

## CASE REPORT

### NIEMANN PICK DISEASE DIAGNOSED ON BONE MARROW ASPIRATION

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**ABSTRACT:** Niemann-pick disease is a rare lysosomal storage disorder affecting 1 in 2,50,000 children. We are describing here, a case of Niemann-pick disease in a 19 months old female baby, who presented with distension of abdomen for 9 months and she was not able to sit or stand until this age. On examination of abdomen there was hepatosplenomegaly. Ultrasound abdomen also revealed hepatosplenomegaly along with multiple mesenteric and periportal lymph nodes. Bone marrow aspiration was done which revealed the presence of numerous large foamy histiocytes.

**KEYWORDS:** Niemann-pick disease, Bone marrow aspiration, histiocytes.

**INTRODUCTION:** Niemann-pick disease is an autosomal recessive disorder affecting 1 in 2,50,000 children<sup>[1]</sup> and is characterised by lysosomal accumulation of sphingomyelin resulting from an inherited deficiency of sphingomyelinase. It is of four common types- Type A, B, C and D. Type A and B disease is common in Ashkenazi Jews. Type A is the severe infantile form due to the missense mutation leading to complete deficiency of sphingomyelinase, causing early death within first three years of life. Type B patients usually survive into adulthood. Type C Niemann-pick disease is a distinct entity from Type A and B which is characterised by accumulation of unesterified cholesterol in the affected cells. Type D is a variant of Type C NPd.

**CASE REPORT:** A 19 months old female baby presented with generalised distension of abdomen for 9 months. Her milestones were delayed, she was not able to sit or stand until this age. She hadn't started complementary feeding till this age. On general examination, her weight was 6 kgs, length 69 cms, upper segment: lower segment ratio was 41: 28, abdominal circumference was 42.5 cms, chest circumference 41 cms, mid arm circumference 10.5 cms. She belonged to Protein energy malnutrition (PEM) grade 3. On ophthalmologic examination, no cherry red spot was seen. Per abdomen examination revealed hepatomegaly about 8 fingers below the costal margin, splenomegaly too about 8 fingers below the costal margin (Figure 1). Central nervous system examination, respiratory system examination and cardiovascular system examination was within normal limits.

Investigations revealed Hemoglobin of 8.3gm%, TLC of 14,000cells/mm,<sup>3</sup> platelet count of 2.50lacs/mm.<sup>3</sup> General blood picture showed normocytic normochromic RBC's.

X-ray (Figure 2) and Ultrasound abdomen revealed moderate hepatomegaly with liver size about 11 cms along with multiple periportal lymph nodes of average size 10x8 mm. There was gross splenomegaly, size about 11.48 cms and multiple mesenteric nodes of average size 14x7.5mm.

Bone marrow aspiration was done which was hyper cellular for age and revealed hyperplastic erythroid series with relative suppression of myeloid series. Along with this there were fair number of large histiocytic cells having central nucleus and vacuolated cytoplasm (Figure 3 & 4). On May grunwald geimsa (MGG) staining, these histiocytes had sea-blue granules and they were negative on PAS staining.

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Thus, keeping in view the clinical history, peripheral blood and bone marrow findings, results of special stains, the diagnosis of Niemann-pick disease type B was suspected. Then acid sphingomyelinase levels were done which were severely decreased and hence confirmed it as a case of Niemann-pick disease type B.

**DISCUSSION:** Albert Niemann published the first description of what is now known as Niemann–Pick disease, type A, in 1914. Ludwig Pick described the pathology of the disease in a series of papers in the 1930s. Acid sphingomyelinase (ASM) deficiency has been categorized in the past as either neuronopathic (Niemann-Pick disease type A [NPD-A]) that results in death by 3 years of age, or non-neuronopathic (Niemann-Pick disease type B [NPD-B]) that is compatible with survival into adulthood.<sup>[2]</sup> There are four most commonly recognized forms of the disease: Types A, B, C, and D. Types A and B are also called Type I. Types C and D are also known as Type II. Type A disease, which has an Ashkenazi Jewish predilection, is a severe neurodegenerative disease of infancy characterized by progressive psychomotor retardation, failure to thrive, hepatosplenomegaly, macular halo or cherry-red macula, and succumbs to death by 3 years of age.<sup>[3]</sup> In contrast, type B symptoms are usually milder, occur in late childhood or adolescence. It is characterized by hepatosplenomegaly, thrombocytopenia, interstitial lung disease and dyslipidemia with most patients having little or no neurologic involvement.<sup>[4]</sup> Liver dysfunction, retinal stigmata, and growth retardation also may be present but are more variable features.

These manifestations occur due to the deficiency of sphingomyelinase which blocks the degradation of lipid resulting in its progressive accumulation within lysosomes, particularly within cells of mononuclear phagocyte system. These lipid laden foam cells are widely distributed in the spleen, liver, lymph nodes, bone marrow, tonsils, gastrointestinal tract, and lungs. Acid sphingomyelinase activity is measured in peripheral blood leucocytes or cultured skin fibroblasts. Affected individuals typically have less than 10% of residual enzyme activity.<sup>[5]</sup> SMPD1 is the only gene known to be associated with acid sphingomyelinase (ASM) deficiency.<sup>[6]</sup> Sequence analysis of SMPD1 detects mutations in more than 95% of individuals with enzymatically confirmed acid sphingomyelinase (ASM) deficiency.

### **Various tests that can be done to confirm the diagnosis Include:**

- Bone marrow aspiration.
- Liver biopsy (usually not necessary).
- Slit-lamp eye examination.
- Sphingomyelinase assays.

Type C usually affects school-aged children, but the disease may occur any time between early infancy to adulthood. It is characterized clinically by a variety of progressive, disabling neurological symptoms including clumsiness, limb and gait ataxia, dysarthria, dysphagia and cognitive deterioration (Dementia).<sup>[7]</sup>

Symptoms of Type D are similar to Type C.<sup>[7]</sup>

Rarely Type E can be seen which occurs in adults. Symptoms include swelling of the spleen and brain and nervous system (neurological) problems. Little is known about this rare type of Niemann-Pick disease.

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### Differential diagnosis Includes:

1. Other Lysosomal storage diseases (LSD) such as Gaucher's disease, confirmed with biochemical testing.
2. Conditions associated with hepatosplenomegaly like Gaucher disease, hexosaminidase A deficiency, Sandhoff disease, Niemann-Pick disease type C, Wolman disease, the mucopolysaccharidoses. These are distinguished on the basis of presence of coarse facial features and dysostosis multiplex in the mucopolysaccharidosis, specific neurologic findings in NPD type C, and enzymatic studies in Gaucher disease and Sandhoff disease.
3. Hepatosplenomegaly can also accompany some infectious diseases and other genetic disorders, including familial hemophagocytic lymphohistiocytosis.
4. Various causes of interstitial lung disease including environmental exposures, connective tissue diseases, and infections come under the differential diagnosis. However, the presence of hepatosplenomegaly in acid sphingomyelinase deficiency helps distinguish it from these other causes of interstitial lung disease.

**Treatment- NPD-A:** At this time, there is no effective treatment for Type A, only supportive treatment can be given which includes physical and occupational therapy; feeding tube for nutrition and sedatives for irritability and sleep disturbance as indicated.

**NPD-B:** Transfusion of blood products for life-threatening bleeding; supplemental oxygen for symptomatic pulmonary disease; treatment of hyperlipidemia in adults; adequate calorie intake. For type B, bone marrow transplantation or stem cell therapy is being studied as a possible treatment,<sup>[8]</sup> along with enzyme replacement therapy and gene therapy.

Carrier testing for at-risk relatives is possible if both disease-causing alleles in the family are known. Prenatal diagnosis for pregnancies at 25% risk is possible by biochemical testing of acid sphingomyelinase (ASM) enzyme activity and/or by molecular genetic testing if both disease-causing alleles in the family are known.

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**FIGURE 1:** A 19 months baby having abdominal distension and hepatosplenomegaly.



**Fig. 1**

**FIGURE 2:** X-ray abdomen showing distension and gas filled bowel loops.

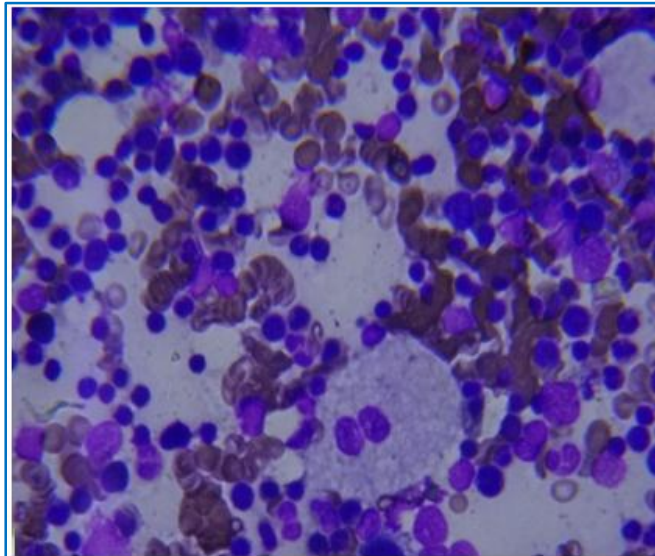


**Fig. 2**

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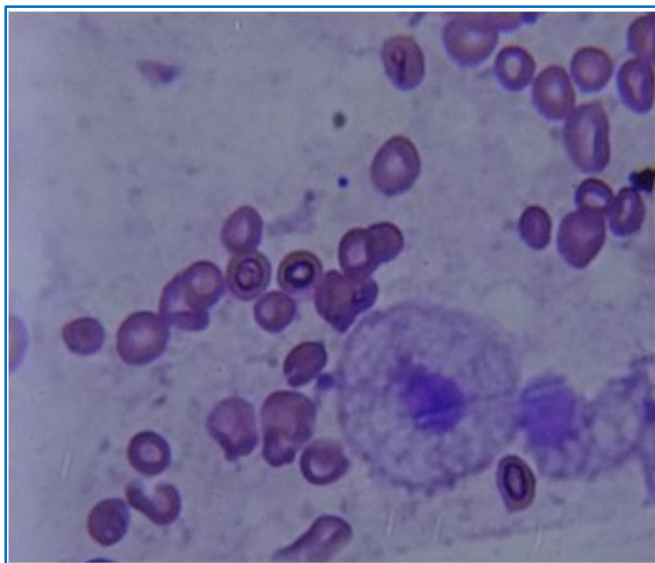
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**FIGURE 3:** High power view of Bone marrow aspirate smear showing large foamy histiocyte (Leishman stain, X400).



**Fig. 3**

**FIGURE 4:** Oil immersion view of Bone marrow aspirate smear showing large histiocyte with central nucleus and foamy cytoplasm (Leishman stain, X1000).



**Fig. 4**

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