

# Secondary IgA Nephropathy

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**Summary:** IgA nephropathy (IgAN) is the most common pattern of primary glomerulonephritis seen in the Western world. In the majority of cases the cause remains unknown. Cases of familial IgAN and secondary IgAN have been reported and these have provided insights into underlying genetic and environmental triggers for this common glomerular disease. Secondary IgAN is seen most commonly in patients with liver disease or mucosal inflammation, in particular affecting the gastrointestinal tract. A number of dietary and microbial antigens have been identified in circulating IgA immune complexes and mesangial IgA deposits, suggesting that environmental factors may play a role in the pathogenesis of IgAN. There is an increasing literature reporting associations between IgAN and other diseases. Whether these reports represent chance associations or genuine shared pathophysiology is discussed.

Semin Nephrol 28:27-37 © 2008 Elsevier Inc. All rights reserved.

**Keywords:** Secondary IgAN, hepatic IgAN, dietary antigens, mucosal inflammation

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IgA nephropathy (IgAN) is the most common pattern of glomerulonephritis identified in all parts of the world where renal biopsy is practiced widely.<sup>1</sup> IgAN is defined by the predominant deposition of IgA in the glomerular mesangium. Light microscopic appearances and clinical features can vary considerably, reflecting the many patterns of histopathologic injury seen in this glomerulonephritis. In most cases IgAN presents as a primary disease, although secondary forms of IgAN have been described, most commonly associated with liver disease.<sup>2</sup> IgAN also has been described in association with inflammatory bowel disease, connective tissue disorders, neoplastic diseases, and chronic infections.<sup>3-8</sup> It is important to appreciate that the entity called *IgAN* is defined by a pattern of glomerular morphology and no assumption can be made that it eventually will prove to be one entity with a single pathogenic mechanism.<sup>9</sup> Evidence from studies of familial and secondary forms of IgAN has suggested that several mechanisms or combinations of mechanisms can produce IgAN.

The potential interrelationship of secondary causes of IgAN with the IgA immune system are summarized in [Figure 1](#).

The strong association between mucosal infection and macroscopic hematuria has provoked intense interest in the mucosal immune system in IgAN (discussed separately by Oortwijn and Suzuki, pp. 58-77). Interaction between mucosal pathogens, environmental antigens, and the mucosal IgA immune system is likely to play an important role in driving the pathogenic processes in IgAN. A number of investigators have looked for a causal link between IgAN and specific bacterial and viral infections as well as dietary antigens.<sup>7,8,10-14</sup> These studies have failed to identify any single antigen to be universally responsible for the development of IgAN, although in some instances specific pathogens and food antigens have been found to drive disease in individual patients.<sup>15</sup>

In this review we discuss the features of secondary IgAN with particular focus on hepatic IgAN. We also discuss the evidence for microbial and environmental triggers in IgAN.

## EPIDEMIOLOGY OF SECONDARY IgA NEPHROPATHY

Compared with primary IgAN very little is known about the incidence of secondary IgAN. In the series from France reported by Berthouex,

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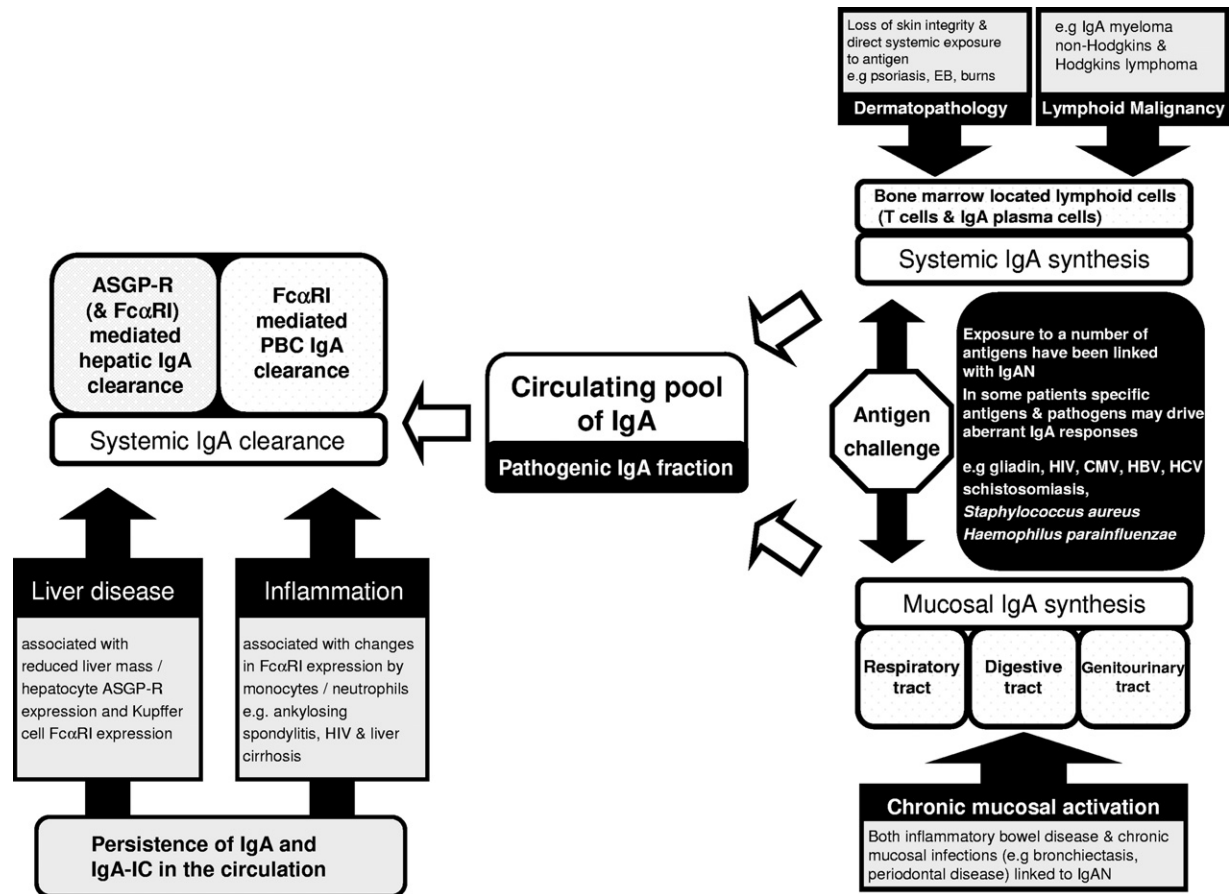
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0270-9295/08/\$ - see front matter

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**Figure 1.** Overview of the interrelationship between the IgA immune system and common diseases linked with the development of secondary IgAN.

pp. 4-9, in this issue IgAN secondary to cirrhosis accounted for 9% of all biopsy-proven cases of IgAN over a 12-year period. Similar to primary IgAN, the apparent prevalence of secondary IgAN will be influenced by renal biopsy practice, for example, in high-risk patients with coagulopathy secondary to hepatic dysfunction. IgAN typically is considered to be a primary diagnosis, and it is unusual in clinical practice for an extensive search to be made for secondary causes. Since 2000 at least 50 separate diseases and pathogens have been linked with the development of IgAN (PubMed, search on "IgA nephropathy") and such case reports account for 15% of all reports cited under "IgA nephropathy" on PubMed between 2000 and 2007. Many of these case reports simply may reflect a chance association. It is important to note the relatively high frequency of subclinical IgAN in supposedly healthy populations. This may be as high as

16% in certain Asian populations and means that the chance of a clinical association between IgAN and another pathophysiologically unrelated condition is high.<sup>16,17</sup>

### PATHOPHYSIOLOGIC RELATIONSHIP OF PRIMARY AND SECONDARY IgA NEPHROPATHY

The initiating event in the pathogenesis of primary and secondary IgAN is the mesangial deposition of IgA. The recurrence of glomerular IgA deposits in up to 60% of patients with primary IgAN who receive renal allografts indicates that mesangial IgA probably is derived from a circulating pool of pathogenic IgA.<sup>18</sup> Not all IgA that deposits in the mesangium triggers a mesangial response characterized by glomerular injury, arguing that mesangial IgA deposition and the development of glomerulonephri-

tis are not linked inextricably.<sup>17</sup> Studies in primary IgAN have identified a number of physicochemical characteristics of circulating IgA that may be associated with mesangial IgA deposition (Table 1).

Evidence is emerging that pathogenic IgA has a mucosal phenotype and that this IgA is synthesized by mucosally primed lymphocytes that have taken up residence in systemic immune sites.<sup>19</sup> Changes in mucosal and systemic IgA immune responses to recall and neoantigens also have been reported and there is some evidence for defects in lymphocyte trafficking along the mucosa–bone marrow axis in primary IgAN (discussed further by Suzuki and Oortwijn in this issue).<sup>9,20</sup> Current data would suggest a fundamental dysregulation of IgA immune responses in primary IgAN, resulting in the appearance in the serum of excessive amounts of pathogenic IgA.

The IgA immune response can be regarded as consisting of 3 basic components: exposure to antigen, IgA synthesis by B cells with T-cell help, and clearance of circulating IgA containing immune complexes (IgA-IC). This framework allows an understanding of the way in which other diseases may contribute to the development of IgAN (Fig. 1).

**EXPOSURE TO ANTIGEN**

**The Role of Environmental and Microbial Antigens**

*Environmental Antigens*

Many studies have found increased circulating IgA-IC containing food antigens in IgAN<sup>12-14,21,22</sup> and a number of studies have reported changes in various clinical and laboratory parameters on exposure to specific foods.<sup>15,22</sup> Circulating IgA antibodies to a variety of milk and egg proteins including casein and bovine serum albumin have been reported in IgAN<sup>15,23</sup> and indirect immunofluorescence has identified mesangial IgA-IC deposits containing casein, soybean protein, and rice protein.<sup>14,23</sup>

Manipulation of dietary antigen exposure has resulted in short-term improvements in some parameters of renal injury in some patients with IgAN. Introduction of a low-antigen diet for 24 weeks has been shown to reduce proteinuria

**Table 1. Properties of IgA in Normal Subjects and Patients With Primary and Hepatic IgAN**

	Normal Subjects			Primary IgAN			Hepatic IgAN		
	Serum IgA	Mucosal IgA	Serum IgA	Serum IgA	Mesangial IgA	Serum IgA	Serum IgA	Mesangial IgA	
IgA isoform	mIgA >> pIgA	pIgA > mIgA	↑ pIgA/IgA-IC	↑ pIgA/IgA-IC	pIgA/IgA-IC	↑↑ pIgA/IgA-IC	pIgA/IgA-IC	pIgA/IgA-IC	
IgA subclass	IgA1 >> IgA2	IgA1 & IgA2	↑ IgA1	↑ IgA1	IgA1	↑ IgA1 / ↑↑ IgA2	IgA1	IgA1	
IgA λ:k light chain use	Normal	Not known	↑ λ Light chain use	↑ λ Light chain use	↑ λ Light chain use	Not known	Not known	Not known	
Net IgA charge	Normal	Not known	↑ Anionic	↑ Anionic	↑ Anionic	Not known	Not known	Not known	
O-glycosylation	Heavily	Variably							
Galactosylation	Galactosylated	Galactosylated	↓ Galactosylation	↓ Galactosylation	↓ Galactosylation	↑ Galactosylation	Galactosylation	Not known	
Sialylation	Sialylated	Sialylated	↑/↓ Sialylation	↑/↓ Sialylation	↓ Sialylation	↓ Sialylation	↓ Sialylation	Not known	
		Depending on site							

Abbreviations: mIgA, monomeric IgA; pIgA, polymeric IgA.

and the extent of IgA/complement/fibrinogen mesangial deposits on repeat biopsy.<sup>24</sup> In a separate study, treatment with 6 months of a gluten-free diet in patients without celiac disease (CD) reduced levels of IgA-IC, dietary antigen-specific IgA, proteinuria, and microscopic hematuria.<sup>15</sup> Pediatric cases also have been described in which meticulous dietary exclusion of specific food antigens and rigid environmental control has led to remission of Henoch-Schönlein purpura.<sup>25</sup>

Although there is no evidence that any specific environmental antigen can induce IgAN, evidence suggests that certain foods may exacerbate underlying primary IgAN, particularly those foods containing specific lectins (a lectin is a protein with a high affinity for specific carbohydrates). The importance of IgA1 glycosylation in IgAN is discussed in other articles in this issue. Indeed, one of the ways IgA1 glycosylation has been measured is by studying the binding of various lectins.<sup>19</sup> Systemic absorption of food lectins with a propensity to bind aberrantly glycosylated IgA1 has the potential to promote the formation of circulating IgA-IC and therefore drive mesangial IgA deposition. There also is evidence that dietary lectins can bind to cell surface carbohydrates including those expressed by mesangial cells and trigger cell activation.<sup>26</sup> At present, little is known about the IgA1 binding properties of lectins in commonly encountered pulses, vegetables, and fruits.

### **Microbial Antigens**

High levels of circulating IgA-IC containing various viral and bacterial antigens also have been described in IgAN,<sup>7,8,10,11</sup> and, perhaps not surprisingly, a large number of pathogens have been reported to drive the development of IgAN. These include common viruses (cytomegalovirus; mumps virus; enterovirus; hepatitis A, B, and C, and human immunodeficiency virus), bacteria (*Staphylococcus aureus*, *Haemophilus parainfluenzae*, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*), and parasites (*Schistosoma haematobium* and *Plasmodium spp*). Predictably, the association is stronger for those pathogens associated with chronic infection (and antigenemia) and disruption

of other facets of IgA homeostasis such as the hepatitis viruses, which can be associated with liver damage and defective clearance of circulating IgA-IC (see later).

Despite the lack of antigen specificity it still is possible that there may be features common to certain pathogens that make them more likely to drive the production of pathogenic IgA. Novak, pp. 78-87, discusses in this issue the possibility that IgG antibodies directed against cell surface polysaccharides of some pathogens may cross-react with underglycosylated IgA1 hinge region O-linked sugars. This raises the concept that in patients with IgAN, exposure to pathogens expressing specific carbohydrate epitopes generates IgG responses appropriate for the infecting pathogen; and that this IgG also contributes to IgA-IC formation, through formation of IgA1-IgG complexes.<sup>27</sup>

What is clear from all these studies is that no single pathogen or environmental antigen is capable of inducing the development of IgAN in human beings. Environmental and microbial antigens may drive the synthesis of pathogenic IgA but this only occurs in individuals who have an inherent dysregulation of their IgA immune system (ie, those patients who already have primary IgAN).

### **Loss of Mucocutaneous Antigen Exclusion**

Patients with primary IgAN show excessive and prolonged systemic IgA responses to mucosal and systemic antigen challenge. The IgA generated is low-affinity polymeric IgA1, and when the antigen is presented at mucosal surfaces the IgA1 is aberrantly O-glycosylated.<sup>19,28</sup> These all are features characteristic of mesangial IgA. Excessive exposure to antigenic stimuli in primary IgAN therefore would be expected to drive the production of pathogenic IgA and consequently mesangial IgA deposition.<sup>29</sup> A permanent or intermittent loss of integrity of mucocutaneous barriers may help explain the relationship of many skin and chronic inflammatory mucosal diseases, such as inflammatory bowel disease, with IgAN.<sup>3,30,31</sup> Combined with a possible defect in oral tolerance this loss of antigen exclusion would be expected to be associated with

high levels of systemic antigenemia and systemic immune activation.

The association of macroscopic hematuria with mucosal infection in IgAN may similarly represent a temporary loss of mucosal integrity and antigen exclusion with marked systemic antigenemia and systemic IgA immune activation. Whether particular pathogens are more or less likely to impair mucosal antigen exclusion and certain individuals more susceptible to these effects is not known.

### IgA SYNTHESIS

IgA synthesis requires close cooperation between B and T lymphocytes and precise regulation of the lymphocytic microenvironment. It is therefore not surprising that clonal disorders of predominantly B-lineage cells (lymphoma and IgA myeloma) have been linked on occasion with excessive IgA production and IgAN.<sup>6,32</sup> Interestingly, in the majority of cases high circulating levels of IgA alone are insufficient to cause IgAN, it is only when the monoclonal IgA has specific physicochemical characteristics (Table 1) that there is the potential for mesangial IgA deposition and glomerular injury. We have reported a case of IgA myeloma in which the monoclonal IgA had the same O-linked glycosylation defect commonly found in primary IgAN.<sup>32</sup> This was associated with extensive mesangial IgA deposition and renal impairment that improved after plasma exchange and cytotoxic treatment of the myeloma. In most of the published case reports successful treatment of the primary lymphoproliferative disorder is associated with complete remission of the secondary IgAN.

In addition to these monoclonal lymphoproliferative diseases, polyclonal immune activation characteristic of many multisystem autoimmune diseases also has been associated with the development of IgAN (systemic lupus erythematosus, Behçets disease, Sjögrens disease, polymyositis, rheumatoid arthritis, and ankylosing spondylitis). The precise interrelationship between these autoimmune conditions, regulation of IgA synthesis, and development of IgAN remain unclear.

### CLEARANCE OF CIRCULATING IgA CONTAINING IMMUNE COMPLEXES

IgA normally is cleared from the circulation by the liver and by leukocytes through receptor-mediated endocytosis. A study in primary IgAN using radiolabelled complexes of IgA and IgG from normal individuals has shown reduced hepatic clearance in IgAN.<sup>33</sup> Hepatocytes express an asialoglycoprotein receptor (ASGP-R) that recognizes asialyl *N*- and *O*-linked carbohydrate chains on a wide variety of glycoproteins including IgA.<sup>34</sup> Hepatic ASGP-R-mediated endocytosis therefore is likely to be an important mechanism for systemic IgA-IC clearance. Kupffer cells also represent an important route of IgA catabolism in laboratory animals, but at present there is no evidence for a role in human beings.<sup>35</sup> Clearly, diseases associated with significant loss of hepatic cell mass are likely to reduce hepatic IgA-IC clearance and promote mesangial IgA deposition through persistence in the circulation of IgA-IC.

Cells of the myeloid lineage express a well-characterized  $Fc\alpha$  receptor, termed *Fc\alpha RI* or CD89. This mediates the activation of inflammatory leukocytes by IgA-IC, and because of the large numbers of such cells in the circulation, also may represent an important catabolic route for IgA and its complexes (discussed further by Moura, pp. 88-95). In primary IgAN it has been shown that some molecular forms of IgA bind less well to myeloid cells than that of healthy controls, and that *Fc\alpha RI*-mediated endocytosis of IgA is defective.<sup>36</sup> Impaired expression and function of *Fc\alpha RI* by myeloid cells also has been described in ankylosing spondylitis, human immunodeficiency virus infection, and alcoholic cirrhosis, all conditions associated with the development of secondary IgAN.<sup>37-39</sup>

### COMMON FORMS OF SECONDARY IgAN Hepatic IgAN

Hepatic IgAN occurs most frequently but not exclusively as a complication of alcoholic liver disease. Hepatic IgAN is associated with alterations in the IgA immune system characterized by high levels of circulating IgA-IC.<sup>40,41</sup> It has been proposed that hepatic IgAN is a chance association of 2 common conditions,<sup>42</sup> how-

ever, most evidence suggests hepatic IgAN is a distinct clinicopathologic entity.<sup>43</sup> Information on hepatic IgAN is based largely on autopsy and biopsy studies.<sup>42,44-50</sup> The incidence of hepatic IgAN in cirrhosis is not known. Where biopsy data have been presented, a wide range of criteria for renal biopsy have been used. The pooled autopsy and biopsy data suggest that between 50% and 100% of patients with alcoholic cirrhosis have glomerular abnormalities on microscopy.<sup>51</sup> Immunofluorescence studies suggest that 30% to 90% of renal specimens display mesangial IgA deposits.<sup>43,51</sup>

### Clinical Features and Natural History

Patients with hepatic IgAN often are asymptomatic. As with primary IgAN the most common urine abnormality is microscopic hematuria. In the series reported by Nakamoto et al<sup>52</sup> 9.6% of cirrhotic patients had microscopic hematuria and/or proteinuria. A small percentage (1.6% in 1 series) of patients present with nephrotic syndrome and renal impairment. Urine abnormalities have been shown to correlate with the degree of mesangial proliferation and severity of glomerular disease.<sup>46</sup>

The risk of progressive chronic kidney disease (CKD) and end-stage renal disease (ESRD) in hepatic IgAN is unknown. Although some reports suggest the risks of CKD and ESRD are low,<sup>51</sup> this has not been our experience. We recently reported the outcome of 8 biopsy-proven cases of hepatic IgAN: 4 developed ESRD, 2 developed progressive CKD, 1 had mild CKD, and 1 had normal renal function after a 4-year follow-up period.<sup>53</sup> The high risk of progression in our reported cases may reflect our policy to perform renal biopsy in chronic liver disease only when there is significant renal impairment, as well as an abnormal urinalysis.

No correlation has been found between the severity of cirrhosis and the risk of CKD and ESRD. There is no specific treatment for hepatic IgAN and the prognosis depends on the course of the liver disease. There is anecdotal evidence of disease regression after abstinence from alcohol, after liver transplantation, or after surgery for portal hypertension.<sup>54</sup> Limited data on repeat renal biopsy, however, suggest that at

least in some cases the glomerular morphology remains static over a number of years.

### IgA in Hepatic IgAN

In alcoholic cirrhosis, only 25% to 45% of circulating IgA is monomeric in contrast with 90% in normal individuals.<sup>55</sup> Both serum IgA1 and IgA2 levels are increased, with IgA2 proportionally higher in some series (Table 1).<sup>56</sup> The ratio of IgA1:IgA2 does not appear to be linked to the severity of liver disease.<sup>57</sup> As liver injury progresses there is an increase in serum secretory IgA levels, possibly through the interruption of normal transepithelial mucosal transport of polymeric IgA.<sup>56</sup> This may be a direct toxic effect of alcohol.

Increased serum IgA antibodies against common food and microbial antigens are reported in hepatic IgAN. This may be a direct result of increased gut permeability and compromised ability of the liver to act as a barrier to gastrointestinal-encountered antigens. Circulating IgA-IC are increased in up to 80% of patients with alcoholic cirrhosis and are even higher in those patients with glomerulonephritis.<sup>48,50</sup> A major proportion of these IgA-IC may be cryoglobulins, which are present in up to 40% of cirrhotic patients. There appears to be no correlation between the levels of IgA-IC and the degree of cirrhosis. Serum IgA levels, however, have been correlated with both the severity of hepatic disease and glomerular lesions in hepatic IgAN, although only in a single case series.<sup>55</sup> Plasma C3 complement levels in hepatic IgAN are depressed. Whether this is caused by underproduction by the cirrhotic liver or increased consumption by immune complexes and cryoglobulins is not clear.

Changes in the O-glycosylation of IgA1 have been reported extensively in primary IgAN and appear to have major pathophysiologic implications (discussed by Novak in this issue). In our case series of biopsy-proven hepatic IgAN we too found marked changes in IgA1 O-glycosylation, but these were distinct from those previously reported in primary IgAN. We identified a minor increase in IgA1 O-galactosylation with reduced O-sialylation and reduced presentation of N-acetylgalactosamine residues compared with healthy subjects.<sup>53</sup> IgA1 from patients with cirrhosis but no glomerular disease displayed a

similar increase in *O*-galactosylation and reduction in *O*-sialylation, but, interestingly, there was no change in the number of *O*-linked *N*-acetylgalactosamine residues. The pathophysiologic significance of these changes is unclear at present.

### Pathology

The light microscopic features of hepatic IgAN are similar to primary IgAN and generally are mild.<sup>58</sup> Mesangial IgA often is associated with less IgG, IgM, and C3 deposition. As with primary IgAN, the presence of IgA deposits may be accompanied by minimal light microscopic changes. Mesangial interpositioning and splitting of the glomerular basement membrane are more common than in primary IgAN. Mesangiocapillary and crescentic patterns of glomerulonephritis also occasionally have been described.

Studies of the IgA subclass distribution in mesangial IgA deposits in hepatic IgAN have been contradictory. An early report suggested that IgA2 was the dominant immunoglobulin in hepatic IgAN, although this same study also overestimated the amount of mesangial IgA2 in primary IgAN, suggesting a possible problem with the methodology.<sup>59</sup> Subsequent studies using more robust staining techniques have reported predominantly polymeric IgA1 mesangial deposits.<sup>60</sup> A recent case report of IgAN secondary to autoimmune hepatitis found mesangial deposits comprising predominantly IgA2.<sup>61</sup> Whether preferential IgA2 deposition reflects a distinct pathologic process in autoimmune hepatitis is unclear.

### Pathogenesis

The cause of hepatic IgAN remains poorly understood. Portosystemic antigen overload and intrinsic abnormalities of the IgA immune system along with defective liver IgA clearance all may contribute to the development of IgAN in patients with liver disease. Similar to primary IgAN, no adequate explanation exists for the variable patterns of glomerular injury and disease progression seen in hepatic IgAN.

### Exposure to Antigen

Increased circulating IgA-IC, characteristic of hepatic IgAN, may represent an appropriate

response of a normal IgA immune system to excess antigen exposure and persistent antigenemia resulting from diminished intestinal mucosal integrity. Furthermore, the altered intestinal milieu in alcoholic cirrhosis may suppress mucosal IgA production and further impair antigen exclusion and contribute to systemic antigenemia.

### Regulation of the IgA Immune System

There also is some evidence for inherent dysregulation of the IgA immune system in hepatic IgAN. In alcoholic liver disease B-cells show increased spontaneous and mitogen-stimulated production of IgA *in vitro* along with abnormal T-cell cytokine patterns and suppressor cell function.<sup>62</sup> Peripheral blood mononuclear cells show enhanced interleukin-6 sensitivity, resulting in excessive IgA secretion from B-cells, which may promote an *in vivo* auto-amplification loop.<sup>63</sup>

### Systemic IgA Clearance

Similar to primary IgAN, fractional catabolism of IgA and its complexes is reduced in alcoholic cirrhosis.<sup>56</sup> This reduced clearance results primarily from impaired hepatic clearance but impaired expression of FcαRI in alcoholic cirrhosis and reduced endocytosis of IgA-IC by myeloid cells also is likely to contribute.<sup>38</sup> Impaired hepatic IgA clearance is likely to occur in a number of ways. In healthy subjects the hepatic ASGP-R is expressed on the sinusoidal/lateral aspect of the hepatocyte, facilitating exposure to circulating IgA-IC. In cirrhosis, loss of hepatic polarity results in aberrant expression of the receptor on the canalicular surface, preventing exposure of the receptor to circulating IgA and IgA-IC.<sup>64</sup> There also is evidence for changes in both the structure of the hepatic ASGP-R and *O*-glycosylation of IgA1-IC in hepatic IgAN, which may result in defective receptor-ligand interactions and impaired hepatic IgA endocytosis.<sup>53</sup> In addition, a reduced hepatocyte number inevitably will result in reduced IgA clearance.<sup>55</sup> It also is likely that with the development of portal hypertension there is shunting of IgA complexes directly to the systemic circulation through opening of portosystemic anastomoses, thereby bypassing the ability of the remaining hepatocytes to endocytose IgA.<sup>54,65</sup>

## IgAN SECONDARY TO BOWEL DISEASE

### Celiac Disease

CD is characterized by malabsorption, chronic mucosal inflammation affecting the small intestine, and villous atrophy. These occur as a direct result of exposure to wheat gluten or related rye and barley proteins. It is associated strongly with HLA-DQ2 and/or DQ8, but there also may be a contributory effect from non-HLA genes.<sup>66</sup> CD has been associated with a wide range of diseases and immune disorders including IgAN.<sup>67</sup> The presence of high levels of IgA against food antigens including gliadin and IgG and IgA antiendomysial antibodies in some patients with IgAN has raised the possibility of a pathophysiologic link between IgAN and CD.<sup>68</sup> Despite these observations few studies have shown improvement in measured renal parameters after gluten withdrawal and there appears to be little correlation between IgA-antigliadin, IgA-antireticulin, and IgA-antiendomysial antibodies or jejunal mucosal atrophy in IgAN.<sup>69,70</sup> Reduction in urinary protein excretion and improvement in creatinine clearance have been described in isolated cases of CD and IgAN after introduction of a gluten-free diet.<sup>71,72</sup> The beneficial effects, however, may not become apparent until 24 months after starting the diet, despite disappearance of antigliadin antibodies and normalization of IgA levels at 6 to 18 months.

In one of the largest cases series reported (223 consecutive adult patients with IgAN), 8 patients were found to have CD and all had the HLA DQ2 or DQ8 haplotype.<sup>73</sup> There was, however, no increase in the frequency of HLA DQ2 or 8 in IgAN, although 14% of those patients with HLA DQ2 had CD. There remains no clear explanation for the interrelationship of CD with IgAN, although a number of investigators have proposed that individuals with a genetic susceptibility to both conditions are more likely to develop clinically apparent disease. It has been suggested that impaired mucosal antigen exclusion and systemic hyperresponsiveness in primary IgAN make the production of IgA-antigliadin, IgA-antireticulin, and IgA-antiendomysial antibodies more likely in patients susceptible to CD. The resultant chronic mucosal inflammation and villous atrophy characteristic of CD

compounds failures in antigen exclusion, further driving the production of pathogenic IgA and mesangial IgA deposition. If this is correct then CD acts more as a disease modifier in patients with primary IgAN rather than a true cause of secondary IgAN.

### Inflammatory Bowel Disease

An association between inflammatory bowel disease (Crohn's disease and ulcerative colitis) and IgAN has been reported.<sup>3,74,75</sup> Most case reports share a common theme in that the clinical course of both diseases follow one another and that treatment of the bowel disease with either immunosuppression or bowel resection is associated with a decrease in serum IgA levels and remission of the IgAN. Similarly, relapse of the bowel disease is associated with significant increases in serum IgA and worsening of urinary abnormalities. The pathophysiologic link between the 2 diseases is not known but one possibility is that relapse of the bowel disease is associated at least in part with loss of mucosal antigen exclusion and increased systemic antigenemia.

## IgAN SECONDARY TO MUCOCUTANEOUS INFECTION

As previously discussed, acute and chronic infection with a range of pathogens can be associated with both acute exacerbation and slow progression of primary IgAN. This is seen most commonly with mucosal infection including tonsillitis, pharyngitis, infections of the upper and lower gastrointestinal tract, urinary tract, and respiratory tract. There are also case reports documenting associations with periodontal disease and tooth abscesses. There is currently no evidence in human beings that IgAN can be induced by exposure to any particular pathogen, although the complement of cell surface carbohydrates may define a group of pathogens more likely to drive pathogenic IgA production in primary IgAN. It appears more likely that it is the frequency and duration of infection that are the main factors driving pathogenic IgA production in primary IgAN and that IgAN secondary to infection is a misnomer.



This is best illustrated in diseases associated with chronic infection such as cystic fibrosis, schistosomiasis, and human immunodeficiency virus.<sup>76-78</sup> These patients often have increased serum IgA levels and IgA-IC, but only a subset of patients go on to develop IgAN. Clearly, those diseases and infections associated with concomitant liver disease such as cystic fibrosis and schistosomiasis may develop hepatic IgAN, but in the absence of liver involvement IgAN will develop only in patients with co-existent primary IgAN.

## CONCLUSIONS

Without a clearer understanding of the pathogenesis of primary IgAN it remains difficult to dissect out those diseases in which there is only a chance association with primary IgAN and those diseases in which there might be shared pathophysiology. In our opinion many of the associations in the literature describe environmental and microbial triggers in primary IgAN, which undoubtedly drive the generation of pathogenic IgA and mesangial IgA deposition, but do not induce fundamental changes in the IgA immune system. Furthermore, a variety of diseases may impair mucocutaneous antigen exclusion and increase the contributory effect of environmental and microbial antigens. Evidence is emerging that shared microbial carbohydrate epitopes and lectin content of common foods may define those antigens more likely to drive pathogenic IgA production in primary IgAN. Clearly, more work is required to define these antigens precisely, but this does raise the possibility of directed antigen exclusion offering a novel therapeutic strategy in the future for selected patients with IgAN.

However, it is unlikely that all reported disease associations are as a direct result of impaired antigen exclusion and excessive systemic antigenemia. There will no doubt be changes to IgA immune regulation in many of the autoimmune diseases associated with IgAN and it is possible that in some of these the IgA immune phenotype resembles that seen in primary IgAN with excessive production of IgA-IC prone to mesangial deposition and triggering of glomerular injury. Progress in understanding the key features of the IgA immune response

that define primary IgAN will clarify the contribution of other diseases to the development of secondary IgAN.

## REFERENCES

1. Barratt J, Feehally J. IgA nephropathy. *J Am Soc Nephrol.* 2005;16:2088-97.
2. Pouria S, Feehally J. Glomerular IgA deposition in liver disease. *Nephrol Dial Transplant.* 1999;14:2279-82.
3. de Moura CG, de Moura TG, de Souza SP, et al. Inflammatory bowel disease, ankylosing spondylitis, and IgA nephropathy. *J Clin Rheumatol.* 2006;12:106-7.
4. Sato M, Kojima H, Koshikawa S. IgA nephropathy in rheumatoid arthritis. *Nephron.* 1988;48:169-70.
5. Corrado A, Quarta L, Di Palma AM, et al. IgA nephropathy in systemic lupus erythematosus. *Clin Exp Rheumatol.* 2007;25:467-9.
6. Cherubini C, Barbera G, Di Giulio SD, et al. Lymphomas and IgA nephropathy. *Nephrol Dial Transplant.* 2001;16:1722-3.
7. Hung KY, Chen WY, Yen TS, et al. Adult primary IgA nephropathy and common viral infections. *J Infect.* 1996;32:227-30.
8. Koyama A, Sharmin S, Sakurai H, et al. Staphylococcus aureus cell envelope antigen is a new candidate for the induction of IgA nephropathy. *Kidney Int.* 2004;66:121-32.
9. Barratt J, Feehally J, Smith AC. Pathogenesis of IgA nephropathy. *Semin Nephrol.* 2004;24:197-217.
10. Chen M, Schena FP, Wang SP, et al. Role of chlamydia pneumoniae (TWAR) in IgA nephropathy. *Nephron.* 1998;80:92.
11. Suzuki S, Nakatomi Y, Odani S, et al. Circulating IgA, IgG, and IgM class antibody against Haemophilus parainfluenzae antigens in patients with IgA nephropathy. *Clin Exp Immunol.* 1996;104:306-11.
12. Jackson S, Moldoveanu Z, Kirk KA, et al. IgA-containing immune complexes after challenge with food antigens in patients with IgA nephropathy. *Clin Exp Immunol.* 1992;89:315-20.
13. Nagy J, Scott H, Brandtzaeg P. Antibodies to dietary antigens in IgA nephropathy. *Clin Nephrol.* 1988;29:275-9.
14. Sato M, Kojima H, Takayama K, et al. Glomerular deposition of food antigens in IgA nephropathy. *Clin Exp Immunol.* 1988;73:295-9.
15. Coppo R, Roccatello D, Amore A, et al. Effects of a gluten-free diet in primary IgA nephropathy. *Clin Nephrol.* 1990;33:72-86.
16. Sinniah R. Occurrence of mesangial IgA and IgM deposits in a control necropsy population. *J Clin Pathol.* 1983;36:276-9.
17. Suzuki K, Honda K, Tanabe K, et al. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. *Kidney Int.* 2003;63:2286-94.
18. Floege J. Recurrent IgA nephropathy after renal transplantation. *Semin Nephrol.* 2004;24:287-91.

19. Barratt J, Smith AC, Feehally J. The pathogenic role of IgA1 O-linked glycosylation in the pathogenesis of IgA nephropathy. *Nephrology (Carlton)*. 2007;12:275-84.
20. Batra A, Smith AC, Feehally J, et al. T-cell homing receptor expression in IgA nephropathy. *Nephrol Dial Transplant*. 2007.
21. Russell MW, Mestecky J, Julian BA, et al. IgA-associated renal diseases: antibodies to environmental antigens in sera and deposition of immunoglobulins and antigens in glomeruli. *J Clin Immunol*. 1986;6:74-86.
22. Feehally J, Beattie TJ, Brenchley PE, et al. Response of circulating immune complexes to food challenge in relapsing IgA nephropathy. *Pediatr Nephrol*. 1987;1:581-6.
23. Yap HK, Sakai RS, Woo KT, et al. Detection of bovine serum albumin in the circulating IgA immune complexes of patients with IgA nephropathy. *Clin Immunol Immunopathol*. 1987;43:395-402.
24. Ferri C, Puccini R, Longombardo G, et al. Low-antigen-content diet in the treatment of patients with IgA nephropathy. *Nephrol Dial Transplant*. 1993;8:1193-8.
25. Sandberg D. Food sensitivity: the kidney and bladder. In: Brostoff J, Challacombe S, editors. *Food allergy and intolerance*. 2nd ed. London: Saunders Ltd; 2002.
26. Freed DJ. Dietary lectins and disease. In: Brostoff J, Challacombe S, editors. *Food allergy and intolerance*. 2nd ed. London: Saunders Ltd; 2002.
27. Tomana M, Novak J, Julian BA, et al. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. *J Clin Invest*. 1999;104:73-81.
28. Smith AC, Molyneux K, Feehally J, et al. O-glycosylation of serum IgA1 antibodies against mucosal and systemic antigens in IgA nephropathy. *J Am Soc Nephrol*. 2006;17:3520-8.
29. Kovacs T, Kun L, Schmelzner M, et al. Do intestinal hyperpermeability and the related food antigens play a role in the progression of IgA nephropathy? I. Study of intestinal permeability. *Am J Nephrol*. 1996;16:500-5.
30. Zadrazil J, Tichy T, Horak P, et al. IgA nephropathy associated with psoriasis vulgaris: a contribution to the entity of 'psoriatic nephropathy'. *J Nephrol*. 2006;19:382-6.
31. Chan SM, Dillon MJ, Duffy PG, et al. Nephro-urological complications of epidermolysis bullosa in paediatric patients. *Br J Dermatol*. 2007;156:143-7.
32. Zickerman AM, Allen AC, Talwar V, et al. IgA myeloma presenting as Henoch-Schonlein purpura with nephritis. *Am J Kidney Dis*. 2000;36:E19.
33. Roccatello D, Picciotto G, Coppo R, et al. Clearance of polymeric IgA aggregates in humans. *Am J Kidney Dis*. 1989;14:354-60.
34. Breifeld PP, Simmons CF Jr, Strous GJ, et al. Cell biology of the asialoglycoprotein receptor system: a model of receptor-mediated endocytosis. *Int Rev Cytol*. 1985;97:47-95.
35. Stad RK, Bogers WM, van Es LA, et al. The involvement of Kupffer cells and liver endothelial cells in the clearance of large sized soluble IgA aggregates in rats. *Adv Exp Med Biol*. 1995;5:1053-5.
36. Monteiro RC. Pathogenic role of IgA receptors in IgA nephropathy. *Contrib Nephrol*. 2007;157:64-9.
37. Montenegro V, Chiamolera M, Launay P, et al. Impaired expression of IgA Fc receptors (CD89) by blood phagocytic cells in ankylosing spondylitis. *J Rheumatol*. 2000;27:411-7.
38. Silvain C, Patry C, Launay P, et al. Altered expression of monocyte IgA Fc receptors is associated with defective endocytosis in patients with alcoholic cirrhosis. Potential role for IFN-gamma. *J Immunol*. 1995;155:1606-18.
39. Grossetete B, Viard JP, Lehuen A, et al. Impaired Fc alpha receptor expression is linked to increased immunoglobulin A levels and disease progression in HIV-1-infected patients. *AIDS*. 1995;9:229-34.
40. Hodgson HJ. Gut-liver interactions in the IgA system. *Scand J Gastroenterol Suppl*. 1985;114:39-44.
41. van de Wiel A, Schuurman HJ, Kater L. Alcoholic liver disease: an IgA-associated disorder. *Scand J Gastroenterol*. 1987;22:1025-30.
42. Bene MC, De Korwin JD, Hurault de Ligny B, et al. IgA nephropathy and alcoholic liver cirrhosis. A prospective necropsy study. *Am J Clin Pathol*. 1988;89:769-73.
43. Axelsen RA, Crawford DH, Endre ZH, et al. Renal glomerular lesions in unselected patients with cirrhosis undergoing orthotopic liver transplantation. *Pathology*. 1995;27:237-46.
44. Sakaguchi H, Dachs S, Grishman E, et al. Hepatic glomerulosclerosis. An electron microscopic study of renal biopsies in liver diseases. *Lab Invest*. 1965;14:533-45.
45. Callard P, Feldmann G, Prandi D, et al. Immune complex type glomerulonephritis in cirrhosis of the liver. *Am J Pathol*. 1975;80:329-40.
46. Nochy D, Callard P, Bellon B, et al. Association of overt glomerulonephritis and liver disease: a study of 34 patients. *Clin Nephrol*. 1976;6:422-7.
47. Berger J, Yaneva H, Nabarra B. Glomerular changes in patients with cirrhosis of the liver. *Adv Nephrol Necker Hosp*. 1977;7:3-14.
48. Sancho J, Egado J, Sanchez-Crespo M, et al. Detection of monomeric and polymeric IgA containing immune complexes in serum and kidney from patients with alcoholic liver disease. *Clin Exp Immunol*. 1982;47:327-35.
49. Kalsi J, Delacroix DL, Hodgson HJ. IgA in alcoholic cirrhosis. *Clin Exp Immunol*. 1983;52:499-504.
50. Coppo R, Arico S, Piccoli G, et al. Presence and origin of IgA1- and IgA2-containing circulating immune complexes in chronic alcoholic liver diseases with and without glomerulonephritis. *Clin Immunol Immunopathol*. 1985;35:1-8.
51. Newell GC. Cirrhotic glomerulonephritis: incidence, morphology, clinical features, and pathogenesis. *Am J Kidney Dis*. 1987;9:183-90.
52. Nakamoto Y, Iida H, Kobayashi K, et al. Hepatic glomerulonephritis. Characteristics of hepatic IgA

- glomerulonephritis as the major part. *Virchows Arch A Pathol Anat Histol.* 1981;392:45-54.
53. Pouria S, Tarelli E, Hendry B, et al. Altered IgA1 O-glycosylation is not unique to primary IgA nephropathy (IgAN): a study of IgA1 O-glycan alterations by MALDI mass spectrometry in patients with renal and hepatic diseases of heterogeneous aetiology. Paper presented at: 12th International Congress of Mucosal Immunology; 2005 June 28; Boston, MA.
  54. Babbs C, Warnes TW, Torrance HB, et al. IgA nephropathy in non-cirrhotic portal hypertension. *Gut.* 1991;32:225-6.
  55. Kutteh WH, Prince SJ, Phillips JO, et al. Properties of immunoglobulin A in serum of individuals with liver diseases and in hepatic bile. *Gastroenterology.* 1982; 82:184-93.
  56. Delacroix DL, Elkom KB, Geubel AP, et al. Changes in size, subclass, and metabolic properties of serum immunoglobulin A in liver diseases and in other diseases with high serum immunoglobulin A. *J Clin Invest.* 1983;71:358-67.
  57. van de Wiel A, Valentijn RM, Schuurman HJ, et al. Circulating IgA immune complexes and skin IgA deposits in liver disease. Relation to liver histopathology. *Dig Dis Sci.* 1988;33:679-84.
  58. Manigand G, Taillandier J, Morel-Maroger L, et al. Glomerular nephropathies in hepatic cirrhosis. *Ann Med Interne (Paris).* 1981;132:178-82.
  59. Andre C, Berthoux FC, Andre F, et al. Prevalence of IgA2 deposits in IgA nephropathies: a clue to their pathogenesis. *N Engl J Med.* 1980;303:1343-6.
  60. Lomax-Smith JD, Zabrowarny LA, Howarth GS, et al. The immunochemical characterization of mesangial IgA deposits. *Am J Pathol.* 1983;113:359-64.
  61. Singri N, Gleason B, Flamm SL, et al. Secondary IgA nephropathy presenting as nephrotic syndrome with glomerular crescentic changes and acute renal failure in a patient with autoimmune hepatitis. *J Nephrol.* 2004;17:125-9.
  62. Giron JA, Alvarez-Mon M, Menendez-Caro JL, et al. Increased spontaneous and lymphokine-conditioned IgA and IgG synthesis by B cells from alcoholic cirrhotic patients. *Hepatology.* 1992;16:664-70.
  63. Deviere J, Content J, Denys C, et al. Immunoglobulin A and interleukin 6 form a positive secretory feedback loop: a study of normal subjects and alcoholic cirrhotics. *Gastroenterology.* 1992;103:1296-301.
  64. Burgess JB, Baenziger JU, Brown WR. Abnormal surface distribution of the human asialoglycoprotein receptor in cirrhosis. *Hepatology.* 1992;15:702-6.
  65. Andre F, Andre C. Letter: cirrhotic glomerulonephritis and secretory immunoglobulin A. *Lancet.* 1976;1:197.
  66. Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med.* 2002;346:180-8.
  67. Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. *Gastroenterology.* 1999;117:297-303.
  68. Pierucci A, Fofi C, Bartoli B, et al. Antiendomysial antibodies in Berger's disease. *Am J Kidney Dis.* 2002; 39:1176-82.
  69. Rostoker G, Laurent J, Andre C, et al. High levels of IgA antigliadin antibodies in patients who have IgA mesangial glomerulonephritis but not coeliac disease. *Lancet.* 1988;1:356-7.
  70. Sategna-Guidetti C, Ferfoglia G, Bruno M, et al. Do IgA antigliadin and IgA antiendomysium antibodies show there is latent coeliac disease in primary IgA nephropathy? *Gut.* 1992;33:476-8.
  71. La Villa G, Pantaleo P, Tarquini R, et al. Multiple immune disorders in unrecognized celiac disease: a case report. *World J Gastroenterol.* 2003;9:1377-80.
  72. Woodrow G, Innes A, Boyd SM, et al. A case of IgA nephropathy with coeliac disease responding to a gluten-free diet. *Nephrol Dial Transplant.* 1993;8:1382-3.
  73. Collin P, Syrjanen J, Partanen J, et al. Celiac disease and HLA DQ in patients with IgA nephropathy. *Am J Gastroenterol.* 2002;97:2572-6.
  74. Forshaw MJ, Guirguis O, Hennigan TW. IgA nephropathy in association with Crohn's disease. *Int J Colorectal Dis.* 2005;20:463-5.
  75. Hubert D, Beaufils M, Meyrier A. Immunoglobulin A glomerular nephropathy associated with inflammatory colitis. Apropos of 2 cases. *Presse Med.* 1984;13: 1083-5.
  76. Stirati G, Antonelli M, Fofi C, et al. IgA nephropathy in cystic fibrosis. *J Nephrol.* 1999;12:30-1.
  77. Barsoum RS. Schistosomiasis and the kidney. *Semin Nephrol.* 2003;23:34-41.
  78. Beaufils H, Jouanneau C, Katlama C, et al. HIV-associated IgA nephropathy—a post-mortem study. *Nephrol Dial Transplant.* 1995;10:35-8.