Nephrotic Syndrome in Autosomal Dominant Polycystic Kidney Disease

Gabriel Contreras, Alvaro Mercado, Victoriano Pardo, and Carlos A. Vaamonde

The Renal Division of the University of Miami School of Medicine was developed in the mid-1960s by Drs. Gorman Hills and William Hulett. It is currently a joint program between the University of Miami/Jackson Memorial Hospital (Dr. Jacques J. Bourgoignie, Division Director) and the Miami Veterans Affairs Medical Center (Dr. Carlos A. Vaamonde, Chair, Nephrology Section). More than 130 fellows have graduated from this combined clinical and research fellowship program since 1968. The program currently supports seven trainees. Eleven full-time and four part-time faculty members supervise the clinical and research activities at both major hospitals as well as at the University of Miami Hospital and Clinics. All institutions are located in a large medical center within walking distance.

The training program provides a 2-yr clinical experience for physicians who have completed their training in internal medicine. Trainees are exposed to a wide range of acute and chronic nephrologic illnesses, extending from the exotic and rare to the most common nephropathies. Training in water, electrolyte, and acid-base disturbances and hypertension is emphasized. About 150 new ESRD patients and 1,000 consultations are seen yearly. About 100 percutaneous renal biopsies and over 4,000 acute dialysis and ultrafiltration procedures are performed yearly. Fellows are trained in the performance and interpretation of renal biopsies. Two large dialysis units provide all modalities of dialytic therapy.

The Division is associated with an active organ transplant program, with two of the nephrologists coordinating the medical aspects of renal transplantation. Kidney transplants average 100 per year. Other transplants include kidney-pancreas, liver, gut, heart, lung, and bone marrow.

A third optional year is available for fellows who desire experience in research. Research is an integral part of the training process with areas of major interest including AIDS and the kidney, the pathophysiology and prevention of progressive renal insufficiency, hepatitis C, drug nephrotoxicity, microvascular renal pathophysiology, hypertension, and renal transplantation. These investigations combine studies in patients and whole animals, as well as investigation in isolated organs and cultured cells, by using modern techniques of physiology, immunology, and molecular biology.

There is an active cycle of conferences, including renal grand rounds, journal club, research, pathophysiology, and renal biopsy conferences. Although faculty and fellows participate jointly in the educational process, trainees are encouraged to present several times during the year. Selected trainees help teach the renal segment of the "Mechanism of Disease" course given to second-year medical students.

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ABSTRACT
Urinary protein excretion is generally less than 1 g/24 h in autosomal dominant polycystic kidney disease (ADPKD), and the association of the nephrotic syndrome with this condition is considered rare. A patient with ADPKD associated with nephrotic-range proteinuria is described. She exhibited a relatively rapid impairment of her renal function. An open renal biopsy revealed focal segmental glomerulosclerosis (FSGS) with features consistent with secondary FGS.
Twenty-one patients with ADPKD and nephrotic syndrome were retrieved from the literature. Fourteen of them (including this case) had a histopathologic evaluation, and FGS was the dominant diagnosis (five patients). Next in frequency were minimal-change disease and membranous nephropathy, with two patients each. Five other patients had a variety of diagnoses. Thus, it is difficult to ascertain if these associations are coincidental or represent a specific pathogenetic relationship. The evaluation of the data also suggests that the presence of proteinuria and nephrotic syndrome accelerates the course of ADPKD toward ESRD.

Key Words: Autosomal dominant polycystic kidney disease, proteinuria, nephrotic syndrome, focal segmental sclerosis, progression to ESRD

We describe a patient with autosomal dominant polycystic kidney disease (ADPKD) associated with nephrotic-range proteinuria. Urinary protein excretion is generally mild in ADPKD, and the association of the nephrotic syndrome with this condition is considered rare (1, 2). This suggests a coincidental relationship between the nephrotic syndrome and ADPKD. Almost every form of glomerular disease has been shown to occur in systemic diseases affecting the kidney. For instance, in diabetes, membranous nephropathy (the most common association), immunoglobulin A (IgA) nephropathy, acute glomerulonephritis, lupus, amyloidosis, mesangiocapillary and crescentic glomerulonephritis, and minimal-change disease have all been reported (3). Likewise, lupus erythematosus may reveal histopathology other than that related to the primary disease such as amyloidosis, HIV nephropathy, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Of interest, however, among the variety of histopathologic lesions reported in ADPKD patients with associated glomerulopathy, focal glomerular sclerosis (FGS) was the more commonly encountered. Thus, it is difficult to be sure whether these associations are simply coincidental or represent a specific pathogenetic relationship.

CASE REPORT

The patient was a 65-yr-old, mildly overweight woman from Colombia with a history of ADPKD known for 25 yr. She had well-controlled hypertension for 25 yr and a strong family history of ADPKD. The patient's mother was hypertensive and died of stroke, two brothers had ADPKD, and two normotensive sons ages 38 and 42 refused screening for ADPKD. A 40-yr-old hypertensive son without ADPKD had FGS and received a renal transplant 8 yr ago.

In December 1990, the physical examination was unremarkable except for a blood pressure of 160/90 mm Hg during clonidine and atenolol treatment; the latter agent was subsequently changed to verapamil because of exacerbation of the patient's mild chronic obstructive pulmonary disease. This was secondary to chronic bronchitis, usually aggravated by smoking. The patient was not O2 or steroid dependent and did not have evidence of sleep apnea. At that time, she was found to have nephrotic-range proteinuria (5.5 g/24 h), with a serum creatinine of 1.0 mg/dL, serum albumin of 3.2 g/dL, hematocrit of 51%, cholesterol of 299 mg/dL, and a 24-h endogenous creatinine clearance (CrCl) of 80 mL/min. As far back as July 1987, + + proteinuria was detected on routine urine examination on several occasions. Renal ultrasonography was performed and showed the right kidney measuring 11.9 cm in length with multiple cysts ranging in diameter from 1.8 to 4.4 cm. The left kidney measured 12.5 cm in length with multiple small cysts; there was a large cyst measuring 6.7 cm in diameter. There was no evidence of cysts in the liver or of mitral valve prolapse. There was no history of urinary tract infections, renal colic, gross hematuria, or abdominal complications. In August 1991, a percutaneous renal biopsy attempted at another institution was unsuccessful.

The patient was referred to the University Clinic on February 1992 with findings similar to those described above. The physical examination was unremarkable, the blood pressure was 150/80 mm Hg, with minimal peripheral leg edema, and her body weight was 73 kg. The laboratory evaluation revealed: hematocrit, 46%; blood glucose, 115 mg/dL; BUN, 17 mg/dL; creatinine, 1.2 mg/dL; serum albumin, 3.7 g/dL; cholesterol, 257 mg/dL; 24-h urine protein, 5.8 g; ANA, 1:80 speckled; anti-dsDNA, anti-Smith, ANCA, anti-SSA, anti-SSB, and anti-RNP, all negative; C3:86, mg/dL; and C4:19, mg/dL. There were no monoclonal bands on immunoelectrophoresis of the serum, and no monoclonal light chains were detected in the urine.

The patient underwent an open kidney biopsy without complications on May 1992. The renal biopsy (Figures 1 and 2) revealed the presence by light microscopy of approximately 50 glomeruli. Some globally sclerosed glomeruli were located in wedge-shaped subcapsular areas that extended deep into the cortex and contained atrophic tubules surrounded by interstitial fibrous tissue. These involved about 25% of the biopsy surface and included collections of mononuclear cells. Glomeruli in other areas exhibited predominantly diffuse mild segmental mesangial hyperplasia. Three glomeruli located deep in the wedge-shaped areas showed typical focal segmental sclerosis (Figure 1). One of the three (not shown) exhibited hyalinosis. Microcystic tubules were present in some biopsy areas (Figure 2). Vessels showed thickened media. There was an increase in mesangial matrix with segmental collapse of capillaries and basement membrane wrinkling by electron microscopic examination. There were no immune-type electron-dense deposits. Epithelial foot processes were swollen in the sclerotic areas of the glomeruli with FGS. However, foot processes ap-
1994, the Ccr had decreased to 38 mL/min and proteinuria remained at 4.1 g/24 h. In the last control available, January 1995, blood pressure was 140/86 mm Hg, proteinuria was 5.5 g/24 h, serum creatinine was 2.1 mg/dL, Ccr was 32 mL/min, and hematocrit was 43%. A liver ultrasound revealed an absence of cysts. In the renal ultrasound, the right kidney length was 13.9 cm with the largest cysts measuring 5.0 cm in diameter. The length of the left kidney was 13.3 cm, with the diameter of the largest cyst measuring 8.0 cm. The presence of FGS in association with ADPKD may explain the absence of large kidneys in this patient.

DISCUSSION

This case report describes one form of glomerular pathology, FGS, associated with nephrotic syndrome in patients with ADPKD. The frequency of proteinuria in ADPKD when qualitatively assessed has ranged in children or nonuremic adults from 14 to 34% to about 80% in adults with advanced renal failure, as recently reviewed by Chapman et al. (2). Those authors have reported a frequency of 18% in a large unselected population of ADPKD in which proteinuria was measured quantitatively. They concluded that those patients with established proteinuria had a significantly higher mean arterial pressure, larger renal volumes, lower creatinine clearances, and a more aggressive course. Proteinuria was found to be more common in ADPKD patients, as compared with essential hypertension, of which a 4 to 7% incidence is usually seen. Of interest, microalbuminuric ADPKD patients with hypertension and left ventricular hypertrophy had a significantly higher filtration fraction and larger renal volumes (2).

In the consultative experience of one of the authors (C.A.V.), the range of protein excretion in 13 consecutive patients with ADPKD (excluding the patient reported here) observed over a period of 17 yr was from 23 to 5,500 mg/24 h. It should be noted that in this referral population, 54% of the patients had proteinuria ranging from 392 to 5,500 mg/24 h (average of 2,270 ± 672 mg/24 h) with lower 24-h Ccr (63 to 8 mL/min, average of 31 ± 8 mL/min) and higher mean blood pressures (113 ± 9 mm Hg) than those ADPKD patients without overt proteinuria (24-h protein, 75 ± 19 mg; P < 0.001) who had an average Ccr of 97 ± 20 mL/min (P < 0.001) and an average mean blood pressure of 101 ± 6 mm Hg (nonsignificant). In none of the patients who had nephrotic-range proteinuria was a renal biopsy performed. The higher incidence of overt proteinuria in this small group of selected patients, compared with large unselected populations (2), may reflect the presence of advanced renal disease, as expected in patients referred for consideration of therapy for ESRD.

In 1957, Dalgaard (4) described three instances of nephrotic-range proteinuria in a report of 122 patients with ADPKD, but unfortunately, renal biopsy

Figure 1. Glomerulus with diffuse increase in mesangial matrix and three areas with segmental sclerosis (arrows) (hematoxylin and eosin, original magnification ×450).

Figure 2. Microcystic tubules in some biopsy areas. Part of a cyst is seen in the lower left corner (hematoxylin and eosin original magnification ×250).
TABLE 1. Patients with ADPKD and nephrotic syndrome with renal histopathologic diagnosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>First Author (Ref. No.)</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Known Duration of ADPKD (yr)</th>
<th>BP (mm Hg)</th>
<th>Hct (%)</th>
<th>Serum Albumin (g/dL)</th>
<th>Ccr (ml/min)</th>
<th>Proteinuria (g/24 h)</th>
<th>Renal Histopathology</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Murphy (9)</td>
<td>44</td>
<td>M</td>
<td>13</td>
<td>Diastolic 110</td>
<td>NA</td>
<td>3.4</td>
<td>(cr 10 mg/dL)</td>
<td>7</td>
<td>FGS</td>
<td>Hemodialysis, 32 months later</td>
</tr>
<tr>
<td>2</td>
<td>Montoyo (10)</td>
<td>35</td>
<td>M</td>
<td>4</td>
<td>140/90</td>
<td>32</td>
<td>2.4</td>
<td>22</td>
<td>14</td>
<td>FGS</td>
<td>Hemodialysis, 3 months later</td>
</tr>
<tr>
<td>3</td>
<td>Dionisio (11)</td>
<td>58</td>
<td>M</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Slight ↓</td>
<td>8</td>
<td>FGS</td>
<td>Prednisone, cytoxan (proteinuria ↓ to 1 g/day). Ccr 52 ml/min 1 yr later</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>This Report</td>
<td>65</td>
<td>F</td>
<td>25</td>
<td>160/90</td>
<td>46</td>
<td>3.7</td>
<td>47</td>
<td>5.8</td>
<td>FGS</td>
<td>Alive, Ccr 38 ml/min</td>
</tr>
<tr>
<td>5</td>
<td>Kida (8)</td>
<td>34</td>
<td>M</td>
<td>1</td>
<td>160/102</td>
<td>NA</td>
<td>32</td>
<td>5.3</td>
<td>FGS/MCD</td>
<td>Prednisone, cytoxan, remission 9 months</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Nakahama (12)</td>
<td>14</td>
<td>M</td>
<td>0</td>
<td>104/64</td>
<td>50</td>
<td>1.7</td>
<td>114</td>
<td>23</td>
<td>MCD</td>
<td>Steroids → proteinuria &lt;300 mg/24 h</td>
</tr>
<tr>
<td>7</td>
<td>Kuroki (13)</td>
<td>18</td>
<td>F</td>
<td>0</td>
<td>130/80</td>
<td>(Hgb 14.9 g/dL)</td>
<td>3.4</td>
<td>64</td>
<td>5.4</td>
<td>MCD</td>
<td>Prednisone, cytoxan, remission 9 months after</td>
</tr>
<tr>
<td>8</td>
<td>Abe (14)</td>
<td>55</td>
<td>F</td>
<td>2</td>
<td>150/92</td>
<td>32</td>
<td>3.0</td>
<td>103</td>
<td>7.7</td>
<td>MGN</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>Shikata (15)</td>
<td>53</td>
<td>F</td>
<td>2</td>
<td>160/100</td>
<td>35</td>
<td>2.2</td>
<td>56</td>
<td>6</td>
<td>MGN</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Licina (16)</td>
<td>69</td>
<td>F</td>
<td>3</td>
<td>170/90</td>
<td>NA</td>
<td>(cr 5 mg/dL)</td>
<td>(3+)</td>
<td>CGN</td>
<td>Responsive to steroid and cytoxan (cr 7.2 mg/dL ↓ to 2.4 mg/dL); no further follow-up after 3 months</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Haritharan (17)</td>
<td>44</td>
<td>M</td>
<td>0</td>
<td>NA</td>
<td>27</td>
<td>2.5</td>
<td>(cr 1.3 mg/dL)</td>
<td>11</td>
<td>IDGS</td>
<td>Hemodialysis, 1 yr later cr 9.2 mg/dL, 3 months later</td>
</tr>
<tr>
<td>12</td>
<td>Panisello (18)</td>
<td>67</td>
<td>F</td>
<td>0</td>
<td>195/105</td>
<td>29</td>
<td>4.4</td>
<td>(cr 6.3 mg/dL)</td>
<td>4.2</td>
<td>IgAN</td>
<td>CAPD 10 months later</td>
</tr>
<tr>
<td>13</td>
<td>Villar (19)</td>
<td>25</td>
<td>M</td>
<td>7</td>
<td>160/110</td>
<td>22</td>
<td>2.7</td>
<td>(cr 5.5 mg/dL)</td>
<td>12</td>
<td>Type 1 MPGN</td>
<td>CAPD 1 yr later</td>
</tr>
<tr>
<td>14</td>
<td>Villar (19)</td>
<td>28</td>
<td>M</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>(cr 5.7 mg/dL)</td>
<td>4.7</td>
<td>Mesangial Proliferative GN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NA, not available; 0, at time of diagnosis of nephrotic syndrome; MCD, minimal-change disease; CGN, crescentic glomerulonephritis; MGN, membranous glomerulonephritis; IDGS, intercapillary diabetic glomerulosclerosis; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; Mesangial proliferative GN, mesangioproliferative glomerulonephritis; cr, serum creatinine; (3+), urinary protein by dipstick; Hct, hematocrit; Hgb, hemoglobin; BP, blood pressure.
data were not reported. Subsequently, four other patients with nephrotic syndrome were reported without histopathologic diagnosis (5–7). To our knowledge, in 1972, Kida et al. (8) published the first case of ADPKD with nephrotic syndrome and a biopsy-proven renal lesion. We could find only 13 cases with the renal lesion documented by histopathology published over the last few decades (Table 1) (8–19). There were six women and seven men with ages ranging from 14 to 69 yr. There were no black patients reported. Fourteen patients had a histopathologic diagnosis (Table 1). Four, including the patient described here, had FGS (9–11). The presence of FGS in the deep nephrons of the patient reported by Kida et al. (8) with the diagnosis of minimal-change disease cannot be excluded with certainty. The decreased Ccr, the short known duration of the disease, the presence of a global increase in mesangial matrix and cells in the glomeruli illustrated (Figure 6 of Reference 8), and the uncertainty about the diagnosis of FGS in the early 1970s favor this interpretation. Of the nine remaining patients, two had minimal-change disease (12,13), two had idiopathic membranous nephropathy (14,15), and five others had crescentic glomerulonephritis (16), diabetic nephropathy (17), IgA nephropathy (18), and membranoproliferative and postinfectious mesangiproliferative glomerulonephritis (19), respectively. Because of the assumed risk as the result of the presence of large cysts or difficulties with obtaining suitable tissue for diagnosis (20), 86% of the procedures (12 of 14) were open surgical biopsies and only 2 were percutaneous (12,17).

FGS was diagnosed in 36% of the nephrotic syndrome cases with histopathology examination (Table 1), including Patient 5. This frequency is twice as high as the 15% frequency of FGS found in the general adult population (21). In contrast, membranous nephropathy, the most common cause of idiopathic nephrotic syndrome in adults with a frequency of 25% (21), was found in 14% of ADPKD patients with nephrotic syndrome, suggesting that FGS may be more than a coincidental finding. We are also aware of two other patients with ADPKD with nephrotic syndrome and FGS not yet reported (Arlene B. Chapman, personal communication). Nevertheless, careful interpretation of this is warranted because the relative frequency of a disease differs according to whether the population is unselected or referred.

Renal failure is the most serious if not the most frequent renal complication of ADPKD. Approximately 45% of patients will reach ESRD by age 60 (22). The rate of the progression of renal failure in ADPKD is slow. It takes decades to reach ESRD, especially when better therapies for hypertension are used (1). Recent data on ADPKD, however, indicate that renal function does not decrease at a constant rate between birth and ESRD, but rather remains well preserved for many years and decreases rapidly at a later stage (23). The risk factors affecting the progression of renal disease in ADPKD have been recently assessed (24). Diagnosis at a young age is associated with worse prognosis, and ADPKD 2 appears to also have a worse prognosis than ADPKD 1. Severe hypertension, gross hematuria, repeated infections, especially in men, and massive kidney size accelerate progression to ESRD (24). The enlargement of cysts by compressing normal parenchyma is a central factor in the pathogenesis of chronic renal failure in this disorder (1). Of note, 11 of the 14 patients listed in Table 1 had decreased Ccr or elevated BUN or serum creatinine concentrations at the time of the reports. Of these 11 patients, at least 5 had moderate to severe hypertension, whereas the others had borderline or normal values. Of the five patients with FGS, two had marked renal failure (serum creatinine of 10 mg/dL, Ccr of 22 mL/min, respectively). There were no data available in the third patient, although he initiated dialysis 6 yr later, suggesting the presence of only moderate renal failure at the time of the report. In the fourth patient (this report), her rapid progression appears to relate more to the proteinuria and hypertension than to the kidney size or other risk factors. The patient of Kida et al. (8) exhibited a Ccr of 32 mL/min at diagnosis, which increased to 52 mL/min 1 yr later after treatment of the nephrotic syndrome. Of the two patients (12,14) with a normal Ccr, one was only 14 yr old with a diagnosis of minimal-change disease and the other had membranous nephropathy. Also, as can be seen in Table 1, patients with ADPKD and associated glomerulopathy and nephrotic syndrome appear to progress rapidly. Of the patients with follow-up information, six were on dialysis therapy less than 6 yr after the nephrotic syndrome was discovered.

FGS and segmental glomerulosclerosis with or without hyalinosis are nonspecific lesions that may be idiopathic or secondary to a chronic adaptive process such as glomerular hyperfiltration. Clinically, it has been suggested that secondary FGS is characterized by less proteinuria, mildly decreased or normal serum albumin, and mild edema in contrast to the more severe presentation of primary FGS (25). Olson et al. reviewed the possibility that FGS may be the histologic manifestation of glomerular hyperfiltration, a process that characterizes many renal diseases and results in a gradual loss of the filtering surface area. Unlike the situation in idiopathic FGS, foot process effacement in FGS due to glomerular hyperfiltration is focal not diffuse (26). The development of similar lesions in the remnant kidney after subtotal nephrectomy suggests that FGS may result from hemodynamic alterations occurring in the residual nephrons (27). Glomerular hyperfiltration also could play an important role in the development of FGS and heavy proteinuria in patients with ADPKD, because glomerular hyperfiltration as assessed by creatinine clearance has been reported in a subgroup of patients with early ADPKD (28).

Polycystic kidney disease has a worldwide distribution, and an estimated 500,000 people have the disease in the United State (22). To our knowledge, the nephrotic syndrome has been reported in only 21
patients (4−19), although it is reasonable to assume that many other similar cases are not published. Almost every form of primary glomerulopathy in ADPKD has been reported, suggesting a coincidental finding. On the other hand, the higher frequency of FGS in ADPKD may suggest that hemodynamic changes might play a role in the progression to ESRD in a subgroup of ADPKD patients. It is interesting that in transgenic mice, renal cyst formation and FGS with proteinuria have been induced (29). However, the number of glomeruli in the experimental and control animals did not differ significantly, suggesting that at least in this experimental model, the native number of nephrons did not appear to influence hemodynamically induced glomerular changes (29).

The progression to ESRD is accelerated in ADPKD mostly as the result of the uncontrolled hypertension and ischemic compression. The data from the 21 ADPKD patients with nephrotic syndrome also support a faster progression to ESRD in the presence of nephrotic-range proteinuria. Seven of 21 patients were on dialysis or had a Ccr of less than 10 mL/min in less than 6 yr, and another 4 patients had a Ccr of less than 56 mL/min or a serum creatinine of more than 5 mg/dL at the time when the nephrotic syndrome was diagnosed. Preliminary data from the Modification of Diet in Renal Disease study in patients with ADPKD also showed a positive correlation between proteinuria and progression of renal disease (30). At present, it is impossible to assess the potential benefit of measures leading to a decrease in the proteinuria in the progression of ADPKD toward ESRD.

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REFERENCES