Lipoprotein Glomerulopathy: A New Role for Apolipoprotein E?

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Nearly 140 years have passed since Virchow first associated lipid abnormalities with renal disease, but despite a large body of clinical and laboratory investigation, the precise role of lipids in the development of kidney diseases has remained elusive. Although it has been demonstrated that abnormalities in lipid metabolism may promote glomerular injury, altered glomerular function can also change lipid metabolism, making it difficult to distinguish primary causes of glomerular disease from secondary consequences. An intriguing report in this issue of the Journal of the American Society of Nephrology suggests for the first time that a specific molecular defect in apolipoprotein E (apo E) may contribute to the pathogenesis of a rare form of nephrotic syndrome and glomerulosclerosis, lipoprotein glomerulopathy (1).

A number of systemic diseases (including rarities such as Fabry’s, Niemann-Pick, and Gaucher’s diseases) include increased intrarenal lipid deposition. Most commonly, however, renal lipidoses is secondary to the nephrotic syndrome, in which hyperlipidemia is a characteristic finding. In this setting, the hyperlipidemia is believed to be a consequence of renal disease, because successful treatment of nephrotic syndrome normalizes plasma lipids, but reduction of lipid levels does not resolve glomerular pathology (2). Nonetheless, some evidence, mainly from animal studies, suggests that hyperlipidemia in the nephrotic syndrome may contribute to the progression of disease (2).

Disorders in which lipid deposition is limited to the kidney are rare and remain poorly understood. Until the late 1980s, only one had been described, a hereditary condition in which cholesterol crystals accumulate within the mesangium (3). Then several reports of a histologically distinct and apparently new entity appeared in the literature, which was named “lipoprotein glomerulopathy” (LPG) (4-6). Of the fewer than two dozen cases thus far reported (4-14), all but two have come from the Far East, the majority from Japan. The histological hallmark of LPG is the presence of laminated thrombi, consisting of lipid droplets, within the lumen of dilated glomerular capillaries. The lipid is demonstrable using oil red-O or Sudan stain and has a layered ultrastructural appearance, suggesting that it has been serially deposited within the glomerulus. Specific immunohistochemical stains show that the lipid contains apo E and apo B, which are normal components of very-low-density lipoprotein particles (VLDL) and their remnants, intermediate density lipoprotein (IDL). Unlike typical thrombi or immune deposits, these lipid thrombi do not typically contain fibrinogen, complement, or immunoglobulin.

Although our understanding of the natural history of LPG is still evolving, the disease has been characterized clinically by the insidious appearance, usually in adulthood, of the nephrotic syndrome, with relatively rapid progression to renal impairment and development of glomerulosclerosis (9,12,14). No other systemic manifestations have been reported. Progression of renal disease in LPG is marked by mesangial expansion, endothelial cell swelling, and segmental sclerosis; however the extraglomerular vessels remain normal. Interestingly, one report notes the recurrence of LPG in a transplanted cadaveric kidney, suggesting that LPG is caused by extrarenal factors (14).

The finding of thrombi consisting of lipoproteins raised the possibility that LPG might be related to a primary abnormality in lipid metabolism. Investigation of the plasma lipoprotein profile in patients with LPG has revealed that many affected patients indeed have features of type III hyperlipidemia, characterized by elevated IDL and high apo E levels. This lipid profile is distinct from the pattern seen in patients with a nephrotic syndrome from other causes, which most often features elevated LDL and VLDL.

These findings beg the question of whether a primary abnormality in apo E might account for the abnormality in the lipid profile and the renal pathology in LPG. Apo E plays an important physiological role in lipid metabolism, serving as a ligand for the binding of lipoprotein particles to the LDL receptor (15). Apo E is polymorphic with three main variants, designated apo E2, E3, and E4, that are present in most human populations; apo E3 is the most common. These isoforms were initially identified by their differing net charges, which confer different migration by isoelectric focusing (IEF). Sequence analysis shows that the three are almost identical, differing only at two amino acid residues. At positions 112 and 158, apo E2, E3, and E4 have cys-cys, cys-arg, and arg-arg residues, respectively (16). Extensive investigation has revealed a variety of other rare apo E variants (17).
Importantly, apo E has been implicated in human disease, with variants affecting both plasma lipid levels and susceptibility to atherosclerosis (18). Recently, the spectrum of diseases associated with inherited variation in apo E has expanded beyond the cardiovascular system, with strong evidence that the apo E4 variant is a major risk factor for development of Alzheimer's disease (19).

Isoelectric focusing of apo E in patients with LPG has provided a possible role for inherited variation in this protein. Although fewer than 15% of the general Japanese population carry the apo E2 allele, virtually all Japanese LPG patients are reported as having apo E2 by IEF. Nonetheless, because heterozygosity for E2 is still much more common than LPG, the precise relationship between apo E and LPG has remained unclear.

The manuscript by Oikawa et al. now provides the first glimpse of what may be the denouement of this story. Studying three LPG patients from two apparently unrelated kindreds, they make the key observation that although all three subjects showed the presence of apo E2 by IEF, DNA sequence analysis revealed that the encoded protein had the residues characteristic of apo E3 at codons 112 and 158. This indicated a discrepancy between protein- and DNA-based typing. The authors reasoned that this discrepancy could arise if the protein migrating as apo E2 by IEF had in fact lost a positive charge at another residue because of a different mutation. Further DNA sequence analysis of apo E in these patients confirmed this suspicion, demonstrating a substitution of proline for the normal arginine at amino acid 145 in all three subjects. The authors have called this mutation apo E-Sendai. Importantly, apo E-Sendai was not found in 100 unrelated Japanese subjects and, moreover, has not been previously reported in the extensive worldwide experience with this protein. These findings indicate association of a novel apo E with LPG. Critically, this amino acid substitution occurs in an α-helical region of the protein that is known to be involved in binding to the LDL receptor (20). Because proline is known to disrupt to α-helices, it is plausible that this mutation could alter receptor binding. This possibility is supported by an earlier report that a different mutation at amino acid 145, substituting cysteine for arginine, alters receptor binding and causes hyperlipoproteinemia, although renal disease was not noted (21).

These findings constitute evidence that LPG is at least in part an inherited disease caused by a specific mutation in the apo E gene. They can potentially explain the characteristic lipoprotein abnormality seen in affected patients and are consistent with the pathological findings of apo E-containing thrombi in glomerular capillaries. Moreover, these observations make the specific prediction that the high prevalence of apo E2 by IEF in other LPG patients will be accounted for by this same mutation in many or all cases. The apparently increased prevalence of this disease in Japan could be explained by a founder effect, with many affected individuals having inherited apo E-Sendai from a remote common ancestor.

How this particular mutation would lead to glomerular damage is unknown at present. The apparent absence of other vascular pathology suggests some specificity of the interaction between mutant apo E and an element of the glomerular capillary endothelial wall. Determining whether this involves a normal receptor or a structure that does not usually interact with apo E will consequently be of interest. In addition, elucidation of the mechanisms whereby these intravascular lipid thrombi can cause glomerular damage (which implies communication between endothelial and other intraglomerular components) may provide new insights into both normal glomerular function and the pathogenesis of other forms of nephrolithiasis.

These intriguing results must however be interpreted with some caution. Only two unrelated LPG patients are reported here, and consequently it will be critical to attempt to replicate this result in additional apparently unrelated LPG patients. In addition, the penetrance of LPG must be determined, because at present the fraction of individuals with this mutation who develop LPG is entirely unknown. This will establish whether apo E-Sendai alone is sufficient to cause development of the disease or whether additional environmental or genetic factors are required. The fact that only three kindreds with more than one affected member have been reported to date (1,7,8) suggests that penetrance may prove incomplete. The identification of apo E-Sendai will permit the penetration of LPG to be readily assessed by genotype-phenotype studies in extended families of index cases. Finally, investigation of the binding of this mutant apo E to LDL receptors will be of considerable interest.

These caveats do not diminish the excitement of these findings. Given the longstanding search for mechanisms responsible for the development of nephrotic syndrome and focal segmental glomerulosclerosis, this report serves not only to expand the pathological role of inherited variation in apo E, but also perhaps as a timely impetus toward redressing the larger questions of the role of lipids in renal disease and the pathogenesis of glomerulosclerosis.

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