IgA nephropathy in children

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Introduction

First described in 1968, IgA nephropathy (IgAN) is the commonest variety of primary glomerulonephritis in the world. It is characterized by mesangial deposits of IgA. It was initially considered a benign disease, however, long-term follow-up studies indicate a progression of the disease to renal failure in 20–50% of adults patients. Likewise the favourable prognosis initially attributed in children with IgAN must be questioned in the light of recent studies.

Epidemiology

The prevalence of IgAN varies widely from one country to another. In Japan, France, Italy, and Australia it accounts for 18–40% of all glomerulonephritis whereas the frequency in the US, UK, and Canada is less, about 2–10%. Ethnic–environmental factors, as well as regional differences in performing routine urinalysis and renal biopsy may account for this variability in the incidence of the disease. In Japan, all children aged 6–18 years are screened annually and those found to have urinary abnormalities are referred for further investigation. Familial clustering is rare in IgAN suggesting that genetic factors play a minor role. Also, significant associations between IgAN and some class I (HLA, B27, B35) and class II (HLA, DR1, DR4) major histocompatibility antigens have been reported.

Aetiology and pathogenesis

Aetiology and pathogenesis of IgA nephropathy remain uncertain. There is substantial evidence that it is an immune complex disease ascribed to the deposition of circulating IgA immune complexes (IgAIC) within the glomeruli. Although many studies revealed high levels of IgAIC during clinically active phases of IgAN, circulating IgAIC were detected in only 30–70% of patients. Attempts to identify antigens inciting IgAN have failed to yield consistent results. In 20–30% of patients alimentary antigens have been detected, but they did not correlate with IgAIC complexes or disease activity and efforts to detect alimentary or viral antigens in glomerular deposits also produced inconsistent results.

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Pathology

Immunofluorescence

The diagnostic immunopathological pattern of IgA nephropathy is the presence of IgA in the glomerular mesangium often extending beyond the mesangio-capillary junctions into the capillary walls. There are...
also deposits of IgG and IgM with lesser intensity. C₃ was observed in 64% of the patients.

**Light microscopy**

The most characteristic abnormality is mesangial enlargement caused by various combinations of hypercellularity and increase in matrix. On the basis of the World Health Organization [5] the histologic changes can be graded into: (i) minimal glomerular lesions, (ii) focal mesangial proliferation, where up to 80% of glomeruli show mesangial proliferation and small crescents are found up to 20% of the glomeruli, and (iii) diffuse mesangial proliferation where more than 80% of the glomeruli are affected and crescents are often found in less than 50% of glomeruli; however, in about 10% of patients more than 50% of glomeruli are involved.

The severity of the tubulointerstitial changes usually reflects the severity of glomerular damage whereas vascular lesions are very unusual in children.

**Clinical features**

IgAN occurs at all ages but is most common during the second and third decades of life. It affects males more frequently than females and the reported man: woman ratio varies from 2:1 to 6:1 [6]. The clinical presentation of IgAN varies from asymptomatic urinary abnormalities to acute renal failure. Five different clinical syndromes can be identified at onset: (i) macroscopic haematuria, (ii) asymptomatic microscopic haematuria and/or proteinuria, (iii) acute nephritic syndrome, (iv) nephrotic syndrome, and (v) mixed nephritic–nephrotic syndrome.

Several studies from Europe [7] and US of IgAN in children have shown that more than 80% of all patients have macroscopic haematuria, but it was the initial feature in only 26% of Japanese children because of the school screening programme which detects asymptomatic urinary abnormalities [2]. In children, the overall incidence of macroscopic haematuria, which often occurs 1–2 days after upper respiratory tract infections, is generally lower than in adults. Nephrotic syndrome is reported in 10% of patients.

Acute renal failure is occasionally associated with episodes of macroscopic haematuria and it is usually reversible. However, a subset of patients with IgAN, characterized by extensive crescents, has a rapidly progressive course. A review of published cases of crescentic IgAN, revealed that 41% of the patients were younger than 16 years of age [8].

**Prognosis**

The overall prognosis of patients with IgAN diagnosed in childhood requires long-term studies and remains to be determined. Based on the data of the EDTA Registry, IgAN represents 1.5% of all cases of end-stage renal failure (ESRF) in Europe [9]. The estimated incidence of ESRF caused by IgAN in different countries increases from 0.77 per million inhabitants (p.m.i.)/year in the UK, to 1.8 p.m.i./year in Italy and up to 2.9 p.m.i./year in France. By 24 years of age, 17% of patients who develop ESRF have started dialysis and 40% by 35 years of age.

Definition of the natural history of IgAN is affected by the pre-selection of cases under study including the referral patterns, the indications for renal biopsy, treatment policies and racial differences. The long-term prognosis has been evaluated by Wyatt et al. [10] in 103 children diagnosed before 18 years of age. The predicted kidney survival from the apparent onset was 94% at 5 years, 87% at 10 years, and 70% at 20 years. A long-term follow-up study of 241 Japanese children [11] indicated that 5% of patients have developed chronic renal failure by 5 years and 11% by 15 years from onset of the disease. The school screening programme leads to a preponderance of mild cases in paediatric studies in Japan.

Factors that are associated with an unfavourable course in patients with IgAN have been defined by several studies and are summarized in Table 1 [12].

**Treatment**

The ideal treatment of IgAN would limit the formation of IgA molecules with altered glycosylation and/or reduce the hyperactive IgA antibody response to exogenous or endogenous antigens. These theoretical approaches are still far from clinical application and IgAN presents a therapeutic challenge [4,13]. Prophylactic antibiotics and tonsillectomy may reduce the frequency of episodes of macroscopic haematuria but the effect on the progression of renal failure is questionable. Treatment by phenytoin or danazol has been tried without beneficial effects. Glucocorticoids may benefit the few patients with nephrotic syndrome and minimal mesangial lesions, but their long-term administration and immunosuppressive treatment do not offer any benefit. However, plasma exchange combined with corticoids and immunosuppressive drugs must be applied to patients with rapidly progressive crescentic IgAN. The Japanese study showed good results with combined treatment

| Race (black) | P = 0.005 |
| ↓GFR at Bx | P = 0.68 |
| Proteinuria at Bx ≥ 2+ | P < 0.0001 |
| ↑BP at Bx | P = 0.003 |
| Type 3 lesions with sclerosis | P < 0.001 |
| ≥ 20% sclerosis + proliferation | P < 0.001 |
| Focal global sclerosis | P = 0.01 |
| Crescents/synechiae | P = 0.03 |
| Tubulointerstitial disease | P = 0.03 |
| Peripheral cap wall deposits (EM) | P = 0.14 |
by prednisone, azathioprine, heparin–warfarin, and dipyridamole for 2 years.

In adults, treatment with fish-oil for 2 years diminished the rate of renal failure progression but the proteinuria was unaffected. Recent studies have indicated that angiotensin-converting enzyme inhibition (ACI) reduces proteinuria and preserves renal function.

Summary

(i) The eventual outcome of IgA in children should be re-evaluated. (ii) The clinical outcome varies considerably from patient to patient. (iii) There is no proven treatment for childhood IgAN. (iv) When considering treatment protocol, an issue of great importance is the selection of appropriate patients. (v) Well-designed randomized, controlled trials in children need to be undertaken. Hopefully this situation will improve soon as controlled trials of the above mentioned therapies are conducted around the world.

References