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Primary IgA Nephropathy: An Update in 2011

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1. Introduction

IgA Nephropathy (IGAN) is also called mesangial IgA glomerulonephritis and was first described by Jean Berger, a French general pathologist, in 1968 in the journal d’Urologie-Néphrologie [1, 2]. Many reviews have been written on the subject [3, 4, 5].

2. Definition [3, 4, 5]

The definition is histopathologic with the characteristic deposition of the immunoglobulin A in the renal mesangium: these deposits are predominant (or codominant with other immunoglobulins, IgG and/or IgM), granular, coarse (with the “en mottes” aspect), generalized in the glomerulus and diffuse to all glomeruli. These deposits are evidenced usually by the technique of direct immunofluorescence on a semi-quantitative scale: traces (+/-), 1+, 2+, and ≥ 3+. There is a general agreement to accept at least 1+ IgA deposits for the definition.

By contrast, the lesions observed by light microscopy are often segmental and focal. The main lesions concern the mesangium with increased matrix and hypercellularity with in addition endocapillary proliferation. The most severe lesions are represented by obsolescent glomeruli (“pains à cacheter”), focal and segmental glomerulosclerosis (FSGS) with capsular adhesions, and extracapillary proliferation with the formation of cellular/hyalinized crescents.

3. The IgA nephritides [3, 4, 5]

The deposition of mesangial IgA has been observed in different types of glomerulonephritis leading to the classification of Primary IgA nephropathy (Berger’s disease) versus the Secondary IgA nephropathies: associated to Schönlein-Henoch Purpura, to patent Alcoholic Liver Cirrhosis, to Systemic Lupus Erythematosus, or to Ankylosing Spondylarthritis. Primary disease represents at least 80% of the cases.

4. Epidemiology [3, 4, 5]

Primary IGAN is worldwide the most frequent glomerulonephritis; it accounts for about a quarter of the percutaneous renal biopsies performed on native kidneys. In France, the incidence is about 30 new cases per million inhabitants (pmp) and its prevalence is closed
to 1000 pmp according to the disease duration from onset to dialysis or to last follow-up (from few months to more than 50 years). All these numbers are of course dependent of the “politic” of renal biopsy: liberal indication or restricted to the most severe cases with already proteinuria over 1g/day or already some degree of renal insufficiency (Glomerular Filtration Rate <60 ml/mn/1.73 m² body surface area).

The disease is more frequent in men than in women, about 70% males, in most continents except in Asia. Age at onset ranges from 5 years to 75 with a peak frequency in adolescents and young adults.

5. Mode of onset/initial presentation [3, 4, 5]

The onset of the disease can be acute/subacute in about 30 to 35% of the patients with the classical intra-infectious gross haematuria: at time of an infectious episode of various origin (pharyngitis, bronchitis, or even intestinal or urinary infection), the patient is urinating blood with colored urine, more brown than red with a color of coffee or coca-cola; this is a total haematuria (sometimes with loin pain) which lasts from few hours to
few days; there is no clot and the characteristics of this gross haematuria is nephrological with the presence on urine cytology of typical red blood cell casts. After such an episode, the patient is usually presenting microscopic haematuria or could be in total remission until the next episode.

The discovery can be chance proteinuria or chance microscopic haematuria at time of systemic urine control for medical check-up at school, at different institutions or at work; the time of onset is therefore imprecise and we should refer to the last negative control if any.

The disease can be diagnosed later on with arterial hypertension (HT) and/or oedema and/or chronic kidney disease stage 3 or up (CKD-3+).

6. Progression of the disease [6-12]

Overall, IGAN is a progressive disease both clinically and pathologically. The clinical progression starts with urine abnormalities, followed by occurrence of HT, sometimes oedema related to massive proteinuria or nephrotic syndrome, and later on occurrence of CKD-3 through CKD-5 and ultimately renal death necessitating chronic dialysis. The progression is also pathological and this was demonstrated by repeated renal biopsies 5 years later [6, 13]: it was shown that the global optical score (GOS) progressed in the majority of the patients with increased glomerular but also vascular and tubular/interstitial indices.

We are taking as example our prospective cohort of primary IGAN patients [12] whose diagnostic biopsy was performed between January 1st 1990 and December 31st 1999 at our institution with loco-regional patients coming from the Saint-Etienne area, the IGAN-STET-CO. This cohort is composed of 332 patients (237 men, 71.4 %) with a mean age of 35.9 at onset, 41.4 at diagnosis and 48.8 years at dialysis/death or at last follow-up visit. The total exposure time was about 13 years. Overall, 32 patients needed dialysis, 13 died before reaching dialysis, and 45 (13.6 %) reached the primary composite outcome while 99 (29.8 %) presented the secondary outcome (CKD-3+).


One very important goal was to sort out the major and independent risk factors (RF), present at diagnosis, able to predict accurately the ultimate final prognosis (dialysis or death as primary end-point). From the literature, we already know that the amount of proteinuria (g per day), the occurrence/presence of HT, and the severity of renal lesions on the initial biopsy were associated with progression [6-11]. Many other risk factors were also described such as gender, overweight/obesity [14], metabolic syndrome, age at onset [15], hypertriglyceridemia/hyperuricemia [16], and also different immunogenetic markers (HLA antigens, different cytokines polymorphisms [17, 18],…) but they were not consistent or controversial in different published cohorts. We recently confirmed [12] that these 3 major risk factors were sufficient to cover the whole prediction in our cohort. These risk factors were simplified, dichotomized for easier use and shown to be independent predictors in a multivariate model of Cox regression: - the most important is the presence of HT (Yes or No) defined according to WHO (≥ 140/90); - the next is the presence of Proteinuria ≥ 1g/d (Yes or No); and - the last is the scoring of the renal lesions; we have used our own global
**optical score** (GOS) developed 20 years ago and integrating all elementary lesions (glomerular from 0 to 6, vascular from 0 to 5, tubular from 0 to 4, and interstitial from 0 to 5) with a GOS up to 20. We set up by ROC analysis that the best cut-off for predicting dialysis was the **presence of GOS ≥ 8 (Yes or No)**. These 3 RF turned out to have a similar weight in the prediction of dialysis/death by the different accuracy parameters and also by the Cox regression ($\beta$/SE ratio of the same magnitude).

In analogy to the absolute cardio-vascular risk (ACVR) of death or major CV events at 10 years [19, 20], we proposed the **Absolute Renal Risk of Dialysis/Death**; this ARR is calculated at diagnosis and is very simply the number of these RF present: 0, 1, 2 or 3. By Kaplan-Meier survival curves, we could calculate the cumulative rate of primary event at 10 and 20 years after onset (time zero); it was respectively 2 and 4 % for ARR=0; 2 and 9 % for ARR=1; 7 and 18 % for ARR=2; and 29 and 64% for ARR=3.

In addition, this ARR integrates gender (less RF for women), age at diagnosis (more RF for older patients), and also body mass index (more RF in overweight/obese patients). We could also use it as prospective with time zero set-up at diagnosis and not at onset; the cumulative incidence of dialysis/death 10 years after diagnosis is 4% for ARR=0, 8% for ARR=1, 18% for ARR=2, and 68% for ARR=3. It is remarkable to underline the similarity of the values obtained 20 y after onset and 10y after diagnosis.

**Distribution of these Risk Factors at time of Diagnosis and at last follow-up (LFU):** HT was present in 120 patients (36.1%) at diagnosis and in 164 (49.4%) at LFU; Proteinuria ≥1g/d was present in 100 patients (30.1%) at diagnosis and in only 61 (18.4%) at LFU; and GOS ≥ 8 was present in 120 patients (36.1%) at time of diagnosis. The distribution of the ARR was as follows at time of diagnosis: 151 patients (45.5%) with ARR=0, 69 (20.8%) with ARR=1, 65 (19.6%) with ARR=2, and 47 patients (14.1%) with ARR=3.

It should be stressed that this cohort is an adequately treated cohort with all RF targeted as soon as they were identified: perfect control of blood pressure (target <130/80) with all antihypertensive agents; persistent reduction of proteinuria with ACEI and ARBs; and prednisolone for severe renal lesions.

### 8. Pathological classification of IgA nephropathy

We have developed our own classification in 1990 [6, 13] with the Global Optical Score already described. During the past decades, the classifications of Haas [21] or Hass modified by Lee [22] were frequently used. The international Oxford classification was published in 2009 [23, 24] and retained only 4 parameters with significant clinical prediction: - mesangial hypercellularity (M score= 0 or 1); - endocapillary hypercellularity (E score= 0 or 1); - segmental glomerulosclerosis (S score= 0 or 1); and - tubular atrophy/interstitial fibrosis (T score= 0 or 1 or 2). Overall, the MEST score ranges from 0 to 5. One limitation is that patients were only included if proteinuria was ≥1g/d in adults and there was no patients with ARR=0 who are in fact the majority of the patients; in addition patients with extracapillary GN (≥ 50% crescents) were also excluded; the two tails of the IGAN cohorts were therefore lacking!

### 9. Principles of treatment in IGAN

The treatment should in fact target all major risk factors when present: hypertension, proteinuria, and severe renal lesions.
The permanent control of HT is a major step; the goal is to lower BP ≤ 130/80. Sodium chloride restriction is recommended with 24 h urinary sodium below 100 mmol/d corresponding to a maximum of 6 g daily sodium chloride. All antihypertensive agents can be used: diuretics, beta blockers, calcium blockers, central-acting, ACE inhibitors, angiotensin-2-receptor blockers (ARBs), and more recently renin inhibitors. However two classes have demonstrated a better protection and should be used alone or in association: ACEI and ARBs [25, 26]. In our prospective cohort [12], we have demonstrated that survival without dialysis/death improved in patients with adequately controlled BP on long term [27].

The significant reduction of proteinuria is another major step [28]; the reduction can be obtained with the use of ACEI and ARBs which have a significant antiproteinuric effect. It is recommended to start with either one of these drugs, to titrate the dose to the effect, and to use the association in case of resistant proteinuria; the goal is to bring proteinuria ≤ 1g/d or ideally < 0.30 g/d. We have also demonstrated [12] that the permanent reduction of proteinuria is associated with a better survival on long-term.

The treatment of severe renal lesions on the biopsy; this could be achieved by Prednisone or Prednisolone treatment [29-31] which should be in theory able to reduce hypercellularity and cellular infiltration within the glomeruli; however in the trial, there was no repeated biopsies at the end of the steroid therapy. For the most severe cases with extracapillary GN (>50 % crescents), the association of high dose steroids and immunosuppressive agents as already proposed might be a good option.

The use of Fish Oil was limited with controversial results [32, 33].

We are still in the need of large randomized controlled trials with a long duration (5 years seems optimal) to draw definite conclusions on the treatment of IGAN.

10. Pathogenesis and patho-physiology of primary IgA nephropathy

Very significant progress has been made during the last decades. The key protein in this disease is the immunoglobulin A and more precisely the subgroup 1; in fact IgA1 is deposited in the mesangium but not IgA2 [34]. The major difference between IgA1 and IgA2 is the presence of an hinge region in IgA1 composed of 23 aminoacids with usually five sugar side chains linked to threonin or serin. There is now a consensus [35-39] about the fact that the main difference between IgA1 in Controls and in IGAN patients is the hypogalactosylation of these glycosylated side chains. The normal complete sugar chain is O-linked to threoin or serin and composed of one molecule of N-acetyl galactosamine (GalNac) and one molecule of Galactose; in addition a molecule of sialic acid can be bound in terminal to Galactose or in lateral to GalNac. In IGAN, more side chains are truncated with loss of terminal Galactose with its terminal sialic acid and is referred to the Galactose-deficient IgA1 (deGal-IgA1). This deGal-IgA1 represents the specific autoantigen in this disease and is present in the serum, within the circulating immune complexes and in the mesangial deposits [40]. This loss in terminal galactose is associated with a down-regulation of the gene controlling the linkage of galactose to GalNac, C1GALT1 [41] and the description of specific polymorphism [42] raising the possibility of genetic predisposition [43].

The loss of terminal galactose unusually exposed the GalNac molecules, which become antigenic with elicitation of a specific antibody response [44, 45]: IgG and/or IgA anti O-GalNac, the specific auto-antibodies. It is now possible to measure the amount of circulating
autoantigen and autoantibodies in patients sera and to discriminate between Controls and IGAN patients [46, 47].

The mesangial deposition of deGal-IgA1 is dependent on physical characteristics of this molecule (more sticky) and the presence of transferrin receptor (CD71) which is able to bind IgA1 variants [48]. After binding, the deGal-IgA1 and the deposited immune complexes are able to activate the different mediators of inflammation both cellular [49] and in fluid phase. There is also the CD89 system [50] that we personally consider as an amplification loop. This is a specific receptor for IgA1 variants, FcαRI, present on circulating monocytes but not in the mesangium; this receptor is able to bind immune complexes with further amplification and longer persistence in the circulation, and may play an additional pathogenic role.

11. Renal transplantation in patients with biopsy-proven IGAN on native kidneys

In cases which progressed to dialysis, renal transplantation should be a strong option and overall the results are similar to the other recipients matched for age and gender. However, there are two specific situations which have strong pathogenic implication.

First, a silent IgA nephropathy can be present on grafted kidney from apparently normal donors leading to the discovery of mesangial IgA deposits on graft biopsies performed early after transplantation; it was demonstrated in few cases that these deposits can regress and disappear demonstrating a contrario that the disease has a systemic (blood) transmission.

Second, the original disease may reappear (recurrence) on the normal grafted kidney after few years and despite immunosuppression [51-59]. The cumulative incidence of clinicopathological recurrence is high reaching 35% or more at 10 years post-transplant [56] and may lead to graft losses in up to 17% at 10 y [57]. The factors associated to recurrence are not well understood: living donors, better HLA matching, short duration of the original disease, etc. There is yet no specific treatment for the recurrent disease; however in a retrospective study [56] we demonstrated that induction treatment with ATG seems able to reduce the incidence of recurrence in comparison to no induction or to induction with Basiliximab. A prospective randomized controlled trial comparing rabbit ATG to Basiliximab has already started, the PIRAT study: Prevention in IgA nephropathy recipients of full Recurrence After renal Transplantation according to induction immunosuppressive therapy: ATG versus Basiliximab. It seems now mandatory to carefully measure the serum levels of the auto-antigen and the auto-antibodies at time of grafting to check for any predicting value of these parameters for recurrence.

12. Conclusions

IgA nephropathy is a frequent disease whose individual prognosis can be totally different: no significant progression for 50 years versus progression to dialysis in few months or years. The clinical challenge is to accurately predict the long term individual prognosis at time of diagnosis (at time of the renal biopsy which is still mandatory for this purpose). We have made significant progress with our new concept: the Absolute Renal Risk of Dialysis/Death (ARR); it takes in account the presence or not of three independent, simplified and dichotomous risk factors: arteria hypertensive; proteinuria ≥1g/d; and severe histopathological lesions appreciated by the Global Optical Score ≥8 (range from 0 to 20). The cumulative incidence rate of primary event (dialysis or death) at 10 years post-
The diagnosis, is 4% for ARR=0; 8% for ARR=1; 18% for ARR=2; and 68% for ARR=3 in our prospective cohort adequately treated/managed on long term.

The pathogenesis of the disease has also made significant progress: it is an **auto-immune disease** with a known **auto-antigen**, the Galactose-deficient IgA1, which can elicit a specific **auto-antibody** response, IgG and IgA anti-O-GalNac. There is formation of specific **immune complexes** which are **circulating** and then **deposited** in the mesangium with creation of the disease. These recent findings will have significant future applications in the diagnosis and in the treatment.

### 13. References


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An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

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