IgA nephropathy

Introduction

Immunoglobulin A (IgA) nephropathy was first described by Jean Berger in 1968, and is now recognized as being the most common form of primary glomerulonephritis worldwide. It is a leading cause of chronic kidney disease and end stage kidney disease, and is believed to affect up to 10% of patients receiving dialysis. Once thought to be a relatively benign condition, it is now known that around 20–30% of affected patients develop progressive kidney disease and end stage kidney disease within 20 years of diagnosis (D'Amico, 2000). Identifying and treating patients at risk of progression is a key aspect to managing this condition. Closely related to IgA nephropathy is Henoch–Schönlein purpura, a systemic condition affecting the kidneys (with histological features indistinguishable from IgA nephropathy), bowel, joints and skin, leading to a characteristic set of features including nephritis, abdominal pain, arthralgia and vasculitic rash.

This review discusses the epidemiology, pathophysiology, clinical and histological features, and management of these conditions.

Epidemiology

IgA nephropathy has a male preponderance in European and North American countries, with the male:female ratio being around 2:1, while this ratio is approximately equal in Asia (Boyd et al, 2012). Peak incidence is between the second and third decade, although IgA nephropathy may affect patients of any age. Reported incidence varies considerably between countries, and this may be partially attributable to differences in diagnostic practice and thresholds for performing a kidney biopsy. For example, in countries where there is a screening programme for non-visible haematuria, the number of cases of IgA nephropathy diagnosed will be higher than in countries with no screening programme. As IgA nephropathy is most common in Asian and Caucasian populations, and is rare in people of African descent, there are also undoubtedly genetic factors, yet to be fully elucidated, which play an important role in the development of this condition (Kiryluk et al, 2010). Familial IgA nephropathy is rare, however, and is thought to cause around 5% of all cases of IgA nephropathy.

Pathophysiology

IgA nephropathy is believed to be a systemic immunological disorder and not confined to the kidneys, as a result of observations that recurrence of IgA deposition may be found in up to 50% of patients after kidney transplantation on biopsy, and that when kidneys with IgA deposits have been inadvertently used for kidney transplantation, repeat biopsy has shown clearance of these deposits (Sanfilippo et al, 1982; Silva et al, 1982).

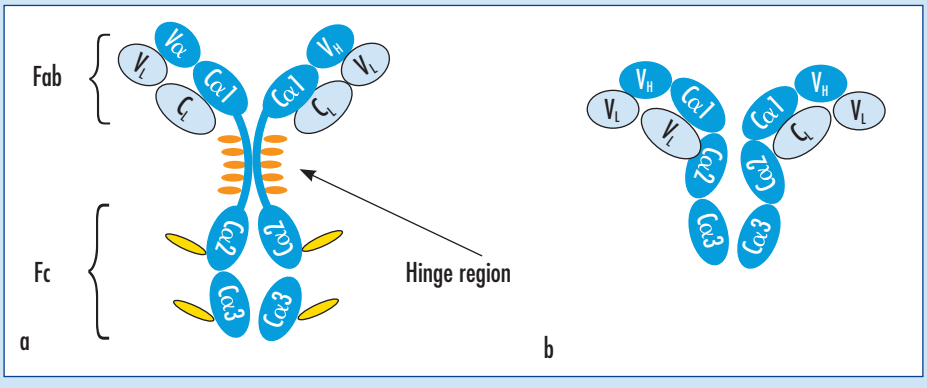
IgA is the most abundant immunoglobulin in humans, and is found in both monomeric and polymeric forms. IgA exists as two isoforms, IgA1 and IgA2 (*Figure 1*). These differ by the presence (IgA1) or absence (IgA2) of a hinge region, which is variably glycosylated by the addition of galactose residues. IgA functions mainly at mucosal surfaces, e.g in the gut, protecting them from invasion by bacteria (Pabst, 2012).

It is now widely accepted that multiple hits are required for the development of IgA nephropathy (Suzuki et al, 2011):

1. Increased production of galactose-deficient IgA1
2. Production of anti-glycan antibodies
3. Formation of pathogenic IgA1-containing circulating immune complexes
4. Subsequent glomerular and tubulointerstitial damage.

In IgA nephropathy, there is an increase in circulating IgA1 which is abnormally underglycosylated in its hinge region (galactose-deficient IgA1) (Moldoveanu et al, 2007). This is thought to stimulate production of autoantibodies against this hinge region 'neo-epitope', leading to formation of circulating IgA1-containing immune complexes (Tomana et al, 1999). These complexes then deposit onto the kidney mesangium, triggering mesangial cell stimulation, proliferation and extracellular matrix formation, damage to podocytes, and ultimately damage to the

Figure 1. Structure of IgA1 and IgA2. a. IgA1 contains a hinge region between Cα1 and Cα2 domains of the heavy chain, which consists of a 26-amino acid sequence rich in proline, serine and threonine residues. Six positions are known to be variably glycosylated by addition of a galactose-containing side chain. In IgA nephropathy there is undergalactosylation of this hinge region, forming galactose-deficient IgA1. This form of IgA1 has the predisposition to form immune complexes and deposit on the mesangium. b. IgA2 lacks this hinge region.



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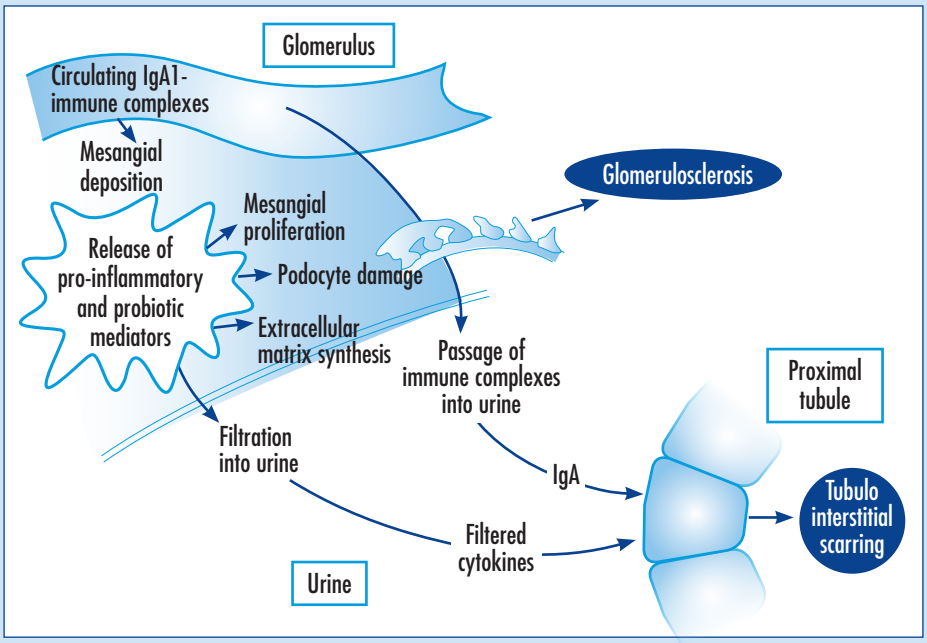


Figure 2. Circulating IgA1 complexes, containing galactose-deficient IgA1, deposit on to the renal mesangium, triggering release of pro-inflammatory and pro-fibrotic mediators, such as tumour necrosis factor-α and fibronectin. These lead to mesangial cell proliferation, damage to podocytes, and synthesis of extracellular matrix components, resulting in damage to the glomerular filtration barrier. Ultimately filtration of these mediators occurs triggering proximal tubular activation and tubulointerstitial fibrosis. In addition, filtered IgA1 that abnormally enters the urinary space may also contribute to this process (Boyd et al, 2012).

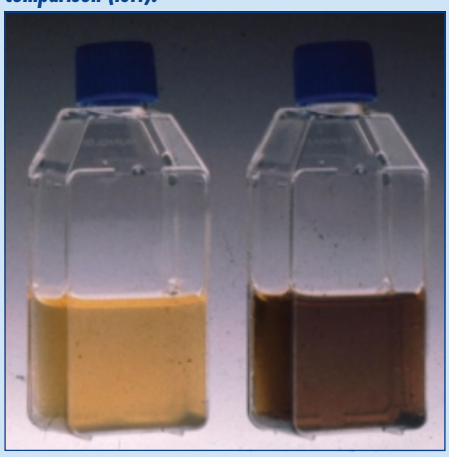
glomerular filtration barrier (*Figure 2*). This results in filtration of mesangial cell-derived cytokines and also IgA, which itself may have toxic effects on the proximal tubule, ultimately leading to tubulointerstitial inflammation and fibrosis, and progressive kidney disease.

Clinical features

Patients with IgA nephropathy typically present in one of two ways. First, patients may be asymptomatic, and have detectable non-visible haematuria, with or without proteinuria, which is found for example during screening or workup for chronic kidney disease or hypertension. Differential diagnoses for persistent isolated non-visible haematuria include hereditary nephritis (Allport's syndrome), an inherited condition associated with deafness and progressive kidney disease leading to end stage kidney disease, and thin basement membrane disease, usually inherited in an autosomal dominant manner and associated with a very good prognosis.

The other mode of presentation is that patients may develop visible haematuria that coincides with an upper respiratory tract infection (synpharangytic haematuria; *Figure 3*). This is more common in younger patients, and is associated with a better prognosis, perhaps partly because patients present at an earlier stage of their disease course. Episodes of synpharangytic haematuria may recur over time, with no long-term detrimental effect on kidney function. The main differential diagnosis is post-streptococcal glomerulonephritis, although in this condition there is usually a delay of around 2 weeks between the upper respiratory tract infection and visible haematuria.

Figure 3. Visible haematuria in IgA nephropathy (right) is typically brown or cola-coloured rather than bright red. Normal urine is shown for comparison (left).



Complement factor H-related protein 5 nephropathy is a familial disease mainly affecting people of Cypriot origin, and is inherited as an autosomal dominant trait (Gale et al, 2010). It is characterized by persistent non-visible haematuria, synpharyngitic haematuria and progressive kidney disease, i.e. features that are clinically indistinguishable from IgA nephropathy. Prognosis is worse than in IgA nephropathy, with more than 80% of males (but a small proportion of females) experiencing a stepwise deterioration of kidney function leading to end stage kidney disease in adulthood.

Less commonly patients may present with nephrotic syndrome, usually associated with underlying minimal change disease, or acute kidney injury, caused either by an obstructive red cell cast nephropathy or a rapidly progressive crescentic glomerulonephritis.

Investigations may reveal impaired kidney function in terms of raised serum creatinine levels, and therefore reduced estimated glomerular filtration rate. Serum IgA levels are raised in 50% of patients, but do not correlate with disease prognosis. Ultrasound scan of the kidneys is usually unremarkable. Galactose-deficient IgA1 may be detected in the serum of patients, and raised levels are associated with progressive kidney disease, although there is great overlap with healthy individuals meaning that it is currently unsuitable as a diagnostic or prognostic test (Zhao et al, 2012).

Glomerular IgA deposition may also occur secondary to other systemic diseases, including liver cirrhosis, coeliac disease and HIV, and therefore these conditions should be excluded.

Histological features

IgA nephropathy can only be diagnosed by kidney biopsy (*Figure 4*). However, as patients who only have non-visible haematuria, without significant proteinuria or impairment of kidney function, have a very good prognosis with little risk of progressive kidney disease, most specialists would elect not to perform a kidney biopsy for diagnostic purposes, and instead maintain a watchful approach. However, patients

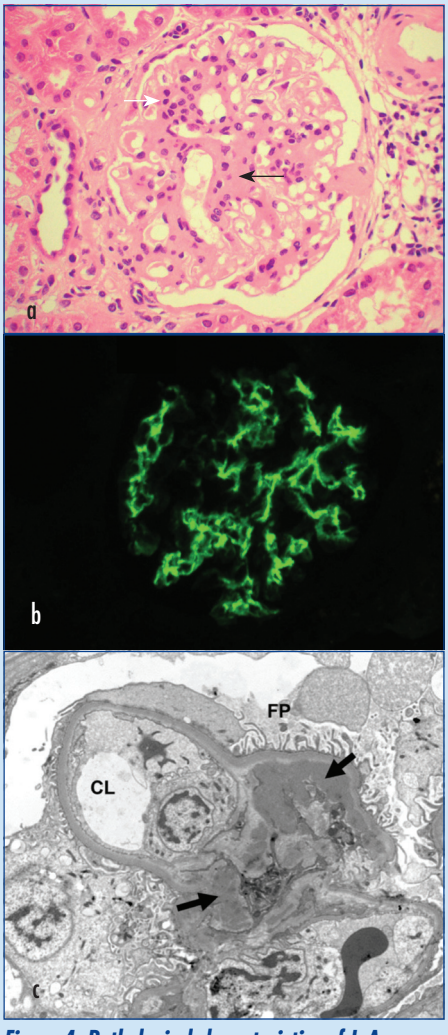


Figure 4. Pathological characteristics of IgA nephropathy. a. Light microscopy typically demonstrates mesangial hypercellularity, defined by four or more cells per mesangial area (white arrow) and mesangial expansion by extracellular matrix (black arrow). b. Immunofluorescence demonstrating diffuse mesangial staining for IgA. c. Electron microscopy of a section of a glomerulus (CL = capillary lumen; FP = foot processes) showing electron dense immune complex deposits (arrowed) within the mesangium, corresponding to IgA deposition.

who have non-visible haematuria and proteinuria, impairment of kidney function, nephrotic syndrome, or suspicion of a rapidly progressive glomerulonephritis indicated by deteriorating kidney function should be biopsied.

Diagnostic features of IgA nephropathy are dominant or co-dominant mesangial deposition of IgA, which occurs alone or with IgG, IgM or both. C3 deposition is often seen, and both the alternative and mannose binding lectin pathways of complement activation have been implicated in this condition (Roos et al, 2006).

Light microscopy findings may include mesangial hypercellularity, mesangial expansion caused by IgA deposition and extracellular matrix formation, focal necrosis, segmental glomerulosclerosis and glomerular crescent formation. Tubulointerstitial fibrosis occurs in progressive disease. Electron microscopy demonstrates mesangial and paramesangial electron-dense deposits which correspond to the IgA deposits.

In 2009, the working group of the International IgA Nephropathy Network and the Renal Pathology Society proposed a new classification for histological features in IgA nephropathy, the Oxford classification. Four pathological variables, mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S) and tubular atrophy/intersititial fibrosis (T) were found to have independent prognostic significance (Cattran et al, 2009).

Management

The management of IgA nephropathy depends upon the clinical stage of presentation:

Non-visible haematuria without proteinuria

Patients with non-visible haematuria only, proteinuria <0.5 g/day and no impairment of kidney function have a very good prognosis and little risk of developing progressive kidney disease. Most specialists would advocate annual follow up with monitoring of kidney function, proteinuria by urine protein:creatinine ratio, urine dipstick and blood pressure.

Non-visible haematuria with proteinuria

Patients who develop proteinuria >0.5 g/day are at risk of developing progressive kidney disease and need to be monitored regularly. All patients should be placed on renin–angiotensin blockade, with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, titrated to maximum tolerated dose, regardless of blood pressure. The aim of treatment is to reduce proteinuria to <0.5 g/d, as this helps to protect against progressive kidney disease (Reich et al, 2007).

If patients have persistent proteinuria >1 g/d, despite optimized supportive care with angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker and blood pressure control for 3–6 months, and have preserved estimated glomerular filtration rate >50 ml/min, current guidelines suggest that a 6-month course of corticosteroids may be beneficial in reducing the degree of proteinuria (KDIGO: Kidney Disease: Improving Global Outcomes guidelines, 2012). However, this guidance is based on randomized controlled trials involving small cohorts with less than optimum use of renin–angiotensin blockade, and larger studies are now underway to try to resolve this aspect of management.

Progressive chronic kidney disease

Patients with progressive kidney disease should be managed as per other kidney conditions, with renin–angiotensin blockade as above, strict control of blood pressure to target <130/80 mmHg (<125/75 mmHg if proteinuria present), and management of other cardiovascular risk factors. As in other kidney conditions, the risk of cardiovascular disease is much greater compared to the general population, and therefore a healthy lifestyle, addressing diet, exercise, blood pressure control and salt restriction, is advocated.

If kidney function continues to deteriorate despite the above measures, then patients should be prepared for renal replacement therapy in the form of dialysis or transplantation (or conservative non-dialytic care if these are not suitable).

Despite the high rate of recurrence of IgA deposition after kidney transplantation, the risk of graft failure as a result of recurrent IgA nephropathy is low (around 5% in total) and often occurs over a long time period, so IgA nephropathy itself is not a contraindication to kidney transplantation (Ponticelli and Glassock, 2010).

Acute kidney injury

Acute kidney injury is a rare form of presentation of IgA nephropathy, and occurs in around 5% of patients. A kidney biopsy should be performed to differentiate between the possibilities of red cell cast obstruction, where management is con-

servative as the acute kidney injury is transient, and a rapidly progressive crescentic glomerulonephritis. This latter condition is rarely associated with IgA nephropathy, and there is little evidence beyond small cohort studies to guide management. Current guidelines are to treat as per other crescentic glomerulonephritides (e.g. anti-neutrophil cytoplasmic antibody (ANCA) -associated vasculitis), with similar immunosuppression protocols including corticosteroids and cyclophosphamide. Unfortunately the prognosis in IgA nephropathy is not as good as other conditions, and many patients will progress to end stage kidney disease and need renal replacement therapy.

Nephrotic syndrome

Nephrotic syndrome is rare with IgA nephropathy and is most commonly associated with underlying minimal change disease. Treatment is the same as for this condition, with a course of corticosteroids.

Henoch–Schönlein purpura

There is little trial evidence to guide treatment of Henoch–Schönlein purpura. Patients who present with flares of Henoch–Schönlein purpura associated with limited kidney involvement, with haematuria, proteinuria and mild impairment of kidney function, usually do not require any specific treatment, and usually resolve spontaneously. Other guidance is similar as for IgA nephropathy, i.e. renin–angiotensin blockade for proteinuria, 6 months of corticosteroids for persistent proteinuria despite the former, and immunosuppression for crescentic Henoch–Schönlein purpura nephritis. Those with rapidly progressive kidney impairment will usually have evidence of crescentic glomerulonephritis on biopsy.

Future questions

There are several unanswered questions in IgA nephropathy. First, does IgA nephropathy represent a single disease entity or different diseases with IgA deposition being the common factor? This may be a possible explanation for the fact that outcomes vary greatly worldwide.

Second, why do some patients develop progressive kidney disease while others may never develop any impairment of kidney function? Mechanisms determining the differences in an individual's IgA and how mesangial deposition occurs may be key to allowing therapeutic targeting.

Finally, what is the best treatment for those with IgA nephropathy who have progressive kidney disease not responsive to standard antiproteinuric and antihypertensive therapies? Two large randomized controlled studies looking at the role of corticosteroids and other more aggressive forms of immunosuppression in IgA nephropathy, the STOP-IGAN study and the TESTING study, are currently underway to address this question. It is clear that there is much more work to be done to unravel the pathogenic mechanisms and optimal management of this condition since its identification over 45 years ago. BJHM

KEY POINTS

- IgA nephropathy is the commonest glomerulonephritis and an important cause of chronic kidney disease.
- Around 20–30% of patients develop progressive kidney disease leading to end stage kidney disease.
- Patients may present with non-visible haematuria or visible haematuria coinciding with an upper respiratory tract infection.
- Diagnosis can only be made by kidney biopsy, which shows mesangial IgA deposition.
- Clinical features associated with a worse prognosis are proteinuria, hypertension and impaired kidney function at diagnosis.
- Management is focused on reducing proteinuria and blood pressure, initially by angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

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