

Increased Risk of End-Stage Renal Disease in Familial IgA Nephropathy

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Abstract. Primary IgA nephropathy (IgAN) is characterized by recurrent episodes of macroscopic hematuria accompanied by upper respiratory tract infections or persistent asymptomatic microscopic hematuria with or without proteinuria. IgAN may involve one or more members of a family. Three generations of a cohort of 110 patients with biopsy-proven IgAN, living in Southern Italy, were checked for urinalysis, and the relative risk (RR) of developing the disease was evaluated. A total of 19 unrelated familial, 37 suspected, and 54 sporadic cases of IgAN were identified. Renal survival was estimated by the Kaplan-Meier method for censored data and compared by use of the log-rank test. More than 50% of the patients with IgAN clustered in kindred with more than two probably affected relatives. In 19 unrelated IgAN families, 8 had single-generation (SG) and 11 multigenerational (MG) involvement showing a prevalent vertical transmission of the trait. The RR was 16 times higher in first-degree relatives (odds ratio [OR], 16.4; 95% confidence interval [CI], 5.7 to 47.8; $P < 0.0001$) and >2 times higher, even if NS, in second-degree relatives (OR, 2.4;

95 % CI, 0.7 to 7.9; $P = 0.145$). The clinical and histologic picture of familial and sporadic IgAN appeared to be similar. The 20-yr renal survival rate from the apparent onset of the disease was significantly poorer in patients with familial (41%) than in patients with sporadic (94%) IgAN ($P = 0.003$). Furthermore, 15-yr renal survival from the time of renal biopsy was significantly worse in familial IgAN ($P = 0.02$); end-stage renal disease was present in 64% of familial and only in 8% of patients with sporadic IgAN. Finally, renal survival was significantly worse in patients belonging to families with SG rather than with MG involvement ($P = 0.03$). These data show, for the first time, that familial IgAN may be considered a nonbenign disease that occurs frequently in first-degree relatives. Familial IgAN has a poorer outcome than sporadic IgAN. Therefore, an accurate family history and urinalysis in all family members is urgently recommended in clinical practice. This procedure might avoid late referral of subjects with persistent and underestimated urinary abnormalities and late diagnosis of the disease.

Primary IgA nephropathy (IgAN) is a worldwide disease characterized by recurrent episodes of macroscopic hematuria, which usually coincide with upper respiratory tract infections, or by asymptomatic persistent microscopic hematuria with or without proteinuria. The disease usually appears in the second and third decades of life and less frequently in the first decade. IgAN is the most common form of glomerulonephritis: ~30% to 40% of all patients with biopsy-proven primary glomerulonephritis have IgAN (1). The incidence of the disease ranges between 8.4 cases per million of population (pmp) in Italy (2), 5.4 to 12.4 patients pmp in Central and Eastern Kentucky, United States (3), and 26 patients pmp in Cotes d'Armor, France (4). The difference in frequency of the disease is due to biopsy policy, because not all subjects with persistent microscopic hematuria with or without proteinuria undergo renal biopsy. In addition, many subjects apparently in good health

refuse renal biopsy, which is the sole methodological approach for a correct diagnosis. IgAN is the most common form of glomerulonephritis responsible for end-stage renal disease (ESRD) worldwide (5–7); 40% of patients develop ESRD 15 yr after the time of the renal biopsy (8,9).

Familial cases of biopsy-proven IgAN were first described by Tolkoff-Rubin *et al.* (10); thereafter, other contributors published articles of families in which two or more relatives were affected by IgAN (11–13). Egido *et al.* (14) distinguished a familial form from a sporadic form for the first time. Identification of a gene that causes the familial disease is the major task. IgAN is, however, difficult to study because a combination of various genes and different environmental factors is probably involved (15). IgAN is a complex disease in which familial clustering is suggestive of inherited genetic predisposition, even though it does not show a typical mendelian transmission pattern. Therefore, this disease may depend on two or more susceptibility loci with a variable contribution from environmental factors. Discovering the major susceptibility locus can be the key to better understanding the causes of the disease. However, a preliminary and accurate epidemiologic study may help to find the most likely modality of transmission and appearance of the disease in family members. Herein we present, for the first time, an epidemiologic study of

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familial IgAN to quantify the magnitude of familial aggregation. Taking into consideration family history and clinical and laboratory data, the outcome of the disease in a series of patients with familial IgAN and sporadic IgAN is reported.

Materials and Methods

IgAN Patient Population

This study is based on a retrospective review of 2830 native kidney biopsies performed at the Institute of Nephrology from January 1971 to December 2000. Seven hundred sixty-eight subjects were diagnosed with primary IgAN. Biopsy-proven IgAN was based on the predominance of IgA deposits in the mesangial area of glomeruli in patients with recurrent episodes of macroscopic hematuria accompanied by upper respiratory tract infections or with persistent microscopic hematuria and/or proteinuria. Histologic grading (G) was based on light microscopy classification proposed by Lee *et al.* (16). Patients with mild renal lesions were placed in G1 and G2 (mesangial matrix expansion and/or mesangial cell proliferation). G3 consisted of moderate lesions (focal segmental glomerulosclerosis, small tuft adhesions, low number of crescents, and small areas of tubulointerstitial damage). G4 and G5 represented severe lesions (diffuse partial or total glomerular sclerosis, diffuse tubulointerstitial damage, and arteriolar thickening with lumen reduction).

Family Study

From January 1988 to December 2000, we studied the families of a cohort of 110 patients with biopsy-proven IgAN (propositus) who visited our outpatient clinic and had given their consent to the study. All families were living in Southern Italy. Cyrillic software, version 2.1 (Cherwell Scientific, Oxford, UK), was used for pedigree drawing and collecting personal and clinical data. Relatives of at least three generations were checked by urinalysis and considered to evaluate the relative risk (RR) after informed consent was obtained according to the protocols approved by the local Ethics Committee. A detailed family history was obtained from all participating relatives. Additional historical information was obtained by family physicians. Information on each family member, including gender, date of birth, history of hypertension, diabetes mellitus, renal disease including renal failure, and family history of blindness or deafness were included in a database. Exposure to presumptive environmental factors, such as type of job, food intake, exposure to solvents, or other stimuli was also considered. Individuals with secondary forms of IgAN (systemic lupus erythematosus, mixed cryoglobulinemia, or chronic hepatitis) were excluded from the study. In this study, all relatives with a history of recurrent episodes of macroscopic hematuria and two relatives with persistent microscopic hematuria underwent renal biopsy. Other relatives with negative urine culture and persistence of microscopic hematuria but who refused renal biopsy received urinalysis, Addis count with contrast phase microscopy, and renal ultrasonography. They were checked systematically once a year. The medical records of all individuals included in the study were reviewed to identify factors pertaining to the clinical presentation of this disease, mode of inheritance, and outcome.

Sporadic IgAN was observed in 54 families, because only one member was affected and relatives had negative urinalysis and nephrologic history. Suspected familial IgAN was found in 37 families in which one member had biopsy-proven IgAN and others (two to three individuals in each pedigree) showed persistent microscopic hematuria and refused renal biopsy. Familial IgAN was diagnosed in 19 unrelated families that contained at least two individuals with biopsy-proven IgAN (Table 1). In these families, affected members were 11

Table 1. Families with IgA nephropathy enrolled in the study

Family	Involved Generations (n)	Affected/Probably Affected Relatives (n)	Family Members ^a (n)
1	2	4	7
2	2	4	24
3	3	5	16
4	2	2	33
5	3	4	21
6	2	3	20
7	3	5	13
8	1	3	13
9	1	1	26
10	3	3	10
11	1	1	9
12	2	3	10
13	2	2	17
14	1	1	13
15	3	2	32
16	1	1	7
17	1	1	3
18	1	1	4
19	1	2	7

^a Total number of family members, including propositus and first- and second-degree relatives.

sibling pairs, 3 parent-children pairs, 2 identical twins, and 4 more distant relatives. Three IgAN families were identified through a variety of sources and referral patterns. There was no difference in the number of first- and second-degree relatives between familial and sporadic IgAN included in the study. At least six relatives were checked for urinalysis in each family with sporadic IgAN.

Within the 19 studied families, subjects were defined as follows:

Affected: those with biopsy-proven IgAN in the absence of secondary forms.

Probably affected: those with persistent microscopic hematuria who refused renal biopsy and family members with chronic renal insufficiency or with ESRD that required renal replacement therapy, such as dialysis or transplantation.

Probably unaffected: subjects without urinary abnormalities and negative nephrologic history.

Status unknown: family members who refused the clinical investigation or those for whom it was not possible to collect historical clinical information.

Affected and probably affected subjects were included in this study.

IgAN families were identified by the presence of the disease (renal biopsy and/or persistent microscopic hematuria) in individuals from one or more generations (Table 1). Families with single-generation (SG) involvement had no more than one generation showing any manifestation of the disease. Families with multiple-generation (MG) involvement evidenced vertical transmission of the trait, with individuals from two or more generations affected.

Clinical Findings

Clinical presentation, hypertension, daily proteinuria, and renal function were reviewed among the clinical events. Hypertension was

considered when resting BP was >130/80 mmHg or if the subject was taking antihypertensive drugs at presentation. Proteinuria was defined mild in the presence of <1 g/d, moderate at 1 to 3 g/d, and severe at >3 g/d. Renal function was defined normal when creatinine clearance (Cockcroft formula) was >70 ml/min per 1.73 m². Mild chronic renal insufficiency was present when creatinine clearance was 51 to 70 ml/min, moderate 30 to 50 ml/min, and severe <30 ml/min. All clinical data were recorded in a database by use of File Maker Pro 3.0 software.

Outcome

Only patients with biopsy-proven IgAN were included in the follow-up. Two outcome measures were considered: (1) doubling of baseline serum creatinine value at the onset of the disease and at the time of renal biopsy and (2) ESRD when the patient received renal replacement treatment (dialysis or renal transplantation).

Statistical Analyses

Statistics was performed by use of Statview 5.0 software. Results were expressed as mean \pm SD or median. Continuous variables were compared by *t* test, and dichotomous and polytomous data were analyzed by the χ^2 test and Fisher's exact test, as applicable. Cumulative incidences of developing end-point events from the onset of the disease and from the time of renal biopsy were estimated by the Kaplan-Meier method for censored data and compared by the log-rank test for stratifying variables. Probability <0.05 was considered significant.

The RR of developing IgAN in relatives of familial patients with IgAN was estimated. The odds ratio (OR) and 95% confidence intervals (CI) were calculated by use of the logistic regression model to estimate RR in first-degree relatives of a patient *versus* control group and second-degree relatives of a patient *versus* control group. The control population was represented by healthy subjects living in Southern Italy who were checked for urinalysis.

Results

Epidemiologic Study

Familial IgAN and suspected familial IgAN were observed in 51% of our population of patients with IgAN. The 19 unrelated IgAN families enrolled in the study are listed in Table 1. Eight families had SG involvement; the number of affected or probably affected individuals ranged between two and four. Eleven families showed MG involvement; three or more affected or probably affected individuals were present. In total, 39 affected subjects and 36 probably affected individuals were present in the 19 unrelated IgAN families. The distribu-

tion of affected and/or probably affected relatives in families with MG involvement suggests either autosomal recessive or autosomal dominant disease with reduced penetrance. The transmission of the trait was irrespective of gender, thus excluding either gender-linked inheritance or mitochondrial DNA disorder. Two families contained one set of identical twins each. Both members of each twin set were affected.

Table 2 shows RR in relatives of familial IgAN. Microscopic hematuria diagnosed according to our protocol reported in the methodology section was considered to be an indicator of disease in first- and second-degree relatives. Thirty-eight subjects with microscopic hematuria among first-degree relatives and 10 among second-degree relatives were reported as affected/probably affected subjects. Four normal subjects had a positive urinalysis for microscopic hematuria. The RR was 16 times higher in the first-degree relatives (OR, 16.4; 95% CI, 5.7 to 47.8; *P* < 0.0001) and >2 times higher, but NS, in the second-degree relatives (OR, 2.4; 95% CI, 0.7 to 7.9; *P* = 0.145).

Demographic and Clinical Presentation

A total of 64 patients with biopsy-proven IgAN were studied. Thirty-nine patients belonged to the 19 familial IgAN families; 25 patients with sporadic IgAN were also considered for this study because they had a long term follow-up (Table 3). Male subjects were more frequently affected by either familial or sporadic IgAN than female subjects. The predominance of male gender was 1.6:1 in familial IgAN and 2.6:1 in sporadic IgAN. No significant difference in predominance of male gender was evident between familial and sporadic IgAN. The disease developed at a mean age of 26.8 yr in the familial cases and 25.2 yr in sporadic IgAN. The onset of the disease was characterized by recurrent episodes of macroscopic hematuria in 50% of patients with familial IgAN. No information from eight patients with familial IgAN was obtained. The same percentage was found in patients with sporadic IgAN. At the time of renal biopsy, no difference was found in laboratory findings, including serum IgA, creatinine, creatinine clearance, and proteinuria between familial and sporadic cases of IgA nephropathy. Mild proteinuria was present in 59% of patients with familial IgAN and in 56% of subjects with sporadic IgAN. Moderate and severe proteinuria occurred in the same percentage of patients with familial and sporadic IgAN. Hypertension

Table 2. Relative risk of the disease developing in relatives of patients with familial IgA nephropathy, estimated by odds ratio (OR)

Subject	<i>n</i>	Age (Median)	Examined (<i>n</i>)	Affected/Probably Affected (<i>n</i>)	Unaffected/Not Tested (<i>n</i>)	OR (95% CI) ^a	<i>P</i>
First-degree relatives	116	46	81	38	78	16.4 (5.7 to 47.8)	<0.0001
Second-degree relatives	150	22	43	10	140	2.4 (0.7 to 7.9)	0.1450
Controls	139	32	139	4 ^b	135		

^a ORs and their 95% confidence intervals (CIs) were calculated by use of the logistic regression model.

^b Healthy subjects with urinalysis positive for microscopic hematuria.

occurred in ~35% of all patients with IgAN in either familial or sporadic form. Normal renal function was present in a higher percentage of patients with sporadic IgAN. Chronic renal insufficiency was more frequent, but not significantly, in familial than in sporadic IgAN.

Renal Biopsy Features

Patients with familial IgAN had mild renal lesions in 45.5% of cases, moderate in 30.3%, and severe in 24.2%. Patients with sporadic IgAN showed mild lesions in 32% of cases, moderate in 56%, and severe in 12% (Table 3). No significant difference was found between the two groups.

Outcome

The mean follow-up of 32 patients with biopsy-proven familial IgAN and 25 with sporadic IgAN was 9.4 ± 8.3 yr from the apparent onset of the disease and 5.8 ± 5.7 yr from the time of renal biopsy, respectively. The cumulative probabilities of reaching the end-point events of doubling of baseline serum creatinine value and ESRD from the apparent onset of the disease were significantly higher in patients with familial IgAN than in patients with sporadic IgAN ($P = 0.006$ and 0.003). During the observation period, 13 and 2 patients with familial and sporadic IgAN, respectively, reached the doubling of baseline serum creatinine value, whereas ESRD occurred in 12 patients with familial IgAN and in 1 subject with sporadic IgAN (Figure 1). The 20-yr renal survival was present in only

41% of patients with familial IgAN, whereas it occurred in 94% of patients with sporadic IgAN. Fifteen years after the time of the renal biopsy, the doubling of baseline serum creatinine value and the rate of ESRD were significantly more frequent in familial IgAN ($P = 0.03$ and 0.02) (Figure 2). ESRD was present in 64% of patients with familial IgAN and in 8% of subjects with sporadic IgAN; the end-point of doubling of baseline serum creatinine value occurred more frequently in patients with familial IgAN (65%) than in subjects with the sporadic form (11%).

Figure 3 shows the renal survival from the time of renal biopsy in patients with familial IgAN with SG or MG involvement. Renal survival was significantly worse in patients with SG involvement, because the doubling of baseline serum creatinine value and ESRD were more frequent in subjects belonging to families with SG involvement ($P = 0.02$ and 0.03).

Discussion

Our epidemiologic study, carried out in a large series of IgAN families, shows that familial clustering of IgAN occurred in >50% of our IgAN population enrolled in the family study. Therefore, IgAN clusters in families more frequently than we may expect. In fact, an RR existed in relatives of patients with IgAN and was higher in first-degree than in second-degree relatives. Even if the decrease of RR in second-degree relatives was higher than expected, this could be explained by the difference of median age between first- and second-degree

Table 3. Clinical findings and laboratory data at the time of renal biopsy

Parameter	No. of Patients (f/s) ^a	Familial	Sporadic	P ^b
No. of families		19	25	
No. of patients		39	25	
Gender (M/F)	39/25	24/15	18/7	NS
MH/mH (onset)	31/25	14/17	13/12	NS
Age of onset (yr)	31/25	26.8 ± 12.6	25.2 ± 11.1	NS
Serum IgA (mg/dl)	14/4	436.7 ± 181.8	388.6 ± 93.8	NS
Serum creatinine (mg/dl)	33/25	1.4 ± 1.0	1.1 ± 0.4	NS
Proteinuria (g/d)	27/25	1.3 ± 1.3	1.1 ± 1.2	NS
Clearance creatinine (ml/min)	27/25	82.9 ± 40.7	93.7 ± 26.9	NS
Proteinuria (no.)	27/25			
mild <1 g/24 h		16	14	
moderate 1 to 3 g/24 h		7	9	NS
severe >3 g/24 h		4	2	
Hypertension (no.) (>130/80)	29/25	12	8	NS
Renal function (no.)	30/25			
normal (Ccr ≥ 70 ml/min)		20	21	NS
reduced (Ccr <70 ml/min)		10	4	
Renal lesions (no.)	33/25			
mild		15	8	
moderate		10	14	NS
severe		8	3	

^a No. of patients included in the study for each parameter. f, familial; S, sporadic.

^b Continuous data were compared by unpaired Student's *t* test; dichotomous and polychotomous data were compared by χ^2 test or Fisher's exact test. NS, not significant.

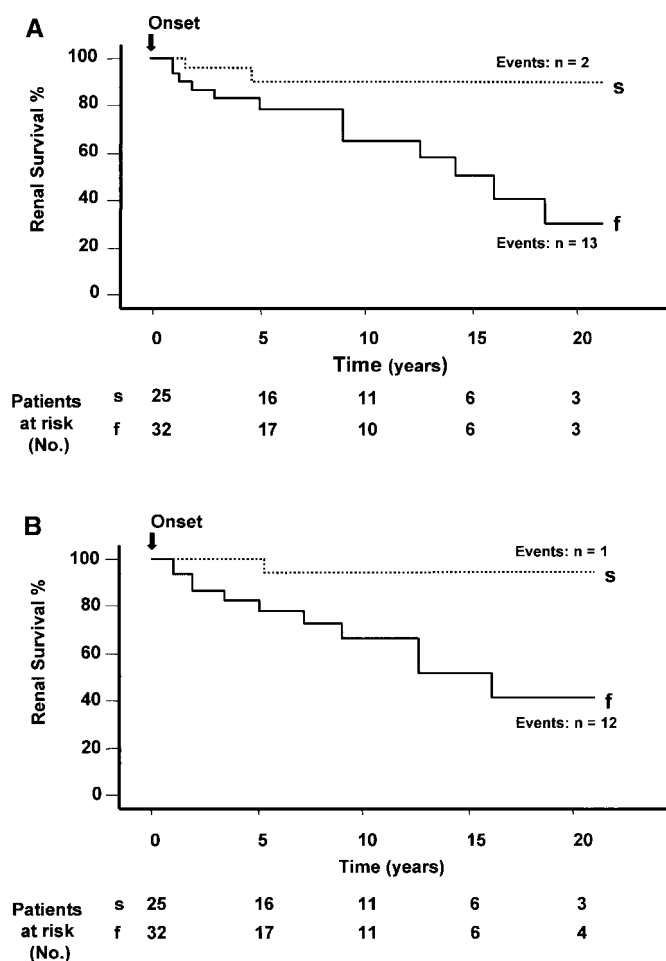


Figure 1. Renal survival in patients with sporadic (s) and familial (f) IgA nephropathy (IgAN) from the apparent onset of the disease. The outcome measures were represented by the doubling of baseline serum creatinine value (A) and end-stage renal disease (ESRD) (B). The number of events was significantly higher in familial IgAN in panel A (log-rank test, $\chi^2 = 7.6$, $P = 0.006$) and panel B (log-rank test, $\chi^2 = 9.0$, $P = 0.003$). Patients at risk were the number of cases in observation at each time.

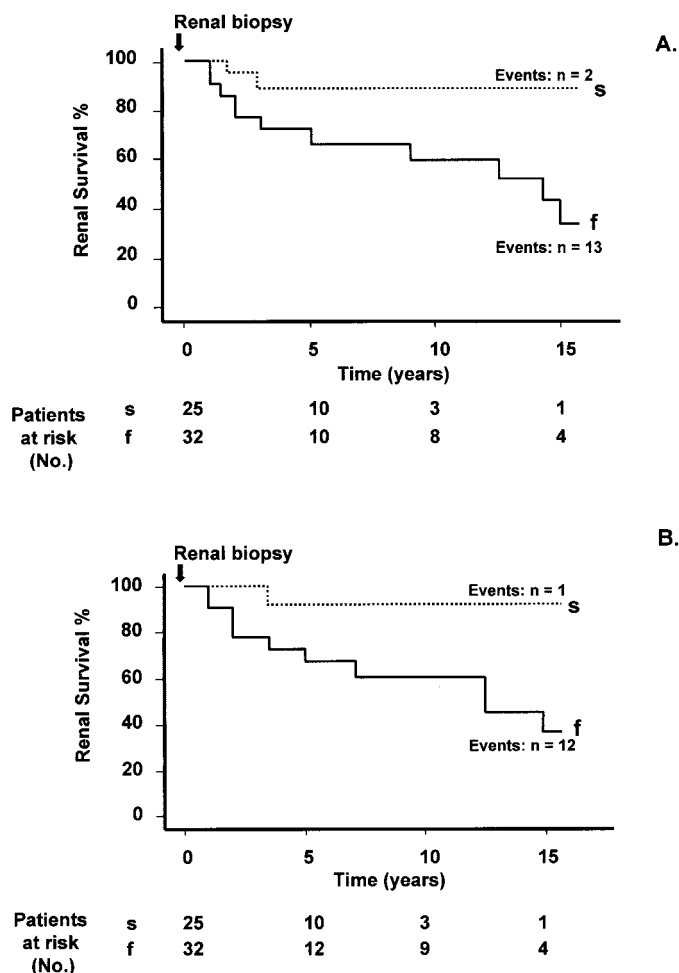


Figure 2. Renal survival in patients with sporadic (s) and familial (f) IgAN from the renal biopsy. The outcome measures were represented by the doubling of baseline serum creatinine value (A) and ESRD (B). The number of events was significantly higher in familial IgAN in panel A (log-rank test, $\chi^2 = 4.6$, $P = 0.03$) and panel B (log-rank test, $\chi^2 = 5.6$, $P = 0.02$). Patients at risk were the number of cases in observation at each time.

relative groups. The high risk of developing the disease in relatives of patients with IgAN suggests that the physician should consider the family history and should examine other family members for urinalysis after informed consent. This procedure might avoid a late referral of subjects with persistent and underestimated urinary abnormalities and late diagnosis of the disease. A family history of chronic glomerulonephritis strongly related to the risk of IgAN was reported by Wakai *et al.* (17) in a case-control study in Japan. In addition, asymptomatic urinary abnormalities, found via the Japanese school screening program, were caused by IgAN in >40% of subjects who subsequently had a deterioration of renal function (18). Therefore, our data and clinical and epidemiologic studies urgently recommend a rapid and early diagnosis of the disease and the differentiation of IgAN from other benign diseases such as thin-membrane disease or normal renal parenchyma.

The cases of familial IgAN reported in this study appear to

be clinically and pathologically similar to sporadic cases of IgAN. The only characteristic was the occurrence of the disease in two or more family members. This finding suggests that a heritable trait for IgAN could be present in certain families and may contribute to the risk of developing renal disease. Considering these different aspects, we approached genetic studies in familial IgAN. We participated in a multicenter study in which 30 IgAN families (24 from Italy and 6 from the United States) were analyzed by whole-genome scanning. Of interest, the linkage analysis showed a close association with the trait 6q22-23 in 60% of familial IgAN, a 6.5-cM region bounded by D6S1702 and D6S262 markers, with a maximum likelihood of odds score of 5.6 at D6S1040 (19). But other suspected traits like chromosome 3p23-24 were showed by linkage analysis. These findings support the hypothesis that familial IgAN is a multifactorial or “complex” disease in which one or more genes, probably in combination with environmen-

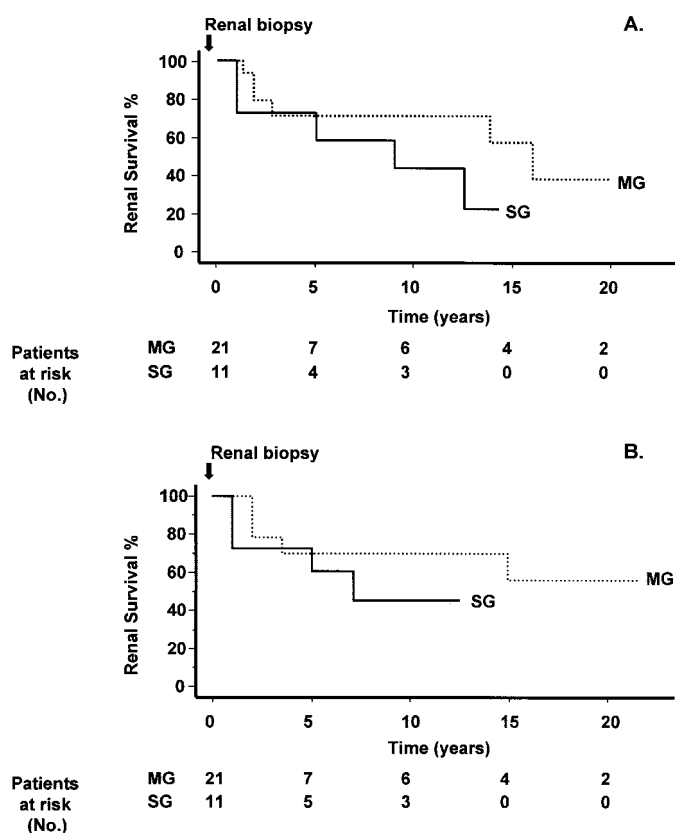


Figure 3. Renal survival in IgAN families with single-generation (SG) and multiple-generation (MG) involvement. The outcome measures were represented by the doubling of baseline serum creatinine value (A) and ESRD (B). Patients at risk were the number of cases in observation at each time. (A) log-rank test, $\chi^2 = 5.2$, $P = 0.02$ and (B) log-rank test, $\chi^2 = 4.4$, $P = 0.03$.

tal factors, may be responsible for the onset of the disease. The more distant family relations of patients with IgAN were studied by US and Italian investigators (20,21). They demonstrated that a high percentage of patients with IgAN were related to at least one other patient. Epidemiologic investigators in one study did not reveal a common environmental factor, because occupations, types of housing, and foods were different (22). These studies on family relations suggest that a genetic mechanism may be more important in the onset of the disease than the environmental factors. In addition, the strongest evidence from human studies of the role of genetic factors in the development of the disease is provided by descriptive reports of familial aggregations of IgAN in which affected sib pairs and parents from a multitude of ethnic backgrounds were present (21,23–32).

We have shown, for the first time, a difference in clinical outcome between patients with familial and sporadic IgAN. Familial patients with IgAN appear to have a more aggressive form of the disease, because a higher number of them showed doubling of baseline serum creatinine value and ESRD 20 yr after the apparent onset of the disease. A significant difference was also evident 15 yr after the time of the renal biopsy. Developments in molecular biology have enabled investigators

to study the influence of candidate genes in the outcome of IgAN (33–42). Genetic association studies have reported contrasting data. The principal bias was represented by the low number of enrolled patients. In addition, those studies were carried out in diverse parts of the globe in which different additional environmental factors influenced the results. Our study shows that an accurate family history and urinalysis of the relatives may reveal kindred with familial IgAN in >50% of the IgAN patient population. Large multiple generation families, sib pairs, and unaffected siblings were obtained. In addition, the population was relatively homogeneous, because all subjects were born and grew up in Southern Italy, namely in the Puglia Region. These characteristics eliminate the bias of population stratification, and the collected familial patients with IgAN may be used to search for gene(s) responsible for the onset and progression of renal damage.

In this study, we analyzed the different pattern of disease distribution in the IgAN families. We assumed the term of SG involvement in which IgAN patient was ascertained in only one generation and the term of MG involvement for the occurrence of the disease in subjects distributed in two or three generations. It is likely that MG involvement occurs in families with autosomal dominant inheritance and SG involvement in those with autosomal recessive inheritance; another possibility is the presence of an autosomal dominant disease with incomplete penetrance. In 11 families we found MG involvement, which suggests a vertical mode of transmission, and the development of the disease in sets of twins also established that a genetic disorder may be present in familial IgAN. We did not find a difference in clinical presentation, but the outcome between the two types of generation involvement was evident, because renal survival was significantly worse in patients with SG involvement. Therefore, SG involvement appears to have a more aggressive form of the disease. It is possible that this more aggressive deterioration in renal function represents the effect of a situation similar to diabetic and lupus erythematosus in which the risk of developing a nephropathy is much higher when two or more first-degree relatives have renal disease (38–42). IgAN is another disease with genetic susceptibility that may be included in the group of non-Mendelian renal diseases at higher familial risk for renal failure. A common environmental exposure was not identified in any of our IgAN families. Because not all family members were affected, phenotypic manifestations of the disease caused by exposure to unknown environmental factors could arise only as a result of epistatic effects on a disease susceptibility gene.

Future investigations of genetic determinants of clinical outcomes may be productive. The identification of susceptibility gene(s) has the potential to identify new targets for early therapeutic intervention to prevent early morbidity and renal mortality. Success in identification of gene(s) conferring susceptibility to end stage renal disease may lead to the development of highly accurate genetic tests permitting the identification of subjects at high risk with specific inherited susceptibility and intervention at a preclinical stage with pharmacogenetic therapies.

In conclusion, we have reported a large series of patients

with IgAN who were clustered in a familial form or sporadic form. Difference in outcome was evidenced and familial IgAN was defined a nonbenign disease, because a higher number of patients with impaired renal function and ESRD occurred than in the sporadic IgAN form. Further genetic studies of these families will contribute to our understanding of the molecular pathogenesis of the disease in the familial IgAN disease.

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