A rare cause of hepatomegaly in the childhood: Lysosomal acid lipase deficiency

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Dear Editor,

Lysosomal acid lipase deficiency (LAL-D) is an autosomal recessive disorder characterized by the accumulation of triglycerides and cholesteryl esters in the lysosome. LAL-D mostly affects the liver; its spectrum ranges from isolated hepatomegaly to cirrhosis. Chronic diarrhea has been reported in some pediatric cases, while calcification of the adrenal glands, which is the hallmark of Wolman disease, can also be seen. Hypercholesterolemia and premature atherosclerosis are other typical manifestations. However, latest studies in the literature have reported on oligosymptomatic cases (1,2).

We report the case of two siblings with LAL-D and with compound heterozygous mutations in the lysosomal acid lipase A (*LIPA*) gene. The index case was a term female from a non-consanguineous family and who had a birth weight of 2800 g. At 6 months, elevated liver function test (LFT) results were obtained. Due to persistent high LFT results [alanine aminotransferase (ALT) level: 102 IU/L, aspartate aminotransferase (AST) level: 133 IU/L, gamma-glutamyl transferase level: 23 IU/L, total bilirubin level: 1 mg/dL, direct bilirubin level: 0.5 mg/dL, alkaline phosphatase level: 236 IU/L] in follow-up visits, a further investigation was initiated. While performing the examination, the liver was palpable at 2 cm below the right costal margin, which was confirmed by ultrasonography. The lipid profile at admission was at the 90th percentile for her age [total cholesterol level: 180 (<170) mg/dL, low-density lipoprotein (LDL) level: 125 (<110) mg/dL, high-density lipoprotein (HDL) level: 33 (40-60) mg/dL, very LDL (VLDL) level: 22 (<30) mg/dL]; therefore, LAL-D was suspected. The diagnosis was confirmed by low acid lipase activity (0.01 nmol/spot/h, N: 0.37-2.3) on a dried blood spot (DBS) card. The second sibling was born at term and weighed 3000 g. She also had hepatomegaly, elevated LFT results (ALT/AST levels: 59/56 IU/L) and dyslipidemia (total cholesterol level: 256 mg/dL, LDL level: 180 mg/dL, HDL level: 59 mg/dL, VLDL level: 17 mg/dL). Her acid lipase activity was low (0.03 nmol/spot/h) on a DBS card. Sanger sequencing of hotspot mutation regions in the *LIPA* gene (exon 6-8) for both siblings revealed compound heterozygous mutations, with one known disease causing mutation (c.894G>A) and one novel likely pathogenic variant [c.616_618dupGTC,p.(Val206dup)]. We confirmed carrier heterozygosity of the mother for c.894G>A and of the father for c.616_618dupGTC. *In silico* analysis of the c.616_618dupGTC variant was shown to alter an exonic splicing enhancer site (Human Splice Finder 3.0). As LAL-D was confirmed, enzyme replacement therapy with sebelipase alfa was launched. Since then, liver and adrenal functions and the clinical status of both siblings have remained stable.

Our index case had hepatomegaly and elevated LFT results and was without typical findings for dyslipidemia. As many patients may remain underdiagnosed as in our case, LAL-D should be suspected when hepatomegaly and/or elevated LFT results and/or hyperlipidemia is present. Hepatomegaly can be detected as the only and most prominent symptom during early childhood or the neonatal period (2). To date, over 48 loss-of-function *LIPA* mutations have been identified. According to Bernstein et al. (3), 89% of cases had the exon 8 splice junction mutation

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in at least one allele. Our siblings showed another likely pathogenic variant [c.616_618dupGTC,p.(Val206dup)], which was not previously defined. The compound heterozygote *LIPA* mutation in our patients showed similar clinical features and biochemical parameters to patients with the homozygous c.894G>A mutation (4). Specific treatment for LAL-D has recently been established. Burton et al. (5) showed the safety and effectiveness of an enzyme replacement therapy referred to sebelipase alfa (Kanuma, Alexion), which was approved by the Food and Drug Administration and European Medicines Agency in 2015. Supportive therapies are also part of treatment; these include low cholesterol diet, vitamin supplements, and 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitors.

Although LAL-D is an uncommon condition and rarely described in the literature, genetic analyses estimate a higher prevalence. Early diagnosis is important as treatment is available and nearly half of the patients die before the age of age 21 when left untreated (5).

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