REVIEW ARTICLE

MEDICAL PROGRESS

IgA Nephropathy

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IgA nephropathy is the most prevalent primary chronic glomerular disease worldwide.[1] However, the requirement of a kidney biopsy for diagnosis hinders delineation of the full consequences of this disease. Since IgA nephropathy was last reviewed in the *Journal* more than a decade ago,[2] advances in analytic approaches have provided better insight into the molecular mechanisms of this disease. These advances offer the potential for the development of noninvasive tests for diagnosis and monitoring of disease activity and an opportunity to envision disease-specific therapy.

PATHOLOGICAL FEATURES

The diagnostic hallmark of IgA nephropathy is the predominance of IgA deposits, either alone or with IgG, IgM, or both, in the glomerular mesangium (Fig. 1). The frequency of IgA without IgG or IgM varies greatly, from 0 to more than 85% across centers.[3,4] Complement C3 and properdin are almost always present. C4 or C4d,[5] mannose-binding lectin,[6] and terminal complement complex (C5b–C9)[7] are frequently detected, whereas C1q is usually absent. These findings suggest involvement of the alternative and lectin pathways of complement activation (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The mesangial IgA is exclusively of the IgA1 subclass and is deficient in galactose,[8-10] a biochemical feature of central importance in the pathogenesis of IgA nephropathy.

The features of IgA nephropathy on light microscopy may vary greatly among patients and within the individual biopsy sample. An increase in mesangial matrix and hypercellularity are common; other glomerular lesions may include focal necrosis (affecting a minority of glomeruli), segmental scarring (affecting only a portion of a glomerulus), and crescents in Bowman's space. An international panel of nephrologists and nephropathologists developed the Oxford classification of IgA nephropathy to standardize the grading of features on light microscopy.[11]

Electron microscopy usually shows electron-dense material corresponding to immune deposits on immunofluorescence microscopy. These are generally observed in mesangial and paramesangial areas but are occasionally present in subepithelial and subendothelial portions of glomerular basement membranes.[3]

Renal histologic features of Henoch–Schönlein purpura nephritis are strikingly similar to those of IgA nephropathy.[12] The diagnosis of Henoch–Schönlein purpura nephritis rests on the concurrent presence of palpable purpura due to leukocytoclastic vasculitis with IgA in the walls of dermal capillaries.

CLINICAL PRESENTATION

In North America, about 75% of children and young adults with IgA nephropathy present with macroscopic hematuria during an upper respiratory or gastrointesti-

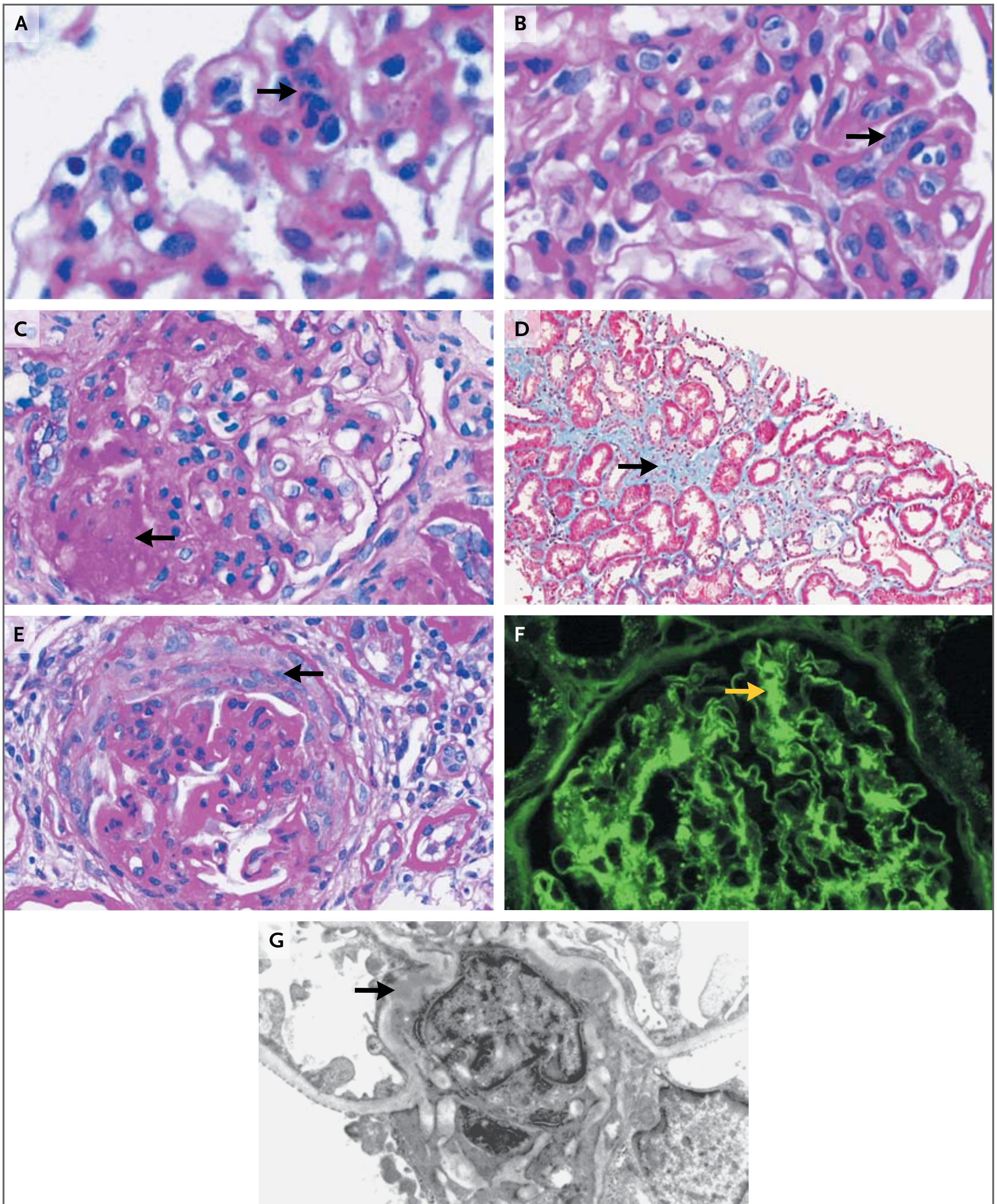


Figure 1. Pathological Characteristics of IgA Nephropathy.

Panel A (periodic acid–Schiff stain) shows mesangial hypercellularity, with four or more cells per mesangial area (arrow). Panel B (periodic acid–Schiff stain) shows segmental endocapillary proliferation with occlusion of the capillary lumen (arrow). Panel C (periodic acid–Schiff stain) shows segmental glomerulosclerosis and adhesion, with focal accumulation of hyaline and obliteration of the capillary lumen (arrow). Panel D (trichrome stain) shows tubular atrophy and interstitial fibrosis, with severe interstitial scarring and loss of tubules (arrow). Panel E (periodic acid–Schiff stain) shows a glomerular crescent; a circumferential layer of epithelial cells surrounds the glomerular tuft (arrow). Panel F (immunofluorescence stain with fluorescein-conjugated anti-IgA antibodies) shows diffuse mesangial staining for IgA (arrow). In Panel G, an electron micrograph of a glomerular capillary tuft in a specimen fixed in osmium tetroxide shows electron-dense material in the mesangial area (arrow), a finding that is consistent with the accumulation of immune complexes.

nal illness.[3,13] Evidence of acute kidney injury may be present. Older adults usually present with proteinuria, microscopic hematuria, or hypertension, alone or in combination.[3,14,15] In the United States, more than 50% of adults older than 30 years of age at diagnosis have chronic kidney disease at stage 3 to 5.[14,15] In North American cohorts, the male-to-female ratio is about 2:1 for children and adults,[3,13,14] whereas the ratio is approximately 1:1 in Asia.[16] The nephrotic syndrome is uncommon at presentation, except in patients with the pathological features of minimal-change disease on kidney biopsy.

PATHOGENESIS

IgA nephropathy appears to be a systemic disease in which the kidneys are damaged as innocent bystanders, because IgA nephropathy frequently recurs after transplantation. Conversely, IgA glomerular deposits in a kidney from a donor with subclinical IgA nephropathy were reported to clear within weeks after engraftment in a patient with a different kidney disease.[17]

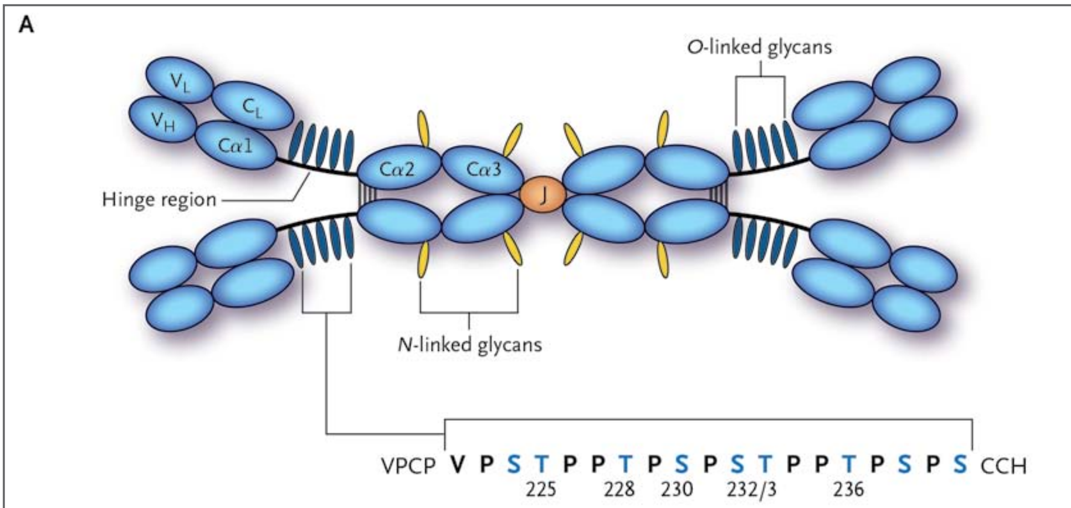
Data from clinical and basic research have led to a multihit hypothesis about the pathogenesis of IgA nephropathy (Fig. S2 in the Supplementary Appendix).[18] Of primary importance is the glycosylation pattern of IgA1. In IgA nephropathy, an increased fraction of circulatory IgA1 has a galactose deficiency in some carbohydrate side chains (*O*-glycans) that are attached to the hinge-region segment of the heavy chain (Fig. 2).[9] The *O*-glycosylated sites are not randomly distributed.[19,20]

This pattern of glycosylation mostly affects polymeric IgA1 produced in mucosal tissues, but galactose-deficient polymeric IgA1 is a minor molecular form in the circulation.[21] Synthesis of poorly galactosylated IgA1 apparently results from an imbalance in the activities of the relevant enzymes in IgA1-secreting cells in patients with IgA nephropathy.[18] Homing of these cells between the mucosal and systemic compartments may be altered, allowing the mucosal cells to reach systemic sites and secrete poorly galactosylated, mucosal-type IgA1 into the circulation.[21,22] Synthesis by IgA1-secreting cells of galactose-deficient IgA1 directed against mucosal pathogens[23] may be influenced by the innate immune system through toll-like receptors.[24] Although microbial or food-derived antigens are occasionally deposited in the mesangium, there is no evidence that these environmental antigens are directly involved in the pathogenesis of IgA nephropathy.

As a consequence of the galactose deficiency, *N*-acetylgalactosamine in truncated IgA1 hinge-region glycans is exposed. Recognition of this IgA1 hinge-region neoepitope by naturally occurring IgG or IgA1 antibodies leads to the formation of immune complexes in the circulation or perhaps in situ after glomerular deposition of galactose-deficient IgA1. On the basis of autoantibody binding to autoantigen, IgA nephropathy is an autoimmune disease.[25]

Virtually all circulating galactose-deficient IgA1 is found within immune complexes bound to a glycan-specific antibody that probably blocks access to the asialoglycoprotein receptor on hepatocytes. This galactose-deficient IgA1 thereby eludes the normal IgA1 catabolic pathway in the liver to reach the glomerular capillary network with large fenestrae overlying the mesangium. Some complexes have IgA1 as the exclusive isotype of anti-glycan antibodies,[20] perhaps explaining why IgA can be the sole immunoglobulin in the mesangium.[3] Glycan-specific IgG antibodies have an unusual structural feature that increases their affinity for binding to galactose-deficient IgA1 *O*-glycans.[25] The third amino acid in the complementarity-determining region 3 of its V_H (variable region of the heavy chain) antigen–binding portion is frequently serine rather than alanine. This alteration arises from a somatic mutation during an active immune response. The origin of anti-glycan antibodies is not fully defined. Some viruses and bacteria express *N*-acetylgalactosamine on their cell surfaces; an infection with such microbes may facilitate synthesis of anti-glycan antibodies that cross-react with galactose-deficient IgA1.

The formation of immune complexes is critical for the nephritogenicity of galactose-deficient IgA1. The addition of uncomplexed galactose-deficient IgA1 to the culture medium for human mesangial cells does not stimulate them to proliferate or become metabolically active.[20] In contrast, galactose-deficient IgA1–containing immune complexes isolated from the blood of patients with IgA nephropathy induce such activity. The biologic properties of IgA1-containing immune complexes may be modulated by various components, such



	225	228	230	232/3	236
O-linked glycan absent	<1	0	~10	0/>50	>50
N-acetylgalactosamine ± sialic acid	<1	1	~33	<1/<25	25
Galactose–*N*-acetylgalactosamine ± sialic acid	99	99	50	99/25	<25

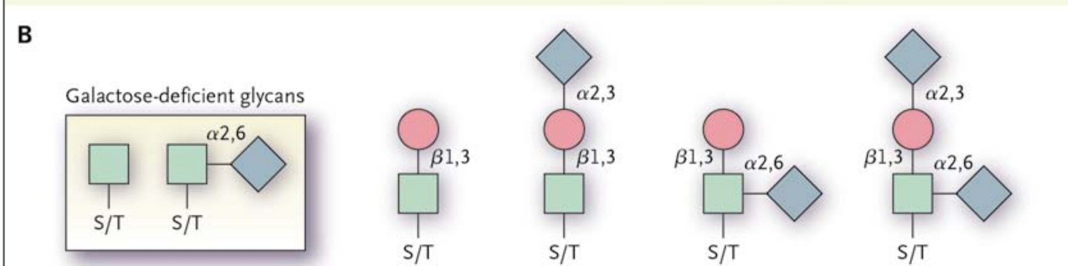


Figure 2. Structure of Human IgA1.

IgA exists in several forms in the circulation: monomers, dimers, trimers, larger polymers, and secretory IgA. The IgA1 dimer depicted in Panel A is composed of two monomers linked by a joining chain. Each heavy chain has two *N*-linked (attached to a nitrogen molecule) glycan (carbohydrate) side chains and a hinge region between the first and second constant-region domains (Cα1 and Cα2, respectively). This hinge region is longer in IgA1 than in IgA2, and the longer IgA1 segment is rich in proline, threonine, and serine amino acid residues. Within the IgA1 hinge region, three to six glycans are attached to an oxygen molecule of a serine or threonine residue (*O*-linked). The dimer depicted has five *O*-linked glycans at each of the four hinge regions. The numbered amino acids indicate the six most common sites of attachment of *O*-glycans. The composition and number of the *O*-glycans differ substantially among the IgA1 molecules in a person, constituting microheterogeneity for the structure of the hinge region. The numbers below the position indicators show the frequency (percentage) of the compositional variations of an IgA1 myeloma protein that mimics the structure of poorly glycosylated IgA1 in patients with IgA nephropathy. As compared with healthy persons, patients with IgA nephropathy have more circulating IgA1 molecules with *O*-linked hinge-region glycans that do not include galactose (galactose-deficient IgA1). Panel B shows *O*-glycan variants of IgA1. Synthesis of the *O*-linked glycans proceeds in a stepwise manner, starting with attachment of *N*-acetylgalactosamine to some of the hinge-region serine or threonine amino acids. The glycan is normally extended by attachment of galactose. Sialic acid can be attached to *N*-acetylgalactosamine, galactose, or both. If sialic acid is attached to *N*-acetylgalactosamine before attachment of galactose, subsequent attachment of galactose is not possible. An imbalance in the activities or expression of specific glycosyltransferases in patients with IgA nephropathy accounts for the increased production of galactose-deficient *O*-linked glycans in the IgA1 hinge region with increased sialic acid residues. Cα denotes constant-region domain on alpha heavy chain, C_L constant-region domain on light chain, V_H variable region on heavy chain, and V_L variable region on light chain. Squares indicate *N*-acetylgalactosamine, circles galactose, and diamonds sialic acid.

as C3b or the soluble form of CD89 — the IgA receptor on macrophages and neutrophils.[26]

In the mesangium, complexed galactose-deficient IgA1 may attach to fibronectin or type IV collagen in the extracellular matrix[27] or the CD71 transferrin receptor or integrins on mesangial cells.[28,29] Activated mesangial cells secrete components of extracellular matrix,[20] enhance the expression of inducible nitric oxide synthase,[30] and release various mediators of renal injury that are not unique to IgA nephropathy: angiotensin II,[31] aldosterone,[31] proinflammatory and profibrotic cytokines,[20,31] and growth factors.[30] The consequences of such events, if extended over prolonged periods, would be mesangial hypercellularity, apoptosis, oxidative stress, activation of complement, expansion of mesangial matrix, injury to podocytes and proximal tubule epithelial cells, increased glomerular permeability, and scarring in the glomerular and interstitial compartments (Fig. 3).[20,31,32] Such renal injury will lead to hypertension, proteinuria, hematuria, and reduced renal clearance.[20,31]

Patients with Henoch–Schönlein purpura nephritis and those with IgA nephropathy have many of the same laboratory abnormalities (Table 1) and pathological features of renal-biopsy specimens. These similarities have led to proposals that the two entities represent opposite ends of the clinical spectrum characterizing a single disease process.[12] It is unknown whether changes in the clinical expression of disease reflect fluctuating serum levels of galactose-deficient IgA1, variations in the composition or precise location of IgA1 hinge-region glycoforms, different binding affinities of anti-glycan antibodies, other factors influencing the formation of galactose-deficient IgA1–containing immune complexes, or variation in the extent of complement- or cytokine-mediated damage in glomeruli.

GENETIC FACTORS

Genetic factors undoubtedly influence the pathogenesis of IgA nephropathy. The serum level of galactose-deficient IgA1 is a heritable trait in diverse racial or ethnic groups.[34] About 75% of patients with IgA nephropathy have a serum galactose-deficient IgA1 level above the 90th percentile for healthy controls[35]; moreover, about 30 to 40% of first-degree relatives have similarly high levels.[36] This pattern is not explained by differences in serum IgA levels.[37] However, most relatives with elevated serum galactose-deficient IgA1 levels never have clinical manifestations of renal disease.[36,38] Thus, other factors must be necessary for the expression of disease.

Genomewide association studies have identified common susceptibility loci in the absence of a priori mechanistic hypotheses.[39] A study involving patients with IgA nephropathy who were of white European ancestry showed an association with the major histocompatibility complex (MHC); the strongest signal was in the DQ locus.[40] A study involving Han Chinese and Europeans identified five susceptibility loci: three on chromosome 6p21 in the MHC, one on chromosome 1q32 in the cluster of genes encoding complement factor H (*CFH*), and one on chromosome 22q12.[41] The 6p21 loci include genes encoding components of the class I and class II MHC response. Products of *CFH* and the cluster of nearby *CFH*-related genes (*CFHR*) modulate activation of the alternative complement pathway, with the combined deletion of *CFHR1* and *CFHR3* conferring a reduced risk of IgA nephropathy. A single deletion in both *CFHR1* and *CFHR3* confers a 30% reduction in the risk of IgA nephropathy. Chromosome 22q12 encodes oncostatin M and leukemia inhibitory factor, cytokines that are implicated in mucosal immunity and inflammation. A meta-analysis with risk-score modeling in 12 cohorts of Asian, European, and African ancestry confirmed all five loci.[42] The IgA nephropathy risk alleles at these five loci have opposing effects on other immune-mediated disorders, including multiple sclerosis, inflammatory bowel disease, and type 1 diabetes mellitus. An independent genomewide association study involving Han Chinese replicated four of the five loci.[43] The 1q32 signal was not detected, probably because this protective allele is rare in Asians.

In a study using a genetic risk score based on the five loci, disease risk varied by a factor of 10 between persons with no protective alleles and those with five or more protective alleles.[44] The frequency of risk alleles paralleled the known ethnic variation in the prevalence of IgA nephropathy: higher in Chinese than Europeans and lowest in blacks.

Thus, common genetic variants influence the risk of IgA nephropathy across ethnically diverse populations and implicate adaptive immunity in the pathogenesis. These loci contain many genes,

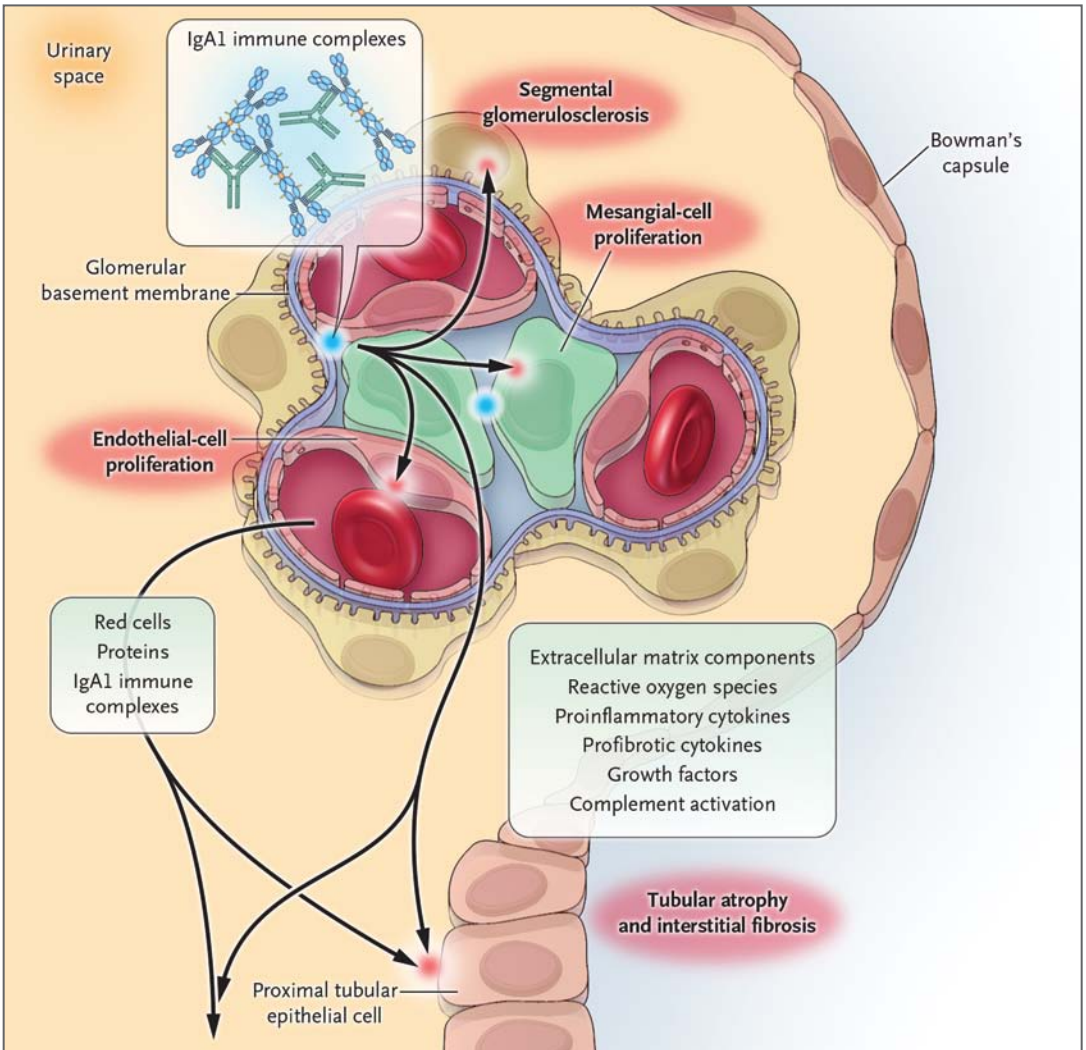


Figure 3. Induction of Glomerular and Tubulointerstitial Injury by Pathogenic IgA1-Containing Immune Complexes.

Galactose-deficient IgA1 may accumulate in the glomerular mesangium by either of two routes: galactose-deficient IgA1 is bound by glycan-specific antibodies in circulating immune complexes that pass through large fenestrae in the glomerular capillary network, or uncomplexed galactose-deficient IgA1 passes through glomerular capillary fenestrae to be "planted" in the mesangium and subsequently targeted by circulating anti-glycan antibodies of the IgG or IgA1 isotype. Attachment of galactose-deficient IgA1 in immune complexes to mesangial cells stimulates the cells to proliferate; secrete various proinflammatory and profibrotic cytokines, components of the extracellular matrix, and growth factors; activate the alternative and lectin complement pathways; and release reactive oxygen species. These mediators activate neighboring mesangial cells and also enter the urinary space, damaging podocytes and proximal tubular epithelial cells (PTECs). Injury to podocytes compromises the filtration-barrier function of the glomerular basement membrane, allowing circulating proteins and IgA1-containing immune complexes to enter the urinary space, and leads to sclerosis of the glomerular tuft. Injury to PTECs causes tubular atrophy and interstitial fibrosis, which is the component of the MEST (mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis or adhesion, and tubular atrophy and interstitial fibrosis) score that is most strongly associated with renal-function outcome.

and fine-mapping studies are needed to uncover the causal genetic variants underlying the signals found in the genomewide association studies. Variations in disease prevalence among populations may also result from the modulation of genetically determined influences by environmental factors such as hygiene or infection.

About 5% of patients with IgA nephropathy

Table 1. Comparative Features of IgA Nephropathy and Henoch–Schönlein Purpura Nephritis (HSPN).*

Feature	IgA Nephropathy	HSPN
Presentation		
Incidence per 1 million	5–50 among children, 10–40 among adults	15–70 among children, 4–13 among adults
Macroscopic hematuria	More common, coincident with mucosal infection	Less common, sometimes after resolution of the Henoch–Schönlein purpura syndrome
Renal histologic findings		
Immunofluorescence	More staining for lambda than kappa light chains	Equal staining for lambda and kappa light chains
Light microscopy	Rare glomerular crescents	More crescents or glomerular-tuft necrosis
Electron microscopy	Rare glomerular capillary-loop deposits	More subendothelial immune deposits
Extrarenal involvement		
IgA in dermal capillaries	Rare (clinically normal skin)	Common in purpuric lesions
Gastrointestinal vasculitis	Rare	Common
Arthralgia	Occasional	Frequent
Pathogenesis		
Serum IgA1 CICs	Contain galactose-deficient IgA1	Contain galactose-deficient IgA1; complexes are larger
Serum galactose-deficient IgA1	High level	High level
Serum anti-glycan antibodies	Increased level	Increased level
Complement activation	Alternative and lectin pathways	Alternative and lectin pathways
Genetic features		
Identical twins, case report	One child with clinical phenotype of IgA nephropathy	Second child with clinical phenotype of HSPN
Familial disease	5% of family members with IgA nephropathy or hematuria; IgA nephropathy and HSPN may occur in same family	Familial disease less common; HSPN and IgA nephropathy may occur in same family
Serum galactose-deficient IgA1	Heritable trait	Heritable trait
Genomewide association studies	Several loci associated with disease	No studies
Familial linkage studies	Several loci linked with disease	No studies
Treatment of native-kidney disease	KDIGO guidelines†	Same, except that for patients with crescents and the nephrotic syndrome, treatment can be the same as that for crescentic IgA nephropathy
Outcome		
Clinical remission	Common	Very common
ESRD	Develops in 20–40% of patients by 20 yr after biopsy	Develops in 1 to 3% of children, with higher risk if clinical onset in adulthood
Transplantation	Macroscopic hematuria rare; histologic recurrence in 50–60% of patients by 5 yr	Extrarenal manifestations rare; recurs as IgA nephropathy (frequency not well defined)

* CIC denotes circulating immune complexes, eGFR estimated glomerular filtration rate, and ESRD end-stage renal disease.

† The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines address specific glomerular diseases.[33]

have a relative with biopsy-confirmed IgA nephropathy, microscopic hematuria, or proteinuria. The mode of inheritance is usually autosomal dominant with incomplete penetrance, suggesting a major gene with a large effect.[34] Linkage studies of multiplex families have linked several chromosomal loci, distinct from those identified in genomewide association studies, in these families.[34] The mutations may be identified by means of genome-sequencing approaches.

BIOMARKERS

Although the serum level of galactose-deficient IgA1 is frequently elevated in patients with IgA nephropathy,[35] the sensitivity and specificity of this laboratory finding are insufficient for the test to replace kidney biopsy as the diagnostic standard. The serum level of glycan-specific IgG antibodies is correlated with the level of urinary protein excretion[25] and the risk of progression to end-stage renal disease (ESRD) or death.[4] This biomarker may prove useful for monitoring disease progression or the response to therapy.

Increased urinary excretion of epidermal growth factor,[45] podocytes,[46] low-molecular-mass proteins,[47] and mannose-binding lectin[48]; increased plasma levels of activated complement C3,[49] advanced oxidative protein products,[50] and fibroblast growth factor 23[51]; an increased serum level of uric acid,[52,53] and decreased serum levels of CD89–IgA complexes[26] are associated with severe histologic changes, severe proteinuria, or a poor clinical outcome. However, these findings may not be unique to IgA nephropathy.

Urinary proteomic analysis can identify patterns of excreted peptides that are unique to diseases, without a priori assumptions about pathogenesis. Analysis of urinary samples by means of capillary electrophoresis coupled with mass spectrometry has differentiated patients with IgA nephropathy from healthy controls and patients with minimal-change disease or IgA–immune-complex nephritis due to chronic hepatitis C infection, even in association with nonpathologic proteinuria.[54,55] Furthermore, the urinary proteomic profile predicts the response to treatment with an angiotensin-converting–enzyme (ACE) inhibitor.[56] Additional studies are needed to determine the potential and cost-effectiveness of urinary proteomic analysis in establishing the diagnosis of IgA nephropathy and making decisions about treatment.

DEMOGRAPHIC AND EPIDEMIOLOGIC CHARACTERISTICS

The prevalence of IgA nephropathy relative to other glomerular diseases is generally inferred from the proportion of cases in biopsy series, but the true prevalence of IgA nephropathy is unknown because diagnosis requires kidney biopsy. The prevalence of clinically silent IgA nephropathy may be surprisingly high; in a Japanese study, 16% of donor kidneys had glomerular IgA deposits and nearly 2% exhibited mesangioproliferative changes with C3 deposits characteristic of IgA nephropathy.[57]

Although data from biopsy series regarding the prevalence of IgA nephropathy in the total population should be interpreted cautiously, several observations are noteworthy. In the United States, IgA nephropathy is the most frequently diagnosed primary glomerular disease in adults and the leading primary glomerular disease causing ESRD in young white adults.[58] Limited data from population-based studies in the United States indicate that the annual incidence of biopsy-documented IgA nephropathy is about 1 case per 100,000 persons,[14,59] representing a lifetime risk of about 1 in 1400. In New Mexico, from 2000 to 2005 the incidence was highest among Native Americans, intermediate among Hispanics, and lowest among non-Hispanic whites.[59] The annual incidence among children in the United States is about 0.5 cases per 100,000[14]; however, in Japan, the incidence is 10 times as high.[60]

CLINICAL OUTCOMES

The clinical course of IgA nephropathy is variable. Estimates of renal survival are often biased because many patients have stage 3 or 4 chronic kidney disease at biopsy or the data are censored for death before patients reach the primary outcome measure of ESRD or percent decrease in the estimated glomerular filtration rate (GFR).[15,61-63]

The likelihood of dialysis or death was recently estimated with the use of three risk factors that are documented at biopsy: urinary protein excretion of more than 1 g per day, hypertension (>140/90 mm Hg), and severe histologic lesions on the basis of glomerular, vascular, tubular, and interstitial features.[64] The 20-year predicted survival without the need for dialysis was 96% among patients with no risk factors versus 36% among those with three factors. The 10-year renal survival rate is about 90% among adults[15,61,65] and children[13,66] with normal renal function at diagnosis.

Some patients have a prolonged clinical remission (normal serum creatinine concentration, normal findings on urinalysis, normal quantitative urinary protein excretion, and normal blood pressure), but repeat biopsy usually shows glomerular IgA.[67] Most patients with acute kidney injury associated with macroscopic hematuria have spontaneous recovery of renal function within several weeks. In the small subgroup of patients with histologic features of minimal-change disease, proteinuria resolves after glucocorticoid therapy.

CLINICAL PROGNOSTIC FEATURES

An impaired GFR, sustained hypertension, and substantial proteinuria independently predict a poor clinical course.[15,68] Although proteinuria at diagnosis has been the focus in many studies, urinary protein excretion calculated as the average of several measurements during serial 6-month intervals after biopsy has better prognostic power.[69,70] Notably, patients with time-averaged urinary protein excretion of more than 1.0 g per day have a risk of ESRD that is 46 times the risk among patients with values of less than 0.5 g per day.[71] Furthermore, the renal outcome is better with a value for time-averaged urinary protein excretion that is less than 0.5 g per day than with a value of 0.5 to 1.0 g per day. For reasons that are not yet clear, the prognosis for patients with IgA nephropathy is worse than that for patients with other glomerular diseases with a similar magnitude of proteinuria.[72]

PATHOLOGICAL PROGNOSTIC MARKERS

The Oxford classification renewed interest in the prognostic value of the histologic features of the diagnostic biopsy and the use of renal histologic analysis for risk stratification in treatment trials.[11] Entry criteria for the Oxford study excluded patients with an estimated GFR of less than 30 ml per minute per 1.73 m^2 of body-surface area (thereby excluding patients with stage 4 or 5 chronic kidney disease), and the outcome measure was progression to ESRD or a decrease in the estimated GFR of more than 50% from the rate at study entry.[11] Three histologic features showed an independent value for predicting the outcome of renal function, even after clinical indicators at the time of biopsy and during follow-up observation were taken into account: mesangial hypercellularity, segmental glomerulosclerosis or adhesion, and tubular atrophy and interstitial fibrosis (Fig. 1).[11] A fourth histologic feature, endocapillary proliferation, showed an interaction with glucocorticoid or immunosuppressive therapy that suggested benefit from treatment. Subgroup analysis of the Oxford cohort validated the classification in children.[73] A recent review of 13 Oxford replication studies confirmed the independent prognostic value of tubular atrophy and interstitial fibrosis in 10 studies, mesangial hypercellularity in 4 studies, and segmental sclerosis in 4 studies.[74] Other histologic features that may be associated with a poor clinical outcome include glomerular deposits of mannose-binding lectin,[6] C4d,[5] and IgG[75,76]; thrombotic microangiopathy[77]; and an increased glomerular diameter.[78]

TREATMENT

Despite a better understanding of pathogenic mechanisms, there is no disease-targeted treatment for IgA nephropathy. Furthermore, relatively few randomized, controlled clinical trials have been conducted. Two expert panels have published approaches to the treatment of glomerular diseases. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines focus on specific diseases,[33] whereas recommendations in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative address broader categories of kidney disease (www.kidney.org/professionals/kdoqi/guidelines).

Both panels emphasized control of proteinuria and blood pressure by suppression of angiotensin II with an ACE inhibitor or angiotensin II–receptor blocker (ARB) (Table 2, and Table S1 in the Supplementary Appendix). The target systolic blood pressure is less than 130 mm Hg with urinary protein excretion of less than 1 g per day but less than 125 mm Hg when the initial urinary protein excretion is more than 1 g per day. For urinary protein excretion that is persistently more than 1 g per day despite 3 to 6 months of proper supportive care (ACE inhibitor, ARB, or both and blood-pressure control) and an estimated GFR of more than 50 ml per minute per 1.73 m^2, the KDIGO guidelines suggest adding fish oil, a 6-month course of glucocorticoids, or both. Intensive immunosuppression (glucocorticoids with cyclophosphamide or azathioprine) is reserved for patients with crescents in more than half the glomeruli and a rapid decline in renal function. Patients with fewer crescents and stable renal function should be treated with an ACE inhibitor or ARB. The KDIGO guidelines do not support the use of mycophenolate mofetil or antiplatelet drugs. Tonsillectomy has been recommended by some centers, particularly in Japan, but this approach was not included in the KDIGO guidelines because of the lack of data from randomized, controlled trials.

Patients presenting with mild disease (normal blood pressure, normal estimated GFR, and a urinary protein-to-creatinine ratio consistently <0.20) do not require treatment. Assessments of renal function and monitoring for proteinuria and hematuria should be performed on a regular schedule, perhaps annually, because progressive disease eventually develops in some patients.

Although an estimated GFR that is persistently less than 30 ml per minute per 1.73 m² poses a substantial risk of progression to ESRD, supportive therapy with cautious use of an ACE inhibitor or ARB should be continued to slow the process. For patients requiring renal-replacement therapy, transplantation is the treatment of choice. Although glomerular IgA deposits frequently recur, occasionally within weeks after transplantation,[79,80] some of these patients never have clinical disease. Recurrence in the allograft is more common in children than in adults[79] and is associated with crescentic disease and a rapid decline in renal function before engraftment.[81] In most transplantation centers, recurrent disease is not more frequent in kidneys from living related donors than in those from deceased donors, although the possibility of familial disease or covert IgA nephropathy mandates careful evaluation before nephrectomy. Whether the circulating level of galactose-deficient IgA1 or anti-glycan antibodies influences the post-transplantation course remains unknown. The KDIGO guidelines did not address the treatment of recurrent IgA nephropathy. Suppression of angiotensin II can reduce proteinuria,[82] and implementation of the other guidelines for treatment of native-kidney IgA nephropathy seems reasonable. IgA nephropathy recurs in at least 50% of patients, leading to allograft loss in 5%.[3] Induction immunosuppressive therapy with antithymocyte globulin[83] and the use of prednisone in the maintenance immunosuppressive regmen[84] may reduce the frequency of recurrent IgA nephropathy.

On the basis of the evolving understanding of the mechanisms underlying IgA nephropathy, new approaches to treatment may be forthcoming.[20,21] Potential therapies are described in Table S2 in the Supplementary Appendix.

Table 2. Treatment of IgA Nephropathy, According to KDIGO Guidelines.*

Recommendation
ACE inhibitor or ARB for urinary protein excretion of >1 g/day; increase dose depending on blood pressure
Suggestions
Proteinuria
ACE inhibitor or ARB if urinary protein excretion of 0.5 to 1.0 g/day; increase dose to the extent that adverse events are acceptable to achieve urinary protein excretion of <1 g/day
6-mo glucocorticoid therapy if urinary protein excretion of >1 g/day continues after 3 to 6 mo of proper supportive therapy (ACE inhibitor or ARB and blood-pressure control) and an eGFR of >50 ml/min/1.73 m²
Fish oil if urinary protein excretion of >1 g/day continues after 3 to 6 mo of proper supportive therapy
Blood pressure: target is <130/80 mm Hg if urinary protein excretion is <1 g/day but <125/75 mm Hg if initial protein excretion is >1 g/day
Rapidly declining eGFR
Glucocorticoids and cyclophosphamide for crescentic IgA nephropathy (>50% glomeruli with crescents) with rapid deterioration in eGFR
Supportive care if kidney biopsy shows acute tubular injury and intratubular erythrocyte casts
Treatments without proven benefit
Glucocorticoids with cyclophosphamide or azathioprine, unless crescentic IgA nephropathy with rapid deterioration in eGFR
Immunosuppressive therapy with an eGFR of <30 ml/min/1.73 m², unless crescentic IgA nephropathy with rapid deterioration in eGFR
Mycophenolate mofetil
Antiplatelet agents
Tonsillectomy

* The approach classified as a recommendation is based on the highest-quality evidence; approaches classified as suggestions have less support, and different choices may be appropriate for different patients. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

CONCLUSIONS

IgA nephropathy is a common glomerular disease and an important cause of kidney failure. Because of the critical interaction between an intrinsic antigen (galactose-deficient IgA1) and circulating anti-glycan antibodies, IgA nephropathy can be considered an autoimmune disease. Advances in understanding the molecular basis of the pathogenesis may lead to earlier diagnosis, better monitoring of the clinical course or response to treatment, and, ultimately, targeted therapy.

Drs. Wyatt and Julian report submitting a patent application related to diagnosing and treating IgA nephropathy, their shares of which are assigned to their respective institutions. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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