Natural History of Primary IgA Nephropathy

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Summary: Primary IgA nephropathy (IgAN) is the most frequent type of primary glomerulonephritis worldwide. The characteristic presentation is gross hematuria at the time of an infectious episode. A renal biopsy still is mandatory for the diagnosis. The natural history of the disease is characterized by clinical and pathologic progression over time, which can vary from a few years to more than 50 years. It is possible to make a broad prediction at the time of diagnosis of the long-term (20 years) risk of progressive chronic kidney disease, and then to end-stage renal disease requiring renal replacement therapy (20-year cumulative end-stage renal disease risk range, 14%-39%). The 3 major independent risk factors are arterial hypertension, proteinuria more than 1 g/d, and severe renal histopathologic lesions including hyalinosis, crescents, or defined by histopathologic scoring systems. When any clinical risk factors are present, patients should be targeted closely by appropriate treatments in the following order: (1) precise control of hypertension, (2) control of proteinuria when persisting for greater than 1 g/d, and (3) evidence-based treatment where available for severe lesions. This is a symptomatic treatment strategy because pathogenesis and etiology still remain unclear.

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IgA nephropathy (IgAN) first was described by the French pathologists Berger and Hinglais[1] in 1968 in Paris in the Journal d'Urologie et Néphrologie, and in 1969 in an international journal.[2] Later, it turned out to be the most frequent type of glomerulonephritis in human beings worldwide.

DEFINITION OF IgAN

The definition of IgAN is pathologic and still needs a renal biopsy which should be examined at least by light microscopy (LM) and by immunofluorescence microscopy. The immunofluorescence microscopy technique, necessary for identification of mesangial IgA deposits, appeared in the late 1960s, explaining why IgAN was not identified earlier. The agreed on definition is the presence of at least 1+ (on a semiquantitative scale: 0, trace, 1+, 2+, and 3+) IgA deposits in the mesangial area (also called *intercapillary tissue*) of glomeruli. The characteristics of these deposits are that they are granular and coarse scattered within the mesangium; global (throughout the glomerular volume) and diffuse (in all glomeruli) contrasting with the lesions seen by LM, which more often are segmental and focal. IgA deposits are dominant or codominant with other immunoglobulins such as IgM and/or IgG. The initial description was IgA with IgG, but in fact IgM deposits are more frequent. Associated C3 mesangial deposits of the same intensity are seen in more than 80% of the cases.

CLASSIFICATION OF IgAN

The spectrum of IgA nephropathies is dominated by idiopathic or primary IgAN, previously also called *Berger's disease*. In our own center,

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an initial cohort diagnosed from 1975 to 1987[3] consisted of 356 patients, with 282 cases (79%) of primary IgAN, 41 cases (11.5%) secondary to Schönlein-Henoch purpura, and 33 cases (9%) secondary to cirrhosis. Similar histologic appearances may be seen in systemic lupus erythematosus, International Society of Nephrology/Renal Pathology Society (ISN/RPS) class II. These were excluded from our cohort. IgAN secondary to liver disease and other less common disease associations are discussed further in this issue by Pouria and Barratt, pp. 27-37.

In this article, we focus only on primary IgAN and on data published mainly within the past decade. We acknowledge 3 recent reviews with extensive references.[4-6]

EPIDEMIOLOGY OF PRIMARY IgAN

IgAN is diagnosed worldwide, and remains the most predominant primary glomerulonephritis. It is frequent in Caucasian and Asian populations, contrasting with its apparent rarity in African populations, especially in African Americans.[7]

Its incidence has been estimated in France to be between 26 and 30 new cases per million population (pmp) in 2 different regions: Britanny[8] and Rhône-Alpes.[9] In Japanese children,[10] the incidence was calculated at 45 pmp (with both sporadically identified cases and systematic school mass screening). The apparent incidence clearly is influenced by the renal biopsy policy: whether it is liberal in cases of isolated microscopic hematuria or restricted to patients with proteinuria greater than 1 g/d and/or with established chronic kidney disease (CKD). In the United States, a report[11] found a 12.4 pmp incidence with equal distribution between whites and blacks.

In our experience, IgAN is the diagnosis in about 20% of all diagnostic renal biopsies and represents about half of all glomerulonephritis.[12]

Its prevalence is more difficult to establish depending on major differences in evolution and follow-up evaluation. From our experience of more than 3 decades, we enrolled about 30 new patients per year, with an active current file of about 700 patients, for a population of 650,000 inhabitants, which gave an incidence of 46 pmp and a prevalence of 1,077 pmp. Another indirect way to estimate prevalence is from the national renal replacement therapy program. Each year in France, about 120 pmp begin renal replacement therapy, of whom 10% (12 pmp) have IgAN.[13] In our experience, 14% of our IgAN patients reached ESRD more than 20 years from disease onset, which would give a prevalence of 1,714 pmp. Elsewhere in France, Simon et al[8] found a prevalence of 2,400 pmp.

The male predominance of IgAN is well established in Europe and America, approximating 70%, but appears not to be so characteristic in Asian countries. These differences remain unexplained, and have not been well investigated.

CLINICAL ONSET OF THE DISEASE

Depending on the renal biopsy policy, extended versus restricted, the proportion of patients diagnosed at the time of an acute episode compared with those who are asymptomatic (urinary screening detection) will vary greatly, ranging from 30%[3] to 80%[14] both in children and adults.

The typical acute presentation is macroscopic hematuria at time of a mucosal infectious event (upper respiratory tract infection, bronchitis, or even urinary tract infection). Episodes last for 2 or 3 days, and usually hematuria is recurrent with each infectious event. The other modalities of acute onset are rarely nephritic syndrome, or nephrotic syndrome. These modalities of onset did not change over time when we compared our historical cohort (retrospective) with our prospective cohort (Table 1). However, there may be some variation in presentation around the world.[7]

The age at onset of the disease is generally the second and third decade of life. From our experience, age at onset has increased significantly between our historical cohort (1975-1989) and our prospective cohort (1990-1999) (Table 1). We have no certain explanation for this increase, although it may represent a general decrease in urinary screening at school, university, military enrollment, and work.

PROGRESSION OF IgAN

The natural history of primary IgAN is progression both clinically and pathologically.

Table 1. Age at Onset and Modalities of Onset in Primary IgAN in 2 Cohorts From the University Hospital of St. Etienne, France

Cohort	Historical 1975-1989 N = 354	Prospective 1990-1999 N = 332
Age at onset, y		
Mean (SD)	28.5 (14.4)	35.6 (15.7)
Median (range)	24.8 (3.8-74.6)	34.4 (2.7-76.6)
Acute onset	**29%**	**25%**
Macroscopic hematuria	23%	20%
Nephritic syndrome	3%	3%
Nephrotic syndrome	3%	2%
Asymptomatic	**61%**	**56%**
Isolated microscopic hematuria	36%	27%
Isolated proteinuria	9%	12%
Proteinuria + microscopic hematuria	16%	17%
Others/late discovery	**12%**	**21%**
Hypertension (±proteinuria hematuria)	10%	14%
Acute or chronic renal failure (± proteinuria ± hematuria ± HT)	2%	7%

Clinical progression is exemplified by our prospective cohort, with collection of 332 new cases over a 10-year period from 1990 to 1999 (Table 2). With time, there is clearly a progression of the number of patients with hypertension (HT), with chronic renal failure (CRF) (defined as stage 3 or 4 CKD [GFR <60 mL/min/1.73 m^2]), or reaching ESRD. The overall prevalence of CRF in other series varied from 9% to 52%, and that of ESRD varied from 7% to 19% in different series.[3-7,15-17] The best way to express progression to CKD and then to ESRD is by survival without either event. For our prospective 1990-1999 cohort, survival without stage 3 CKD was 79.4% and 72.0% at 10 and 20 years from onset, respectively. Survival without ESRD was 95.8% and 86.1% at 10 and 20 years past onset, respectively. Comparison between series is difficult because of varying definitions of CRF and the choice of time zero (either onset of the disease or date of the first renal biopsy procedure). The 20-year cumulative rate for ESRD ranged from 14% to 39%.[16,17]

Table 2. Clinical Progression in a Prospective IgAN Cohort Diagnosed Between 1990-1999 at University Hospital, St. Etienne, France

Cohort	Time of First Renal Biopsy		
	Onset	Diagnosis	Last FU
Macrohematuria	20% (68)	20% (68)	29% (97)
Proteinuria ≥1 g/d	data unavailable	29% (97)	13% (43)*
Hypertension	21% (69) (pre-existing in 14%)	35% (115)	45% (151)
CKD (GFR <60)	7% (24) (acute in 3 %)	21% (69)	26% (87)
ESRD	0% (0)	1.2% (4)	8.1% (27)

*Actively treated by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

The natural history of primary IgAN also shows progression of pathologic lesions. There are few studies on serial renal biopsies in IgAN.[18,19] Our experience[3,18] was progression of a global optical score (GOS), which includes a range of LM changes in about 55% of the patients. Progression was caused mainly by arteriolar and interstitial lesions, IgA deposit magnitude did not correlate with progression. There is no internationally accepted pathologic classification of IgAN and a number of groups have developed their own systems.[17,20–22] An international group has been convened to develop a new consensus classification.[23]

Severe histopathologic lesions such as the percentage of glomeruli with focal or segmental glomerulosclerosis/hyalinosis, and/or with crescents and/or obsolescence are additional markers of progression.

The hallmark of the natural history of IgAN is progression, but over a very wide time range from a few years (rapidly progressive) to more than 50 years (such cases will apparently be stable over a short follow-up period). Finally, the apparent differences in outcome, observed between the continents, are most likely to represent bias in inclusion of patients and/or in follow-up time.[24]

PREDICTIVE RISK FACTORS OF PROGRESSION IN IgAN

A major step to be performed at the time of diagnosis in each individual case is to establish as accurately as possible the long-term prognosis with an appropriate management plan and follow-up procedure.

There is now a consensus about the 3 major risk factors predictive of progression toward CKD and ESRD.

The occurrence of arterial HT is the most important. By Cox regression analyses (univariate, then multivariate), HT occurring at any stage of the disease is an independent and strong risk factor for progression: this includes presence at onset, presence at diagnosis, occurrence during follow-up evaluation, and presence at the latest review. By contrast, the absence of HT during the disease course is a strong protective factor.

The quantitative proteinuria (g/d) is also a major risk factor, both as a continuous variable (amount of proteinuria expressed in g/d) or as a dichotomous variable (>1 g/d, which is the usual accepted cut-off level). There is also increasing evidence that sequential information about HT and proteinuria during treatment and follow-up evaluation improves the accuracy of prognosis.[25–27]

The existence of severe lesions on initial renal biopsy such as hyalinosis, crescents, and/or defined by quantitative scoring. Our own GOS is the sum of glomerular, vascular, tubular, and interstitial lesions seen on LM and scored by specific indices on a scale from 0 to 20. A GOS of 8 or more is an independent risk factor for progression toward CKD and then ESRD.

In our 1990-1999 cohort, the combination of these 3 risk factors (HT, proteinuria, and GOS) was highly predictive of CKD and ESRD after 20 years. However, using the Cox model, the presence of CRF at diagnosis means that HT and proteinuria are no longer independent predictive factors for ESRD.

There are additional risk factors that have been found in some series but not others: hypertriglyceridemia,[28] overweight/obesity,[29] and age at onset.[30] The predictive value of genetic factors, for example, CCR5,[31,32] remains controversial. Sex has no impact on outcome.

The isolation of these 3 independent risk factors predictive for CKD and then ESRD has major consequences for treatment that should target each factor.

First, the ideal control of HT with a target of 130/80 or less mm Hg or 125/75 or less mm Hg in cases with proteinuria greater than 1 g/d. This control could be obtained by a low-salt diet and all classes of antihypertensive agents with special emphasis on angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers.

Second, the control of proteinuria (including residual proteinuria >1g/d after control of HT) with the use of an angiotensin-converting enzyme inhibitors[33] and/or an angiotensin receptor blocker[34] as antiproteinuric and protective drugs.

Third, the control of severe renal biopsy lesions should be approached by strategies that may include the use of fish oil,[35] corticosteroids,[36] or corticosteroids with immunosup-

pressive agents (eg, cyclosporine or cyclophosphamide).[37] The role of immunosuppressive therapies remains controversial and is reviewed by Floege and Eitner, pp. 38-47.

CONCLUSIONS

The natural history of IgAN is dominated by clinical and pathologic progression. The rate of progression to CKD and ESRD is highly variable among patients, from very fast to very slow (ie, from a few years to >50 years). It is possible to predict long-term prognosis at the time of initial diagnosis with 3 independent risk factors: occurrence of arterial HT, amount of proteinuria, and severity of some renal lesions. The natural history of the disease should be observed carefully and every effort should be made to target risk factors in the following order: (1) HT, (2) proteinuria or residual proteinuria greater than 1 g/d, and (3) specific renal lesions such as crescents and focal hyalinosis. Nevertheless, primary IgAN remains an important cause of ESRD (about 10% of all incident cases).

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