CASE REPORT

Infant case of lysosomal acid lipase deficiency: Wolman's disease

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SUMMARY

Lysosomal acid lipase (LAL) deficiency is a rare autosomal recessive disorder which causes two distinct clinical phenotypes: Wolman's disease and cholesterol ester storage disease. LAL hydrolyses LDL-derived triglycerides and cholesterol esters to glycerol or cholesterol and free fatty acids. Its deficiency leads to accumulation of intracellular triglycerides and/or cholesterol esters. In early onset LAL deficiency, clinical manifestations start in the first few weeks of life with persistent vomiting, failure to thrive, hepatosplenomegaly, liver dysfunction and hepatic failure. Adrenal calcification is a striking feature but is present in only about 50% of cases. We report a case of an infant presenting with vomiting, diarrhoea, hepatosplenomegaly and poor weight gain that was subsequently diagnosed as Wolman's disease. He was entered into a clinical trial for LAL replacement therapy. This case reinforces that early onset LAL deficiency should be considered in a baby presenting with failure to thrive, gastrointestinal symptoms and hepatosplenomegaly.

BACKGROUND

Lysosomal acid lipase (LAL) deficiency presenting in infants also known as Wolman's disease is a rare lipid storage disorder which presents with vomiting, diarrhoea, poor weight gain and hepatosplenomegaly. Affected infants, irrespective of treatment, almost always die within the first year of life, with some very rare exceptions who survived after bone marrow transplant. Enzyme replacement has been used successfully for the treatment of other lysosomal storage diseases and clinical trials are now investigating the effects of enzyme replacement in LAL deficiency. The rarity and rapidity of progression of LAL deficiency presenting in infants means that disease awareness is low and diagnosis is further complicated by the relatively non-specific clinical manifestations. Diagnosis is often delayed and there are a number of published cases where the correct diagnosis was only made after death. Given the rapidly progressive nature of the disease, improved knowledge of the disease leading to more rapid diagnosis is critical, particularly given the recent availability of a novel investigational, recombinant human enzyme replacement therapy (ERT) in clinical development. We describe a case that highlights the diagnostic challenges when adrenal calcification is not present and its impact in the context of a rapidly progressive disease.

CASE PRESENTATION

A male baby was born at term to non-consanguineous parents with a normal antenatal history by emergency caesarean section for failure to progress. He was born in good condition and did not require any resuscitation at birth.

He fed well with standard infant formula milk in the first week of life but subsequently developed watery diarrhoea from day 8. He presented to hospital at 2 weeks of age with poor weight gain, diarrhoea and vomiting but no hepatosplenomegaly was found at that stage. He was initially thought to have cow's milk protein intolerance and started on amino acid based formula milk following which his symptoms improved to an extent, and he was discharged home.

He presented to the hospital again at 5 weeks of age with continued vomiting, poor weight gain and gluteal wasting. On this occasion, he was started on gaviscon and ranitidine for possible reflux and fed by nasogastric tube and monitored as an inpatient. However he continued to have vomiting and poor weight gain in the hospital, despite input from the dietician. During this admission he was also noted to have hepatosplenomegaly so the possibility of a metabolic condition was raised and investigated. The preliminary metabolic screen was normal and he was transferred to a tertiary centre for further metabolic work-up.

Vacuolated lymphocytes were found on the blood film so a diagnosis of Wolman's disease (LAL deficiency) was suspected. White cell acid esterase (ie, LAL) levels were subsequently found to be low and the diagnosis was confirmed by genetic testing which revealed homozygosity for LIPA gene deletion.

INVESTIGATIONS

At initial presentation at 2 weeks of age, apart from a mildly elevated aspartate aminotransferase (AST) of 44 IU/L, all blood tests including full blood count, liver function tests, renal function tests and thyroid stimulating hormone were within normal limits. When he re-presented at 5 weeks of age, his haemoglobin levels had dropped from 14 to 9 g/dL, and the AST had risen to 75 IU/L, along with an alkaline phosphatase of 270 IU/L, but rest of full blood picture was normal.

Immunoglobulin levels including subclasses, galactosaemia screen, plasma amino acids, very long chain fatty acid levels, urinary amino acid and organic acids were also within normal limits. A lipid profile was not performed. Stool cultures and virology were negative, as were investigations for cystic fibrosis.

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Abdominal X-ray was unremarkable with no evidence of adrenal gland calcification and abdominal ultrasound confirmed hepatosplenomegaly with some debris in the gallbladder.

At 10 weeks of age, peripheral blood film revealed vacuolated lymphocytes and plasma chitotriosidase was markedly elevated (7839 nmol/h/mL; normal range 0–170) indicating macrophage activation, suggestive of an underlying metabolic storage disorder. White cell acid lipase levels were 38 µmol/g/h (normal range 74–390).

Genetic sequence analysis for LIPA gene revealed homozygosity for one base pair deletion at the nucleotide position 398 in exon 4 (c.398delC) which confirmed the diagnosis as Wolman's disease. Both parents were confirmed as heterozygotes.

DIFFERENTIAL DIAGNOSIS

- ▶ Cow's milk protein intolerance was a differential at initial presentation.
- ▶ Niemann-Pick disease, Gaucher's disease.
- ▶ Familial haemophagocytic lymphohistiocytosis.

TREATMENT

Following confirmation of diagnosis at 10 weeks of age, the baby was initially managed by nasogastric tube feeding with amino acid-based formula milk and energy-rich carbohydrate-based formula. However weight gain remained suboptimal despite adequate calorie intake. He received a blood transfusion for anaemia.

Subsequently, at 12 weeks of age, he was transferred to another hospital for participation in a clinical study of investigational ERT, sebelipase alfa (SBC-102). He continues with ERT and receives a modular low-fat feed via gastrostomy.

OUTCOME AND FOLLOW-UP

His progress is currently being monitored under a clinical trial. As he is part of a clinical trial, the final outcome will only be known when the trial is completed.

DISCUSSION

Wolman's disease is a rare lysosomal storage disorder, with an incidence of about 1 in 350 000 births. As an autosomal recessive disease, it occurs in higher frequencies in populations where consanguinity is common. In 1956, the disease was first described by Abramov, Scorr and Wolman in an infant with abdominal distension, hepatosplenomegaly and massive calcification of the adrenal glands. In 1961, Wolman went on to report the same clinical findings in two siblings of the original patient, and also showed that the accumulated lipids were mainly cholesterol esters and triglycerides. In 1965, Crocker first introduced the term 'Wolman's disease'.¹

The defect in Wolman's disease is in the LIPA gene which is located on chromosome 10q23.2–q23.3 and comprises 10 exons; mutations of which result in the deficiency of LAL. Several mutations have been identified, some of which lead to almost complete loss of enzyme activity with early presentation, which is the typical phenotype of Wolman's disease; whereas others cause only a partial disruption of the enzyme activity leading to a clinically more benign condition called cholesteryl ester storage disease (CESD), the onset of which is later on in life.¹

Early onset LAL deficiency (Wolman's disease) presents shortly after birth and is rapidly fatal within the first year of life with severe malabsorption, growth failure and liver failure. In contrast, late onset LAL deficiency also known as CESD can present across a wide age spectrum from 2 to 68 years with dyslipidaemia

(high cholesterol and triglyceride levels) and hepatomegaly often being the main abnormalities at presentation, which can subsequently progress to liver cirrhosis. A vast majority of patients with CESD can remain underdiagnosed due to overlapping features with non-alcoholic fatty liver disease and cryptogenic cirrhosis.^{2–4}

In Wolman's disease, the LDL triglycerides and cholesteryl esters that enter the cells cannot be hydrolysed due to deficiency of the LAL. The consequences appear mainly in the adrenal glands, reticuloendothelial system and gastrointestinal system. A feature of the disease in many patients is adrenal calcification due to necrosis of adrenocortical cells that are overloaded with hydrophobic lipids. The reticuloendothelial system promotes endocytosis of lipoproteins in the liver, spleen and lymph nodes. These cells are unable to process the fatty esters in Wolman's disease because they lack the acid lipase. Therefore they are swollen and transformed into foam cells. This occurs in other organs as well including heart, blood vessels and brain. Vacuolated lymphocytes may not always be present in the peripheral blood film but bone marrow aspirate always shows presence of foamy histiocytes. The extreme degree of lipid storage that occurs in the small intestinal mucosa, specifically in the lamina propria macrophages, in Wolman's disease is responsible for the malabsorption of fats and steatorrhea which is responsible for severe and early marasmus. The accumulations of lipids in the liver leads to rapid fibrosis, cirrhosis and liver failure.^{1–7}

A definitive diagnosis of Wolman's disease can only be reached by measuring acid lipase activity in leucocytes and fibroblasts, although a more recently developed test of enzyme activity using dried blood spot has shown promise. Abdominal X-ray, ultrasound or CT scan showing adrenal gland calcification is strongly suggestive. Bone marrow aspiration will show foamy histiocytes, and liver biopsy shows characteristic elliptical 'cholesterol clefts' on electron microscopy and microvesicular steatosis with expansion of Kupffer cells on light microscopy. Genetic studies have been developed recently for gene sequence analysis of the LIPA gene which can be carried out using extracted DNA or by nested PCR from dried blood spots.^{1–7}

There is no definitive treatment available for Wolman's disease, and death is usually within the first year of life (median age of death according to the recently presented natural history data is 3.4 months). Although there is one reported case of Wolman's disease successfully treated by haematopoietic stem

Learning points

- ▶ Lysosomal storage disorders are a rare group of conditions that often present with non-specific signs and symptoms making their timely recognition challenging; their diagnosis requires specialist metabolic laboratories.
- ▶ An index of clinical suspicion of Wolman disease should be entertained in newborn infants presenting with gastrointestinal symptoms, rapidly developing failure to thrive and hepatosplenomegaly.
- ▶ Initial non-invasive tests such as a peripheral blood smear to look for vacuolated lymphocytes and abdominal X-ray or ultrasound to look for adrenal calcification and hepatosplenomegaly may be helpful.
- ▶ Current management strategies are mainly supportive, including nutritional support with low-fat formula.
- ▶ The feasibility of novel treatments like enzyme replacement therapy can be considered.

cell transplantation (HSCT) in a 6-month-old child, most patients treated with HSCT for Wolman's disease have experienced serious complications including death.⁸

Current management strategies are aimed at nutritional supplementation (with specialised low-fat milk formula or parenteral nutrition), blood transfusions for anaemia and steroid replacement therapy for adrenal insufficiency.

ERT with a recombinant form of human LAL is currently under investigation in clinical trials. The recombinant ERT is currently under investigation in the phase 3 of clinical trials in infants with LAL deficiency and the final results of this trial will be published after it is completed.⁹ Gene therapy may also hold promise for the future.

Contributors MS was involved in the initial management of the patient when he first presented. She also performed background research to write up the case report and was the main person in writing up the case report with suggestions from other authors. AS was involved in performing background research on the disease and was actively involved while writing up the case report. RV was actively involved in the confirmation of diagnosis, the management of the patient and currently also the patient's follow-up. She also contributed actively in providing guidance in the writing of the case report. BB was the consultant under whom the patient was admitted when he first presented and has been involved in his management from the very beginning. He was also involved in actively providing guidance in writing up the case report.

Competing interests None.

Patient consent Obtained.

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