

# Berger's disease

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**Creation Date: June 2001**

**Update: January 2004**

**Scientific Editor: Professor Francesco Scolari**

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## Abstract

*Berger's disease, also called IgA nephropathy (IgAN), is characterized by prominent mesangial IgA deposition, with variable degrees of mesangial proliferation. Typical clinical features include hematuria with or without proteinuria and episodes of gross hematuria. Approximately 30% of the patients develop chronic renal failure. The pathogenesis of IgA nephropathy (IgAN) is unknown. It has been suggested that structural abnormalities of O-glycosylation of the IgA1 hinge region play a key role in mesangial deposition. That genetic factors may be important in disease susceptibility was recently confirmed by a genetic study performed in 30 multiple IgAN families. This study provided evidence that a single gene on chromosome 6 influences the disease. IgAN affects up to 1% of the population worldwide and accounts for 25-50% of renal biopsy diagnoses. Only a subset of IgAN patients with adverse prognostic features, such as hypertension, proteinuria > 1 g/24 hour, slowly progressive renal failure, and severe histologic changes may be candidates for therapy. Treatment options include general measures (e.g. treatment of hypertension, low-protein diet, good hydration, etc.), steroids, cytotoxic drugs, and fish oil. For patients who progress to end-stage renal failure, treatment consists of dialysis or a kidney transplant. The success rate of transplantation is good, although de novo IgA deposits appear in the transplanted kidney in about half the patients.*

## Keywords

Berger's disease, chronic renal failure, genetic factors, hematuria, IgA nephropathy

## Disease name

Berger's disease

## Synonyms

IgA nephropathy (IgAN)

## Diagnosis criteria

Typical clinical features include onset before age 40 with hematuria with or without proteinuria.

Episodes of gross hematuria ("tea-colored urine") following mucosal infections are also common; 30% of the patients may present or progress to renal failure. Although the presence of blood with or without protein in the urine may suggest a diagnosis of IgAN, a renal biopsy is necessary to confirm the diagnosis. The pathognomonic finding is revealed by

immunofluorescence microscopy which shows IgA deposits in the mesangium and, to a lesser degree, in the glomerular capillary wall. By light microscopy, focal or diffuse mesangial proliferation and matrix expansion can be observed. A variable degree of segmental crescents or glomerulosclerosis may also be present. Skin biopsy, looking for IgA deposition in the dermal capillaries, has been investigated as a diagnostic test but is not sufficiently specific or sensitive to avoid renal biopsy. The conventional recommended approach is to restrict biopsy to patients with proteinuria of > 1 g/24 hour and microhematuria, since only these patients are candidates for the emerging treatment. However, IgAN is not an entirely benign condition, even when microhematuria is the only clinical finding at presentation. In addition, when a renal biopsy is systematically taken in patients with isolated hematuria, IgAN is the most frequent finding, but Alport's syndrome and thin membrane nephropathy are also found. Since the latter two are Mendelian hereditary diseases, the correct diagnosis is important for subsequent management. These considerations seem to argue in favor of more extensive indications for renal biopsy.

#### Differential diagnosis

A number of glomerular diseases have symptoms similar to those of IgAN, particularly thin membrane nephropathy and Alport's syndrome. Although a family history of renal failure with or without deafness may be helpful, the diagnosis of any of these disorders can only be made by renal biopsy.

#### Prevalence

IgAN seems to affect up to 1.3% of the population worldwide and 100,000 people in the United States. Moreover, demographic studies revealed that, among patients undergoing renal biopsy, IgAN is the most common glomerulonephritis in the world, accounting for 25-50% of renal biopsy diagnoses. However, the true population prevalence for IgAN is difficult to obtain, since the definitive diagnosis depends on policies governing renal biopsy, which vary considerably from country to country. Thus, a dramatic variation in the prevalence of diagnosed IgAN (ranging from less than 5% to more than 40% worldwide) has been reported. For example, in a study from Singapore, 94 out of 100,000 military inductees were diagnosed with IgAN, reflecting the practice of mandatory routine screening for urinary abnormalities of all army recruits. In addition, a random autopsy kidney-biopsy study revealed that IgAN may affect up to 4% of the general population, suggesting the possible existence of a large proportion of clinically silent and undetected

IgAN. However, it is noteworthy that some racial differences in the disease prevalence cannot be explained for by local biopsy criteria alone. IgAN is uncommon in blacks, and is more common among American Indians and Hispanics than whites. These findings provide indirect support for the existence of genetic factors that determine susceptibility to the development of IgAN.

#### Clinical description

IgAN was first described by Berger and Hinglais in 1968. This clinicopathological entity is characterized by prominent mesangial deposition of IgA detected by immunofluorescence microscopy, with variable degrees of mesangial expansion and proliferation seen by light microscopy. It is the only primary glomerular disease defined by immunohistochemical findings rather than light microscopy. Over the last 30 years, IgAN has evolved from being a curiosity to being the most common glomerulonephritis seen in all parts of the world where renal biopsy is widely practiced. In the majority of the patients, IgAN may present as an isolated renal disease (primary IgAN). However, a number of other clinical conditions may be associated with IgAN (secondary IgAN), such as Henoch-Schönlein purpura (IgA-mediated systemic vasculitis), ankylosing spondylitis, Reiter's syndrome, celiac disease, dermatitis herpetiformis, and chronic liver disease. Although IgAN usually develops randomly in affected individuals, it may aggregate within families in a substantial number of cases, suggesting a genetic contribution to the disease. From a clinical point of view, approximately 40-50% of patients with IgAN present with recurrent gross hematuria, usually concomitantly with upper respiratory tract infections. Microscopic asymptomatic hematuria (isolated or associated with non-nephrotic proteinuria) is the presentation in 30 to 50% of the patients in most series. Nephrotic syndrome is an uncommon presentation (5%) of IgAN; in this setting, the possible coincidence of IgAN and minimal change disease (particularly in children but also in adults) should be considered. Acute renal insufficiency is an infrequent presentation of IgAN (5%) and it is usually associated with gross hematuria. Alternatively, it may be due to crescentic IgAN. To distinguish between these two clinical conditions, renal biopsy is mandatory in acute renal insufficiency unless recovery of renal function is rapid. In 10-20% of the patients, IgAN presents with chronic renal failure; in this context, it is difficult to determine the exact time of onset of the glomerular disease, since these patients are already azotemic when they first consult. The natural history of IgAN is characterized by an

extreme variability in clinical course and sometimes by the unpredictability of the ultimate outcome. Actuarial renal survival at 10 years in adults was between 80% and 85% in most of the European and Asian studies, but it was lower in studies from the United States (57-67%) and exceeded 90% in the few studies on children. After 20 ys of follow-up, end-stage renal failure is reported to develop in 20- 30% of patients with IgAN. Impaired of renal function, severe proteinuria, and arterial hypertension can be considered the strongest and most reliable clinical predictors of an unfavorable outcome.

### Management including treatment

There are no widely accepted medical treatments for IgAN except during the latest stages of the disease. In the early years after the first description of IgAN, the approach was to wit and no therapy was initiated because early reports suggested a benign evolution in most cases. However, with increased awareness that IgA nephropathy was a progressive disease in many patients, treatment issues began to be more widely discussed. Thus, the situation now seems to be changing, and there is growing evidence that a number of therapies can be effective in delaying the deterioration of kidney function. A diagnosis of IgAN, however, should not be a justification for a rush to treat. IgAN patients with normal renal function, normal blood pressure, isolated microhematuria with proteinuria < 1 g/24 hour who have only minor histological changes on biopsy usually show a benign course; thus, no specific treatment is recommended for these patients who should be managed conservatively.

Only a subset of IgAN patients with one or more adverse prognostic features, such as hypertension and/or proteinuria of more than 1 g/24 hour, slowly progressive renal failure, and severe changes of renal biopsy histology, may be candidates for therapy.

Since many prospective randomized trials are still in progress, it is quite difficult to summarize the most practical recommendations. Keeping this consideration in mind, treatment options include, steroid, cytotoxic therapy, fish oil and general measures. The latter most importantly include aggressive therapy of hypertension, initially with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists alone or in combination with diuretics and/or non-dihydropyridine calcium channel blockers. Smoking should be discouraged because it increases the risk of renal failure and a moderate dietary protein restriction may offer some benefit in patients with progressive course. Patients with acute renal failure associated with gross hematuria but no crescents in the renal biopsy should receive good supportive care, such as

good hydration and antibiotics when necessary, with the expectation that they will recover renal function.

If the bouts of gross hematuria are precipitated by recurrent tonsillitis, these patients may benefit from tonsillectomy; otherwise, the role of tonsillectomy is unproven. Patients with rapidly progressive glomerulonephritis associated with extensive crescents should be treated aggressively with high-dose steroids combined with cyclophosphamide for 6 months. Treatment of patients with nephrotic range proteinuria associated with minimal glomerular changes should consist of glucocorticoid regimens similar to those used to treat minimal change disease idiopathic nephrotic syndrome. Patients with proteinuria > 1g/24 hour and serum creatinine < 1.5 mg/dl, with moderate glomerular abnormalities in the renal biopsy should receive ACE-inhibitors or angiotensin II receptor antagonists with the goal of reducing proteinuria to at least 50% of baseline values or to < 1 g/24 hour.

In patients who maintain proteinuria > 1g/24 hour, a course of steroids (intravenous methylprednisolone for once montly for 3 months plus 0.5 mg/kg on alternate days for 3-6 months) may be indicated. For patients with impaired renal function (serum creatinine > 1.5 mg/dl) and severe proteinuria (> 1.0-2.0 g/d) accompanied by moderate renal histological alterations, steroids alone will probably not be of much benefit. In patients with proteinuria > 1 g/24 hour or with slowly progressive renal failure, fish oil (eicosapentaenoic acid 1.8 g/d plus docosahexanoic acid 1.2 g/d) has also been recommended. However, conclusive data on the benefit of fish oil are not available.

Patients presenting with advanced renal failure (serum creatinine > 4 mg/dL) and severe chronic lesions in the biopsy should be treated conservatively with ACE-inhibitors and other antihypertensive agents. Dietary protein restriction may have some added value. For patients who progress to end-stage renal failure, treatment will consist of dialysis or kidney transplantation. The success rate of transplants is good in IgAN patients, even though de novo IgA deposits appear in the transplanted kidney in about half the patients. The clinical relevance of recurrent IgAN seems largely to be a function of the time posttransplantation. Recurring disease need not be treated routinely unless renal failure ensues associated with extensive crescents. Aggressive therapy with high-dose prednisone and mycophenolate mofetil may be helpful in this situation.

### Etiology

In spite of considerable research, the precise etiology and pathogenesis of IgAN remain poorly

understood, and the true mechanism of mesangial targeting of IgA is still unknown. The lack of an adequate animal model - those available are models of IgA deposition rather than models of IgAN- significantly hinders progress in the pursuit of the fundamental pathogenic mechanism of IgAN. Many reports have been devoted to the mechanisms governing the deposition of IgA in the renal mesangium. Clinical and experimental studies have pointed to an immune complex-mediated form of glomerulonephritis. Abnormalities in the immune regulation of the IgA system, resulting in high IgA plasma levels, have been suggested as the mechanism underlying the disease. However, the rarity of IgAN in patients with AIDS and IgA myeloma, despite high circulating IgA levels, suggests that some qualitative alteration of IgA is required before mesangial deposition will occur.

Recent data indicate that structural abnormalities of O-glycosylation of the IgA1 hinge region may play a key role in its mesangial deposition. However, there is little direct evidence to confirm the putative abnormalities in IgA1 behaviour induced by altered O-glycosylation.

In the last few decades, observations have accumulated indicating that genetic factors may be important in disease susceptibility. First, demographic and racial differences have been observed in the prevalence of IgAN (varying from < 5% to > 40% worldwide), not explained by local biopsy criteria alone. IgAN is uncommon in blacks, and is more common among American Indians and Hispanics than whites. Second, abnormalities of the IgA immune system may be detected not only in patients with IgAN, but also in their healthy family members. Third, several instances of familial IgAN have been described in different ethnic groups, suggesting that familial predisposition is common.

Recently, genetic analyses were carried out in 24 Italian & 6 American that had multiple members with the disease. No evidence of abnormalities in the genes that govern the synthesis, modification or clearance of IgA from the kidneys was found. Genome-wide linkage analysis carried out in these 30 multiplex IgAN kindreds demonstrated linkage of the *IgAN* gene to 6q22-q23 under a dominant model of transmission with incomplete penetrance, with a limit of detection (lod) score of 5.6 and 60% of the kindreds linked. Thus, surprisingly, the study provided very strong evidence that a single gene on chromosome 6 (region 6q22-23) influences the disease in about 60% of families studied. Discovering the gene and tracing its physiological effects will open the way to better understanding the cause of IgAN and will have major impact on IgAN treatment.

### Genetic counseling

Familial IgAN is commonly inherited in a multifactorial manner. It should be noted that any genetic test in a multifactorial disease, which shows both a polygenic and environmental components of causative factors, will never answer the question as to whether the subject will or will not develop the disease. In contrast to the Mendelian forms of disease, which are the result of a single gene defect, multifactorial genetic disease is a consequence of complex interplay between several disease-susceptibility genes and environmental factors. An individual who inherits a particular combination of interacting genes has a relative risk of developing disease. When these genetic components interact with certain environmental factors, a biological threshold is crossed, and disease expression occurs. Thus, genetic counseling for a subject with a sporadic form of IgAN and their family members must be relatively nonspecific. It should be pointed out that IgAN is the most common chronic glomerulonephritis in adults worldwide. Although the risk of developing the disorder may be considered to be slightly higher in family members of a sporadic IgAN patient, the probability is currently unknown. Finally, in multiplex families with IgAN, the presence of more than one family member with IgAN probably further increases the risk for close relatives; however the magnitude of that increase, is unknown.

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