Mechanisms of Orthostatic Proteinuria: Lessons From a Transplant Donor

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Abstract
Orthostatic proteinuria accounts for 60% of all children and 75% of adolescents with proteinuria. Despite its frequent occurrence, the underlying pathophysiological mechanisms remain unclear. The following three possibilities have been reviewed: (1) a normal variant; (2) a glomerular abnormality; (3) a hemodynamic abnormality. On the basis of the experience with an individual who had orthostatic proteinuria and who was a donor of a living-related kidney transplant, novel insights and a potentially unifying hypothesis for the pathogenesis of this condition are presented. It is suggested that individuals with orthostatic proteinuria may be predisposed by a subtle glomerular abnormality. However, a precipitating factor, in the form of an exaggerated response to the upright position, appears to be essential to unmask the condition.

Key Words: Proteinuria, orthostatic proteinuria

Orthostatic proteinuria is a common condition encountered in nephrology. However, its pathogenesis remains unclear. We report an individual with orthostatic proteinuria who was the donor of a living-related kidney transplant. Novel insights into
the mechanisms of this condition, gleaned from the subsequent clinical course of the donor and recipient, are presented.

CASE REPORT

A 40-yr-old woman was referred to the adult nephrology service for evaluation as a renal donor for her son. She had no history of renal or other illnesses. However, she had been monitored by an internist for mild proteinuria, which had been quantitated three times in the previous 6 months to be in the 500 to 600 mg/day range. Her 12-yr-old son was suffering from ESRD secondary to posterior urethral valves. Absence of significant or postural proteinuria in him had been documented on two occasions by split 24-h urinary protein determinations.

Her physical examination was benign, as was her urine sediment. Split 24-h urine collections on two separate occasions revealed more than 300 mg of protein excretion when she was upright, but less than 100 mg when she was supine. Her renal ultrasound, IV pyelogram, and arteriogram were normal. She was diagnosed to have orthostatic proteinuria and was cleared for renal donation.

Intraoperatively, a kink was detected in the renal vein of the donor kidney. After the surgery, her proteinuria resolved. A split 24-h urine collection 4 months after nephrectomy showed only 140 mg of protein when she was upright and 10 mg when she was in the supine position. Her son is now over a year posttransplant and has normal renal function. He continues to be completely free of proteinuria, as documented by split 24-h urinary protein determinations.

BACKGROUND

Orthostatic proteinuria has been defined as a "laboratory syndrome requiring the absence of qualitative proteinuria during recumbency, and its appearance during quiet upright ambulation or upon standing" (1). The total daily protein excretion should usually be less than 1,000 mg, with the majority appearing in the upright position. Individuals with this entity should have no known renal disease or hypertension and should have normal urinary sediment and renal function.

INCIDENCE AND NATURAL HISTORY

Orthostatic proteinuria accounts for 60% of all children with proteinuria and 75% of adolescents with proteinuria (2). It can be detected in 2 to 5% of normal adolescents (3). The incidence gradually decreases in the second decade of life, and it is rare in persons over 30 yr of age.

Very rarely, orthostatic proteinuria may be the first symptom of renal disease (1,4). This condition has also been documented in the resolving phases of acute glomerulonephritis and the nephrotic syndrome. However, the excellent long-term prognosis for the vast majority of individuals with this diagnosis has been borne out by several studies. Springberg et al. reported a 20-yr follow-up of 43 patients with fixed and reproducible orthostatic proteinuria; 83% showed complete resolution of proteinuria, and there were no relapses (5). All 43 patients had normal renal function. In another study, Ryland and Spreiter reported a follow-up of six patients diagnosed to have orthostatic proteinuria 42 to 50 yr ago; all six had resolution of the condition and had normal renal function (6).

PATHOGENETIC MECHANISMS OF ORTHOSTATIC PROTEINURIA

Despite its frequent occurrence, the mechanisms leading to orthostatic proteinuria are unclear and subject to controversy. We will consider the following three possibilities, as listed in Table 1: (1) Is it a normal variant? (2) Is there a glomerular abnormality? and (3) Is there a hemodynamic abnormality?

Is It a Normal Variant?

Some investigators have suggested that orthostatic proteinuria is merely an exaggerated variant of the normal, on the basis of the following two findings. First, "normal" proteinuria (less than 150 mg/day) is also posture dependent. Mahurkar et al. have shown that 20% of normal volunteers exhibit increased urinary protein excretion upon assuming the upright position, although the total amount of proteinuria remained within accepted limits (7). In another study, of 116 normal adolescents, Houser et al. demonstrated a significant rise in the urine protein/creatinine ratio in the upright versus recumbent position (8).

Second, orthostatic proteinuria, like normal proteinuria, is rather selective. Frey et al. compared 14 individuals who showed orthostatic proteinuria with 14 patients who had biopsy-proven glomerulonephritis. The selectivity of proteinuria was clearly greater in those with orthostatic proteinuria (9). Furthermore, there was an increase in selectivity when these individuals were upright, whereas patients with glomerulonephritis continued to exhibit nonselective proteinuria when upright.

Is There a Glomerular Abnormality?

Renal biopsies of individuals with orthostatic proteinuria have revealed few minor and inconsistent findings on light or electron microscopy (1,10–12).
About half of the biopsies showed mild focal and segmental mesangial hypercellularity, focal or diffuse capillary wall thickening, and occasional focal foot process fusion. Two electron microscopic studies did not detect any abnormalities (11,12). However, immunofluorescence showed mesangial and capillary deposits of C3, immunoglobulin G, and immunoglobulin in 10 out of 12 patients with orthostatic proteinuria. The significance of these findings is unclear. It is conceivable that these patients may have suffered subclinical immune injury to the kidney (see reference 17), which might render them more susceptible to other (hemodynamic) factors that mediate orthostatic proteinuria.

Is There a Hemodynamic Abnormality?

The upright position normally causes venous pooling in the legs, renal vein congestion, and decreased RBF (with resultant activation of angiotensin II), all of which increase efferent arteriolar resistance and protein filtration (13,14). It is possible that in individuals with orthostatic proteinuria, this hemodynamic response is exaggerated. An experimental model supporting this mechanism has been described: acute partial renal vein obstruction in rats caused a marked reduction in glomerular filtration, a rise in efferent arteriolar resistance, and a 15-fold increase in proteinuria (15). These changes were normalized by pharmacologic blockade of angiotensin II.

Recently, an additional mechanism for renal vein obstruction has been described, independent of angiotensin II (16). Of 15 normal children with orthostatic proteinuria, 13 demonstrated an entrapment of the left renal vein by the aorta and superior mesenteric artery, with typical prestenotic dilation, by ultrasonography. These findings were enhanced by the upright position and were relieved by the supine position. However, the control group was 80 healthy children, 9 of whom also showed left renal vein entrapment. It was unclear why these children displayed renal vein entrapment but did not have proteinuria.

On the basis of the above considerations, we offer the following hypothesis (Figure 1). Individuals with orthostatic proteinuria may be predisposed by a sub-"normal" proteinuria to an exaggerated response to the upright position, mediated by anatomic (renal vein entrapment) or functional (angiotensin II) mechanisms.

The case report described here lends support to this hypothesis. The mother may have suffered an immune injury to her kidneys but probably required the kink in her renal vein to precipitate orthostatic proteinuria. When this kidney was transplanted into her son, her proteinuria resolved because the precipitating factor was removed. The renal injury alone was not sufficient to cause proteinuria in the absence of the kink, because her son has received that kidney but has shown normal urinary protein excretion.

TABLE 1. Putative mechanisms of orthostatic proteinuria

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Supporting Evidence</th>
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<tbody>
<tr>
<td>Normal Variant</td>
<td>Normal proteinuria is posture dependent</td>
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<tr>
<td>Glomerular Abnormality</td>
<td>Both normal and orthostatic proteinuria are selective</td>
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<tr>
<td>Hemodynamic Abnormality</td>
<td>Capillary wall thickening and mesangial hypercellularity seen</td>
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<tr>
<td></td>
<td>Mesangial/capillary deposits of IgG, IgA, and C3 reported</td>
</tr>
<tr>
<td></td>
<td>Animal model of angiotensin II-mediated efferent arteriolar constriction and proteinuria</td>
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<td></td>
<td>Left renal vein entrapment syndrome</td>
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</table>

Devarajan

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