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Familial glomerulonephritis

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Abstract. Between 1970 and 1984, the diagnosis of glomerulonephritis was made in 860 patients on the basis of a nephritic sediment and/or renal biopsy; of these patients, 86 (10%) had at least one first-degree relative with glomerulonephritis. These patients originated from 45 families and 1674 family members were screened; 172 had glomerulonephritis, of whom 101 could be classified. The diagnostic breakdown of the 101 patients showed that 50.5% had classical Alport's syndrome; 21.8% had atypical forms; 17.8% had familial IgA glomerulonephritis; 1.9% had focal segmental glomerulosclerosis with Wolff-Parkinson-White syndrome; and 7.9% had benign familial haematuria. The proportion of patients with glomerulonephritis who had familial disease was higher than expected. The family history is an important point to consider in the examination of patients with glomerulonephritis.

Key words: Familial glomerulonephritis – Alport's syndrome – Alport's variants – Benign haematuria – IgA glomerulonephritis – Focal glomerulosclerosis

Introduction

In the 19th century, several authors recognized that some renal diseases tended to run in families [1]. In 1902 Guthrie [2] described a family with haematuria and a defined mode of genetic transmission. In the same family, Alport [3] later pointed out the constellation of nephritic urinary sediment, early hearing loss and rapid progression into renal failure in males. This syndrome was later named "Alport's disease".

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Recently, it has been recognized that in some families glomerular disease may occur which differs in important aspects from Alport's disease [4, 5]. Familial occurrence of haematuria without progression to renal failure has been classified as "familial benign hematuria" [6]. In addition, prognostically more adverse variants of non-Alport glomerulonephritis (GN) may occur in families.

In order to define the prevalence of glomerular disease in family members of patients with GN, we examined systematically the families of all patients in whom the diagnosis of GN had been verified either clinically or by renal biopsy between the years of 1970 and 1984. In this study we have analysed the prevalence of the various forms of familial GN.

Patients and methods

Between 1970 and 1984 the diagnosis of GN was made in 860 patients (aged 13–82 years) from the Outpatient Department of the Division of Nephrology, Department of Internal Medicine, University of Heidelberg. The diagnosis was based on the finding of haematuria without urological causes and/or nephritic sediment. Renal biopsy confirmation was obtained in 302 patients. Eighty-six patients fulfilled the following criteria of familial GN: presence of haematuria and/or nephritic sediment (with or without renal biopsy) in at least one first-degree relative within three generations; exclusion of urological disease.

Consequently, familial GN, thus defined, was present in 10% of all patients with GN. These 86 patients came from a total of 45 families. Our further investigation comprised 1674 family members in these 45 families. In addition to the above 86 index patients, we were able to identify an additional 86 patients within the 45 families who fulfilled the criteria for familial GN. A nephritic urinary sediment was defined as the presence of granular or erythrocyte cell casts. Chronic renal insufficiency was defined as the persistent elevation of plasma creatinine above 125 μmol/l.

Results and discussion

The findings in 172 patients with familial GN are listed in Table 1. The type of GN could be classified in 101 patients, of whom 51 (50.5%) had classic Alport's syndrome. This group included the greatest proportion of classifiable patients with hereditary progressive GN with sensory hearing loss in the proband and at least one family member. These patients demonstrated typical glomerular basement membrane lesions (e.g. splitting of lamina densa) on electron microsocopy. Of the 51 patients, 21 (41%) with classical Alport's syndrome developed renal failure, i.e. serum creatinine >125 µmol/l, at a median age of 35 years (range 16–66 years). Twenty patients developed terminal renal failure (14 male, 6 female; median age at renal death in males 36.5 years, in females 31.5 years). This contrasts with other reports which detail a more favourable course in females [5]. Only 17 of the 51 patients (33%) had concomitant sensory hearing loss; 5 of these patients had normal renal function and 12 patients had renal failure at the time of the last audiometric examination. Terminal renal failure was reached at a median age of 39 years (range 16–52 years) in patients with sensory hearing loss and at a median age of 29 years (range 17–53 years) in patients without sensory hearing loss. Other authors [6, 7] have reported a more rapid progression of renal failure in patients with sensory hearing loss. Of the 51 patients with Alport's syndrome, 25 had a detailed ophthalmological check-up; 2 patients had a congenital cataract; in a third patient, the cataract was diagnosed at the age of 28 years. Perimacular spots, frequently described as a common lesion in Alport's syndrome, were found in only 1 of the 25 patients.

Hereditary progressive GN with glomerular basement membrane splitting but without sensory hearing loss, in the patient or more than one other family member, was present in 12 of the 101 patients (11.9%). These patients demonstrated splitting of the lamina densa in the proband and/or at least one family member with GN. Four patients developed terminal renal failure.

Hereditary progressive GN with isolated thinning of basement membrane without sensory hearing loss was present in 10 of the 101 patients (9.9%). Electron microscopy showed isolated thinning of the glomerular basement membrane without areas of thickening or splitting. There was progression to renal failure in the proband and/or at least one family member.

Table 1. Prevalence of various types of familial glomerulonephritis (GN) in 45 German families

Type of glomerulonephritis	Number of families involved	Number of patients (%)	Male/female	Age at diagnosis median (range)	Number of biopsies	Chronic renal insufficiency S-crea > 125 µmol/l	End-stage renal failure
1. Alport's syndrome	14	63 (62.4)	33/30	18 years (3 months–65 years)	18	27	24
a) classical	12	51 (50.5)	25/26	16.5 years (3 months–65 years)	16	21	20
b) variants	2	12 (11.9)	8/4	22 years (3–32 years)	2	6	4
2. Hereditary progressive GN with isolated thinning of glomerular basement membrane (GBM)	2	10 (9.9)	7/3	26 years (3–33 years)	7	4	3
3. Benign familial haematuria with isolated thinning of GBM	1	8 (7.9)	0/8	38.5 years (3–82 years)	2	0	0
4. Familial IgA-GN	6	18 (17.8)	7/11	21.5 years (3–71 years)	8	4	3
5. Familial idiopathic nephrotic syndrome with focal-segmental glomerulosclerosis	1	2 (1.9)	2/0	26 years (25–27 years)	2	2	2
Subtotal	24	101 (100)	49/52		37	37	32
6. Familial progressive GN, not classified	16	61 (35.5)	31/30	21 years (3–74 years)	12	33	30
7. Familial non-progressive GN, not classified	5	10 (5.8)	5/5	18 years (8–41 years)	3	0	0
Total	45	172	85/87	20.5 years (3 months–82 years)	52	70	62

One particular problem was the classification of patients who failed to exhibit splitting of basement membrane on electron microscopy. We propose that this merely represents a variant of Alport's syndrome, since progressive renal failure was noted in the families of such patients. On the whole, the clinical course in such patients appeared to be more benign and renal failure supervened only at a higher age. However, in one female, renal biopsy performed at age 35 years showed only isolated basement membrane thinning; nervertheless; this woman progressed to terminal renal failure. Two other cases with progression into renal failure were observed in this family, in the presence of isolated GBM thinning. This finding illustrates that adverse clinical outcome is not excluded by the finding of isolated basement membrane thinning [8], as had previously been proposed by its classification as benign familial haematuria.

In 18 of the 101 patients (17.8%) the diagnosis of familial IgA GN, with typical predominantly mesangial deposits of IgA on immunofluorescence, was established on the basis of renal biopsy in the proband. However, biopsy confirmation in the family members was available in only one of the six families. At the last examination 14 patients had normal renal function and 4 patients were in renal failure, 3 of whom were on dialysis.

In 2 patients, both from one family, taken from 101 patients (1.9%) who had severe idiopathic nephrotic syndrome, renal biopsy showed the presence of focal segmental glomerulosclerosis. The diagnosis was made after the exclusion of an immune complex GN on immunofluorescence and after exclusion of defined basal membrane lesions by electron microscopy. Both patients progressed to terminal renal failure. It is worthy of note that both patients also had Wolff-Parkinson-White syndrome, a combination not described hitherto in association with familial GN.

Non-progressive hereditary GN, i.e. benign familial haematuria, was diagnosed in 8 of 101 patients (7.9%) who came from one family. All patients were female and the disease could be followed over three generations. The clinical examination showed isolated microhaematuria and cylindruria without proteinuria, hypertension or impaired renal function. In two patients in whom biopsy was performed, segmental glomerular thinning of basal membranes was found on electron microscopy, with absence of hearing loss, significant proteinuria (>200 mg/die), renal failure or perimacular eye changes.

Of the 172 patients, 61 (35.5%) from 16 families had familial progressive GN which could not be properly classified because neither immunofluorescence nor electron microscopy were performed on the renal biopsy specimens. None of the patients had sensory hearing loss. Of the 61 patients, 33 (54.1%) developed renal failure at a median age of 48.5 years (range 32–70 years), and terminal renal failure occurred in 30 patients at a median age of 44.5 years (range 6–76 years).

In 10 of 172 patients (5.8%), familial non-progressive GN was diagnosed with absence of renal failure in either patients or diseased first-degree relatives. Renal biopsy did not allow uncontroversial classification if neither immunohistology nor electron microscopy were performed. It is interesting to note that in one family, four members suffered from sensory hearing loss dating back to early adolescence, whereas in the subsequent generation, a nephritic syndrome developed in a 44-year-old female patient (biopsy not performed) without sensory hearing loss.

On the whole, the above observations show that familial GN encompasses a whole spectrum of diseases with diverse clinical presentations and renal prognosis. In 80% of the above patients, renal disease in a further family member was not known to the patient and was discovered only upon systematic investigation. In 20% of the family members, urological disease, mostly cystitis and pyelonephritis, had been diagnosed previously. In 10% of patients with glomerulonephritis a familial disease was found, drawing attention to the need for screening of the relatives of patients with haematuria [9].

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