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Eight-Year-Old Girl with Hepatomegaly

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CASE DESCRIPTION

An 8-year-old girl was referred for abdominal pain and elevated liver transaminases. She was previously healthy and was not on any medications. There was no prior history of blood transfusions, toxin exposures or parenteral nutrition. Her parents were nonconsanguineous, and of French and Irish descent. Her family has no history of liver diseases but maternal and paternal grandparents have elevated cholesterol.

Her weight was 25.5 kg (27th percentile), height 127 cm (21st percentile) and body mass index (BMI) was 15.8 kg/m^2 (42nd percentile). On abdominal examination, both liver and spleen were enlarged. There was no scleral icterus or abnormal skin findings or xanthomatosis.

Her liver enzymes revealed elevated transaminases. Total bilirubin was high at 32.7 (<17) μmol/L and direct bilirubin was 5 μmol/L. There was no coagulopathy. Abdominal ultrasound demonstrated her liver to be at near the 95th percentile while her spleen was also enlarged. Doppler study of liver vasculature was normal with no evidence of portal hypertension. Laboratory investigations are outlined in Table 1. Given the hepatomegaly, a lipid profile was performed, demonstrating elevated cholesterol of 6.11 (≤5.20) mmol/L and low HDL cholesterol of 0.83 (≥1.30) mmol/L. Further studies led to the diagnosis.

CASE DIAGNOSIS: LYSOSOMAL ACID LIPASE (LAL) DEFICIENCY (CHOLESTERYL ESTER STORAGE DISEASE)

Studies for infectious and autoimmune hepatitis, α-1 antitrypsin, Wilson's disease and celiac disease were negative. She had elevated cholesterol at 6.11 mmol/L and low HDL cholesterol at 0.83 mmol/L. Liver biopsy revealed severe diffuse, microvesicular steatosis with bridging fibrosis (Batts–Ludwig stage ¾) and abundant foamy macrophages (Figure 1A and 1B).

Further metabolic testing showed low activity of LAL of 13 (80–230) pmol/h/dried blood dot punch. Plasma chitotriosidase activity was also elevated at 545 (6–121) nmol/h/mL, which is a marker enzyme for various lysosomal storage disorders. She was diagnosed with lysosomal acid lipase deficiency (LALD), also known as cholesteryl ester storage disease. Genetic testing confirmed this diagnosis, showing two pathogenic mutations in the lysosomal acid lipase gene (LIPA) (c.684delT and c.894G>A). A low fat diet was initiated to address her dyslipidemia. Lipid-lowering agents such as statins were not initiated as evidence for efficacy was poor. The use of enzyme therapy, specifically sebelipase alfa is available for adults in USA but it is currently waiting for approval in Canada.

LALD is an autosomal recessive, metabolic condition characterized by mutations in the LIPA. Deficient LAL activity leads to accumulation of cholesteryl esters in the liver, spleen, lymph nodes, thymus, adrenal gland and small bowel. This condition can present early as the infantile form called Wolman disease (WD) or later in life as LALD affecting children and adults. It occurs with an incidence of 1/300,000 to 1/500,000 in the Caucasian population, with the highest incidence in the German population of 1/40,000 (1).

Infants with WD present around 2 to 4 months of age with massive hepatosplenomegaly, feeding difficulties and failure to thrive. These findings in combination with adrenal calcification are pathognomonic for WD. The presentation in patients with late-onset LALD can be subtle and thus, unrecognized. Almost all individuals will have hepatomegaly with or without splenomegaly. Other nonspecific gastrointestinal symptoms include vomiting, diarrhea, failure to thrive and abdominal pain. Eighty to ninety per cent of individuals have elevated transaminases, low HDL cholesterol, high total cholesterol and triglycerides. Hepatic steatosis may be seen on ultrasound. Liver biopsy shows microvesicular steatosis from lysosomal accumulation of CE and triglycerides plus foamy

Table 1. Investigations summary

Investigation	Result	Range
Aspartate aminotransferase (U/L)	**117**	≤33
Alanine aminotransferase (U/L)	**86**	≤32
Alkaline phosphatase (U/L)	308	≤300
Gamma-glutamyltranspeptidase (U/L)	28	≤31
International normalized ratio	1.2	0.9–1.1
Total bilirubin (μmol/L)	**32.7**	3.4–17.1
Direct bilirubin (μmol/L)	5	≤5
Partial thromboplastin time (s)	28	23–32
Albumin (g/L)	45	38–54
Hemoglobin (g/L)	132	110–160
Platelets (×10^9/L)	320	150–400
White blood count (×10^9/L)	4.8	5–12
Cholesterol (mmol/L)	**6.11**	≤5.20
Triglycerides (mmol/L)	1.26	≤1.70
HDL cholesterol (mmol/L)	**0.83**	≥1.30
LDL cholesterol (calc) (mmol/L)	4.71	—
Non-HDL cholesterol (mmol/L)	5.28	—
Cholesterol: HDL ratio	7.4	—
Ferritin (μg/L)	51.9	13–150
Alpha-fetoprotein (μg/L)	2.4	≤5
Acylcarnitine (profile, total and free)	Normal	—
Urine organic acids	Negative	—
Plasma amino acids	Negative	—

Investigations were completed to rule out other causes of hepatomegaly. Abnormal values are bolded.

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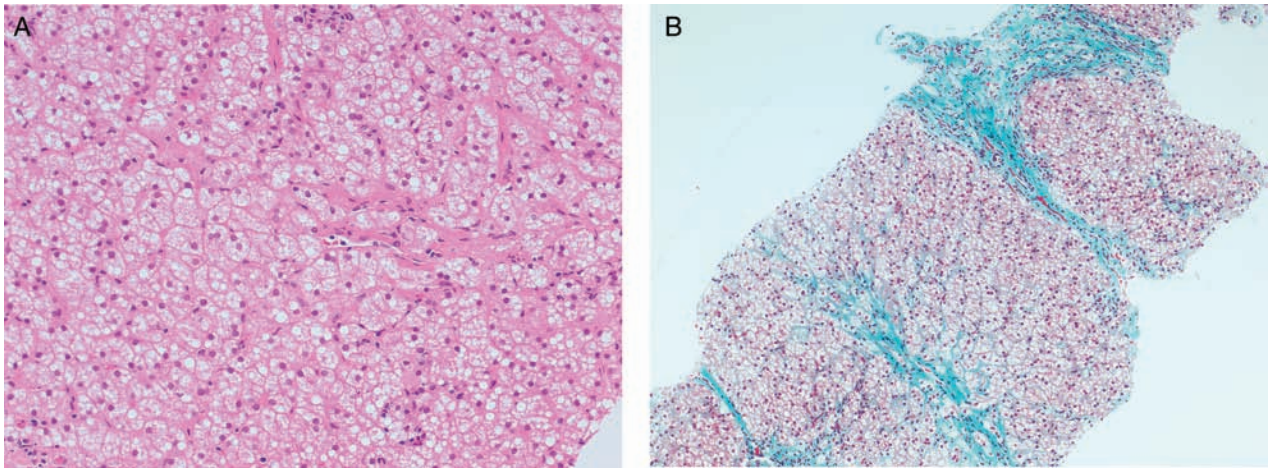

Figure 1. Liver biopsy. (A) Liver biopsy showing diffuse micro vesicular steatosis. (B) Bridging fibrosis seen with Masson trichrome stain (blue).

macrophages with lipid and ceroid. This condition can progress to liver fibrosis and micronodular cirrhosis. Diagnosis is based on finding reduced LAL level in peripheral blood leukocytes. Reduced LAL activity in affected individuals ranges from 1% to 12% of normal, with residual enzymatic activity correlating with disease onset and rate of disease progression (2). Gene sequencing of the LIPA is also available.

The differential diagnosis for hepatomegaly includes inflammation (infections, toxins, autoimmune diseases), inappropriate storage of different materials like lipids or glycogen, primary or metastatic liver malignancies and hepatic vascular congestion (veno-occlusive disease, heart failure, hepatic vein thrombosis). Clinicians should suspect this condition if a patient presents with raised transaminases and an abnormal lipid profile, especially in a non-obese child. Early recognition is essential to halt progression to cirrhosis, which has been seen in patients as young as 5 years of age. Those with hepatic fibrosis can have complications such as portal hypertension, ascites and esophageal varices. Treatment with statins has not been effective in improving liver disease. Those with liver failure may require transplantation. A recombinant human LAL, sebelipase alfa, has demonstrated improvements in transaminases and lipid profile. Children with LALD should be monitored for hepatic fibrosis. Evaluation should include annual liver enzymes and function tests, lipid panel and chitotriosidase (a macrophage inflammatory marker found to be elevated in LALD). Liver and spleen imaging should occur periodically along with cardiovascular assessment. Genetic counselling should be considered for parents of the affected child for future pregnancies.

CLINICAL PEARLS

- Paediatricians encountering patients with hepatomegaly should consider a broad differential diagnosis. In children with fatty liver disease, consideration should be given to screening for metabolic diseases like LALD, mitochondrial hepatopathy and Wilsons, especially if their BMI is normal.
- Due to the nonspecific presentation of LALD, suspicion for this diagnosis should be high, especially in the context of hepatosplenomegaly, elevated transaminases and abnormal lipid profile.
- Early recognition of this under-recognized condition will facilitate management by specific enzyme replacement therapy to halt progression of the disease.

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