EDUCATIONAL REVIEW

Idiopathic immunoglobulin A nephropathy in children and adolescents

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Abstract Immunoglobulin A nephropathy is now recognized as the glomerular disease most often associated with progressive renal failure in patients around the world. In many cases it is not known when the disease starts to inflict glomerular injury, but recent studies that have shown genetically determined abnormalities in glycosylation of the IgA molecule suggest that this may begin in early life. This review focuses on recent advances in our understanding of IgA nephropathy, with special emphasis on clinical aspects of the disease when it presents in children and adolescents. In addition, the sections dealing with therapeutic options for patients with IgA nephropathy concentrate on studies that have been carried out on children. Whenever possible, data from randomized controlled clinical trials have formed the basis for recommendations. Unfortunately, this is not always possible, because of the lack of such trials in patients with IgA nephropathy.

Keywords Berger's disease · Chronic kidney disease · Glycosylation · Glomerular disease

Introduction

Immunoglobulin A nephropathy (IgAN), a condition originally called Berger's disease, is defined by the presence of IgA deposits in glomerular mesangial areas, sometimes associated with IgA deposits in other areas of the glomeruli [1, 2]. These deposits may be accompanied by other immunoreactants, but the IgA deposits are always dominant or co-dominant. Early descriptions of the condition in children indicated that it was relatively mild [3, 4]. However, it is now known that histologic abnormalities and the clinical course of patients with IgAN may range from almost normal to very severe—in both children and adults [5–8]. In the later stages of disease, glomerulosclerosis may predominate. Although the renal lesions in children with Henoch–Schönlein purpura (HSP) are also characterized by mesangial IgA deposition [9], the features of HSP nephritis are not considered in this review.

Epidemiology

IgAN was first described by Jean Berger in 1968 [1]. Since then, it has become recognized as the most common form of glomerulonephritis in both children and adults in many parts of the world. This is particularly evident in countries such as Japan and Korea, where annual mass screening of school children is carried out [10, 11]. In those countries, IgAN is diagnosed in 30–40% of the patients who have undergone a kidney biopsy to determine the diagnosis in children with hematuria with or without proteinuria.

Diagnosis

The diagnosis of IgAN requires a renal biopsy. Although elevated levels of serum IgA are sometimes observed in patients with IgAN, this finding is too inconsistent to be of diagnostic help. Currently, there are no non-invasive techniques that can establish the diagnosis of IgAN.

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Biopsy findings

The degree of histopathologic injury varies between patients [2, 5–8]. In most cases, there is focal or diffuse mesangial hypercellularity that may vary from mild to severe. Mesangial hypercellularity is accompanied by an increase in mesangial matrix. Endocapillary lesions, which may be proliferative or sclerosing, are also seen in some patients. Crescentic glomerulonephritis, in which more than 50% of glomeruli contain crescents, is observed in approximately 5% of cases [2]. In patients with progressive disease, tubular injury often results in fibroproliferative changes. Immunofluorescence studies are mandatory for the diagnosis of IgAN. The presence of IgA in the glomeruli is usually demonstrated by immunofluorescence of unstained frozen sections. Complement component 3 (C3) is usually present and IgG and IgM are seen in approximately 50% of biopsies [2, 8]. Electron microscopy usually shows electron-dense deposits only in mesangial areas. However, capillary-wall deposits may also be seen in approximately 30% of biopsies. In rare cases there may be a membranoproliferative pattern.

Clinicopathologic correlations

The presence of glomerulosclerosis, fibrous crescents, interstitial fibrosis, or tubular atrophy provides the most reliable histologic indicator of a poor outcome. It is important to distinguish between chronic irreversible lesions and potentially reversible lesions that may respond to therapy.

Etiology

The etiology of IgAN remains unclear [12]. The fact that hematuria following an episode of upper respiratory infection is observed in many patients with IgAN has led to the view that IgAN is a complication of such infections, but no individual viral or bacterial organism has been consistently associated with IgAN. It has also been proposed that IgAN might be caused by hypersensitivity to food antigens. However, there is no evidence of hypersensitivity to food antigens in most patients with IgAN.

Pathogenesis

IgA is produced in two forms, IgA1 and IgA2, and is secreted from mucosal surfaces, with very little reaching the systemic circulation [12]. Increased levels of circulating

IgA immune complexes have been documented in some patients with IgAN. However, attempts to correlate these complexes with disease activity have not produced consistent findings. It has recently been proposed that some patients with IgAN have IgA molecules with some abnormal characteristics that lead to mesangial deposition. This proposed molecular abnormality involves a defect in glycosylation of the IgA1 hinge region [12]. Initial reports of abnormal galactosylation of IgA1 *O*-glycans involved studies that demonstrated abnormalities in the molecular structure of serum IgA, but recent studies have shown the same *O*-glycosylation abnormalities in IgA immune deposits in the glomeruli of IgAN patients [13]. Abnormally galactosylated IgA has also been found in the urine of patients with IgAN. Altered sialylation of IgA1 has also been described.

Genetics

It has been postulated that both genetic and environmental factors may be responsible for the variable prevalence of IgAN around the world, which is most pronounced in southeast Asia. In recent years many families with biopsy-proven IgAN have been described. Some patients share with their asymptomatic blood relatives the abnormality in glycosylation of the IgA1 molecule discussed above. In contrast, individuals who married into these families did not exhibit this defect in glycosylation.

The potential role of an individual's genetic predisposition to the development of IgAN in the USA was established by a large study that was carried out in eastern Kentucky [14]. It was found that 53 of 96 (55%) IgAN patients in eastern or central Kentucky had at least one relative with IgAN. In some parts of Europe up to 10% of patients with IgAN have a family history of renal disease. If hematuria is used as the criterion for IgAN, familial disease may be responsible for 10–15% of all cases in northern Italy and eastern Kentucky. However, it is likely that most of a cohort's family members will not develop clinically progressive disease.

Clinical presentation

The initial clinical features observed in children with IgAN are quite variable, with some being identified as a result of urinary screening as opposed to others who develop overt clinical symptoms or signs. A good example of the first situation exists in Japan and Korea, where many children are diagnosed with IgAN after hematuria with or without proteinuria has been discovered during the annual school screening programs that exists in these two countries [10,

11]. This is exemplified by two recent Japanese clinical trials, wherein 63 (59%) of 106 patients enrolled in the trials were diagnosed after they were found to have urinary abnormalities via the Japanese school screening program [15, 16]. A similar situation was recently reported by Park et al., who described biopsy findings in 113 children who were identified by the Korean school screening program [11]. Thirty-four of 51 (66%) biopsied children with hematuria/proteinuria were diagnosed with IgAN.

Other children with IgAN present with more overt clinical findings. The original descriptions of the disease emphasized synpharyngitic presentations, i.e. an episode of gross hematuria coincident with an upper respiratory infection [1, 2]. This is the most frequent mode of presentation in children and young adults in the Western hemisphere [2, 4, 8]. A smaller number of patients show clinical signs of the nephritic or nephrotic syndrome.

Natural history and prognosis

The natural history of IgAN is quite variable [2–8]. Some children have recurrent episodes of gross hematuria, whereas others remain asymptomatic and may show no overt clinical features. When they occur, the episodes of hematuria are often associated with upper respiratory infections but are usually short-lived, sometimes resolving within a day or two. Up to 20% of pediatric patients with IgAN have progressive disease, leading eventually to end-stage renal disease [5, 6]. In most such cases the rate of progression of disease is usually very slow. This makes it very difficult for the nephrologist to evaluate the level of success of any therapeutic intervention that is employed.

Clinical features which mark a poor prognosis include moderate to severe degrees of proteinuria, renal insufficiency at the time of renal biopsy and hypertension [3–6]. Renal biopsy features that portend a poor prognosis include glomerulosclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis [3–8]. In most patients the level of proteinuria appears to correlate closely with the severity of renal parenchymal disease and risk of progression. Although none of these prognostic indicators has sufficient specificity to identify the outcome of an individual patient, it is clear that children with hypertension and/or severe proteinuria are most likely to have progressive disease and should be regarded as prime candidates for therapeutic intervention [2, 5, 6].

Approach to therapy in children with IgAN

At some point in the future it is likely that the focus of treatment for patients with IgAN will be to reverse the pathogenetic processes that result in the disease. Hence, the therapy might correct defects in IgA1 glycosylation, and/or prevent mesangial deposition of IgA immune complexes. However, such treatment options are not currently available. At the present time, therapeutic strategies are directed at downstream immune and inflammatory processes in the glomerulus and the tubulo-interstitium that are associated with proteinuria and progressive renal damage.

Current options for therapy of individual patients

One of the guiding principles that should be foremost in the minds of pediatric nephrologists when approaching a child or adolescent with IgAN is that aggressive therapeutic measures should not be employed for patients who are not likely to develop progressive disease. This is also true for patients for whom there is no realistic chance of recovery, i.e. patients with diffuse glomerulosclerosis who have reached chronic kidney disease stages 4 or 5 [17]. These patients are considered to have reached "the point of no return". The following sections consider how treatment should be tailored to patients with varying degrees of disease severity. Unfortunately, most of the recommendations are based on less than stellar evidence [18].

(a) Patients with microscopic hematuria and/or low-grade proteinuria: it is not known whether therapy is necessary for such patients, although they should undergo regular follow-up examinations. Some reports indicate that vitamin E supplements may be efficacious in this group of patients [19]. A threshold for more aggressive therapy that has found general acceptance is proteinuria greater than 1 g/1.73 m^2 body surface area per 24 h. This level of proteinuria is equivalent to a urine protein:creatinine ratio of 0.6 in male patients and 0.8 in female patients. Recent reports favor the initiation of treatment with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) for patients with these grades of proteinuria. This is discussed below.

(b) Patients with recurrent gross hematuria: episodes of gross hematuria appear to be of little long-term consequence for patients with IgAN. Most studies of adults even report that a history of gross hematuria is associated with a better prognosis. Studies of this issue in children have produced mixed results. Tonsillectomy has been recommended by some investigators for patients with IgAN complicated by gross hematuria, especially those with a history of frequent episodes of tonsillitis. Reports of this approach in children have been predominantly retrospective studies and have not included adequate

controls [18]. Some proponents have presented evidence that tonsillectomy induces long-term renal protection. However, most of the patients reported in these studies have also received concomitant medications such as corticosteroids. This makes the data difficult to interpret [18]. In general, it is recommended that a conservative approach be maintained for children with recurrent gross hematuria unless they develop additional risk factors.

(c) Children with combined clinical and pathologic risk factors: as noted above, more aggressive treatment measures should be reserved for children and adolescents with features consistent with a high risk of progressive renal dysfunction, such as hypertension, severe proteinuria and/or reduced glomerular filtration rate (GFR) at the time of renal biopsy, plus histologic lesions such as glomerulosclerosis and/or proliferation. Unfortunately, large controlled studies with prolonged follow-up that compare the various treatment strategies in such patients are lacking [18]. Even well-designed studies of progressive IgAN that have been recently published have involved relatively few patients and short periods of follow-up [20]. In addition, many trials of children with IgAN have depended mainly on clinical entry criteria—typically the presence of hypertension and proteinuria—in patients who may have a wide array of pathologic findings [18, 20, 21].

A variety of approaches has been employed in attempts to prevent, or at least delay, progressive renal damage in children and adults with severe manifestations of IgAN.

Many authors propose that the initial goals in IgAN patients with hypertension and/or proteinuria should be to establish a normal blood pressure, based on age, gender and height [22], and to reduce proteinuria via blockade of the renin–angiotensin system (RAS) without resorting to immunosuppressive drugs. A recent multicenter collaborative study in Europe has shown that this approach may provide significant reduction in proteinuria and preservation of GFR [20].

Other investigators believe that the initial treatment of children with high-risk IgAN should incorporate immunosuppressive medications and that therapy oriented towards the renin–angiotensin system is of less importance. The large multicenter studies in Japan have concentrated on immunosuppressive medications and have even prohibited the use of ACEis in their study patients. A third approach to therapy is to employ a stepwise strategy wherein ACEi is tried first and immunosuppressive medications are reserved for patients who show a poor response to ACEis [21]. The next few sections describe the various approaches that have used corticosteroids with or without other immunosuppressive medications in children with IgAN.

Corticosteroids as monotherapy

A trial of high doses of corticosteroids should be considered for children presenting with clinical features of nephrotic syndrome and renal biopsy findings that are otherwise consistent with minimal change disease (MCD) [23–25]. This scenario is relatively rare, but the response of the patients is usually comparable to that seen in children with MCD without IgA deposits. The relationship between the two conditions is unclear.

Results obtained with corticosteroids in children with more significant renal lesions are less certain.

The short-term effect of prednisone on the severity of hematuria in 20 children with milder degrees of proteinuria was examined by Welch et al. [26]. The patients were randomly chosen to be given either placebo or prednisone (2 mg/kg per day) for 2 weeks, followed by the same doses on alternate days for 10 weeks. No difference in the severity of hematuria was reported in the two groups. It should be noted, however, that most of the patients in that study showed relatively mild histologic changes.

In a retrospective study of patients with more severe renal histologic changes, Waldo et al. compared 13 children with IgAN who received prednisone on alternate days for 2 years with 15 children who received no therapy [27]. Whereas none of the 13 treated patients progressed to end-stage renal disease (ESRD), this did develop in five of 15 untreated patients. At last follow-up, 12 of the treated patients had normal findings in their urinalyses.

Corticosteroids plus azathioprine

The efficacy of combination therapy using prednisone and azathioprine was evaluated by Andreoli and Bergstein [28]. They employed a tapering dose of prednisone in addition to azathioprine (2–3 mg/kg per day) for 1 year. Proteinuria fell by 61% from baseline, and the renal biopsy activity score improved. However, the chronicity score was unchanged. There was no control group in this study.

In a subsequent randomized controlled trial (RCT), the Japanese Pediatric IgA Nephropathy Treatment Group evaluated the efficacy of a 2-year course of prednisone, azathioprine, heparin, warfarin, and dipyridamole [29]. The control group received heparin, warfarin and dipyridamole. The group receiving prednisone and azathioprine had a significant reduction of proteinuria (1.35→0.22 g per day), whereas the control did not (0.98→0.88 g per day). Follow-up biopsies showed that progression of glomerular sclerosis had occurred only in the control group.

The same Japanese group then conducted a second RCT, which evaluated the efficacy of prednisone, azathioprine, warfarin and dipyridamole versus a control group

receiving prednisone alone [15]. They found that protein-uria fell to less than 10 mg/m^2 per day in 92% of the group receiving combination therapy versus 74% of the group receiving prednisone (P difference=0.007). As in their first study, they found that the percentage of glomeruli showing sclerotic changes was unchanged from baseline in the group receiving combination therapy but that it had increased significantly in those receiving prednisone alone.

Corticosteroids plus cyclophosphamide

Murakami et al. evaluated the efficacy of a 6-month course of low doses of prednisone combined with cyclophospha-mide and dipyridamole in 17 pediatric patients who had proteinuria >1 g/m^2 per day [30]. The authors noted significant improvement in proteinuria, but post-therapy biopsies showed persistent signs of chronic disease. Additional follow-up in these patients over a period of 5–6 years revealed rebound deterioration of proteinuria.

Mycophenolate mofetil and mizoribine in children with IgAN

The use of mycophenolate mofetil (MMF) has shown mixed results in studies of adults with IgAN, but it has not been studied adequately enough in children for a treatment recommendation to be made.

Mizoribine, an agent that blocks purine synthesis in a manner similar to that of MMF, has been reported to be effective in reducing proteinuria in Japanese children with IgAN [31, 32]. A recent report by Yoshikawa et al. indicated that when mizoribine was substituted for azathi-oprine as part of the combination therapy approach described above, proteinuria fell from 1.19 g/m^2 per day to 0.05 g/m^2 per day [16]. In addition, 18 of 23 children gained complete remission of their proteinuria. The Japanese Study Group has subsequently embarked on an RCT to determine if they can confirm the results obtained in this pilot study.

Omega 3 fatty acids

Based upon the limited evidence available, it is difficult to recommend the use of omega 3 fatty acids for treatment of IgAN in pediatric patients, although data from the North American IgA Nephropathy Trials, which included both children and adults, indicate that such therapy may be efficacious in reducing proteinuria in such patients [33].

Children with crescentic (rapidly progressive) IgAN

The prognosis for children with crescentic IgAN is very poor in the absence of effective therapy [34]. Although there are no controlled trials of treatment regimens for children with crescentic IgAN, Niaudet et al. described a good response to intravenous treatment with methylprednisolone for 2 weeks at a dose of 1 g/1.73 m^2 q.o.d., followed by 1 month of prednisone daily (1 mg/kg) and then prednisone on alternate days for 23 months [35]. The authors also described good long-term outcomes in most of these patients.

Conclusions

It is apparent from this consideration of IgAN in children that we still have much to learn about this condition. Until more specific interventions are discovered, it is recommen-ded that non-immunosuppressive regimens be tried first in patients with signs of slowly progressive disease, with subsequent use of immunosuppressive medications in patients who do not show a good response.

Questions

(Answers appear following the reference list)

1. Children with IgA nephropathy may present with:

   a. gross hematuria
   b. microscopic hematuria
   c. nephrotic syndrome
   d. acute renal failure
   e. all of the above

2. Characteristic renal biopsy findings in patients with IgA nephropathy include:

   a. IgG deposits in glomerular capillary walls
   b. subepithelial deposits on electron microscopy
   c. mesangial hypercellularity plus increase in mesangial matrix
   d. none of the above
   e. all of the above

3. Which of the following statements is true?

   a. IgA nephropathy can be diagnosed on the basis of characteristic light and electron microscopy findings
   b. IgA nephropathy is a rare diagnosis in Korean children with hematuria and proteinuria
   c. patients with progressive renal disease associated with IgA nephropathy usually develop end-stage disease soon after the diagnosis has been made
   d. none of the above
   e. all of the above

4. Gross hematuria is a frequent finding in patients with IgA nephropathy. Which of the following is true?

    a. episodes of gross hematuria indicate a rapidly progressive course
    b. in most patients episodes of gross hematuria persist for 1–2 weeks
    c. gastroenteritis often precedes an episode of gross hematuria
    d. none of the above
    e. all of the above

5. Which of the following statements is true?

    a. treatment of children with corticosteroids has been found to be ineffective in all studies involving children diagnosed with IgA nephropathy
    b. abnormal glycosylation of the IgA molecule may be the underlying problem in some patients with IgA nephropathy
    c. omega 3 fatty acids are well established as an effective treatment for children with IgA nephropathy
    d. none of the above
    e. all of the above

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Answers:

1. e.
2. c.
3. d.
4. d.
5. b.