JAOA
CASE REPORT

Lecithin-cholesterol acyltransferase deficiency: First report of case in a United States citizen

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Lecithin-cholesterol acyltransferase is responsible for the formation of most cholesteryl esters in plasma. Absence of this enzyme can result in a rare syndrome that includes diffuse corneal opacities, normocytic normochromic anemia, proteinuria, renal failure, and premature arteriosclerosis. The deficiency can be inherited in an autosomal recessive manner, or it can be acquired through liver disease. Diagnosis requires a high index of suspicion and documentation of impairment of enzyme mass or activity (or both). This article includes a case report of the first United States citizen known to have lecithin-cholesterol acyltransferase deficiency. The authors review the literature related to this disease.

(Key words: Lecithin-cholesterol acyltransferase deficiency, cholesteryl esters, corneal opacities, lipoprotein metabolism, proteinuria, arteriosclerosis, renal failure, anemia, inherited metabolic disease)

We herein report the first case of a United States citizen with lecithin-cholesterol acyltransferase (LCAT) deficiency. In all, 26 families with a total of 50 affected members have been reported.[1] The deficiency was first described as a rare inherited disorder by Gjone and Norum[2] in 1968. Gjone[1] recognized the paucity of US citizens with this disorder. There have been no complete case discussions reviewed in the literature since that study. Albers and associates[3] refer to an American possibly having low LCAT mass and activity, but, to our knowledge, that case was not formally described.

Lecithin-cholesterol acyltransferase is responsible for the formation of most cholestryl esters in plasma. Lecithin-cholesterol acyltransferase deficiency is inherited as an autosomal recessive trait.[4] The disease is characterized clinically by diffuse corneal opacities, normocytic normochromic anemia with target cells, proteinuria, renal failure caused by lipid deposits in the kidneys, and premature arteriosclerosis.[1]

Report of case

A 24-year-old man born in Flint, Mich, of unrelated parents, and with no evidence of inbreeding through his family tree over four generations, was seen at Flint Osteopathic Hospital in January 1989. His maternal grandparents had both died of myocardial infarctions late in life, and his paternal grandparents had lived to their mid-60s and died of causes unknown. The patient's father, now in his early 50s, is of French Canadian/Hungarian descent and has a history of hypertension. The patient's mother, also in her early 50s, is of Irish descent and has a history of adult onset, insulin-dependent diabetes mellitus and hypertension. The patient has two siblings: one brother with obesity and hypertension and another brother with kidney disease. Both are in their late 20s.

In 1982, at age 16, the patient was seen by a nephrologist for a workup of proteinuria (2+). His medical history was significant only for jaundice at birth and exercise-induced asthma. The surgical history included a rhinoplasty secondary to fracture and a tonsillectomy and adenoidectomy. The patient had no known allergies. As a high school student, he smoked two packs of cigarettes per day and occasionally drank alcohol. There was no history of intravenous drug abuse or blood transfusions.

The original workup for proteinuria had revealed

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urine total protein of 1025 mg/24 h and a urine volume of 500 mL. Urinalysis revealed occult blood (3+) with few hyaline casts. The patient was found to be anemic, and a hematology consultation was sought. A peripheral blood smear revealed the following: a white blood cell count of 4700/mm^3; a red blood cell count of 3870/mm^3; hemoglobin, 12.7 g/dL; hematocrit, 36.2%; mean corpuscular volume, 94 μm^3; mean corpuscular hemoglobin, 33.0 pg; mean corpuscular hemoglobin concentration, 35.2 g/dL; platelet count, 2400/mm^3; erythrocyte sedimentation rate, 6 mm/h; and reticulocytes, 1.4%. Stomatocytes were present in the peripheral blood smear suggesting hereditary stomatocytosis as a cause of hemolytic anemia.

The lactate dehydrogenase level was 242 U/mL; total bilirubin, 2.8 mg/dL; and serum heptoglobin was depressed at 242 mg/dL. A liver-spleen scan revealed the spleen size to be in the upper limits of normal. A nephrotomogram and a renal scan and flow study showed no abnormality, as did an ultrasound examination of the kidneys. A kidney biopsy performed in 1982 was interpreted as showing mesangium capillary nephritis type II. The patient was referred to an ophthalmologist after a routine eye evaluation revealed abnormalities. The patient was noted to have what appeared to be arcus senilis and corneal dystrophy at that time.

The patient was referred to our clinic in 1989 for evaluation of his hypercholesterolemia and hypertension. A review of his history, physical findings, and laboratory values led to the speculation that the problem was LCAT deficiency/disorder. Laboratory studies at that time revealed the following values: total lipids, 1400 mg/dL; α-lipids (high-density lipoprotein), 2.8%; pre-β lipids (very-low-density lipoprotein), 46.9%; chylomicrons, 50.3%; total cholesterol, 381 mg/dL; high-density-lipoprotein cholesterol, 16 mg/dL; low-density-lipoprotein cholesterol, 244 mg/dL; very-low-density-lipoprotein cholesterol, 121 mg/dL; triglycerides, 606 mg/dL; cholesteryl esters, 21%; indirect bilirubin, 1.3 mg/dL; total bilirubin, 1.4 mg/dL; creatinine, 1.3 mg/dL; blood urea nitrogen, 12 mg/dL; hemoglobin, 13.4 g/dL; and urinalysis, 2+ protein.

Blood samples were drawn and transported the next day to a Seattle research laboratory. That laboratory reported the LCAT mass to be 0.36 μg/mL (low, 5.8 μg/mL) and LCAT activity to be null.

Discussion

Lecithin-cholesterol acyltransferase is responsible for catalyzing the transfer of a fatty acid from the 2-position of lecithin to the 3–hydroxyl group of cholesterol to form cholesteryl ester.[5] This process is simplified in the *Figure*.[6] The enzyme is secreted by the liver into the plasma, where it plays a crucial role in lipoprotein metabolism. The enzyme has a molecular weight of approximately 68,000, of which 24% is accounted for by carbohydrates. This enzyme is encoded by a gene located on chromosome 16 (16q21 to q22).[7]

Deficiencies of this enzyme can be inherited in

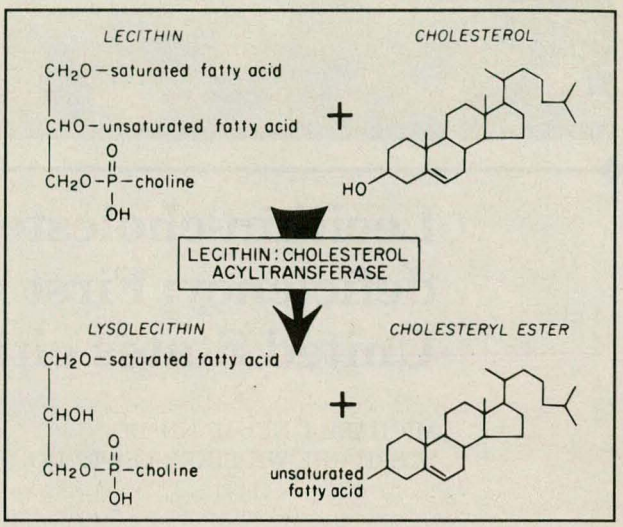

Figure. *Principal lipid reactants in the plasma lecithin-cholesterol acyltranferase reaction. (Reprinted with permission from Glomset J, Norum K, Gjone E: Familial lecithin-cholesterol acyltransferase deficiency, in Stanbury J, Wyngaarden J, Fredrickson D, et al [eds]:* The Metabolic Basis of Inherited Disease, *©1983, McGraw-Hill, Inc, p 644.)*

an autosomal recessive manner[4,7] with the obligate heterozygotes having normal levels of serum lipoproteins and no clinical features, but half the normal levels of circulating enzyme. The inherited disorder may be reflected by the complete absence of enzyme mass and activity, or by the presence of partially inactive or functionally defective enzyme.[3] The case reported here was characterized by low enzyme mass and null activity. Lecithin-cholesterol acyltransferase deficiencies can also be acquired through liver disease or obstructive jaundice.[8]

The ocular manifestations have been described in depth by Gjone.[1] On gross inspection, the cornea can have a cloudy or hazy appearance. This can be evident in early childhood in LCAT-deficient patients. Slit lamp examination reveals innumerable, evenly distributed, minute, grayish dots localized to the parenchyma. The dots can increase near the limbus to form a grayish ring that resembles arcus senilis. Although these dots are presumed to be fat deposits, routine conventional stains and frozen section stains for lipids have produced negative results.

Renal involvement in LCAT deficiency is inevitable and is the major cause of death; death usually occurs in the fourth or fifth decade.[1] Proteinuria is a classic manifestation of renal involvement. When disease is present, typical biopsy reports refer to the presence of foam cells in the glomerular tuft lumens, glomerular capsular thickening, and lipid deposition in the glomerular basement membrane and mesangial regions, but an absence of foam cells in the glomeruli.[9] Several

patients with LCAT-induced renal failure had kidney transplants, but this procedure did not change LCAT levels in serum, and lipoprotein abnormalities did not reverse.

Mild anemia is another manifestation of this disease and is secondary to a hemolytic process with reduced compensatory erythropoiesis. Target cells result from increased amounts of cholesterol and lecithin within red blood cell membranes and this, in turn, results in increased mechanical fragility, increased sensitivity to membrane lipid peroxidation, and reduced osmotic fragility.[10] Frolich and coworkers[11] suggest that the anemia and renal disease are causally related and are not the direct result of each other.

Diagnosis of LCAT deficiency requires a high index of suspicion, as demonstrated by the delayed confirmation in the patient described here. The diagnosis should be suggested by findings of corneal opacities, arcus senilis, target cells in peripheral serum, proteinuria, and a reduction in esterified cholesterol. Criteria for the diagnosis include one of the following: the complete absence of enzyme mass and activity, a low level of enzyme mass and activity, and the presence of partially inactive or functionally defective enzymes as discussed earlier.[3]

No singular approach to the management of LCAT-deficient patients has been established. One goal of treatment is to decrease the cholesterol and abnormal lipoproteins in the patient's serum. Dietary treatment aimed at lowering dietary fat may benefit some patients. Strict dietary guidelines and counseling must be instituted and cholesterol-lowering agents, such as cholestyramine, may be useful in limiting damage to vital organs.

A potential treatment modality involves replacement of the deficient enzyme. Highly purified LCAT enzymes have been prepared from outdated human plasma,[12] and LCAT cDNA clones have been isolated.[13] This technique may one day permit mass enzyme replacement. Until such time as better treatment is developed, other palliative options, such as dialysis, must be used. As our understanding of the disease increases, perhaps many of the mysteries of lipid control, and therefore of atherosclerosis, may be discovered.

Comment

Lecithin-cholesterol acyltransferase deficiency is responsible for a rare syndrome manifested by diffuse corneal opacities, normocytic normochromic anemia, proteinuria, renal failure, and premature arteriosclerosis. Lecithin-cholesterol acyltransferase is an important enzyme that forms cholesteryl esters from cholesterol. The deficiency can be inherited in an autosomal recessive manner, or it can be acquired secondary to liver disease. The diagnosis of this disorder requires a high index of suspicion through familiarity with symptoms and by documenting impairment of enzyme mass or activity (or both). Presently, strict dietary guidelines and lipid-lowering agents are the mainstay of therapy. In the future, exogenous forms of LCAT replacement may be a therapeutic option.

Syndromes involving LCAT deficiency may be rare, but they may also be underidentified. Perhaps by better understanding LCAT disorders, we will gain valuable insight into the mechanisms of arteriosclerosis and other lipid disorders.

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