

# IgA NEPHROPATHY: NEW ASPECTS IN PATHOPHYSIOLOGY AND PATHOGENESIS

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## ABSTRACT

Knowledge of the pathophysiology of immunoglobulin A nephropathy (IgAN) has progressed significantly, with this disease being clearly identified as an autoimmune disease with a peculiar autoantigen (galactose-deficient IgA1 [Gd-IgA1]), specific autoantibodies (IgG and IgA1 anti-glycans), and formation followed by mesangial deposition of circulating immune complexes with the involvement of other players, such as mesangial transferrin receptor (TfR), monocyte Fc $\alpha$  receptor (CD89), and glomerular transglutaminase 2 (TG2). The pathogenesis still requires additional clarifications in order to explain the initiation of the disease and to establish the respective role of genetics, environment, and hazard concordance in the cascade of events/steps. The clinical application of this new knowledge is spreading slowly and includes possible measurement of serum Gd-IgA1, IgG anti-Gd-IgA1, IgA anti-Gd-IgA1, soluble CD89, and soluble TfR in the urine of patients with IgAN.

**Keywords:** IgA nephropathy, autoimmune disease, IgA1 molecule, glycosylation, genetics, pathogenesis, pathophysiology.

## INTRODUCTION

Immunoglobulin A nephropathy (IgAN) was first described in 1967 by Jean Berger,<sup>1</sup> a general pathologist in Paris. The primary form represents 90% of all cases and was also called Berger's disease. The secondary forms are seen in Henoch-Schönlein purpura (HSP), in a few cases of systemic lupus erythematosus-induced nephritides, and also in some cases of nephritis associated with overt liver cirrhosis. The classification between primary and secondary forms is based exclusively on clinical grounds. The definition<sup>2,3</sup> is pathological in nature and still requires a renal biopsy in order to accurately establish the diagnosis. The biopsy should be processed for both immunofluorescent (IF) and optical microscopies. The characteristic lesions observed in IF microscopy are mesangial IgA deposits with the following patterns: granular, coarse, generalised, or diffuse, and these patterns can also be dominant or codominant with other immunoglobulin deposits (IgM and/or

IgG) or complement-factor deposits (mainly C3). Examination by light microscopy allows the evaluation of elementary lesions and establishment of an International/Oxford classification<sup>4</sup> using 'MEST' scoring: M for mesangial hypercellularity (M0 or M1), E for endocapillary hypercellularity (E0 or E1), S for segmental glomerulosclerosis (S0 or S1), and T for tubular atrophy/interstitial fibrosis (T0, T1 or T2); by combining these indices, the maximal score is 5 (M1+E1+S1+T2). The MEST score has been validated as an independent risk factor for prediction of progression to end-stage renal failure (dialysis or Stage 5 estimated glomerular filtration rate), with renal lesions indicative of poor prognosis being present when the MEST score is  $\geq 2$  (unpublished data from our group).

This pathological risk factor should be evaluated with the two other independent clinical risk factors already described and internationally approved: proteinuria  $\geq 1$  g/day and the presence of arterial hypertension, and this has permitted our group<sup>5</sup> to establish the absolute renal risk (ARR) for

dialysis/death. We demonstrated that these three simplified risk factors: proteinuria  $\geq 1$  g/day (yes or no), arterial hypertension (yes or no), and severe pathological score ( $\geq 8$  for our local classification or MEST  $\geq 2$  for the Oxford classification; yes or no), were independent and equipotent in the prediction of dialysis/death. The scoring of ARR is simply the number of these three risk factors that are present at initial diagnosis (0, 1, 2, or 3); this ARR allows an accurate estimation of the risk of dialysis/death at 10 years post-diagnosis or at 20 years post-disease onset: approximately 5%, 10%, 20%, and 60% for ARR 0, 1, 2, or 3, respectively. This ARR scoring was also validated for IgAN secondary to HSP.<sup>6</sup>

## PATHOPHYSIOLOGY OF IgAN

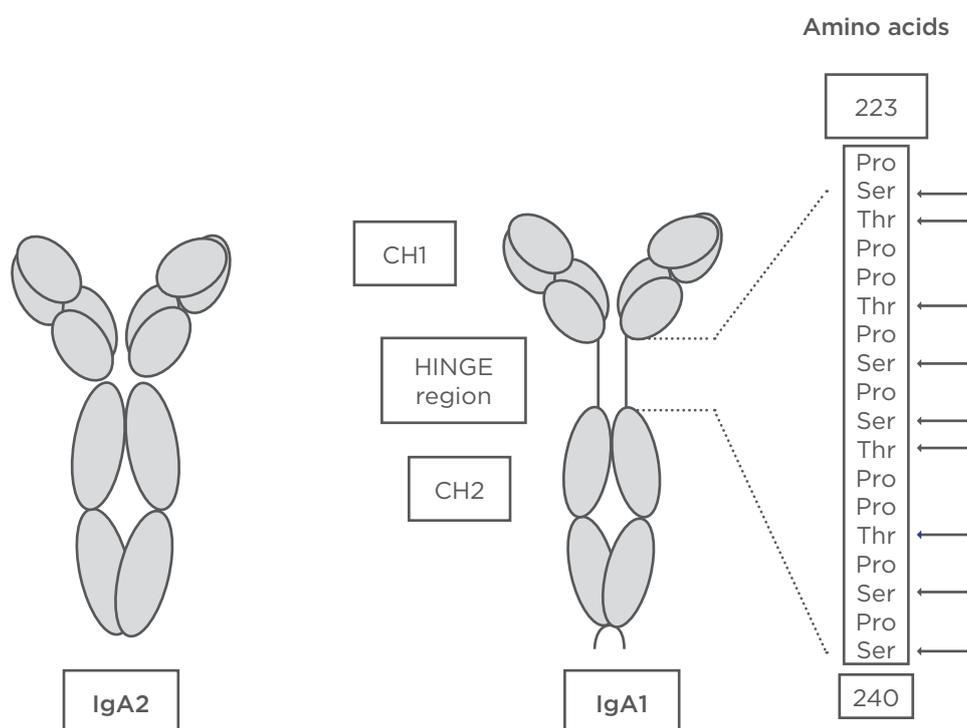
### Mesangial Deposits of IgA1 Subclass

The main characteristic of IgAN is the deposition of IgA in the mesangial area, it has been known since 1980<sup>7</sup> that this deposition is highly selective and concerns only the IgA1 subclass and not IgA2. In normal individuals, the majority (approximately

84%) of serum IgA is monomeric with IgA1 being predominant, although these percentages are highly variable (range: 65-94%).

### IgA1 Subclass and Unique Hinge Region

The major difference between IgA1 and IgA2 resides in the presence of a unique long hinge region in IgA1 (Figure 1). This hinge region is a chain of 18 amino acids (5 serine, 4 threonine, and 9 proline) that can attach up to six lateral sugar chains fixed to the threonine or serine residues by an oxygen linkage (O-glycosylated chains). A complete glycosylated chain is composed of a first molecule of sugar, the N-acetylgalactosamine (GalNAc) fixed on either threonine or serine by a specific enzyme called GalNAc transferase 2, the second molecule of sugar is galactose (Gal) fixed on GalNAc by a specific enzyme called  $\beta 1,3$ -galactosyltransferase ( $\beta 1,3$ GT), and a third molecule of sialic acid (also called N-acetylneuraminic acid) can be attached to the terminal Gal by a specific enzyme called  $\alpha 2,3$ -sialyltransferase ( $\alpha 2,3$ ST) and/or attached to the lateral GalNAc by the specific enzyme called  $\alpha 2,6$ -sialyltransferase ( $\alpha 2,6$ ST).

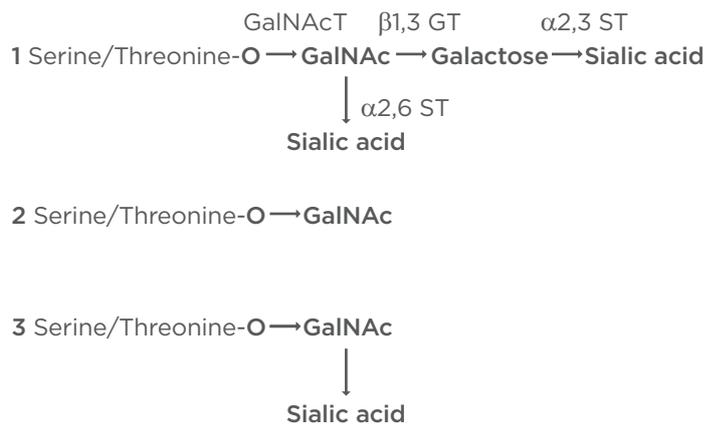


**Figure 1: Molecular differences in IgA1 and IgA2.**

IgA1 molecules are characterised by the presence of a hinge region that can bind lateral sugar chains on the main protein chain, and which is composed of 18 amino acids. The binding is exclusively possible on serine or threonine residues with an oxygen linkage, the O-glycosylated lateral chains. There are nine potential sites for fixation, but only up to six lateral chains are attached.

IgA: immunoglobulin A; CH: constant heavy chain domains; Pro: proline; Ser: serine; Thr: threonine.

O-Glycosylated lateral chains: complete or truncated



**Figure 2: Complete or truncated lateral sugar chains.**

The first step is the binding of an N-acetyl galactosamine (GalNAc) molecule to serine/threonine residues, which is controlled by the enzyme GalNAc transferase (GalNAcT). The second step is the transfer of a galactose (Gal) molecule, which is controlled by the enzyme  $\beta 1,3$ -galactosyltransferase ( $\beta 1,3$ GT). The final step is the addition of a terminal sialic acid molecule to Gal, which is controlled by the enzyme  $\alpha 2,3$ -sialyltransferase ( $\alpha 2,3$ ST), and the GalNAc molecule can be laterally sialylated under the control of the enzyme  $\alpha 2,6$ -sialyltransferase ( $\alpha 2,6$ ST). In IgA nephropathy, these sugar chains are often lacking Gal, and are referred to as Gal-deficient IgA1. These chains are truncated with the loss of Gal and the terminal sialic acid, if present; the simplest chain is O-GalNAc.

Besides these complete sugar chains, there are incomplete sugar chains lacking terminal or lateral sialylation or lacking Gal; the simplest chain is O-GalNAc (Figure 2).

### Differences in O-glycosylation of IgA1 Between Controls and IgAN Patients

Compared with healthy individuals, there is a significant decrease in the number of completely glycosylated lateral chains, with a loss of Gal (under-galactosylation), in serum samples from IgAN patients; this is a quantitative but not a qualitative difference. In healthy individuals, the majority of O-chains are complete with Gal (i.e., at least four of the six chains are complete), while the majority of chains in IgAN patients are incomplete or truncated (i.e., no more than two of the six chains are complete). This IgA1 abnormality in IgAN patients was first described by Hiki et al. in 1998,<sup>8,9</sup> largely confirmed by many other groups,<sup>10-12</sup> and is now a well-established fact.

This under-galactosylation of IgA1 molecules in IgAN patients is not only evident in circulating (serum) IgA1, but is also present in mesangial-deposited IgA1,<sup>13,14</sup> IgA1 produced by B

lymphocytes (peripheral or in bone marrow), in mucosa-associated lymphoid tissue (MALT), and in IgA1 extracted from tonsils.<sup>15</sup> Therefore, this is a generalised abnormality. Compared with healthy individuals, an increased number of sialic acid molecules in the serum of IgAN patients has been described,<sup>16</sup> and this was despite the loss of Gal molecules with possible terminal sialic acid moieties; this implies an increase in lateral sialylation of GalNAc. There is currently a lack of consensus regarding this observed abnormality.

### Differences Between IgAN Patients and Controls at the Enzyme and Gene Levels

Three enzymes control the addition of sugar molecules to the O-glycosylated lateral chains:

- i) The enzyme  $\beta 1,3$ GT controls the transfer of Gal molecules to GalNAc and its activity is diminished in lymphocytes from IgAN patients.<sup>17-19</sup> This enzyme requires a chaperone molecule, referred to as CosmC, to gain full activity,<sup>20</sup> and the genes encoding these two proteins have been identified: *C1GALT1* and *C1GALT1C1*, respectively. There is decreased gene expression of *C1GALT1* and also

an association with a particular gene polymorphism in IgAN patients;<sup>21</sup> the results for the *C1GALT1C1* gene are discordant.

- ii) The enzyme  $\alpha$ 2,6ST controls the lateral binding of sialic acid molecules to GalNAc. In IgAN patients, its activity is increased with an increased expression of the gene *ST6GALNAC2*,<sup>22</sup> but with a controversial paper.<sup>23</sup>
- iii) The enzyme  $\alpha$ 2,3ST controls the terminal binding of sialic acid molecules to Gal. No difference between this enzyme's activity in IgAN patients and healthy individuals has been found.

### The IgAN Autoantigen

The hallmark of IgAN patients is an under-(hypo-)galactosylation of circulating IgA1 (Gal-deficient IgA1, Gd-IgA1) compared with healthy individuals and with patients with other renal diseases. The consequence is an 'overexposure' of terminal GalNAc molecules, which are often sialylated, and these glycans become immunogenic and constitute the autoantigen. The measurement of this autoantigen within serum samples is either very sophisticated, e.g. by mass spectrometry techniques,<sup>8,13</sup> and therefore limited, or by a more simple indirect enzyme-linked immunosorbent assay (ELISA) that relies on the specific binding of the lectin *Helix aspersa* agglutinin (HAA) to terminal GalNAc molecules; the percentage binding/reactivity to HAA is proportional to the amount of Gd-IgA1 within the sample.<sup>24,25</sup>

For clinical use, this assay should be performed on desialylated samples (pretreated with neuraminidase) and the total Gd-IgA1 calculated by multiplying the normalised HAA binding (units) obtained by the amount of IgA1 in the sample (units/ml). The serum level of Gd-IgA1 is significantly elevated in IgAN patients versus healthy individuals and patients with other renal diseases; subsequently, an association was shown with the subgroup of progressive IgAN patients.<sup>26,27</sup> It should be remembered that total serum IgA is globally increased in IgAN patients compared with healthy individuals, with a significant individual increase (over 350 mg/dl) in more than 50% of patients. It has subsequently been shown that this is also true for total IgA1, with the majority being polymeric and more anionic.

### The Specific Autoantibodies in IgAN: IgG and IgA Subclasses

Specific anti-glycan antibodies were first described by the group of Jan Novak,<sup>22,24,28</sup> with IgG anti-Gd-IgA1 and IgA (including IgA1) anti-Gd-IgA1; circulating immune complexes were also demonstrated. Therefore, IgAN is clearly an autoimmune disease, similar to membranous glomerulonephritis in which the most common autoantigen is phospholipase A2 receptor and there is specific IgG autoantibody. In the clinical situation, it is possible but difficult to measure serum IgG and serum IgA anti-Gd-IgA1 by specific ELISA assays.<sup>26,29</sup> The results were normalised (units per 0.5  $\mu$ g of IgG or per 1  $\mu$ g of IgA) and then multiplied by the amount of IgG or IgA in the sample (units/mg). We recently demonstrated that the respective serum levels of Gd-IgA1 and of the autoantibodies (IgG and IgA subclasses) are associated with potential progression of the disease, which is reflected by the ARR for dialysis/death.<sup>26</sup> Hastings et al.<sup>30</sup> provide a thorough review of these clinical results.

### Circulating Immune Complexes and Monocyte Fc $\alpha$ Receptor (CD89) Amplification Loops

Before reaching the kidneys, immune complexes composed of Gd-IgA1-IgG and Gd-IgA1-IgA can bind to the receptor CD89 expressed on the surface of monocytes and macrophages in the circulation; this receptor is a specific ligand for the Fc $\alpha$  chain and has been well described by the group of Renato Monteiro in Paris, France.<sup>31</sup> These complexes can then be transported by these cells or circulate freely as a tri-molecular complex composed of antibody, antigen, and soluble CD89 (sCD89); this sCD89 is a truncated chain of the receptor. This constitutes the systemic CD89 amplification loop. Recently, it was shown that this tri-molecular complex can bind directly to the transferrin receptor (TfR) within the mesangium,<sup>32</sup> locally initiating the expression of a new molecule, transglutaminase 2 (TG2),<sup>33</sup> with a local amplification loop (increased expression of TfR with greater IgA1 deposition). In the clinical situation, serum levels of sCD89 have been measured with conflicting results: one study showed elevated levels in IgAN patients compared with healthy individuals,<sup>31</sup> whereas others showed lower sCD89 in progressive IgAN or no differences between the non-progressive IgAN patients versus healthy individuals or patients with other renal diseases.<sup>34,35</sup>

## Gd-IgA1 Mesangial Deposition and Creation of Renal Lesions

These Gd-IgA1 molecules and immune complexes have modified characteristics and are more prone to deposit passively within the kidney (because they are more 'sticky'), as well as actively within the mesangium due to the presence of TfR that can bind IgA1 (non-specific ligand), and which results in an overexpression of these receptors. Binding of Gd-IgA1 to TfR is increased compared with normal IgA1. As described above, sCD89 can also bind TfR with a local amplification loop. In the clinical situation, it has been possible to measure soluble TfR in concentrated urine: the median value was higher in progressive IgAN and HSP nephritis (HSPN) compared with quiescent IgAN/HSPN and all other renal diseases.<sup>36</sup>

The initiation of renal lesions is dependent on the activation of humoral and cellular mediators of inflammation,<sup>37,38</sup> the role of complement deposition, and the local production of cytokines and receptors such as interleukin (IL)-6, IL-4, tumour necrosis factor  $\alpha$ , Toll-like receptor, and many others. The details of this process are not well understood but it allows the initiation of acute kidney lesions starting at the glomerular/mesangial level (increased matrix, mesangial, and endocapillary proliferation, focal and segmental hyalinosis, crescent formation, etc.). These lesions will not spontaneously heal, but instead lead to a chronic process with arteriolar, interstitial, and tubular lesions and their clinical consequences (massive proteinuria, hypertension, and progressive renal failure). This chronicity could be the result of different acute episodes or a permanently low level of stimulation.

## PATHOGENESIS OF IgA NEPHROPATHY

### Systemic Disease

The mechanism of this disease is systemic with two long-known clinical situations in favour: IgAN is prone to recurrence after renal transplantation in patients with biopsy-proven IgAN in the native kidney and in those who progressed to end-stage renal disease and dialysis.<sup>39</sup> After renal transplantation, one-third to one-half of these patients exhibit clinicopathological recurrence at 10 years post-transplant with typical IgAN on transplant biopsy.<sup>40</sup> Two renal recipients may have inadvertently received a donor kidney containing subclinical mesangial IgA deposits, in this situation

the IgA deposits usually disappear rapidly as proved by subsequent graft biopsy.<sup>41</sup>

### Implication of Mucosal IgA1 and Bone Marrow IgA1 Production with Crosstalk

The typical presentation of patients (about one-third) with such disease is the occurrence of gross haematuria episodes at the time of a mucosal infection (tonsillitis, intestinal infection, etc.). At that time, increased production of Gd-IgA1 with probable specific autoantibodies was demonstrated. This implies a predominant role of MALT in local production of protective secretory IgA molecules, followed in these IgAN patients by a rapid production of Gd-IgA1 at the mucosal site and also by a systemic production in the bone marrow. The connections between mucosal and bone marrow B lymphocytes (plasmocytes) are complex and partly unknown: direct migration of lymphocytes and production of cytokines with a special role in homing and addressing.

### The Potential Causes of the Early Initiation/Occurrence of the Disease

There are different possibilities, which are not mutually exclusive. The genetic background/predisposition for this disease is based on initial description of familial cases among siblings,<sup>42</sup> followed by specific classical genetic-linkage studies leading to the isolation of the first locus on chromosome 6 within the human leukocyte antigen region, *IgAN1*.<sup>43</sup> More recently, the genome-wide association studies isolated different loci on different chromosomes.<sup>44</sup> The Gd-IgA1 abnormality observed in affected patients was also observed in unaffected family members.<sup>45</sup> Some specific single nucleotide polymorphisms in the genes controlling different humoral and/or cellular mediators of inflammation may potentially be involved. Abnormal microRNA expression may also play a significant role in IgAN.<sup>46</sup> The overall impact of genetics in the occurrence of this disease is complex and multigenic, but probably also limited.

This disease may also be acquired depending on numerous environmental factors: exposure to certain exoantigens (infectious organisms, food, etc.), involvement of specific cytokines that can induce the production of Gd-IgA1, and modification of the different players potentially involved (immune response to autoantigens, abnormalities in receptors such as TfR and CD89, tissue TG2 status, etc.).

In any case, the initiation of the disease is dependent on a 'multi-hit theory',<sup>38</sup> which implies a concordance of events at different steps: exposure to certain antigens; Gd-IgA1 production at the mucosal and bone marrow levels; deposition of mesangial Gd-IgA1; response/activation of the mediators of inflammation, which all ultimately result in acute glomerular lesions with disease expression. The transition to chronicity depends on the repetition of acute events, and also on renal pathology and clinical factors involved in progression. Current treatment for IgAN targets the late renal lesions/inflammation (with steroid treatment) and also the clinical factors for progression (optimal control of hypertension, reducing proteinuria with angiotensin-converting

enzyme inhibitors and angiotensin II receptor blockers); in the future the target will be the early pathogenic events.

## CONCLUSION

IgAN is clearly an autoimmune disease with a precisely identified autoantigen and specific autoantibodies, and is characterised by circulating immune complexes with mesangial deposition in the kidneys. There is a multi-step, multi-hit process required to achieve the full expression of this clinicopathological disease. The intimate mechanisms involved in the key early events are still obscure and the pathogenesis is not yet fully elucidated.

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