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Case Study

A kindred with fish eye disease, corneal opacities, marked high-density lipoprotein deficiency, and statin therapy

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HDL Map;
Cholesterol esterification

Abstract: A kindred affected with fish eye disease (FED) from Oklahoma is reported. Two probands with corneal opacification had mean levels of high-density lipoprotein (HDL) cholesterol (C), apolipoprotein (apo) A-I, and apoA-I in very large alpha-1 HDL particles that were 9%, 17%, and 5% of normal, whereas their parents and 1 sibling had values that were 61%, 77%, and 72% of normal. The probands had no detectable lipoprotein-X, and had mean low-density lipoprotein cholesterol (LDL-C) and triglyceride levels that were elevated. Their mean lecithin cholesterol acyltransferase (LCAT) activities, cholesterol esterification rates, and free cholesterol levels were 8%, 42%, and 258% of normal, whereas their parents and 1 sibling had values that were 55%, 49%, and 114% of normal. The defect was due to 1 common variant in the LCAT gene in exon 1: c101t causing a proline34leucine substitution and a novel mutation c1177t causing a threonine37methionine substitution, with the former variant being found in the father and 1 sibling, and the latter mutation being found in the mother, and both mutations being present in the 2 probands. FED is distinguished from familial LCAT deficiency (FLD) by the lack of anemia, splenomegaly, and renal insufficiency as well as normal or increased LDL-C. Both FLD and FED cases have marked HDL deficiency and corneal opacification, and FED cases may have premature coronary heart disease in contrast to FLD cases. Therapy, using presently available agents, in FED should be to optimize LDL-C levels, and 1 proband responded well to statin therapy. The investigational use of human recombinant LCAT as an enzyme source is ongoing.

In the absence of liver disease or marked hypertriglyceridemia, marked high-density lipoprotein cholesterol (HDL-C) deficiency (<10 mg/dL) is observed in patients with homozygous apolipoprotein (apo) A-I deficiency, Tangier disease, familial lecithin cholesteryl acyl transferase (LCAT) deficiency, and fish eye disease (FED). These cases can readily be distinguished by the measurement of plasma or serum apoA-I levels and the determination of apoA-I in individual HDL particles by immunoblotting following 2-dimensional gel electrophoresis.[1,2] Patients with apoA-I deficiency have defects in the apoA-I gene, undetectable plasma apoA-I, normal low-density lipoprotein cholesterol (LDL-C), may have tuboeruptive xanthomas, and have strikingly premature

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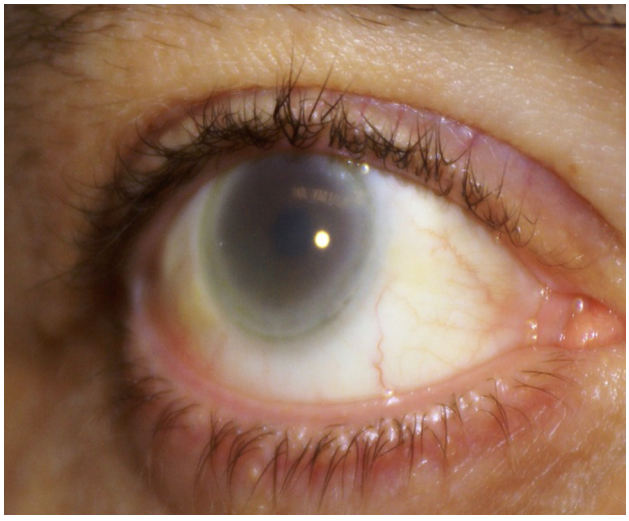

Figure 1 Photograph of the marked diffuse corneal opacification in a patient with homozygous LCAT deficiency (previously published[7]).

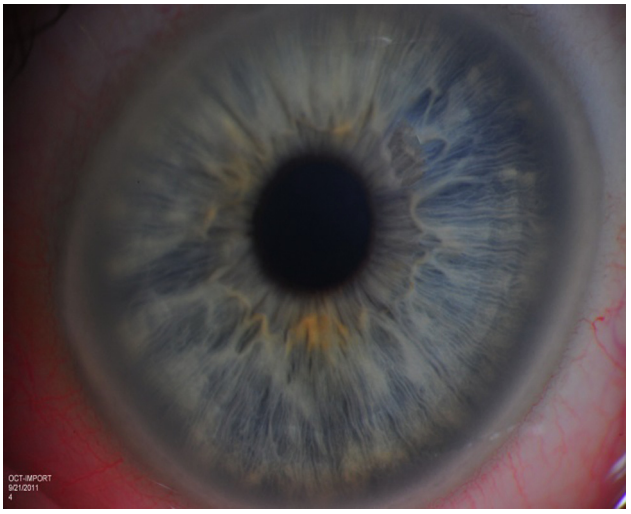

Figure 2 Photographs of eye findings in the index case for this kindred with fish eye disease. In contrast to the diffuse corneal opacification seen with lecithin cholesterol acyltransferase deficiency in Figure 1, in this case we see mainly peripheral lipid deposition.

coronary heart disease (CHD). Patients with Tangier disease have defects in the ATP-binding cassette transporter A1 (ABCA1) gene, and usually have hepatosplenomegaly, mild corneal opacification, orange mucosa and tonsils, peripheral neuropathy, premature CHD, mild hypertriglyceridemia, low LDL-C levels, and only pre-beta-1 HDL particles.[1] Patients with familial LCAT deficiency (FLD) have defects in the LCAT gene, marked corneal opacification (Fig. 1), splenomegaly, anemia, often kidney failure, hypertriglyceridemia, abnormal and low LDL, and the presence of both pre-beta-1 and alpha-4 HDL particles.[2] Patients with FED, as presented here, have defects in the LCAT gene and marked corneal opacification, and the presence of both pre-beta-1 and alpha-4 HDL particles. However, these patients, in contrast to FLD, do not have splenomegaly, anemia, or kidney failure. Moreover, FED patients have moderately elevated triglyceride and LDL-C levels, and may develop premature CHD.[3–17]

Materials and methods

Report of kindred

A 23-year-old female presented in good health with known marked HDL deficiency. Her HDL cholesterol levels have generally been $<$ 10 mg/dL. She was noted to have corneal haze or opacification by an ophthalmologist (Fig. 2). Her height was 165 cm, her weight was 74.5 kg, her body mass index was 27, and her blood pressure was 120/70 mmHg. Her pulses were normal throughout, and no xanthomas were noted. Examination of her heart, chest, abdomen, and legs was within normal limits. Carotid intima-media thickness test was normal and showed no evidence of plaque formation. A calcium score of the coronary artery carried out using computed tomographic analysis was negative. She had 1 brother, age 26, who also had corneal opacification, was otherwise in good health, and was also noted to have an HDL-C level of $<$ 10 mg/dL. Another brother, age 28, was in good health, had no corneal opacification, and had an HDL-C value of 23 mg/dL. The father, age 62, was in good health, had no corneal opacification, had an HDL-C value of 32 mg/dL, and was on statin therapy. The mother, age 55, also was in good health, had no corneal opacification, and had an HDL-C value of 38 mg/dL.

Laboratory analysis

Samples of blood from the 2 probands off any lipid-altering medication as well as of both her parents and 1 brother drawn after an overnight fast were sent to Boston Heart Diagnostics, Framingham, MA. Results from this laboratory, which maintains lipid standardization with the Centers for Disease Control and apolipoprotein standardization with the Northwest Lipid Research Clinics Research Laboratory, University of Washington, are shown in Table 1. The method used for lipid, lipoprotein cholesterol, apolipoproteins, and HDL particle analysis was by 2-dimensional gel electrophoresis. Direct LDL-C, small dense LDL-C, and sterol analysis was done. The index case had very low levels of HDL cholesterol, with increased levels of LDL cholesterol and small dense LDL cholesterol. Her values are shown in Table 3. Her lipoprotein(a) (Lp(a)) level was 8 mg/dL (optimal and low). She was placed on statin therapy with atorvastatin 80 mg daily and her lipid values in milligrams per deciliter on 2 occasions were: total cholesterol 93 and 88, triglycerides 80 and 86, LDL cholesterol 78 and 62, HDL cholesterol 6 and 4, and apoA-I level of 39 and 43. Therefore statin therapy resulted in marked reductions in total cholesterol, triglycerides, and LDL cholesterol (mean 55% reduction in LDL-C), with little change in HDL cholesterol or apoA-I levels. These levels were measured as previously described.[2] The proband and her father have apoE genetic type of 3/4.