Review Article

Medical Progress

IgA Nephropathy

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IgA nephropathy is a relatively newly recognized disease, first described by Berger and Hinglais in 1968.[1] It is now generally known to be the most common form of primary glomerulonephritis throughout the world.[2-4]

Primary IgA nephropathy is an immune-complex–mediated glomerulonephritis defined immunohistologically by the presence of glomerular IgA deposits accompanied by a variety of histopathologic lesions.[5,6] Although primary IgA nephropathy receives the most attention, many other diseases are also associated with glomerular IgA deposits (Table 1). The most common of these is Schönlein–Henoch purpura. This condition may indeed be indistinguishable from primary IgA nephropathy and may represent a systemic form of the disease process.[6,7]

Although primary IgA nephropathy was considered a benign condition for many years, it is now clear that a large number of cases eventually progress to renal failure.[8-11] Indeed, IgA nephropathy is the main cause of end-stage renal disease in patients with primary glomerular disease who require renal-replacement therapy.[10,12,13]

DEMOGRAPHIC FEATURES

Primary IgA nephropathy occurs at any age, most commonly with clinical onset in the second and third decades of life.[8-11] There is a male:female ratio ranging from less than 2:1 in Japan to as high as 6:1 in northern Europe and the United States. In addition, whites and Asians are more prone to IgA nephropathy than are blacks from the United States and from South Africa.[14,15] The lower prevalence in blacks is unexplained. The frequency seems to be low in Polynesians from New Zealand[16] and high in Native Americans from New Mexico[17] and in Australian aborigines.[18]

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INCIDENCE

Few epidemiologic studies have examined the incidence of primary IgA nephropathy in various populations around the world. The reported incidence in three regions in France[19-21] and one each in the Netherlands,[22] Germany,[23] and Italy[24] varied from 15 to 40 new cases per million population per year. In contrast, one study in the United States reported an increase from 5 cases (from 1975 to 1979) to 12 cases (from 1990 to 1994) per million population per year (in eastern and central Kentucky).[25]

In most reports from cohort studies in referral-based centers, prevalence rates are expressed as a percentage of cases of primary glomerulonephritis or as a percentage of a total series of renal biopsies.[2,3,6,10] Prevalence appears highest in Asia (Singapore, Japan, and Hong Kong), Australia, Finland, and southern Europe (20 to 40 percent). In the United Kingdom, Canada, and the United States, prevalence rates are much lower. In the United States, for example, prevalence rates of IgA nephropathy are only 2 to 10 percent, with the exception of Native Americans from New Mexico, in whom the prevalence rate is 38 percent.[26]

Although genetic differences may in part explain the regional variations in disease prevalence, the renal-biopsy practices in a given locale may contribute. For example, IgA nephropathy will be detected more frequently if patients with minor urinary abnormalities undergo biopsy. In Japan, routine screening for urinary abnormalities is performed in all school-aged children.[27] In addition, symptom-free persons with microscopic hematuria are more likely to undergo renal biopsy, leading to increased diagnosis of IgA nephropathy.

Conversely, in the United Kingdom, Canada, and the United States, it is common practice not to recommend renal biopsy for patients presenting with isolated hematuria or mild proteinuria; examination of renal tissue is reserved for those in whom increasing proteinuria or worsening renal function develops. Such reluctance to perform biopsies inevitably reduces the number of cases of IgA nephropathy reported in the general populations of these countries.

CAUSES AND GENETIC FACTORS

The cause of primary IgA nephropathy is unknown. No consistent infectious or environmental agents have been identified that can be considered responsible for the IgA-antibody response.

Isolated cases of IgA nephropathy are common, and

TABLE 1. DISEASES ASSOCIATED WITH GLOMERULAR DEPOSITION OF IgA.

Primary causes
IgA nephropathy
Schönlein–Henoch purpura
Secondary causes
Diseases of the liver: alcoholic, primary biliary, or cryptogenic cirrhosis; hepatitis B (where endemic); chronic schistosomiasis
Diseases of the intestine: celiac disease; chronic ulcerative colitis; Crohn's disease
Diseases of the skin: dermatitis herpetiformis; psoriasis
Diseases of the bronchus or lung: sarcoidosis, idiopathic pulmonary hemosiderosis; cystic fibrosis; bronchiolitis obliterans
Neoplasia: carcinoma of the lung, larynx, and pancreas; mycosis fungoides
Infection: human immunodeficiency virus; leprosy
Other systemic or immunologic disorders: systemic lupus erythematosus; rheumatoid arthritis; cryoimmunoglobulinemia; psoriatic arthritis; ankylosing spondylitis; Sjögren's syndrome; Behçet's syndrome; Reiter's syndrome; familial immune thrombocytopenia; autoantibody-mediated (monoclonal IgA–mediated) Goodpasture's syndrome
Diseases coincident with IgA nephropathy: antineutrophilic cytoplasmic antibody–associated vasculitis; diabetic nephropathy; membranous nephropathy; Wegener's granulomatosis

the disease is not considered to be familial. There have, however, been suggestions that there may be immunogenetic factors that predispose some persons to IgA nephropathy, and familial clustering has been reported.[28] For example, some studies have established a link between the occurrence of IgA nephropathy and disease progression and certain HLA antigens, whereas others have not.[6,28,29]

No consistent genetic abnormalities have been identified that predict the development or progression of IgA nephropathy. Genetic analysis of familial IgA nephropathy is the most promising approach to the identification of IgA disease or IgA susceptibility genes.[28,29] For example, in a recent multicenter study, 30 families with IgA nephropathy (24 from Italy and 6 from the United States) were analyzed with the use of whole-genome scanning.[30] The analysis showed a close association, in 60 percent of kindreds linked, with the trait 6q22–23, a 6.5-cM region bounded by the D6S1702 and D6S262 polymorphic markers on chromosome 6, with a maximal likelihood-of-odds score of 5.6 at D6S1040. Such findings support the suggestion that familial IgA nephropathy is a complex disease initiated by one or more genes in combination with environmental conditions.

PATHOGENESIS

Clinical observations of patients who have undergone renal transplantation have provided strong support for the notion that IgA nephropathy is a systemic disease. Histologic evidence of recurrent IgA nephropathy is observed in over 35 percent of patients who receive renal allografts as treatment for end-stage renal disease due to IgA nephropathy.[31] When a kidney obtained from a donor with asymptomatic IgA nephropathy is transplanted into a recipient with end-stage renal disease due to a disease other than IgA nephropathy, the deposits in the donor kidney rapidly disappear.[32] Some but not all patients with IgA nephropathy have elevated serum IgA levels or elevated levels of IgA in a complex with fibronectin.[33,34] However, no antigen has been consistently detected in circulating immune complexes containing IgA or in biopsy specimens from the kidneys of patients with IgA nephropathy.[35]

Humans produce two isotype subclasses of IgA — IgA1 and IgA2. Plasma cells associated with the gastrointestinal tract and respiratory tract produce both IgA1 and IgA2, whereas plasma cells in the bone marrow, lymph nodes, and spleen produce predominantly IgA1.[36] The glomerular deposits of IgA in IgA nephropathy appear to be exclusively of the IgA1 subclass.[37] Despite intensive investigation, the mechanism underlying glomerular IgA deposition in IgA nephropathy has not been defined. Potential mechanisms are outlined in Figure 1.

The onset of IgA nephropathy may be associated with infections in the upper respiratory tract. It has therefore been proposed that IgA nephropathy results from hyperactivity of the mucosal immune system.[38] However, current evidence suggests that mucosal immunity, which is in part directed by IgA, is decreased in patients with IgA nephropathy.[39] Mucosal T cells isolated from patients with IgA nephropathy show reduced expression of the genes encoding Vγ3 and Vδ3, as compared with normal controls.[40] These variable regions are among those most commonly expressed by mucosal γ/δ T cells in normal persons. Potential mechanisms whereby this mucosal T-cell defect, which produces no clinically apparent symptoms, promotes

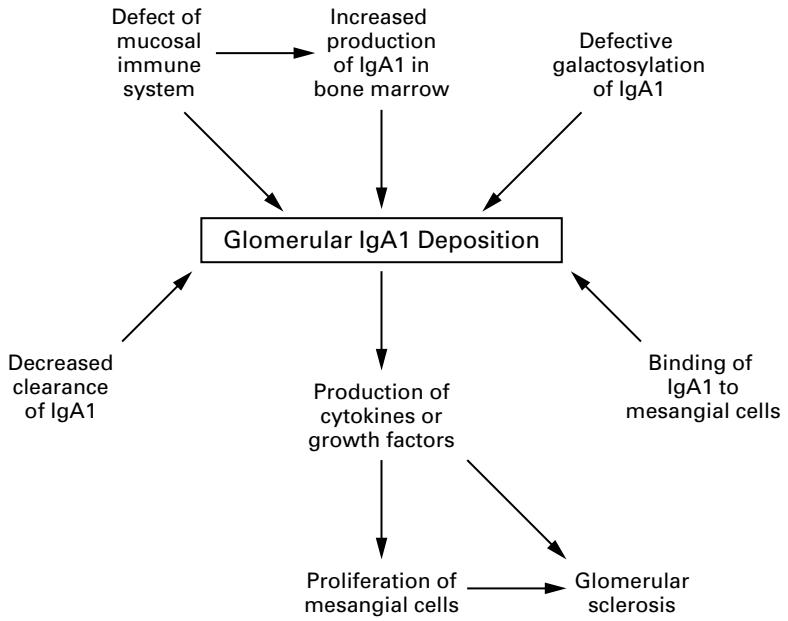

Figure 1. Potential Mechanisms Underlying Glomerular Deposition of IgA and Progression of Renal Disease in IgA Nephropathy.

Decreased IgA response to mucosal antigens may promote increased production of polymeric IgA1 by the bone marrow, leading to increased serum levels of IgA1. Defective galactosylation of IgA1, perhaps due to decreased β1,3-galactosyl transferase activity, may decrease hepatic clearance of IgA1 and promote binding of IgA1 complexes to glomerular mesangial cells. IgA1 deposits in the kidney trigger the production of a variety of cytokines and growth factors by renal cells and by circulating inflammatory cells, leading to the characteristic histopathological features of mesangial-cell proliferation and extracellular-matrix deposition.

glomerular deposition of IgA in patients with IgA nephropathy await definition. In some patients with IgA nephropathy, production of IgA1 in the bone marrow is increased and may be responsible for the observed increase in serum IgA1 levels.[33,41,42]

Increased production of IgA is not sufficient to produce IgA nephropathy. For example, patients with IgA-secreting myelomas or patients infected with the human immunodeficiency virus often have markedly elevated serum IgA levels yet rarely have IgA nephropathy.[43,44] Therefore, recent studies have focused on potential abnormalities of the IgA molecule as a factor in the pathogenesis of IgA nephropathy.[45-47] IgA1, like other immunoglobulins, is heavily glycosylated. Sugars are attached to proteins through two types of linkages. N-linked sugars are complex structures linked to asparagine residues and are common on circulating proteins; O-linked sugars consist of simple sugar chains connected to serine or threonine residues. O-linked sugars are widespread on cell-surface proteins but are uncommon on circulating proteins. A unique feature of IgA1 is the presence of multiple O-glycosylation sites within the hinge region; IgA2 and other immunoglobulins do not possess these sites (Fig. 2A). These O-linked sugars consist of *N*-acetyl galactosamine O-linked to serine or threonine. Galactose is attached to *N*-acetyl galactosamine through a β1,3 link, and sialic acid is added to galactose or *N*-acetyl galactosamine through α2,3 links and α2,6 links, respectively (Fig. 2B).

Recent studies have shown that there is a defect in galactosylation of IgA1, both in serum and in IgA1 eluted from nephrectomy specimens obtained from patients with IgA nephropathy.[45-47] IgA1 from patients with IgA nephropathy injected into mice survives longer in the circulation than IgA1 isolated from healthy controls.[48] Incubation of IgA1 obtained from normal patients with β-galactosidase increases its binding to human mesangial cells.[48] This observation suggests that mesangial cells possess a receptor for IgA1, which may show specificity for undergalactosylated IgA1.[48] However, the nature of this putative IgA1 receptor on mesangial cells awaits characterization.[49] Recent studies have found that leukocyte β1,3-galac-

tosyl transferase activity is decreased in patients with IgA nephropathy.[50] Decreased activity of this enzyme, which promotes the addition of galactose to *N*-acetyl galactosamine residues on O-linked glycans, may be responsible for the deficient galactosylation of IgA1 in patients with IgA nephropathy. The basis for decreased β1,3-galactosyl transferase activity in IgA nephropathy is not known.

Hepatic clearance of IgA1 is decreased in patients with IgA nephropathy.[51] The asialoglycoprotein receptor in the liver, which recognizes terminal galactose residues,[52] is the principal site of IgA catabolism. However, the role of this receptor in the clearance of undergalactosylated IgA1 in IgA nephropathy has not been defined.[39]

Once deposited in the kidney, IgA1-containing immune complexes are associated with glomerular inflammation. A number of cytokines and growth factors have been linked to the development and progression of renal injury in patients with IgA nephropathy. For example, a serum factor, probably a lectin, present in patients with IgA nephropathy, induces expression of interleukin-6 by peripheral mononuclear cells.[53] Lectins can also promote interleukin-6 secretion by mesangial cells.[54] Interleukin-6 promotes proliferation of mesangial cells and synthesis of extracellular-matrix macromolecules.[55] Increased renal expression and urinary excretion of interleukin-6 correlate with the extent of renal damage in patients with IgA nephropathy.[38,56] Platelet-derived growth factor has been implicated in the proliferation of mesangial cells in patients with IgA nephropathy and other glomerular diseases.[57] Transforming growth factor β1 (TGF-β1) has emerged as a predominant fibrogenic cytokine, which leads to glomerulosclerosis, interstitial fibrosis, and tubular atrophy.[58,59] Renal localization of TGF-β1 correlates with the severity of tubulointerstitial damage in patients with IgA nephropathy.[60] Most of the therapies currently employed for IgA nephropathy are directed at these non–immune-mediated mechanisms of renal-disease progression.

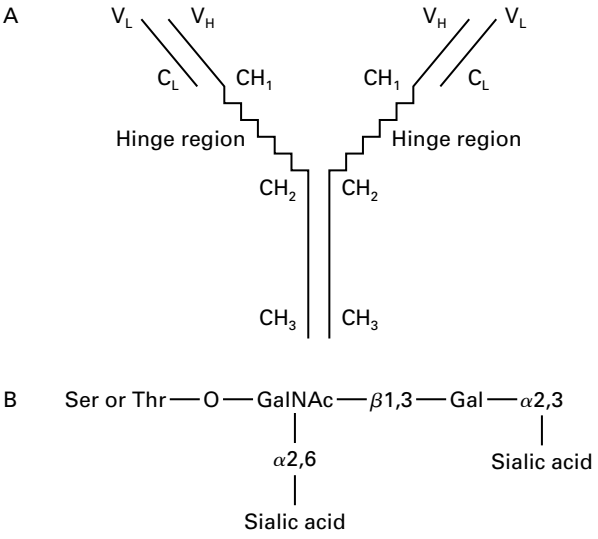

Figure 2. The Structure of a Normal IgA1 Molecule (Panel A) and the Structure of Carbohydrates O-Linked to Serine or Threonine Residues within the Hinge Region of Normal IgA1 (Panel B).

CH_1, CH_2, and CH_3 designate constant regions of the heavy chain, and V_H designates the variable region of the heavy chain. C_L and V_L refer to the constant and variable regions, respectively. The IgA1 heavy chain contains a hinge region between the CH_1 and CH_2 domains. *N*-acetyl glucosamine (GalNAc) is O-linked to serine (Ser) or threonine (Thr) residues within the hinge region of the IgA1 molecule. *N*-acetyl glucosamine is linked to galactose (Gal) through the action of the enzyme β1,3-galactosyl transferase. Sialic acid is linked to galactose through an α2,3 link and to *N*-acetyl glucosamine through an α2,6 link.

PATHOLOGY

Typical features of IgA nephropathy as identified by light microscopy, immunofluorescence studies, and electron microscopy are illustrated in Figure 3. The most common alteration associated with IgA nephropathy identified by light microscopy is focal or diffuse expansion of mesangial regions, with cells and matrix. Mesangial-cell and matrix expansion is in no way specific to IgA nephropathy and can be observed in a number of other renal diseases, including diabetic nephropathy, focal segmental glomerulosclerosis, and a variety of glomerular lesions associated with systemic disease. Furthermore, a wide variety of lesions identified by light microscopy may be seen in patients with IgA nephropathy, including diffuse endocapillary proliferation, segmental sclerosis, segmental necrosis, and cellular crescent formation.

Since the features of IgA nephropathy identified by light microscopy are nonspecific, immunofluorescence or immunoperoxidase studies demonstrating a predominant deposition of IgA are essential to establish a definitive diagnosis of IgA nephropathy. The immune-complex deposits are found predominantly within mesangial regions of glomeruli, with focal paramesangial or subendothelial extension. A variety of other immunoglobulins and complement are frequently codistributed with IgA, including IgM, IgG, C3, lambda light chain, and kappa light chain.[9,61] Electron-dense deposits are identified by electron microscopy, predominantly within mesangial regions of glomeruli. Focal or diffuse expansion of mesangial regions — with cells, matrix, or both — may also be noted.

In addition to the glomerular alterations, a variety of tubulointerstitial and vascular changes may be identified in patients with IgA nephropathy, including interstitial fibrosis, tubular atrophy, interstitial inflam-

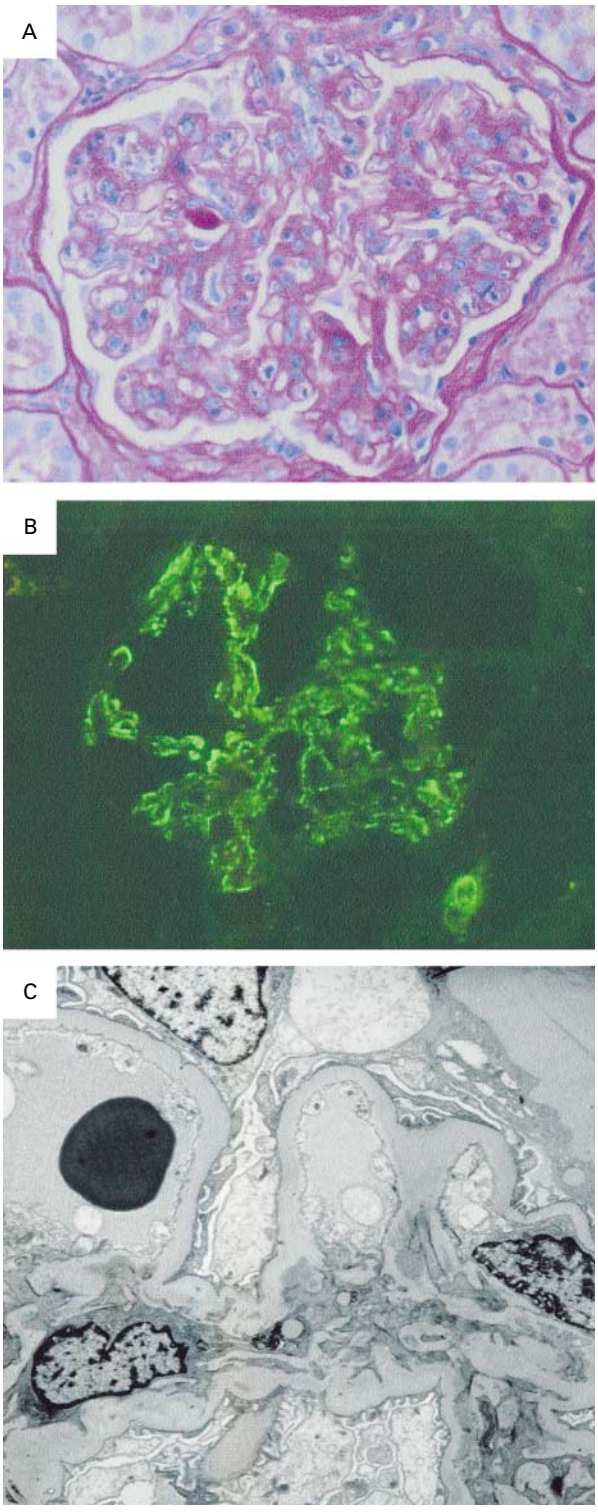

Figure 3. Typical Morphologic Alterations in IgA Nephropathy.
In Panel A, light microscopy (×400) demonstrates expansion of mesangial regions, with cells and matrix (periodic acid–Schiff stain). In Panel B, immunofluorescence microscopy (×400) demonstrates the deposition of IgA, predominantly within mesangial regions of glomeruli. In Panel C, an electron photomicrograph (×6000) demonstrates electron-dense deposits within mesangial regions.

mation, vascular sclerosis, or red-cell casts and proteinaceous casts within the tubules. These features may be seen in progressive renal disease of any cause. Nevertheless, assessment of these features may provide important prognostic information for patients with IgA nephropathy.[9,62]

CLINICAL FEATURES

In the early stages of the disease, many patients have no obvious symptoms and are unaware of any problems. In these patients, IgA nephropathy may be suspected only during routine screening or investigation of another condition. However, some patients may present with aggressive disease.

In general, there are few characteristic clinical signs; however, microscopic hematuria and proteinuria may be persistently or intermittently detected for many years. Patients with IgA nephropathy usually present with one of the following[10,61,63,64]: episodes of macroscopic hematuria (tea-colored urine) that may coincide with an infection of the upper respiratory tract (this presentation usually occurs in patients under 40 years of age, and loin pain often accompanies hematuria), or abnormal sediment in the urine and proteinuria in patients without symptoms (this presentation is usually more common in older patients but is observed in patients of all ages).

It is important that patients undergo further investigations at an early stage (Table 2), despite the tendency of many physicians not to act until renal function is severely impaired. A definitive diagnosis of IgA nephropathy can be made only by renal biopsy and immunohistologic examination. Up to 20 percent of patients with IgA nephropathy present with severe azotemia that represents long-standing disease that differs from the classic presentations, either because the patient's condition did not come to early medical attention or because the patient was referred late without an established diagnosis.

As previously discussed, the decision by a nephrologist to recommend renal biopsy in a patient without symptoms who has microscopic hematuria and mild proteinuria varies from region to region and remains a matter of debate even when IgA nephropathy is highly suspected. This relates in part to the lack of effective treatment in the early stages of the disease and the realization that none may be necessary. Moreover,

TABLE 2. DIAGNOSIS OF IgA NEPHROPATHY.

TEST	CLINICAL IMPORTANCE
Urinalysis	On the first morning, the urine sediment in a freshly voided sample is examined for the presence of erythrocytes, leukocytes, and erythrocyte casts, which are indicative of glomerular injury
Urinalysis for proteinuria	Physicochemical testing by dipstick (e.g., Albustix) or Coomassie blue is more sensitive to albumin than globulins; tests may miss proteinuria in patients with tubular proteins or abnormal globulins, such as myeloma proteins
24-Hr protein determination	This test requires accurate collections of urine that are cumbersome in large numbers of patients — for example, in patients enrolled in a multicenter clinical trial
Protein:creatinine or protein:osmolality ratio	A random or first morning urine sample is collected that accurately determines abnormal protein excretion, especially in patients with a greater degree of proteinuria; the test can be used to determine the efficacy of therapy and avoids inaccuracies of 24-hr collections of urine
Renal function	Serial direct or reciprocal serum creatinine determinations measure the change in renal function over time (slope); estimates of glomerular filtration rate (e.g., inulin, iothalamate, and creatinine clearance) are more accurate measures of renal function than serum creatinine but less clinically useful
Renal biopsy	Immunohistologic examination is required to make an accurate diagnosis of IgA nephropathy, with a finding of predominant or codominant deposition of IgA, mostly within mesangial regions of glomeruli

although some mild cases progress to renal failure, there are no consistent genetic, immunologic, clinical, or morphologic markers that predict progressive disease in a patient without symptoms who has minor urinary abnormalities.

OUTCOME

Primary IgA nephropathy is characterized by a highly variable course ranging from a totally benign condition to rapidly progressive renal failure. From 15 to 40 percent of patients will eventually have end-stage renal disease.[8-11,65-70] Chronic, slowly progressive renal failure develops in most of these patients.

Over the past decade or so, many studies from around the world, involving large cohorts of patients, have reported clinical, laboratory, and pathological characteristics that predict progressive renal disease.[8-11,62,65-70] In both children and adults, hypertension, high glomerular histopathological scores,[9] persistent microscopic hematuria and proteinuria of more than 1 g per 24 hours, and impaired renal function at the time of diagnosis stand out as consistent and strong predictors of poor renal survival. For the majority of patients, prognostic indicators are weak on a case-by-case basis. On the other hand, it is useful to establish a profile of clinicopathological features in order to determine which patients are most at risk for progression to renal failure; for these patients, treatment strategies can then be designed in an attempt to slow or halt progression. A better understanding of the pathogenesis of the disease may help in the design of methods to assess activity as a basis for prognosis.

In a recent development concerning the assessment of prognosis, controversy arose about whether polymorphisms in the genes encoding angiotensin-converting enzyme and angiotensinogen are associated with a hyperfunctioning renin–angiotensin system in primary IgA nephropathy.[28] The hypothesis is that increased production or activity of angiotensin II and decreased levels of bradykinin play a detrimental part in the glomerular response to injury, leading to progressive loss of renal function. After the discovery of an insertion–deletion (I/D) polymorphism in intron 16 of the gene encoding human angiotensin-converting enzyme, reports of strong associations between the D allele and cardiovascular illnesses — including myocardial infarction, left ventricular hypertrophy and hypertension, and progressive diabetic and nondiabetic nephropathies — were published. Initial positive results in primary IgA nephropathy have not been confirmed in follow-up studies.[28,71,72]

TREATMENT

Until recently, there was no effective treatment available for patients with IgA nephropathy. Although there remains no cure, treatment options that slow dis-

ease progression are becoming available. Since IgA nephropathy may affect up to 1.3 percent of the population,[2,3,73,74] there is a need for novel therapeutic agents capable of preserving renal function.

For patients with only minor urinary abnormalities who do not have hypertension, the general consensus is not to offer specific treatment but to follow such patients prospectively over many years. Up to 23 percent of patients will have a complete remission.[8-10,65-67,75]

Substantial progress has been made in the past several years in preventing progressive renal disease in at-risk patients with the use of several modes of treatment that include angiotensin-converting–enzyme inhibitors, corticosteroids, and n−3 polyunsaturated fatty acids.

Angiotensin-Converting–Enzyme Inhibitors

It has been established that angiotensin-converting–enzyme inhibitors reduce the risk of progressive renal disease in patients with type 1 diabetic nephropathy, hypertensive nephrosclerosis, and chronic, nondiabetic glomerular and interstitial renal disease.[76] However, no study has shown that angiotensin-converting–enzyme inhibitors preserve renal function in patients with IgA nephropathy.

A reduction in proteinuria is considered by many investigators to be the hallmark of effective treatment in preserving renal function in nondiabetic renal diseases.[77] However, in IgA nephropathy, three randomized clinical trials[78-80] and a large retrospective cohort study[81] found that a variety of angiotensin-converting–enzyme inhibitors moderately lowered urinary protein excretion without an accompanying improvement in renal function. Additional long-term studies are needed to determine whether a reduction in proteinuria is associated with improved or preserved renal function.

Limited data are available on the effects on proteinuria of combination therapy with angiotensin-converting–enzyme inhibitors and angiotensin II type 1 receptor antagonists. In two small studies in patients with IgA nephropathy, the combination of losartan and angiotensin-converting–enzyme inhibitors appeared to have an additive effect on the reduction of urinary protein excretion, whereas doubling the dose of monotherapy had no effect.[82,83]

Despite their lack of efficacy in preserving renal function in patients with IgA nephropathy in these short-term trials, angiotensin-converting–enzyme inhibitors are used widely to lower blood pressure and decrease proteinuria, both of which are considered modifiable risk factors for progressive disease.[77]

Corticosteroids

Corticosteroids have been used for over 20 years in the treatment of IgA nephropathy because of their antiinflammatory and immunosuppressive properties. In a recently reported randomized, controlled trial, treatment with steroids (1 g of intravenous methylprednisolone per day for three days at the beginning of months 1, 3, and 5, plus 0.5 mg of oral prednisone per kilogram of body weight on alternate days for six months) was shown to lower proteinuria by 50 percent after six months and to reduce the risk of a 50 percent increase in the serum creatinine level by 36 percent after five years.[84] Two other randomized trials in small cohorts of patients showed a similar lowering of urinary protein levels with steroid therapy, but no effect on renal function was observed.[85,86] Nephrotic relapses and steroid dependence were also described.[85] A trial comparing corticosteroids plus azathioprine with corticosteroids alone is in progress in Italy[87]; this study is aimed at determining whether the combination could be more effective and less toxic than steroid therapy alone.

n−3 Polyunsaturated Fatty Acids

The rationale for the use of n−3 polyunsaturated fatty acids, provided in dietary fish-oil supplements, involves potential mechanisms that reduce renal inflammation and glomerulosclerosis, both hallmarks of progressive renal disease.[88,89] The efficacy of fish oil has been tested in patients with IgA nephropathy in four randomized trials, with varying results; two showed that treatment stabilized renal function,[90,91] and two reported a decline in renal function.[92,93] A meta-analysis of these four randomized trials plus a small, nonrandomized study[94] showed that the probability of at least a minor beneficial effect on the preservation of renal function was 75 percent.[95]

The largest study[91] was a randomized, placebo-controlled trial in patients with persistent proteinuria (more than 1 g per 24 hours) and deteriorating renal function (a serum creatinine level of less than 3.0 mg per deciliter [265 μmol per liter] at study entry). That study provided strong evidence that treatment for two years with a daily dose of 1.8 g of eicosapentaenoic acid and 1.2 g of docosahexaenoic acid reduced the risk of a 50 percent increase in the serum creatinine level by 82 percent. Treatment also lowered the risk of death or end-stage renal disease by 67 percent. The annualized median change in creatinine clearance was an increase of only 0.3 ml per minute per 1.73 m^2 of body-surface area in patients treated with fish oil, as compared with a decrease of 7.1 ml per minute per 1.73 m^2 in patients given placebo. These benefits persisted after 6.4 years of follow-up.[96]

More recently, the effects of daily high-dose treatment (3.76 g of eicosapentaenoic acid and 2.94 g of docosahexaenoic acid) as compared with standard-dose treatment (1.88 g of eicosapentaenoic acid and 1.47 g of docosahexaenoic acid) with polyunsaturat-

ed fatty acids contained in a highly purified ethyl ester concentrate (Omacor, Pronova Biocare) were assessed in patients with severe IgA nephropathy.[97] The doses showed a similar slowing of the rate of loss of renal function, particularly in patients with moderately advanced renal disease (defined by serum creatinine levels of up to 3.0 mg per deciliter [265 μmol per liter] and proteinuria of more than 500 mg per 24 hours).

Given the discrepancies in the results of the four clinical trials of fish oil, a randomized, placebo-controlled trial in children and young adults is under way in the United States[98] to attempt to resolve the issue of which is the better treatment in patients at risk for progressive renal disease — corticosteroids or n−3 polyunsaturated fatty acids.

Other Treatments

Anecdotal reports have shown stabilization or improvement of renal function after treatment with intravenous immunoglobulins, plasmapheresis, mycophenolate mofetil, and intravenous steroids plus cyclophosphamide in patients with a rapidly progressive course (a decrease in renal function of 50 percent or more over a three-month period).[99,100] In a recent controlled trial in 38 patients with moderately rapidly progressive disease, combined treatment with prednisolone and oral cyclophosphamide for three months, followed by azathioprine for two years or more, resulted in better preservation of renal function and a lower degree of proteinuria than did placebo.[101]

Finally, tonsillectomy, a popular practice in France and Japan, might be beneficial in patients with IgA nephropathy who have recurrent tonsillitis along with macroscopic hematuria. A group of patients in France who underwent tonsillectomy had subsequent reductions in episodic hematuria and proteinuria.[102] A prospective controlled study of the effect of tonsillectomy is needed because of the high degree of variability of IgA nephropathy; no study to date has shown long-term preservation of renal function in patients who undergo tonsillectomy.[103]

No convincing evidence has been provided to support the use of angiotensin-converting–enzyme inhibitors, n−3 polyunsaturated fatty acids, or tonsillectomy in children with IgA nephropathy, and controlled studies comparing these treatments have not been conducted.

RENAL TRANSPLANTATION

For patients in whom end-stage renal disease develops, renal transplantation is the best option for the treatment of IgA nephropathy, since such patients tend to be younger, otherwise healthy adults. In one report from the United States, IgA nephropathy accounted for 10 percent of renal transplants among patients with primary glomerulonephritis.[104] In Europe and Australia, IgA nephropathy accounted for 7 to 20 percent of patients in long-term dialysis and renal-transplantation programs.[4]

Survival of both patients and renal allografts is excellent, comparing favorably with patient and graft survival after transplantation for non-IgA nephropathy.[31,61] However, from about five years after transplantation, IgA nephropathy recurs in 20 to 60 percent of grafts, with the higher percentages reported from centers that perform serial biopsies of renal allografts in every recipient.[61] Recurrent IgA nephropathy results in declining renal function and graft loss (of up to 15 percent) that is distinct from previous graft failure due, for example, to allograft rejection.[61,64] Recurrence of IgA nephropathy is divided equally between cadaveric kidneys and kidneys from living, related donors,[61,105] a finding that dispels earlier, unsubstantiated data that reported an allegedly higher frequency of IgA nephropathy in kidneys from living, related donors as a result of HLA antigens shared by the donor and the recipient that increase the risk of recurrence. With the solid data that show equal rates of recurrence in cadaveric kidneys and kidneys from living, related donors, the transplantation of kidneys from living, related donors should not be discouraged.

It remains to be proved whether newer immunosuppressive regimens — for example, the use of mycophenolate mofetil — can prevent recurrent IgA nephropathy (as has been suggested recently[31]) or can reduce the loss of renal function in patients who have a recurrence.

DIFFERENTIAL DIAGNOSIS

There are two conditions that must be distinguished from primary IgA nephropathy: Schönlein–Henoch purpura and thin glomerular basement membrane disease. Schönlein–Henoch purpura is a clinical syndrome with a peak incidence in the first two decades of life.[6,7] Schönlein–Henoch purpura is distinguished from IgA nephropathy by the presence of systemic symptoms, including purpuric rash, arthralgias, and abdominal pain.[6,7] Whereas Schönlein–Henoch purpura usually has an acute onset and is self-limited, progressive renal failure is the principal cause of morbidity. Although the clinical manifestations of Schönlein–Henoch purpura and IgA nephropathy are distinct, the histopathological alterations observed in these diseases are similar.

In biopsy specimens obtained from the skin of patients with Schönlein–Henoch purpura, the dermal vessels frequently contain IgA deposits. However, IgA deposits have been identified in clinically normal skin obtained from patients with both Schönlein–Henoch purpura and IgA nephropathy.[106] Morphologic alterations observed on renal biopsy in patients with Schönlein–Henoch purpura are identical to those seen

in patients with IgA nephropathy. Like the deposits in IgA nephropathy, the glomerular deposits in patients with Schönlein–Henoch purpura consist exclusively of IgA1. Serum IgA1 isolated from patients with Schönlein–Henoch purpura has glycosylation defects similar to those described in IgA1 isolated from patients with IgA nephropathy.[107] On the basis of family studies, including studies of identical twins, it is recognized that Schönlein–Henoch purpura may develop in one family member and IgA nephropathy may develop in another family member who has been exposed to similar environmental factors.[108] These observations support the notion that Schönlein–Henoch purpura and IgA nephropathy are variants of the same pathologic process. However, factors leading to systemic activation of IgA-containing immune complexes in Schönlein–Henoch purpura or localized activation of IgA-containing immune complexes in IgA nephropathy have not been identified.

Thin glomerular basement membrane disease is a common condition that occurs more often in female patients and has a benign clinical course.[109] Although microscopic hematuria, proteinuria, and hypertension are common presentations in both thin glomerular basement membrane disease and IgA nephropathy, patients with IgA nephropathy are likely to have more hematuria and proteinuria.[109,110] End-stage renal disease does not develop in patients with thin glomerular basement membrane disease.[109,110] Renal biopsy distinguishes the two disorders. A diagnosis of thin glomerular basement membrane disease is established by electron-microscopical evaluation of glomerular capillary loops. In thin glomerular basement membrane disease, the basement membranes are diffusely attenuated. No significant expansion of mesangial regions is shown by light microscopy, and immunofluorescence studies fail to demonstrate IgA deposits within glomeruli.

The presence of mesangial IgA deposits is also associated with many other diseases (listed as secondary causes in Table 1); the IgA deposits are often incidental findings with unclear pathogenesis or clinical significance. The many secondary conditions are distinguished from primary IgA nephropathy by their distinctive clinical expressions. Because IgA nephropathy is a prevalent disease, it may be found in association with other glomerular diseases (Table 1).

SUMMARY

IgA nephropathy, the most common form of primary glomerular disease in the world, is an immune-complex–mediated glomerulonephritis defined immunohistologically by the presence of glomerular IgA deposits accompanied by a variety of lesions identified histopathologically in the absence of systemic disease.

Occurring at all ages and more frequently in male patients, the disease shows regional variations in frequency that may be explained by genetic differences and by differences in renal-biopsy practices. The cause of the disease and the mechanism underlying glomerular deposition of immune complexes containing IgA1 are unknown. The two most common clinical presentations are episodic macroscopic hematuria, often coincident with upper respiratory infection, in younger patients, and abnormal urine sediment and proteinuria in patients without symptoms. Fifteen to 40 percent of patients will eventually have end-stage renal disease. In both children and adults, severe glomerular pathological features, persistent microscopic hematuria, proteinuria of more than 1.0 g per 24 hours, impaired renal function, and hypertension are associated with a poor prognosis.

There is no cure for the disease, but recent two-year clinical trials testing the efficacy of corticosteroids, with and without immunosuppressive agents, and n−3 fatty acids have shown these treatments to have favorable effects on the progression of renal disease. In short-term trials, a variety of angiotensin-converting–enzyme inhibitors have been shown to control hypertension and reduce proteinuria, both of which are modifiable risk factors for progressive disease. These positive effects, however, are tempered by the studies reporting no benefits with these categories of therapeutic agents.

Renal transplantation is the treatment of choice for patients in whom end-stage renal disease develops. Although both patient and renal-allograft survival compare favorably with survival among patients with non-IgA nephropathy who have undergone renal transplantation, IgA nephropathy recurs in 20 to 60 percent of grafts five years or more after transplantation, and renal function declines and graft loss occurs in up to 15 percent of patients. The recurrences are divided equally between kidneys from cadaveric donors and those from living, related donors; therefore, the use of transplants from living, related donors should not be discouraged.

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