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Steroid pulse therapy transiently destroys the discriminative histological structure of tonsils in IgA nephropathy: Tonsillectomy should be performed before or just after steroid pulse therapy

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ABSTRACT

Objective: Tonsillectomy combined with steroid-pulse therapy is a widely accepted method for the treatment of IgA nephropathy (IgAN) in Japan. However, the indication of tonsillectomy for IgAN is still controversial, and the timing of tonsillectomy is not clearly defined for the protocol of this therapy. Based on the results of a randomized control trial in Japan, the Evidence-Based Clinical Practice Guidelines for IgA nephropathy 2014 (edited in Japan) recommended tonsillectomy combined with steroid-pulse therapy for Grade C1. However, this is not widely accepted worldwide. To clarify the validity and timing of tonsillectomy, we evaluated how the three-consecutive steroid-pulse therapy method affects the tonsil tissues of IgAN patients.

Methods: We examined tonsil specimens from 35 IgAN patients and 8 chronic tonsillitis patients. We compared the proportion of follicular area to total tonsillar area and the number of germinal centers between each group on hematoxylin and eosin stained pathological specimens to clarify the histopathological characteristics of tonsils from IgAN patients. Based on these findings, we examined the tonsils of patients after three-consecutive steroid-pulse therapy treatments (n = 34) to determine the influence of this therapy on the tonsil tissues of IgAN patients. Moreover, we observed chronological changes in tonsil tissues after steroid-pulse therapy.

Results: The extrafollicular area was enlarged in IgAN patients before steroid-pulse therapy compared with chronic tonsillitis patients. Just after steroid-pulse therapy, the follicles became very small with blurry outlines, and the number of germinal centers was remarkably decreased. With a gradual decrease in oral prednisolone, the tonsil tissue structure was gradually restored.

Conclusion: Tonsillectomy combined with steroid-pulse therapy is considered a reasonable treatment for IgAN. Steroid-pulse therapy-induced histological changes in tonsils were transient, indicating tonsillectomy should be performed before or just after steroid-pulse therapy.

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1. Introduction

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis especially in Asia. The outcome of IgAN is poorer than first expected: 30%–40% of patients reach end stage renal disease within 20 years from its onset [1,2].

A reliable pathogenesis of IgAN is difficult to obtain; therefore, a specific treatment method for IgAN has not yet been fully established. Since Hotta et al. [3] reported that tonsillectomy combined with steroid-pulse therapy had the potential to induce the complete remission (CR) of IgAN, this therapy has become one of the most widely accepted methods for the treatment of IgAN in Japan [4]. The Evidence-Based Clinical Practice Guidelines for IgA nephropathy 2014 (edited in Japan) [5] graded this therapy as C1. However, the indication of tonsillectomy for IgAN is still controversial, and the timing of tonsillectomy has not been clearly defined in the protocol of this therapy.

Moreover, the recent Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines for glomerulonephritis [6] suggested that tonsillectomy should not be performed. Because the contents of KDIGO cannot be compared simply with the results in Japan, the current Japanese standard treatment for IgAN differs substantially from the global standard treatment.

Among otolaryngologists, tonsillectomy is empirically used as an effective treatment for nephritis. Some reports showed that renal function was maintained better in patients with tonsillectomy than in those without tonsillectomy [7–9]. In addition, following the report by Hotta et al. many studies revealed the effectiveness of tonsillectomy combined with steroid-pulse therapy compared with steroid-pulse therapy alone [10–13]. According to the results of a randomized control trial in Japan [10,13], the percentage decrease in proteinuria during the 12 months from baseline was significantly larger in the tonsillectomy combined with steroid-pulse therapy group than in the steroid-pulse therapy alone group.

In contrast, when tonsillectomy was not performed in combination with steroid-pulse therapy, Rauen et al. [14] reported no difference in outcomes between a group with added immunosuppressant administration and a supportive care group following the recommended KDIGO guidelines [6]. Paradoxically, tonsillectomy appears to be effective for the treatment of IgAN.

Because IgAN is a disease caused by tonsillar focal infection [15,16], some cases have an episode of upper respiratory infection at the onset [17,18]. Collapse of the mucosal immune response was suspected to participate in the onset and progress of IgAN. Histologically, the tonsil structure contains crypt epithelium, and a follicular germinal center with a mantle zone and extrafollicular area, which all participate in the immune response [19]. Previous studies reported discriminative histopathological findings in the tonsils of IgAN patients. An enlarged extrafollicular area [20,21] and inhibition of the reticulation of tonsillar crypt epithelium [22,23] were discriminative histopathological findings in the tonsils of IgAN patients. In addition, the proportion of IgA-producing cells was significantly increased [23], and a large number of IgA1 positive cells were present in the follicular dendritic cells in the tonsils of IgAN patients [24].

If the tonsillar immune system is related to the development and progress of IgAN, it is important to understand what type of influence steroid-pulse therapy might have on tonsillar tissue. No studies have evaluated the chronological changes in tonsil tissue after steroid-pulse therapy. Such a study might provide evidence for the advantage of tonsillectomy combined with steroid-pulse therapy over steroid-pulse therapy alone. In the present study, we clarified the characteristic histopathological findings of tonsils from IgAN patients. We also examined the influence of steroid-pulse therapy on tonsil tissues by comparing its effect with that of the characteristic histopathological findings. Finally, we observed chronological changes in the tonsil tissue after steroid-pulse therapy.

2. Patients and methods

2.1. Patients and controls

The study protocols were approved by the Ethical Committee of our hospital (authorization number 2015-2). We obtained written informed consent from each participant. From January 2005 to December 2005, 218 patients underwent tonsillectomy in the Department of Otolaryngology. Overall, 178 patients had a diagnosis of IgA nephropathy by renal biopsy, and they received tonsillectomy as a series of treatments. Among these patients, we chose patients who received 0.5 g/day of methylprednisolone intravenously for 3 consecutive days for less than six months before or after tonsillectomy. The patients were also given oral prednisolone at an initial dose of 0.5–0.6 mg/kg on alternate days, with a decrease of 0.1 mg/kg every 2 months. The control group consisted of patients with chronic tonsillitis, but without episodes of hematuria or kidney disease.

All patients were eligible for the current study if the following criteria were satisfied: older than 20 years old at the time of tonsillectomy; no clinical or biological evidence (no history or complication) of systemic disease such as Henoch–Schönlein purpura nephritis; systemic lupus erythematosus and other collagen diseases; diabetes mellitus; viral hepatitis; systemic infectious disease such as syphilis or tuberculosis; malignant disease; or no previous treatment with corticosteroids or immunosuppressive drugs.

2.2. Data sorting and evaluation

Both sides of excised tonsils were embedded in paraffin, sliced to a thickness of 3 μm, and stained with hematoxylin and eosin (HE). To define the histological characteristics of tonsillar tissue, we examined two consecutive fields (magnification ×40) of each specimen from both sides of tonsils by digital microscopy KEYENCE BZ 9000 (KEYENCE, Osaka, Japan). First, we counted all confirmed follicles with a germinal center in the two consecutive fields. Next, these follicles and the tonsillar tissue area in the same fields were traced by a measurement module in the digital microscope, and the total area of the follicles and the tonsil tissue area were determined. Finally, we calculated the number of germinal centers per equivalent unit area and the ratio of extrafollicular to follicular areas.

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