.5 cm from left costal margin along its long axis (Fig-3 There was no ascites. Eye examination revealed cherry red spot at macula (Fig-4). With these clinical findings, we kept two differentials in our mind, Niemann Pick disease type A and Gaucher disease type 2.

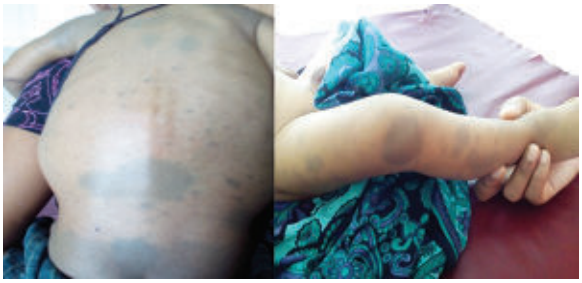

Fig.-2: *Hyperpigmented skin lesions*

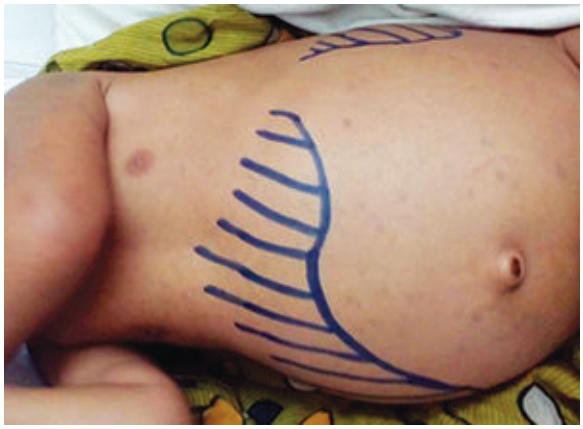

Fig.-3: *Hepatosplenomegaly*

His Haemoglobin level was 6.7 gm/dl with dimorphic picture in peripheral blood film. His LDH level was 1403U/L (Normal: 230-460 U/L). Ultrasonogram of whole abdomen revealed hepatosplenomegaly. Bone marrow examination showed normoblastic hyperactive marrow and 'Sea Blue' histiocyte like cells suggestive of Niemann Pick disease (Fig-5). Lipid profile and thyroid function were normal.

On the basis of clinical manifestations, presence of cherry red spot on both eyes and Niemann-Pick cells in bone marrow our patient was ultimately diagnosed as a case of Niemann Pick disease Type A. The patient was discharged after 2 weeks with genetic counselling and supportive management including blood transfusion, iron, folic acid and multivitamin. Developmental therapy was also started. Enzymatic confirmation could not be done due to unavailability.

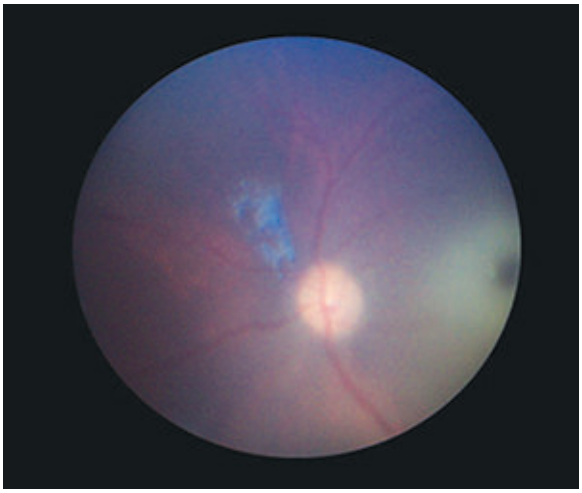

Fig.-4: *Cherry red spot at macula*

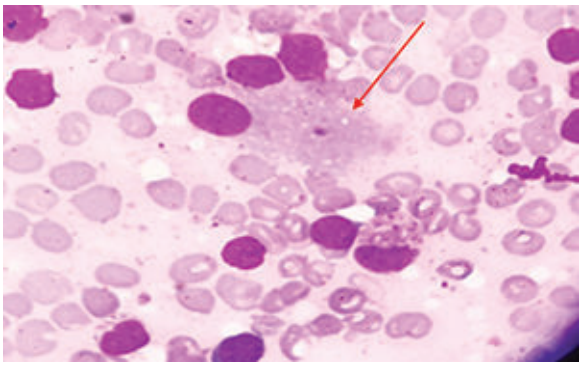

Fig.-5: *Bone marrow- 'Sea Blue' cells*

Discussion:

Our patients's clinical features comprising of gradual neurodevelopmental regression and organomegaly were consistent with both NPD type A and Gaucher disease type 2. Gaucher disease type 2 presents in infancy with neuropathic and visceral involvement. However after doing the bone marrow examination in our patient, the presence of 'Niemann Pick' cells excluded the possibility of Gaucher disease in our patient. Niemann Pick disease has been described as a very rare disease in childhood. [7] There are three types, A, B and C. All form of NPD present with neurological deficit except type B, which is non-neuropathic form. Mutations in types A and B are seen in SMPD1 gene, but in type C disease are seen in NPC1 and NPC2 genes. Types A and B result from the deficient activity of sphingomyelinase and the SMPD1 gene located on bands 11p15.1-p15.4 and are referred to as acid sphingomyelinase deficiency (ASMD).[8] Type C is a neuronopathic form that results from defective cholesterol transport.[1] The most common form of Niemann pick disease is Type A, i.e., Acute neuropathic form which presents in the first months of life with marked hepatosplenomegaly, lymphadenopathy and psychomotor retardation, followed by neurodevelopmental regression. Half of the patients have a cherry red spot in the macula as was also seen in our patient.[7] Cherry red spot develops due to deposition of sphingomyelin in retinal ganglionic cell. In NPD type A death usually occurs by 3 years of age.[9] Type B NPD often presents in mid-childhood. The clinical features are similar to that of type A but less severe with additional short stature and delayed bone age. The survival rate in type B is usually up to late adulthood.[9] NPD type C often presents with prolonged neonatal jaundice and may remain normal for the first 1- 2 year of life ultimately leading to slowly progressive and variable neurodegenerative course. Hepatosplenomegaly is less common and these patients may survive into adulthood.[8] Furthermore, they also may present with ataxia, vertical supranuclear gaze palsy and dystonia.[10]

This case coincides with the type A NPD and the patient ultimately died at 18 months of age. The child had come to us with gradual abdominal distension with gross organomegaly and developmental regression from 7 month of age. Bari I et al eported a similar case of NPD type A where the child presented with developmental regression from 5 month of age and gradual abdominal distension.[6] A case report of NPD type A by Shubhankar M et al stated that their patient had Mongolian spots in different parts of the body which was an isolated finding.[10] Similar Mongolian spots were also found in our patient.

In developed countries, diagnosis of NPD is established by enzyme assay and mutation analysis. In type A and B NPD the enzyme level is markedly decreased whereas in type C the level is normal or slightly decreased. However, in developing countries, these modalities are expensive and usually not available. Common practice in such circumstances is demonstration of NP (Niemann Pick) cells by Bone marrow aspiration.[11] Bone marrow examination in our patient revealed typical 'sea blue' cells which was consistent with the diagnosis. Enzyme assay and mutation analysis could not be done in our patient due to unavailability and the patient passing away within a few months of being diagnosed. Since this was a chronic disease the patient was also anaemic. His LDH level was high as found in all storage diseases.

Currently there is no specific treatment for NPD.[1] Symptomatic treatment is the mainstay to maintain and improve quality of life. Bone marrow transplantation or liver transplantation has also been advised but was of no avail. Transplantation is not effective in treating type A NPD because of the severe neurological symptoms but encouraging results have been reported supporting early hematopoietic stem cell transplantation in NPD type B patients.[12,13] Currently Miglustat (N-butyldeoxynojirimycin) is the only disease-specific oral therapy approved to treat progressive neurological manifestation of NPD type C.[14] Cholesterol lowering agents may partially reduce the cholesterol load in the liver but does not improve the neurological

manifestations.[15]

All forms of Acid sphingomyelinase deficiency (NPD-A, NPD-A/B, and NPD-B) are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SMPD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Once the *SMPD1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible. Biochemical prenatal diagnosis for a pregnancy at 25% risk is also possible by testing of acid sphingomyelinase enzyme activity and/or molecular analyses of cultured amniocytes or chorionic villi.[16,17] The only effective method for prevention of NPD appears to be the identification of heterozygotic individuals and the prevention of marriage of such individuals with each other.[6]

Niemann pick disease is a rare fatal disease of infancy. Till date there is no definitive treatment for the disease. The main diagnostic tool is enzyme assay but this is not available in Bangladesh. Along with clinical findings bone marrow aspiration helps us to establish the diagnosis. Early diagnosis and treatment of complications can improve life expectancy. Although rare in our country when a child presents with organomegaly and neurological regression, the possibility of Niemann Pick disease should be kept as a possible differential diagnosis.

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