Coincidence of Niemann-Pick Disease and beta-Thalassemia; a Case Report

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Abstract

Background: Niemann-Pick disease and β-thalassemia are distinct conditions with specific clinical and morphological manifestations. β-thalassemia is the most common inherited blood disorder in Iran whereas Niemann-Pick disease, a lysosomal storage disorder, is rarely found in this country.

Case Presentation: This 5-month old girl, a known case of β-thalassemia major was hospitalized for failure to thrive and hepatosplenomegaly. Because of unusual splenomegaly and liver enzymes disturbance that was not compatible with the first diagnosis, further evaluation revealed cherry red spot and high lipid profile suggestive of lysosomal storage disease. Foamy cells in the bone marrow and low activity of the specific enzyme led to the diagnosis of Niemann-Pick disease.

Conclusion: This unique case illustrates the importance of looking for a second pathological condition in a patient whose clinical profile does not support the first diagnosis in its entirety.

Key Words: Niemann-Pick disease; Beta-Thalassemia; Liver enzyme; Lipidosis; Hemolytic anemia

Introduction

Niemann-Pick disease¹ and β-thalassemia² are distinct conditions with specific clinical and morphological manifestations.

Beta-thalassemia major (BTM) is the term applied to patients who have either no effective production (as in homozygous β/0 thalassemia) or severely limited production of beta globin. These hemoglobinopathies are relatively common in Iran, since Iran is located on the "thalassemia belt", with estimated three million carriers in population³⁴. For this reason all patients could be recognized early in life and usually receive appropriate supportive
management. However, Niemann-Pick disease (NPD) as a subgroup of lysosomal storage diseases is one of the inherited autosomal recessive metabolic disorders characterized by intracellular accumulation of sphingomyelin, with prevalence rate of 1/248000[1].

Here we report an infant girl with a diagnosis of β-thalassemia major who coincidentally received a diagnosis of Niemann-Pick disease after clinical suspicion of a second pathological condition due to partly unusually abnormal liver tests which was otherwise consistent with β-thalassemia.

To our knowledge, there are no previous reports of these two conditions diagnosed in the same individual.

**Case Presentation**

At 7.5 months of age the girl was brought to our attention with poor weight gain. The patient was 5th born child of seemingly healthy related parents with family history of sibling death at 9 months with similar features.

A concern of possible β-thalassemia arising from hemoglobin decrement started from 5th month leading to seek medical attention. Investigation including hemoglobin electrophoresis came to diagnosis of β-thalassemia whereupon she regularly received transfusions. Hemoglobin electrophoresis of the patient and her parents is shown in Table 1.

Physical examination revealed all her growth indexes being under normal range for age. A firm 4-cm liver edge in the midclavicular line with estimated span of 10 cm and a 4cm splenic tip under the left costal margin was detected in abdominal examination. Mild palmar erythema was present without digital clubbing. General muscle tone and the result of developmental assessment including head lag was not appropriate for the age. Cherry red maculae were reported in ophthalmic evaluation as an unexpected finding.

Laboratory tests are shown in Table 2. These were abnormal for hemoglobin, pliatet, alanin aminotransferase (ALT), Aspartate aminotransferase (AST), cholesterol and triglycerides. Alkaline phosphates, renal function, blood glucose, serum bilirubin, albumin and total protein as well as coagulation tests were normal. Abdominal sonography demonstrated increased volume of liver with homogenous parenchyma, normal biliary structure and normal vasculature. Spleen was larger than normal. Other visceral organs were normal. Reticular pattern of both lungs in chest X-ray was reported. Bone marrow aspiration was performed and foamy cells were detected suggesting lysosomal storage disease.

In the analysis of lysosomal enzymes from dried blood enzymatic acid sphingomyelinase activity was below the normal range, which was indicative of NPD A or B. Molecular genetic testing was not available.

The infant received monthly blood transfusions and waited to receive bone marrow transplantation, which is chosen option for the disease. She was brought to our outpatient clinic regularly and received supportive nutritional treatment. At 12 months of age she was admitted to a local hospital for severe pneumonia and thrombocytopenia, where she expired after a few days.

**Discussion**

Starting during the first year of life, BTM patients have profound and life-long transfusion-
Table 2: Hematologic indices of the patient*

| Parameter         | patient     | Normal range for age |
|-------------------|-------------|----------------------|
| WBC               | 6.26×10³/µL | 4.1-10.9×10³/µL      |
| Polymorphonuclear cells | 36%,        | 35-80%               |
| Lymphocytes       | 56%         | 20-50%               |
| Hb                | 9.5 gr/dl   | 10.5-14 gm/dl        |
| MCV               | 71.8 fl     | 76-80 fl             |
| Platelet          | 120×10³/µL  | 140-450×10³/µL       |
| AST               | 183 IU/L    | 5-40 IU/L            |
| ALT               | 202 IU/L    | 10-50 IU/L           |
| ALK               | 589 IU/L    | 180-1200 IU/L        |
| Bilirubin, total  | 1.1 mg/dl   | 0.2-1.3 mg/dL        |
| Bilirubin, direct | 0.3 mg/dl   | <0.3 mg/dL           |
| TG                | 206         | 40-140               |
| Cholesterol       | 233         | 120-220              |
| INR               | 1.1         |                      |

* She had received packed bed blood cells recently;

ALK: Alkaline Phosphatase; ALT: Alanin aminotransferase; AST: Aspartate aminotransferase

dependent anemia, hepatosplenomegaly, and skeletal deformities due to bone marrow expansion; they are prone to infection and skeletal fractures and unless appropriately treated, die during adolescence of iron overload syndromes.

Due to increased red cell destruction as well as extramedullary erythropoiesis, liver enlargement tends to be somewhat more prominent in children with BTM than in other causes of congenital hemolytic anemia. Later in the first decade of life, hepatomegaly becomes fixed and not reducible by blood transfusion, because of development of cirrhosis secondary to increased iron deposition. The platelet count is usually normal. However, hypersplenism can lower both white blood cell and platelet counts[4]. Thalassemia can be cured by bone marrow transplantation.

Nonetheless, NPD: also called sphingomyelin-cholesterol lipidosis) belongs to a group of autosomal recessive lysosomal storage disorders which present within the first 6 months of life with enlarged liver and spleen and failure to thrive. In type A, history of pulmonary infections and abnormal neurological examinations may also be noted and often leads to death within 3 years. In contrast to type A, type B patients have little or no neurodegeneration, and frequently survive into adulthood[5].

Recently, patients with phenotypes intermediate between types A and B NPD have also been described[7,8].

Most affected patients have thrombocytopenia secondary to hypersplenism. Liver involvement can be severe, with infiltration of foamy histiocytes, ballooning of hepatocytes, and fibrosis[6]. Other systemic manifestations include short stature with delayed skeletal maturation, interstitial lung disease, and ocular abnormalities (macular halos and cherry red maculae)[9]. Other laboratory abnormalities may include liver dysfunction, decreased high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia and increased low-density lipoprotein cholesterol (LDL-C)[10]. The diagnosis of NPD first depends on an appreciation of the variable phenotypic manifestations followed by demonstration of acid sphingomyelinase deficiency, with residual acid sphingomyelinase activity <10 percent of controls. The definitive diagnosis of NPD-A and NPD-B requires genetic study[11].

The current treatment of NPD is purely symptomatic awaiting the use of enzymatic replacement therapy which has been successfully experimented in animal models[12]. Bone marrow transplantation has been undertaken in several NPD patients with variable results[6].
Considering this case, liver involvement and developmental delay are not common signs in β-thalassemia major, in addition, neither cherry red spot nor interstitial infiltration in lungs are seen in β-thalassemia. These findings prompted us to continue investigation including lysosomal enzyme assay of dried blood spot. It was also strengthening the suspicion that bone marrow aspiration showed foamy cells.

Low level of acid sphingomylinase led to diagnosis of NPD. This disease could have caused the condition that was not explainable by first diagnosis.

This is the only patient, as far as we are aware, in whom coincidence of β-thalassemia major and NPD has been diagnosed. It is of interest to recall that the genes responsible for the two disorders are on different chromosomes.

**Conclusion**

This unique case illustrates the importance of looking for a second pathological condition in a patient whose bone marrow aspiration and clinical profile do not support the first diagnosis in its entirety.

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