| Case Report |

Niemann Pick disease: a rare lysosomal storage disease

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Abstract

Niemann Pick Disease (NPD) is a rare autosomal recessive lysosomal storage disease characterized by lysosomal lipid storage. The disease is caused by deficiency of enzyme, acid sphingomyelinase (ASM) which leads to accumulation of sphingomyelin & other lipids in reticuloendothelial cells of various organs like liver, spleen, bone marrow, lymph node, brain, nerves and kidney. Four types of the disease have been identified i.e. A, B, C and D. We report a case of Niemann Pick Disease type C. The patient was a 2.5 years female child who presented with developmental regression, recurrent seizures, failure to thrive and hepatospleenomegaly. Bone marrow (BM) aspiration was performed which showed hypercelluler marrow with few fat laden macrophage resembling foam cell that are characteristics of this disease.

Introduction:

Dr Noor-A- Sabah Liza: Lysosomal storage diseases describe a heterogeneous group of rare inherited disorders characterized by the accumulation of undigested or partially digested macromolecules, which results in celluller dysfunction and clinical abnormalities. Mutation in the genes for the lysosomal enzymes are responsible for more than 50 different human genetic disorders, which are collectively known as Lysosomal Storage Disease. Niemann pick disease is autosomal recessive rare lysosomal storage disease.[1]

Niemann pick disease (NPD) is of four types - A, B, C and D. NPD type A and B are due to deficient activity of sphingomyelinase, a lysosomal enzyme encoded by the SMPD1 gene located on chromosome bands 11p15.1-p15.4. The incidence of type A & B in general population is estimated to be 1 in 250,000. NPD type A is more common in Ashkenazi Jewish population with estimated incidence of 1 in 40,000 .Both sex are affected equally.[1]

Here, we report the case of a 2.5 years female child who presented with developmental regression, recurrent seizures, failure to thrive and hepato-splenomegaly. Bone marrow (BM) aspiration was performed which showed foam cell that is characteristic of this disease.

However, this case suggests that neuro-degenerative disorders with organomegaly in infancy NPD could be a possible cause.

Presentation of Case

Dr Sk Serjina Anwar: A 2.5 years old girl 2nd issue of his nonconsanguineous parents got admitted with the complaints of developmental regression for 1 year, seizure for two occasions , not growing well for the same duration and respiratory distress for 15 days. She developed fever which was high grade, intermittent in nature and subsided by taking anti pyretics. After that she developed regression of developmental milestone in the form of unable to sit and stand and regression of speech. The mother also noticed swelling of abdomen not associated with pain. There was history of seizure for two occasions 7 days apart which was generalized tonic clonic in nature persisted for 2-3 minutes and after cessation of seizure the child became drowsy. There is also history of cough and respiratory distress for 15 days. There was no history of unconsciousness, vomiting, visual and

hearing abnormality, abnormal body and urine odour. There was family H/O two abortions of the mother and her prior development was age appropriate.

Dr. Meher Nigar Nishi: On examination, the child was ill looking, mildly pale, vitally stable, anthropometrically severely wasted and stunted, weight for age -5SD and height for age -3.15 SD. Ophalmoscopic examination revealed normal findings. On systemic examination, the liver was enlarged about 6 cm, spleen was 4cm enlarged, bilateral crepitation was present in both lung fields, decreased tone in all four limbs, deep tendon reflexes were decreased and planter was bilaterally flexor. Cranial nerves and all modalities of sensory function were intact and cerebellar function was also normal.

Investigations showed normal blood count. Electroencephalogram was normal. Chest X ray revealed reticulogranular mottling in both lung field (Figure-1). Neuroimaging of brain showed generalized cortical atrophy (Figure-2 & 3). Bone marrow examination revealed hyper cellular bone marrow with few fat laden macrophages which was resembling foam cells. (Figure-4)

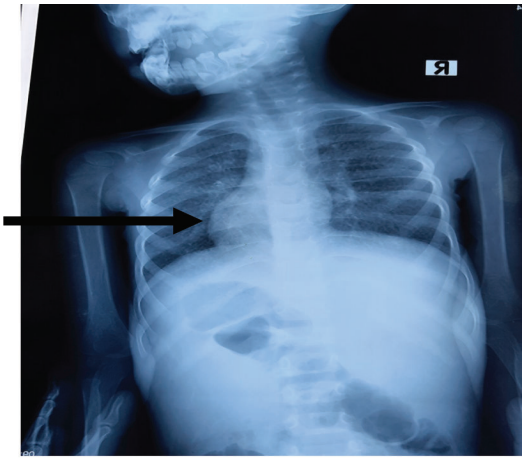

Figure-1: Chest X ray showing reticuiogranular mottling suggestive of interstitial lung disease

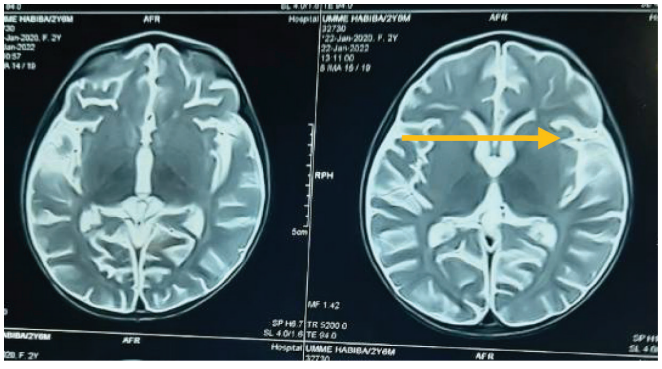

Figure-2 : MRI of Brain T2 image showing generalized cortical atrophy

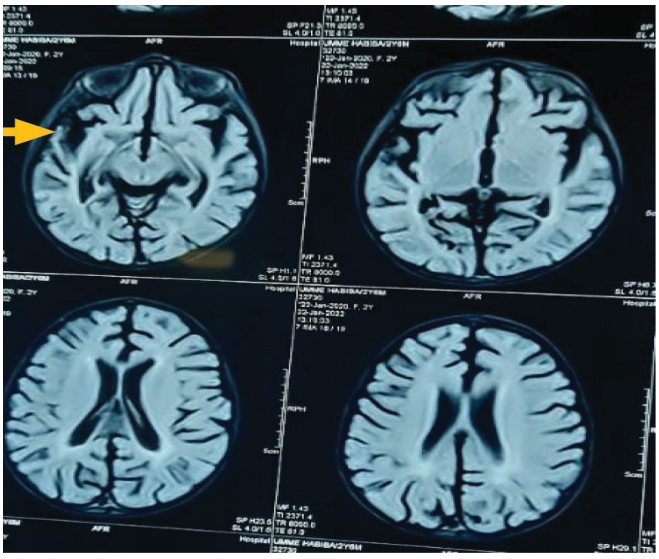

Figure-3 : MRI of Brain flair image showing generalized cortical atrophy

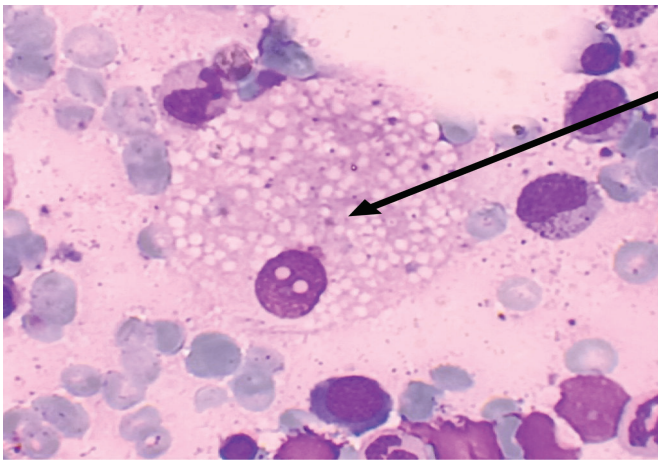

Figure - 4: Bone marrow showing foam cell

Provisional Diagnosis

Niemann Pick Disease

The patient was treated with the protocol of protein energy malnutrition along with multivitamins and multiminerals and other supportive management including developmental therapy.

Differential diagnosis

Gaucher disease

Dr. Mohammad Arbab Sarker: Gaucher's disease is the autosomal recessive variety of lysosomal storage disease in which glucocerebroside accumulates in cells and certain organs. The disorder is characterized by bruising, fatigue, anemia, low blood platelet count, enlargement of the reticuloendothelial system, progressive neurological

deterioration and is caused by a hereditary deficiency of the enzyme glucocerebrosidase.[2-4] When the enzyme is defective, glucocerebroside accumulates, particularly in white blood cells and especially in macrophages (mononuclear leukocytes). Glucocerebroside can collect in the spleen, liver, kidneys, lungs, brain, and bone marrow.[3]

Manifestations may include enlarged spleen and liver, liver malfunction, skeletal disorders or bone lesions that may be painful, severe neurological complications, swelling of lymph nodes and (occasionally) adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelet count, and yellow fatty deposits on the white of the eye (sclera).[4] Initial laboratory testing may include enzyme testing. Less than 15% of mean normal enzymatic activity is considered to be diagnostic. Diagnosis can also be implied by biochemical abnormalities such as high alkaline phosphatase, angiotensin-converting enzyme, and immunoglobulin levels, or by cell analysis showing "crinkled paper" cytoplasm and glycolipid-laden macrophages.[2,3]

Though the clinical findings of our case had some similarities with Gaucher's disease, the presence of radiological findings and lipid laden macrophage exclude Gaucher's disease.

Sandhoff Disease

Dr. Sanjida Ahmed: Sandhoff disease is another lysosomal genetic, lipid storage disorder caused by the inherited deficiency to create functional beta-hexosaminidases A and B. The first signs and symptoms begin before 6 months of age and the parents' notice when the child begins regression of developmental milestone.[5,6] There are several symptoms that begin to appear such as muscle/motor weakness, sharp reaction to loud noises, blindness, deafness, inability to react to stimulants, mental retardation, seizures, respiratory problems and infections, cherry red spots in the retina, enlarged liver and spleen (hepatosplenomegaly).[7]

Diagnosis is based on enzymetic assay for hexosaminidase, lipid laden macrophage in bone marrow and membranous concentric bodies in electron microscope.[5,6]

Our case although bear some similar neurological pictures along with chest and bone marrow findings, but absence of the typical age of onset of Sandhoff disease along with the hyper reactivity to loud noises exclude our differential.

Discussion

Dr. Syeda Tabassum Alam: Niemann Pick Disease is a rare autosomal recessive disease. NPD type A is a rapidly developing metabolic illness.[8]

The name Niemann-Pick is derived from two German pediatricians - Albert Niemann, who first identified the Type A in 1914, and Ludwick Pick, who first identified the Type B in 1927.[9,10]

Classically Niemann Pick Disease is classified into four sub type.[8,9]

1. Niemann Pick Disease type A: classic infantile
2. Niemann Pick Disease type B: visceral
3. Niemann Pick Disease type C: sub acute /juvenile
4. Niemann Pick Disease type D: Nova Scotian

Some intermediate forms are also present.

A review of English medical literature shows that 1,200 cases of NPD type A and NPD type B worldwide have been reported with the majority being Type B or an intermediate form.[11] Our patient is probably the intermediate form.

Type A NPD 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, intellectual impairment, spasticity, rigidity that may lead to death by 2 – 4 years of age.[12] In the classic infantile type-A variant, a missense mutation causes complete deficiency of sphingomyelinase. It is more common in Ashkenazi Jewish population.[13] There is also association of interstitial lung disease in type B and intermediate form on Niemann pick disease. Our patient also had interstitial lung disease but we did not perform HRCT due to financial constraint.

Like other reports, our patient also had failure to thrive, hepatosplenomegaly and neurological manifestation.[8,12] MRI of Brain shows generalized cortical atrophy. Chest radiology revealed evidence of interstitial lung disease. Bone marrow morphology showed foam cells but enzyme activity could not be seen due to lack of facilities.

Dr. Sharmina Afrin Sheemu: Prenatal diagnosis of NPD type A and B is possible by doing sphingomyelinase assay.[14] Prognosis is very bad in type A. About 85% die before 18 months.[15] Newer modalities like bone marrow transplantation, enzyme replacement therapy and gene therapy are likely to be useful for NPD type B.[16]

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. Genetic counseling and genetic testing is recommended for families who may be carriers of Niemann –Pick disease. No specific treatment is known for type A, but symptoms are treated. Early diagnosis and management of complication will help to increase the life span of the child.

Follow up

Dr. Mohammad Abdul Quddus: Although definitive follow up schedule has not yet been published, we made a follow up plan monthly for 6 months, then 3 monthly for 2 years, then

yearly. In 2 subsequent follow up our patient improved clinically in terms of nutritional status and there was no further deterioration of neurological symptoms and signs.

Final Diagnosis

Niemann Pick Disease

Conclusion

Though uncommon in South East Asian countries including Bangladesh, NPD should be kept in differential diagnosis of children presenting with failure to thrive, hepatosplenomegaly and neuroregression. Acid sphingomyelinase activity was not performed for this case report due to lack of facilities.

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