PATHOLOGY OF IgA NEPHROPATHY

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ABSTRACT
Idiopathic IgA Nephropathy (IgAN) has been recognized as the most common form of glomerulonephritis worldwide since its original description by Berger and Hinglais. Initially considered as a benign disease, the natural history has changed considerably with studies showing an incidence of chronic renal failure ranging from 20 to 40%. The highly variable clinical course has resulted in efforts to determine clinical, laboratory, and histologic features that predict the development of renal failure in IgAN. Light microscopic appearances and clinical features can vary considerably, reflecting the many patterns of histopathologic injury seen. Closely associated with IgAN is Henoch – Schonlein purpura (HSP), a small vessel systemic vasculitis characterized by small blood vessel deposition of IgA predominantly affecting the skin, joints, gut, and kidney. The nephritis of HSP is also characterized by mesangial IgA deposition and may be histologically indistinguishable from IgAN. This article focuses on IgAN considering especially information regarding its prevalance, histopathologigal, immunofluorescence findings and in particular, focussing on growing understanding of the pathogenesis of IgAN.

Keywords: IgAN, Henoch – Schonlein purpura (HSP), immunofluorescence (IF), glomerulonephritis.

INTRODUCTION

It is almost forty two years since Jean Berger was able to describe IgA nephropathy as recent group of primary GN. Berger discovered IgA nephropathy using immunohistochemistry (IH) and renal biopsy examination (Berger and Hinglais, 1968). Fluorescent labelled antibodies were first used by Coons and Kaplan (Coons and Kaplan, 1950) and by Mellors and Ostega on renal tissue (Mellors et al, 1957). Iverson and Brun introduced the technique for percutaneous renal biopsy (Iverson and Brun, 1951). In 1963, discovery of antibodies against clans specific epitopes of immunoglobulin (Ig) light chains were available for IgG, IgM, and IgA. In 1965, IgA immune system was discovered by Tomasi (Tomasi et al, 1965). So it all leads to the discovery of new disease entity "Mesangial IgA / IgG deposition", in Necker hospital, Paris. Jean Berger and Nicole Hinglais observed that immunostaining of IgA dominates the IgG staining in "Bergers' Disease" (Berger, 1968). In 1969, Berger had seen IgA nephropathy in transplanted patients, as fifty percent of the patients who were transplanted had to face graft rejection due to recurrence of IgA nephropathy in transplanted kidney (Berger, 1969).

Now Berger disease is considered as a syndrome having uniform morphology but clinical features show great diversity hence variable prognosis (Clarkson et al, 1977). Woo et al, showed that IgA nephropathy has renal survival after five years as 89%, after ten years it is 81%, and after twenty years it is 65%. The deterioration is a slow and progressive process, taking an average 7.7 years (Woo et al, 1986).

Epidemiology

IgA nephropathy prevalence shows distinct geographic variation as it is highest in Singapore, Hong Kong, Japan, Australia, Finland and southern Europe where it accounts for 20% - 40% of cases of primary GN. While in US, England and Canada the prevalence is very low (Schena, 1990). The incidence of IgA nephropathy in Italy is 8.4 patients per million population per year. IgA nephropathy accounts for 21.5% for primary GN and its frequency is higher in males i.e. 39.3%, in females 27.8% and in children it is 18.8% (Gesualdo et al, 2004), (Schena, 1997). In France the prevalence is 2.4 in thousand persons and it is 3.6 in thousand males while 1.3 in thousand females (Simon et al, 2004). IgA nephropathy is the most common primary GN that accounts for 17.2% in adults and 19.5% in children in Spain (Rivera et al, 2002). In Brazil among the non nephritic patients, IgA nephropathy accounts for 28 – 29.4% (Bahiense – Oliveira el al, 2004). The United States Renal Data System shows increase in cases up to 12.4 cases/ pmp/year for the period of 1990 – 1994, males have 2.2 times higher incidence than females, however incidence in blacks and whites is similar. In end stage renal disease it is 5.5 cases / pmp / year (Wyatt et al, 1998). In 2006, according to the study conducted by Nair and Walker IgA nephropathy is the most common primary glomerulopathy in

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USA (Nair and Walker 2006). The frequency of IgA nephropathy in Hong Kong is 35% (Lai and Wang 1994) while in Singapore, Sinniah reported 34% and in Korea it is 22.1% (Choi et al, 2001). IgA nephropathy accounts for 47.4% of primary GN (Research Group on Progressive Chronic Renal Disease, 1999) and incidence is 4.5 cases / 1,00,000 children / yr (Utsunomiya et al, 2003) while in adults it is up to 143 cases / pmp / year (Yamagata et al, 2002). In India, Chandrika observed in a retrospective study consisting of 1592 renal biopsies, that the frequency of IgA nephropathy is 14.26% that is second to focal segmental glomerulosclerosis (FSGS) (Chandrika, 2007).

In a report from Pakistan it was observed that the frequency of IgA nephropathy as 12.65%. In a total of 105 renal biopsy samples in which only 1 biopsy turned out to be of Henoch Schonlein nephritis (HSN). The male to female ratio is 1.5 to 1 (Muzaffar et al, 2003). In the previous two studies conducted in southern part of Pakistan, the prevalence of IgA nephropathy is 2% with application of immunoperoxidase technique (Khan et al, 1988) and 5.9% in another study (Khan et al, 1990). The study conducted in northern part of Pakistan reported 7.9% prevalence of IgAN (Lakhnana et al, 1995). Recently a study was carried out by Noor in northern areas of Pakistan and according to that prevalence was reported to be 20.83% (Noor et al, 2007).

IgA deposits are seen in 4%-16% of healthy adults, living and cadaveric donors on immunofluorescence (IF) studies, which shows that studies carried out on biopsies do not predict the actual prevalence of IgA nephropathy (Sinniah, 1983) (Suzuki et al, 2003).

The variation in prevalence of IgA nephropathy reflects ancestral differences, clinical policies to conduct renal biopsies and role of an incremental antigen (Levy and Berger, 1988). The annual screening of urines in Japan and Singapore in schools and army recruitment offices may contribute to the higher detection of IgAN (Yamagata et al, 2008). A community urine analysis survey done in Karachi using dipstick method showed that in asymptomatic individuals haematuria was present in 25% and proteinuria in 15% (Raaz et al, 2002). So the incidence reported in Pakistan is rightly called "Tip of the iceberg", and actual prevalence would be high if studies are conducted on larger population (Mubarak, 2009).

Pathophysiology

In some cases IgA nephropathy has association with many other aetiological factors and diseases and is termed as secondary IgA nephropathy but if no association is seen, it is termed as primary IgA nephropathy. In secondary IgA nephropathy, the renal lesions are the consequences of the major extra renal disease (Fouria and Barratt, 2008). Secondary diseases related to IgA nephropathy includes celiac disease, Crohn's disease, ulcerative colitis, cirrhosis, HIV, HBV, Schistosomiasis, Brucellosis, leprosy, ankylosing spondylites, systemic lupus erythematosis, Wegner's granulomatosis and with carcinomas of renal cell types, laryngeal and bronchial types (Barratt and Feechally, 2005). In classical IgA nephropathy, it is suspected that formation of immune complexes is triggered by exogenous antigen. These exogenous antigens have been studied in detailed by various groups. These antigens include food antigen (Coppo et al, 1991), viral antigens like adenovirus, herpes simplex, varicellazoster (Tomino et al, 1989), bacterial antigens like haemophilus parainfluenzae (Woodroffe et al, 1980), S Aureus, (Shimizu et al, 2007), biliary and dermal antigens.

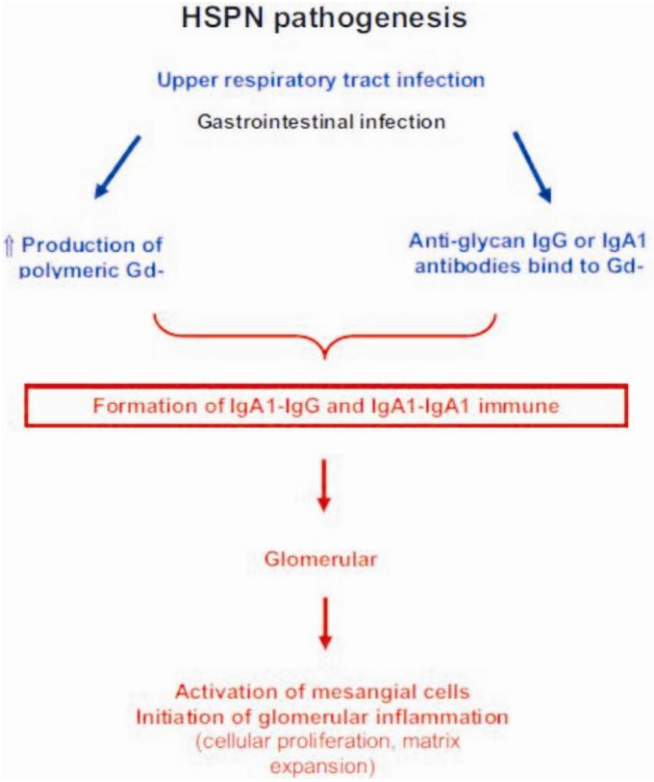

Fig. 1: *Possible role of IgA1 and IgA1 - containing immune complexes in the pathogenesis of HSPN.*

Henoch Schonlein Purpura (HSP) is the systemic form of primary IgA nephropathy in which mesangial deposits of IgA are seen with IgA - mediated vasculitis in small vessels. The only difference in IgA nephropathy and Henoch Schonlein Purpura nephritis (HSPN) is of extra renal manifestations (Figure 1).

The main clinical manifestations of HSPN include Purpura, intestinal colic, heamaturia, arthralgia (Sanders and Wyatt, 2008). Schonlein termed the HSP as "Peliosis Rheumatica" after discovering the relationship of purpura with joint pain. In 1899, Henoch described the renal involvement in HSP (Rai et al, 1999). In United Kingdom, the incidence is 14 - 20 per

100,000 children per year and estimated annual incidence is highest between 4 - 6 years of age. In Henoch Schonlein Nephritis (HSN), the principal manifestation of HSP, occurs in 40 - 50% of cases (Halling et al, 2005). There is 20 fold disparity in incidence between adults and children that is 1.3 versus 22.1 per/100,000 (Gardner - Medwin et al, 2002).

The most important pathogenic factor in primary or autoimmune IgA nephropathy is the alteration in IgA biology. IgA is the main immunoglobulin (Ig) in mucosal secretions as it plays an important role in mucosal defense against bacterial and viral infections. IgA is produced by mucosal tissue as secretory IgA (SIgA) and also by plasma cells in bone marrow. Both of these production houses are inter linked with each other and termed as "mucosa - bone marrow axis" (Suzuki and Tomino, 2007). IgA is mainly produced as dimeric form and before secretion; it binds to polymeric Ig receptor (pIgR) at mucosa and secreted with proteolitically cleaved, pIgR (Mostov, 1994). IgA has two sub classes i.e., IgA1 and IgA2. The basic difference in these two sub classes is of 18 amino acids hinge region which is absent in IgA2 (Kerr, 1990). The distribution of these two sub classes is variable at different mucosal sites. In nasal mucosa relative contribution of IgA1 is high (93%) while in distal colon it is low accounting 36% (Brandtzaeg and Johansen, 2005). IgA is mainly produced in mucosa but it is present in concentration of 2 - 3 mg/ml in systemic compartment. Serum IgA mainly exists as IgA1, 90%, in monomeric form. (Mestecky et al, 1999).

In IgA nephropathy, the IgA1 molecule contains reduced glycosylation of O-linked glycan in hinge region resulting in the formation of terminal GalNac residues (Coppo and Amore 2004). IgA1 level in the plasma is elevated in 50% of the patients of IgA nephropathy (van den Wall Bake et al, 1988). Normally small amounts of IgA are seen in circulation but the relative level of IgA is higher in IgA nephropathy than in normal subjects (Oortwijn et al, 2006). Almost 40% of IgA nephropathy patients experience episodes of macroscopic haematuria after upper respiratory tract infection, which demonstrates the pathogenic role of IgA (Nicholls et al, 1984). Therefore, in IgA nephropathy, both qualitative and quantitative abnormalities of IgA are seen due to the defective regulation of mucosal IgA immune response.

Induction of IgA secretion is mediated by T cell dependent and T cell independent mechanisms. The T-cell dependent mechanism is purely dependent on CD40 - CD40 ligand interaction and cytokines like TGFB, IL-2 and IL-10 (Figure 2) (Zan et al, 1998). On the other hand in T cell independent mechanism, B-cells are activated via local cytokines, Ag-specific activation signal through B-cell receptors, antigen presenting cells and TNF family (Figure 3).

It has been seen that dendritic cells (DC) derived

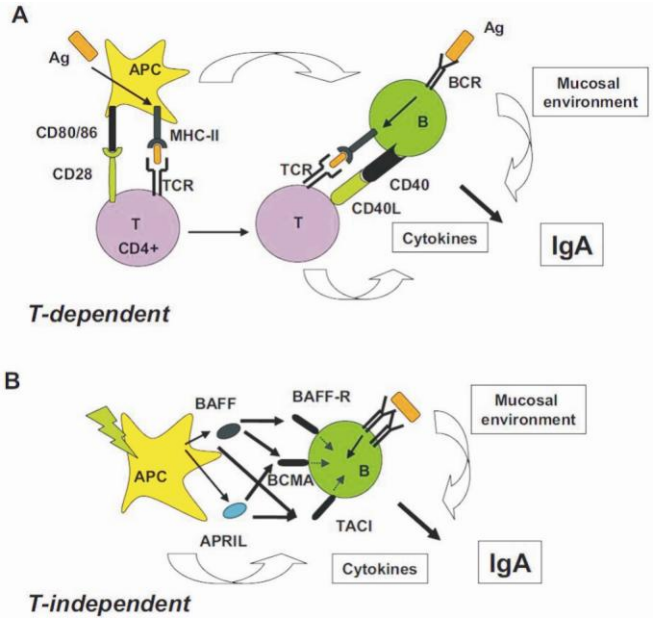

Fig. 2: *(a): T cell - dependent and, (b): T cell - independent mechanisms of B cell maturation. (Courtesy: Recent Advances in IgA Nephropathy, Page. 168).*

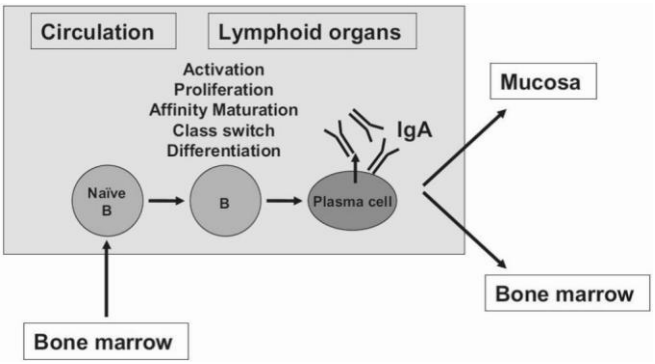

Fig. 3: *Maturation of B Cells and Synthesis of IgA. (Courtesy: Recent Advances in IgA Nephropathy, Page. 166).*

from IgA nephropathy patients have reduced ability to induce production of IgA in the presence of IL-10 due to the functional defect in dendritic cells (Castigli et al, 2004). There is an increase in subepithelial DC-SIGN positive DC and epithelial CD1-a positive DC in nasal mucosa of IgA nephropathy patients due to compensatory phenomenon to increase IgA production (Eijgenraam et al, 2008). IgA is the dominant or co dominant Ig with IgG or IgM or both with significant amounts of C3 (Emancipator, 1998). In IgA nephropathy it is observed that there is an increase in IgA and IgA containing immune complexes with IgG in circulation (Tomana et al, 1999). The patients of HSPN also have raised levels of galactose deficient IgA1 and IgA-IgG circulating complexes (Allen et al, 1998).

The resultant IgA1 complexes are relatively larger

and because of their size they are not cleared from circulation are deposited in mesangium (Mestecky et al, 2008). Another cause for decreased clearance of IgA1 complexes is that hepatocytes express asialo-glycoprotien receptor and they bind to glycoproteins via terminal galactose. However, in aberrantly galactosylated IgA1 that is linked to sialic acid or covered by antibody is not recognized by hepatic receptors, so they are not catabolised (Novak et al, 2002). The aberrantly glycosylated IgA1 also interact with CD22 molecules which modulates signaling of B-cells hence production of aberrant pIgA1 by long lived plasma cells (Lai et al, 2005).

IgA nephropathy basically occurs in three phases, after the production of aberrant pIgA1 molecule by B-cells, two IgA receptors, FcαR1 and TfR intervene at different steps of IgA nephropathy. FcαR1 is expressed on haematopoietic cells and when aberrant pIgA1 binds with FcαR1(CD89), it induces shedding of extracellular domain of FcαR1.After the cleavage of extracellular domain of FcαR1, it results in the release of pIgA / FcαR1complexes into the circulation and later on it get deposited in mesangium. Due to deposition in mesengium, there is priming and recruitment of inflammatory cells (Kanamaru et al, 2007). Similarly binding of aberrant pIgA to tranferrin receptor TfR (CD71) causes mesangial activation, secretion of proinflammatory and profibrogenic cytokines and mesangial cell proliferation (Moura et al, 2005). Over expression of TfR is also seen in the mesangium of patients having HSPN (Haddad et al, 2003).

In the secondary phase, polymeric IgA causes activation of complement system via alternative pathway directly (Zwirner et al, 1997) and lectin pathway via mannose binding lectin (MBL) (Neth et al, 2000). The serum IgA/C3 ratio reflects the histological severity of IgAN (Nakayama et al, 2008) and it could be used to determine the progression of IgA nephropathy. The activation of macrophages due to binding of sialoadhesin to sialyl-Tn ligand as pIgA1-IC deposits which cause enhanced cytokine production and cross link to tubulo-interstitial compartment causes T-cell mediated injury in tertiary stage. T-cell mediated injury occurs through CD4+ and CD8+ cells. The tubular and interstitial T-cell infiltrations are associated with tubulointerstitial injury leading to progression of IgA nephropathy (Lai, 2005).

The tubular atrophy is a sign of regression of renal function. Interepithelial lymphocytes in renal tubules are used as an initial marker for the progression of IgAN towards end stage renal failure in 20% - 40% of patients (Van Es et al, 2008; Boyman et al, 2007). Patients of IgA nephropathy present with hypertension, persistent macroscopic or microscopic haematuria, proteinuria more than 1 gram / 24 hours and a range of normal to impaired renal functions.

The observations on histology made by Berger and Hinglais are still authenticated and constitute the basics of IgA nephropathy. As they stated:

"*The duration of the nephropathy from the first symptom to the biopsy varied from several months to 12 years. Thus, it appears that in majority of cases of chronic focal glomerulonephritis, there are diffuse intercapillary deposits associated with the focal lesions. This observation, in addition to its theoretical interest, has some practical implications. Immunofluorescence microscopy allows an easy diagnosis of this syndrome in cases in which the kidney is either normal or shows other lesions.*" (Berger, 1968).

Light microscopy shows histological variability in this disease, ranging from minimal change to diffuse proliferative glomerulonephritis (GN) to crescenteric GN. Mesangial hypercellularity (figure 4) is seen when the mesangial cells exceed three per segmental area and it is mainly focal segmental and sometimes it is accompanied by mesangial matrix expansion (To et al, 2000).

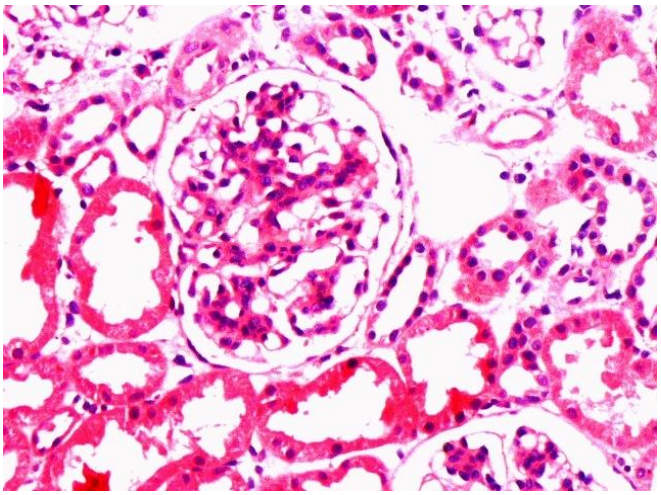

Fig. 4: *Photomicrograph of Diffuse mesangial proliferative glomerulonephritis showing a glomerulus with mesangial hypercellularity and increase in mesangial matrix (H&E).*

When there is disruption of capillary wall, mesangiolysis, leucocytic infiltration, nuclear fragmentation, fibrinous deposits and cellular crescents, they are termed as necrotising lesions. They are seen in about 10% of IgAN patients and in 50% of HSPN (D'Amico et al, 2001). Glomerular sclerosis accompanied by capillary collapse with accumulation of proteinaeous hyaline and degenerative foam cells, capsular adhesions, distortion of capillary tufts, segmental sclerosis finally going into global sclerosis is frequently seen. The loss of renal function is correlated with the extent of glomerular sclerosis hence it parallels with progressively declined functional nephrons (Feehally et al, 2007).

The extent of tubular atrophy with interstitial fibrosis progresses with glomerulosclerosis. One third of

patients of IgAN experience hyaline arteriosclerosis due to hypertension. Grading of IgAN is done on chronicity based indices comprising of glomerulosclerosis, tubular atrophy, interstitial fibrosis and hyaline arteriosclerosis (Lai et al, 2002).

So IgA nephropathy is defined by the presence of IgA-dominant or co-dominant immune deposits within glomeruli. Biopsy specimens meeting these diagnostic criteria have a range of histological changes that are reflected in the variable clinical course of IgA nephropathy. The impact of histology on outcomes in IgA nephropathy has been clarified in a number of large retrospective clinicopathological studies. These studies have consistently demonstrated that the stage of disease at presentation, as indicated by the extent of interstitial fibrosis and tubular atrophy in the biopsy, is the strongest histological predictor of renal survival. Future challengs include improving the reproducibility of histological scoring, particularly for the presence and extent of endocapillary lesions, and to improve prognostic modeling by combining histological data with clinical variables and biomarker data (Ian, 2014).

The immunofluorescent microscopic study of IgA nephropathy shows mesangial deposits of IgA - C3 (Figure 5) predominantly with IgG or IgM. The deposition of immune complexes is diffuse intercapillary irrespective of light microscopic lesions, whether or not they are focal and segmental (Berger et al, 2000).

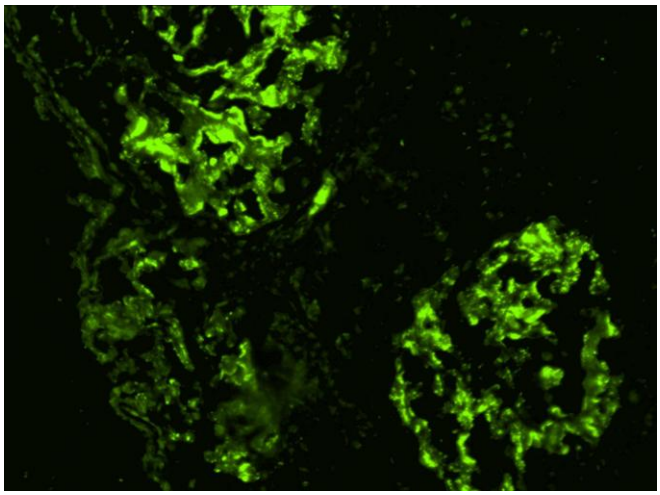

Fig. 5: *Immunofluorescent staining of Glomeruli section showing IgA deposits in the mesangial region.*

The capillary wall distribution of immunoreactants is rarely seen in IgA nephropathy. In case of advanced stage of glomerulosclerosis, the mesangial distribution of predominantly IgA - C3 might not be clear then presumptive diagnosis should be made (Lee et al, 1989). Immunoglobulin (Ig) A nephropathy (IgAN) is characterized by mesangial deposits of IgA1 and C3, often with co-deposits of IgG. Mesangial IgG deposition is associated with more severe clinical features in patients with IgAN (Wada, 2013). In majority of cases of IgA nephropathy, only electron microscopy can confirm the diagnosis previously made by the aid of light microscopy and immunofluorescent technique (Woodrow et al, 1989). Electron microscopy helps in making the diagnosis of minimal change nephropathy overlapping on IgA nephropathy (Lai et al, 1986) and also membranous nephropathy co-existing with IgA nephropathy (Lai et al, 1994).

Activation of the complement system was involved in renal damage and was identified through deposition of C4d in the glomerulus and tubules. Positive C4d staining in the glomerulus and the tubules may be associated with functional damage related to glomerular filtration and poor renal outcome (Maeng, 2013).

Table 1: *Classification systems for IgAN and HSN.*

Histological classification of IgA nephropathy of Haas	
Class I	Minimal Histological Lesion
Class II	FSGS
Class III	Focal Proliferative GN
Class IV	Diffuse Proliferative GN
Class V	Advanced Chronic GN (or end stage renal disease ESRD)
ISKDC(International study of kidney disease in childhood) Classification of HSN	
CLASS I	Minimal Histological Lesion
CLASS II	Pure Mesangial Proliferation
CLASS III	IIIa: Focal
	IIIb: Diffuse Mesangial Proliferation with less than 15% crescents
CLASS IV	IVa: Focal
	IVb: Diffuse Mesangial Proliferation with 15 - 75% crescents
CLASS V	Va: Focal
	Vb: Diffuse Mesangial Proliferation with more than 75% crescents
CLASS VI	Membranoproliferative like GN

Many classification systems have been introduced and these classifications favored glomerular injury over injury to blood vessels and interstitium (Table 1). Mostly Haas classification is used to grade the IgA nephropathy (Kim et al, 1999). No consensus had been made in comparing the findings reported from centers using different methods to access prognosis, hence International IgA nephropathy Network has formulated

the "Oxford Classification", on review of biopsy specimen and clinical data of 5 years from 300 patients from different parts of the world. According to the Oxford classification, six pathological changes need to be observed, i.e., mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, cellular crescents, interstitial fibrosis and hyaline arteriosclerosis. Out of these mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity and interstitial fibrosis have independent value in predicting renal outcome (Roberts et al, 2009). However this classification needs to be validated in routine practice and also it should be thoroughly investigated for a correlation with immunofluorescence and electron microscopic findings (Mubarak, 2009). Park and his group suggested that the Haas and the Oxford classifications are comparable in predicting progression of IgAN (Park, 2014).

Prognosis

The features which presents worst prognosis include male sex (Neugarten et al, 2000), older age (Geddes et al, 2003), obesity (Tanaka et al, 2007), insulin resistance (Kaartinen et al, 2007), microscopic haematuria (Shen et al, 2007), serum creatinine level, decline in GFR, proteinuria > 1000 mg/day (Reich et al, 2007), Albuminuria>30mg/day, hypertriglyceridemia (Syrjanen et al, 2000), hypercholesterolemia and increased uric acid level (Myllymaki et al, 2005), whereas on light microscopy, worst prognosis is indicated by decreased number of podocytes per glomerulus (Hishiki et al, 2001), endothelial cellular proliferation, focal necrosis, focal segmental scars, extra capillary cellular proliferations and global sclerosis (Coppo and D'Amico, 2005). Histologic classification can identify the magnitude of the risk of progression to ESRD and is useful for predicting long-term renal outcome in IgAN (Kawamura, 2013). In immunofluorescent studies, the worst prognosis is shown by the presence of IgG in the mesangial immune deposits (Nieuwhof et al, 1998) and on confocal laser scanning microscopy by decrease amount of anionic sites in glomerular basement membrane (Sakagami et al, 2004). In electron microscopy, immune deposits in capillary loops have worst prognosis (Berthoux et al, 1996). In serum high IgA/C3 ratio is correlated with worst histological lesion (Komatsu et al, 2004) and increased level of oxidation products show worst prognosis (Descamps-Latscha et al, 2004). Excretion of IL-6 (Harada et al, 2002), IL-8 (Huang et al, 2001), TGF-β, increase ratio of urinary epidermal growth factor to MCP-1 is associated with worst prognosis in urine (Torres et al, 2008).The increased interstitial expression of iNOS is associated with clinical indicators of poor prognosis in IgAN. Macrophages have the potential to cause renal injury by inducing production of reactive oxygen species, nitric oxide and various pro-inflammatory cytokines. (Stambe et al, 2004).

The future prospects for IgA nepropathy are focused on fundamental genetic, molecular and cellular events involved in the disease pathogenesis. Theses approaches will bring forward the novel biomarkers that could be used in diagnosis, prognosis and therapy of the enigmatic disease that is diagnosed every year in as many as 2,00,000 people worldwide.

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