DOI: 10.4274/tpa.292

Niemann-Pick disease and hemophagocytic syndrome

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Summary

Hemophagocytic syndromes represent a severe hyperinflammatory condition with the cardinal symptoms of prolonged fever, cytopenias, hepatosplenomegaly and hemophagocytosis induced by activated, morphologically benign macrophages. Hemophagocytic syndrome may be primary or it may be secondary to malignancy, metabolic diseases, collagen vascular diseases and bacterial, viral and fungal infectious diseases. Niemann-Pick disease is a fatal lysosomal storage disease related to progressive neurodegeneration secondary to abnormal intracellular accumulation of cholesterol. In this article, we describe the first reported case of Niemann-Pick disease that demonstrated hemophagocytosis in Niemann-Pick cell (lipid loaded macrophage). *(Turk Arch Ped 2012; 47: 220-222)*

Key words: Hemophagocytic syndrome, Niemann-Pick disease

Introduction

Niemann-Pick disease (NPD) is an autosomal recessive lipid storage disease characterized by hepatomegaly-splenomegaly of varying degrees and progressive psychomotor retardation. Niemann-Pick disease is divided into four classes (1). While sfingomyelinase deficiency is shown in Niemann-Pick type A and B, sfingomyelinase levels are normal or near normal in Niemann-Pick type C and D. In the studies performed later, it was shown that intracellular metabolism of external cholesterol was deficient in NPD and the clinical picture developed as a result of accumulation of unesterified cholesterol in lysosomes (2).

Hemophagocytic syndrome (HPS) is a disease characterized by abnormal growth of macrophages and increase in cytokines. Clinically, it presents with fever, hepatomegaly-splenomegaly and cytopenia. If untreated, it results in accumulation of T lymphocytes and activated macrophages as a result of erroneous triggering of apoptosis and decrease in cytotoxic effect. It is studied in two groups as primary and secondary HPS (3,4). The secondary form may be related to infection (viral, bacterial, fungal and parasitic), malignancy, metabolic disease and rheumatic diseases.

In this article, a 38 day-old male subject who presented with complaints including jaundice, fever and hepato-splenomegaly, who was considered to have NPD and whose bone marrow examination revealed hemophagocytosis in lipid-loaded macrophages (foam cells) was presented, since this association was observed for the first time.

Case

A 38 day-old male patient presented to our clinic with jaundice. In his history, it was learned that jaundice started from the birth and increased gradually, there was no consanguinity between the mother and the father and he was the first child of the family. Physical examination revelaed that the body temperature was 39°C (axillary) and the height and weight were in the 25th percentile. The patient had tachypnea and tachycardia and appeared pale and dirty yellow. The liver was

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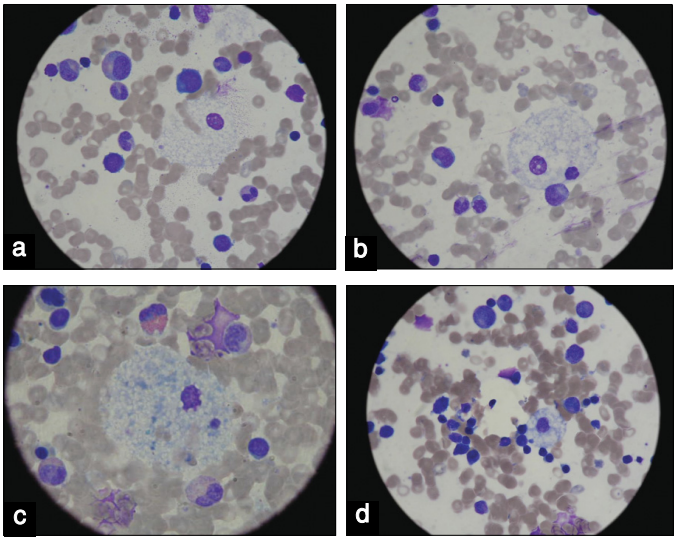
palpable at 6-7 cm below the costal magrin and the spleen was palpable at 4-5 cm below the costal magrin. Complete blood count findings were as follows: hemoglobin: 7.9 g/dL, white cells 7360/mm^3, platelets: 93000/mm^3. On peripheral blood smear, erythrocyte and segmented cell structures were found to be normal and no extraordinary cells were observed. Blood biochemistry findings were as follows: renal function tests: normal, AST: 100U/L, ALT: 116U/L, total protein: 3.5 g/dL, albumin: 2.3 g/dL, total biluribin: 14,4mg/dL, direct bilirubin 8.4 mg/dL, gamma glutamyl transferase (GGT): 112 U/L, LDH: 2094 U/L, triglyceride: 307 mg/dL, cholesterol: 159 mg/dL. Coagulation tests were found to be normal. Ferritin: 750 ng/mL, fibrinogen: 86 mg/dL. Urinary organic acid levels were found to be normal. Tandem MS test and plasma and urinary amino acids were found to be normal. Lysosomal sfingomyelinase activity which was tested considering Niemann-Pick disease was found to be 0,32 nmol/h/mg (N:0.86-2.8). Alpha-1 antitrypsin, hepatitis markers, immunglobulins, cytomegalovirus infection (CMV), Epstein-barr virus (EBV), Parvo virus and Adeno virus were found to be negative. Hemoculture and other cultures were found to be negative. On abdominal ultrasonography, the choledoc, intrahepatic bile ducts, portal vein and gallbladder were found to be normal. The liver had a craniocaudal lenght of 110 cm and the spleen had a size of 90x40 mm both with a homogeneous echo. On bone marrow examination, foam cells and marked hemophagocytosis inside the cells (erythrocytes, platelets and lymphocytes) were observed (Picture 1 a-d).

Liver biopsy could not be performed, since the general status of the patient was poor. Although hemophagocytic lymphohistiocytosis treatment protocol was planned, only intravenous immunglobulin (IVIG) was given at a dose of 0,8 mg/kg/day. In the follow-up, liver failure findings progressed and the patient died on the 13th day of the follow-up.



Picture 1 a-d. Foam cells and hemophagocytosis of erythrocytes, lympocytes and platelets on bone marrow examination

Discussion

Niemann Pick disease is an autosomal recessive lipidosis which results in accumulation of unesterified cholesterol in lysosomes because of a defect in intracellular metabolism of external cholesterol (1). Although the clinical findings of the disease are considerably variable, the known phenotype is characterized by hepato-splenomegaly, vertical supranuclear ophthalmoplegia, progressive ataxia, dystonia and dementia. In the infantile type which is the most severe form of the disease, findings include jaundice starting in the newborn period, cholestasis, giant cell hepatitis and hepato-splenomegaly. Neurological signs and symptoms may not be evident. The late infantile type is observed more frequently and the first signs generaly start at the ages of 2-4 years. Neurological signs are evident and varies depending on the age of onset of the disease. While hypotonia and pause in development are observed in infants, cerebellar ataxia may be the first sign in older children. Although it is observed in 90% of the patients with hepato-splenomegaly, it is not as evident as in NPHA (2). While the patients show normal development until the age of 2, afterwards the abilities obtained previously are lost and ataxia, psychomotor retardation, diffuse tonic clonic convulsions and dystonia occur. Death usually occurs at the age of 10-20 years because of lung infection and aspiration. In our patient, we considered NPH type B because of jaundice which started from the time of birth as the first finding, hepato-splenomegaly, anemia, thrombocytopenia and absence of neurological findings. However, we could not determine the genotype.

Hemopagocytic syndrome is a clinical picture characterized by fagocytosis of blood cells by macrophages accompanied by fever, hepato-splenomegaly and cytopenia of at least two series (5). Fagocytic action of macrophages directed to blood cells are mostly observed in the bone marrow, spleen, liver and lypmh nodes. Hemopgagocytic syndrome may be primary or secondary. The primary type is named familial erythrophagocytic lymphohistiocytosis. The secondary type is usually observed with viral infections (4). Secondary HPS cases have been defined during infections with Epstein-Barr virus and other viruses, bacteriae, protozoae and fungi, during diagnosis or treatment of various malignant diseases, during metabolic disease, different system diseases, autoimmun diseases, following blood transfusion, stem cell transplantation, organ transplantation and drug administration or intravenous feeding with lipids (6). In our patient, primary HPS was considered because the disease occured at an early age, but genetic analysis could not be performed.

The diagnostic criteria of hemophagocytic syndrome include clinically prolonged fever, hepato-splenomegaly, bicytopenia, increased triglycerides, decreased fibrinogen, increased ferritin and cytokines (7,8). Metabolic diseases should be considered among secondary causes. HPS has

been reported in individuals with amino acid metabolism defects (especially lysinuric protein intolerance) (9). In this condition, absorbtion of basic amino acids (lysin, arginin, ornitin) is defected in the intestines, kidneys and liver. Avoidance of food containing protein, growth retardation, hepato-splenomegaly and osteoporosis are present. Hemophagocytosis related to the lung, kidney, pancreas and bone marrow has been reported. Until the present time, hemophagosytosis in lipid storage diseases has not been published. Since we could not perform genetic analysis in our patient, it is difficult to make an interpretation if HPS was secondary to NPD or there was a coincidental association of NPD and HPS.

Conclusively, HPS should be considered in the presence of fever, splenomegaly and cytopenia in lipid storage diseases. Invesigating hemophagocytosis by bone marrow aspiration before futher tests is important for diagnosis and planing of treatment.

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