IgA Nephropathy: Evidence of Abnormal Mucosal Immunity

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Background: IgA nephropathy (IgAN) is the most prevalent form of glomerulonephritis in countries where renal biopsy is widely practised. It is characterized clinically by the association of macroscopic haematuria and mucosal infection, and pathologically by the predominant deposition of IgA in the mesangium.

Summary: The epidemiological and clinical aspects of the disease are considered and immunodysfunction summarized. The known abnormalities within the gastrointestinal lamina propria are discussed in the context of the mucosal plgA response and oral tolerance. Prognosis, and the lack of an effective treatment is outlined.

Conclusions: Although there is overwhelming evidence of widespread abnormalities within the IgA immune systems in IgAN, our present techniques have not allowed us to pinpoint the origin of glomerular IgAN. However there is increasing evidence that abnormalities of mucosal immunity may result in an impaired ability to handle the normal environmental antigen load. This may play an important role in the pathogenesis of this common glomerulonephritis

Keywords: IgA nephropathy, J chain, Mucosal immunity, Oral tolerance.


Twenty-five years have lapsed since the disease we now call IgA nephropathy (IgAN) was first described by the French pathologists Berger & Hinglais. The application of immunofluorescence techniques to renal biopsy material had allowed the identification of a group of patients with glomerular disease defined by the presence of mesangial IgA. Since that report the frequency of the condition and its potential for progressive renal injury have fuelled the interest shown in the condition by clinicians, pathologists and immunologists alike.

Definition

In these individuals IgA was shown to be the dominant immune reactant present in the glomerular mesangium. The definition excludes other groups of patients with glomerular IgA deposition including those with lupus nephritis and alcoholic liver disease. In these conditions glomerular IgA (with or without other immune reactants) is found within a characteristic clinical and pathological setting.

The associated light microscopic abnormalities in IgAN are wide ranging, however mesangial
proliferative changes with increased mesangial matrix are the predominant form.\textsuperscript{2,3} IgA may be found alone or coincident with IgG, IgM or C3. Neither the presence of co-deposits or the intensity of IgA deposits correlate with the degree of glomerular structural damage.

Mesangial electron dense deposits are characteristically identified on electron microscopy.\textsuperscript{2}

**Epidemiology**

IgAN presents most commonly in the second and third decades of life, although it may occur at any age.\textsuperscript{2} It is two to six times more common in males than females.\textsuperscript{4-7} The frequency of IgAN varies significantly world-wide. The apparent differences range from 5 to 10\% of renal biopsies in North America (excluding native Americans), the UK and the Netherlands, through 18–30\% in Continental Europe, Australia and native Americans, to 25–45\% in Japan and Asia.\textsuperscript{2,8} It is therefore the most common form of glomerulonephritis found in countries where renal biopsy is widely practised.\textsuperscript{2}

Although perceived differences world-wide may reflect true fluctuations in prevalence, there is little doubt that the facilities for health screening and local renal biopsy policies contribute to observed disparities.\textsuperscript{2,9,10} Despite the most aggressive health screening and biopsy policies IgAN is thought to go unrecognized in a considerable number of individuals.\textsuperscript{2}

**Clinical Features**

The most consistent feature of IgAN is haematuria. Indeed it may be the only manifestation of renal disease. Macroscopic haematuria may occur spontaneously or may rapidly (<24 h) follow a 'stress', most frequently intercurrent respiratory or gastrointestinal infection. In a small number of patients macroscopic haematuria is precipitated by exercise or vaccination, or by operative intervention, such as tonsillectomy or dental extraction. Macroscopic haematuria is typically painless and self limiting but may be associated with reversible impaired renal function and the development of a nephritic syndrome.\textsuperscript{11}

More frequently, however, haematuria is asymptomatic and detected by chance after an uneventful course and unknown duration on routine urine testing.

Mild proteinuria (<1 g/24 h) is commonly an associated feature although rarely the sole abnormality. Heavy proteinuria occurs much less frequently, nephrotic individuals accounting for <5\% of the total.

Renal impairment and hypertension may also be significant features as with other forms of glomerulopathy.

The characteristic clinical presentations of IgAN vary with age. Macroscopic haematuria is usually the presenting symptom in younger patients (10–30 years). In contrast, individuals presenting with asymptomatic urine abnormalities, chronic renal failure, hypertension and nephrotic syndrome tend to be older.

**Henoch–Schönlein Purpura (HSP)**

The debate as to whether HSP and IgAN are separate disease entities or are two poles of a spectrum is long-standing.\textsuperscript{12,13} Clinical evidence supports the latter view although HSP is typically a disease affecting a younger population. Histologically the same renal lesion is seen in HSP as in IgAN, but it is seen in the clinical setting of a systemic vasculitis with IgA deposition in many organs. Although many immunological parallels exist between HSP and IgAN,\textsuperscript{14} recent studies have highlighted a significant immunological distinction between the two conditions, in that IgA antineutrophil cytoplasmic antibodies have been shown to occur in individuals with HSP but not in IgAN.\textsuperscript{15}

**Pathogenesis**

A comprehensive understanding of the immune mechanisms involved in the development of IgAN is awaited. However, the recurrence of IgAN after renal transplantation\textsuperscript{16,17} and the subsequent clearing of IgA deposits from donor kidneys used for transplantation into a 'normal' host,\textsuperscript{18,19} suggest that IgAN is a 'downstream' disease in which an abnormal immune environment mediates the deposition of IgA (on a regular or continuous basis) in an essentially normal mesangium.

In the light of these findings, investigation has concentrated on abnormalities of IgA and the IgA systems in IgAN.

Multiple abnormalities of the IgA immune system have been described in IgAN (see below). A view that has gained wide acceptance proposes that the IgA immune system is hyper-responsive in IgAN and that either circulating IgA antibody–antigen complexes become trapped in the mesangium, or that IgA antibodies are directed against endogenous or exogenous glomerular antigen.\textsuperscript{14,20,21}
Immune Abnormalities in IgAN

Glomerular deposits
Deposited mesangial IgA in IgAN is, at least in part, polymeric.\textsuperscript{22-29} It is also principally restricted to the IgA\textsubscript{1} subclass.\textsuperscript{22,30-33} The origin of mesangial pIgA\textsubscript{1} (mucosal or systemic) remains controversial. The chief source of polymeric IgA (of both subclasses) is the mucosal IgA immune system, most circulating IgA, however, is monomeric IgA\textsubscript{1} and is bone marrow derived. There is experimental evidence to support both claims, of a systemic\textsuperscript{34} or mucosal\textsuperscript{35} origin.

Circulating IgA
Elevated total serum IgA occurs in 30–60\% (14) of patients. More specifically pIgA and pIgA\textsubscript{1} levels are raised,\textsuperscript{36-39} especially during acute relapses.\textsuperscript{34,40,41}

Abnormalities within lymphoid tissue

Tonsils
Tonsils contain an excess of IgA and IgA\textsubscript{1} producing plasma cells in patients with IgAN.\textsuperscript{42-45} Furthermore, two studies have reported an excess of J chain positive IgA plasma cells in tonsils (J chain is the 15 kDa bridging protein only found in IgA in its polymeric form). These findings therefore suggest an abnormal emphasis on pIgA production within the tonsils.\textsuperscript{43,45}

Small bowel
There are three reports in the literature concerned with the immune abnormalities in this area (see below).

Bone marrow
Studies from a single centre have reported an increase in IgA\textsubscript{1} plasma cells in the bone marrow aspirates from individuals with IgAN\textsuperscript{46} but no increase in IgA\textsubscript{1} cells able to bind secretory component.\textsuperscript{47}

Circulating lymphocytes
Some investigators have defined an increase in circulating IgA-bearing lymphocytes in IgAN.\textsuperscript{48,49} Abnormalities of B alpha cell numbers and T cell subset abnormalities have also been reported.\textsuperscript{50-54}

In vitro studies

Tonsils
Isolated tonsillar lymphocytes produce an excess amount of pIgA after stimulation.\textsuperscript{43,55}

Bone marrow
Spontaneous immunoglobulin synthesis in bone marrow culture has shown a shift to IgA\textsubscript{1} synthesis.\textsuperscript{46}

Circulating lymphocytes
Spontaneous IgA production by mixed lymphocyte cultures and pokeweed mitogen driven IgA production has received mixed reports.\textsuperscript{40,56,57} There is some evidence from co-culture experiments to suggest that T cells derived from patients enhance IgA production by normal B cells more so than T cells from controls.\textsuperscript{53,58}

Immune response to a known antigen
Specific IgA antibody production after vaccination with a variety of known environmental antigens has supported the propensity to IgA immune hyperactivity in IgAN.\textsuperscript{59-63} The hyper-responsiveness appears to be limited to the IgA\textsubscript{1} subclass,\textsuperscript{62} but is probably of both isomeric forms.\textsuperscript{61,62}

Abnormal Mucosal Immunity
The undeniable immunohistological abnormalities demonstrated within the tonsils in IgAN\textsuperscript{42} and the clear clinical link between mucosal infection and macroscopic haematuria are strong evidence to suggest that abnormalities of the mucosal IgA immune system play a fundamental role in the pathogenesis of IgAN. However only three studies have investigated the lamina propria—the main synthetic and effector site of the IgA mucosal immune system.\textsuperscript{64-66}

In complete contrast to the findings within the tonsil,\textsuperscript{42} two studies have found a reduction in numbers of IgA plasma cells and an increase in IgG cells within the small bowel lamina propria.\textsuperscript{64,65} Although the results of a smaller third study were in line with these findings, they failed to reach significance.\textsuperscript{66} No evidence for an abnormality of IgA cell subclass abnormality was forthcoming from any of these studies.

Recent studies from our laboratory take the mucosal story much further.\textsuperscript{64} The primary function of the mucosal system is the production of pIgA and its transport into luminal secretions.
In vitro studies suggest that the factor most closely correlated with high level plg secretion is the level of expression of J chain mRNA. The bridging protein is only found in IgA in its polymeric form. A novel technique of combined non-isotopic in situ hybridization (for J chain mRNA) and immunofluorescence (for cytoplasmic IgA) has demonstrated a downregulation of J chain mRNA expression within the IgA cells of the lamina propria. This suggests a shift away from lamina propria plgA production and secretion in IgAN and highlights a possible flaw in mucosal immunity.

Such a situation would render the systemic immune system prone to excess and prolonged stimulation by mucosally derived antigen. This notion provides an explanation for increased serum levels of circulating antibodies to food antigens and common respiratory and gastrointestinal pathogens. In addition these findings also suggest that the lamina propria is unlikely to be the source of excess circulating IgA or deposited glomerular IgA in this condition.

Oral Tolerance and Mucosal Function/Permeability

Oral tolerance is the T cell orchestrated process by which mucosal immunity (IgA) and systemic tolerance (IgG) for a mucosal antigen is maintained. The pattern of mucosal abnormalities demonstrated in IgAN (reduced J chain but increased IgG expression) is associated with a general abrogation of oral tolerance. There is experimental evidence to support the link between defective mucosal antigen handling, defective oral tolerance and glomerular immune deposits. In certain murine models of IgA nephropathy a failure of oral tolerance appears to be central to the development of nephritis. These animal studies have led to the proposition that patients with IgAN display abnormal mucosal antigen handling and impaired oral tolerance, and that persistent or episodic environmental antigen challenge elicits mixed isotype responses, although IgA predominates.

In inflammatory bowel disease antigen stimulus is believed to be heavy and continuous. Similar alterations in J chain and IgG expression have also been demonstrated in such circumstances. This lends further support to the view that mucosal antigen handling is abnormal in IgA nephropathy.

Non-specific physical mucosal permeability is probably normal in adults with IgA nephropathy, despite one report to the contrary in children. In contrast, however, a significant number of studies support the view that specific ‘immune permeability’ is not.

A defect in mucosal immunity would therefore point to the potential pathogenetic significance of systemic immune responses to antigen which were under normal circumstances mucosally encountered and excluded.

Prognosis

The term ‘benign recurrent haematuria’ was in the past applied to IgAN. However, long-term follow-up of large numbers of patients with IgAN from different centres over decades had shown that between 20 and 30% of patients progress to end-stage renal failure and renal replacement therapy or transplantation. After a 20-year follow-up only 50% will have serum creatinine levels within the normal range, which is a significant finding in a disease with a peak incidence in the second and third decades of life. Haematuria should not be taken lightly, therefore, in otherwise healthy young individuals. Such patients should remain under long-term observation and a diagnosis is being established in an increasing number of centres by the use of percutaneous renal biopsy. The frequency of urological causes of haematuria is uncommon in those under 40; in the context of normal renal tract imaging, nephrolithic rather than urological assessment is therefore preferable.

Treatment

No effective treatment for IgAN is yet available. A number of therapeutic approaches have been used, often in uncontrolled trials. The lack of a logical approach to the problem results from our ignorance concerning the pathogenetic processes involved. Although IgA (± other immune reactants) deposition may be the primary glomerular insult, non-immunological factors probably influence progression.

The most extensively used agents have been corticosteroids. There is evidence that these agents confer benefit on the small minority of patients who are frankly nephrotic; they may also be beneficial in those with rapidly progressive crescentic disease. Although some trials from Hong Kong and Japan have given encouraging results there are no prospective, randomized controlled data to suggest they have any ameliorative effects in the majority of patients with IgAN.
IgA Nephropathy

The effectiveness of any therapy will require extensive controlled therapeutic trials, and the answer to each proposed treatment modality may take 20 years to emerge. Therefore careful follow-up, the treatment of hypertension, and the dietary and metabolic measures taken in any form of progressive renal disease remain for the moment the corner-stone of management.

The Future

While our understanding of the immune mechanisms involved in the development of IgAN is deficient a specific treatment will remain elusive. If the source of mesangial IgA can be defined and the control of its aberrant synthesis understood, progress towards a therapeutic solution may be made in IgAN—a condition which world-wide is responsible for 10% of individuals being on chronic renal dialysis.

References

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