The Egyptian Journal of Medical Human Genetics (2016) 17, 277–280

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The Egyptian Journal of Medical Human Genetics

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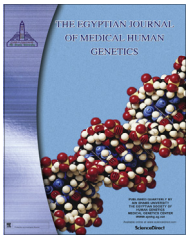

ORIGINAL ARTICLE

Wolman disease in patients with familial hemophagocytic lymphohistiocytosis (FHL) negative mutations

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Available online 26 September 2015

KEYWORDS

Wolman disease;
Familial hemophagocytic lymphohistiocytosis;
Hepatomegaly;
Splenomegaly;
Fever

Abstract *Background:* Familial hemophagocytic lymphohistiocytosis is a rare autosomal recessive disease that is usually evident in the first few months or years of life. Major signs and symptoms include hepatomegaly, splenomegaly, anemia, leucopenia or thrombocytopenias which resemble many inborn errors of metabolism and lysosomal storage diseases in which hemophagocytic lymphohistiocytosis has also been reported as a secondary association.

Case reports: We report three children with hemophagocytic lymphohistiocytosis for whom mutation screening for the known four genes of FHL ((*PRF1* (FHL2), *UNC13D* (FHL3), *STX11* (FHL4), and *STXBP2* (FHL5)) revealed no mutation, while sequencing of the *LIPA* gene confirmed the diagnosis of Wolman disease. Peculiar characteristics of these patients included absence of prominent fever, huge hepatomegaly and a severe failure to thrive.

Conclusion: Wolman disease should be excluded in patients with clinical and laboratory characteristics of FHL and negative molecular testing especially if the fever is not prominent and is associated with relatively huge hepatomegaly and/or severe failure to thrive.

1. Introduction

Familial hemophagocytic lymphohistiocytosis (FHL) presents within the first months or years of life with prolonged fever (more than 7 days), cytopenias, hepatosplenomegaly, liver dysfunction, neurological dysfunction and hemophagocytic cells in the bone marrow [1]. Secondary (acquired or reactive) hemophagocytic lymphohistiocytosis (HLH) is difficult to distinguish from FHL (primary) by clinical or histologic findings alone. The diagnosis of secondary HLH is usually made in association with infection by viruses, bacteria, fungi, or parasites or in association with lymphoma, autoimmune disease, or metabolic disease [2,3]. Inborn errors of metabolism including biotinidase deficiency [4], lysinuric protein intolerance [5], galactosemia [6], multiple sulfatase deficiency, Gaucher disease, Pearson syndrome, galactosialidosis, methylmalonic acidemia, and propionic acidemia [7] have all been reported

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Peer review under responsibility of Ain Shams University.

http://dx.doi.org/10.1016/j.ejmhg.2015.08.005

in association with secondary HLH in some individuals. The main challenge to the physician in these cases is the diagnosis of the underlying IEM.

1.1. Case report (1)

Is a 2.5 month old boy, the second in birth order of double cousin parents who presented at the age of one month with abdominal distension. He had a history of mild fever for the last 5 days (37.7 °C). On examination, the patient's weight was 3 kg (birth weight was 3.250 kg), he had huge hepatomegaly and pallor. CBC showed hemoglobin level of 5 g/dl, total white blood cell count (WBC) of 3800/μl and platelets of 98,000/mm^3. Bone marrow aspiration revealed moderate hypercellular bone marrow. Erythropoiesis was the most stimulated and showed abundance of the marrow precursors. Late normoblasts showed defective hemoglobinization and deficient stainable iron. Granulocytopoiesis was stimulated to a lesser extent and showed normal morphology and normal maturation sequence. Myeloblasts were 2% of the nucleated marrow elements. The myeloid: erythroid series ratio was decreased to 1.7: (1) Megakaryocytes were increased and showed occasional young forms. Free platelets were decreased in count. Lymphocytes were normal in count (11%) and morphology. Plasma cells were normal, macrophages were markedly increased and showed features of activation with phagocytosis of intact blood cells and marrow elements.

Serum ferritin was 2363 ng/ml (normal; range 10–120), serum LDH was 1612 U/L (normal range 266–500), and serum triglyceride was 528 mg/dl. EBV IGM and CMV IgM were both negative

Abdominal ultrasound revealed markedly enlarged liver measuring 9.8 cm in span in mid clavicular line with homogenous echopattern with no focal lesion and no dilatation of intrahepatic or extrahepatic bile ducts. The spleen was mildly enlarged measuring 11.2 cm in its long axis with no focal lesions. Both kidneys showed normal site, size and shape with normal thickness and echopattern, with no stones or back pressure changes. Pancreas and para aortic region were free. There was no ascites, no abdominal or pelvic masses or abnormal fluid collection.

Segregation of polymorphic markers study at *PERFORINE*, *UNC13D*, *STXBP2* and *SYNTAXIN 11* genes did show any homozygous haplotype. Sequencing of *LIPA* gene revealed homozygous G969A (W130X) mutation leading to the diagnosis of Wolman disease.

1.2. Patient (2)

Is a 3 month old girl, the second in birth order of double cousin marriage. She had a similar affected brother who died at the age of 3 months and a maternal cousin (girl) who died at the age of one month with a provisional diagnosis of FHL without molecular confirmation, Fig. 1. The patient presented with abdominal distension, pallor and mild fever (38 °C) that decrease with antipyretics. On examination the patient had severe failure to thrive, liver was hugely enlarged 6 cm below the costal margin, and the spleen was 8 cm below the costal margin. CBC showed hemoglobin level of 6.9 g/dl, total leukocytic count of 5.6×10^3/mm^3 and platelets of 95,000/mm^3. Bone marrow aspiration revealed a marrow infiltrated with

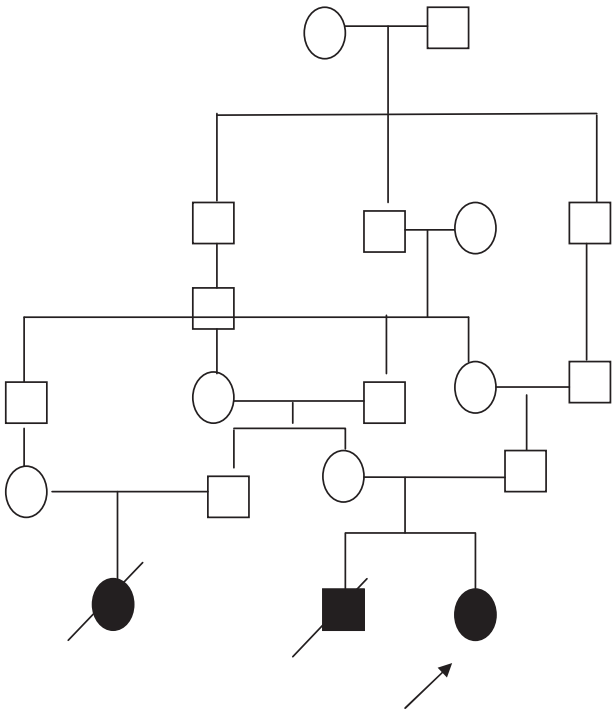

Figure 1 Family pedigree of patient (2).

giant macrophages which showed compressed nuclei due to extensive cytoplasmic vacuolation. These vacuoles contained unstainable contents. In addition many sea-blue histiocytes were seen. Phagocytosis of intact and/or damaged hematopoietic cells was rarely seen. The patient had an initial diagnosis of Niemann–Pick disease and so Beta-glucocerebrosidase enzyme was done and showed normal level of 5.3 μmol/h/g of protein (normal 1–5), sphingomyelinase was also measured with the level of 2.7 umol/gmpt/h (normal 1.5–5 nmol/h/g) excluding both Niemann–Pick type A and Gaucher disease. Then, the patient was referred to the genetics clinic because of the family history of a genetic disease.

Plasma fibrinogen level was 150 mg/dl (normal value: 150–350), Serum ferritin was 1664 ng/ml (normal; range 10–120), serum LDH was 1612 U/L (normal range 266–500), serum triglyceride was 266 mg/dl, ALT was 17 U/ml (normal up o 30), AST was 78 U/ml (normal up to 40), albumin was 2.2 mg/dl.

Segregation of polymorphic markers study at *PERFORINE*, *UNC13D*, *STXBP2* and *SYNTAXIN 11* genes did show any homozygous haplotype. Sequencing of all coding sequences of *LIPA* gene revealed homozygous mutation c.438delC (p.S112X) leading to the diagnosis of Wolman disease.

1.3. Patient (3)

Is a 3 month old boy, the third in birth order of first cousin parents. The pregnancy was uncomplicated and he was delivered by CS with a birth weight of 3.5 kg. His condition started at the age of 2.5 months when the mother noticed progressive abdominal enlargement, failure to thrive and pallor. On examination, his weight was only 3 kg, length was 52 cm and had no fever except after one week of presentation (38 °C). His liver