

Minireview

Nephrotic syndrome and autosomal dominant polycystic kidney disease

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Abstract

Background. Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder characterized by the development and growth of cysts in the kidneys and other organs. In ADPKD patients, nephrotic range proteinuria is unusual and needs to be investigated further to exclude coexisting glomerular disease. Among the anecdotal case reports of ADPKD associated with nephrotic syndrome, focal segmental glomerulosclerosis occurs most frequently.

Methods. We report the case of a 26-year-old male with ADPKD and concomitant nephrotic syndrome, in which an ultrasound (US)-guided renal biopsy showed a mesangioproliferative glomerulonephritis. We treated the patient with prednisone 1 mg/kg/day, because of the failure of treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker association.

Results. After 6 months of steroid treatment, we observed a stability of his GFR and a reduction of proteinuria.

Conclusion. This case report and other cases of the literature underline the importance of a renal biopsy in patients with ADPKD and nephrotic syndrome in order to make an accurate diagnosis and an appropriate treatment/prevention of renal function deterioration.

Keywords: autosomal dominant polycystic kidney disease; glomerulonephritis; nephrotic syndrome; renal biopsy

Introduction

Autosomal dominant polycystic kidney disease (ADPKD), the most common heritable renal disease, with an estimated incidence of 1:800 live births, is a disorder characterized by the development and growth of cysts in the kidneys and other organs [1]. This disease is genetically heterogeneous; in ~85% of the cases, the disease is caused by a mutation localized on chromosome 16 (PKD1) and in 15% by a mutation localized on chromosome 4 (PKD2), while a few families have been identified in which the disease is caused by a mutation in an unmapped locus [2]. However, within the two identified forms of the disease, there is a remarkable variability in clinical features. Proteinuria and microalbuminuria (MA) also occur with a highly variable severity and are associated with a more progressive course of the disease [3, 4]. Mild proteinuria, usually <2 g/24 h, is a common finding on routine examination in ADPKD patients; however, the association of nephrotic syndrome with ADPKD is considered rare [4, 5] and needs to be investigated further to exclude coexisting glomerular disease. Among the anecdotal case reports of ADPKD associated with nephrotic

syndrome, focal segmental glomerulosclerosis occurs most frequently [6].

We report the case of a 26-year-old male with ADPKD and concomitant nephrotic syndrome, in which the renal biopsy showed a mesangioproliferative glomerulonephritis

Case report

In April 2009, a 24-year-old man was referred to our hospital with a history of ADPKD. The patient's father had a diagnosis of ADPKD and the mother was affected by a membranous nephropathy. At first observation, laboratory studies showed a daily urinary protein excretion of 3.19 g, serum creatinine 106.08 $\mu\text{mol/L}$ (1.2 mg/dL), and eGFR (estimated glomerular filtration rate) 84.7 mL/min/1.73 m². We thus started therapy with an angiotensin-converting enzyme inhibitor (ACEi), ramipril 5 mg/day. After 6 months, his proteinuria decreased to 1.13 g/day, so we added an angiotensin receptor blocker (ARB), losartan potassium 50 mg/day. His proteinuria remained about 1.8–2 g/day until the end of 2010.

In July 2011, urine analysis showed a daily protein excretion of 7.4 g and 15 red blood cells per high power field; the patient had neither peripheral leg oedema nor other symptoms; urine culture was sterile; tests for HBsAg and HCVAb and anti-nuclear antibodies were negative; IgG, IgA, IgM, C3, C4 were normal; there were no monoclonal bands on immunoelectrophoresis of the serum and no monoclonal light chains were detected in the urine. An abdomen ultrasound (US) analysis showed the right kidney measuring 11.4 cm in length with multiple cysts ranging in diameter from 1.6 to 3.2 cm, and the left kidney measuring 13.4 cm in length with multiple cysts. There were no cysts in the lower pole of the left kidney. Due to the persistent presence of nephrotic-range proteinuria, a US-guided biopsy was performed, the diagnosis of which was mesangioproliferative glomerulonephritis. Because of the failure of treatment with ACEi/ARB association, we added prednisone to the antiproteinuric agents at the initial dose of 1 mg/kg/day. After 6 months of steroid treatment, we observed an eGFR stability, a gradual reduction of proteinuria until ~2 g/24 h and an increase of the serum albumin. After 3 months from the end of steroid therapy the proteinuria was 0.5 g/24 h.

Discussion

Proteinuria and MA occur with a highly variable severity in ADPKD patients and proteinuria is usually <2 g/24 h. The frequency of occurrence of proteinuria in ADPKD ranges from 14 to 34% in non-uraemic adults to ~80% in adults with advanced renal failure [4], even if a high prevalence of MA was found in normotensive adults and children with ADPKD [7, 8]. Chapman *et al.* have demonstrated that both overt proteinuria and MA in ADPKD patients were associated with a higher mean arterial pressure, lower GFR, larger renal volume, worse renal prognosis [4] and with an increased cardiovascular morbidity [9]. The association of nephrotic syndrome with ADPKD is considered rare [4, 5] and, when possible, should be investigated by histological studies to exclude the possibility of a superimposed glomerular disease.

In 1957, Dalgaard described three instances of nephrotic range proteinuria (>5 g/day) in a report of 122 cases with ADPKD; but renal biopsy data are not available in these series [10]. Subsequently, four other ADPKD patients with nephrotic syndrome were described without histopathologic diagnosis [11–13]. In 1972, Kida *et al.* [14] reported the first case of ADPKD with nephrotic syndrome due to biopsy-proven minimal change nephrotic syndrome. In 1995, Contreras *et al.* [6] reviewed 14 cases of ADPKD in which the renal lesions had been evaluated by histopathological studies. In 2006, Hiura *et al.* [15] expanded Contreras' review adding seven more Japanese cases. Our review of the literature reveals that since 1972 to the present there have been only 29 cases (including this report) of ADPKD, associated with nephrotic syndrome, in which the renal lesions were evaluated by histopathological studies (Table 1); but it is reasonable to assume that many other similar cases were not investigated or published. This may be due in part to the reluctance of nephrologists to perform an open renal biopsy in ADPKD patients and in part to the real risk and complexity of percutaneous renal biopsy in these patients. Since the presence of multiple bilateral cysts has been listed as relative contraindication to percutaneous renal biopsy,

Table 1. Renal histology in patients with ADPKD and nephrotic range proteinuria^a

First author	Age	Sex	Renal biopsy	Renal histopathology
Contreras <i>et al.</i> [6]	65	F	O	FSGS
Murphy <i>et al.</i> [17]	44	M	O	FSGS
Montoyo <i>et al.</i> [38]	35	M	O	FSGS
Dionisio <i>et al.</i> [18]	58	M	O	FSGS
Maeshima <i>et al.</i> [19]	23	M	P	FSGS
Savaj <i>et al.</i> [20]	29	M	O	FSGS
Kida <i>et al.</i> [14]	34	M	O	MCD
Nakahama <i>et al.</i> [21]	14	M	P	MCD
Kuroki <i>et al.</i> [12]	18	F	O	MCD
Nishimura <i>et al.</i> [23]	62	M	O	MCD
Kurosu <i>et al.</i> [24]	50	F	O	MCD
Abe <i>et al.</i> [25]	55	F	O	MN
Shikata <i>et al.</i> [26]	53	F	O	MN
Oguro <i>et al.</i> [27]	59	M	P	MN
Peces <i>et al.</i> [28]	38	M	P	MN
Saxena <i>et al.</i> [29]	Data not available			MN
Panisello <i>et al.</i> [32]	67	F	O	IgAN
Hiura <i>et al.</i> [15]	70	M	O	IgAN
Licina <i>et al.</i> [34]	69	F	O	CreGN
Hariharan <i>et al.</i> [35]	44	M	P	IDGS
Villar <i>et al.</i> [36]	25	M	O	MPGN I
Villar <i>et al.</i> [36]	28	M	O	Post-Inf. GN
Mizutani <i>et al.</i> [33]	50	F	O	AMYLOID
Sar <i>et al.</i> [16]	39	M	GR	AMYLOID
Wan <i>et al.</i> [5]	49	F	CT	MLN
D'Cruz <i>et al.</i> [37]	35	M	O	D-PGN
Seyrec <i>et al.</i> [31]	Data not available			MES-PGN
Okubo <i>et al.</i> [30]	51	M	O	MES-PGN
Visciano (This report)	26	M	P	MES-PGN

^aP, percutaneous biopsy; O, open surgical biopsy; CT, computed tomography-guided biopsy; GR, gingival rectum biopsy; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MN, membranous nephropathy; IgAN, IgA nephropathy; CreGN, crescentic glomerulonephritis; IDGS, intercapillary diabetic glomerulosclerosis; MPGN I, membranoproliferative glomerulonephritis type I; Post-Inf GN, post infectious mesangial proliferative glomerulonephritis; MLN, membranous lupus glomerulonephritis; D-PGN, diffuse proliferative glomerulonephritis; MES-PGN, mesangial proliferative glomerulonephritis.

due to the presumed risk of complications and difficulties in obtaining suitable tissue for diagnosis, a majority of ADPKD patients received an open surgical biopsy. In fact, of the 26 patients whose methodological data were available, only 5 (including our patient) received a percutaneous renal biopsy, 1 patient received a computerized tomography (CT)-guided renal biopsy, in 1 patient the diagnosis of amyloidosis was supposed on the basis of a gingival and intestinal biopsy [16]. The 20 remaining patients received an open surgical biopsy.

Of the 29 cases evaluated by biopsy procedures, focal segmental glomerulosclerosis (FSGS) [6, 17–20] (6 patients), minimal change nephropathy [14, 21–24] (5 patients) and membranous nephropathy [25–29] (5 patients) were the dominant diagnoses. Next were non-IgA mesangial proliferative glomerulonephritis [30, 31], (with three patients including ours), IgA nephropathy [15, 32] (with two patients) and amyloidosis [16, 33] (with two patients). Other types of glomerulonephritis diagnosed were crescentic glomerulonephritis [34], diabetic nephropathy [35], membranoproliferative glomerulonephritis [36], membranous lupus glomerulonephritis [5], diffuse proliferative glomerulonephritis [37] and postinfectious mesangial proliferative glomerulonephritis [36] (each with one patient). Of the 27 patients whose data were available, 18 were male and 9 were female and only 1 female had a diagnosis of focal segmental glomerulosclerosis; the mean age was 44 ± 16 years (40 ± 15 years for male and 53 ± 15 years for female). It is difficult to be certain

whether these associations are coincidental or whether they demonstrate a specific pathogenetic relationship with ADPKD. The frequency of focal segmental glomerulosclerosis (6/29, 20%) is higher than the 15% frequency of focal segmental glomerulosclerosis found in the general adult population. In contrast, membranous nephropathy, the most common cause of idiopathic nephrotic syndrome in adults, with a frequency of 25%, was found in 17% (5/29) of the ADPKD patients with nephrotic syndrome, which suggests that FSGS may be more than a coincidental finding and glomerular hyperfiltration could play an important role in the development of FSGS and heavy proteinuria in patients with ADPKD. Moreover, the coincidence of ADPKD and FSGS can be caused by two independent concurrent genetic mutations which are not necessarily related or one single mutation, which is unknown yet. It is possible that different mutations in these patients could clarify the nature of this coincidence. However, in a histological study of kidneys of 12 ADPKD patients without nephrotic syndrome, Montoyo et al. [38] reported that interstitial fibrosis and tubular atrophy were found to be the main determinants of the development of chronic renal failure in ADPKD. In a study of 18 cases, Zeir et al. [39] reported interstitial fibrosis and arteriolar sclerosis to be the most important lesions in the kidney of ADPKD patients, whereas FSGS was observed in <5% of the glomeruli.

Interestingly, in our patient, the severe increase of proteinuria after about 2 years of ACEi/ARB association and the peculiar family history (father with a diagnosis of ADPKD and mother affected by membranous nephropathy) induced us to perform a US-guided biopsy. We chose the percutaneous biopsy because the lower pole of the left kidney of our patient still had a good representation of the renal parenchyma. Although the treatment of mesangioproliferative glomerulonephritis is not well defined, we decided to use corticosteroids for our patient with a good clinical response. In addition to our report, there are two other cases of mesangioproliferative glomerulonephritis in ADPKD patients in the literature. In the first one, the data are not available [30], and in the second one, Seyrek et al. [31] described a case of a 56-year-old woman with flank pain, haematuria, proteinuria (0.5 g/day) and normal renal function, in which a kidney biopsy revealed the presence of mesangioproliferative glomerulonephritis. The patient received prednisone 0.5 mg/kg/day and her haematuria and proteinuria improved and during the following years, urinary sediments occasionally showed microscopic haematuria. At the time of kidney biopsy, a representation of renal morphology was not possible due to some technical deficiencies. Five years later, a CT diagnosed ADPKD, showing two kidneys and the pancreas occupied by numerous cysts; moreover, the family history revealed that her sister was a haemodialysis patient. Of the patients with follow-up information, six were on dialysis therapy from 3 months to 6 years after the nephrotic syndrome was discovered; six patients presented a reduction of the proteinuria and a stability or an improvement of the renal function after steroid and/or cytotoxic therapy in a follow-up from 2 months to 5 years; one patient had reduced proteinuria and normalized renal function after salt restriction and antihypertensive medications (losartan potassium and amlodipine); two patients showed worsened renal function.

This evidence supports the need for performing a renal biopsy in patients with ADPKD and nephrotic syndrome. A kidney biopsy is an invasive examination procedure,

and should only be indicated on an individual basis, depending on the patient's characteristics and after careful consideration of the risks and benefits for each particular case [40], such as the case of an ADPKD patient with a nephrotic syndrome. With the use of real-time ultrasonography for guiding the biopsy procedure and the use of automatic biopsy needles, the success rate has improved in 95% of cases [41]. A CT-guided percutaneous renal biopsy is an alternative when the kidneys cannot be properly visualized. Alternative methods have been attempted for obtaining samples of kidney tissue in patients with contraindications for the percutaneous approach. Although open or surgical renal biopsies have been performed for over 40 years as a standard procedure in patients with contraindications for the percutaneous approach, there are other less invasive alternatives. These include laparoscopic, transurethral or transvenous renal biopsy [42–44]. Recently, a technique has been proposed which combines the laparoscopic approach with a percutaneous needle biopsy [45]. However, a kidney biopsy allows an accurate diagnosis and an appropriate treatment/prevention of renal function deterioration. The treatment for various histopathological subtypes leading to nephrotic syndrome is different, with corticosteroids beneficial in some conditions and useless in other cases. Reaching a firm diagnosis based on histopathology and immunofluorescence studies will help the physician to give an appropriate treatment and to avoid empirical therapy with potentially toxic agents. The enlargement of cysts by compressing normal parenchyma is a central factor in the pathogenesis of chronic renal failure in this disorder [1]. At present, it is impossible to assess the potential benefit of measures leading to a decrease in proteinuria in the progression of ADPKD toward end-stage renal disease. The data related to follow-up of the ADPKD patients treated with immunosuppressive therapy are too few to evaluate if steroid or other cytotoxic agents may influence the course of the ADPKD and if the progression of this disease may depend on the histological subtype of associated glomerulonephritis.

Conflict of interest statement. None declared.

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