TYPE B NIEMANN-PICK DISEASE: REPORT OF A CASE WITH MILIARY PATTERN ON CHEST X-RAY

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A 10-year-old girl was admitted to the hospital because of gross hematuria and abdominal pain. She had hepatosplenomegaly and a miliary pattern on chest X-ray and CT-scan. Histopathologic studies of bone marrow and liver revealed findings in favor of type B Niemann-Pick disease (NPD). This is a fatal and nonneuropathic form of NPD that is usually detected as an incidental finding during routine physical examination.

Keywords: Lung • Niemann-Pick disease

Introduction

Niemann-Pick disease is a form of lipidosis and consists of six subtypes (A to F), that are inherited as autosomal recessive traits and result from allelic mutations within the acid sphingomyelinase (ASM) gene. These patients have a deficient activity of ASM, a lysosomal enzyme that hydrolyzes sphingomyelin (SPM) to phosphorylcholine and ceramid and results in the pathologic accumulation of SPM and other lipids in the monocyte-macrophage system, the primary site of pathology.1, 2

Case Report

A 10-year-old girl was admitted to the hospital because of abdominal pain and gross hematuria for 3 days. She was well until one week prior to admission, when she experienced otitis media and was placed on antibiotics. The parents are first cousins. She has two healthy sisters—3 and 5 years old—and her grandfather has a history of renal stones. On physical examination, vital signs were within normal limits. She was not ill or toxic and had no distress. Severe tenderness on both flanks, suprapubic region, and right upper quadrant of the abdomen were detected on palpation and percussion. Liver was palpable 4 cm below costal margin with a span of 12.5 cm. Spleen was also palpable 5 cm below costal margin.

Lymphadenopathy was not present. Examination of both eyes, including retinoscopy by ophthalmologist, did not show any abnormality. Laboratory findings and imaging studies suggested hemorrhagic cystitis and bilateral pyelonephritis, which were treated with antibiotics. Liver function tests were normal. A diffuse miliary pattern was detected on chest X-ray (Figure 1). The patient had BCG scar and the Mantoux test was negative after 72 and 96 hours. Ultrasonography of the abdomen and pelvis was normal except for hepatosplenomegaly (liver span 12.9 cm, spleen 13 cm).

Chest CT scan with double contrast showed a diffuse miliary pattern in both lungs. Abdominal CT was unremarkable. Bone survey showed hypodensity of bones and delayed bone age, 2.5 years on average. Whole body bone scan was normal.

Bone marrow aspiration and bone marrow and liver biopsies showed characteristic NPD foam cells (Figures 2 and 3) and revealed no findings in favor of metastatic lesions or granulomatous reaction. Polymerase chain reaction (PCR) performed on bone marrow and liver specimens were negative for tuberculosis.
Discussion

Type A NPD, with Ashkenazi Jewish predilection, 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 and intellectual capabilities, spasticity, and rigidity that leads to death by 2 – 4 years of age. Except for type B, other types of NPD also have a variable neurodegenerative course. Type B disease is panethnic and is characterized by hepatosplenomegaly, hyperlipidemia, and variable survival to adulthood. Cherry red spot or haloes are rarely seen in the maculae of type B patients. They do not have neurodegeneration and have normal IQ and intellectual capabilities. Most cases have decreased pulmonary diffusion due to infiltration of both alveoli and interstitium. Sea blue histiocytes become evident in late childhood. Progression happens by 15 – 20 years of age and may cause life-threatening bronchopneumonia and corpulmonale. In severe forms, liver involvement leads to life-threatening cirrhosis, portal hypertension, ascites, and pancytopenia due to hypersplenism that may require splenectomy. However, this should be avoided as splenectomy leads to the progression of pulmonary involvement.

Liver dysfunction, pulmonary disease, retinal stigmata, and growth restriction may also be present, but are features that are more variable. Although the clinical manifestations in type A patients are uniform, there is marked variability in the phenotype among type B patients, ranging from severe disease in childhood to patients with milder course. Duchateau et al reported an asymptomatic 22-year-old man with NPD type B diagnosed by bone marrow biopsy and ASM assessment. Pulmonary involvement was discovered inciden-
tally during the evaluation of a dry cough. Chest X-ray and CT scan showed smooth interlobular septa thickening and a subtle ground glass pattern. Gonzalez-Reimers et al also reported another asymptomatic 39-year-old male patient in whom pulmonary involvement became evident as the initial diagnosis. Abnormal linear growth and delayed skeletal maturation are common in children and adolescents with type B disease; short stature and low weight are significantly correlated with large organ volumes, delayed bone age, and low insulin-like growth factor-1 (IGF-1) levels.

NPD is diagnosed by demonstrating foam cells in bone marrow and liver biopsies, which are characteristic NPD cells and are seen in all types. Type B is the only type with pulmonary involvement characterized by a micronodular or miliary pattern on chest X-ray and CT scan. ASM activity is also reduced in isolated leukocytes or cultured cells and two mutations within the ASM gene may be identified. Many ASM mutations have been identified in unrelated type A and B patients. Three of these, R496L, L302P, and FsP330, account for 95% of the mutant alleles in Ashkenazi Jewish type A patients and a single mutation, Delta R608, has been reported to occur commonly in patients with type B disease. In contrast to patients with other mutations, individuals homozygous for the Delta R608 mutation had normal height and weight, markedly less hepatosplenomegaly, and bone age delay, as well as normal IGF-1 levels.

He X et al suggest that high performance liquid chromatography (HPLC), using plasma instead of leukocytes, is a very reliable and highly sensitive technique to determine ASM activity and that plasma is a very reliable and simple source for the accurate diagnosis of NPD patients and carriers based on ASM activity. Our patient showed similar findings as in the literature. Genetic studies or ASM activity was not performed. So far, there is no specific treatment for NPD type B nor for the pulmonary involvement. Whole-lung lavage may be a potentially useful modality of treatment for patients with pulmonary involvement. Prenatal diagnosis of NPD type A and B is routinely accomplished by sphingomyelinase assay. 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.

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References