



# Immunopathological predictors in immunoglobulin A nephropathy; an update to current knowledge

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## Abstract

Immunoglobulin A nephropathy is the most common glomerulopathy throughout the world. Immunoglobulin A nephropathy is not continuously benign, and it should determine factors either clinical or morphological have prognostic significance. It is necessary to found which individuals are at risk of a disease evolution and to recommend the exact therapy to the patients. Several morphological, biological and clinical parameters have been defined and are presently applied to a better understanding of individuals at risk, to suggest the exact therapy and to monitor the treatment impact and the immunoglobulin A nephropathy evolution over time. In this regard, more attention to immunostaining data and investigating their possible prognostic significance suggests.

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## Introduction

Immunoglobulin A nephropathy is the most common glomerulopathy throughout the world (1,2). The underlying pathogenesis of this autoimmune disease includes the formation of immune complexes, containing glycan-specific IgA1 or IgG antibodies and also an aberrant glycosylation of IgA1. The dominant mesangial or mesangiocapillary IgA deposits characterize the diagnostic hallmark of immunoglobulin A nephropathy. IgA mesangial deposits is supposed as the initiative element in the pathogenesis of IgA nephropathy. IgA mesangial deposits, results to activation local complement system (1-3). Immunoglobulin A nephropathy is clinically and morphologically heterogeneous and have a slow progress in patients, leading to kidney failure in 15%–20% of patients over a decade and in 20%–30% over two decades (2-4). The clinical highlights in this disease are highly variable, ranging from a simple hematuria with normal renal function to a rapidly progressive loss of kidney function. Progression to end-stage renal disease is variable in different ethnics and depend to various factors consisting morphological elements. Importantly, IgA nephropathy is recognized to have an aggressive course in Asians (1-5). Thus, immunoglobulin A nephropathy is not continuously benign, and it should determine factors either clinical or morphological have prognostic significance. Numerous efforts have been conducted to

## Key point

It is necessary to found which IgA nephropathy patients are at risk of a disease evolution and to recommend the exact therapy to the patients. Several morphological, biological and clinical parameters have been defined and are presently applied to a better understanding of individuals at risk, to suggest the exact therapy and to monitor the treatment impact and the immunoglobulin A nephropathy evolution over time. In this regard, more attention to immunostaining data and investigating their possible prognostic significance suggests.

explain factors that predict those individuals expected to have poor outcomes or finding the parameters, which have significance during follow up (2-5). In fact, the main problem for the physicians is to found which individuals are at risk of a disease evolution and to recommend the exact therapy to the patients. Indeed, various morphological, biological and clinical parameters have been defined and are presently applied to a better understanding of individuals at risk, to suggest the exact therapy and to monitor the treatment impact and the immunoglobulin A nephropathy evolution over time (1-7).

## Materials and Methods

For this mini-review, we used a variety of sources by searching through PubMed/



Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents such as IgA nephropathy, Oxford classification, extracapillary proliferation, chronic kidney disease, crescent, and end-stage renal disease, immunoglobulin A nephropathy, immunostaining data, and endocapillary proliferation.

### Oxford classification for immunoglobulin A nephropathy

Variables of Oxford classification included M; mesangial proliferation, E; endocapillary proliferation, S; segmental sclerosis, T; tubular atrophy/interstitial fibrosis) known as MEST variables too (1,2). Of the morphologic lesions, non-included not included yet in Oxford classification, which may have prognostic significant, is extra-capillary proliferation (crescent) or immunostaining findings (1,2). However more investigations in different ethnics of the world requires to find, whether they had prognostic significance? In fact immunoglobulin A nephropathy is considered to be an immune complex-mediated glomerulonephritis (1). The presence of electron-dense deposits may have value for the evaluation of the disease activity. Additionally, the site of deposited immunoglobulins (pure mesangial versus mesangial-capillary) is also may had prognostic significance (2-9). We therefore suggest more studies on the prognostic significance of deposited antibodies in this disease, especially in different parts (1-3).

### Predictive factors for immunoglobulin A nephropathy

Several investigations detected that, proteinuria and decrease renal function and the presence of fibrosis in tubulointerstitial region and glomerular sclerosis at presentation may be predictors of loss of renal insufficiency (2-5). However, it is well not defined yet, whether the immunostaining findings have clinical significance or whether, they have any correlation with clinical and morphologic lesions in IgAN (5-9). While least studies had been conducted on this aspect of immunoglobulin A nephropathy, the present studies have conflicting results. Indeed immunoglobulin A nephropathy is a leading cause of chronic renal failure through the world. Thus finding the aggravating factors, affects the disease progress, monitoring of disease activity and a chance to envision disease-specific therapy have of especial importance. In immunoglobulin A nephropathy, the diagnostic hallmark is the preponderance of IgA deposits, with C<sub>3</sub> in the mesangial area of the glomeruli (4-9). IgG or IgM may also deposited, however they are in lower intensity than IgA (3-9). C<sub>1</sub>q deposition is absent and its absence, is a diagnostic tool for this disease (1,2). In some patients, the mesangial deposits may extend to capillary loops too (1,4-9). In this subject, the questions bear in mind is, firstly that, clinical significance of the amount of the deposits, or whether deposition of other antibodies such as IgG or IgM, had any clinical significance? Also, the mesangial-capillary versus pure mesangial deposits may have some clinical importance. Bellur et al conducted a study on 265 IgAN patients. Location of glomerular IgA

(mesangial-capillary versus pure meningeal) and the presence of IgG deposits correlate with mesangial and endocapillary hypercellularity. This study confirms the significance of IgG deposits and capillary wall IgA depositions in the progress of proliferative changes in immunoglobulin A nephropathy (10). While, the Oxford classification for immunoglobulin A nephropathy did not comprise pattern of immunostaining in its classification, we sought to study the possible association between the immunostaining findings and morphologic features of Oxford classification (MEST) and some clinical and demographic features of patients with immunoglobulin A nephropathy. In this study, a total of 114 renal biopsies were studied (70.2% were male). Mean age of the individuals was  $37.7 \pm 13.6$  years. In this investigation, we found C3 deposits had a significant association with levels of serum creatinine. Other antibodies consisting IgA, IgM and IgG had no meaningful association with value of serum creatinine. This investigation also revealed that IgA deposited intensity score had significant positive association with presence of endocapillary hypercellularity and presence of segmental glomerulosclerosis as the variables of Oxford classification (11). Furthermore, IgM deposited intensity score had positive correlation with presence of segmental glomerulosclerosis. Moreover no significant correlation of IgG deposited intensity score with all four morphologic features of MEST classification. Finally, we found a significant relationship of C3 deposited intensity score with S and E variables of MEST classification (11). Recently much attention had been made toward the deposition of C4d in glomerular disease. C4d positivity shows that complement activation happens via alternative pathway. C4d positivity at the time of kidney biopsy can be related to poor prognosis in immunoglobulin A nephropathy. To find the correlation of glomerular C4d deposition with some demographic data in immunoglobulin A nephropathy patients, we carried out a preliminary investigation. The study was conducted on 29 patients (68% were male). The Mean  $\pm$  standard deviation (SD) of serum creatinine value and the proportion of proteinuria were  $1.72 \pm 1.2$  mg/dL and  $1582 \pm 1214$  mg/day, respectively. In this study, we found  $54.2 \pm 25$  percent of glomeruli in all biopsy fragments were positive for C4d. The study showed a statistically significant associations of percent C4d positivity with the serum creatinine ( $r=0.61$ ,  $P=0.0005$ ), proportion of proteinuria ( $r=0.72$ ,  $P=0.0001$ ) and the proportion of totally sclerotic glomeruli ( $r=0.43$ ,  $P=0.02$ ) and also the magnitude of tubulointerstitial fibrosis ( $r=0.54$ ,  $P=0.0023$ ) (12).

Recently Maeng et al, conducted a retrospective investigation on 23 immunoglobulin A nephropathy. They found that, 56.5% were positive for C<sub>4</sub>d staining in the glomeruli and 47.8% were positive in the tubular epithelium. They also detected that glomerular C<sub>4</sub>d deposits were associated with albuminuria and tubular C<sub>4</sub>d deposition was associated with a higher grade of immunoglobulin A nephropathy. They detected that activation of the complement system was interacted in renal damage and was identified through deposition of C<sub>4</sub>d in the glomeruli and

tubules of immunoglobulin A nephropathy. Positive C<sub>4</sub>d staining in the glomeruli and the tubules may be associated with functional injury related to glomerular filtration and poor kidney outcome (13). While deposition of IgA, IgG or C<sub>3</sub> was not still justified to be included as a factor for treatment or follow up study. However, the mentioned studies on immunostaining data may be potentially helpful in predicting the severity of IgAN in some patients. By contrast to the one of the mostly important points of diagnosis of IgAN, that, C<sub>1</sub>q deposits, should not be more than trace (1), Lee and colleagues, conducted a study on the correlation of C<sub>1</sub>q deposition with kidney involvement in IgA nephropathy. They aimed to test the correlation between co-deposition of C<sub>1</sub>q, clinicopathological features, and kidney outcomes in immunoglobulin A nephropathy. Study included 221 patients with primary IgAN who were divided in two groups: C<sub>1</sub>q-positive and C<sub>1</sub>q-negative. They found, C<sub>1</sub>q-positive patients had higher mean systolic blood pressure values and more impaired renal function than the unmatched C<sub>1</sub>q-negative patients (14). This association was not found when the C<sub>1</sub>q-positive patients were compared with the matched C<sub>1</sub>q-negative patients. They concluded that, mesangial C<sub>1</sub>q deposition in the glomeruli is associated with a poor kidney outcome and severe pathologic features in patients with immunoglobulin A nephropathy. They also concluded that, deposition of C<sub>1</sub>q in immunoglobulin A nephropathy could therefore serve as an indicator of a poor kidney prognosis (14). As mentioned above, it is well found that, the pathologic diagnosis of immunoglobulin A nephropathy necessitates the documentation of IgA-dominant mesangial or mesangial-capillary immune deposits through immunostaining study in absence of significant C<sub>1</sub>q deposits (1-3). Indeed, C<sub>1</sub>q deposition in more than trace amount provoke the presence of diseases other than IgAN, mostly lupus nephropathy and in rare conditions, C<sub>1</sub>q Nephropathy (1-8). As the working group of the international immunoglobulin A nephropathy network and the renal pathology society, mentioned in their publication in July 2009 for pathology definition of immunoglobulin A nephropathy (1,2), that, the presence of C<sub>1</sub>q staining in more than trace intensity should bring up evaluation of nephropathy of lupus which also mentioned in the recent articles too (1,2). Thus each work to show any significant positivity of the C<sub>1</sub>q in the background of immunoglobulin A nephropathy in not correct and the diagnosis of IgAN will be questioned and will challenged with diagnosis of immunoglobulin A nephropathy (14-17). However, this study had some interesting points.

### Conclusion

Indeed, after publication of Oxford classification for immunoglobulin A nephropathy in 2009 much attention has been directed toward finding other morphologic lesions which had prognostic significant while, they are not included to the Oxford classification yet. In this regard, more attention to immunostaining data and investigating their possible prognostic significance suggests (16-19).

### Author's contribution

HN is the single author of the paper.

### Conflicts of interest

The author declared no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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