Abstract

IgA nephritis (IgAN) is an autoimmune disease characterized by deposits of IgA in the glomerular mesangium. Clinically, the disease may be punctuated by episodes of macroscopic haematuria often associated with pharyngotonsillitis or may be oligosymptomatic with microscopic haematuria and mild proteinuria. The natural course of IgAN may be indolent and benign; however, some 30–50% of patients may progress to end-stage renal disease when follow-up is extended to ≥20 years. In patients with IgAN, circulating IgA1 molecules have an aberrant structure of O-glycans in the hinge region, which is characterized by abbreviated glycans composed of N-acetylgalactosamine, with or without sialic acid. These aberrant IgA1 trigger the production of autoantibodies, with formation of immune complexes that deposit in the mesangium causing inflammation and production of extracellular matrix. A number of experimental and clinical data outlined a possible pathogenic role of tonsillitis. As a consequence, tonsillectomy has been frequently performed in Japan. Observational studies, made in patients with normal renal function and mild proteinuria, reported that tonsillectomy could reduce the episodes of macrohaematuria as well as the entity of microhaematuria and proteinuria. However, the available studies had short-term follow-up and could not assess the role of tonsillectomy in protecting from renal function deterioration. In a longitudinal retrospective study, Isseki et al. compared the outcome of tonsillectomized patients with IgAN with that of IgAN patients who did not receive tonsillectomy. Tonsillectomized patients had a higher number of remissions and a better slope of glomerular filtration rate in comparison with controls. These data are interesting and suggest that tonsillectomy may prevent renal dysfunction in patients with IgAN and normal renal function. However, the retrospective nature of the study and the presence of some confounding factors require further investigations to confirm these promising data.

Keywords: IgA nephritis; pathogenesis of IgA nephritis; tonsillitis; tonsillectomy and IgA nephritis

IgA nephritis (IgAN) is a glomerular disease characterized by the presence of diffuse mesangial deposits of immunoglobulin A (IgA) usually associated with mesangial proliferation and expansion of the mesangial matrix. IgAN often presents in children or young adults with recurrent episodes of macrohaematuria associated with upper respiratory infection. However, in a number of patients, the disease may be asymptomatic and is detected by the presence of microscopic haematuria or mild proteinuria at screening or check-up visits. It has also been reported that 16–24% of Asian kidney living donors without clinical signs of nephropathy showed deposits of IgA in the mesangium of the donated kidney [1, 2].

IgA is mostly produced in mucosal areas as a result of a cooperation between plasma cells that produce polymeric IgA and mucosal epithelial cells that express a polymeric immunoglobulin receptor, which is released from the nearby activated plasma cells. IgA exist in two isotypes, IgA1 that accounts for ~90% of IgA and IgA2. Human IgA1 has a unique mucin-like structure in its hinge region. It can carry up to six sugar chains, called O-linked glycans. In patients with IgAN, circulating IgA1 molecules have an aberrant structure of O-glycans, characterized by abbreviated glycans composed of N-acetylgalactosamine, with or without sialic acid [3]. These aberrant IgA1 might act as autoantigens and generate the synthesis of glycans-specific antibodies or as antigens for cross-reactive anti-microbial antibodies [4]. The binding of antibodies to antigens forms circulating immune complexes that accumulate in the glomerular mesangium, with activation of mesangial cells, proliferation of extracellular matrix and release of cytokines and chemokines that can initiate and perpetuate glomerular injury [3–5]. Furthermore, binding of polymeric IgA1 to mesangial cells may recruit the lectin pathway of the complement and contribute to create an inflammatory environment [6] that alters the permselectivity barrier (Figure 1). The passage in the tubular lumen of IgA immune complexes together with mesangial cell-derived mediators may promote inflammatory and profibrotic transformation of proximal epithelial cells that can eventually result in interstitial fibrosis and tubular atrophy [4, 7, 8]. Genetic factors are likely to influence the pathogenesis of IgAN. In a genome-wide association study, three independent loci in the major histocompatibility complex as well as a common deletion of CFHR1 and CFHR3 at chromosome 1q32 and a locus at chromosome 22q12 were identified. These five loci can explain 4–7% of the disease variance and up to a 10-fold variation in inter-individual risk [9].

The natural course of IgAN may be variable. Many patients with IgAN can maintain a stable renal function...
Production of IgA1 with galactose-deficient O-glycans in the hinge region (genetic factors?)

Production of autoantibodies which recognize the poorly glycosylated IgA1 hinge region

Formation of circulating IgA-IgG immune complexes

Deposition of immune complexes in the mesangium

Activation of mesangial cells, proliferation of extracellular matrix, release of cytokines and chemokines. Activation of complement

Glomerular inflammation, decreased permeability of the glomerular barrier.

Dysmorphic haematuria, proteinuria

Fig. 1. Sequence of pathogenetic events leading to mesangial deposition of IgA1. Patients with IgAN produce IgA1, which have an aberrant structure of O-glycans in their hinge region. This may trigger the production of autoantibodies (IgG) against the circulating abnormal IgA1, with formation of circulating IgG/IgA immune complexes, that deposit in the glomerular mesangium. Here immune complexes may induce inflammation, activate mesangial cells, induce proliferation of extracellular matrix and release cytokines and chemokines. The consequent damage of the glomerular barrier may permit the passage in the tubular lumen of erythrocytes (dismorphic erythrocytes) and proteins.

but over follow-up of ≥20 years, 30–50% of patients show progression to end-stage renal disease [10, 11]. Due to the variable course of the disease, many efforts have been made to identify clinical or biological prognostic markers. There is general agreement that isolated microscopic haematuria in the absence of proteinuria can predict a favourable prognosis. Among factors that may indicate a poor prognosis, the most important are impaired renal function [12, 13], arterial hypertension [12], proteinuria exceeding 1 g/day at presentation [10] and persistent proteinuria over 500 mg/day [10]. Less clear is the prognostic significance of macrohaematuria. Some investigators found that macroscopic haematuria can carry an increased risk of acute renal failure [14, 15] but others found that the long-term prognosis was favourable in patients with recurrent episodes of macrohaematuria [16–18]. Several histological features have been related to a poor prognosis. To identify specific pathological features that can more accurately predict the risk of progression of renal disease in IgAN, an international network of experts proposed a new clinico-pathological classification, the so-called Oxford classification. Taking into account all clinical indicators available at the time of renal biopsy as well as during follow-up, four features have been found to have prognostic significance, namely mesangial hypercellularity score, segmental glomerulosclerosis, endocapillary hypercellularity and tubular atrophy/interstitial fibrosis [19]. Further studies validated the new classification, although some investigators found that renal function at baseline seems to be of a greater importance than pathological lesions impairment [13], while others suggested to include also extra-capillary proliferation in the Oxford classification [20].

Numerous treatments have been attempted in IgAN. The effects of fish oil, calcineurin inhibitors, purine synthesis inhibitors and cyclophosphamide were modest at best. Controlled trials showed that inhibitors of the angiotensin-converting enzyme can reduce proteinuria and slow the progression of renal disease in IgAN [21, 22]. These data have been confirmed in the clinical practice, and today, most centres are using inhibitors of the renin–angiotensin system (RAS) as a primary treatment of IgAN. Controlled trials showed that glucocorticoids also proved to significantly reduce proteinuria and protect from renal function deterioration, at least in patients with moderate proteinuria and normal or subnormal renal function [23, 24]. The frequent association between tonsillitis and macroscopic hematuria focused the attention of clinicians and researchers on the possible pathogenetic role of tonsillitis and the potential usefulness of tonsillectomy. The palatine tonsils and the nasopharyngeal tonsil are lymphoepithelial tissues that provide a first line of defence against inhaled foreign pathogens. The molecular pattern of viruses and bacteria is recognized by toll-like receptors (TLRs) and other trans-membrane or cytosolic receptors of the cells of the innate immunity. TLRs recruit adaptor proteins and activate a number of kinases that amplify the danger signal and transmit it to transcription factors that enter the nucleus and encode proinflammatory genes. In turn, the inflammatory environment favours the maturation of dendritic cells that capture the antigen and migrate to lymphatic system where they activate immunocompetent cells. Once activated, tonsillar B cells can produce all the five major immunoglobulin classes, but they can release in particular IgA. Some arguments may play for a possible pathogenetic role of tonsil IgA in IgAN: (i) in patients with IgAN, both IgA produced by tonsillar cells and IgA deposited in glomerular mesangium are mainly J chain-positive polymeric IgA [25]. (ii) In a murine model of IgAN, nasal challenge with CpG-oligodeoxynucleotides, which are ligands for TLR9, aggrivated renal injury, led to strong Th1 polarization, and increased serum and mesangial IgA [27]. (iii) In patients with IgAN, an association was observed between TLR9 polymorphisms and disease progression [28]. (vii) It is a common experience that tonsillitis and recurrent pharyngitis are frequently observed in patients with IgAN and are often associated with episodes of macrohaematuria. (vii) In patients with IgAN, tonsillectomy can reduce the episodes of macrohaematuria, improve urinary findings and improve mesangial
proliferation and IgA deposits, particularly when associated with glucocorticoids [25, 29, 30]. It is therefore possible to hypothesize that in response to chronic tonsillitis or repeated episodes of pharyngotonsillitis, genetically (?) predisposed subjects can produce high amounts of abnormally glycosylated IgA1, so favouring the formation of IgA immune complexes and their deposition in the glomerular mesangium (Figure 2).

Tonsillectomy is being frequently used in Japan, while Western nephrologists are more reluctant to adopt tonsillectomy as a treatment for IgAN, mainly because there is no evidence that tonsillectomy can protect renal function in the long-term. In this issue of the Journal, Isseki et al. report the outcome of 200 Japanese patients with biopsy-proven IgAN followed for up to 7 years after renal biopsy. When first admitted to the hospital, patients had normal glomerular filtration rate (GFR), mild proteinuria and microscopic haematuria. Among them, 70 patients received tonsillectomy because of chronic tonsillitis, frequent episodes of acute tonsillitis or gross haematuria in correspondence with a sore throat. Most of them also received glucocorticoids and RAS inhibitors. These patients had significantly increased incidence of remission and reduced incidence of decline in GFR in comparison with patients who were not tonsillectomized. These data led the authors to conclude that tonsillectomy can be associated with a favourable renal outcome of IgAN in terms of clinical remission and delayed renal function deterioration.

**Fig. 2.** The possible involvement of tonsils in the pathogenesis of IgAN. In the tonsils, the pattern recognition receptors of the innate immunity recognize the pathogen-associated molecular patterns (PAMPs) released by pathogens during a pharyngotonsillitis. PAMPs and TLRs may also activate the complement cascade. Through the mediation of adaptor proteins and kinases, TLRs transmit the signal to transcription factors that encode the inflammatory genes of granulocytes, monocyte-macrophages and natural killer cells that together with complement attack the pathogens and create an inflammatory environment. In the presence of inflammation, dendritic cells capture the antigen, mature and migrate to lymphatic system where they present the antigen to immunocompetent cells. B cells produce plasmocytes and immunoglobulins, mostly IgA which are abnormal in patients with IgAN. Therefore, a new clone of B cells will produce IgG against the aberrant IgA, so forming immune complexes that deposit in the glomerular mesangium.

Compared with previous reports, this longitudinal retrospective study has the advantage of a longer follow-up since patients were followed on average for >5 years. Therefore, this is the first study that could evaluate the slope of GFR after tonsillectomy. Moreover, different from many other papers, the participants in this study were adults with ages ranging between 23 and 50 years on admission. This eliminates a possible bias, since children have a higher tendency to spontaneous remission of microhaematuria and mild proteinuria in comparison to adults. Although important, this study has some limitations. An issue is represented by the retrospective nature of the study and by the presence of confounding factors. Many demographic characteristics were similar in the two groups, but there were some significant differences at baseline. In comparison with the control group, renal biopsy in tonsillectomized patients showed more frequently endocapillary hypercellularity, one of the four pathological predictors of poor outcome in the Oxford classification [19]. On the other hand, >70% of tonsillectomized patients received glucocorticoids and RAS inhibitors while only 15% of control patients received glucocorticoids and 45% received RAS inhibitors. These drawbacks were partly contended with by using different models for Cox’s proportional analysis. The authors were able to show that the hazard ratio for remission remained significantly higher in tonsillectomized patients even after adjustments for historical and treatment variables. Similarly, the higher risk of GFR decline in non-tonsillectomized patients (4.8 per 100 person-years versus 0.5 per person-year) remained significantly more elevated after adjustment for laboratory, historical and treatment variables. Two other findings raise some perplexity. Surprisingly, patients who were given RAS inhibitors had a higher risk for GFR decline in comparison with untreated patients. This datum is in contrast with the current evidence showing a renoprotective effect of these agents in IgAN as well as in other glomerular diseases. Also, strange is the better outcome observed in tonsillectomized patients who had worse pathological features at initial renal biopsy, although one might speculate that this was attributable to the beneficial effect of tonsillectomy combined with glucocorticoids and RAS inhibitors. However, the main issue is represented by the different slopes of GFR observed at presentation. The baseline slope of GFR was stable in patients who received tonsillectomy (0.03 mL/min/year) while there was a tendency to decrease in non-tonsillectomized patients (−1.3 mL/min/year). Although the difference was not significant, one may presume that the trends observed at presentation maintained also during a longer follow-up eventually enhancing the difference (0.6 versus −1.6 mL/min).

In conclusion, there is evidence that recurrent pharyngotonsillitis may play a pathogenetic role in IgAN. The paper of Isseki et al. shows that tonsillectomy may represent a promising approach in the treatment of IgAN not only in children but also in adults. Their data also outline that the association of tonsillectomy with glucocorticoids and RAS inhibitors may protect renal function in the long-term at least in patients with preserved renal function and mild proteinuria. However, the retrospective nature of their study and the presence of some confounding factors require further investigations to confirm their conclusions.
Moreover, some questions still remain unanswered: are the beneficial effects of tonsillectomy different in different ethnicities? Can tonsillectomy be of benefit also in IgAN patients without previous tonsillitis or pharingitis? Is tonsillectomy of any benefit in IgAN patients with more severe proteinuria or reduced GFR?

Acknowledgements. C.P. was a consultant of Novartis Italy until December 2011.

Conflict of interest statement. None declared.

(See related article by Maeda et al. Tonsillectomy has beneficial effects on remission and progression of IgA nephropathy independent of steroid therapy. Nephrol Dial Transplant 2012; 27: 2806–2813.)

References


Received for publication: 18.2.2012; Accepted in revised form: 24.2.2012