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LETTER TO THE EDITOR

The silent course of liver steatosis and fibrosis in an adult patient with Cholesteryl Ester Storage Disease

KEYWORDS
Cholesteryl ester storage disease;
Lysosomal acid lipase deficiency;
Liver steatosis;
Liver fibrosis;
Dyslipidemia.

Lysosomal acid lipase deficiency (LAL-D) is a genetic autosomal recessive disease caused by a mutation of the *lipase A* (*LIPA*) gene, which is responsible for the coding of the lysosomal acid lipase (LAL), resulting in a loss of the enzyme function by decreasing it's activity and inducing a clinical lysosomal storage disease. Prevalence ranges worldwide from 1 in 40,000 to 1 in 300,000 [1].

Children and adults with LAL-D experience a range of clinical manifestations as a result from accumulation of fat in many organs including the liver, spleen, gut and blood vessels. Children present the most aggressive spectrum of the disease known as Wolman's disease, and may present with abdominal swelling, diarrhea, vomiting, and intestinal malabsorption with weight loss. As the disease progresses, severe complications can occur as anaemia, physical wasting and because of increasing fat accumulation in the liver they can present liver dysfunction and cirrhosis. Children, adolescents and adults can present the mildest form of the disease known as cholesteryl ester storage disease (CESD) with a wide range of signs and symptoms that overlap with other disorders, overt disease usually begins before 12 years of age but on rare occasions it can start in adulthood, and because of dyslipidemia and high cardiovascular risk, patients may present with sudden cardiac death [1,2].

LAL-D can be caused by a wide range of homozygous and compound heterozygous mutations in the *LIPA* gene that result in a reduced or absent enzymatic activity. The diagnosis of LAL-D is performed with an enzyme-based biochemical blood test demonstrating an absent activity of LAL [3].

LAL-D can be treated with sebelipase alfa which is a recombinant form of LAL that works as enzyme replacement therapy and that has been recently approved for this disease [4].

CESD is a rare and under-diagnosed disease in adults, so here we report a case of an adult patient with this condition that presented with silent dyslipidemia and liver steatosis with fibrosis [2].

We present de case of a 36 year-old female with a family history of a father who died at 64 years from complications of cirrhosis, two children who died at 3 and 4 months from acute liver failure and a living child with Wolman's disease. After genetic counselling she was referred to our centre for evaluation. At that time she referred to be asymptomatic. Physical examination was unremarkable and she had a body mass index of 23. Laboratory analyzes presented normal blood cell count, blood chemistry and liver function tests, negative viral hepatitis profile, glycosylated haemoglobin of 5.2%, lipid profile with triglycerides of 134 mg/dL, total cholesterol of 317 mg/dL, low-density lipoprotein cholesterol (LDL-c) of 254 mg/dL and high-density lipoprotein cholesterol (HDL-c) of 37 mg/dL. Abdominal ultrasound revealed increased echogenicity of the liver parenchyma suggestive of mild liver steatosis and cholelithiasis without other abnormalities. Liver biopsy was performed and hystopatological analysis reported mixed macro and micro-vesicular steatosis, lipid inclusions in Kupffer cells and bridging fibrosis (Fig. 1). An analysis of lysosomal acid lipase activity was performed in a dry blood sample with an activity of < 40 pmol/h/spt, whereby a Sanger dideoxy sequencing of the *LIPA* gene was performed in which a compound heterozygous pathogen variant was devised by identification of two pathogenic alleles in the exon 8; c.894G > A (p.delSer275_Gln298) and c.894G > C (p.Gln298His).

Abbreviations: LAL-D, Lysosomal Acid Lipase Deficiency; *LIPA*, *Lipase A*; LAL, Lysosomal Acid Lipase; CESD, Cholesteryl Ester Storage Disease; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; ALT, Alanine Transaminase; E8SJM, Exon 8 Splicing Junction Mutation.

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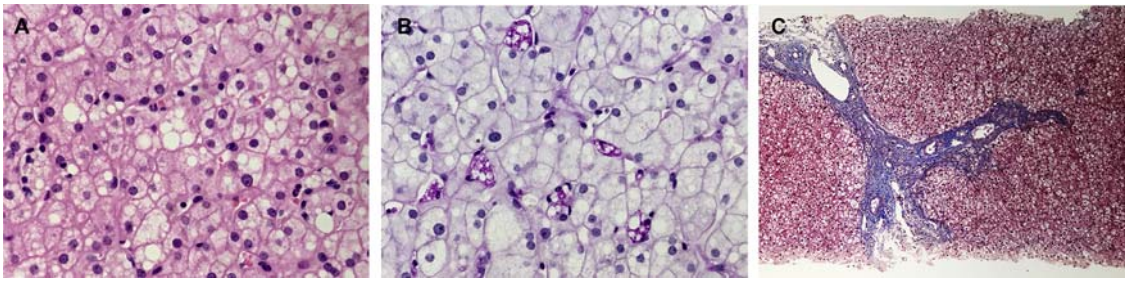

Figure 1 Liver biopsy. (A). Haematoxylin and eosin stain, liver lobule with mixed macro and micro-vesicular steatosis. (B). PAS/Diastase stain, histiocytes with cytoplasmic foamy inclusions that are PAS positive and resistant to diastase digestion, suggestive of lipid lysosomal accumulations. (C). Masson stain, bridging fibrosis.

Therefore, she was diagnosed with mixed dyslipidemia and cholesteryl ester storage disease. She started treatment of dyslipidemia with atorvastatin and remained under clinical surveillance.

According to the latest consensus regarding this disease, deficiency in the activity of lysosomal acid lipase should be considered in patients with certain liver abnormalities as unexplained hepatomegaly, cryptogenic cirrhosis, micro-vesicular and/or mixed hepatic steatosis, persistently elevated alanine transaminase (ALT) with LDL-c $\geq$ 130 mg/dL or HDL-c $\leq$ 45 mg/dL and suspected non-alcoholic fatty liver disease or non-alcoholic steatohepatitis with any of the following from persistently elevated ALT, LDL-c $\geq$ 130 mg/dL, HDL-c $\leq$ 45 mg/dL, normal weight, elevated ALT despite weight loss and rapidly progressive fibrosis/cirrhosis [1,4].

The diagnosis in this case was made by a suppressed LAL enzymatic activity in dry blood test, and the molecular testing of the *LIPA* gene demonstrated the p.delSer275_Gln298 pathogenic allele variant also known as ''Exon 8 Splicing Junction Mutation'' (E8SJM) which is considered as the most frequent allele mutation associated with LAL-D, and the other p.Gln298His pathogenic allele variant has only been reported in one case with LAL-D [2,5].

This case highlights the importance of considering this disease in first-degree relatives with positive history for LAL-D or patients with non-alcoholic fatty liver disease with normal weigh and/or with dyslipidemia. It is also important to make an early diagnosis in patients with high suspicion as they may have advanced liver or cardiovascular damage despite being asymptomatic as this patient with a high degree of liver fibrosis and no symptoms.

In summary, adult patients with CESD whom are compound heterozygotes for pathogenic *LIPA* gene alleles can present with liver disease from early steatosis to liver fibrosis and cirrhosis, and as this disease is under diagnosed in adults, it should be sought in high-risk patients, like those with positive family history for LAL-D or those with non-alcoholic fatty liver disease with normal weigh, LDL-c $\geq$ 130 mg/dL or HDL-c $\leq$ 45 mg/dL.

Contribution of authors

All authors contributed to the conception, design, acquisition, analysis and interpretation of data, drafting, revising and final approval of the manuscript.

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Ethical approval

The patient gave written informed consent.

Disclosure of interest

The authors declare that they have no competing interest.

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