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PERSPECTIVES IN RENAL MEDICINE

Relationship between tonsils and IgA nephropathy as well as indications of tonsillectomy

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Relationship between tonsils and IgA nephropathy as well as indications of tonsillectomy. Although there are many papers about IgA nephropathy (IgAN) and tonsils, respectively, reviews about the relationship between tonsils, tonsillitis, tonsillectomy, and IgAN are limited. In this review, we introduced the structure, development, and function of tonsils, difference of tonsils with and without IgAN, consistency of both tonsillar IgA and glomerular IgA, the effect of tonsil stimulation, tonsil infection, and tonsillectomy on IgAN showed some evidences in which tonsils were closely related to IgAN and polymeric IgA1 deposited in glomerular mesangium were at least in part of tonsillar origin. Tonsillectomy can improve the urinary findings, keep stable renal function, improve mesangial proliferation and IgA deposit, have a favorable effect on long-tern renal survival in some IgAN patients, and do not cause significant immune deficiency and do not increase incidence of the upper respiratory tract infections, and can be used as a potentially effective treatment. The indications of tonsillectomy in patients with IgAN include mainly the deterioration of urinary findings after tonsillar infection, mild or moderate renal damage. However, tonsillectomy may not be enough and may not change the prognosis in IgAN patients with marked renal damage.

Immunoglobulin A nephropathy (IgAN), that is, nephropathy with mesangial IgA-IgG deposits, was first reported by Berger and Hinglais in Frence in 1968 [1] and described by Berger in English in 1969 [2]. Studies for more than 30 years demonstrated that primary IgAN is an immune complex–mediated glomerulonephritis defined immunohistologically by the presence of glomerular IgA deposits [3]. It is now generally known to be the most common form of primary glomerulonephritis throughout the world [4–6]. Although primary IgAN was considered a benign condition for many years, it is now clear that a large number of cases eventually progress to renal failure [7–11]. Indeed, IgAN is the main cause of end-stage renal disease (ESRD) in patients with primary glomerular disease who require renal replacement therapy [12, 13]. However, the cause of primary IgAN, source of IgA deposited in glomeruli and the mechanism underlying mesangial IgA deposition in IgAN, is unclear and there is no effective treatment available for patients with IgAN [14].

The IgA deposited in glomerular mesangium in patients with IgAN appears to be exclusively of the IgA1 subclass [15] and IgA produced by tonsillar lymphcytes in patients with IgAN is mainly polymeric IgA1, about half of patients with IgAN their serum IgA levels increase [16] and tonsillectomy decreases the levels of serum IgA, suggesting there is any relationship between tonsils and IgAN. Recently, we demonstrated that the tonsillectomy has a favorable effect on long-term renal survival in patients with IgAN [17].

Although there are many papers about IgAN and tonsils, respectively, reviews about the relationship between tonsils, tonsillectomy, and IgAN are limited. In this review, we introduce the structure, development, and function of tonsils, difference of tonsils with and without IgAN, consistency of both tonsillar IgA and glomerular IgA, the effect of tonsil stimulation, tonsil infection, and tonsillectomy on IgAN, show some evidences in which tonsils were closely related to IgAN and polymeric IgA1 deposited in glomerular mesangium were at least in part of tonsillar origin, and present the indications of tonsillectomy in patients with IgAN.

STRUCTURE, DEVELOPMENT, AND FUNCTIONS OF TONSILS

Structure of tonsils

Human tonsils include the palatine tonsils, nasopharyngeal tonsil (adenoid), lingual tonsil and the tubal tonsils [18] (Fig. 1). The palatine tonsils are the largest ones in four types of tonsils in human beings. Histologically, tonsil tissues consist of four well-defined microcompartments,

Key words: tonsils, tonsillectomy, IgA nephropathy, treatment, indication.

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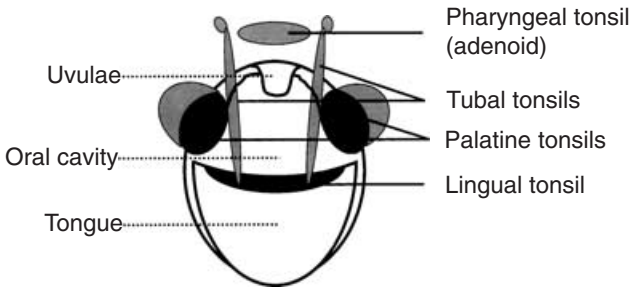

Fig. 1. Anatomy of the tonsils.

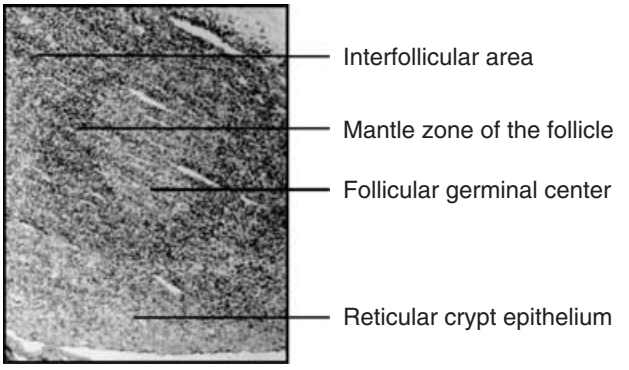

Fig. 2. Histologic structure of tonsils. The sample originated from tonsil tissues after tonsillectomy because of chronic tonsillitis in 8-year-old, male patient. The cellular nuclei of the section were stained with hematoxylin (original magnification ×50).

which all participate in the immune response: the reticular crypt epithelium, the interfollicular (extrafollicular) area, the mantle zone of lymphoid follicles, and the follicular germinal center [19] (Fig. 2). Cell biologically, immunocyts of tonsil tissues contain predominantly B cells (approximately 65%), approximately 30% $CD3^+$ T cells, and 5% macrophages. The T cells were primarily of the $CD4^+$ subset (approximately 80%) [20]. Quantitative immunohistochemistry reveals that IgG-containing B cells predominate in all lymphoid compartments, including follicles, extrafollicular areas, and reticular epithelium, whereas IgA cells are found predominantly in extrafollicular areas, especially subepithelial area, and IgM cells are in follicles. J chain is present within IgM and some IgA cells. The IgG:IgA:IgM class ratios of the overall tonsillar immunocyte population are 13:8:2. Cells containing IgD and IgE are rare [21]. In clinically normal tonsils, the overall percentage distribution of these cells is 65:30:3.5:1.2 for the IgG, IgA, IgM. and IgD classes, respectively. In recurrent tonsillitis, these figures are 53:39:4.7:4.4; in hyperplastic tonsillitis, 67:25:4.0:4.5; and in idiopathic tonsillar hyperplasia, 50:33:7.2:10, respectively [22]. In comparison with the clinically healthy tonsils, the number, the size of the germinal centers and the density of the immunocytes in tonsils are very large in the hyperplastic tonsils, large in chronic cryptic tonsillitis, but remarkably decreased in acute tonsillitis [23]. The study regarding the distribution and proportion of Ig subclasses producing cells in chronic tonsillitis show that the percentage ratios of IgG1:IgG2:IgG3:IgG4 were 53.1:35.9:4.7:6.3, respectively. Proportional ratios of IgA1:IgA2 are approximately 80:20 [24].

Development of tonsils

The development of the palatine tonsils starts during the 14th gestational week when the mesenchyme underlying the mucous membrane of the tonsillar cavity becomes invaded by mononuclear wandering cells. In fetuses of about the 16th gestational week epithelial crypts grow down into the connective tissue and are infiltrated by T lymphocytes. At the same time, precursors of interdigitating cells can be identified among the epithelial cells. Primary follicles develop in earlier fetal stages than in all other secondary lymphoid organs. They contain precursors of dendritic reticulum cells and lymphoid cells that belong to the B-cell line. These primary follicles may be considered as the first assemblage of B-cell regions in human fetal lymphoid tissue [25]. The formation of the follicular germinal centers reflecting B-cell activation by exogenous antigens takes place shortly after birth [26]. The immunohistochemical study show the morphometric features of tonsils below the age of 8 years are more active than those above the age of 8 years. Total number of IgA immunocytes is the highest at the age of 5 to 7 years with a decline by age. The serum IgA and salivary secretory IgA concentrations reach to adult's level at the age of 11 to 13 years. These results suggest that tonsils in preschool children are important as a local immunological defense mechanism [27].

Functions of tonsils

Tonsil tissues are located at the gateway of the respiratory and alimentary tract and belong to the mucosa-associated lymphoid tissue. The generation of B cells in the germinal centers of the tonsil is one of the most essential tonsillar functions. The major function of tonsils is as a first line of defense against viral, bacterial, and food antigens that enter the upper aerodigestive system. Secretory dimeric IgA produced by B cells has particular hydrophilic properties and is capable of preventing adsorption and penetration of bacteria and/or viruses into the upper respiratory tract mucosa [28]. With the uptake of antigen by microfold cells (membrane cell, M cells) present in the cryptepithelium a process is initiated, which ultimately results in the generation and dissemination of antigen-specific memory and mainly dimeric IgA-producing effector B lymphocytes. This process requires successful cognate interactions between antigen-presenting cells and lymphocytes and mutually between lymphocytes, which depend not only on antigen-specific

Table 1. Difference of tonsils with (+) and without (−) IgA nephropathy (IgAN)

Characteristic of tonsils	IgAN(+)	IgAN(−)	Reference number
T cell area (T nodules)	Expanded	Not expanded	29
Reticulization of crypt epithelium	Reduced	Not reduced	31
IgA cells:IgG cells	>1	<1	32–34
Polymeric IgA cells	Increased	Not changed	32–34
Polymeric IgA:IgA	Increased	Not changed	35
Follicular dendritic cells	IgA1+	IgA1−	36
J chain mRAN-positive cells	Increased	Not changed	37
Adhesion molecules CD31, CD54	Increased	Not changed	38
CD5+ B cells	Increased	Not changed	39

signals, but also on the expression of various complementary adhesion and costimulatory molecules [19]. In additional, Mitogen-triggered T cells from tonsils produced both of Th1- and Th2-type cytokines, clearly exhibiting their pluripotentiality for support of cell-mediated and antibody responses. The antigen-specific T cells produced interferon-gamma (INF-γ) and lower levels of interleukin-5 (IL-5). These results suggest that tonsils of the nasopharyngeal-associated lymphoreticular tissues represent a distinct component of the mucosal-associated lymphoreticular tissues with features of both systemic and mucosal compartments [20].

DIFFERENCE OF TONSILS WITH AND WITHOUT IgA NEPHROPATHY

There are significant differences in histologic structure, proportional ratios of cells, and cell adhesion molecules in tonsils with and without IgAN (Table 1).

Difference of tonsillar histologic structure

The enlarged primary T nodules in tonsils, which are defined as sum of the small areas of accumulating T lymphocytes and apparent nodule, composed predominantly of small T lymphocytes, were a characteristic feature of tonsils in patients with IgAN. Most T nodules in patients with IgAN were enlarged, especially in younger patients, and a few T nodules contain high endothelial venules and nonlymphoid cells. In contrast, T nodules in patients with habitual tonsillitis do not expand, and nonlymphoid cells and high endothelial venules are distributed peripherally around the nodules [29]. The basic structure and functional unit of reactive lymph nodes is composed of two separate T nodules and B-lymphoid follicles. These composite nodules play a major role in the triggering, helper T-cell–dependent stimulation and subsequent maturation of antigen-responsive B cells into antibody-secreting plasma cells [30]. With regard to his relationship between T-cell and B-cell domains, the enlarged primary T nodules reminds us that extrafollicular maturation of the stimulated B lymphocytes into plasma cells may occur more frequently in the tonsils of patients with IgAN than in patients with habitual tonsillitis. Another study demonstrated abnormal reticulization of tonsillar crypt epithelium in patients with IgAN. Tonsils of controls with recurrent tonsillitis or tonsillar hypertrophy showed well-developed reticular crypt epithelia with lymphoepithelial symbiosis, and the nonreticulated area was less than 7% of the total crypt epithelia per overall section. In IgAN tonsils, however, nonreticulated crypt epithelium was frequently observed and, in the advanced stage of IgAN, exceeded 50% of total crypt epithelia [31].

Difference of tonsillar cells

Primary IgAN is characterized by renal deposits of polymeric IgA (J chain-positive), the origin of which is not confirmed, yet. The study by Bene et al [32] showed that in controls with recurrent tonsillitis, IgG secreting cells were predominant (IgG secreting cells 65% and IgA plasma cells 29%), while in the IgAN patients, the plasma cells percentages was of an inversion (IgG 37% and IgA 56%). This increment in the IgA population was paralleled by an augmentation of the number of dimeric IgA secreting cells (75% of IgA plasma cells), stained both for cytoplasmic IgA and J chain [32]. The study by Nagy and Brandtzaeg [33] and a later multicenter study by Bene et al [34] also demonstrated a similar result. In additional, after 7 days of culture with pokeweed mitogen, the percentage of tonsillar cells producing polymeric IgA is significantly higher in the IgAN patients than in the controls suffering from chronic tonsillitis [35]. The IgA1 subclass was found in follicular dendritic cells (FDC) of the tonsil of IgAN patients, but not in FDC of non-IgAN controls. On the other hand, IgA2, IgG, IgM, and C3 did not show any differences in distribution between the two groups [36]. In situ hybridization (ISH) study for the detection of J chain mRNA within IgA plasma cells revealed J chain mRNA-positive cells were identified in germinal centres, and within the subepithelial and interfollicular zones of tonsils. Combined immunofluorescence and fluorescent ISH showed a greater proportion of J chain mRNA-positive interfollicular IgA cells in the patient tonsils compared with the controls. In additional, the finding of excess numbers of J chain-positive IgA-negative cells was found within germinal centers of tonsils in IgAN patients [37]. These results demonstrate immune abnormalities within the tonsil as a central feature of abnormal polymeric IgA biology in IgAN, which is in keeping with the hypothesis favoring a tonsil origin for the mesangial IgA present in their kidneys.

Abnormalities in the partition of IgA- and IgG-producing cells in the tonsils of patients with IgAN have been suggested to result from a dysregulation of cell

trafficking and homing through high endothelial venules in this lymphoid tissue. Study demonstrated a significant enhancement of cell adhesion molecules, CD31 and CD54, expression on high endothelial venules of tonsils from patients with IgAN compared with controls [38]. In additional, the number of $CD5^+$ B cells isolated from the tonsil germinal centers of IgAN patients is increased. These $CD5^+$ B cells are likely IgA1 antibody-producing cells. Moreover, these $CD5^+$ B cells show a reduced susceptibility to Fas-mediated apoptosis [39].

RELATIONSHIP BETWEEN TONSILLAR IgA AND GLOMERULAR IgA

Both IgA produced by tonsil cells and IgA deposited in glomerular mesangium with IgAN are mainly J chain-positive polymeric IgA [35, 37, 40, 41]. Studies demonstrated they were consistent in some cases. The antibodies eluted from renal tissues of patients with IgAN specifically bound with the nuclear regions of tonsillar cells. The binding of eluted antibodies and tonsillar cells was completely inhibited by the addition of antihuman IgA antisera, but not inhibited by human IgA myeloma proteins. The eluted antibodies bound with tonsillar cells from the same patients, but only 10% of them bound with the tonsillar cells obtained from other patients with IgAN. This result suggests that IgA antibodies deposited in glomeruli specifically bind with tonsillar cells obtained from patients with IgAN [42]. The study by Tokuda et al [43] offered another evidence of binding of IgA produced by tonsillar B lymphocytes to the glomerular mesangium of IgAN. They first made heterohybridoma cells of human tonsillar B lymphocytes from IgAN patient with mouse myeloma cells and cultured them. The culture medium was analyzed by Western blot analysis using antihuman IgA antibody, and both IgA1 and IgA2 were demonstrated to be produced. The specimens of the biopsied kidney tissue of IgAN were washed with 0.02 mol/L citrate buffer (pH 3.2) to remove deposited IgA from glomerulus. The specimens were then incubated with the culture media of hybridoma cells, and immunofluorescence analysis using fluorescein isothiocyanate (FITC)-conjugated antihuman IgA antibody was performed. The result demonstrated that IgA deposit was efficiently removed by washing with citrate buffer and was recovered after incubation with the culture medium of hybridoma cells [43].

TONSIL STIMULATION AND IgAN

Method and judging criteria of tonsil provocation test

The methods of tonsil provocation test include direct or indirect tonsil stimulation using Tonsil Provocator producing an ultrashort wave (each tonsil for 5 minutes), mechanical tonsil stimulation (tonsil massage, each tonsil for 5 minutes) and injecting hyaluronidase (2000 U/mL, each tonsil for 0.5 mL) into tonsils. In general, four criteria are used to judge the results of tonsil provocation test. Any one of four criteria positive is regarded as tonsil provocation test positive: (*1*) an increase of white blood cell count over 1200/mm^3 after 3 hours; (*2*) an increase in body temperature over 0.55°C after 15 minutes; (*3*) enhancement of erythrocyte sedimentation rate over 12 mm after 1 hour; and (*4*) worsened skin eruption or deterioration of urinary findings after 3 hours, which is defined as urinary protein increased by more than 30 mg/dL or erythrocyte count in the sediment increased by more than 10/hpf, as compared with that before the test [44, 45].

Effect of tonsil stimulation on IgAN

Although the pathogenesis of IgAN still remains uncertain, it is well known that IgAN patients often show gross hematuria or deteriorated urinary findings after upper respiratory tract infections such as tonsillitis, it is supposed that tonsil inflammatory stimulation may be related to IgAN. Masuda et al [46] reported that a tendency of decreasing levels of serum complement combined with an increase of CIC was observed within 1 week after tonsil provocation test in several cases of IgAN associated with chronic tonsillitis [46]. Shiraishi et al [44] performed the tonsil provocation test in 11 cases with pustulosis palmaris et plantaris (PPP) and seven cases with IgAN. Analysis of the provocation test proved positive in three of 11 cases (27%) with PPP and in five of seven cases (71%) with IgAN [44]. Yamabe et al [45] studied effect of ultrashort wave stimulation of tonsils on urinary findings in patients with IgAN. In 62 patients with IgAN and 20 patients with other renal diseases, tonsils were directly stimulated by Tonsil Provocator producing an ultrashort wave to 40.68 MHz each tonsil for 5 minutes. Forty (65%) of 62 patients with IgAN showed deterioration of urinary findings after the stimulation compared with 6 (30%) of 20 patients with other renal diseases. The deterioration of urinary findings was significantly more frequent in IgAN than in other renal diseases. In additional, previous episodes of gross hematuria following upper respiratory tract infections and the level of serum secretory IgA were higher in IgAN patients with deterioration of urinary findings after tonsil stimulation than in those without deterioration [45]. Matsuda et al [47] evaluated the effects of the mechanical tonsil stimulation on the serum and urinary concentrations of macrophage-colony-stimulating factor (M-CSF) in patients with IgAN associated with chronic tonsillitis. The serum and urinary levels of M-CSF in the groups with mild and severe IgAN were significantly higher than those in the chronic tonsillitis group without IgAN. Enhanced urinary excretion of M-CSF prolonged for 7 days after tonsil stimulation in the severe IgAN group; in contrast, the urinary M-CSF

level was increased for only 2 days after tonsil stimulation in the mild IgAN group. The urinary M-CSF level was not changed in the chronic tonsillitis group after tonsil stimulation. These results suggest that tonsil stimulation contributes to the progression of IgAN via enhancement of glomerular production of M-CSF [47].

However, the usefulness of the tonsillar provocation test in IgAN is now doubted. Even otolaryngologists [46] who initially claimed that the tonsillar provocation test was of clinical value in patients with IgAN have already changed their opinion. Their late results showed that there was no statistically significant difference between positive and negative patients in the rate of remission of proteinuria based on any parameter of the tonsillar provocation test at any time after surgery [48, 49]. Moreover, the Japan Society of Stomato-Pharyngology officially reported the lack of value of tonsillar provocation test in determining the indications for tonsillectomy in IgAN patients [50]. We think that an increase of white blood cell count, an increase of body temperature and enhancement of erythrocyte sedimentation rate after tonsillar provocation test may not be of any clinical value in patients with IgAN, but deterioration of urinary findings after tonsillar stimulation may be significant and suggest that tonsils are related to kidneys. A questionnaire survey also showed that 51.6% of 154 medical doctors who had reported case of IgAN answered that urine protein was the most important factor in any estimation of the provocation test [51].

TONSILLAR INFECTION AND IgAN

Tonsillar bacterial infection and IgAN

Suzuki et al [52] reported that the antigen and antibodies of outer membranes of *Haemophilus parainfluenzae*, a common bacterium on the tonsils, were present in glomerular mesangium and sera of IgAN, respectively, suggesting that *H. parainfluenza* infection may have a role in the etiology of IgAN [52]. Further studies showed that tonsillar lymphocytes from patients with IgAN revealed a significantly higher stimulation index to *H. parainfluenza* antigens (thymidine incorporation in tonsillar lymphocytes with *H. parainfluenza*/thymidine incorporation in unstimulated tonsillar lymphocytes) than controls. The lymphocytes from patients with IgAN also showed a significantly higher level of IgA antibody and IgA1 antibody against *H. parainfluenza* antigens in culture supernatants than lymphocytes from controls [53]. In vivo study showed that mouse glomerular deposition of *H. parainfluenza* outer membrane antigens and IgA, and increases in the amount of mesangial matrix were observed after administration of *H. parainfluenza* outer membrane antigens orally or intraperitoneally, respectively. Levels of IgA antibodies against *H. parainfluenza* outer membrane antigens were significantly increased in administration groups compared with controls. That is, administration of *H. parainfluenza* outer membrane antigens to mice may induce glomerular deposition of IgA and mesangial proliferation, resembling the changes seen in IgAN, with increases in IgA antibodies against *H. parainfluenza* outer membrane antigens [54]. Furthermore, production of cytokines IL-10 and transforming growth factor-β (TGF-β) was enhanced by stimulation with *H. parainfluenza* outer membranes in tonsillar mononuclear cells from IgAN [55]. These results suggest that *H. parainfluenza* antigens stimulate tonsillar T and B lymphocytes in patients with IgAN to produce cytokines and IgA antibody and that an immune response to *H. parainfluenza* antigens may play a role in the pathogenesis of IgAN in some cases.

In additional, Rekola et al [56] reported that 38 of 187 IgAN patients had possible acute glomerulonephritis at the onset of their disease. Antistreptococcal antibodies increased in forty-three percent of the patients. Thirty-three percent of the patients had different groups of beta-hemolytic streptococci isolated from their throats. This result indicates a possible role of beta-hemolytic streptococci, a most common bacterium in tonsils or throat, in the pathogenesis of some IgAN cases [56].

Tonsillar viral infection and IgAN

Regarding relationship between viral infection in tonsils and IgAN, there is a adult case report in which granular depositions of adeno- and herpes simplex viral antigens were detected in the glomerular mesangial areas in IgAN patients associated with episodes of recurrent tonsillitis and in the tonsillar epithelial cells by *H. parainfluenza* immunofluorescence [57]. The later study showed that the detection ratio of Epstein-Barr virus in the patients with glomerular lesions, such as IgAN and membranous nephropathy, was significantly greater than those without. However, the detection of Epstein-Barr virus was not disease specific [58]. Kunimoto et al [59] investigated viral infections in the tonsils, pharynx, and renal tissues of patients with IgAN using cell culture, polymerase chain reaction, and immunofluorescent techniques, and measured antibody titers against numerous types of viruses. As a result, no evidence was obtained that the viral infections play a significant role in the pathogenesis of IgAN [59].

EFFECT OF TONSILLECTOMY ON IgAN

Effect of tonsillectomy on immune system

As described above, human tonsil tissues are located at the gateway of the respiratory and alimentary tract, belong to the mucosa-associated lymphoid tissue, and play a role in the systemic immune and the local mucosal immune. What effect does tonsillectomy have on

Table 2. Effect of tonsillectomy on urinary findings and renal function

Author	Year	Tonsillectomy +/−	Follow-up *months*	Urinary remission	Urinary improvement	Renal survival	Reference number
Masuda	1988	16/0	36	56.3%			46
Tamura	1993	26/0	24		46%		71
Sugiyama	1993	28/0	61	32%	60.7%		79
Bene	1993	34/0	48	UP 3.5 g/day →	0.9 g/day	Stable	69
Iino	1993	35/15	36	54.8%/53.8%	61%/46%	96.8%/76.9%	78
Tomioka	1996	104/0	12	38%	94%		80
Barta	1996	35/40	144	6m UP 1.4 g/day →	0.92 g/d	88.6%/80.0%	70
Rasche	1999	16/39	41			NS	74
Hotta	2001	250/79	75	Total 48%			81
Xie	2003	48/70	193			89.6%/63.7%	17

Abbreviations are: UP, urine protein; NS, non-statistic difference.

the systemic and local mucosal immune? Studies demonstrated that tonsillectomy decreased the levels of serum IgA and salivary secretory IgA, especially in children, several months or years after operation [60–62]. However, these changes do not cause significant immune deficiency and are clinically insignificant. Moreover, these alterations do not increase incidence of immunomodulated diseases, such as infections of the upper respiratory tract [63]. These may be because the concentrations of serum IgA and salivary secretory IgA are higher before operation in some tonsillectomy cases than that of nontonsillectomy controls. Tonsillectomy decreased significantly the IgA levels compared with preoperation, but there is no significant difference compared with normal nonoperative controls [27]. Recent study demonstrated children with chronic tonsillitis have increased levels of $CD19^+$ B lymphocytes compared to healthy controls in the pre-operative period. The percentage of B lymphocytes bearing CD23 was found to be significantly higher in patients, most likely representing in vivo B lymphocyte activation due to chronic antigenic stimulation. After the tonsillectomy, despite ongoing B lymphocyte activation, $CD8^+$ T lymphocyte levels increased and B cell levels returned to normal [64].

Tonsillectomy may also lead to certain changes in the cellular immune systems in some boys, including slightly increased percentages of $CD21^+$ cells, raised counts of $CD4^+$ cells, absolute and relative increases in DR^+ cells and a raised $CD4^+DR$ count [63]. Peripheral blood $CD8^+$ cells, $CD45RA^+CD4^+$ cells, and $CD8^+CD11b^-$ cells increase significantly after tonsillectomy, compared with their preoperative values in patients with IgAN accompanied by chronic tonsillitis. In some cases, the preoperative serum tumor necrosis factor-alpha (TNF-α), and INF-γ levels were higher than normal before surgery, but decreased after surgery. These results suggest that tonsillectomy suppresses a decrease in suppressor T cells in patients with IgAN and corrects abnormal cell-mediated immune responses in these patients [65].

In additional, tonsillectomy has no effect on complement and saliva-derived nonimmunoglobulin host defense factors, such as lysozyme, salivary peroxidases, thiocyanate, hypothiocyanite, and agglutinins, except lactoferrin, which declined significantly [66]. The effects of tonsillectomy on serum and salivary secretory IgG, IgM, and IgE remain still controversial [67, 68].

Effect of tonsillectomy on urinary finding and renal function

Studies demonstrated that tonsillectomy can improve the urinary finding and keep stable renal function in some patients with IgAN (Table 2). Bene et al [69] followed up the evolution of urinary protein and serum creatinine in 34 patients with IgAN, and Barta et al [70] followed up 35 IgAN patients after tonsillectomy. The urinary protein and microhematuria decreased significantly from 6 months after tonsillectomy than that before operation, and no significant variation was observed in the levels of creatininemia [69]. Furthermore, tonsillectomy stopped gross hematuria in more than two thirds of patients [70]. Tamura et al [71] reported that 46% IgAN patients with chronic tonsillitis showed distinct improvement in urinary findings after the tonsillectomy. Akagi et al [48] followed up 24 patients with IgAN for more than 2 years after tonsillectomy. Remission of proteinuria was observed in 41.7% of the patients 6 months after surgery and in 50.0% 2 years after surgery [48]. The clinical remission rate of urinary finding and the stable renal function rate in tonsillectomy patients with IgAN were significantly higher than that in nontonsillectomy patients [72].

Effect of tonsillectomy on renal histologic findings

A repeat renal biopsy study for 35 patients demonstrated that renal histologic finding improved distinctly after the combined therapy of methylprednisolone pulse, prednisolone, antiplatelet, and tonsillectomy in IgAN patients [73]. The interval between the first and second biopsy was 18 to 138 months (mean, 77.1 months) in that study. Mesangial proliferation and interstitial mononuclear cell infiltration were significantly reduced in second biopsy specimens. Acute inflammatory glomerular lesions, such as endocapillary proliferations, glomerular tuft necrosis, and cellular crescents, were present in 32

	1979	1989	2001
BP (mm Hg)	132/88	120/80	120/80
UP (g/d)	0.4	0.4	0.5
U-RBC (/hpf)	2.3	2	2
Scr (mg/dL)	1.0	1.1	1.4
Ccr (mL/min)	113	78.9	56

Fig. 3. Effect of tonsillectomy on renal histological findings. This patient was born in 1952, diagnosed with IgA nephropathy (IgAN) by the first renal biopsy in 1979, received tonsillectomy in 1982, discovered hypertension in 1985, and received antihypertensive therapy. The patient underwent the second biopsy in 1989 and the third biopsy in 2001. Renal specimen was performed by periodic acid-Schiff (PAS) staining (original magnification ×50).

patients in first biopsy specimens, whereas these were no longer present in any of the second biopsy specimens. Although there was no significant difference in percentage of globally sclerotic glomeruli between the first and second biopsy specimens, the percentage of segmentally sclerotic glomeruli was significantly lower in second biopsy specimens. The distribution of IgA mesangial deposits had diminished in most patients, and no IgA deposits were seen in second biopsy specimens from eight patients. Impact of isolated tonsillectomy on renal histologic findings was unknown. We followed up a repeated biopsy patient with IgAN and tonsillectomy. He did not receive other drug therapy except for antihypertension. The first renal biopsy showed the marked mesangial proliferation, marked IgA deposit in glomerular mesangium, and almost normal renal tubules and blood vessel. After 10 years, the second biopsy showed the moderate mesangial proliferation, moderate IgA deposit, mild-to-moderate renal tubular atrophy, and mild arteriole sclerosis. The third biopsy after 22 years showed the enlarged glomeruli, mild mesangial proliferation, negative IgA deposit, marked tubular atrophy, and moderate arteriole sclerosis. The results of this patient demonstrated that tonsillectomy can improve IgA deposit and mesangial proliferation and cannot impact renal damage induced by other causes such as hypertension (Fig. 3).

Effect of tonsillectomy on long-term renal survival

Rasche, Schwarz, and Keller [74] reported that there was no significant correlation between tonsillectomy and ESRD by observing 16 IgAN patients with tonsillectomy and 39 patients without tonsillectomy, and introduced that tonsillectomy does not reduce the risk of developing renal failure [74]. The mean observation time after renal biopsy was relatively short (3.4 ± 4 years) in that study. Another study demonstrated that ESRD was detected in four of 35 IgAN patients after 10 years after tonsillectomy, in eight patients of 40 nontonsillectomy controls [70]. We [17] followed up 118 patients with idiopathic IgAN patients, including 48 tonsillectomy patients and 70 nontonsillectomy patients, for 192.9 ± 74.8 months (48∼326 months). In that study, we used three different statistical methods, including the chi-squared test, Kaplan-Meier method with log-rank test, and Cox regression proportional hazards model in order to establish the efficacy of tonsillectomy in IgAN patients. Baseline characteristics at the time of renal biopsy, pathologic finding, and therapy during observation were not significant different between tonsillectomy and nontonsillectomy patients. A mean 15 years after diagnostic biopsy, only five (10.4%) of 48 tonsillectomy patients entered dialysis, whereas 18 (25.7%) of 70 nontonsillectomy patients required dialysis, by chi-squared test, $P = 0.0393$. Kaplan-Meier analysis showed the renal survival rates of tonsillectomy patients were statistically higher than those of non-tonsillectomy (log-rank test, $P = 0.0329$). For example, renal survival rates were 89.6% and 63.7% in the patients with and without tonsillectomy, respectively, at 240 months after renal biopsy. Cox regression analysis showed that the relative risk for terminal renal failure in patients with tonsillectomy was lower compared to nontonsillectomy patients (hazard ratio 0.22, 95% CI 0.06 to 0.76, $P = 0.0164$). The results of these three statistical analyses were consistent. All revealed that tonsillectomy had a favorable effect on long-term renal survival in patients with IgAN [17].

Indications and limitations of tonsillectomy

Tonsillectomy and adenoidectomy procedures are among the oldest surgical procedures still performed today. Otolaryngologically, the two main indications for tonsillectomy are upper airway obstruction due to tonsillar hypertrophy and recurrent acute or chronic tonsillitis. Adenoid hypertrophy with upper airway or eustachian tube obstruction and recurrent acute or chronic adenoiditis or otitis media are main indications to perform an adenoidectomy [75]. Nephrologically, indications for tonsillectomy are to date still unclear. In fact, many factors have effect on the efficacy of tonsillectomy in patients with IgAN, such as urinary finding and grades of renal damage. In general, the efficacy of tonsillectomy in patients with hemoturia type IgAN, especially presenting hemoturia after tonsil infection, is good [76]. We have showed that with a mild renal damage condition, in which the amount of urine protein excretion was less than 1.0 g/24 hours and global glomerular sclerosis less than 25%, none of 26 patients with tonsillectomy needed dialysis, whereas five (13.2%) of 38 patients without tonsillectomy required dialysis [17]. The percentage entering

dialysis in the tonsillectomy patients with moderate renal damage, such as urinary protein was more than 1.0 g/24 hours, but global glomerular sclerosis was less than 25% of total, was less than half of that in the nontonsillectomy patients [17]. On the other hand, the patients with a marked renal damage, in whom both the amount of urine protein excretion was more than 1.0 g/24 hours and global glomerular sclerosis was more than 25% of total or crescent formation was more than 25% of total might develop renal failure even if tonsillectomy was performed, that is, tonsillectomy is mainly indicated for patients with mild or moderate IgAN [17, 77, 78]. Rupture of the glomerular basement membrane occurred more frequently in the noneffective tonsillectomy than in the effective tonsillectomy group [79, 80]. Hotta et al [81] conducted a retrospective investigation of the renal outcome in IgAN patients with a median observation period of 75 months after tonsillectomy and steroid pulse therapy. Their results showed that there were no significant differences between the tonsillectomy and nontonsillectomy groups regarding the incidence of progressive renal functional loss defined as a 50% increase in baseline serum creatinine, but a combination of tonsillectomy and steroid pulse therapy had a significant impact on clinical remission by multivariate Cox regression analysis [81]. Sato et al [82] retrospectively investigated 70 patients with advanced IgAN (serum creatinine $\geq$1.5 mg/dL) classified into three groups according to their treatment regimens, that is, steroid pulse with tonsillectomy (30 patients), conventional steroid (25 patients), and supportive therapy (15 patients). During the mean follow-up period of 70.3 (12 to 137) months, 41.4% of patients reached ESRD (13.3% vs. 56.0% vs. 73.3%). The incidence of ESRD in the patients treated by steroid pulse with tonsillectomy was significantly lower than that in the patients treated by conventional steroid and supportive therapy at a baseline creatinine level of 1.5 to 2 mg/dL, but no statistical difference was observed at a level of >2 mg/dL [82]. These results suggest tonsillectomy combined with steroid pulse therapy may be effective in the IgAN patients with a baseline creatinine level of $\leq$2 mg/dL, whereas when serum creatinine >2 mg/dL, tonsillectomy may not change renal outcome even if that combines steroid therapy.

CONCLUSION

First, human tonsils are lymphoid organs and play a role in production of antibodies and local mucosal immune, especially in children. Tonsillectomy decreases the levels of serum IgA and salivary secretory IgA, but these changes do not cause significant immune deficiency and do not increase incidence of the upper respiratory tract infections. Second, tonsils are closely related to IgAN and polymeric IgA1 deposited in glomerular mesangium is at least in part of tonsillar origin. However, it is unclear that why do IgA-producing cells be predominant in tonsils with IgAN and how does IgA produced by tonsils deposit in mesangium. Third, tonsillectomy can improve the urinary findings, keep stable renal function, and have a favorable effect on long-tern renal survival in some IgAN patients. The indications of tonsillectomy in patients with IgAN include mainly the deterioration of urinary findings after tonsillar infection, mild or moderate renal damage. However, tonsillectomy may not be enough and may not change the prognosis in IgAN patients with marked renal damage. Unfortunately, studies regarding tonsillectomy were performed until now in a retrospective style and little information has been available about the side effect or complication of the operation in IgAN patients. In order to further clarify the clinical efficacy and security of tonsillecteomy, randomized prospective controlled trials are necessary because of the high degree of variability of IgAN.

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REFERENCES

1. Berger J, Hinglais N: Les depots intercapillaires d'IgA-IgG. *J Urol Nephrol* (Paris) 74:694–695, 1968
2. Berger J. IgA glomerular deposits in renal disease: *Transplant Proc* 1:939–944, 1969
3. Emancipator SN: IgA nephropathy: morphologic expression and pathogenesis. *Am J Kidney Dis* 23:451–462, 1994
4. D'Amico G: The commonest glomerulonephritis in the world: IgA nephropathy. *Q J Med* 245:709–727, 1987
5. Julian BA, Waldo FB, Rifai A, Mestecky J: IgA nephropathy, the most common glomerulonephritis worldwide: A neglected disease in the United States? *Am J Med* 84:129–132, 1988
6. Levy M, Berger J: Worldwide perspective of IgA nephropathy. *Am J Kidney Dis* 12:340–347, 1988
7. D'Amico G, Colasanti G, Barbiano di Belgioioso G, *et al*: Long-term follow-up of IgA mesangial nephropathy: Clinico-histological study in 374 patients. *Semin Nephrol* 7:355–358, 1987
8. Ibels LS, Gyory AZ: IgA nephropathy: Analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine* (Baltimore) 73:79–102, 1994
9. Hogg RJ, Silva FG, Wyatt RJ, *et al*: Prognostic indicators in children with IgA nephropathy—Report of the Southwest Pediatric Nephrology Study Group. *Pediatr Nephrol* 8:15–20, 1994
10. Radford MG Jr, Donadio JV Jr, Bergstralh EJ, Grande JP: Predicting renal outcome in IgA nephropathy. *J Am Soc Nephrol* 8:199–207, 1997
11. Nishi S: The prognosis of IgA nephropathy—Favorable or poor? *Intern Med* 40:679–680, 2001
12. Maisonneuve P, Agodoa L, Gellert R, *et al*: Distribution of primary renal diseases leading to end-stage renal failure in the United

States, Europe, and Australia/New Zealand: Results from an international comparative study. *Am J Kidney Dis* 35:157–165, 2000
13. Briganti EM, Dowling J, Finlay M, *et al*: The incidence of biopsy-proven glomerulonephritis in Australia. *Nephrol Dial Transplant* 16:1364–1367, 2001
14. Donadio JV, Grande JP: IgA nephropathy. *N Engl J Med* 347:738–748, 2002
15. Lomax-Smith JD, Zabrowarny LA, Howarth GS, *et al*: The immunochemical characterization of mesangial IgA deposits. *Am J Pathol* 113:359–364, 1983
16. Tomino Y, Sakai H, and Special Study Group (IgA Nephropathy): Clinical guidelines for immunoglobulin A (IgA) nephropathy in Japan, second version. *Clin Exp Nephrol* 7:93–97, 2003
17. Xie Y, Nishi S, Ueno M, *et al*: The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. *Kidney Int* 63:1861–1867, 2003
18. Hellings P, Jorissen M, Ceuppens JL: The Waldeyer's ring. *Acta Otorhinolaryngol Belg* 54:237–241, 2000
19. van Kempen MJ, Rijkers GT, Van Cauwenberge PB: The immune response in adenoids and tonsils. *Int Arch Allergy Immunol* 122:8–19, 2000
20. Boyaka PN, Wright PF, Marinaro M, *et al*: Human nasopharyngeal-associated lymphoreticular tissues. Functional analysis of subepithelial and intraepithelial B and T cells from adenoids and tonsils. *Am J Pathol* 157:2023–2035, 2000
21. Matthews JB, Basu MK: Oral tonsils: An immunoperoxidase study. *Int Arch Allergy Appl Immunol* 69:21–25, 1982
22. Brandtzaeg P, Surjan L Jr, Berdal P: Immunoglobulin-producing cells in clinically normal, hyperplastic and inflamed human palatine tonsils. *Acta Otolaryngol Suppl* 360:211–215, 1979
23. Goumas P, Troubouki D, Toska N, *et al*: Immunohistochemical study of the palatine tonsils. *Laryngol Rhinol Otol* (Stuttg) 67:34–37, 1988
24. Moro I, Komiyama K, Iwase T, *et al*: Immunoglobulin subclasses in chronic tonsillitis. *J Oral Pathol* 17:475–477, 1988
25. von Gaudecker B, Muller-Hermelink HK: The development of the human tonsilla palatina. *Cell Tissue Res* 224:579–600, 1982
26. Brandtzaeg P: The B-cell development in tonsillar lymphoid follicles. *Acta Otolaryngol Suppl* 523:55–59, 1996
27. Jung KY, Lim HH, Choi G, Choi JO: Age-related changes of IgA immunocytes and serum and salivary IgA after tonsillectomy. *Acta Otolaryngol Suppl* 523:115–119, 1996
28. Bernstein JM: Mucosal immunology of the upper respiratory tract. *Respiration* 59 (Suppl 3):3–13, 1992
29. Kawaguchi M, Sakai T, Sakamaki A, *et al*: Expanded primary T nodules in the palatine tonsils from patients with IgA nephropathy. *Acta Otolaryngol Suppl* 508:36–42, 1993
30. van den Oord JJ, de Wolf-Peeters C, Desmet VJ: The composite nodule. A structural and functional unit of the reactive human lymph node. *Am J Pathol* 122:83–91, 1986
31. Sato Y, Hotta O, Taguma Y, *et al*: IgA nephropathy with poorly developed lymphoepithelial symbiosis of the palatine tonsils. *Nephron* 74:301–308, 1996
32. Bene MC, Faure G, Hurault de Ligny B, *et al*: Immunoglobulin A nephropathy. Quantitative immunohistomorphometry of the tonsillar plasma cells evidences an inversion of the immunoglobulin A versus immunoglobulin G secreting cell balance. *J Clin Invest* 71:1342–1347, 1983
33. Nagy J, Brandtzaeg P: Tonsillar distribution of IgA and IgG immunocytes and production of IgA subclasses and J chain in tonsillitis vary with the presence or absence of IgA nephropathy. *Scand J Immunol* 27:393–399, 1988
34. Bene MC, Hurault De Ligny B, Kessler M, Faure GC: Confirmation of tonsillar anomalies in IgA nephropathy: A multicenter study. *Nephron* 58:425–428, 1991
35. Egido J, Blasco R, Lozano L, *et al*: Immunological abnormalities in the tonsils of patients with IgA nephropathy: inversion in the ratio of IgA: IgG bearing lymphocytes and increased polymeric IgA synthesis. *Clin Exp Immunol* 57:101–106, 1984
36. Kusakari C, Nose M, Takasaka T, *et al*: Immunopathological features of palatine tonsil characteristic of IgA nephropathy: IgA1 localization in follicular dendritic cells. *Clin Exp Immunol* 95:42–48, 1994
37. Harper SJ, Allen AC, Bene MC, *et al*: Increased dimeric IgA-producing B cells in tonsils in IgA nephropathy determined by in situ hybridization for J chain mRNA. *Clin Exp Immunol* 101:442–448, 1995
38. Kennel-De March A, Bene MC, Hurault de Ligny B, *et al*: Enhanced expression of CD31 and CD54 on tonsillar high endothelial venules in IgA nephropathy. *Clin Immunol Immunopathol* 84:158–165, 1997
39. Kodama S, Suzuki M, Arita M, Mogi G: Increase in tonsillar germinal centre B-1 cell numbers in IgA nephropathy (IgAN) patients and reduced susceptibility to Fas-mediated apoptosis. *Clin Exp Immunol* 123:301–308, 2001
40. Rifai A, Small PA Jr, Teague PO, Ayoub EM: Experimental IgA nephropathy. *J Exp Med* 150:1161–1173, 1979
41. Harper SJ, Feehally J: The pathogenic role of immunoglobulin A polymers in immunoglobulin A nephropathy. *Nephron* 65:337–345, 1993
42. Tomino Y, Sakai H, Endoh M, *et al*: Cross-reactivity of IgA antibodies between renal mesangial areas and nuclei of tonsillar cells in patients with IgA nephropathy. *Clin Exp Immunol* 51:605–610, 1983
43. Tokuda M, Shimizu J, Sugiyama N, *et al*: Direct evidence of the production of IgA by tonsillar lymphocytes and the binding of IgA to the glomerular mesangium of IgA nephropathy patients. *Acta Otolaryngol Suppl* 523:182–184, 1996
44. Shiraishi S, Tomoda K, Matsumoto A, *et al*: Investigation of the local provocation test to PPP and IgA nephritis. *Acta Otolaryngol Suppl* 523:178–181, 1996
45. Yamabe H, Osawa H, Inuma H, *et al*: Deterioration of urinary findings after tonsil stimulation in patients with IgA nephropathy. *Acta Otolaryngol Suppl* 523:169–171, 1996
46. Masuda Y, Terazawa K, Kawakami S, *et al*: Clinical and immunological study of IgA nephropathy before and after tonsillectomy. *Acta Otolaryngol Suppl* 454:248–255, 1988
47. Matsuda M, Shikata K, Wada J, *et al*: Increased urinary excretion of macrophage-colony-stimulating factor (M-CSF) in patients with IgA nephropathy: Tonsil stimulation enhances urinary M-CSF excretion. *Nephron* 81:264–270, 1999
48. Akagi H, Nishizaki K, Hattori K, *et al*: Prognosis of tonsillectomy in patients with IgA nephropathy. *Acta Otolaryngol Suppl* 540:64–66, 1999
49. Akagi H, Hattori K, Doi A, *et al*: Tonsillar provocation test for tonsillectomy in patients with IgA nephropathy. *Stomato-pharyngol* 11:297–305, 1999
50. Kataura A: Evaluation of the provocation test of tonsils: A report from the Committee for the standardization of diagnostic criteria for tonsillar focal infections. *Stomato-pharyngol* 9:213–221, 1997
51. Akagi H, Kosaka M, Doi A, *et al*: Results of a survey of the relationship between palatine tonsil and IgA nephropathy. *Nippon Jibiinkoka Gakkai Kaiho* 102:305–310, 1999
52. Suzuki S, Nakatomi Y, Sato H, *et al*: *Haemophilus parainfluenzae* antigen and antibody in renal biopsy samples and serum of patients with IgA nephropathy. *Lancet* 343:12–16, 1994
53. Suzuki S, Fujieda S, Sunaga H, *et al*: Immune response of tonsillar lymphocytes to *Haemophilus parainfluenzae* in patients with IgA nephropathy. *Clin Exp Immunol* 119:328–332, 2000
54. Yamamoto C, Suzuki S, Kimura H, *et al*: Experimental nephropathy induced by *Haemophilus parainfluenzae* antigens. *Nephron* 90:320–327, 2002
55. Fujieda S, Suzuki S, Sunaga H, *et al*: Bacterial infection and production of immunoglobulin in the tonsil. *Rinsho Byori* 47:724–729, 1999
56. Rekola S, Bergstrand A, Bucht H, Lindberg A: Are beta-haemolytic streptococci involved in the pathogenesis of mesangial IgA-nephropathy? *Proc Eur Dial Transplant Assoc Eur Ren Assoc* 21:698–702, 1985
57. Tomino Y, Yagame M, Omata F, *et al*: A case of IgA nephropathy associated with adeno- and herpes simplex viruses. *Nephron* 47:258–261, 1987
58. Iwama H, Horikoshi S, Shirato I, Tomino Y: Epstein-Barr virus detection in kidney biopsy specimens correlates with glomerular mesangial injury. *Am J Kidney Dis* 32:785–793, 1998

59. Kunimoto M, Hayashi Y, Kuki K, *et al*: Analysis of viral infection in patients with IgA nephropathy. *Acta Otolaryngol Suppl* 508:11–18, 1993
60. Ostergaard PA: IgA levels and carrier rate *of Haemophilus influenzae* and beta-haemolytic streptococci in children undergoing tonsillectomy. *Acta Pathol Microbiol Scand* [C] 84:290–298, 1976
61. D'Amelio R, Palmisano L, Le Moli S, *et al*: Serum and salivary IgA levels in normal subjects: comparison between tonsillectomized and non-tonsillectomized subjects. *Int Arch Allergy Appl Immunol* 68:256–259, 1982
62. Cantani A, Bellioni P, Salvinelli F, Businco L: Serum immunoglobulins and secretory IgA deficiency in tonsillectomized children. *Ann Allergy* 57:413–416, 1986
63. Bock A, Popp W, Herkner KR: Tonsillectomy and the immune system: A long-term follow up comparison between tonsillectomized and non-tonsillectomized children. *Eur Arch Otorhinolaryngol* 251:423–427, 1994
64. Ikinciogullari A, Dogu F, Ikinciogullari A, *et al*: Is immune system influenced by adenotonsillectomy in children? *Int J Pediatr Otorhinolaryngol* 66:251–257, 2002
65. Kanamoto Y, Shibata R, Ozono Y, Harada T: Effect of tonsillectomy on peripheral blood T cell surface markers and cytokine production in patients with IgA nephropathy accompanied by chronic tonsillitis. *Nippon Jinzo Gakkai Shi* 36:1296–1302, 1994
66. Kirstila V, Tenovuo J, Ruuskanen O, *et al*: Longitudinal analysis of human salivary immunoglobulins, nonimmune antimicrobial agents, and microflora after tonsillectomy. *Clin Immunol Immunopathol* 80:110–115, 1996
67. Ostergaard PA: IgA levels and carrier rate of pathogenic bacteria in 27 children previously tonsillectomized. *Acta Pathol Microbiol Scand* [C] 85:178–186, 1977
68. Sainz M, Gutierrez F, Moreno PM, *et al*: Changes in immunologic response in tonsillectomized children. I. Immunosuppression in recurrent tonsillitis. *Clin Otolaryngol* 17:376–379, 1992
69. Bene MC, Hurault de Ligny B, Kessler M, *et al*: Tonsils in IgA nephropathy. *Contrib Nephrol* 104:153–161, 1993
70. Barta J, Kovacs T, Fazekas A, *et al*: Does tonsillectomy cause any change in long-term course of IgA nephropathy? *Orv Hetil* 137:2903–2906, 1996
71. Tamura S, Masuda Y, Inokuchi I, *et al*: Effect of and indication for tonsillectomy in IgA nephropathy. *Acta Otolaryngol Suppl* 508:23–28, 1993
72. Kosaka M: Long-term prognosis for tonsillectomy patients with IgA nephropathy. *Nippon Jibiinkoka Gakkai Kaiho* 101:916–923, 1998
73. Hotta O, Furuta T, Chiba S, *et al*: Regression of IgA nephropathy: a repeat biopsy study. *Am J Kidney Dis* 39:493–502, 2002
74. Rasche FM, Schwarz A, Keller F: Tonsillectomy does not prevent a progressive course in IgA nephropathy. *Clin Nephrol* 51:147–152, 1999
75. Paulussen C, Claes J, Claes G, Jorissen M: Adenoids and tonsils, indications for surgery and immunological consequences of surgery. *Acta Otorhinolaryngol Belg* 54:403–408, 2000
76. Zhou WG, Wang TF, Xue Y, *et al*: Chronic tonsillitis and IgA nephropathy. *Chin Med J* (Engl) 106:770–772, 1993
77. Hattori K: Therapeutic effects and prognostic factors of tonsillectomy for IgA nephropathy in long-term follow-up. *Nippon Jibiinkoka Gakkai Kaiho* 101:1412–1422, 1998
78. Iino Y, Ambe K, Kato Y, *et al*: Chronic tonsillitis and IgA nephropathy. Clinical study of patients with and without tonsillectomy. *Acta Otolaryngol Suppl* 508:29–35, 1993
79. Sugiyama N, Shimizu J, Nakamura M, *et al*: Clinicopathological study of the effectiveness of tonsillectomy in IgA nephropathy accompanied by chronic tonsillitis. *Acta Otolaryngol Suppl* 508:43–48, 1993
80. Tomioka S, Miyoshi K, Tabata K, *et al*: Clinical study of chronic tonsillitis with IgA nephropathy treated by tonsillectomy. *Acta Otolaryngol Suppl* 523:175–177, 1996
81. Hotta O, Miyazaki M, Furuta T, *et al*: Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. *Am J Kidney Dis* 38:736–743, 2001
82. Sato M, Hotta O, Tomioka S, *et al*: Cohort study of advanced IgA nephropathy: Efficacy and limitations of corticosteroids with tonsillectomy. *Nephron Clin Pract* 93:c137–c145, 2003