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Case Report

A rare constellation of imaging findings in Wolman disease

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ARTICLE INFO

Article history:

Received 13 June 2013

Accepted 16 February 2014

Available online 26 April 2014

Keywords:

Bilateral adrenal calcification

Infant

Radiology

Wolman disease

Case report

A 4-month-old male infant patient, an issue of second-degree consanguineous marriage and born normally at full-term, was brought to this hospital with progressive abdominal distension, vomiting and listlessness noted over the last one month. There was no history of fever, diarrhoea or jaundice. The first three months of the baby's life were uneventful with normal weight gain and achievement of milestones. There was no history of similar illness in the family. The baby's parents came from a poor socio-economic strata and he was suspected to be suffering from protein-energy malnutrition.

On examination, the baby weighed 4.5 kg. He was pale and had a protuberant abdomen. There was evidence of hepatosplenomegaly with the liver span measuring 9.0 cm and the spleen palpable 3.0 cm inferior to the costal margin. The neurological examination and fundus were normal. Laboratory investigations revealed microcytic hypochromic anaemia with a haemoglobin of 10 g/dL, leucopaenia with a total leucocyte count of 3000/mm³ and thrombocytopaenia with a platelet count of 75,000/mm³. Vacuolated lymphocytes were noted in the peripheral blood smear. The serum albumin was 2.5 g/dL. The liver function tests were deranged with raised serum bilirubin (2.0 mg/dL) and elevated transaminases (alanine transaminase – 150 IU/L, aspartate transaminase – 300 IU/L). The prothrombin time (PT) and partial thromboplastin time (PTT) were prolonged and measured 23 s and 48 s,

Introduction

Bilateral adrenal calcification in infants is an infrequent occurrence and often presents a diagnostic dilemma. Wolman disease is a very rare autosomal recessive lysosomal storage disease that is caused by severe deficiency of lysosomal acid lipase (LAL) enzyme and is fatal within the first year of life. Most literature on the subject describes the characteristic bilaterally enlarged calcified adrenals on imaging. This article presents a rare constellation of other imaging findings in Wolman disease.

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<http://dx.doi.org/10.1016/j.mjafi.2014.02.006>

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respectively. The international normalized ratio (INR) was elevated to 1.7. Hypercholesterolaemia (230 mg/dL) and hypertriglyceridaemia (240 mg/dL) were also noted. Faecal fat was evident on 'Sudan staining'. Radiograph of the chest and abdomen revealed a protuberant abdomen with suggestion of hepatosplenomegaly and bilateral paraspinal triangular calcific lesions (Fig. 1). Ultrasonography of the abdomen revealed hepatosplenomegaly, a contracted calcified gallbladder and bilaterally enlarged calcified adrenals (Fig. 2). A subsequent computerized tomography (CT) scan of the abdomen showed hepatomegaly with steatosis, calcified contracted gallbladder, splenomegaly, retroperitoneal lymphadenopathy and ascites apart from the calcified adrenal glands (Figs. 3 and 4). The enlarged adrenal glands maintained their triangular configuration and revealed dense peripheral calcification. Based on the clinical presentation, laboratory investigations and constellation of radiological findings, the diagnosis of Wolman disease was arrived at. The infant's poor health and deranged coagulation profile precluded any attempts at corroborative liver or bone marrow biopsy. Despite supportive therapy, the infant died after a week of admission. Post-mortem liver biopsy revealed 'foamy' histiocytes and 'cholesterol clefts' in the Kupffer cells, which confirmed the diagnosis. The parents were counselled about the genetic nature of the disease and actions to be taken at the next conception.

Fig. 1 – Radiograph of the chest and abdomen reveals a protuberant abdomen with bilaterally enlarged calcified adrenal glands (white arrows).

Fig. 2 – Ultrasonographic image showing hepatomegaly. Also note the enlarged calcified adrenal glands casting distal acoustic shadowing (arrows).

Discussion

Wolman disease is a very rare autosomal recessive lysosomal storage disease that is caused by severe deficiency of the lysosomal acid lipase (LAL) enzyme and is fatal within the first year of life. It is named after Moshe Wolman, an Israeli neuropathologist.¹ The disease is characterized by lipid deposition in multiple organs and was first described in 1956 in an infant who presented with vomiting and pallor and had calcified adrenal glands.^{1–3} About 80 cases have been reported globally till 2008 and only 5 cases from India till date.^{4–6}

The gene for LAL is located on chromosome 10q23.2-q23.3 and it contains 10 exons.³ The type of defect in the LAL genotype determines the residual enzymatic activity and consequently the severity of the phenotype – residual acid lipase activity within 3–8% of normal LAL leads to the more benign cholesteryl ester storage disease (CESD) and absence of any residual activity leads to Wolman disease.⁷ The exact pathogenesis of Wolman disease is unclear. In tissues rich in LDL-receptors, there is efficient uptake of plasma LDL with liberation of cholesterol by LAL. This cholesterol in turn down-regulates the LDL receptor. In Wolman disease, the downregulation of LDL-receptors does not occur, leading to accumulation of LDL cholesteryl esters in lysosomes. The over-uptake of LDL-associated toxic molecules and oxidation of LDL in these tissues (e.g. adrenals, reticuloendothelial system) leads to cytotoxicity.⁸

A characteristic feature of Wolman disease is bilaterally enlarged calcified adrenal glands. This occurs due to the saponification of fatty acids and their subsequent calcification.^{2,3} The calcified adrenals may be detected on plain radiography, ultrasonography and computerized tomography. On magnetic resonance imaging (MRI), the enlarged fatty adrenal glands reveal signal intensity similar to abdominal fat on T1- and T2-weighted images and the calcifications are seen in the

Fig. 3 – Panel of axial, coronal and sagittal CT images. Bilateral adrenal glands are enlarged with dense peripheral calcification. Also seen are contracted calcified gallbladder (black arrow), ascites (white arrow) and low attenuation of the liver consistent with steatosis.

cortex as hypointense areas on both these sequences.² Plasma cortisol and ACTH usually remain normal despite the glandular involvement.³ Other causes of bilateral adrenal calcification in infants include haemorrhage (due to prematurity, trauma of labour, hypoxia and other stresses), tumours (eg. neuroblastoma) and infection (tuberculosis, meningococcal septicaemia).⁹ Adrenal haemorrhage usually results in globular calcification in shrunken glands.¹ Calcification in neuroblastoma is usually speckled or curvilinear, and associated with a mass distorting the normal configuration of the adrenal gland.¹

The deposition of lipid-filled histiocytes in the small bowel mucosa impairs absorption and results in malabsorption, diarrhoea, steatorrhoea, and accounts for the severe and early marasmus.^{2,3} On imaging, the small bowel walls appear thickened. At autopsy, the inner surface of the bowel is velvety and bright yellow.¹

Accumulation of lipoproteins in the cells of the reticulo-endothelial system leads to their swelling and transformation into 'foam cells'. Apart from the liver, spleen and lymph nodes, this transformation is also seen in the heart,

blood vessels, and brain.³ The hepatic involvement may proceed to fibrosis.¹⁰ CT reveals hepatosplenomegaly with low parenchymal attenuation due to lipid deposition. The intensity of the spleen and liver on T1-weighted MRI images is higher than normal due to lipid deposition. Enlarged retroperitoneal lymph nodes also reveal low attenuation on CT scan and signal intensity similar to the abdominal fat on MRI.²

Bone marrow aspirate reveals the presence of 'foamy' histiocytes. Haemophagocytosis may be noted in the bone marrow and vacuolated lymphocytes in the peripheral blood. These findings may be noted in other lipidoses also, but 'cholesterol clefts' in the Kupffer cells on liver biopsy is seen only in Wolman disease.

Pulmonary lipid deposition also occurs and it may progress to fibrosis.¹⁰

The confirmation of diagnosis is by assaying LAL activity in leucocytes and cultured skin fibroblasts.^{3,5,6} Prenatal diagnosis can be made by assessing the enzyme levels in cultured chorionic villi or amniocytes.⁵

No definite treatment for the condition exists, however early bone marrow and umbilical cord blood transplantation hold promise.^{4,10,11} Other therapeutic strategies have included withholding breast milk and formula feeds that contain triglycerides and cholesterol esters, percutaneous administration of unsaturated fats like sunflower oil, vitamin supplementation, and use of lovastatin and antioxidants like α -tocopherol.^{2,3,6,8}

Other diseases that may have some common presenting features include congenital and disseminated tuberculosis, and lipidoses like Niemann–Pick disease and Chanarin Dorfman disease. In congenital tuberculosis, the affected infant is often born premature with development of fever, respiratory distress, lethargy, poor feeding, irritability, abdominal distension and failure to thrive. Hepatosplenomegaly and lymphadenopathy are common. The revised diagnostic criteria for congenital tuberculosis by Cantwell (Proven tuberculosis lesions in the infant plus one of the following: (i) Lesions occurring in the first week of life, (ii) A primary hepatic complex, (iii) Maternal genital tract or placental tuberculosis, and (iv) Exclusion of postnatal transmission by thorough investigation of contacts) may help in the diagnosis.¹² Niemann–Pick disease is associated with hepatosplenomegaly, jaundice, psychomotor regression and

Fig. 4 – Axial CT section of the abdomen shows retroperitoneal lymphadenopathy (open arrow). Ascites is also noted (solid white arrow).

neurological symptoms. Chanarin Dorfman disease is characterised by non-bullous ichthyosiform erythroderma, leucocyte vacuolation and hepatomegaly with steatosis, hearing and visual impairment.

The constellation of imaging findings in Wolman disease as reported in this article is indeed very rare and probably not reported in the same patient elsewhere.

Conclusion

Wolman disease is a very rare autosomal recessive lysosomal storage disease caused by the deficiency of lysosomal acid lipase (LAL) enzyme and is fatal within the first year of life. Normal-shaped bilaterally enlarged adrenals with dense cortical calcification and 'cholesterol clefts' in Kupffer cells are pathognomonic of this condition and reduced LAL activity in leucocytes and cultured skin fibroblasts is confirmatory.

Conflicts of interest

All authors have none to declare.

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