

WHAT'S YOUR DIAGNOSIS?

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FIGURE 1.



FIGURE 2.

History

A 20-month-old Saudi female child presented with gradual abdominal distention, failure to thrive and delayed psychomotor development from the age of eight months. She had had three hospital admissions for respiratory infections, otherwise she remained afebrile. The child was born normally after a full-term uneventful pregnancy. The parents were first-degree cousins. Two other siblings and both the parents were healthy. On examination, the patient's weight was below the 3rd percentile and corresponded to the median weight of a 9-month-old girl. Height and head circumference were normal. Her vital signs were normal. She had marked hepatosplenomegaly and no signs of chronic liver disease. She was not anemic and had no lymphadenopathy. She was hypotonic with normal reflexes. She could sit without support but could neither crawl nor stand. She could see and hear, and speak 2 to 3 meaningful words. Other examinations were unremarkable. Laboratory investigations showed Hb 112 g/L, white cells $15.59 \times 10^9/L$, platelets $121 \times 10^9/L$, ESR 15

mm in the first hour, normal differential count and blood film study. Her blood glucose, blood urea nitrogen, serum electrolytes, uric acid, lactate, ammonia, bilirubin and proteins were normal. Prothrombin and thromboplastin times were also normal. Alanine aminotransferase was 312 U/L (normal 30-65), aspartate aminotransferase was 358 U/L (15-37), alkaline phosphatase was 277 U/L (100-350), serum cholesterol was 6.4 mmol/L (2.4-6.4), and triglycerides were 4.6 mmol/L (0.34-2.8). Serology for Epstein-Barr virus, cytomegalovirus, hepatitis viruses, brucella and salmonella, and tuberculin test were negative. Skeletal x-rays were normal. Ultrasound of the abdomen showed liver span more than 11 cm with uniformly enhanced echo, and the spleen was 10 cm with normal echo, normal gallbladder, bile ducts, portal vein and renal system.

1. What does the bone marrow smear show?
2. What important eye finding and simple radiological investigation has not been mentioned?
3. What's the diagnosis?

ANSWER TO WHAT'S YOUR DIAGNOSIS? (PREVIOUS PAGE)

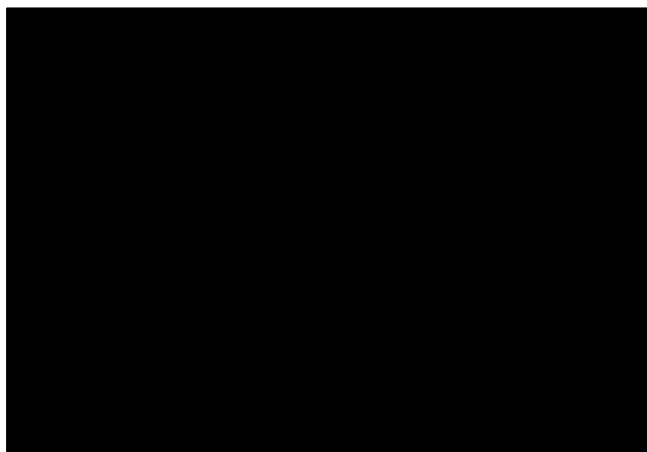


FIGURE 1. Bone marrow shows foamy histiocytes with normal hematopoietic cell lines.

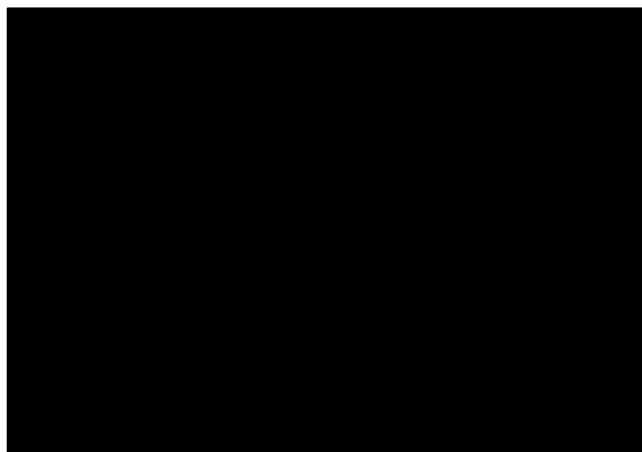


FIGURE 2. Chest x-ray, PA view: lung fields show multiple miliary opacities.

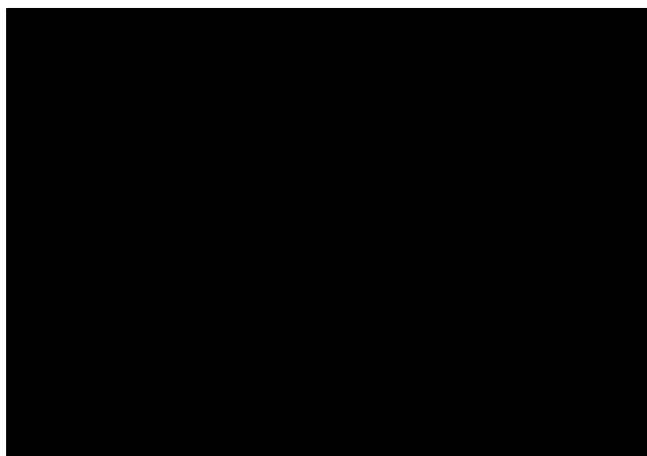


FIGURE 3. Fundoscopy shows macular cherry red spot.

Diagnosis: Niemann-Pick disease (NPD).

Differential Diagnoses: At the initial stage of evaluation of such a young patient with progressive hepatosplenomegaly one should consider infective causes such as Epstein-Barr virus, cytomegalovirus, typhoid, brucella, tuberculosis, malaria, kala-azar, toxoplasma, etc. Hemolytic disorders, malignancies, primary liver diseases can also cause hepatosplenomegaly. However, the absence of prolonged fever, lymphadenopathy, anemia, thrombocytopenia, and normal blood film ruled out these diagnoses. A storage disorder should be considered in such a child with developmental delay. Storage disorders include glycogen, lipid, mucolipid or glycoprotein storage diseases and mucopolysaccharidosis (MPS).¹ Glycogen³ storage disease presents with various combinations of hepatomegaly,

hypoglycemia, myopathy and cardiomyopathy.¹ MPS presents with coarse features, skeletal changes, corneal clouding and mental retardation. Mucopolysaccharidosis and glycoprotein storage disorders also have coarse features and skeletal involvement like MPS, but no mucopolysacchariduria.² The presence of foamy histiocytes in bone marrow with hepatosplenomegaly suggests the diagnosis of a lipid storage disease (LSD) such as Niemann-Pick disease, Gaucher's disease, Wolman's disease or gangliosidosis.³ The foamy cells of NPD have uniform-sized vacuoles and are prominent throughout the film, which gives a typical "mulberry appearance."¹ Nuclear debris and engulfed erythrocytes may be present in the cell in rare cases. The nucleus of the cell is eccentric. If lipid pigments are abundant, the cell is packed with blue staining granules and is termed "sea-blue histiocyte."³ Cytoplasm of the Gaucher cell, on the other hand, shows "crumpled tissue paper appearance."^{1,3} Typical storage cell of Wolman's disease shows "sky-blue cytoplasm."³ Pulmonary infiltrates may be found in NPD and Gaucher's disease.² Gaucher's disease and Wolman's disease do not show a cherry red spot.² Many patients with Wolman's disease show adrenal calcification.² Cherry red spot may also be found in GM2 gangliosidosis (no hepatosplenomegaly), mucopolysaccharidosis (coarse features, skeletal changes), and GM1 gangliosidosis (coarse features).²

Discussion: NPD is a lipid storage disease with several different subtypes, due to accumulation of sphingomyelin and other lipids, mainly in the cells of the reticuloendothelial (RE) system and sometimes in the central nervous system. It is of autosomal recessive inheritance.⁴ The disease was first described in 1914 by

Niemann in Berlin, in an Ashkenazi Jewish female infant.⁵ Pick later identified several cases.⁶ Crocker in 1961 classified the disease clinically into subtypes A to D.⁷ Recently, a new classification has been proposed, based on enzyme defects and different genetic mutations.^{4,8}

The disease Ia (formerly classified as A) is very rare except in Ashkenazi Jews, among whom the incidence of this disease is 1 in 40,000 and carrier frequency is 1 in 90.⁴ Type IIs (D) disease is found in Acadians in Nova Scotia.^{5,8} The biochemistry and histopathology of the disease are as follows: Acid sphingomyelinase (ASM) breaks sphingomyelin into its component parts. Type I disease shows more accumulation of sphingomyelin and type II more cholesterol.⁴ In NPD, lipid droplets and lipid pigments are accumulated in the lysosomes of RE cells of many organs. The cytoplasm of the cell is distended by vacuoles containing lipid droplets, which gives them a foamy or mulberry appearance, and lipid pigments give the cell sea-blue appearance by Wright or Giemsa stain.³ In the liver, both the Kupffer cells and hepatocytes contain lipids. In the spleen, accumulation appears in the pulp and around the arteries. The bone marrow contains numerous typical foamy cells and sea-blue histiocytes. Retinal lipid accumulation around the macula is shown as a cherry red spot on funduscopy.⁵ In type Ia disease the brain is atrophied, the accumulation is in the cortical neurons and spares the subcortical regions. Lung alveoli contain foamy histiocytes.

Clinically, type Ia (A) disease is a progressive neurodegenerative disorder with hepatosplenomegaly of infancy, such as in the present patient.^{1,4} It presents with hypotonia, usually from 6 months of life. Later, hearing loss, visual deterioration and mental retardation become obvious. Hepatic impairment may be mild to severe. Hypersplenism may occur later. Infiltration in lung fields gives miliary mottling and predisposes to recurrent chest infection and pulmonary insufficiency. Cherry red spot is found in about 50% of cases.^{1,5} Vomiting, diarrhea, osteoporosis, etc., may occur. Death usually occurs by 2-3 years of age.⁴ Type Is (B) disease typically develops in early childhood and the patient usually survives into adulthood. Hepatosplenomegaly is the most important clinical presentation. There is no or subtle CNS involvement, but lung and bones are involved. The cherry red spot may be found in 30% of cases.²

NPD type IIs (C) presents with prolonged neonatal jaundice. A normal first 2-year period is followed by a slowly progressive neurodegenerative course. The hepatosplenomegaly in these cases is less severe. The patients have a variable course, and some may survive into adulthood.⁸

Diagnosis of NPD type I is confirmed by determining ASM activity in cultured skin fibroblast or leukocytes. Genetic analysis may diagnose common mutations.⁴ Type II disease has normal ASM activity; diagnosis is confirmed

by the rate of cholesterol esterification when skin fibroblasts are cultured with LDL-derived tritiated oleate. Filin staining shows accumulation of free cholesterol in lysosomes.⁸ Both types may be diagnosed perinatally. Type Is disease is curable by early bone marrow transplantation.^{2,4} There is no satisfactory treatment for other types.

Splenectomy may increase the risk of lung disease and is to be reserved for severe hypersplenism.⁴ Other supportive care includes prompt treatment of infections, nutritional support and physiotherapy. Enzyme replacement therapy is not effective as in Gaucher's disease. In IIs disease cholesterol lowering agents have been tried without much success.⁸ Early diagnosis is possible from the history and the examination, including funduscopy and simple laboratory tests such as bone marrow and radiological studies, even without confirmatory tests. This may help to predict the ultimate outcome and therapeutic decision.

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