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Original Article

Immune-mediated acquired lecithin-cholesterol acyltransferase deficiency: A case report and literature review

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BACKGROUND: Recessive inherited disorder lecithin-cholesterol acyltransferase (LCAT) deficiency causes severe hypocholesterolemia and nephrotic syndrome. Characteristic lipoprotein subfractions have been observed in familial LCAT deficiency (FLD) with renal damage.

OBJECTIVE: We described a case of acquired LCAT deficiencies with literature review.

METHODS: The lipoprotein profiles examined by gel permeation–high-performance liquid chromatography (GP-HPLC) and native 2-dimensional electrophoresis before and after prednisolone (PSL) treatment.

RESULTS: Here we describe the case of a 67-year-old man with severely low levels of cholesterol. The serum LCAT activity was undetectable, and autoantibodies against it were detected. The patient developed nephrotic syndrome at the age of 70 years. Renal biopsy revealed not only membranous glomerulonephritis but also lesions similar to those seen in FLD. We initiated PSL treatment, which

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resulted in remission of the nephrotic syndrome. In GP-HPLC analysis, lipoprotein profile was similar to that of FLD although lipoprotein X level was low. Acquired LCAT deficiencies are extremely rare with only 7 known cases including ours. Patients with undetectable LCAT activity levels develop nephrotic syndrome that requires PSL treatment; cases whose LCAT activity levels can be determined may also develop nephrotic syndrome, but spontaneously recover.

CONCLUSION: Lipoprotein X may play a role in the development of renal impairment in individuals with FLD. However, the effect might be less significant in individuals with acquired LCAT deficiency.

Introduction

Lecithin-cholesterol acyltransferase (LCAT) is a key molecule during the synthesis of Cholesteryl ester (CE),[1] and loss of its activity causes severely low high-density lipoprotein cholesterol (HDL-C) levels. Two rare syndromes are caused by the recessive inherited mutations of the LCAT gene: familial LCAT deficiency (FLD) and fish eye disease (FED). Although both diseases have defects in LCAT enzyme activity on HDL particles, FLD is known to lead to renal failure,[2] whereas FED does not.

In this report, we describe a case of immune-mediated acquired LCAT deficiency with nephrotic syndrome who showed similar lipid profile with FLD with renal damage.[3] Immune-mediated acquired LCAT deficiency is extremely rare, we only know of 6 reports other than this one in the literature.[4–9] Moreover, this is the first report of this kind containing the analyses of lipoprotein subfractions before and after treatment. We also reviewed the available literature to expose the characteristic of acquired LCAT deficiency with and without nephrotic syndrome.

Materials and methods

Informed consent

Patient provided written informed consent.

Measuring anti-LCAT activity

Serum LCAT activity was measured using an exogenous substrate method (Anasorb LCAT; Sekisui Medical, Tokyo, Japan), according to the manufacturer's protocol.

Mixing test

Sera obtained from the patient before prednisolone (PSL) treatment and a healthy control were mixed at several ratios (10:0, 8:2, 5:5, 2:8, and 0:10) and incubated at 37°C for 1 hour. LCAT activities were subsequently measured.

Immunoprecipitation

To separate immunoglobulin G (IgG) fragments from serum, 1 mL serum from a healthy control or the patient before and after PSL treatment was incubated with protein G-sepharose beads (Protein G Sepharose 4 Fast Flow; GE Healthcare) at 4°C for 2 hours. The beads were subsequently centrifuged at 15,000 × *g* for 10 seconds, washed using ice-cold phosphate buffer solution (PBS) several times, mixed with 1 ml serum obtained from another healthy control, and incubated for overnight at 4°C. The beads were washed with ice-cold PBS several times, boiled in Laemmli sample buffer at 95°C for 5 minutes, and centrifuged. They were then separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidenedifluoride membranes (Immobilon-P; Millipore). The membranes were blocked in phosphate buffer solution-tween (PBS-T) containing 5% nonfat dry milk at room temperature for 1 hour, and incubated with anti-LCAT antibodies (EPR1384Y; Epitomics; 1:10,000) at room temperature for 1 hour. After incubation with HRP-linked anti-rabbit IgG (GE Healthcare; 1:2000) at room temperature for 1 hour, the signals were visualized using an enhanced chemiluminescence western blotting detection system (GE Healthcare). Images were captured using ChemiDoc MP Imaging System (Bio-Rad).

Lipoprotein fraction analysis

Lipoprotein fraction (Fr.) analysis was performed using the patient's serum isolated before and after PSL treatment via gel permeation–high-performance liquid chromatography (GP-HPLC).[10]

Native 2-dimensional electrophoresis

Patient plasma samples obtained before and after PSL treatment were separated using native 2-dimensional (2D) gel electrophoresis (1st dimension, 0.75% agarose gel; 2nd dimension, 2%–15% polyacrylamide gradient gel) was performed as previously described.[11,12] Immunoblotting was performed using anti-Apolipoprotein (Apo) A-I antibodies (PC085; the binding site; 1:20,000). After incubation with HRP-linked anti-sheep IgG (Invitrogen; 1:100,000), images were Quant Las 4000 (GE Healthcare). Then, we stripped off the antibodies bound to the membranes, and reblotted the same membranes using anti-ApoE antibodies (AB947; Millipore; 1:20,000) and anti-goat IgG (Invitrogen; 1:100,000). The distribution of ApoE was determined by the method described previously.