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Review Article

The Oxford Classification of IgA nephropathy: A review of literature

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ABSTRACT

IgA nephropathy is one of the commonest forms of primary glomerulonephritis in the world, most commonly among Asian population. Though usually slowly progressive, it is one of the important causes of chronic renal failure. Abnormal IgA1 are formed which leads to formation of IgG antibodies which deposit in the mesangium. It presents with synpharyngitic hematuria and can have variable histopathological patterns. The Oxford classification was devised in order to categorize the histopathological patterns, correlate with clinical course and modify treatment accordingly. Different histopathological criteria are assessed in the classification, which include mesangial proliferation (M), endocapilary proliferation (E), segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).The classification has become widely accepted around the world but still needs further validation studies and incorporation of newer parameters.

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INTRODUCTION

IgA nephropathy is the most common of primary glomerulonephritis in the world. It has been shown to account for 30-40% of biopsy proven glomerulonephritis. Though the course is quite variable, it has been shown to be one of the causes of end stage renal disease within 10-20 years from its onset.[1]

First described in 1968 by Berger and Hinglais who correlated the findings of upper respiratory tract infections, hematuria, and proteinuria. It is regarded as the commonest glomerular disease in the world, with slowly but eventually progressive course, with 30-40% of patients developing end stage renal disease in 20-30 years. Another important characteristic of this lesion is that it typically affects younger patients.[2]

The kidneys are supposed to be innocent bystanders within a systemic process, which causes formation of immune complexes which are eventually deposited in the kidneys.

It also shows frequent recurrence in allografts.[3]

IgA nephropathy is a relatively newly discovered disease, but it has become the most common primary glomerular disease worldwide. It is more common in Western Europe, parts of Asia and Australia. It is relatively less common in U.S., Africa, and the Middle East. In addition, some of these centers in developing countries may not have immunofluorescence facilities and screening of patients is not being done on a regular basis. Hence, the frequency of cases may actually be higher in that countries.[4]

The frequency of IgA nephropathy is quite variable according to geographic location, as already mentioned. Studies in North America and Northwestern Europe have frequency of 5-10% of all kidney biopsies.[5] However, in Italy, it has been shown to be as high as 35%.[6] In South East Asia and Japan, frequency of the disease ranges from 25-50%.[7,8] A South African study showed low prevalence in black people (only 0.7%).[9] In a study in Brazil, IgA nephropathy accounted for 20.1% of all glomerular diseases and 9.6% of all kidney biopsies.10 Studies from India have shown frequency to be from 7 to 16%.[11-13]

Clinical Presentation

Recurrent episode of hematuria occurring concurrently or immediately following upper respiratory infection, also known as synpharyngitic hematuria, is the most common presentation. Less than half of these patients may present with microscopic hematuria and mild proteinuria. A small number may present with nephrotic syndrome or rapidly progressive glomerulonephritis, characterized by renal insufficiency, edema, hypertension and hematuria.[5]

Asymptomatic hematuria with minimal proteinuria may be detected in places with screening programs. Progressive kidney disease is associated with development of hypertension, proteinuria and decreased glomerular filtration rate.[14]

Nephrotic range proteinuria is also not uncommon, and usually responds well to steroid therapy. IgA nephropathy with rapidly proliferative course occurs when more than 50% glomeruli show crescents. Though rare, many of these patients with crescents may progress to end stage kidney disease.[14]

Etiopathogenesis and Morphology

IgA is produced mainly in the mucous membranes and a small fraction of this is present in the circulation. Human polymeric and monomeric IgA exists as IgA1 and IgA2. IgA1 production becomes aberrant and becomes deficient in galactose, i.e. galactose deficient IgA1 (Gd-IgA1). This leads to exposure of its hinge region N-acetylgalactosamine. Antibodies are formed against the exposed region, mainly of the IgG type, and form immune complexes (IgG-Gd-IgA1). (fig. 1) These IgA1 molecules are resistant to hepatic removal and are have affinity to mesangial cells.[10]

There is presence of genetically determined increased levels of IgA1 with galactose-deficiency in the blood of patients with IgA nephropathy. Antibodies against these galactose deficient IgA1 molecules lead to synthesis of immune complexes, which are eventually deposited in the mesangium of glomeruli.[3]

In the mesangial cells of the kidney, these immune complexes bind to fibronectin, type IV collagen, CD71 or mesangial cell integrins. Activated mesangial cells secrete matrix and other inflammatory mediators, eventually leading to oxidative stress, apoptosis, mesangial hypercellularity and expansion.[10]

Formation of abnormal Gd-IgA1 molecules is probably done by abnormal B lymphocyte clones, decreased hepatic clearance (because these molecules do not bind to hepatocytes as well as normal IgA molecules), and host immune response. In addition, local complement activation and cytokines like PDGF-B and TGF-B have also been implicated.[10]

IgA nephropathy has a range of histopathological presentations, ranging from minimal histological changes to extensive proliferation or scarring with chronicity. These features are variable, and include no change at light microscopy (10%), mesangial cell proliferation with matrix expansion, endocapillary/extracapillary proliferation, segmental sclerosis, interstitial fibrosis and tubular atrophy (fig.2). [2,10]

The diagnosis of IgA nephropathy requires presence of mesangial IgA deposits by immunofluorescence microscopy. Some cases also show presence of deposition in capillary loops. Direct immunofluorescence should show dominant or co-dominant expression of IgA. It is important to note that IgA deposits have been seen in 3-16% of healthy individuals as well, termed as "IgA deposits of undetermined significance". Other immune deposits may also be present in lesser amount, including IgG and C3. Electron microscopy is not mandatory for the diagnosis; however, it can be useful to identify the presence and location of these mesangial deposits.[2,3]

Some new potential diagnostic and prognostic markers are being evaluated. In the blood, serum levels of galactose-deficient IgA1 may have some use as a diagnostic marker. These levels have been shown to be elevated long before the disease is diagnosed. In the urine, these aberrantly glycosylated IgA may be present in immune complexes which have been identified. In addition, genetic biomarkers need to be investigated, as Africans have protective alleles, whereas Asians have fewer protective alleles and hence highest prevalence, which may eventually have some therapeutic significance.[3]

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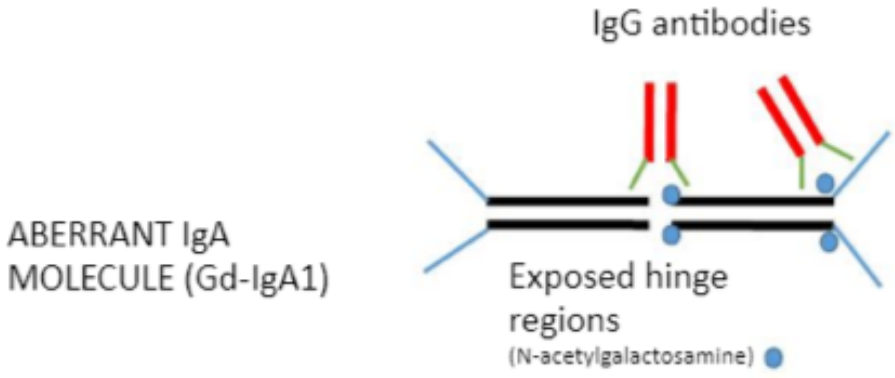

Figure 1: *Formation of immune complex, with IgG antibodies against exposed IgA hinge regions*

There are also approaches for disease specific therapy. Interventions to reduce galactose-deficient IgA or anti-glycan antibodies may be useful to decrease the formation of immune complexes. Interruption in the alternate pathway or blocking mesangial cell signal pathways by using protein-kinase inhibitors are other methods which may be useful.[3]

Classification of IgA Nephropathy

Previous classifications by Lee and Haas were used, along with modifications by Alamartine which resembled the different classes of lupus nephritis, and hence they were widely used. Eventually, further standardization was attempted with the Oxford classification.[3,14] All these classifications had one goal in common, which was an attempt to some form of semi-quantitative scoring which correlated clinical outcome and individual morphologic findings with each other.[15]

The most recent and widely used has been the Oxford classification, which was developed over a five-year period and published in 2009 and later, updated in 2016.[16-18]

In 2004, a proposal to develop and consensual clinico-pathological classification was done by Renal Pathology Society and research groups around the world. The aim of the classification was to enable both clinicians and pathologists to improve patient prognostication. 265 patients from eight countries in four continents from China, Japan, France, U.K., Italy, Canada, U.S.A., and Chile were included in this research. 30% of the patients were children.[16]

In the Oxford (MEST) classification, four main histopathological parameters were assessed in the renal biopsy, namely: (M) mesangial hypercellularity, (E) endocapillary hypercellularity, (S) segmental glomerulosclerosis, and (T) tubular atrophy/interstitial fibrosis. During the 2016 revision of the classification, a further parameter was recommended to be scored which was C (crescents).[17,18]

Other parameters which need evaluation, but not yet incorporated into the IgA score include pattern of IgA deposition, quantification of glomerular macrophages and biomarkers.[18]

The main aim for development of the classification is to provide prognostic information for patients. Incorporation of the MEST-C score to the clinical data has been shown to provide better predictive outcomes in patients.

Validation Studies

In the studies during the Oxford classification formulation, mesangial score, segmental glomerulosclerosis, endocapillary hypercellularity, and extracapillary proliferation showed strong association with proteinuria and were independently predictive of clinical outcome.[16] Patients with endocapillary and extracapillary lesions were treated with immunosuppression. Since then, there have been several validation studies which were done to further confirm the initial findings. Some examples are given below.

Sixty nine patients at Soonchunhyang University in Seoul, South Korea were evaluated and followed up for more than 3 years. In this study, 9% of patients showed reduction of GFR and 14% progressed to end stage renal disease. Both E and T lesions were shown to have prognostic significance. However, E lesions were shown to have less of an impact on outcome of East Asians when compared to European patients.[19]

Interstitial fibrosis and tubular atrophy (T) was the only pathological finding which was independently associated with renal outcomes in a study done on Chinese pediatric population. In addition, segmental sclerosis (S) had a relatively weak influence on renal outcome.[20]

Another review and meta-analysis by Jincheng Lv et al concluded that all the Oxford parameters, except E lesions were strongly associated with progression of kidney disease, and were rightly included in the Oxford classification.[21]

A study on Greek patients revealed that E, S and T lesions, were associated with a worse outcome and proteinuria. If

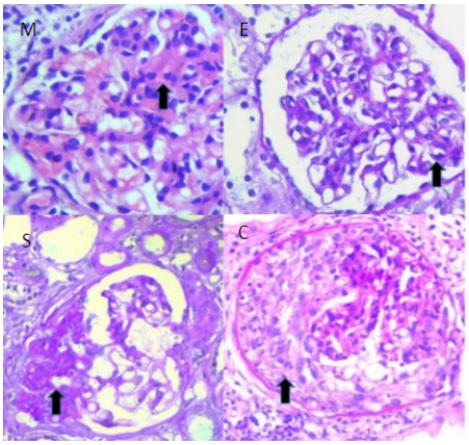

Figure 2: *Glomerular histopathology of IgA nephropathy, labelled with arrows, M (mesangial cell and matrix proliferation), E (endocapillary proliferation), S (Segmental sclerosis) and C (crescent- cellular)*

treated aggressively, C lesions were not associated with a worse outcome.[22]

Similarly, Troyanov et al in their validation analysis also mentioned that M lesions may not be associated with proteinuria, and they questioned the validity of the M score. In addition, it has been the parameter with the worst reproducibility among pathologists.[23]

Benefits of the Classification

IgA can have a variable outcome and presentations, similar to lupus nephritis. If there is low proteinuria, the disease will usually not progress. If there is predominantly scarring, immunosuppression will not help. And finally, crescentic IgA nephropathy cases should be treated as vasculitis.[24,25]

MEST-C system differs from previous classifications by the fact that there is stepwise methodology to diagnosis, and factors with poor reproducibility have been removed. As mentioned above, we can use the scoring system to predict the long term prognosis of patients. It is also immensely useful for therapeutic purposes, as E and C lesions have to be treated more aggressively. These treatment modifications have been shown to help to preserve renal function for a longer duration.[25]

Comparing the MEST scoring system to clinical parameters, Hezenberg et al found that the histopathological scoring was superior to clinical assessment methods in prediction of renal function decline. If both clinical and pathological variables were combined, the prediction was even better.[24]

Similarly, Barbour et al analyzed data from North American, Oxford and VALIGA validation studies. They also found that the MEST score provided earlier risk prediction and significantly improved prediction of clinical outcome.[25]

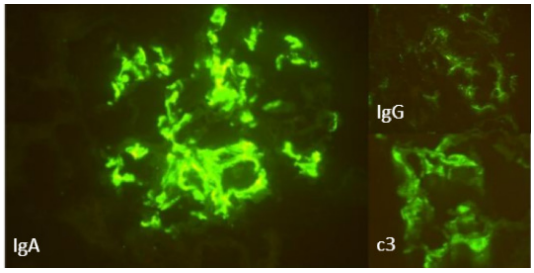

Figure 3: *Immunofluorescence of IgA nephropathy, with strong IgA positivity and moderate IgG and C3 positivity.*

CONCLUSION

Oxford classification has been widely accepted by clinicians and pathologists worldwide, and helps produce simple and reproducible reports. However, there are still some challenges with inconsistencies in scoring which need to be streamlined26. Further review of the current histopathology parameters along with addition of clinical parameters, immunofluorescence findings, and newly developed biomarkers may help to further improve prediction of disease progression and modify treatment in these patients.

Conflict of Interest: None

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