Case Report

Stability of lipids on peritoneal dialysis in a patient with familial LCAT deficiency

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Case

A 37-year-old man of northern European descent with familial lecithin:cholesterol acyltransferase (LCAT) deficiency started peritoneal dialysis (PD) one year ago, for end-stage renal failure.

Proteinuria and an abnormal lipid profile were first noted in his early 20s. At the age of 29, he suffered an alkali burn to his right eye. When assessed by an ophthalmologist, diffuse lipid deposition in the corneas with accentuated arcus and preservation of his visual acuity were noted. At the age of 30 (in 1999), the following clinical findings were observed at nephrology and lipid specialist appointments: blood pressure 140/80, weight 112 kg (BMI 33), and marked arcus cornealis bilaterally. He was anaemic (haemoglobin 11.4g/dl), but had preserved renal function. Urinalysis revealed proteinuria and microhaematuria. A 24-h urine collection showed nephrotic range proteinuria at 6 g/day. His total cholesterol (TC) was 270 mg/dl (6.99 mmol/l), triglycerides (TG) 946 mg/dl (10.68 mmol/l) and HDL-C 15 mg/dl (0.38 mmol/l).

Familial LCAT deficiency (FLD) was confirmed by LCAT assay. Interestingly, he was found to be a compound heterozygote for two novel missense mutations in the LCAT gene, namely V28M in Exon 1 and A211T in Exon 5.

Our patient was evaluated 5 years later (August 2004) because of severe hypertension (180/100 mmHg) and renal failure with serum creatinine 6.7 mg/dl (593 μmol/l). He was a heavy smoker and a heterozygous carrier for Factor V Leiden. His physical examination was essentially unremarkable, apart from striking opacification of his corneas (Figure 1). Laboratory investigations are outlined in Table 1. A renal ultrasound demonstrated normal-sized kidneys and renal biopsy showed changes characteristic of LCAT deficiency with mesangial and capillary wall lipid accumulation. Renal damage was already quite advanced with extensive glomerulosclerosis, tubular atrophy and interstitial fibrosis (Figure 2).

A PD tube was inserted in December 2004. His medication profile included labetolol, felodipine, furosemide, calcium carbonate, iron polysaccharide, darbepoetin alfa and multivitamins. His initial

Fig. 1. Still stereo image of (L) eye demonstrating corneal opacification. Visual acuity 20/20. Cornea shows generalized haziness in stromal layer with accentuation at the periphery forming a circumferential corneal arcus. The high corneal lipid content creates a refractile surface and results in reflection of the camera flash.
prescription was continuous cycling PD (CCPD) over 8 hours, using 2 l fills of 1.5% dextrose, last fill 1.5 l of 2.5% dextrose (total 15.5 l/day), dry weight 90 kg. He had significant residual renal function with urine output >1.8 l/day. He met current adequacy guidelines on his first peritoneal equilibration test and was a low-average transporter.

Over the first 6 months of PD he remained hypertensive, gained 8 kg in weight and was non-compliant with medications. CCPD was increased to 8.5 h/night with an extra daytime exchange and these parameters slowly improved. He developed worsening secondary hyperparathyroidism, and was started on vitamin D. Laboratory values during his first year on PD are outlined in Table 1.

His lipid profile remained stable despite exposure to dextrose-containing PD solutions (Table 2). Given his multiple traditional and non-traditional cardiovascular risk factors (obesity, hypertension, smoking, dyslipidaemia, end-stage renal failure and secondary hyperparathyroidism) he underwent a battery of investigations. Echocardiogram demonstrated left ventricular ejection fraction of 55%, left ventricular hypertrophy and a mildly calcified aortic valve. Carotid ultrasound revealed minimal plaque on the left side of no haemodynamic consequence and Persantine MIBI demonstrated multiple areas of attenuation artefact secondary to his obesity, but no reversible ischaemia. He recently experienced an episode of congestive heart failure and a subsequent coronary angiogram revealed no lesions.

Table 1. Laboratory values

<table>
<thead>
<tr>
<th></th>
<th>Six months prior PD start (August 2004)</th>
<th>PD start (January 2005)</th>
<th>PD 1 year (January 2006)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>8.5</td>
<td>8.6</td>
<td>9.5</td>
<td>14–17 g/dl</td>
</tr>
<tr>
<td>Transferrin Sat.</td>
<td>0.12</td>
<td>0.27</td>
<td>0.36</td>
<td>0.20–0.50</td>
</tr>
<tr>
<td>Ferritin</td>
<td>–</td>
<td>97</td>
<td>–</td>
<td>15–200 ng/ml</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6.7</td>
<td>8.8</td>
<td>11.9</td>
<td>0.7–1.3 mg/dl</td>
</tr>
<tr>
<td>eGFR</td>
<td>7.3</td>
<td>5</td>
<td>5</td>
<td>0.7–1.3 mg/dl</td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>88</td>
<td>3.7</td>
<td>3.4</td>
<td>3.5–5.5 g/dl</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.6</td>
<td>8.6</td>
<td>8.9</td>
<td>9–10.5 mg/dl</td>
</tr>
<tr>
<td>Calcium</td>
<td>5.6</td>
<td>8.2</td>
<td>8.2</td>
<td>3–4.5 mg/dl</td>
</tr>
<tr>
<td>Phosphate</td>
<td>24.3</td>
<td>75.7</td>
<td>75.7</td>
<td>1.0–5.5 pmol/l</td>
</tr>
<tr>
<td>Intact PTH</td>
<td>8.35</td>
<td>–</td>
<td>–</td>
<td>&lt;0.15 g/d</td>
</tr>
</tbody>
</table>

Transferrin Sat, Transferrin saturation; eGFR calculated using modified MDRD equation; PTH, parathyroid hormone. To convert hemoglobin in g/dl to g/l, multiply by 10. To convert ferritin in ng/ml to ug/l, multiply by 2.24. To convert creatinine in mg/dl to mmol/l, multiply by 88.4. To convert glucose in mg/dl to mmol/l, multiply by 0.05551. To convert albumin in g/dl to g/l, multiply by 10. To convert calcium in mg/dl to mmol/l, multiply by 0.2495. To convert phosphate in mg/dl to mmol/l, multiply by 0.3229.

Discussion

Familial LCAT deficiency was first described in three Norwegian sisters by Gjone and Norum [1] in 1967. It is extremely rare with only ~40 families described in the world literature [2,3]. The first cases were reported in people of Northern European descent, but since then there have been reports of patients from other parts of the world.

FLD is inherited in an autosomal recessive fashion. To date, ~55 mutations in the human LCAT gene on chromosome 16 have been reported [2]. Sequence analysis of our patient’s genomic DNA using an established method revealed compound heterozygosity for two novel missense mutations in the LCAT gene, namely V28M in Exon 1 and A211T in Exon 5 [4]. These mutations were absent from the genomes of 150 healthy normolipidaemic individuals. Homozygotes or compound heterozygotes for mutations in the LCAT gene are classified into two distinct clinical syndromes based on biochemical criteria: FLD, where plasma LCAT is either absent or completely lacks catalytic activity, and fish eye disease, where LCAT lacks activity towards HDL-C lipids, but esterifies cholesterol bound to apo-B containing lipoproteins [2].
Table 2. Lipid profile

<table>
<thead>
<tr>
<th></th>
<th>TC (&lt;200)</th>
<th>TG (&lt;205)</th>
<th>HDL-C (&gt;35)</th>
<th>LDL-C (&lt;130)</th>
<th>apo-AI (&gt;110)</th>
<th>apo-B100 (&gt;125)</th>
<th>Lp(a) (&lt;30)</th>
<th>VLDL-C (&lt;40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2000</td>
<td>380</td>
<td>1082</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Aug 2004</td>
<td>139</td>
<td>535</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Jan 2005</td>
<td>122</td>
<td>357</td>
<td>–</td>
<td>–</td>
<td>43</td>
<td>47</td>
<td>&lt;3.5</td>
<td>–</td>
</tr>
<tr>
<td>Jan 2005*</td>
<td>168</td>
<td>728</td>
<td>–</td>
<td>–</td>
<td>48</td>
<td>48</td>
<td>–</td>
<td>57</td>
</tr>
<tr>
<td>April 2005</td>
<td>148</td>
<td>283</td>
<td>9</td>
<td>84</td>
<td>53</td>
<td>53</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sept 2005</td>
<td>124</td>
<td>246</td>
<td>3</td>
<td>71</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nov 2005</td>
<td>161</td>
<td>893</td>
<td>&lt;1</td>
<td>62</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*All units mg/dl.

To convert mg/dl to g/l (apoAI, apo-B100), multiply by 0.01. To convert Lp(a) in mg/dl to mg/l, multiply by 10.

FV Leiden

ESRD

Proteinuria

Fig. 3. Family pedigree. Proband is indicated by arrow. Square: male, circle: female. Black symbols indicate clinical FLD who are (presumed) compound heterozygotes of LCAT deficiency similar to our patient. Hatched symbols indicate heterozygote carriers. White symbols indicate unknown status.

The family pedigree of our patient demonstrates that three of four brothers are affected, making their parents obligate heterozygotes (Figure 3).

LCAT catalyses esterification of free cholesterol in the following reaction [3]: Free cholesterol (FC) + lecithin (PL) ⇔ Cholesterol ester + lysolecithin. It plays a key role in the formation and maturation of HDL-C, and it is an intermediary in the reverse cholesterol transport pathway [5].

The lipid profile of an FLD patient is characterized by a severe deficiency of normal HDL-C particles, resulting in low plasma HDL-C, increased free cholesterol: cholesterol ester ratio, decreased apo-AI (the major lipoprotein of HDL), decreased apo-B (the major lipoprotein of LDL) and elevated triglycerides [2]. Inheritance of an abnormal LCAT genotype causes a gene-dose-dependant alteration in the plasma lipid/lipoprotein profile. Thus, heterozygote carriers of mutant genes have a biochemical phenotype intermediate between carriers of zero or two copies of the mutant alleles [6].

Lipid deposition in tissues leads to the classic clinical triad of LCAT deficiency: corneal opacification, anaemia and proteinuria [7]. While FLD is often diagnosed in adulthood, corneal clouding is frequently manifested already in childhood [3]. These lesions consist of minute greyish dots throughout the corneal stroma that are accentuated towards the periphery. Opacification of the cornea progresses slowly, and visual acuity is usually normal or only slightly reduced [8]. A mild haemolytic anaemia resulting from instability of the red blood cell membrane is observed, with anisopoikilocytosis, target cells and stomatocytes seen on peripheral blood film [5].

Kidney disease is the major cause of morbidity and mortality observed in patients with FLD. Albuminuria is noted in childhood and progresses to nephrotic syndrome by the fourth to fifth decades of life [9]. Urinalysis often reveals proteinuria, microhaematuria and granular casts. Hypertension and progressive renal failure leading to end-stage renal disease (ESRD) is frequent and necessitates renal replacement therapy. In those who undergo transplantation, FLD tends to recur in the renal allograft, sometimes within weeks; however, graft function is usually preserved and long-term graft survival has been described [9,10].

Light microscopy demonstrates mesangial expansion with varying degrees of mesangial hypercellularity, capillary wall thickening, and foam cells in the capillary walls, mesangium and occasionally in the interstitium [7]. Segmental sclerosis and eventual global sclerosis of glomeruli are observed as the disease advances. Electron microscopy shows lipid deposition in many areas (epi- and intra-membranous, subendothelial, mesangial, within epithelial foot processes and arteriolar endothelial and medial cells) and there may be focal or diffuse effacement of the epithelial foot processes [7,11,12]. The lipid deposits are partly lucent with osmiophilic inclusions, and have been shown by immunoflorescence to contain large amounts of apo-B [7].

There are anecdotal reports of kidney disease associated with high circulating levels of Lipoprotein-X (LP-X: lipoprotein rich in free cholesterol (FC) and phospholipid (PL) in those with FLD who develop kidney disease. A Toronto group has recently
described a mouse model of LCAT deficiency with high circulating levels of LP-X and demonstrated progressive renal disease with proteinuria and renal pathology findings similar to those observed in humans with FLD [11]. They observed an up-regulation of inflammatory biomarkers as a result of lipid deposition and postulated that LP-X may stimulate an inflammatory reaction leading to proteinuria, progressive glomerulosclerosis and ultimately ESRD. The overproduction of LP-X in FLD is likely to occur from hepatically derived very-low density lipoprotein cholesterol (VLDL) or intestinally derived chylomicrons, which in the absence of LCAT, results in the accumulation of FC and PL and formation of LP-X [11].

Is there an increased risk of premature atherosclerosis in LCAT deficiency? While a case report of FLD has documented increased atherosclerotic burden [13], a 25-year follow-up of a Canadian LCAT-deficient kindred documented no clinical vascular events and only minimal atherosclerosis with no evidence of endothelial dysfunction in two affected siblings, one of them with ESRD [14]. Interestingly, the heterozygote carriers in this family had evidence of vascular disease on carotid sonograms. Similarly, in a report of an Italian cohort no cardiovascular events in FLD patients were mentioned, although two of the heterozygote carriers had suffered from stroke [2]. Our patient did not have any clinical manifestations of cardiovascular disease, apart from an episode of congestive heart failure. Likewise, coronary angiogram showed no lesions, despite his many risk factors. Why patients with such profound lipid abnormalities do not develop premature atherosclerosis is not known. Ayyobi et al. [14] postulate that LCAT activity may not be essential for reverse cholesterol transport and that cholesterol efflux may be unaltered in FLD patients. Also, these patients have very low levels of atherogenic lipoproteins, thus lowering their atherosclerotic risk. In contrast, heterozygotes may have ‘dysfunctional’ high density lipoprotein (HDL) which in association with higher intermediate-density lipoprotein (IDL) levels and hypertriglyceridaemia, may lead to premature atherosclerosis [14].

To our knowledge, there are no published reports on PD in LCAT deficiency. It is well documented that various components of the lipid pathway are up- or down-regulated in chronic renal failure, resulting in worsening of the lipid profile [15]. In addition, PD patients tend to have more ‘atherogenic’ lipid profiles than those on haemodialysis, with higher levels of TC, LDL-C, Lp(a), oxidized LDL-C, TG, apo-B and lower HDL-C cholesterol levels [16]. The use of dextrose-based solutions is also of concern, as patients can absorb significant amounts of glucose. This may contribute to development of the metabolic syndrome and undesirable effects on lipids. Our patient has been treated exclusively with dextrose-based PD solutions, has not been placed on any lipid-lowering therapy and to date, his lipid profile is not markedly different from pre-dialysis values.

Conclusions

FLD deficiency is a rare disease manifest by corneal opacification, anaemia, proteinuria, and in many cases, ESRD. While these patients have an abnormal lipid profile characterized by very low levels of HDL-C, apo-AI, apo-B and increased triglyceride levels, they do not appear to have an increased risk of cardiovascular disease. Deposition of LP-X, rich in free cholesterol and lecithin likely stimulates an inflammatory reaction, leading to proteinuria and ultimately renal failure. PD with dextrose-based solutions can be used to successfully treat those patients who develop ESRD.

Conflict of interest statement. None declared.

References

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