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Clinical Heterogeneity in Familial IgA Nephropathy

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Abstract
Background: IgA nephropathy is the most common primary glomerulonephritis worldwide and a significant cause of end-stage renal disease (ESRD). While most cases of IgA nephropathy are considered sporadic, familial cases have been reported. ***Methods:*** We performed a national audit of 1,809 patients attending renal clinics and dialysis units to identify a family history among patients with kidney disease. We reviewed all renal biopsies performed at our institution spanning a 30-year period. Paediatric cases were not included. ***Results:*** We identified 14 families involving 41 affected individuals with biopsy-proven IgA nephropathy and at least one other member with either biopsy-proven IgA nephropathy or ESRD. Detailed family histories were obtained, medical records reviewed and family pedigrees constructed. Retrospective application of the MESTC criteria to all familial IgA biopsies was performed. Seven families had 2 or more members with biopsy-proven IgA nephropathy, equating to 23 (1.8%) of 1,283 biopsies with IgA nephropathy over the last 30 years. A complex inheritance pattern was observed, with autosomal dominant and autosomal recessive families identified with varying penetrance. There was a male preponderance (68%), and a complex heterogeneity in the clinical and histopathological features of familial IgA patients (age range 16–60 years; creatinine range 60–350 μmol/L). We observed a high rate (66%) of progression to ESRD, with a mean time to progression of 5.13 years (SD 1.8 years; range 2–8 years). Among those patients who had undergone transplantation, recurrence of disease was reported in 5 (50%) cases. ***Conclusion:*** These data suggests familial aggregation of IgA nephropathy, confirm the clinical and histopathological heterogeneity and raise the possibility of monogenic inheritance.

Introduction

First described in 1968 [1], IgA nephropathy is increasingly recognized as the most common type of primary glomerulonephritis. It is an important cause of end-stage renal disease (ESRD) worldwide, with an estimated population incidence of between 5 and 50 per million [2–4]. Characterized histologically by focal glomerulonephritis and primarily mesangial IgA deposits, the disease

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manifests clinically with varying degrees of proteinuria, hypertension, haematuria and reduced renal function [4]. The mainstay of treatment is focused on the control of these sequelae, with immunosuppression reserved for selected aggressive cases [5]. In addition, the lack of any alternative to invasive biopsy as a means of diagnosis represents a further clinical challenge for nephrology [6].

Given the heterogeneity in clinical presentation, and regional differences in urine dipstick screening, an accurate epidemiological picture of IgA nephropathy is yet to emerge [8]. Nevertheless, some broad conclusions have been possible. The disease is generally more prevalent in Asia [9–10], Australia [11] and Europe [12–14], when compared to North America [3, 15]. There is a geographically dependent male preponderance [16], and it associates clinically with mucosal infections and a range of hepatic, intestinal and autoimmune conditions [17].

Two features point to a genetic basis for the disease: racial and familial aggregation. There is an increased incidence among Caucasians and Asians when compared to African and Hispanic ancestry [17–19], and differences in prevalence between separate racial groups within specific geographical regions have also been noted. For example, in Australia and North America, a higher prevalence has been noted among Australian aborigines [20] and Native Americans [21–23], respectively, when compared to their Caucasian compatriots. Similar differences in prevalence between distinct racial groups have also been observed in New Zealand [24].

Familial aggregation of the disease was first observed by Julian et al. [25], who reported a series of 3 pedigrees from central and eastern Kentucky with evidence of disease inheritance. Familial aggregation of the disease has since been reported throughout the world. While there are some reports of an autosomal recessive mode of inheritance, the predominant mode appears to be autosomal dominant, albeit with incomplete penetrance [25–30]. The presence of reports of both forms of inheritance, together with the lack of complete penetrance, has led to the description of IgA nephropathy as a complex disease process, wherein both genetic and environmental factors contribute to disease expression [16]. Thus, the continued identification of large pedigrees with familial IgA nephropathy may allow further identification of inheritance patterns and susceptibility loci to help elucidate the complex interplay between hereditary and environmental factors in the pathogenesis of the disease. Here we present our findings with respect to family history, clinical and associated pathological findings, and their relationship to long-term prognosis in a series of 14 families with IgA nephropathy.

Methods

A national cross-sectional analysis of 1,809 patients attending renal clinics and dialysis units was performed to identify the presence of a family history among patients with kidney disease (The Irish Kidney Gene Project) [31]. The Irish Kidney Gene Project and several other data sources were accessed to identify all cases. The records of 8,033 adult native kidney biopsies performed at our institution over the period 1986–2016 were reviewed to calculate the incidence of IgA nephropathy over the study period. Non-familial paediatric biopsies were not included, as these are not performed at our institution. Families that contained at least one individual with biopsy-proven IgA and at least one other affected individual with kidney disease were identified and studied in more detail. In order to be included in this analysis, each family had to have at least one member with biopsy-proven IgA nephropathy and a second family member with either biopsy-proven IgA nephropathy or ESRD. IgA nephropathy was defined as the presence of dominant IgA deposits in the mesangial regions of the glomerulus, detected by immunofluorescence microscopy at renal biopsy, wherein IgA was the dominant immunoglobulin. Detailed family pedigree data were obtained from all participating families. Extensive medical and histological data were collected. For histological analysis, retrospective application of the MESTC criteria to all available biopsy slides was performed by 2 of the authors, where possible, according to previously published guidelines [6, 7]. In cases where the biopsy sections were no longer assessable microscopically due to the retrospective nature of the study, biopsy reports were used to determine MESTC scores. In these cases, reports of mild and/or focal increases in mesangial hypercellularity were assigned an M score of 0, while reports of moderate and/or diffuse increases were assigned an M score of 1. Deposition of C3, C4, IgG and IgM was recorded for all biopsies.

Results

Familial Aggregation of IgA Nephropathy

In order to determine the prevalence of familial IgA nephropathy, we reviewed the records of renal biopsies performed at our institution during the period 1986–2016. A review of 8,033 adult native kidney biopsies was carried out, of which 1,283 (16%) were assigned a diagnosis of IgA nephropathy. Twenty-three (1.8%) of these were familial cases. This represented 14 separate families (Table 1). All of these families were living in Ireland and belonged to the Caucasian race. Thirteen were of Irish descent and one was of Eastern European descent. Of these 14 families, 5 had 2 affected family members, 6 had 3 affected family members, 2 had 4 affected family members and 1 had 5 affected members, giving a total of 41 affected individuals for the study. Seven families had 2 or more members with biopsy proven IgA nephropathy (Table 1).

Four families comprised only a single affected generation, suggesting autosomal recessive inheritance. Ten

Table 1. Familial aggregation of IgA nephropathy

Family	Number of members affected	Number of generations affected	Number with ESRD	Number with biopsy proven IgA	Mode of inheritance
F91	5	3	5	2	Unclear
F141	4	4	3	1	AD
F224	4	1	2	3	AR
F39	3	2	3	1	Unclear
F74	3	2	1	3	AD
F312	3	2	1	2	AD
F315	3	2	3	2	AD
F421	3	4	2	2	AD
F326	3	4	2	1	Unclear
F404	2	2	1	1	Unclear
F229	2	1	0	2	AR
F256	2	1	1	1	AR
F268	2	2	1	1	Unclear
F104	2	1	2	1	AR
Total (14)	41	Range (1–4)	27 (66%)	23 (56%)	Unclear 5 AD 5 AR 4

IgA, immunoglobulin A; AD, autosomal dominant; AR, autosomal recessive.

families had individuals affected from multiple generations. In 5 families, we identified individuals with biopsy-proven IgA nephropathy born to an affected parent, suggesting an autosomal dominant mode of inheritance. In the remaining 5 families, affected individuals were born to non-affected parents, but with multigenerational disease involvement. The pattern of inheritance here was unclear. A representative sample of family pedigrees is shown in Figure 1.

Clinical Features of Familial IgA Nephropathy

Regarding the 41 affected patients, 28 (68%) were male and the remaining 13 (32%) were female (Table 2). The mean age at diagnosis was 35 years (range 16–60 years; Table 2). Clinical presentation data and biopsy reports were available for 23 of the 41 affected patients. The mean creatinine at presentation was 150.13 μmol/L (SD 77.7 μmol/L; range 67–350 μmol/L). Nineteen (83%) patients had microscopic haematuria at presentation, while 20 (87%) had proteinuria. Hypertension was reported in 5 patients (22%), and 5 patients (22%) reported macroscopic haematuria. Four patients (17%) were diagnosed following acute kidney injury, and 4 patients (17%) were diagnosed incidentally following urine dip (Table 2). No cases of Henoch-Schonlein purpura were identified in the study. Of the 41 patients, 27 (66%) had progressed to ESRD. Eight (20%) were deceased, 9 (22%) were currently on dialysis, and 10 (24%) had been transplanted. The remaining 14 patients (34%) were classified at various stages of chronic kidney disease. In those transplanted, recurrence of disease was reported in 5 (50%) cases following re-biopsy for investigation of a decline in graft function and/or abnormal urine dip analysis. The mean time to progression to ESRD from diagnosis was 7.92 years (SD 5.2 years; range 0–10 years; Table 2).

Histopathological Features of Familial IgA Nephropathy

The MESTC criteria comprise five histological lesions useful as independent prognostic factors in IgA nephropathy: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T) and crescents [7]. Regarding the 23 patients with biopsy-proven IgA nephropathy, MESTC criteria were retrospectively applied to all biopsies. Fifteen (65%) biopsies showed a moderate and diffuse increase in mesangial hypercellularity (M score 1; Table 2). Six (26%) showed no increase or only a very focal increase in mesangial hypercellularity (M score 0). In 2 (9%) biopsies, all of the glomeruli were globally sclerosed making assessment of mesangial hypercellularity impossible. Endocapillary loop inflammation was seen in 11 (48%) of the 23 biopsies (E score 1; Table 2) and segmental sclerosis was seen in 14 (61%; S score 1; Table

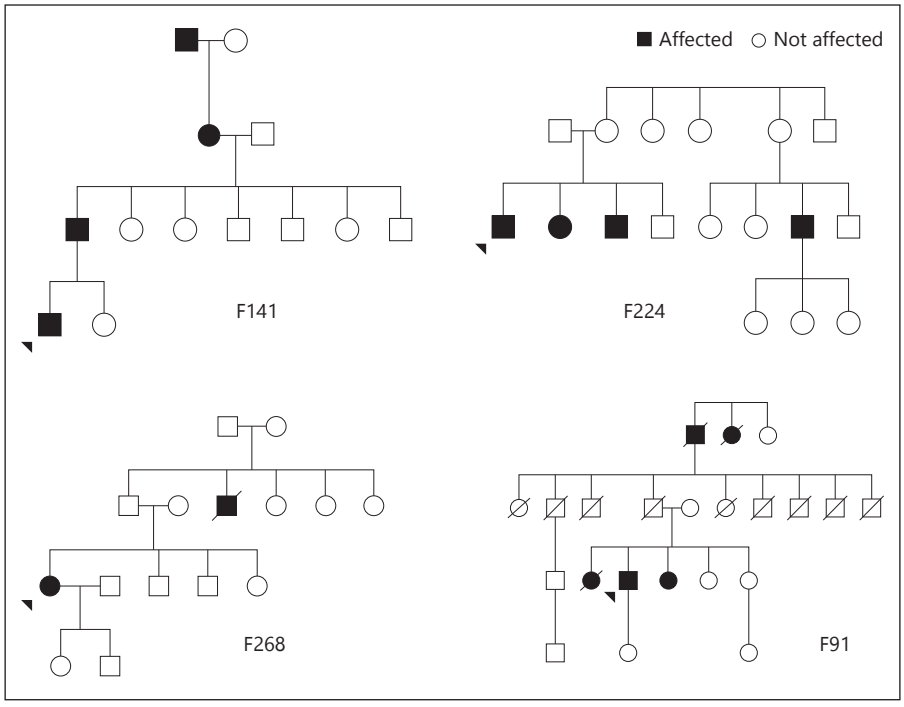

Fig. 1. Familial aggregation of IgA nephropathy. Four family pedigrees showing inheritance and familial aggregation of IgA nephropathy. F141, autosomal dominant; F224, autosomal recessive; F268 and F91, mode of inheritance unclear.

2). Seven (30%) biopsies showed extensive (>50%) tubulointerstitial fibrosis (T score 2; Table 2), while 8 (35%) biopsies showed moderate (25–50%) tubulointerstitial fibrosis (T score 1). The remaining 8 (35%) biopsies showed no or only mild (0–25%) tubulointerstitial fibrosis (T score 0). Cellular crescents were seen in 6 (26%) biopsies. C3 deposition was seen in 19 (82%) of biopsies, C4 in 2 (9%) biopsies, IgG in 2 (9%) biopsies and IgM deposition in 11 (48%) biopsies.

Discussion

In this report, we present a series of 14 families with at least 1 member with biopsy-proven IgA nephropathy and at least 1 other affected family member with either IgA nephropathy or ESRD. We report a relatively low prevalence of familial IgA nephropathy when compared to sporadic disease incidence. We have identified heterogenous inheritance patterns in addition to clear autosomal dominant and recessive modes of transmission. We also report clinical and histopathological heterogeneity of familial IgA nephropathy. Progression to ESRD was a common occurrence in affected individuals, and a relatively high rate of disease recurrence was observed in transplanted patients.

Familial IgA nephropathy was first described in the United States in 1985 and has since been seen throughout the world [25–30]. While some of these reports detail isolated large families with disease aggregation [25, 27, 29] a larger series of 10 families comprising 26 individuals was reported by Scolari et al. [28], who noted a range of different possible inheritance patterns. The largest series to date is that of the Cooperative Study of the Societe Francaise de Nephrologie [26], which reported 34 families, each comprising 2 or 3 family members with biopsy-proven IgA nephropathy. Similar to Scolari et al. [28], the authors noted a range of different possible inheritance patterns including a father and 2 sons with IgA nephropathy, an uncle and a nephew with IgA nephropathy and several families demonstrating aggregation of IgA nephropathy with Henoch-Schonlein Purpura.

We report a prevalence of familial IgA of just 1.8% of total adult IgA cases over a 30-year period in the present study. This highlights the relatively low prevalence of familial IgA in our population. We note the report of the Cooperative Study of the Societe Francaise de Nephrologie, who collected a total of 90 families with 1 family member with biopsy proven IgA nephropathy and at least 1 other member with urinary abnormalities or ESRD, wherein the clinicians strongly suspected IgA nephropathy, but diagnostic histopathological data were not available [26]. Indeed, in the present study, we also observed a significant number of families wherein reports of family members with IgA nephropathy or ESRD were made

Table 2. Clinical characteristics of familial IgA nephropathy

Gender, *n* (%)	
Male	28 (68)
Female	13 (32)
Age at presentation, years, mean (range)	35 (16–60)
Creatinine at presentation, μmol/L, mean (SD; range)	150.13 (77.7; 67–350)
Progression to ESRD, *n* (%)	27/41 (66)
Time to progression to ESRD, years, mean (SD; range)	5.13 (1.8; 2–8)
Pathologic features and MESTC scores	
Mesangial hypercellularity	Score 0–6 (26%) Score 1–15 (65%) Sclerosed –2 (9%)
Endocapillary inflammation	Score 0–12 (52%) Score 1–11 (48%)
Segmental sclerosis	Score 0–9 (39%) Score 1–14 (61%)
Tubulo-interstitial fibrosis	Score 0–8 (35%) Score 1–8 (35%) Score 2–7 (30%)
Cellular crescents	C0–17 (74%) C1–3 (13%) C2–3 (13%)
Additional features	C3–19 (82%) C4–2 (9%) IgG–2 (9%) IgM–11 (48%)
Presenting features, *n* (%)	
Proteinuria	20/23 (87)
Microscopic haematuria	19/23 (83)
Hypertension	5/23 (22)
Macroscopic haematuria	5/23 (22)
Incidental via urine dip	4/23 (17)
Acute kidney injury	4/23 (17)
Progression of chronic kidney disease	3/23 (9)
Recurrent urinary tract infection	1/23 (4.3)
Back pain	1/23 (4.3)
Clinical status, *n* (%)	
Deceased	8/41 (20)
Receiving dialysis	9/41 (22)
Transplanted	10/41 (24)
CKD	14/41 (34)

For a detailed description of MESTC criteria, please see Trimarchi et al, 2017 [7].

that could not be verified due to the retrospective nature of the study (data not shown). This suggests that the true prevalence of familial IgA nephropathy may be much higher than observed.

Similar to previous reports, we have also identified families with autosomal dominant, autosomal recessive and other more complex inheritance patterns [25–30]. This complexity has made identification of a precise inherited defect elusive to date [16, 32]. Scolari et al. [28] have reported an increased incidence of Human Leucocyte Antigen-DRB1*08 in cases of familial IgA nephropathy. In addition to other genetic linkage studies associating IgA nephropathy with Human Leucocyte Antigens (HLA) [33–34], more recent whole genome-wide association studies have identified several discrete susceptibility loci for IgA nephropathy [35–38]. Interestingly, these comprise both HLA and non-HLA loci, including several prominent signaling and adhesion molecules of the innate immune system, some of which are directly involved in the regulation of IgA-producing cells in response to pathogens at mucosal barriers such as the intestine [38]. This may well prove significant, given the well-described association between IgA nephropathy and inflammatory bowel disease [16], in addition to observations of elevated levels of serum IgA in family members of those affected with IgA nephropathy [39–42]. A model therefore emerges, describing a genetic susceptibility requiring environmental factors, possibly from the intestine, for full disease expression.

Interestingly, and consistent with previous reports [43–44], we have observed a relatively high level of both progression to ESRD (66%) and recurrence of disease post renal transplantation in those affected by IgA nephropathy (50%). This observation gives further weight to the conception of IgA nephropathy as a complex disease process involving both genetic and environmental pathogenic mechanisms. This may well be reflected in the heterogeneity of data observed in our clinical data and biopsy series.

Familial aggregation of IgA nephropathy raises the possibility of monogenic inheritance. Studies of Focal Segmental Glomerular Sclerosis have been very successful in identifying numerous different genes involved in the pathogenesis of Focal Segmental Glomerular Sclerosis [45–52]. Genetic sequencing of IgA nephropathy families may lead to the identification of genes causing familial IgA, which in turn may shed light on sporadic IgA nephropathy.

The present study is limited by its retrospective nature and small sample size. Due to the retrospective nature, often spanning multiple generations in large family pedigrees, it was not possible to verify the precise aetiology of ESRD in all family members. However, given that primary kidney disease is sufficiently uncommon, for the purposes of this analysis, we feel it is reasonable to consider these cases of ESRD as likely IgA nephropathy. Another limitation of the present study is that paediatric cases were not included in the analysis, which may have affected the overall incidence of familial IgA nephropathy. Nevertheless, we have identified 14 cases of familial IgA

nephropathy, displaying autosomal dominant, autosomal recessive and other more heterogenous modes of inheritance. Consistent with previous reports, we observed a male preponderance, with a high rate of progression to ESRD and recurrence post renal transplant in affected individuals, and a complex heterogeneity in our clinical and histopathological data. These data suggests a complex pathogenesis of IgA nephropathy, where both genetic and environmental factors may contribute to disease expression. Genetic analysis of familial IgA may aid identification of genes involved, and shed light on sporadic IgA nephropathy.

Ethics Statement

The authors declare that all patients in this study have provided informed written consent and that the study protocol and design were subject to appropriate Ethics Committee approval.

Disclosure Statement

The authors declare no conflicts of interest with regard to the results presented in the above paper. We confirm the results presented in this paper have not been published previously in whole or in part, except in the abstract format.

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