exceptional case

Progressive kidney disease in three sisters with elevated lipoprotein(a)

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Introduction

Lipoprotein(a) [Lp(a)] is an atherogenic, LDL-like particle of unknown physiologic function. Elevated serum concentrations of Lp(a) have been linked conceptually and epidemiologically to cardiovascular disease [1–3], but their relationship to the progression of renal disease remains much less clear, despite several hypothesized mechanisms by which this could occur [4–12].

We present a unique case of three sisters with profound elevations in serum Lp(a), progressive but unexplained impairment of kidney function, and renal biopsies demonstrating benign nephrosclerosis and apolipoprotein(a) [apo(a)] deposition.

Case report

Sisters A and B came to our attention independently after screening laboratory examinations revealed asymptomatic elevations in their serum creatinine, while Sister C was referred for assessment in light of her siblings’ renal impairment. Clinical and laboratory data for each sister, and limited data for their parents, are presented in Table 1.

At initial presentation, Sister A had no significant medical history. She denied substantial antecedent non-steroidal anti-inflammatory (NSAID) use. She had stopped smoking 10 years previously.

Sister B’s medical history was significant for recurrent attacks of gout, which she treated with 2- to 3-day courses of indomethacin. One of these episodes occurred during pregnancy, an exceedingly rare occurrence, and this was reported in the medical literature [13]. Ten years earlier, she had seen a nephrologist regarding an elevated creatinine of 133 µmol/L (eGFR = 45 mL/min/1.73 m²). At that time, she had a benign urine sediment with no evidence of proteinuria or haematuria, and her elevated creatinine was felt to represent normal variance. She had not been re-evaluated until her presentation to our clinic.

Sister C’s medical history was significant only for an abnormal lipid profile and four complication-free pregnancies. She had quit smoking 7 years previously and denied substantial antecedent NSAID use.

None of the sisters had a history of hypertension, diabetes mellitus, atherosclerotic disease, nephrolithiasis or abnormalities of the urogenital tract. All three sisters reported participating in aerobic exercise for a minimum of 45 min on three occasions per week. Their parents were known to have hypercholesterolaemia, but there was no family history of kidney disease or premature cardiovascular events. Their physical examinations at presentation were unremarkable aside from the averaged blood pressures listed in Table 1.

All three sisters had remarkably similar findings on renal biopsy. Histologically, there were a number of obsolete glomeruli (29%, 44% and 13% for Sisters A, B and C, respectively), while the remaining glomeruli appeared normal. Focal tubular atrophy and fibrosis were present. Intimal sclerosis of interlobular arteries was moderate-to-severe in one biopsy and mild-to-moderate in two. Focal intimal arteriolar hyalinosis was observed in two of the biopsies. Electron microscopy and direct immunofluorescence (IF) did not demonstrate any significant abnormality of glomerular ultrastructure. In two of the biopsies, IF for IgG, IgM, IgA, C1q, C3, F and light chains was negative, while in the third there was weak mesangial staining for IgG and C3. The latter was interpreted to represent an epiphenomenon of no pathogenetic significance in view of the histological finding of normal-appearing viable glomeruli. The final pathological diagnosis was benign nephrosclerosis, moderate in Sisters A and B and mild in Sister C.

Clinical course

Even with close clinical monitoring and standard chronic kidney disease (CKD) care, there has been progressive decline in renal function for Sisters A and B. Sister A’s eGFR has fallen from 29 to 13 mL/min/1.73 m².

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Table 1. Clinical and laboratory results

<table>
<thead>
<tr>
<th>Test (normal range, units)</th>
<th>Sister A</th>
<th>Sister B</th>
<th>Sister C</th>
<th>Father</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (years)</td>
<td>43</td>
<td>40</td>
<td>39</td>
<td>66</td>
<td>59</td>
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<tr>
<td>Smoking history (pack-years)</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>40</td>
<td>0</td>
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<tr>
<td>Average BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td>150/100</td>
<td>132/83</td>
<td>118/77</td>
<td>129/73</td>
<td>145/79</td>
</tr>
<tr>
<td>Current</td>
<td>146/84</td>
<td>114/77</td>
<td>116/85</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>V4-MDRD eGFR (mL/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Presentation</td>
<td>29</td>
<td>29</td>
<td>55</td>
<td>56</td>
<td>67</td>
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<tr>
<td>Current</td>
<td>13</td>
<td>19</td>
<td>61</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>ΔGFR</td>
<td>--16</td>
<td>--10</td>
<td>6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Urinary protein (g/d)</td>
<td>0.08</td>
<td>0</td>
<td>0.14</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Lipid panel</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chol (2.00–5.19 mmol/L)</td>
<td>7.28</td>
<td>6.51</td>
<td>6.33</td>
<td>6.38</td>
<td>6.94</td>
</tr>
<tr>
<td>TG (0.45–2.29 mmol/L)</td>
<td>2.41</td>
<td>1.38</td>
<td>1.22</td>
<td>1.55</td>
<td>5.27</td>
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<tr>
<td>LDL (1.50–3.39 mmol/L)</td>
<td>5.07</td>
<td>4.72</td>
<td>4.28</td>
<td>4.6</td>
<td>3.24</td>
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<tr>
<td>HDL (&gt;1.10 mmol/L)</td>
<td>1.11</td>
<td>1.16</td>
<td>1.5</td>
<td>1.52</td>
<td>1.28</td>
</tr>
<tr>
<td>TChol/HDL ratio (&lt;4.4)</td>
<td>6.56</td>
<td>5.6</td>
<td>4.22</td>
<td>4.49</td>
<td>4.42</td>
</tr>
<tr>
<td>Lp(a) (75 percentile &lt; 280 mg/L)</td>
<td>1439</td>
<td>1163</td>
<td>1365</td>
<td>2887</td>
<td>1485</td>
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<td>Homocysteine (&lt;11 mmol/L)</td>
<td>12.6</td>
<td>14.7</td>
<td>13.1</td>
<td>9.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Uric acid (140–400 µmol/L)</td>
<td>575</td>
<td>564</td>
<td>412</td>
<td>--</td>
<td>200</td>
</tr>
<tr>
<td>Fasting glucose (3.9–6.0 mmol/L)</td>
<td>4.6</td>
<td>4.8</td>
<td>4.8</td>
<td>5.3</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Note: Dashes (–) indicate information not available. Bold text indicates abnormal values.

a 'Average' denotes the mean systolic and diastolic blood pressures at the first three ('Presentation') and last three ('Current') clinic visits.

Recommended targets for blood pressure have been difficult to achieve, despite adherence to appropriately prescribed antihypertensive agents. At the age of 51, she is awaiting living donor transplantation. Sister B’s eGFR has fallen from 29 to 19 mL/min/1.73 m² despite excellent blood pressure control on similar medications, and she, too, has been referred for transplantation assessment. Sister C’s blood pressure control has been excellent and her kidney function has remained stable. Of note, Sister C has developed episodes of severe ankle pain, which were presumed to be gout, though no confirmatory diagnosis has been sought via synovial fluid aspiration.

As they were dyslipidaemic at presentation, all three sisters were assessed in a specialized lipid clinic. On the basis of their family history and fasting lipid panels (see Table 1), each of the sisters were diagnosed with familial combined dyslipidaemia with substantially elevated Lp(a). Lipid abnormalities have responded relatively poorly to folic acid, escalating doses of HMG-CoA reductase inhibitors and the more recent addition of ezetimibe.

Despite markedly abnormal lipid panels and progressive kidney dysfunction, none of the three sisters have evidence of cardiovascular disease. They deny symptoms of angina, congestive heart failure, stroke, transient ischaemic attack and peripheral arterial disease. Sister A has undergone a pre-transplant echocardiogram, which demonstrated a normal visually-estimated left ventricular ejection fraction and borderline left ventricular hypertrophy (LV mass index 106 g/m²). Sisters A and B’s pre-transplant exercise 2-methoxy isobutyl isonitrile (MIBI) cardiac scans have revealed normal calculated ejection fractions and no evidence of ischaemia or previous infarction. Four years after their presentation, Sisters B and C underwent carotid ultrasound studies in order to ascertain the presence of asymptomatic atherosclerotic disease. In both sisters, minimal plaques were present bilaterally, and carotid intimal-medial thickness was minimally increased above the 75th percentile for age and gender, suggesting no substantial atherosclerotic burden. No additional cardiac investigations have been undertaken.

The father and mother of these sisters were also diagnosed with familial combined dyslipidaemia and profoundly elevated Lp(a) levels. Neither parent had any clinically apparent adverse vascular event, and both have relatively preserved renal function. There is no family history of premature vascular disease.

Further Lp(a) and biopsy investigations

Further characterization of the sisters’ Lp(a) included an apo(a) isofrom phenotype analysis, performed as described in Part I of the Web Appendix. Phenotyping demonstrated a single apo(a) band in all three sisters, consistent with a small apo(a) isofrom with 16 repeats of the plasminogen kringle IV-like domain.

Immunohistochemical staining of the kidney biopsies for apo(a) was also performed, according to a method described in Part II of the Web Appendix. This demonstrated strongly positive apo(a) localization in biopsy specimens from all three sisters.

Control patients

In order to provide experimental controls for our case series, the St Paul’s Hospital (Providence Health Care, Vancouver, Canada) Renal Biopsy Database was searched to provide a listing of all female patients with a final diagnosis of nonhypertensive nephrosclerosis. The three patients whose age at the time of renal biopsy most closely matched those of
Sisters A, B and C were contacted and asked to participate in the clinical study. After providing informed consent, blood was drawn and serum Lp(a) concentration was determined. Their renal biopsies were retrieved from storage and were also stained by immunohistochemical methods for apo(a).

Serum Lp(a) concentrations for control patients 1, 2 and 3 were 247, 287 and 697 mg/L, respectively, values that are considerably lower than those found in the three sisters and their parents (see Table 1). However, all three control patient renal biopsies demonstrate strongly positive apo(a) localization. We are unaware of a standardized and validated method to quantify the intensity of staining in all six biopsy samples, so no comment correlating serum Lp(a) concentration and degree of Lp(a) deposition can be made.

**Discussion**

We present a unique case of three sisters with the following findings: progressive impairment of kidney function beginning prior to age 50 and in the absence of traditional CKD risk factors, profound elevations in serum Lp(a), a pathological diagnosis of benign nephrosclerosis with positive immunohistochemical reactivity for apo(a), and no evidence of clinically apparent cardiovascular disease. Importantly, renal function has deteriorated despite the use of medications known to slow its progressive decline, and despite the absence of proteinuria or other adverse prognostic signs. It is intriguing to speculate as to the possible role that the high serum Lp(a) levels have played in the clinical course of this family.

Lp(a) is a co-dominantly inherited, low-density lipoprotein (LDL)-like particle of unknown function. It is differentiated from LDL by the presence of apo(a), a highly polymorphic glycoprotein covalently linked to the apoB-100 moiety of LDL. Apo(a) shares several domains with plasminogen. One of these domains is present within apo(a) in a variable number of copies (plasminogen kringle IV type 2 repeated sequences), and this confers a substantial size polymorphism to the apo(a) protein. Over 30 kringle size isoforms of apo(a) have been identified to date. Serum Lp(a) concentration is inversely proportional to the molecular weight of the expressed isoforms, with the smallest isoforms corresponding to the greatest elevation in Lp(a).

High plasma Lp(a) concentrations have been associated with cardiovascular events, cerebrovascular disease and peripheral atherosclerosis [1–3]. Serum Lp(a) concentrations predict the presence of target-organ damage in the setting of essential hypertension [11], and may predict the development of diabetic proliferative retinopathy [14]. Independent of their tendency to produce higher Lp(a) serum levels, smaller apo(a) isoforms have been shown to predict atherosclerotic disease [15]. The correlation between high serum Lp(a) and progressive atherosclerosis appears to hold particularly true in familial hypercholesterolaemia and in renal disease, conditions which are also associated with higher Lp(a) levels [2,3].

The association between Lp(a) and the pathogenesis of kidney disease remains much less clear. Some evidence suggests that Lp(a) may play a causative or propagative role. Triglyceride-rich, apoB-containing lipoproteins are known to hasten the progression of renal insufficiency [4]. Moreover, an extensive literature using in vitro animal models has described many putative mechanisms by which Lp(a) may induce or exacerbate renal dysfunction [6–10,12], and it has been proposed that glomerulosclerosis and atherosclerosis evolve by analogous pathobiological processes [5]. In one study of unselected paediatric chronic renal failure patients, proliferative renal biopsy specimens staining positive for apo(a) were noted to contain more crescents, more macrophage infiltration and more severe mesangial proliferation than those that did not, while patients with non-proliferative disease and apo(a) positivity fared more poorly than their apo(a) negative counterparts [16]. A second observational study found higher serum Lp(a) concentrations in patients with co-localization of apoB and apo(a) within renal biopsy specimens, compared with those without lipoprotein in biopsy samples [17].

Clinical evidence linking elevated serum Lp(a) and apo(a) deposition to the initiation or acceleration of renal dysfunction is far from definitive. Song et al. observed that serum Lp(a) levels were weakly predictive of the progression to diabetic nephropathy in Korean patients with dipstick-positive proteinuria [18]. However, an observational study of unselected non-diabetic CRF by Samuelsson et al. found that plasma levels of Lp(a) do not predict progression of renal dysfunction [19]. While the localization of apo(a) within the renal biopsies described by Sato et al. may indicate a pathogenic role for Lp(a), it may also be an epiphenomenon, its accumulation made possible by an initiating injury, and its purpose a mechanism of wound healing or simply a marker of inflammation [17].

Our unique cases add to this debate. First, in the absence of traditional risk factors for CKD, two of three young women have progressed to end-stage renal disease (ESRD). The combination of high serum Lp(a) and biopsies strongly positive for apo(a) initially suggested that Lp(a) may be playing a pathogenic role in the development of ESRD. However, with only mild elevations in serum Lp(a), the control patients also demonstrate intense deposition of apo(a) within their kidney biopsies. This suggests that renal apo(a) deposition occurs in non-hypertensive nephrosclerosis at any serum Lp(a) concentration. The role that this deposition may play in the initiation, promotion or acceleration of CKD is still unclear.

Second, although Sisters A and B progressed to ESRD, Sister C and both parents have stable renal function. If Lp(a) indeed plays a role in the development of chronic kidney disease, there must be other initiating or accelerating factors that determine its progression in this family. Perhaps even relatively minor elevations in blood pressure act in concert with Lp(a) to provoke lipid deposition and progressive renal dysfunction [7]. Hyperuricaemia could directly damage glomeruli, potentiate hypertensive or Lp(a)-mediated damage, or both [20]. There may also be other as-yet unknown synergistic determinants.

Third, if Lp(a) deposition is responsible for their progressive CKD, we must consider the possibility that it may recur in a transplanted organ as well. How might this affect decisions regarding the appropriateness of transplantation?
Progressive kidney disease in three sisters with elevated lipoprotein(a) have these sisters progressed to ESRD in the absence of clinically significant vascular disease? This is particularly interesting, given CKD itself is now widely recognized as a risk factor for vascular disease. We may postulate a number of explanations: their particular Lp(a) isoform is universally toxic once deposited but is preferentially nephrotropic in deposition; Lp(a)’s deleterious effects required an initiating glomerular injury and/or nephrosclerotic promoters that remain unidentified; an arterioprotective rescue mechanism exists in this family; or, Lp(a) merely shadows glomerular injury but is of no pathogenic significance. Although several of these postulated explanations may be at play, the strong family history of lipid disorders without premature vascular disease suggests a heritable ‘rescue mechanism’ that thwarts atherogenesis but may allow glomerulosclerosis to proceed.

Although the interplay between renal disease, cardiovascular disease and Lp(a) remains incompletely defined, rigorous evaluation of unique familial conditions can help to frame relevant, testable hypotheses. In this case report, we have described familial concordance of elevated serum Lp(a) levels, progressive renal failure with histologic deposition of apo(a), and the absence of clinically apparent vascular disease. We hope that this report inspires further appreciation and investigation of the complex interaction between vascular and renal pathologies.

Conflict of interest statement. None declared.

Supplementary material

Supplementary material is available online at http://ndt.oxfordjournals.org/.

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