IgA Nephropathy: The Presence of Familial Disease Does Not Confer an Increased Risk for Progression

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• ***Background:*** **Immunoglobulin A (IgA) nephropathy is the most common form of glomerulonephritis worldwide. Familial and sporadic cases are recognized, and a locus associated with the familial form of the disease was mapped to chromosome 6. Recent data suggest the familial IgA nephropathy form may have a poorer outcome than the sporadic form.** ***Methods:*** **We tested the hypothesis of unequal survival rates between the 2 forms of disease by analyzing time from biopsy to end-stage renal disease in patients of Italian ancestry; 589 patients with sporadic and 96 patients with familial IgA nephropathy.** ***Results:*** **Overall 10- and 20-year renal survival probabilities of the cohort as a whole were 71% and 50%, respectively. Macroscopic hematuria was the modality of clinical presentation in 51% of patients with familial IgA nephropathy and 39% of patients with sporadic IgA nephropathy. At univariable analysis, the sporadic form of IgA nephropathy was associated significantly with increased risk for renal death. However, patients with the sporadic form tended to be more hypertensive and diagnosed later, with signs of more advanced renal disease than those with familial disease at baseline. In the regression model, form of disease lost any independent effect. Only male sex, lower baseline glomerular filtration rate, greater proteinuria, and histopathologic score proved to be independent predictors of disease progression. Treatment with steroids or angiotensin-converting enzyme inhibitors was associated with improved outcomes.** ***Conclusion:*** **Our study does not confirm that familial IgA nephropathy has a worse prognosis than the sporadic form. The similar renal phenotype may support a common pathogenic mechanism underlying familial and sporadic IgA nephropathy.** ***Am J Kidney Dis*** **47:761-769.**

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INDEX WORDS: Familial immunoglobulin A (IgA) nephropathy; glomerular filtration rate; renal survival; risk factors; sporadic immunoglobulin A (IgA) nephropathy.

IMMUNOGLOBULIN A (IgA) nephropathy is a relatively newly recognized disease, first described by Berger and Hinglais[1] in 1968. After their seminal article, the disorder soon was recognized as the most common primary glomerulonephritis in the world, comprising 25% to 50% of renal biopsy diagnoses.[2,3] Once considered a relatively benign condition, longitudinal follow-up studies showed that 40% of patients progressed to end-stage renal disease by 15 years after the time of renal biopsy.[4] In the last 20 years, many studies involving large cohorts of patients reported clinical, laboratory, and pathological characteristics that predict progressive renal disease.[5-12] Impaired renal function at the time of renal biopsy, high glomerular histopathologic scores, proteinuria with protein greater than 1 g/24 h, and hypertension have emerged as strong predictors of poor renal survival.

Despite considerable research, the pathogenesis of IgA nephropathy is poorly understood, and the true mechanism of mesangial IgA targeting

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remains hypothetical.[13] However, observations have accumulated indicating that genetic factors may be important in disease susceptibility.[14] Recently, the role of genetic factors in the development of IgA nephropathy was definitely established, and a chromosomal position of the trait was identified on 6q22-23.[15] Traditionally, the strongest evidence of a role of genetic predisposition in the development of IgA nephropathy was provided by descriptive reports of familial aggregation of the disorder that appears to be very common. To date, more than 100 families with multiple members with IgA nephropathy have been reported from several ethnic backgrounds.[16,17] Moreover, in some series, familial forms of the disease may represent up to 15% to 20% of cases of primary disease.[18]

To date, only 2 studies examined the renal phenotype of patients with familial IgA nephropathy. According to Julian et al,[19] familial and nonfamilial IgA nephropathy cannot be differentiated by clinical features of the disease. However, more recently, Schena et al[20] reported that patients with familial IgA nephropathy had a poorer outcome than those with sporadic IgA nephropathy. However, none of those studies was powerful enough to provide a reliable estimate of any association with disease progression while considering potential confounders.

The purpose of the present work, including a large cohort of adults with biopsy-proven IgA nephropathy, is to compare the renal phenotype of patients with sporadic and familial IgA nephropathy, accounting for baseline clinical characteristics and other risk factors known to impact on renal outcome.

METHODS

IgA Nephropathy Patient Population

This historical cohort study includes 685 Italian patients with IgA nephropathy recruited by the European IgA Nephropathy Consortium: 589 patients had sporadic disease and 96 patients had familial IgA nephropathy. Patients with familial IgA nephropathy belonged to 40 families; 34 were nuclear families, including 2 or more first-degree affected members; and 6 were extended families, including, in addition to at least 2 first-degree affected members, other more distant affected relatives. Demographic, clinical, and pathological data from adults with biopsy-proven IgA nephropathy were collected from databases in Brescia and Bari, the 2 Italian coordinating centers of the European IgA Consortium, a collaborative study group including nephrologists and geneticists from Italy, Germany, and Greece. Data were collected retrospectively from university hospitals and associated tertiary-care centers by using biopsy registries, clinical inpatient and outpatient records, and discharge summaries at each institution. The study was approved by the local ethical review committees. All individuals participating in the study gave informed consent according to the Helsinki Declaration.

Diagnostic Criteria and Definitions

Biopsy-proven IgA nephropathy was based on the predominance of IgA deposits in the mesangial area of glomeruli in patients with recurrent macroscopic hematuria or persistent microscopic hematuria and/or proteinuria. Individuals with secondary forms of IgA nephropathy were excluded from the study. A detailed family history was obtained from all patients with IgA nephropathy. Moreover, all first-degree family members of patients with IgA nephropathy underwent urinalysis. Sporadic IgA nephropathy was diagnosed when the presence of the disease occurred only in the patient and family members had negative results at urinalysis. Familial IgA nephropathy was diagnosed when at least 2 first-degree family members had biopsy-proven IgA nephropathy.

Baseline Clinical, Laboratory, and Histopathologic Data

At the time of renal biopsy (baseline data), the following demographic and clinical data were collected: age, sex, blood pressure, urinary protein excretion (grams per 24 hours), serum creatinine (milligrams per deciliter [SI, micromoles per liter]), and glomerular filtration rate (GFR; milliliters per minute [SI, milliliters per second]). Treatment with an angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin II receptor blocker (ARB) and immunosuppressive therapy with steroids also were considered. Proteinuria was categorized as mild for protein less than 1 g/24 h, moderate at 1 to 3 g/24 h, and severe at greater than 3 g/24 h. GFR was estimated based on the 4-variable Modification of Diet in Renal Disease (MDRD) formula.[21] Categories of renal function deterioration are defined based on the National Kidney Foundation–Dialysis Outcomes Quality Initiative classification as absent/mild at greater than 60 mL/min (>1.00 mL/s), moderate at 60 to 30 mL/min (1.00 to 0.50 mL/s), and severe/advanced at less than 30 mL/min (<0.5001 mL/s).[22] Hypertension is defined as systolic blood pressure of 130 mm Hg or greater and/or diastolic blood pressure of 80 mm Hg or greater; patients are defined as having arterial hypertension if they had a history of hypertension requiring treatment or developed hypertension at the time of diagnosis. The existence or absence of at least 1 documented episode of macroscopic hematuria was investigated. Histopathologic renal lesions were graded according to the World Health Organization classification.[23] Three grades (G) were identified: (1) G1 (mild disease): normal renal parenchyma or evidence of mild mesangial cell proliferation or mesangial matrix expansion (minimal lesions); (2) G2 (moderate disease): focal and segmental glomerular sclerosis with the presence of floccular adhesions to Bowman capsule, low number of extracapillary proliferations (crescents), and mild interstitial infiltrates (focal and segmental

lesions); and (3) G3 (severe disease): severe involvement of glomeruli (partial or total glomerular sclerosis), tubules (tubular atrophy and thickness of basement membranes), interstitium (numerous infiltrates and severe interstitial fibrosis), and vessels (intimal thickening and arteriolar thickening with lumen reduction).

Follow-Up and Outcome

During follow-up, clinical and laboratory data for patients with familial and sporadic IgA nephropathy were obtained at different times, with frequency depending on the severity of renal disease. Patients were followed up after diagnosis until they died or reached end-stage renal disease (ESRD). To avoid loss to follow-up, patients were contacted by telephone between September 1 and December 31, 2004 (study end date), if they were not known to already be on dialysis therapy or dead. Two outcome measures were considered at the end of follow-up: (1) the composite end point of halving the GFR value or ESRD (dialysis or renal transplantation), and (2) reaching ESRD only. Death and loss to follow-up were considered in sensitivity analysis (see statistical analysis).

Statistical Analysis

Study power and sample size. Previous reports described a median time to ESRD of 25 to 30 years in patients with the sporadic forms of IgA nephropathy[5,11] and risk for progression up to 100% greater in those with familial forms of the disease.[20] On this basis, we expected that the Italian population of the European consortium (~700 subjects with a 6:1 ratio of sporadic to familial form) would permit detection of a relative risk for event occurrence of 0.6 or less or 1.7 or greater with a power of 0.9 and a type I error probability of 0.05.

Survival functions. Times from diagnosis (biopsy date) to event (halving the GFR or renal replacement therapy start dates) or censoring (last scheduled visit date, death, or loss to follow-up) were described by using the Kaplan-Meier method. Univariable comparisons were conducted by using log-rank test. The Cox proportional hazards procedure was used to model time to event as a function of the form of IgA nephropathy (sporadic versus familial). Potential correlation within family members was accounted for by correcting the robust variance–covariance matrix of the estimators with the matrix of the independent groups' (clusters) efficient score residuals.[24] Covariates considered to develop the survival model included all risk factors previously described unless violation of the hazard proportionality was present. Stratification was used to build the final regression model and check its consistency. Furthermore, the largest possible meaningful model initially considered included clinically consistent and interpretable interaction terms, following the rule of 10 (1 parameter/10 events) and considering the overall model fit and hazard proportionality. The final model was stratified by referral coordinating centers (Brescia and Bari) and age tertiles because they did not satisfy the proportionality assumption and age was included in the MDRD formula. Strata were obtained by factoring these 2 variables into the 6 possible combinations. Proteinuria and baseline renal function were tested as both continuous and categorical variables. A maximum-likelihood procedure was used to estimate regression coefficients, and contribution of the covariates to explain the dependent variable was assessed by means of a 2-tailed Wald test, with P less than 0.05 considered significant. The –2 log likelihood ratio statistic was used for goodness-of-fit comparison. Model specification and overall fit were checked by reestimation; formal tests based on Schoenfeld, martingale, and Cox-Snell residuals; and testing the interaction with time of variables in the model. Influence analysis was conducted based on efficient score residuals. Sensitivity analysis was conducted considering the length of observation time and reasons for loss to follow-up. All analyses were performed using STATA 9 SE (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

Table 1 lists demographic and baseline characteristics of the study cohort as a whole and by patients with the familial versus sporadic IgA nephropathy forms. The study population at the time of renal biopsy had an average age of 34.8 ± 14.8 (SD) years; 75.4% of patients were men, 40.6% were hypertensive, and 41.1% had macroscopic hematuria at onset. Baseline GFR was 78.5 ± 41.1 mL/min (1.30 mL/s); serum creatinine, 1.47 ± 1.13 mg/dL (130 μmol/L); and proteinuria, 1.24 ± 1.31 g/24 h or protein. At the time of renal biopsy, frequency of arterial hypertension, severity of histological lesions, serum creatinine levels, and proteinuria were significantly greater (Table 1) in patients with sporadic IgA nephropathy compared with those with familial disease. Of note, macroscopic hematuria was the modality of clinical presenting feature in 51% of patients with familial IgA nephropathy and 39.2% of patients with sporadic disease ($P = 0.010$).

Renal Outcome

After a mean follow-up of 77 months (median, 55 months; range, 3 to 378 months), 177 patients reached the combined end point of halving GFR or ESRD (4,423 patient-years at risk; incidence rate, 3.4/100 patient-years). By univariate analysis, in the entire population, renal survival probabilities were 0.67 (95% confidence interval [CI], 0.62 to 0.72) at 10 years and 0.38 (95% CI, 0.29 to 0.46) at 20 years. Of those censored, 9 patients died and 11 patients were lost to follow-up. Event occurrence was appreciably greater among patients with sporadic forms (4.4 versus 2.3/100 person-years). Considering ESRD only and censoring patients with halving of GFR, events

Table 1. Characteristics of the Cohort as a Whole and by Type of IgA Nephropathy at Time of Renal Biopsy

Variable	All (N = 685)	Sporadic (n = 589)	Familial (n = 96)	*P*
Age (y)	34.8 ± 14.8	35.28 ± 14	32.23 ± 14	0.064
Male sex	517 (75.4)	451 (76.5)	66 (68.7)	0.099
Hypertension	306 (40.6)	278 (47.2)	28 (29.1)	**0.001**
Macrohematuria	282 (41.1)	231 (39.2)	51 (53.1)	**0.010**
Serum creatinine (mg/dL)	1.47 ± 1.13	1.51 ± 1.18	1.24 ± 0.71	**0.002**
GFR ($MDRD_4$; mL/min)	78.5 ± 41.1	77.0 ± 39.4	87.7 ± 49.7	**0.047**
Proteinuria (g/L)	1.24 ± 1.31	1.27 ± 1.28	1.12 ± 1.5	0.370
Chronic kidney disease				
Absent-mild	467 (68.1)	395 (67)	72 (75)	
Moderate	140 (20.4)	121 (20.5)	19 (19.7)	0.104
Severe-advanced	78 (11.3)	73 (12.3)	5 (5.2)	
Proteinuria (g/L)				
<1	353 (51.5)	291 (49.4)	62 (64.5)	
1-3	253 (36.9)	227 (38.5)	26 (27)	**0.002**
>3	79 (11.5)	71 (12)	8 (8.33)	
Histological grade				
1	231 (33.7)	184 (31.2)	47 (48.9)	
2	266 (38.8)	239 (40.5)	27 (28.1)	**0.003**
3	188 (27.4)	166 (28.1)	22 (22.9)	
Steroid and ACE-inhibitor/ARB use	108 (15.7)	101 (17.1)	7 (7.29)	
ACE inhibitor/ARB only	211 (30.8)	185 (31.4)	26 (27)	**0.015**
Steroid only	32 (4.6)	24 (4)	8 (8.3)	
Neither drug	334 (48.7)	279 (47.3)	55 (57.2)	

NOTE. Qualitative variables expressed as absolute frequency and percentage, and quantitative variables expressed as mean ± SD. Chi-square and *t*-tests were used for comparisons. Results that have $P < 0.05$ are indicated in bold. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; GFR in mL/min to mL/s, multiply by 0.01667.

occurred in 143 patients. With this outcome measure, renal survival probabilities were 0.71 (95% CI, 0.66 to 0.76) at 10 years and 0.50 (95% CI, 0.41 to 0.58) at 20 years. As expected, older age, male sex, presence of hypertension (Fig 1C), onset type with microhematuria (Fig 1B), higher histological grade (Fig 1A), lower GFR, and greater proteinuria were associated with significantly worse survival. As far as the main exposure of interest was concerned, patients with the familial form showed crude survival probabilities (combined end point of halving GFR or ESRD) of 0.77 and 0.63 at 10 and 20 years versus 0.64 and 0.28 for the sporadic forms ($P = 0.003$; Fig 1D), respectively. To obtain an unbiased estimate of the exposure–outcome relationship of interest, the mentioned confounding factors were controlled with multivariable analysis. In the Cox model, male sex, severity of histological lesions, baseline GFR, and proteinuria level were all strong and independent predictors of disease progression. Patients administered converting-enzyme inhibitors and those treated with steroids had a significantly decreased risk for event occurrence. Conversely, the association of the sporadic form with renal failure was no longer present (Fig 2; Table 2). No significant second-order interaction was found between any combination of these variables. Results were the same when the outcome was ESRD only (and patients halving GFR were censored), excluding patients with follow-up shorter than 1 year (n = 71) or censoring those with follow-up longer than 25 years (n = 14), as well as assuming that the 20 subjects lost to follow-up before the study end date had developed the event of interest.

DISCUSSION

This study describes the long-term outcome of one of the largest cohorts of patients with IgA nephropathy reported to date. Considering the entire population (familial and sporadic cases) and ESRD as outcome measure, overall 10- and 20-year renal survival rates were 71% and 50%, respectively. This is similar to previous reports. Actuarial renal survival at 10 years reported by the majority of studies performed in Europe,

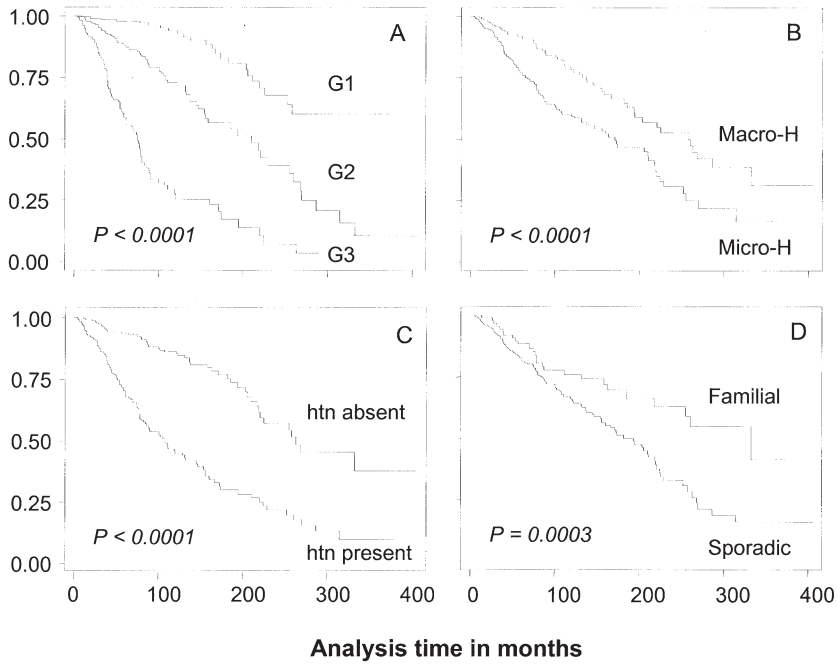

Fig 1. Kaplan-Meier renal survival functions by (A) histological grade, (B) macrohematuria versus microhematuria, (C) presence of hypertension, and (D) sporadic versus familial IgA nephropathy from the renal biopsy, with halving of baseline estimated GFR and ESRD as the combined end point.

Asia, and the United States during the last 2 decades is highly variable, ranging from 57% to 94%.[5-12] This variability in long-term outcome of patients with IgA nephropathy may reflect differences in genetic influences, frequency of urinary screening, and criteria for renal biopsy. A review of patients from 3 continents suggests that a lead-time bias in establishing the diagnosis contributes to the variation in long-term outcomes by different centers.[25]

In our study, the size of the entire cohort and length of follow-up allowed meaningful comparison of factors that affected long-term outcome. By using univariate analysis, multiple risk fac-

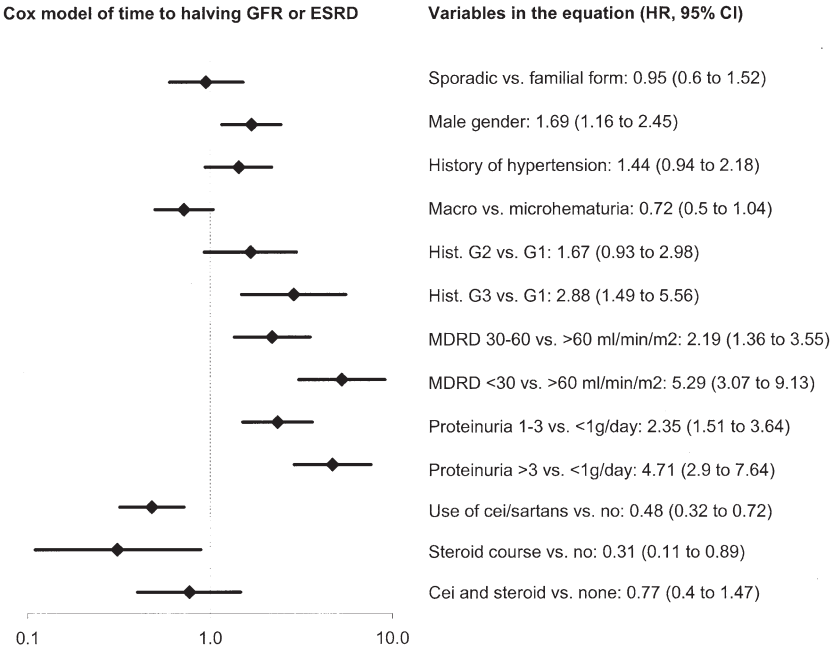

Fig 2. Stratified Cox model of time to halving of baseline estimated GFR and ESRD (see Table 2 for details). Log-scale plot of hazard ratios (HRs) and 95% CIs for disease progression. To convert GFR in mL/min to mL/s, multiply by 0.01667.

Table 2. Stratified Cox Proportional Hazards Procedure of Time to Halving GFR or ESRD

Variable	B	SE	*P*	Hazard Ratio	95% CI for Hazard Ratio
Sporadic *v* familial	−0.042	0.236	0.858	0.95	0.60-1.52
Sex (male *v* female)	0.527	0.189	**0.005**	1.69	1.16-2.45
Hypertension (yes *v* no)	0.365	0.213	0.086	1.44	0.94-2.18
Macrohematuria *v* microhematuria	−0.321	0.184	0.081	0.72	0.50-1.04
Histological grade (G2 *v* G1)	0.512	0.296	0.084	1.67	0.93-2.98
Histological grade (G3 *v* G1)	1.059	0.335	**0.002**	2.88	1.49-5.56
GFR (30-60 *v* >60 mL/min)	0.788	0.245	**0.001**	2.19	1.36-3.55
GFR (<30 *v* >60 mL/min)	1.667	0.278	**<0.001**	5.29	3.07-9.13
Urinary protein (1-3 *v* <1 g/d)	0.855	0.223	**<0.001**	2.35	1.51-3.64
Urinary protein (>3 *v* <1 g/d)	1.550	0.246	**<0.001**	4.71	2.90-7.64
ACE inhibitor only (*v* neither)	−0.722	0.202	**<0.001**	0.48	0.32-0.72
Steroid only (*v* neither)	−1.131	0.528	**0.031**	0.31	0.11-0.89
Steroid + ACE inhibitor (*v* neither)	−0.257	0.330	0.436	0.77	0.40-1.47

NOTE. N = 177 events. Hazard ratios and 95% CIs of hazard ratios for progression associated with covariates in the final model are listed. Center effect (Brescia and Bari) and age (tertiles) are accounted for by stratification, discussed in Methods. SEs are adjusted for clustering on family code. The model is highly significant (Wald chi-square[13] = 272.18; $P < 0.0001$). There was no violation of the proportional hazards assumption. Results that have $P < 0.05$ are indicated in bold.

tors were associated significantly with poorer outcome. They included older age, male sex, arterial hypertension, absence of history of macroscopic hematuria, higher histological grade, lower GFR, and greater proteinuria. However, considering multiple risk factors simultaneously, only male sex, baseline GFR, proteinuria level, and high histopathologic score proved to be significant and independent predictors of disease progression. These findings are consistent with data from most published studies, in which poor renal function and heavy proteinuria at the time of biopsy or initiation of the disease and severity of histological lesions emerged as independent predictors of poor outcome.[5-12] In the present study, absence of episodes of gross hematuria and male sex showed only a borderline effect on prognosis, a finding concordant with previous studies in which, with few exceptions, these risk factors lost their prognostic value when evaluated by using multivariate analysis.[5]

The role of treatment with steroids and ACE inhibitors/ARBs on survival rate was not analyzed in previous studies of familial versus sporadic IgA nephropathy. In the present large cohort of adult patients with IgA nephropathy, multivariate analysis showed for the first time an independent protective effect of ACE-inhibitor/ARB and steroid therapy. Although not statistically significant, a trend toward an additional survival advantage compared with either treatment alone was observed in patients treated with both ACE inhibitors/ARBs and steroids. The observational design of our study precludes the establishment of causality. However, these results confirm the beneficial influence of ACE inhibitors and steroids on the course of IgA nephropathy, already described in different and appropriate studies.[26-28]

More recently, a new factor was reported that might have an independent effect contributing to the progression of IgA nephropathy: the presence of familial disease. Familial IgA nephropathy seems to have a much worse prognosis than the sporadic form.[20]

Comparison of the renal phenotype of patients with the familial and sporadic forms of IgA nephropathy, with particular emphasis on risk for progression, was the major aim of our study. Thus, the present study is designed to detect, if present, a clinically relevant difference in renal outcome between the 2 types of disease (familial/sporadic relative risk for progression to ESRD <0.6 or >1.7), with a power of 90% and a probability of rejecting the null hypothesis when it is true (α error) of 0.05. Although there still remains a risk of 10% of failing to reject the null hypothesis of effect equality when it is actually false (β error), to our knowledge, this study provides the most powerful answer to the prognostic questions related to type of IgA nephropathy.

To date, only 2 studies examined in detail the renal phenotype of patients with sporadic and familial IgA nephropathy, giving controversial results. In the first study, Julian et al[19] compared 11 patients with familial IgA nephropathy and 17 patients with the sporadic form of disease. According to Julian et al,[19] clinical findings, such as mean age at apparent clinical onset of disease, age at time of renal biopsy, degree of microscopic hematuria, history of macroscopic hematuria, magnitude of daily proteinuria, and renal prognosis, were similar in patients with familial and sporadic disease. In addition, histological findings and frequency of the immunoglobulin isotype and C3 in renal biopsy specimens did not differ.

More recently, Schena et al[20] reported that patients with familial IgA nephropathy appeared to have a more aggressive form of disease. Renal phenotype was compared in 39 patients with familial and 25 patients with sporadic IgA nephropathy. Predominance of male sex, mean age at time of renal biopsy, and history of macroscopic hematuria were similar in those with familial and sporadic IgA nephropathy. Moreover, at the time of renal biopsy, no difference was found in laboratory findings, including serum IgA level, creatinine clearance, and proteinuria, between the 2 groups, as well as severity of histological lesions. However, despite this clinical and histological similarity, renal survival was significantly worse in patients with familial IgA nephropathy. According to that study, familial IgA nephropathy may be considered a nonbenign disease, characterized by a poorer outcome than the sporadic form of IgA nephropathy.

These studies may just have inadequate sample size to draw firm conclusions. For this reason, larger epidemiological studies appear necessary to test the hypothesized association between form of IgA nephropathy and renal outcome.

In our study population, at the time of renal biopsy, the group of patients with sporadic disease was composed of more severely ill symptomatic subjects, suggested by greater serum creatinine levels, more severe histological lesions and proteinuria, and increased frequency of arterial hypertension. This probably reflects different times of diagnosis, rather than different severity of the 2 forms. In other words, our clinical practice to obtain an accurate family history and perform urinalysis in all family members of patients with IgA nephropathy may favor earlier detection of the disease in the subset of patients with familial IgA nephropathy with asymptomatic and possibly less severe illness. Stronger clinical suspicion, leading to earlier diagnosis, may lead to a phenomenon known as lead-time bias in survival studies. In an ideal prognostic study, an inception cohort should be assembled with a common time zero for time-to-event analysis. Practically, this time zero is when the diagnosis is made, but this can vary in relation to the true disease course. Lead-time bias occurs if there is a systematic difference between groups in the timing of diagnosis in relation to disease course. Lead-time bias confers an apparent survival advantage to individuals diagnosed in the preclinical phase of the disease, and it may be very difficult to introduce corrections of this measurement bias once detection by screening has occurred more often in 1 of the exposure groups. One way to correct the effect of lead-time bias in prognostic studies in nephrology is to subtract time segments from those who were screened and enrolled earlier in the course of their disease (or prolong time of those not screened) by using renal function at baseline and rate of renal function deterioration. However, this can be done only under the assumption that renal function declines linearly and independently of any intervention undertaken after diagnosis to decrease progression and irrespective of other factors known to impact on progression, such as hypertension or proteinuria. These assumptions clearly are untenable, and the validity of this correction is very uncertain. Furthermore, the time of biopsy-proven diagnosis remains the least vague starting point to measure time-to-event occurrence in this kind of disease, and prognostically important markers of renal disease severity, such as renal function, proteinuria, and histological score, can be incorporated usefully into a regression model to provide a less biased estimate of the association of interest.

For all these reasons, although univariate analysis suggested that the sporadic form of IgA nephropathy was associated significantly with increased risk for renal death, this detrimental effect on renal survival disappeared in multiple Cox regression. This suggests that the sporadic disease was not an independent predictor of renal

survival and confirms the role of known confounders.

Our study has limitations. It is an observational investigation; thus, any exposure-disease relationship must be interpreted cautiously as association and not causality. Despite successful handling of confounding issues, the possibility of design limitation and residual confounding cannot be ignored. The likelihood of selection bias seems low because of the meticulous record search in different registries and centers and efficient variable definitions. However, we acknowledge that these same risk factors for renal mortality, such as hypertension and proteinuria, were assessed only at the study start and not during follow-up, precluding analysis of the impact of their change over time. Finally, our analysis is limited with respect to exploring other potential recently identified predictors of the development of ESRD, such as obesity, smoking, and inflammation markers.[29-31]

In summary, results of the present study suggest that one cannot differentiate between familial and nonfamilial IgA nephropathy with respect to clinical features of disease. In particular, we are unable to confirm previous suggestions that patients with familial IgA nephropathy have a much worse prognosis than those with sporadic forms of IgA nephropathy because a similar clinical long-term outcome between the 2 groups of patients was observed. Thus, today, familial disease cannot be added to the growing list of independent factors contributing to the overall prognosis of patients with IgA nephropathy.

To conclude, we can speculate that the similarity of renal phenotype may represent a compelling argument in favor of a common pathogenic mechanism underlying familial and sporadic IgA nephropathy. This offers the possibility that identification of the gene(s) for familial IgA nephropathy might shed light on the pathogenesis of the sporadic form of the disease.

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