

Cholesteryl ester storage disease in a young child presenting as isolated hepatomegaly treated with simvastatin

Buket Dalgıç¹, Sinan Sarı¹, Mehmet Gündüz¹, Fatih Ezgü¹, Leyla Tümer¹

Alev Hasanoğlu¹, Gülen Akyol²

Department of ¹Pediatrics, and ²Pathology, Gazi University Faculty of Medicine, Ankara, Turkey

SUMMARY: Dalgıç B, Sarı S, Gündüz M, Ezgü F, Tümer L, Hasanoğlu A, Akyol G. Cholesteryl ester storage disease in a young child presenting as isolated hepatomegaly treated with simvastatin. Turk J Pediatr 2006; 48: 148-151.

Cholesteryl ester storage disease (CESD) is an autosomal recessive disorder resulting from lysosomal acid lipase deficiency and is usually characterized by hepatomegaly and hyperlipidemia. This paper reports a two-year-old boy who had hepatosplenomegaly, hyperlipidemia and hypertransaminasemia determined incidentally. The liver biopsy sample was orange-yellow in appearance. Microscopically, microvesicular steatosis and birefringent crystals were seen in liver biopsy. The diagnosis of CESD was confirmed by the reduced human acid lipase activity in peripheral leukocytes. Simvastatin therapy was given and tolerated without side effects. Our patient is the youngest reported case in the literature treated with 3-hydroxy 3-methyl glutaryl (HMG) CoA reductase inhibitor.

Key words: cholesteryl ester storage disease, 3-hydroxy 3-methyl glutaryl CoA reductase inhibitors, lysosomal acid lipase.

Cholesteryl ester storage disease (CESD), due to the deficiency of lysosomal acid lipase (LAL), is a rare autosomal recessive lysosomal storage disorder¹. LAL is present in lysosomes of all nucleated cells and catalyzes the hydrolysis of highly hydrophobic cholesteryl esters and triglycerides. Deficient activity of LAL results in massive accumulation of cholesteryl esters and triglycerides in many organs, particularly the liver¹. Two forms of LAL deficiency have been recognized: Wolman disease is the severe clinical form and a fatal disorder of infancy, whereas CESD is a milder late-onset form, usually characterized by hepatomegaly and hypercholesterolemia. Liver dysfunction, splenomegaly, xanthelasma, and premature atherosclerosis are the other clinical findings. Adrenal calcification and intestinal and muscle involvement have been reported less frequently¹⁻⁴.

Here we report a patient with incidentally discovered hepatomegaly who was finally diagnosed as CESD.

Case Report

A two-year-old boy was referred to our clinic for the etiological evaluation of hepatomegaly. He was the second child of nonconsanguineous healthy parents and his brother was also in good health. On physical examination his weight and height were both at the 25th percentile for age. The liver edge was palpable 10 cm below the costal ridge and the spleen was palpable 3 cm below the left costal margin.

Hemoglobin, hematocrit, leukocyte and platelet counts were normal. He had elevated plasma cholesterol and triglycerides (Table I). Except for slightly increased transaminase levels (aspartate transaminase-AST: 56 IU/L, alanine aminotransferase-ALT: 43 IU/L), all other laboratory findings including alkaline phosphatase, γ -glutamyl transferase, total bilirubin, albumin, calcium, and prothrombin time were within normal limits. Serologic tests for hepatitis B and C virus, human immunodeficiency virus (HIV), Epstein Barr virus, cytomegalovirus, herpes simplex virus,

Table I. Transaminases and Plasma Lipid Levels Before and After HMG CoA Reductase Inhibitor Therapy

	Normal range	Before therapy	After HMG CoA reductase inhibitor therapy			
			1 st month	2 nd month	3 rd month	5 th month
AST (IU/L)	0-40	56	54	56	49	49
ALT (IU/L)	0-40	43	43	46	51	43
Cholesterol (mg/dl)	45-182	303	217	233	232	214
Triglycerides (mg/dl)	30-86	277	157	164	162	230
HDL-C (mg/dl)	35-84	44	50	50	46	45
LDL-C (mg/dl)	60-140	203	135	149	154	123

AST : Aspartate transaminase.

ALT : Alanine aminotransferase.

HDL : High-density lipoprotein.

LDL : Low-density lipoprotein.

HMG CoA: 3-hydroxy 3-methyl glutaryl CoA.

and rubella were negative. Serum α -1 antitrypsin and ceruloplasmin levels were within normal limits. Abdominal ultrasonography showed hepatosplenomegaly with normal parenchymal echogenicity and no adrenal calcifications.

Percutaneous liver biopsy was performed. The liver biopsy sample was orange-yellow in appearance. Microscopically in the parenchyma, hepatocytes showed widespread microvesicular steatosis and areas of rare focal necrosis, and in some portal tracts mild dilatation with minimal mononuclear cellular infiltration was seen (Fig. 1). Under polarized light microscope, multiple cytoplasmic spindle-shaped small aggregates showing birefringence, concordant with cholesterol crystals, were seen. Periodic acid-Schiff stain revealed no glycogen storage in hepatocytes.

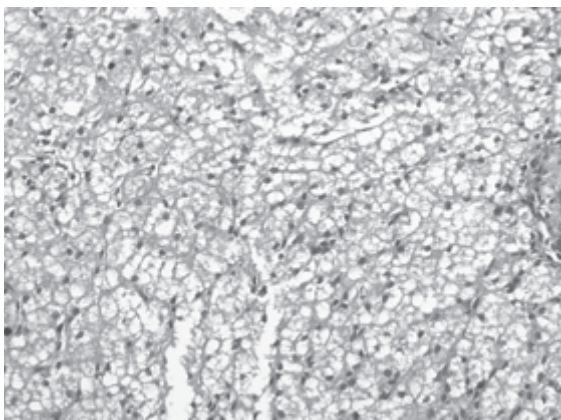


Fig. 1. Diffuse steatosis and hydropic degeneration (H&E X 100).

The diagnosis of CESD was suspected based on orange-yellow biopsy samples and birefringent crystals in liver tissue. For the confirmation of diagnosis, human acid lipase activity in peripheral leukocytes was measured in Royal Manchester Children's Hospital, England. Enzyme activity was assayed as 37 U/mol/g.h (N:350-2000).

Discussion

Cholesteryl ester storage disease is a rare disease, inherited as an autosomal recessive trait. The gene has been localized to chromosome 10q22.2-22.3, and over 20 mutations have been described (Human Gene Mutation Database). Some available data suggests a genotype-phenotype correlation for CESD⁵.

The marked deficiency in LAL activity results in the massive accumulation of cholesteryl esters and triglycerides especially in the liver, but also in the spleen, adrenal glands, lymph nodes, intestinal mucosa, vascular endothelium, and muscle¹. Although CESD is not a frequent cause of hepatomegaly, it is usually presented with hepatomegaly, hyperlipidemia or elevated transaminase levels in routine controls or found coincidentally during examination for other health problems^{1,4,7-9,14,15}. CESD may be easily confused with glycogen storage disease. In both disorders, marked hepatomegaly and hyperlipidemia may appear, but differential diagnosis can be made by laboratory tests (i.e. hypoglycemia and lactic acidosis in glycogen storage disease), liver biopsy and enzymatic analyses^{1,8}. Other clinical features of CESD include splenomegaly,

adrenal calcifications, premature atherosclerosis, diarrhea, steatorrhea, failure to thrive, and neurologic disturbances^{1-3,8,13}. Our case had only hepatosplenomegaly, determined incidentally; the rest of the physical examination was normal.

Most of the patients with CESD have slightly increased transaminases, high cholesterol and low-density lipoprotein (LDL), reduced high-density lipoprotein (HDL), and variable triglyceride levels^{1,6}. Abdominal ultrasonography can show increased echogenicity of the hepatic parenchyma, hepatosplenomegaly, and rarely adrenal calcification⁷. Our case had hypercholesterolemia and hypertriglyceridemia with slightly increased transaminases and LDL cholesterol levels. Also, ultrasonographic examination showed hepatosplenomegaly.

Although microscopic examination of liver biopsy is suggestive of the disease, it is very difficult to differentiate CESD and Wolman disease even with electron microscopic examination. Liver histology usually reveals enlarged and vacuolated hepatocytes and Kupffer cells as well as large numbers of foamy histiocytes. Periportal fibrosis and rarely cirrhosis may also be seen⁸. Vacuolation of hepatocytes as seen in our patient can also be observed in Niemann-Pick disease type B, mucopolysaccharidoses, and GM1 gangliosidosis by light microscopy. These disorders can be easily distinguished from CESD by clinical findings and enzyme assays. Heat-sensitive birefringent crystals in liver tissue are not observed in other lysosomal disorders. These are highly sensitive for CESD in frozen section¹. Foamy cells may also be seen in bone marrow, spleen, adrenal glands, lymph nodes, and small intestine⁹. The diagnosis of CESD is based on clinical picture, biochemical abnormalities and liver biopsy findings. The confirmation is made by demonstration of acid lipase deficiency in liver, cultured skin fibroblasts or peripheral mononuclear leukocytes.

Specific treatment for CESD has not yet been determined. In addition to the supportive therapies with low-cholesterol diet, fat soluble vitamin supplements, and cholestyramine, 3-hydroxy 3-methyl glutaryl (HMG) CoA reductase inhibitors have been reported to be efficacious and well tolerated¹⁰⁻¹⁴. Liver transplantation is a choice of treatment for progressive liver disease¹⁵⁻¹⁷. Enzyme replacement and gene therapy might be possible in the future.

Simvastatin, an HMG CoA reductase inhibitor available in our country, was given to our patient. It was taken orally at a dose of 10 mg per day (0.65 mg/kg) for five months and was well tolerated without side effects. Plasma lipids were minimally reduced with this therapy (Table I). Our patient is the youngest reported CESD patient in the literature treated with HMG CoA reductase inhibitor. Long-term follow-up is needed to observe the possible side effects due to medication and also progression of the disease.

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