Case Report

Atypical presentation of Niemann-Pick disease

Mysore Lakshmikantha Keshavamurthy, G V Basavaraja, G R Rajeshekarmurthy, K S Sanjay, R Premalatha
From Department of Pediatric Intensive Care, Indira Gandhi Institute of Child Health, Bangalore, Karnataka, India
Correspondence to: Dr. M L Keshavamurthy, No.F-6, Srivari Asharya Apts, 1st Main, 2nd Block, Devarachikkannahalli Main Road, BTM Layout 4th Stage, Bangalore - 560 076, Karnataka, India. Phone: +91-9845701759, E-mail: keshml@yahoo.co.in
Received – 24 December 2014 Initial Review – 15 January 2015 Published Online – 27 February 2015

Abstract

Niemann-Pick (NP) disease is a distinct disorder with specific clinical and morphological manifestations. We report a 2-year-old girl who presented with normal development, acute onset of pallor, lethargy, and massive splenomegaly, which made us to think of hemolytic anemia as the initial diagnosis. Her bone marrow done, after initial hematological work up being normal, showed NP cells. As the child did not have any neurological abnormality, she was diagnosed as NP Type B (NPD-B) storage disease. We report it as a typical presentation of NPD-B.

Key words: *Child, Hemolytic anemia, Niemann-Pick, Storage disorder*

Niemann-Pick disease (NPD) comprises a clinically heterogeneous group of disorders involving lysosomal accumulation of sphingomyelin and cholesterol [1]. Clinically, there are three variants classified as Type A (classical infantile neuronopathic form), Type B (non-neuronopathic visceral form) and Type C (juvenile form). The Types A and B are inherited as autosomal recessive disorders and are the result of allelic mutation in the acid spingomylinase (ASM) gene, which leads to deficiency of the ASM enzyme and the resultant accumulation of sphingomyelin in the reticulo-endothelial system.

In NP Type A (NPD-A), characterized by a severe deficiency of ASM, the breakdown of sphingomyelin into ceramide and phosphorylcholine is impaired, resulting in excessive accumulation of sphingomyelin in all the phagocytic cells and neurons. Spleen, liver, bone marrow, lymph nodes and lungs are the organs most affected, because of their high content of phagocytic cells. The central nervous system, including the spinal cord and ganglia, is also affected. Death usually occurs within the first 3 years of life [2].

NPD-B, which is panethnic, is a non-neuronopathic disease characterized by hepatosplenomegaly, hyperlipidemia, and pulmonary involvement, with most patients living into adulthood. Other, more variable features of NPD-B may include liver dysfunction, cardiac disease, retinal stigmata, and growth retardation [3].

NPD-C is an autosomal recessive genetically distinct disorder resulting in defective cholesterol transport, the pathogenesis of NPD-C is unclear, usually characterized by hepatosplenomegaly and severe progressive neurological dysfunction. We report a 2-year-old girl presenting with acute onset of pallor, with no other significant history, who was diagnosed later as NPD-B.

CASE REPORT

A 2-year-old girl was brought to our department with acute onset pallor, lethargy and irritability. Her parents were consanguineously married, and she was their first child. She had one healthy sibling. Her birth history was uneventful. She was developmentally normal and was apparently healthy till now.

On initial examination, her weight and height corresponded to 10th centile of WHO growth reference curves. She was pale and anxious. She had tachycardia (heart rate-180 beats/min), and tachypnea (respiratory rate-52/min), with Spo2 of 88% in room air and normal capillary refill time. Systemic examination revealed splenomegaly (11 cm below left subcostal margin); however, liver was not enlarged. Central nervous system examination and developmental assessment were unremarkable with normal cardiovascular and respiratory system examination. Her ophthalmologic examination was normal (no cherry red spots).

Initial investigation showed hemoglobin of 3.1 g/dl, normal total and differential counts, erythrocyte sedimentation rate-45 mm at 1st h, and C-reactive protein<6 mg/dl. Her random blood sugar was 84 mg/dl and serum ferritin was 561.6 µg/l. Serum calcium was 8.2 mg/dl, ionized calcium was 4.6 mg/dl and phosphorus was 5.1 mg/dl. Serum electrolytes, renal function tests and lipid profile were within normal limits. Biochemical investigations showed mild elevation of alanine

transaminase (137 IU/ml) and AST (105 IU/ml), with the rest of the liver functions being within normal limits. Her coagulation profile was also normal.

Peripheral smear showed microcytic hypochromic anemia, moderate anisopoikoilcytosis with few nucleated and fragmented red blood cells and thrombocytopenia. Investigations were planned to establish the underlying cause of hemolytic anemia showed corrected reticulocyte count of 2.5% and normal hemoglobin electrophoresis. Bone marrow examination revealed normocellular marrow with maintained erythroid to myeloid ratio (3:1), and adequate megakaryocytes with normal morphology. There were good numbers of histocytes, which were large in size having central/peripheral nucleus and abundant vacuolated cytoplasm. This was suggestive of NP storage cells (Figs. 1 and 2). Her chest X-ray showed pulmonary infiltrates.

During the course in our hospital, she had a fever for 5 days. She was started on the first line anti-biotics and received blood transfusion along with supportive care. On day 5, she was afebrile, and her septic screening including blood and urine cultures were negative, so anti-biotics were stopped. Her repeat hemoglobin showed improvement, she was discharged with advice to follow up on an outpatient basis. After 3 months of follow-up, she was asymptomatic.

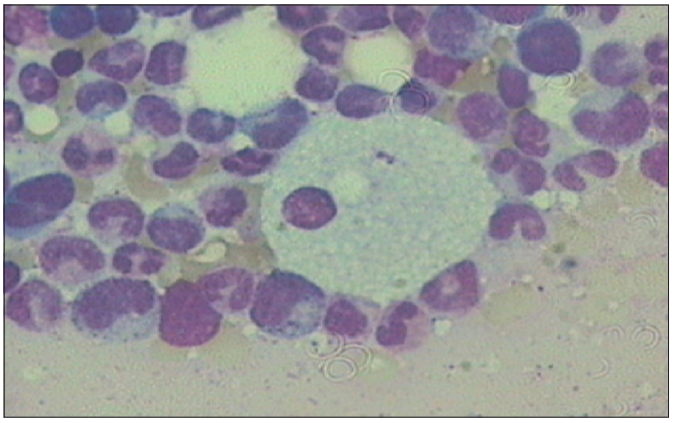

Figure 1: Histo-pathological examination showing bone marrow storage cells

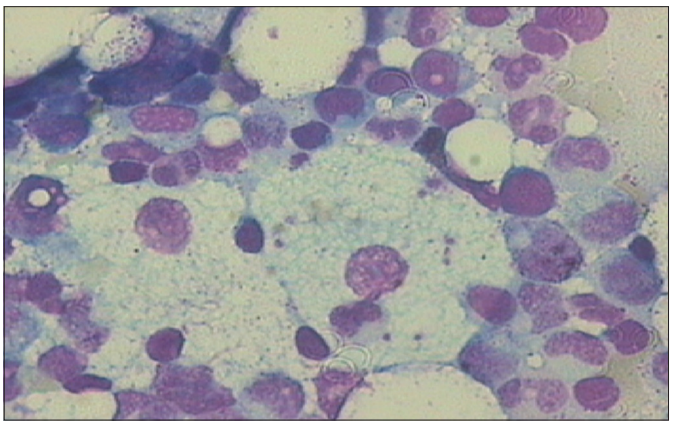

Figure 2: Histo-pathological examination showing storage cell myelopoiesis

DISCUSSION

In Types A and B NPD, the affected enzyme is encoded by the sphingomyelin phosphodiesterase 1 gene located on chromosome bands 11 p15.1-p15.4, resulting in primary ASM deficiency with 1-10% of normal enzyme activity. Pathological sphingomyelin deposition results in infiltration of bone marrow, spleen, liver and lymph nodes with NP cells. NPD-A is invariable evident by 6 months of age in contrast to NPD–B, which has a variable presentation and course. Most patients of NPD-B are diagnosed in infancy or childhood due to detection of liver or spleen enlargement in a routine examination [4].

The natural history of NPD-B is characterized by hepatosplenomegaly with progressive hypersplenism, worsening atherogenic lipid profile, gradual deterioration in pulmonary functions, and stable liver dysfunction [3]. The hematologic complications include decreasing leukocyte and platelet counts with age, whereas the hemoglobin concentration remains stable [3]. Most of the patients present with following symptoms and/or signs: Splenomegaly (78%) or hepatomegaly (73%), bleeding (49%), shortness of breath (42%), pulmonary infections (42%), and joint and/or limb pain (39%) [5].

Our patient presented with acute onset of severe pallor with no other bleeding manifestation or systemic illness. She was fairly healthy till date with unremarkable systemic examination except for splenomegaly and severe pallor. Initially, hemolytic anemia was thought of and was supported by the peripheral smear; however, hemoglobin electrophoresis was within normal limits. Second possibility was hypersplenism in view of thrombocytopenia, but it could not explain low hemoglobin levels. Therefore, possibility of storage disorders with infiltration of bone marrow was suspected and bone marrow examination was done to rule out any storage disorder, which showed NP cells.

As she had splenomegaly with no neurological manifestation, chest X-ray showing pulmonary infiltrates, with hemolytic work-up being normal and bone marrow showing NP cells, child was diagnosed as NPD-B. However, we could not confirm our diagnosis by genetic work-up due to financial constraints and non-availability of the facility in our setup. Hemoglobin electrophoresis should essentially be done in these patients to rule out other hemoglobinopathies, as case reports are available in literature on coexistent beta - thalassemia and NPD-B in the same patient [6].

CONCLUSION

We report this case as an unusual presentation of NP Type B presenting as hemolytic anemia. Therefore in a case of hemolytic

anemia, bone marrow examination should be performed to rule out storage disorders.

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Funding: None; Conflict of Interest: None Stated

How to cite this article: Keshavamurthy ML, Basavaraja GV, Rejeshekarmurthy GR, Sanjay KS, Premalatha R. Atypical presentation of Niemann-Pick disease. Indian J Child Health. 2015;2(1):40-2.