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Wolman's disease in a Jordanian infant

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Summary We report a case of Wolman's disease that is apparently the first to be reported in a Jordanian infant. The clue to diagnosis was the radiological evidence of bilateral adrenal calcifications and foam cells in bone marrow. The disease was confirmed by skin fibroblast culture which showed decreased 'acid esterase' activity.

Introduction

In 1956, Abramov and colleagues reported an infant of Iranian-Jewish origin with a peculiar lipidosis syndrome who died at 2 months of age with hepatosplenomegaly and adrenal calcifications.[1] In 1961, Wolman *et al.* from Israel described two siblings with a similar condition and named it 'primary familial xanthomatosis with involvement and calcification of the adrenals'.[2] In 1964, Cracker *et al.* reported the first three cases from the United States and they were the first to suggest the name 'Wolman's disease' for this entity.[3] Since 1964, the disease has been observed in patients from many ethnic backgrounds (Dutch, Rumanian-Irish, German-English, Japanese, Iraqui-Jew, Greek) and were reviewed elsewhere by Patrick and Lake.[4] Recently, the disease has been described in female twins of Libyan-Arab origin.[5]

This is the first reported instance from Saudi Arabia and apparently the first in a Jordanian infant.

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Case report

The patient, a 2-month-old boy of a consanguineous Jordanian-Arab couple, was referred to us from a peripheral hospital for evaluation of abdominal distension and hepatosplenomegaly. He was the product of a normal pregnancy and delivery and was thought to have had a normal birthweight. There was no family history of a similar condition. The patient was well until 3 weeks of age when abdominal distension was noted. He continued to appear alert and well, except for increasing abdominal distension, until we saw him at 8 weeks of age. On physical examination he was pale and had marked abdominal distension. His height was at the 50th percentile and his weight and head circumference were at the 10th percentile. There were no dysmorphic features. His liver was enlarged by 5 cm and his spleen by 6 cm. There were no palpable lymph nodes. Fundal examination was essentially normal.

The haemoglobin was 9.7 g/dl, and the white blood count 6.6×10^9/l, with 48% neutrophils, 46% lymphocytes, 5% monocytes and 1% eosinophils. Platelets were 220×10^9/l. Biochemical values were normal except for an albumin concentration of 29 g/l

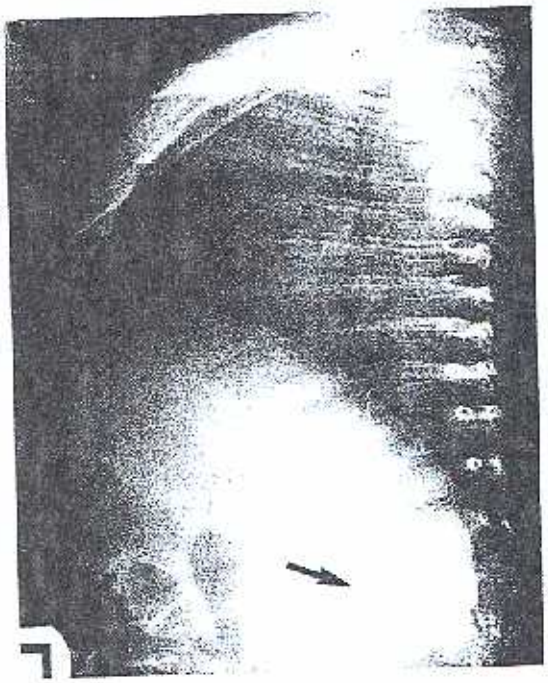

Fig. 1. Lateral radiograph of abdomen showing bilateral adrenal calcifications.

(normal 35–50 g/l) and slightly elevated liver enzymes. Tests for hepatitis B surface antigen and congenital infections were negative. Serum cholesterol and triglycerides were normal. Abdominal X-rays and ultrasound revealed enlarged adrenals with extensive bilateral calcifications (Fig. 1). Bone marrow aspiration showed heavy infiltration with large foamy cells. These findings were compatible with Wolman's disease. Low acid esterase activity in skin fibroblast culture confirmed the diagnosis of Wolman's disease.

The child's condition progressively deteriorated over the next 2 months; he developed severe marasmus, progressive hepatosplenomegaly and died at 4 months of age. Post mortem examination was not done. Following the death of this child the family had another infant who died in a peripheral hospital with a similar condition before the age of 6 months. The diagnosis was made in view of bilateral adrenal calcifications shown on X-ray of abdomen.

Materials and methods

Following informed consent, the patient's inner thigh was cleansed with alcohol swabs and anaesthetized with 0.5 cc of 1% xylocaine injected subcutaneously with a 23-gauge needle. A punch biopsy, including dermis, was obtained using a 4 mm disposable circular blade (Fisher). The biopsy specimen was submerged in 15 cc of IX Minimum Essential Medium (MEM) for fibroblast culture.

Enzyme assays were performed locally by 'The Inborn Error of Metabolism Research Laboratory' at King Faisal Specialist Hospital and Research Centre, Riyadh. The acid esterase activity was measured in patient cultured skin fibroblasts using 4-Methylumbelliferyl palmitate (Sigma Chemical Co., St Louis, Mo., USA) as a substrate. The substrate was first dissolved in 1% Triton X-100 and petroleum ether; after the evaporation of the solvent, the gummy residue was dissolved in Glycine 100 mM, pH = 3.93. The final substrate concentration was 0.2 mM, Triton X-100 4%, and fibroblast protein 0.1–2.5 mg/ml. The incubation time was 15 minutes and the fluorescence of the free 4-methylumbelliferone was measured after terminating the reaction with 10X volume 0.4 M glycine, pH = 9.0. The excitation wavelength was 365 nm, and emission wavelength was 450 nm. Previous values obtained for normal cell lines, including control normal cell lines determined parallel to the patient, were used to express the deficiency of the enzyme as % of normal.

Results

Acid esterase activity level in the patient's fibroblasts was 116.1 μmol/mg/min. Normal controls' ($n = 8$) mean (SD) value was 956(200) μmol/mg/min. Thus, acid esterase activity in skin fibroblast culture was 12% of control level, a value highly suggestive of Wolman's disease.

Discussion

Wolman's disease is a rare familial lipidosis resulting from deficiency of an intracellular

lysosomal enzyme 'acid esterase' that normally degrades triglycerides and cholesterol esters within the lysosomes.[6] It is thought to be of autosomal recessive inheritance. The typical clinical profile, which usually emerges in the 1st few weeks of life, includes abdominal distension, anaemia, failure to thrive and hepatosplenomegaly.[7,8] The crucial clue to diagnosis is the evidence of bilateral adrenal calcifications on routine radiological examination of the abdomen and the presence of foamy histocytes in the bone marrow.[1,2] Ultrasound and computerized tomographic (CT) scanning of the abdomen are useful new modalities in the evaluation of this disease.[9] Demonstration of absent or significantly deficient activity of lysosomal acid esterase in liver biopsy material, leucocyte or skin fibroblast culture, confirms the diagnosis.

Autopsies performed on patients who have died of Wolman's disease have shown that the adrenals are symmetrically enlarged, very firm, bright yellow and that calcifications are observed on the cut surfaces in the deep cortical areas.[10] Histopathological studies also show evidence of disseminated, lipid-laden foam cells, most notable in the liver, spleen, lymph nodes, bone marrow, thymus, intestinal mucosa and pulmonary interstitium.[3,10] The brain is externally normal but ultrastructural examination shows evidence of lipid accumulation in oligodendrocytes and astrocytes.[11] Unfortunately, autopsy was not done in our patient. Tissue biopsies and autopsies are difficult to obtain in Saudi Arabia because of local customs and religious beliefs.

Wolman's disease as a form of lipidosis has to be differentiated from Niemann-Pick disease. The confusion is increased by the presence in both syndromes of foam cells in the bone marrow. The localization pattern of adrenal calcifications is unique to Wolman's disease. In neuroblastoma adrenal calcifications may occur, but are usually unilateral. In adrenal haemorrhage, calcifications may be bilateral but the adrenals usually decrease in size.

The deficiency of acid esterase is expressed in a number of distinct phenotypes.[10,12] Wolman's disease is the severe expression of the disease and in infancy is nearly always fatal. Cholesterol ester storage disease (CESD) is a comparatively mild form of the disease and characterized by hepatomegaly which may not be detected until adulthood.[13] A new variant of Wolman's disease, characterized by short stature, obesity, deafness, psychomotor regression, seizures, acanthosis nigrans, hepatomegaly and severe acid esterase deficiency, has been reported.[14]

There is no effective treatment for Wolman's disease. Therapeutic attempts with cholestyramine, clofibrate or a medium chain triglyceride diet have hitherto failed. Prenatal diagnosis of the disease, through cultured chorionic villus cells and fetal skin fibroblast, is now possible.[15] Carriers of the disease can also be identified by skin fibroblast culture.[16] The only hope which has yet to be explored is bone marrow transplantation, a procedure which has recently been found to be of therapeutic benefit in children with lysosomal storage diseases.[17]

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