Does tonsillectomy have a role in the treatment of patients with immunoglobulin A nephropathy?

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Immunoglobulin A nephropathy (IgAN) is an immune-complex mediated glomerulonephritis characterized by deposition of polymeric IgA (mainly IgA1) in the mesangium of the kidney [1]. It is the most common form of primary glomerulonephritis worldwide and is prevalent among all ages and racial demographics [2]. Its pathogenesis has been under investigation for the last several decades and one of the key players is the aberrant glycosylation pattern of IgA1. There is now convincing evidence that the hinge region of IgA1 heavy chain has defective glycosylation with a reduction in the galactose and sialic acid residues [3]. As a result, the N-acetylgalactosamine in the IgA1 hinge region is exposed and recognized by IgG antibodies. This in turn leads to formation of IgG-IgA immune complexes and their deposition in the mesangium and renal injury that subsequently ensues [4–7]. It should be noted that aberrantly glycosylated IgA1 can also be seen in circulation in normal subjects following an immune response triggered by exposure to mucosal antigens such as food, bacteria or viruses. Thus, other factors, including genetic predisposition, are likely to influence the pathogenesis of IgAN [8].

The renal outcomes of IgAN vary significantly between individuals ranging from minimal proteinuria and stable renal function to development of end-stage renal disease (ESRD) in up to 50% of the cases [9]. Markers of poor prognosis include impaired kidney function at presentation, hypertension and persistent proteinuria >1 g/day in adults, and 0.5 g/day in children [10–12].

In addition, the recent Oxford classification has identified MEST (mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis) as an independent renal biopsy indicator of poor renal outcome [13]. Treatments aiming to block the angiotensin II system, the use of corticosteroids, either alone or in combination with cytotoxic medications have been used in patients with IgAN with variable success [14–18]. In some patients, renal disease progresses despite treatment and thus a search for additional forms of therapy have been carried out including the use of tonsillectomy.

What is the rationale behind performing tonsillectomy in patients with IgA nephropathy? First, recurrent tonsillitis is the most common extrarenal clinical manifestation in IgAN and there is a clear recognition that in some patients episodes of macroscopic hematuria and proteinuria are often associated with tonsillitis (synpharyngitic hematuria) [19, 20]. In fact, studies have shown that episodes of macroscopic hematuria can be reduced following tonsillectomy [21, 22]. Second, tonsils provide the first line of defense against inhaled pathogens. The foreign antigens, particularly bacterial polysaccharides, activate the Toll-like receptors (TLRs) of the cells of innate immunity, which ultimately results in activation of tonsillar B-cells and production of immunoglobulins particularly polymeric IgA1. Third, tonsils from patients with IgAN have an increased number of polymeric IgA1 compared with controls [23]. Forth, the polymeric IgA1 deposited in the kidney are, in part, of tonsillar origin. This was based on the evidence that IgA1 eluted from the mesangium of patients with IgAN specifically bound the nuclear regions of tonsillar cells obtained from the same patient and the binding was completely inhibited by the addition of antihuman IgA sera [24]. Fifth, abnormal IgA-secreting cells which predominantly produce polymeric IgA1 are found in the tonsillar tissue of patients with IgAN in contrast to IgG-secreting cells that predominate in tonsils of patients without IgAN [20, 25–27]. Taken together, it has been postulated that chronic tonsillitis in a susceptible patient may lead to increased production of aberrantly glycosylated IgA1, formation of IgG-IgA immune complexes and their deposition in the glomeruli triggering an inflammatory response [28]. As such, tonsillectomy has been suggested as a possible treatment modality in patients with IgAN. Several retrospective studies have evaluated the efficacy of tonsillectomy in treatment of IgAN with conflicting results as shown in Table 1 [21, 22, 29–35]. Most of the studies, however, are from an era prior to
routine use of renin-angiotensin system (RAS) blockade and/or concomitant corticosteroid therapy.

In the only prospective non-randomized trial, Komatsu et al. found an increased rate of clinical remission in patients with IgAN when tonsillectomy was combined with pulse steroids suggesting a possible role for tonsillectomy [21]. Similarly in a meta-analysis by Wang et al. in which seven retrospective studies were included, there appeared to be a beneficial effect for tonsillectomy when it was combined with steroids [36]. Importantly, in some of these studies, the beneficial effect of tonsillectomy was not seen until 5–10 years after the procedure [22, 32]. Currently, even though tonsillectomy is not recommended as part of treatment of IgAN by Kidney Disease: Improving Global Outcomes Guidelines [12], tonsillectomy remains a common practice in Japan [37]. Given that tonsillectomy is not without risks, there has remained a definite need for a randomized clinical trial (RCT) to evaluate the role of tonsillectomy in treatment of IgAN.

In the current issue of NDT, Kawamura et al. report the results of the first randomized controlled trial of tonsillectomy combined with pulse steroids in treatment of patients with IgAN [38]. Eighteen centers across Japan participated in this study and total of 80 patients were recruited. Patients were randomized into two groups and followed for 12 months. Group A underwent tonsillectomy in addition to pulse steroids (500 mg of intravenous methylprednisolone per day for 3 days at 1 and 3 weeks and then at 2 and 4 months in addition to oral prednisolone at a dose of 0.5 mg/kg for 6 months), whereas Group B only received steroid therapy similar to Group A. Patients with IgAN who presented with nephrotic syndrome, serum creatinine >1.5 mg/dL, or recent immunosuppressive therapy or contra-indications to surgery were excluded. Percentage decrease in urinary protein from baseline and clinical remission defined as disappearance of proteinuria and hematuria were primary end points. Doubling of serum creatinine and change in estimated glomerular filtration rate (eGFR) were secondary end points.

There were equal numbers of males and females in the study with mean age of 38 years. The renal function was similar between the groups and well-preserved (mean eGFR of 72 mL/min/1.73 m²). The renal biopsies, however, suggested a relatively poor or a poor prognosis in 95% of the patients with a mean 24-h proteinuria of 1.6 g/day. Only half the patients were on treatment with renin-angiotensin inhibitor (RAS-I) at the time of randomization. At 12 months, patients who underwent tonsillectomy in Group A had a larger percentage decrease in proteinuria compared with Group B. The authors do not provide data on the absolute reduction in the amount of proteinuria in each group or the mean 24-h urinary protein in follow-up, which weakens interpretation of the results. In addition, even though the percentage decrease in the degree of proteinuria was statistically significantly higher in Group A, the actual difference was only ~10–15% between the two groups and thus relatively small in actual terms. Moreover, there were no differences in the percentage of patients who had disappearance of proteinuria at 12 months. Similarly, the disappearance of hematuria was no different between the two groups and the rate of clinical remission remained similar at 12 months.

**Table 1. Summary of non-randomized studies evaluating the efficacy of tonsillectomy in treatment of patients with IgAN.**

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient population</th>
<th>No.</th>
<th>Age (mean ± SD)</th>
<th>Gender (M/F)</th>
<th>Duration of follow-up (Y/N)</th>
<th>Use of steroids</th>
<th>Outcome Favors tonsillectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasche et al. [29]</td>
<td>European</td>
<td>55</td>
<td>39 ± 15.6</td>
<td>36/19</td>
<td>36.0 ± 8.4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Piccoli et al. [30]</td>
<td>European</td>
<td>61</td>
<td>28.3 ± 10.9</td>
<td>39/22</td>
<td>250 (12–300)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chen et al. [31]</td>
<td>Chinese</td>
<td>112</td>
<td>27.3 ± 9.5</td>
<td>66/46</td>
<td>130 ± 50.3</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hotta et al. [22]</td>
<td>Japanese</td>
<td>329</td>
<td>36.1 ± 12.8</td>
<td>178/151</td>
<td>823 ± 38.2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Maeda et al. [34]</td>
<td>Japanese</td>
<td>200</td>
<td>31.6 (25.2–48.5)</td>
<td>67/133</td>
<td>624 ± 24</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kawaguchi et al. [35]</td>
<td>Japanese</td>
<td>388</td>
<td>38.8 ± 11.5</td>
<td>177/214</td>
<td>213/34</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Komatsu et al. [21]</td>
<td>Japanese</td>
<td>55</td>
<td>39 ± 11.5</td>
<td>21/34</td>
<td>54 ± 21.2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CR, complete remission. *This is median with minimum and maximum range.*
An advantage of the current study was that it is the first randomized study evaluating the use of tonsillectomy in IgAN. A major issue is the small size of the study and the potential lack of power to answer the questions proposed considering that 7/40 (17.5%) of the patients in the tonsillectomy/corticosteroid arm were discontinued from the study leaving 33 patients for the analysis. This is further confounded by the fact that two patients in the corticosteroid alone arm underwent tonsillectomy after randomization and one patient in the tonsillectomy/corticosteroid arm did not undergo tonsillectomy but were included in the intent-to-treat analysis. Another problem recognized by the authors is that <50% of the patients had been treated with an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). This form of therapy was added at the discretion of the treating physician and in seven cases it was added after randomization. As reported by Praga et al., ACE-I has a significant effect in protecting renal function and reducing proteinuria and current recommendations are to titrate RAS-I before adding immunosuppressive therapy [14]. When taken together, all these imbalances can have significant effects when dealing with studies involving small number of patients.

Whether the small additional reduction in percentage proteinuria in Group A translates to better renal outcome long-term is yet to be determined. Even though previous retrospective studies performed in the Japanese population showed reduced proteinuria and increased rate of clinical remission in patients who underwent tonsillectomy, this RCT which also included the Japanese population shows no benefit in the short term. This is consistent with the data presented by the European Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA) network at the American Society of Nephrology Kidney Week 2013. The study included 1147 European patients with IgAN that were followed for 5 years and evaluated 41 patients with tonsillectomy that were matched to 41 patients that did not undergo tonsillectomy and showed that tonsillectomy provided no additional benefit in reducing the rate of ESRD or GFR loss in patients with IgAN that were followed for 5 years [39]. In addition, the current study does not answer the question of the role of tonsillectomy plus corticosteroid therapy in patients with IgAN and higher risk of progression (i.e. Scr >1.5 mg/dL and proteinuria >3 g/dL), although the study by Xie et al. showed no benefit for tonsillectomy in patients with proteinuria >1 g/24 h or glomerular sclerosis >25%. This study does confirm that corticosteroid therapy is effective in reducing proteinuria in IgAN.

Finally, the follow-up in this study is of short duration and many of the secondary outcomes in particular renal outcomes and need for renal replacement therapy were not reached. This may have been in part because patients had excellent renal function to begin with and use of estimated GFR to detect small changes in renal function may not be as useful, and more sensitive methods for quantifying GFR such as iothalamate clearance could have detected smaller trends in GFR. Regardless, a slowly progressive disease such as IgAN requires a more prolonged follow-up (i.e. >5 years) in order to assess renal prognosis.

An interesting finding of the study was that tonsillectomy had no additional effect on hematuria. If mucosal infection coincides with episodes of gross hematuria in classical cases of IgAN and abnormally glycosylated IgA1 that are secreted from the mucosal compartment are the key step in the development of IgAN, why is it that removing the tonsils does not improve the rate of clinical remission? First, activation of intestinal lymphoid tissue, rather than tonsillar, may also play a role in the pathogenesis of IgAN [40] and tonsils represent only a small part of the gut-associated lymphoid tissue (GALT) mass [41]. Second, in patients with IgAN, polymeric IgA-secreting plasma cells are increased systemically in particular in the bone marrows [42, 43]. As such, it should not be surprising that tonsillectomy alone does not result in long-term depression in secretory IgA. In fact, data from the VALIGA study showed that even though the serum degalactosylated IgA1 levels were lower in tonsillectomized patients compared with non-tonsillectomized individuals, the levels were still significantly higher than controls [44]. Finally, increased production of galactose-deficient IgA1 is only one step in the development of IgAN and other factors including production of IgG-anti-IgA antibodies and activation of complement pathway in the renal mesangium play a major role [7].

The current study does not support the role of tonsillectomy in addition to corticosteroid in treatment of IgAN based on the short-term outcome. Tonsillectomy is an invasive surgery that is not without risk. Whether there would be any long-term improvement in renal outcomes in patients who underwent tonsillectomy in addition to RAS blockade and corticosteroid therapy is yet to be seen, but the current data do not support the use of this surgery in the absence of clear otorhinolaryngological indication.

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**CONFLICT OF INTEREST STATEMENT**

The authors have no conflict of interest.

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