

Original Article

Advanced membranous nephropathy-like lesion in a Chinese patient with familial lecithin-cholesterol acyltransferase deficiency

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Abstract: Familial lecithin cholesterol acyltransferase (LCAT) deficiency is a rare autosomal recessive disorder, and often present with corneal opacities, anemia, low high-density lipoprotein (HDL) and renal involvement with varying degrees of proteinuria and progressive renal insufficiency in some cases. However, characteristics of renal lesions of LCAT deficiency are seldom described. Here, we reported a 40-year-old woman with a two-month history of proteinuria and hematuria. She also had mild anemia, remarked low HDL and corneal greyish opacities. Laboratory test showed absent activity of LCAT and genetic analysis showed a homozygous pathogenic mutation (c. 491G>A, p.164A>H) in LCAT gene. Renal biopsy revealed irregular glomerular basement membrane (GBM) thickening and vacuolization with mesangial expansion. Immunofluorescence findings are only positive for IgM. Electron microscopy showed diffuse vacuoles with a lucent appearance in the mesangial matrix and the GBM, which induced irregular thickening of the GBM, and some vacuoles contained osmiophilic lamellar structures. It was a typical feature of renal disease associated with familial LCAT deficiency. After maintaining a low-fat diet and receiving lipid-lowering agents, erythropoietin (EPO) and angiotensin receptor blockers (ARB), the patient's HDL levels remained low with mild proteinuria and normal renal function during 24 months of follow-up.

Keywords: Lecithin-cholesterol acyltransferase deficiency, fish-eye disease, FLD, HDL, membranous nephropathy, renal biopsy

Introduction

Lecithin-cholesterol acyltransferase (LCAT) is a key enzyme for the esterification of cholesterol in circulating plasma lipoproteins that promotes the maturation of discoidal pre-high-density lipoprotein cholesterol (HDL-c) to spherical mature HDL particles. LCAT deficiency (OMIM, #245900) is a rare autosomal recessive disorder of lipoprotein metabolism and causes a typical triad of diffuse corneal opacities, anemia and renal lesion. It is caused by mutation in LCAT gene and resulted from loss of LCAT activity. Although kidney involvement characterized by proteinuria with progressive renal dysfunction is often reported in LCAT deficiency, only a few study demonstrated the feature of renal lesions associated with such diseases. We report a case with biopsy-proven renal damage, which is caused by hereditary deficiency of LCAT.

Case report

Clinical history and initial laboratory data

A 40-year-old Chinese woman was admitted with a two-month history of 3+ proteinuria and + hematuria with decreased serum albumin (33.3 g/L), hemoglobin (92 g/L) and normal blood pressure. Corneal opacities gave her eyes the appearance of those of boiled fish (**Figure 1A**), and mild splenomegaly were observed. The remainder of physical examination was normal. Her parents were first cousins and **Figure 1B** is a pedigree of her family. Her older brother had corneal greyish opacities, and one older sister had impaired vision both with normal urinalysis and renal function which was not available in the remaining family members.

The main laboratory findings at renal biopsy time was list as follow: hemoglobin 91 g/dL;

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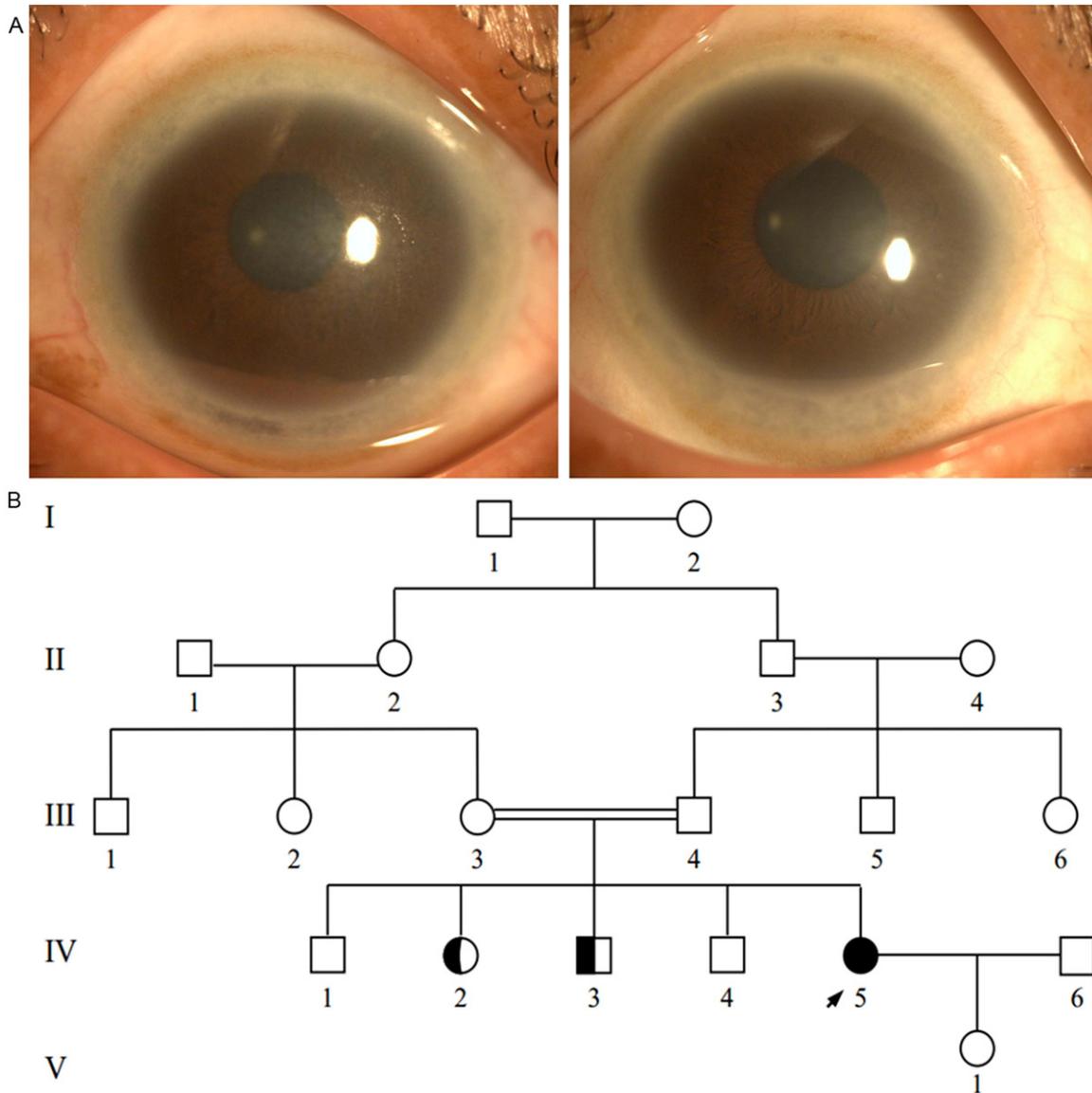


Figure 1. A. Corneal greyish opacities resembling a fish eye were observed by slit-lamp examination. B. Pedigree of the family investigated. The arrow shows the proband. Her father and mother were first cousins. Her older brother had corneal greyish opacities, and one older sister had impaired vision with normal urinalysis and renal function. Urinalyses of the rest of the family members were not available.

creatinine 0.69 mg/dL; albumin 40.7 g/L; total cholesterol 2.22 mmol/L (normal: 3-6); triglycerides 3.64 mmol/L (normal: 0.28-2.2); HDL-c 0.16 mmol/L (normal: 1.0-1.8); low-density lipoprotein cholesterol (LDL-c) 0.35 mmol/L (normal: 1.5-3.12); apolipoprotein (Apo) AI 0.39 g/L (normal: 10-16); apo-B 0.53 g/L (normal: 6-10); apo-E 7.02 mg/dL (normal: 3-5); and lipoprotein (a) 9.00 mg/L; proteinuria 0.69 g/24 h (normal: 0-300). Coomb's test and autoantibodies were negative. Serum complement levels were within normal ranges.

Kidney biopsy

The patient's kidney biopsy revealed 29 glomeruli and 5 global scleroses. The remaining glomeruli exhibited mild mesangial widening with glomerular basement membrane (GBM) thickening and vacuolization, resemble those seen in advanced membranous nephropathy (MN) (**Figure 2A, 2B**). Toluidine blue-stained semithin sections showed dark blue structures in the mesangial area and GBM (**Figure 2C**). There were no foam cells in the glomeruli. Focal

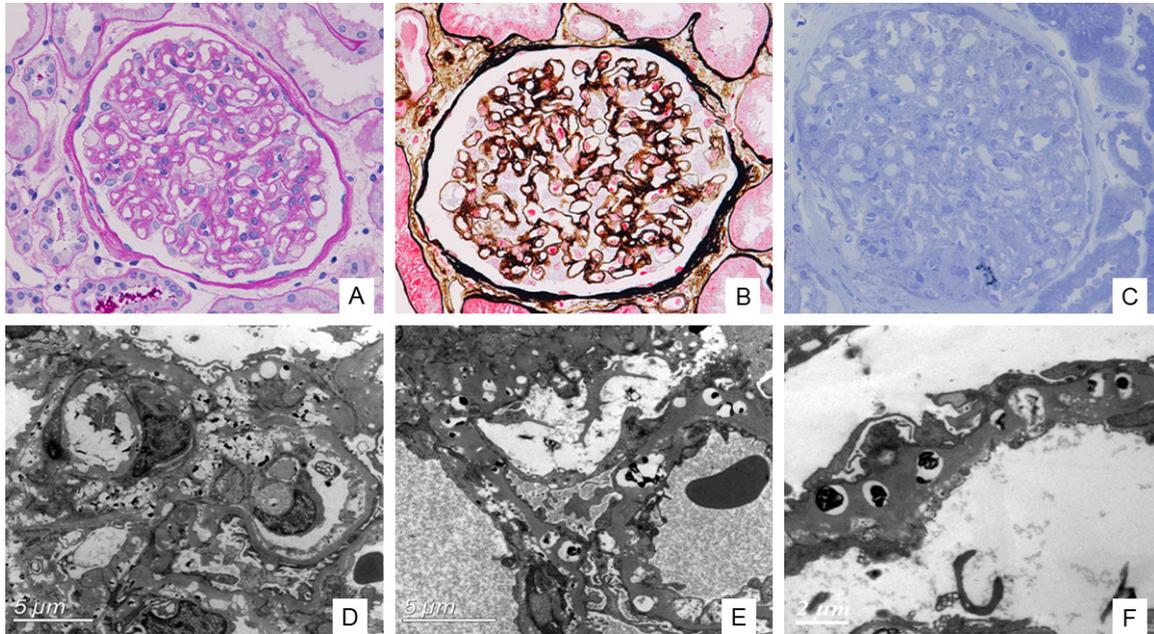


Figure 2. Histological findings. A. Mild mesangial widening with GBM vacuolization (PAS, original magnification, $\times 400$). B. Thickening and vacuolization of the GBM, similar to that seen in MN (PASM, original magnification, $\times 400$). C. Toluidine blue-stained semithin sections show dark blue structures in the mesangial area and GBM (Toluidine blue stain, original magnification, $\times 400$). D, E. Vacuoles with a lucent appearance in the mesangial matrix and the GBM (EM). F. Some vacuoles contained osmiophilic lamellar structures (EM).

interstitial fibrosis with proportional tubular atrophy was observed. There was a mild intimal fibrosis of interlobular arteries and focal mild arteriolar hyalinosis. Immunofluorescence showed granular IgM (+) deposition in the mesangial area and along the capillary loops. IgG, IgA, C3, and C1q stains were negative. Electron microscopy (EM) examination showed diffuse vacuoles with a lucent appearance in the mesangial matrix and the GBM, which led to irregular GBM thickening (**Figure 2D, 2E**). Some vacuoles contained osmiophilic lamellar structures (**Figure 2F**). There was focal and segmental endothelial cell detachment from the GBM due to the widening of the subendothelial region.

Detection of LCAT activity and mutation

LCAT activity was barely detectable in this patient compared with 20 normal volunteers according to the LCAT Activity Fluorometric Assay Kit (EMD Bioscience, San Diego, CA, USA). Further DNA sequences of all exons and exon-intron join regions of LCAT gene revealed a homozygous missense mutation (c. 491G>A) in exon 4, which resulted in an amino acid change at codon 164 from arginine to histidine.

Diagnosis

Familial LCAT deficiency (FLD) was finally confirmed in this patient based on the combination of clinical features, HDL-c concentration, LCAT activity, LCAT gene detection and renal biopsy.

Treatment and clinical follow-up

After maintained a low-fat diet and given lipid-lowering agents, erythropoietin (EPO) and angiotensin receptor blockers (ARB), the patient's HDL levels remained extremely low with mild proteinuria and normal renal function during 24 months of follow-up (**Table 1**).

Discussion

This patient presented with minor proteinuria, hematuria, normal blood pressure and renal function. Renal biopsy showed vacuolization of the GBM, which resembled advanced MN. Routine immunofluorescence staining was negative, except IgM. EM examination revealed diffuse vacuoles with a lucent appearance in the mesangial matrix and GBM without electron-dense deposits. Thus, a diagnosis of MN was not supported. Some vacuoles also contained osmiophilic lamellar structures, which highly

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Table 1. The follow-up of this proband

TIME (M)	N	-0.5	Biopsy	1	2	5	7	10	12	15	19	24
Urbc (*10 ³ /ml)	≤100	720	200	160	80	140	220	20	20	10	10	40
Upro (g/24 h)	≤0.4	0.86	0.86	0.49	0.83	0.44	0.43	0.55	0.47	0.31	0.26	0.55
Alb (g/L)	35-55	51.6	40.7	45.7	43.7	47.5	47.3	44.8	50.3	47.5	45.2	
SCr (mg/dl)	0.35-1.24	0.79	0.69	0.81	0.68	0.70	0.63	0.70	0.75	0.65	0.71	0.67
TC (mmol/l)	3-6	2.43	2.22	2.58	2.50	1.91	1.73	1.80	2.58	2.08	1.95	2.75
TG (mmol/l)	0.28-2.2	2.40	3.64	2.88	3.11	1.53	1.98	2.50	2.26	1.39	1.73	2.71
Hb (g/l)	110-150	107	91		97	90	100			95	92	
HDL-c (mmol/l)	1-1.8		0.16				0.25		0.18		0.24	0.28
LDL-c (mmol/l)	1.5-3.2		0.35				0.37		0.46		0.32	0.57
Apo-E (mg/dl)	3-5		7.02						9.20		5.07	5.53
Apo-AI (g/l)	1-1.6		0.39				0.45		0.44		0.37	0.41
Apo-B (g/l)	0.6-1.00		0.53				0.47		0.46		0.53	0.57
Lp (a) (mg/l)	0-300		9.00				13.00		9.20		41	19

M: months; N: normal range; Urbc: Hematuria; Upro: Proteinuria; Alb: Albumin; SCr: Serum creatinine; TC: Total cholesterol; TG: Triglycerides; Hb: Hemoglobin; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; Apo-E: Apolipoprotein E; Apo-AI: Apolipoprotein AI; Apo-B: Apolipoprotein B; Lp (a): Lipoprotein (a).

suggested that the lesions were related to the deposition of lipids. The significantly decreased HDL level, the presence of corneal greyish opacities, led us to the diagnosis of a lipid metabolism disorder with renal disease. The extremely low LCAT activity and identification of mutations in the LCAT gene confirmed that renal disease in this patient was caused by familial LCAT deficiency with a scattered incidence worldwide [1-3]. It is the first reported renal biopsy-proven case in a Chinese patient.

LCAT is a 63-kDa glycoprotein that is synthesized in the liver and released into circulation. LCAT possesses both α -LCAT activity and β -LCAT activity. Alpha-LCAT activity catalyzes cholesterol in HDL particles and requires apo-AI and apo-AIV as cofactors. Beta-LCAT mainly catalyzes the cholesterol in LDL or very low-density lipoprotein (VLDL) without the help of any cofactor [4]. LCAT catalyzes the transacylation of the sn-2 fatty acid of lecithin to the free 3 β -OH group of cholesterol to form lysolecithin and a cholesteryl ester. This process promotes the transformation of discoid premature HDL3 to spherical mature HDL2. LCAT also participates in reverse cholesterol transport. Therefore, LCAT is essential for the maturation of HDL and the maintenance of HDL levels in the plasma.

LCAT deficiency is divided into two forms: familial LCAT deficiency (FLD) and fish-eye disease

(FED) [4]. FLD presents absent or diminished α -LCAT and β -LCAT activity, which causes an increase in non-esterified cholesterol. The symptoms and signs of FLD primarily include corneal opacity, normochromic hemolytic anemia and renal lesion. The loss of α -LCAT activity leads to FED, which exhibits normal or mildly increased non-esterified cholesterol.

FLD patients only show mild abnormal laboratory tests in early childhood, including a decreased HDL level and increases in non-esterified cholesterol and triglyceride levels [5]. Corneal opacity first appears during childhood, anemia and renal insufficiency progress with age, especially during adulthood. Proteinuria often occurred in their third or fourth decades of life [3] or sooner [6], which progresses to end-stage renal disease (ESRD) in the fourth to fifth decades. Renal failure is the leading cause of death in FLD patients. Most LCAT deficiency were caused by mutations in the LCAT exons, but some were due to intron mutation [7] or abnormal translation or post-translation [8]. Notably, the same genetic mutation among relatives may present with different clinical manifestations [1], and multiple factors may contribute to the renal lesions. For instance, lipoprotein-X (Lp-X) plays a major role in renal lesions; this lipoprotein contains a high content of phospholipids and non-esterified cholesterol but a low content of protein cholesterol esters and triglycerides. The serum level of Lp-X in FLD

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Table 2. The differentiation of renal involvement in the hereditary disorder of lipid metabolism

	Fabry's disease	Gaucher disease	Niemann-Pick disease	Type III hyperlipoproteinemia	LCAT deficiency
Deficient enzyme	α-galactosidase A	β-glucocerebrosidase	Sphingomyelinase	Apo E3	LCAT
Stored material	Glycosphingolipids	Glucocerebroside	Sphingomyelin	Chylomicron remnants and IDL	Unesterified cholesterol
Hereditary form	X-linked	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Clinical manifestation	Angiokeratoma, acroparesthesia, hypohidrosis, proteinuria	Hepatosplenomegaly, severe neurologic complications, bruising, fatigue, anemia, low blood platelets,	Hepatosplenomegaly, degenerative disease of the central nervous system.	Palm xanthoma, high cholesterol, high triglycerides, β-VLDL, VLDL-ch/TG>0.3	Diffuse corneal opacities, target cell hemolytic anemia, proteinuria, HDL↓.
Light microscopy	Fine vacuolization of podocyte with honey-comb appearance	Glomerular mesangial area and capillary loops filled with Gaucher' cells (endothelial or macrophage origin) with wrinkled-paper "fluffy" appearance	Swollen of glomerular endothelial and epithelial cells with lipid vacuoles in cytoplasm like foam cell	Foam cells in the mesangium and distending the capillary lumens	Foam cells in capillary loops and mesangial area; lipid deposition in the GBM; GBM vacuolization and thickening
Electron microscopy	Lamellar lipid inclusions in podocyte and tubular epithelial cells	Membrane-bound tubular structures consisting of fibrils 60 to 80 nm in diameter.	Electronic translucent vacuoles in the cytoplasm of macrophages, inside the bubble there is a ring of layered myeloid bodies.	Lipid vacuoles and different lamellated electron-dense osmiophilic bodies in foam cells	Deposition of lipid in GBM, subendothelial and mesangial area leads to vacuolization, and some containing layered osmiophilic substance

LCAT: Lecithin cholesterol acyltransferase.

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patients is increased, which contributes to LCAT deficiency-related nephropathy [9]. However, the precise pathogenic mechanisms of renal glomerular injury are uncertain.

The LCAT gene is located on the q21-22 region of chromosome 16, which consists of 6 exons separated by 5 introns and encompasses a total of 4.2 kilobases. The human genetic mutation database (HGMD) has collected 97 mutation loci in the LCAT gene; 58 of these mutations cause FLD, and 7 mutations cause FED. The other mutations exhibit manifestations between FLD and FED, and some other mutations have undetermined significance. LCAT deficiency can also be caused by mutations in the LCAT intron [7] or abnormal translation or post-translation [8]. The present case showed a missense mutation in exon 4 of the LCAT gene, which resulted in an amino acid change at codon 164 from arginine to histidine. Steyrer *et al* [10] has given strong evidence that this mutation directly leads to complete LCAT deficiency. Samples from family members were not available.

Light microscopy showed no or mild mesangial expansion and GBM thickening. However, we observed vacuole-like, lipid-like material with a honeycomb or foamy appearance distributed in the thickened GBM and widening mesangial region. These GBM changes were best visualized on silver and PAS stains and resembled the changes seen in stage IV MN. Double contouring of the GBM may also be observed, foam cells are present occasionally in glomeruli and rare in interstitial area. Focal segmental and global glomerulosclerosis may develop as the disease progresses. Lipid deposits in the endothelial or smooth muscle cells of the arterial wall appear occasionally. Tubular atrophy, tubular base membrane thickness and interstitial fibrosis developed in advanced stages. Immunofluorescence staining for immunoglobulins or complement is negative or nonspecific for deposition. Apo-B or apo-E staining may be positive. EM is an important tool for the diagnosis of FLD; using this technique, lipids appear as various-sized vacuoles or layered osmiophilic substances and are first deposited in the intra-GBM and subepithelial layer, followed by the subendothelial and mesangial regions [11].

The diagnosis of FLD should be considered in patients presenting with the following charac-

teristics. First, mild proteinuria or nephrotic syndrome (NS) and insensitivity to glucocorticoid therapy may be observed. Second, FLD patients may show lipid metabolism disorders beyond the abnormality caused by NS, including sharply increased non-esterified cholesterol and VLDL, especially with a severe decrease in apo-AI and HDL. Third, the existence of a vacuole-like appearance in the mesangial area or the thickening GBM resemble advanced MN with negative immunofluorescence staining is suggestive of FLD. Finally, EM examination can confirm vacuole and osmiophilia formation in the mesangial area and intra-GBM. The detection of LCAT activity and screening of the LCAT gene is needed to confirm the diagnosis of FLD, and a family history can add evidence for the diagnosis.

In addition to genetic deficiency, acquired LCAT deficiency syndrome, such as the presence of inhibitory anti-LCAT antibody in the serum [12, 13] or LCAT loss accompanied by massive proteinuria [14]. Differential diagnosis between LCAT deficiency and apo-AI deficiency or Tangier disease is also needed [4, 15]. A decrease in LCAT activity may be caused by liver dysfunction [16], malignancy [13], chronic renal failure [17], nephrotic syndrome [14], thyroid dysfunction [18], or as a side effect of numerous drugs. Therefore, the required diagnosis for FLD is gene testing. In addition, similar histological lesions, such as lipid deposition in kidney, can also be observed in Alagille syndrome [19, 20], and the presence of foam cells and lipids in the capillary loop and/or mesangial area can also be seen in Gaucher's disease [21], Fabry's disease [22] and type III hyperlipoproteinemia [23], which are listed in **Table 2**.

There are no effective therapies for FLD. Lipid-lowering agents, blood pressure control and reduction in proteinuria constitute the conventional treatments, and hemodialysis can prolong life in patients with ESRD. Transplantation is another treatment choice in ESRD patients, and although lipids will deposit in the glomerulus several weeks after renal transplantation, the function of the allografts remains normal for a long period of time [24-26]. In addition, enzyme replacement represents a new therapy for LCAT deficiency [27-29]. Following treatment, the HDL and apo-AI levels in our patient remained low during the follow-up period (**Table 1**).

Conclusion

LCAT deficiency is an extremely rare lipid metabolism disorder due to loss of LCAT activity which includes corneal opacity, anemia and renal lesions constitute the triple-symptom complex of FLD patients. The renal characteristic histological lesions in FLD patients include vacuoles and osmiophilic substance deposition in the mesangial region and GBM with negative immunofluorescence. The detection of LCAT activity and screening of the LCAT gene are needed to confirm the diagnosis of heredity LCAT deficiency.

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Disclosure of conflict of interest

None.

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