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Case Study

Paradoxical fall in proteinuria during pregnancy in an LCAT-deficient patient—A case report

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Abstract: A 29-year-old lady was diagnosed with lecithin:cholesterol acyltransferase (LCAT) deficiency having presented with bilateral corneal clouding, severely reduced high density lipoproteins cholesterol, and proteinuria. She is a compound heterozygote with two *LCAT* gene mutations, one of which is novel, c.321C>A in exon 3. Surprisingly, the level of proteinuria significantly improved during pregnancy, despite stopping the angiotensin-converting enzyme inhibitor. However, LCAT concentration and activity remained identical during pregnancy and postpartum. Her pregnancy was complicated by rising triglyceride levels from the second trimester requiring treatment with omega-3 fatty acid and fenofibrate. In the last trimester, a further complication arose when she became hypertensive and proteinuria worsened. She was diagnosed with pre-eclampsia and had an emergency cesarean section at 39 weeks delivering a healthy baby. This case adds to the knowledge of the pathophysiology of LCAT deficiency during pregnancy and will be useful in future patient management.

Introduction

Phosphatidylcholine:sterol-O-acyltransferase, more commonly called lecithin:cholesterol acyltransferase (LCAT), is a lipoprotein-associated enzyme designated as enzyme commission number 2.3.1.43.[1] LCAT, a hepatic produced protein, is the only enzyme responsible for cholesterol esterification in plasma and acts within plasma high density lipoproteins (HDL) (alpha activity) and apoB-containing particles (beta activity). LCAT deficiency is an extremely rare autosomal recessive condition with prevalence less than 1:1,000,000 caused by mutations in the *LCAT* gene. The *LCAT* gene is found on Chr 16 q21-22 and is primarily expressed in the liver. It is composed of 6 exons separated by 5 introns and the gene is made of 4.2 kilobase pairs. Over 80 pathogenic mutations have been identified. Two syndromes have been described: familial LCAT deficiency (FLD, OMIM #245900) with complete loss of LCAT activity and fish-eye disease (FED, OMIM #136120) due to loss of alpha LCAT activity.[2] LCAT deficiency results in accumulation of unesterified cholesterol in the cornea, kidneys, spleen, and liver. The clinical features of both FLD and FED include corneal clouding and extremely low HDL-cholesterol (HDL-C). FLD cases may also have proteinuria, renal failure, and

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anemia.[2] The pathogenesis or renal disease in FLD is not completely understood but is likely due to the presence in plasma of large molecular weight low density lipoproteins (LDL) particles[3] and abnormal lipoproteins such as lipoprotein X (LpX).[4] Although there is currently no definitive treatment, recombinant human LCAT is a potential future treatment.[5]

This is the first case report in the literature of the natural history, outcome, and management challenges of LCAT deficiency during pregnancy.

Methods

Case report

A 29-year-old female initially presented with discomfort, photophobia, and decreased vision in both eyes, which had been present for a few months. She was noted to have bilateral corneal clouding, severely reduced HDL cholesterol, and proteinuria (albumin-to-creatinine ratio (ACR) 1006.2 mg/g creatinine). She had a history of childhood asthma for which she used inhalers, psoriasis, and eczema but was otherwise well. Her body mass index was 24 kg/m^2. At the time of diagnosis, she had two children, one of whom had asthma. Of her 7 siblings, none had any history of eye problems but one sister and one brother have since been diagnosed with LCAT deficiency. In both corneas, there was a generalized haze, which appeared to be localized to the stroma. There was also a ring-like condensation in the corneal periphery resembling a corneal arcus. Her visual acuity was 6/6 right eye and 6/18 in the left eye. Central corneal thickness was 477 microns in both eyes.

The corneal findings, severe reduction in HDL-C, and proteinuria were consistent with LCAT deficiency. The spleen size was within the normal reference range for her age.

This lady was treated with a low-fat diet and angiotensin-converting enzyme (ACE) inhibitor. The ramipril was titrated to 5 mg, but she had dizziness limiting further titration. There was a reduction in her albuminuria initially to 322.1 mg/g creatinine 1 month after starting ramipril, but this coincided with an acute infection. The ACR level plateaued at 796.5 to 973.4 mg/g creatinine, while her blood pressure (BP) control remained well controlled at 127/78 mmHg. The ACE inhibitor was stopped when her third pregnancy was confirmed. She did not require any antihypertensives during pregnancy, and her BP remained at prepregnancy levels.

Biochemical analyses

Fasting blood samples were collected, at the different times, into tubes containing Na_2-EDTA and centrifuged at 4°C. Plasma aliquots were immediately frozen and stored at −80°C before shipment in dry ice for analysis. Plasma levels of total and unesterified cholesterol, HDL-C, triglycerides, phospholipids, and creatinine were determined by standard enzymatic techniques. LDL-cholesterol was calculated using Friedewald formula. Apolipoprotein A-I (apoA-I), apoA-II, and apoB levels were determined by immunoturbidimetry, using commercially available polyclonal antibodies. Fresh sample of blood was used for the determination of hemoglobin. Urinary albumin and creatinine were measured by immunoturbidimetric and enzymatic methods, respectively.

Cholesterol esterification in plasma was assessed by calculating the unesterified/total cholesterol ratio.[6] The esterification of cholesterol within endogenous lipoproteins (cholesterol esterification rate) or incorporated into an exogenous standardized substrate (LCAT activity) was determined as previously described.[6] Plasma LCAT concentration was measured by immunoenzymatic assay. Plasma lipoprotein profile was analyzed by fast performance liquid chromatography using a Superose 6 HR 10/30 column (GE Healthcare, UK). Samples of 350 microliter of plasma were applied to the column, 1.2-ml fractions were collected, and lipid levels determined by enzymatic methods.[6]

Results

Laboratory analysis at diagnosis

The biochemical changes at diagnosis and during her pregnancy are reported in Table 1. Laboratory analysis showed a severe reduction in HDL-C <5 mg/dL, creatinine 66 μmol/L, and ACR 1006.2 mg/g creatinine (reference values, <31). At presentation, no evidence of other renal disease such as vasculitis or autoimmune disease was found on laboratory testing. She had normal complement levels C3 1.03 g/L (0.75–1.65), C4 0.25 g/L (0.14–0.54), antinuclear antibodies, anti-GBM antibody, c-ANCA, and p-ANCA; MPO/PR3 antibodies were all <0.2 U/L negative; she had a low IgM 0.4 g/L (0.5–2), normal IgG 8.3 g/L (6–16), and IgA 2.89 g/L (0.8–4); no paraprotein was detected on electrophoresis. No renal biopsy was performed.

The initial lipid results at diagnosis prompted further lipoprotein analysis confirming low HDL-C, apoA-I, and apoA-II levels, normal total and LDL-cholesterol, apoB and triglycerides levels (Table 1). The ratio unesterified to total cholesterol was very high (Table 1), thus suggesting impairment of the esterification system. Molecular analysis confirmed the clinical diagnosis of LCAT deficiency. Two heterozygous mutations of the *LCAT* gene were identified: c.321C>A (p.Tyr107 * exon 3) has not previously been reported, and c.1034C>T (p.Thr345Met exon 6) was previously reported in FED.[7]

Laboratory analysis during pregnancy and postpartum

Plasma lipids and ACR were monitored throughout her pregnancy. Her prepregnancy triglyceride was 128 mg/dL