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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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

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