CASE REPORT

Familial LCAT deficiency: from renal replacement to enzyme replacement

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ABSTRACT

Familial LCAT deficiency (FLD) is a recessive lipid disorder ultimately leading to end-stage renal disease (ESRD). We present two brothers with considerable variation in the age at which they developed ESRD. Kidney biopsies revealed both tubular and glomerular pathology. To date, no causal therapy is available, yet enzyme replacement therapy is in development.

KEYWORDS

Familial LCAT deficiency, FLD, LCAT, renal failure

What was known on this topic?
Familial LCAT deficiency (FLD) leads to end-stage renal disease (ESRD). No causal therapy is available to date.

What does this add?
We show considerable variation in the age at which ESRD occurs in FLD, demonstrate that FLD causes tubular pathology besides glomerular pathology, and discuss the development of enzyme-replacement therapy.

INTRODUCTION

Patients with familial lecithin-cholesterol acyltransferase (LCAT) deficiency (FLD), a rare autosomal recessive disorder, are characterised by progressive corneal opacification, glomerulopathy, mild haemolytic anaemia and very low plasma levels of high-density lipoprotein cholesterol (HDL-c).[1] The molecular defect underlying FLD is homozygosity or compound heterozygosity for mutations in the gene encoding LCAT. LCAT is a pivotal enzyme in cholesterol metabolism, by virtue of its ability to esterify cholesterol molecules in HDL and low density-lipoprotein (LDL) particles, anchoring them in the lipophilic cores of these lipoproteins.[2,3]

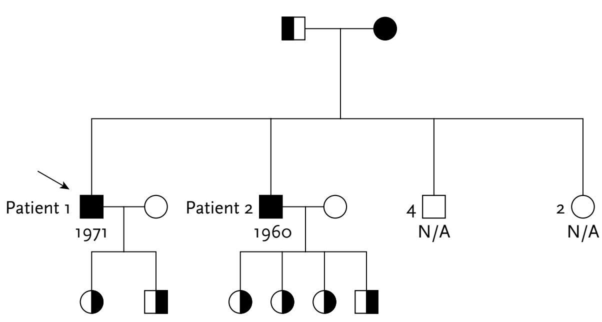
With no causal therapy currently available, FLD patients often develop end-stage renal disease in the fourth decade of life.[4] Here, we describe FLD in two brothers of Turkish descent. One recently received a kidney transplant, the other developed severe renal insufficiency. The described cases illustrate the need for enzyme-replacement therapy, currently in preclinical development.[5]

CASE REPORT

Patient 1 was referred at the age of 25 because of generalised oedema. The patient had bilateral corneal opacification. Upon physical examination signs of lung oedema were noted. Blood pressure was 140/95 mmHg. Clinical characteristics are depicted in *figure 1*. Blood sample analysis revealed increased glomerular filtration and hypoalbuminaemia, complete HDL-C deficiency and low apolipoprotein A-I. In addition, a mild microcytic anaemia was shown. Proteinuria was noted in the absence of leucocyturia or erythrocyturia. Upon ultrasonography, no structural renal abnormalities were found.

Quinapril, furosemide and candesartan were started, resulting in resolution of the oedema and a decrease in proteinuria and renal clearance (12.4 g/l to 9.4 g/l and from 165 ml/min to 130 ml/min). Notwithstanding, the

Figure 1. *Pedigree of FLD patients*



	Patient 1	Patient 2
Albumin:	14 g/L	47 g/L
eGRF	165 mL/min	28 mL/min
Haemoglobin	7.0 mmol/L	7.6 mmol/L
MCV	78 fL	93.3 fL
Urine protein	12.4 gr/L	++
TC	5.7 mmol/L	3.6 mmol/L
LDL-C	2.2 mmol/L	1.02 mmol/L
HDL-C	< 0.10 mmol/L	0.12 mmol/L
TG	7.1 mmol/L	5.47 mmol/L
Apo A-I	0.38 g/L	--
Apo B	0.30 g/L	--

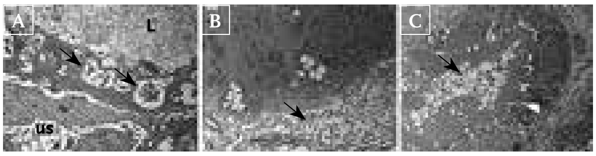
Squares are males, circles females; arrow in pedigree indicates proband. Filled symbols indicate homozygotes for $LCAT^{T345M}$, half-filled symbols indicate heterozygotes. Four brothers and two sisters of the patients were not available for analysis (N/A). eGFR = estimated glomerular filtration rate; MCV = mean corpuscular volume, TC = total cholesterol; LDL-C = low density lipoprotein-cholesterol; HDL-C = high density lipoprotein-cholesterol; TG = triglycerides; Apo A-I = apolipoprotein A-1; Apo B = apolipoprotein B.

patient developed ESRD at the age of 37. His brother – Patient 2, 50 years old – was evaluated as a kidney donor, but upon assessment he was shown to suffer from corneal opacification, HDL-C deficiency and severe proteinuria as well.

Electron microscopy of a renal biopsy of Patient 1 showed accumulation of electron-lucent vacuoles with or without osmiophilic particle cores in the glomerular basement membrane, Bowman's capsule, the tubular basement membrane and the lumen of tubules. Segmental foot process effacement, foam cell accumulation in the mesangium and a distorted architecture of the glomerular and tubular basement membrane were also noted (*figure 2*).

The patients' parents were first cousins (*figure 1*), and the presence of FLD as underlying disease was anticipated. Plasma LCAT activity, measured as the ability of plasma LCAT to esterify free cholesterol in proteoliposomes,[6] was severely reduced in both patients: 0.75 nmol cholesterol ester/h/ml (normal: 25 nmol/h/ml). Upon DNA analysis,[3] both patients were found to be homozygous carriers of an ACG→ATG mutation in exon 6, resulting in the p.T345M substitution in LCAT.[7]

Figure 2. *Electron microscopy of renal biopsy of patient 1*



A: Glomerulus. Glomerular basement membrane with accumulation of lipids. US: urinary space, L: capillary lumen, arrows: osmiophilic structures.
B: Tubular basement membrane with osmiophilic structures (arrow).
C: Tubule. L: Lumen with osmiophilic structures (arrow).

DISCUSSION

Here we report familial LCAT deficiency (FLD) in two brothers of Turkish descent. We show that the age at which end-stage renal disease develops is variable and we also demonstrate that renal pathology in FLD is not only characterised by glomerular changes, but also by profound tubular changes.
To date, 88 mutations in *LCAT* have been described.[8] Severe mutations lead to complete inactivation of the LCAT enzyme, and consequentially to FLD. The T345M mutation identified in our two patients was originally described in a Sardinian patient.[7] The threonine residue at position 345 is conserved up to C. elegans, but it is currently unknown why this specific residue is crucial for normal enzyme function.

Patients with FLD suffer from progressive proteinuria and renal dysfunction, on average leading to ESRD in the fourth decade of life.[1] Patient 1 indeed developed ESRD at the age of 37, but Patient 2, his full brother, was 50 years old when severe renal insufficiency was noted during a work-up for renal transplantation. The reason for the variable course of renal disease progression in our two FLD patients is unknown and remarkable given the fact that the two brothers had a comparable lifestyle; neither had any comorbidity influencing renal function such as diabetes mellitus, hypertension or cardiovascular disease.

The exact pathogenesis of renal disease in FLD is unknown. Due to the absence of functional LCAT, excess unesterified cholesterol and phospholipid are present in these patients, leading to the formation of lipoprotein X, a protein-free aberrant particle containing FC and PL, associated with glomerular endothelial damage.[9] The composition of typical vacuoles in the glomerular basement of FLD patients has not been fully characterised to date.[9-10] The presence of foam cells in the mesangium of our patient, however, suggests that excess lipid is important in the pathogenesis of the renal damage observed in our FLD patient.

To date no causal treatment for FLD is available. As a consequence, symptomatic treatment encompassing lipid lowering and antihypertensive therapy is commonly started in FLD patients. This combination has been shown to result in decreased proteinuria and stabilisation of pathological sequelae in FLD patients.[11] Beneficial effects of corticosteroid administration have also been described.[12] FLD patients who develop ESRD require haemodialysis or kidney transplantation. Despite evidence of early histomorphological changes consistent with FLD in renal grafts after transplantation, acceptable long-term results have been reported.[13]

Both LCAT gene replacement and enzyme replacement are under development. In a model described by Kuroda and co workers,[14] autologous adipocytes are transfected with human LCAT via a retroviral vector. LCAT secreted by these cells is able to restore enzyme activity in plasma of FLD patients. Recombinant human LCAT (ACP-501)[15] showed excellent results in LCAT knockout mice, rapidly restoring LCAT activity, cholesterol efflux and lipid profiles. rhLCAT is currently being evaluated in FLD patients in a phase I trial.[5]

CONCLUSION

FLD is a recessive lipid disorder ultimately resulting in ESRD. The clinical course of the disease is variable, even in related FLD patients. We demonstrate that apart from glomerulopathy, FLD is also characterised by tubular pathology. Finally, our patients stress the need for LCAT enzyme replacement therapy, which is currently under development in a phase 1 clinical trial.[5]

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