Auris Nasus Larynx 51 (2024) 761–773

Contents lists available at ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Guidance of clinical management for patients with tonsillar focal disease

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ARTICLE INFO

Keywords:
Tonsillar focal disease (TFD)
Palmoplantar pustulosis (PPP)
IgA nephropathy (IgAN)
Sternocostoclavicular hyperostosis (SCCH)
Tonsillectomy

ABSTRACT

Tonsillar focal diseases (TFDs) are defined as "diseases caused by organic and/or functional damage in organs distant from tonsil, and the disease outcome is improved by tonsillectomy." Although several reports and reviews have shown the efficacy of tonsillectomy for TFDs, no guidelines for the clinical management of the diagnosis and treatment of TFDs have been reported. Therefore, the Society of Stomato-pharyngology established a committee to guide the clinical management of patients with TFDs, and the original guide was published in May 2023. This article summarizes the English version of the manuscript. We hope that the concept of TFDs will spread worldwide, and that one as many patients with TFDs will benefit from tonsillectomy.

1. Introduction

Tonsillar focal diseases (TFDs), previously known as tonsillar focal infection, are defined as "a diseases are caused by organic and/or functional damage in organs distant from tonsil, and the disease outcome is improved by tonsillectomy." The diseases were called "tonsil induced autoimmune/ inflammatory syndrome: TIAS" because it may have been triggered by the failure of immune system tolerance for the tonsil's indigenous bacteria [1,2].

TFDs had been already mentioned in a cuneate document about the relationship between disease and the tooth caries of the King in 650 B.C, and in Hippocrates's note about an association between oral disease and articular rheumatism. In the past decade, the pathogenesis of TFDs has been thought to be caused by inflammatory substances, including toxins, that spread from the original inflammation focus. Therefore, most TFDs were rheumatic diseases such as glomerulonephritis after the β-hemolytic streptococcus infection, rheumatic fever, acute articular rheumatism, endocarditis, and myocarditis until the early 20th century. However, the formation of TFD has been radically altered by the development of antibacterial agents.

Palmoplantar pustulosis (PPP) [3,4], IgA nephropathy (IgAN) [5-7], and sternocostoclavicular hyperostosis (SCCH) [3,4] are recognized as typical TFDs because many reports have shown the high efficacy of tonsillectomy. In addition to these diseases, there are many candidate diseases such as psoriatic diseases [8,9], IgA vasculitis [10,11], reactive arthritis [12], and periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome [13,14]. Although several reports and reviews on TFDs have been published [1–5], no clinical management guidelines for the diagnosis and treatment of TFDs have been reported. Therefore, the diagnosis and treatment of TFDs were left to the discretion of the otorhinolaryngologist who examined the patients. For the standardization of diagnosis and treatment, the Japan Society of Stomato-pharyngology established a committee to guide the clinical management of patients with TFDs. Committee members provided

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https://doi.org/10.1016/j.anl.2024.05.010
Received 30 March 2024; Accepted 20 May 2024
Available online 14 June 2024

evidence-based recommendations on how general otolaryngologists clinically manage patients with TFDs. Moreover, the recommendations were supported by public comments from specialists belonging to other departments and suggestions from an academic panel belonging to the Society of Otorhinolaryngology-Head and Neck Surgery. Finally, the original guidelines were published in May 2023 by the Committee and Society [15]. As a next step, we hoped that the concept of TFDs would spread worldwide and thus developed a summarized English version of the guidelines. In addition to the previous version, these recommendations indicated one standard management option for TFDs, which should be decided by the responsible otolaryngologist based on the individual clinical situations. Therefore, these guidelines do not provide legal support.

2. Diagnosis

As a matter of fact, we do not have any examination which correctly diagnose TFDs at present. Therefore, we perform the examinations shown below, and diagnose TFDs holistically from these results.

2.1. Medical interview

Important points in medical interviews differ depending on the TFD. Patients with TFDs generally present to an otolaryngologist in a referral form written by an attending doctor in another department. The otolaryngologist should carefully read the form and ask questions about any additional topics that may need clarification.

2.1.1. Palmoplantar pustulosis (PPP)

Important questions in the medical interview include a history of cigarette smoking and the presence of anterior chest wall pain. Most patients with PPP are smokers [16], and the rate of improvement of the PPP rush by tosillectomy reportedly decreases in patients who fail postoperative smoking cessation [4]. Therefore, patients should ensure preoperative smoking cessation. The presence of anterior chest wall pain may indicate pustulotic arthroosteitis (PAO), which can be diagnosed using imaging tests, such as magnetic resonance imaging (MRI) and bone scintigraphy [17]. PAO is associated with 20–30 % of patients with PPP, and PAO pain frequently improves with tonsillectomy [4,18]. In addition, patients with PAO experience more favorable outcomes of PPP rash by tonsillectomy than those without PAO [4].

2.1.2. IgA nephropathy (IgAN)

It is important to confirm that IgAN can be definitively diagnosed using renal biopsy. If a renal biopsy has not been performed, the attending otolaryngologist should ask the reason. In addition, patients sometimes take antiplatelet drugs to treat IgAN. Drugs should be checked and not be taken a few days before tonsillectomy. Although there are many reports describing the relationship between the severity of IgAN and the efficacy of tonsillectomy, consensus standards showing the severity level for the indication of tonsillectomy are unclear [19]. Therefore, the indications cannot be determined based on the severity level at present.

2.1.3. Sternocostoclavicular hyperostosis (SCCH)

More than 80 % of American patients with SCCH also experience PPP. Therefore, the presence or absence of a PPP rush must be confirmed. Sometimes, patients are diagnosed with Syndrome Acne-Pustulosis-Hyperostosis-Osteitis (SAPHO), which includes SCCH and PAO [20].

2.1.4. IgA vasculitis (IgAV)

IgA vasculitis was not associated with a poor prognosis. However, purpura nephritis concomitant with IgAV may induce renal failure and influence long-term prognosis [21]. Tonsillectomy has also been reported to have favorable outcomes for purpura nephritis [10], and patients with purpura nephritis have more clinical benefits from tonsillectomy. Therefore, the presence or absence of concomitant purpura nephritis should be considered as a stronger recommendation for tonsillectomy.

2.1.5. Psoriasis vulgaris

Some patients with psoriasis vulgaris experience exacerbation of their skin condition during upper airway inflammation. These patients reportedly have more favorable outcomes after tonsillectomy [22]. Therefore, the presence or absence of exacerbation should be considered when making a stronger recommendation for tonsillectomy.

2.1.6. Periodic fever, aphthous stomatitis, and pharyngitis and cervical adenitis (PFAPA) syndrome

When a child with recurrent tonsillitis visits the Department of Otolaryngology, the presence or absence of periodic fever should be considered. If tonsillitis and fever recur periodically, the child should be referred to a pediatric doctor to exclude PFAPA syndrome. The first-line treatment for PFAPA syndrome is medication until spontaneous remission is achieved.

2.2. Physiological and examination findings

There were no specific physiological or examination findings in patients with TFDs. On pharyngeal inspection, the palatine tonsils are generally buried and show non-specific inflammatory changes, such as mild redness and attachment of a pus plug. In fact, it has been reported that the degree of tonsillar hypertrophy does not correlate with the outcome of tonsillectomy in patients with PPP [4]. In addition, blood test results, including anti-streptolysin O antibody (ASO), anti-streptokinase (ASK), and rheumatoid factor (RF), are reportedly unrelated to the outcome of tonsillectomy in patients with TFDs [4,23,24]. However, the symptoms and findings specific to each TFD, such as diagnostic palmoplantar exanthema in patients with PPP and painful swelling of the sternocostoclavicular joint in patients with SCCH, should be confirmed.

2.3. Bacterial examination

TFDs may be caused by chronic inflammation of the palatine tonsils. The tonsils are located on the outward border and are always exposed to various microorganisms, including harmful and commensal microorganisms, leading to chronic inflammation. Excessive immune responses may evoke mistakes in self- and non-self-recognition, resulting in tissue damage in distant organs where autoantibodies or autoreactive immune cells flow from the tonsils. The identification of pathogenic microorganisms in the tonsils is important for understanding their pathogenesis. Specific microorganisms have been suggested to participate in the pathogenesis.

2.3.1. Palmoplantar pustulosis (PPP)

The detection rate of *Streptococcus salivarius*, a resident oral bacterium, is higher in the palatine tonsils of patients with PPP than in those with chronic tonsillitis [25]. Tonsillar immune cells from patients with PPP are known to show an excessive immune response to these resident bacteria [2], and this excess may provide a background for immune disorders that induce focal diseases such as PPP.

2.3.2. Psoriasis

Patients with psoriasis vulgaris show exacerbation of upper respiratory tract infections caused by *beta-hemolytic streptococci* [26]. Some prospective controlled trials have shown the superior effectiveness of tonsillectomy in patients belonging to the group [26]. In addition, these bacteria increase the expression of skin-homing receptors on tonsillar T cells [26].

2.3.3. IgA nephropathy

Infection with *Haemophilus parainfluenzae* in the tonsils has been suggested to contribute to the pathogenesis of IgA nephropathy. Suzuki et al. [27,28] and Fujieda et al. [29] reported that bacterial tests showed a higher detection rate of *H. parainfluenzae* in the palatine tonsils of patients with IgA nephropathy, and tonsillar lymphocytes responded excessively to *H parainfluenzae*. More recently, *Streptococcus mutans* [30], *Treponema sp*., and *Campylobacter rectus* [31], which frequently induce dental caries and periodontal disease, were predominant in the tonsils of patients with IgA nephropathy and were related to the severity of IgA nephropathy and the therapeutic effect of tonsillectomy and steroid pulse therapy [30,31]. Furthermore, Kusano et al. reported the presence of *Helicobacter pylori* in all 55 tonsils of patients with IgA nephropathy [32].

2.3.4. PFAPA syndrome

Microbiome analysis has revealed a higher detection rate of *cyanobacteria* in the palatine tonsils of patients with PFAPA syndrome than in those with other diseases [33]. Additionally, Lantto et al. reported that biofilm formation was predominant in the tonsils from PFAPA patients by electron microscope examination [34]. Since control of infections caused by biofilms usually requires removal of the infection focus, the authors suggested that this may be one of the reasons why tonsillectomy was effective in patients with PFAPA syndrome [34].

2.3.5. Role of bacterial testing in tonsil focal disease

In view of the above-mentioned reports, it is currently difficult to decide on an indication for tonsillectomy based on the results of a tonsil bacterial test. Furthermore, because of the limitations of the current bacterial culture tests and discrepancies in results among sampling sites (surface or core), the results should be carefully interpreted [35]. Recently, new testing methods such as microbiome analysis using next-generation sequencers targeting bacterial 16S rRNA have been introduced, and the results of tonsillar microbiome analysis using this method have been reported [31,33,34,36]. Accumulation of these data will provide evidence for identifying the specific bacterial species responsible for the development of TFDs.

2.4. Tonsillar provocation and annulation test

Because TFDs generally do not develop typical local symptoms such as sore throat, diagnosis of TFDs is often difficult until tonsillitis exacerbates the original symptoms or findings of TFDs. Therefore, a definitive diagnostic procedure was devised. Currently, two examinations, the tonsillar provocation test and the annulation test, can potentially diagnose TFD.

2.4.1. Tonsillar provocation test

The tonsillar provocation test measures the response of the entire body or the original symptoms of TFDs by physical or electromagnetic stimulation of the palatine tonsils. The test was first reported by Nosaka in 1961 as local provocation method of the focus [37]. Nosaka showed stimulation procedures by ultrashort waves or tonsil massage to the bilateral palatine tonsils for 5 min each. Moreover, he proposed criteria for a positive diagnosis by ultra-short wave provocation method as follows: more than 0.45 °C increase of body temperature from 15 min to 3 h after the test, more than 1000/mL increase of peripheral white blood cell count 3 h after the test, or more than 10 mm/h increase of erythrocyte sedimentation rate 3 h after the test. These procedures and criteria continue to be valid. Because the test may cause the patients to distress, informed consent should be obtained before the procedure.

2.4.2. Tonsillar annulation tests

Tonsillar annulation tests include the tonsillar crypt rinsing and Impletol tests [37]. The tonsillar crypt rinsing test involves washing out post-inflammatory debris in tonsillar crypts with physiological saline for 5 to 7 consecutive days. A radar tonsillar suction tube was used to remove debris. This test can be used for not only diagnosis but also treatment of tonsillar febricula. The Impletol test involves injecting Impletol containing a local anesthetic agent around the palatine tonsils once a day for 5 consecutive days [38]. However, this test has rarely been conducted.

2.4.3. Re-evaluation of the diagnostic criteria for tonsillar provocation tests

Since Nosaka proposed the diagnostic criteria for tonsillar provocation tests, the number of diseases categorized as TFDs has been increasing, and immunological disorders are gradually being recognized as the pathogenesis of TFDs. Therefore, a re-evaluation of these criteria, including the introduction of new immunological parameters, is required. In response, the Society of Tonsil Problems (Society of Stomato-Pharyngology) created a committee for the standardization of tonsillar provocation test criteria in 1987. The standardization process has been summarized in a series of reports from the committee [39,40]. As a result of the reevaluation of the diagnostic criteria, the negative predictive value was extremely low, whereas the positive predictive value was high. Hence, the committee concluded that the criteria had been revised.

2.4.4. Current significance of the tonsillar provocation tests

According to these results, we would have to say that the criteria in tonsillar provocation tests is of less diagnostic importance [40]. In fact, in the indications for tonsillectomy in IgAN reported by Akagi et al. [41], the tonsillar provocation test was categorized as a reference criterion. However, the test procedure is thought to be reasonable for the detection of a direct response from the palatine tonsils. Nosaka's criteria were proposed in 1961 when TFD mainly consisted of rheumatic diseases. As the diseases comprising TFDs change drastically, the criteria should change accordingly. From this perspective, new parameters representing the pathogenesis may be necessary. Candidate parameters have already been reported as follows: uric blood [41], macrophage colony-stimulating factor (M-CSF) in urine for IgA nephropathy [42], and temperature of the palms and soles for palmoplantar pustulosis [43]. Our responsibility is to further improve the criteria of tonsillar provocation tests, which the pathfinders formulated and developed, to adapt them to the present TFDs.

3. Treatment outcome of tonsillectomy for each tonsillar focal disease

3.1. Palmoplantar pustulosis (PPP)

PPP is characterized by a unique exanthema, showing that small sterile pustules, followed by erythema and scaly plaques, are limited to the palms and soles. A prevalence of PPP was reported to be about 0.09 % in Japan, and fall to about one-tenth in United States [44]. PPP affects many middle-aged women and occasionally causes local haphalgesia, resulting in grip and gait disorders. PPP is conventionally treated with external preparations and/or phototherapy. However, it often becomes chronic.

3.1.1. Efficacy of tonsillectomy

PPP is a TFD caused by marked improvement in skin lesions after tonsillectomy. The main outcomes are summarized in Table 1 [3,4,45-47]. In 1934, Andrews first demonstrated that three patients with PPP were completely cured after tonsillectomy [48]. In 1977, Ono et al. [45] subjectively evaluated skin condition after tonsillectomy in Japanese patients with PPP and reported that the rate of skin lesions was significantly better in the 73 patients undergoing tonsillectomy than 83 patients who received other treatments (84 % vs. 39 %, $p < 0.01$). After that, they additionally did a questionnaire survey for patients with PPP, and their Kaplan–Meier analysis showed that 72 % and 20 % cure rates after a year's observation period in 40 tonsillectomized and 24

Table 1
Outcome of tonsillectomy for a patinet with palmoplantar pustulosis.

Author	Year	Treatment	Number of patients	Obsevation priod month (median)	Number of patients with disappeance of skin lesion	Number of patients with improvement of skin lesion	Evaluation method	Factor affecting favarable outcome of tonsillectomy
Ono [45]	1977	tonsillectomy	73		39 (53 %)	58 (79 %)*	Doctor's evaluation	Shorter period between onset of PPP and tonsillectomy
		others	84	>3	23 (27 %)	32 (38 %)		
Kuki [46]	1992	tonsillectomy	117		54 (48 %)	87 (76 %)	Doctor's evaluation	History of tonsillitis
		others	62		21 (35 %)	36 (58 %)		
Kataura [3]	1996	tonsillectomy	211	>3	(54 %)	(88 %)	Doctor's and Patient's evaluation	Shorter period between onset of PPP and tonsillectomy
Yamakita [47]	2009	tonsillectomy	26	18	(46 %)	(85 %)*	Doctor's evaluation (prospective study)	
		others	37		(15 %)	(35 %)		
Takahara [4]	2018	tonsillectomy	138	3–120	60 (43 %)	128(93 %)	Patient's evaluation	Intercurrent PAO Smoking cessation after tonsillectomy
		tonsillectomy	80	(12)	42 (53 %)	72 (90 %)	PPPASI	

* Statistically significant difference, PAO: palmoplantar pustulotic arthro-osteitis, PPPPASI: palmoplantar pustulosis area and severity index.

conservatively treated patients, respectively, suggesting that tonsillectomy conduced a significant higher cure rate, for the conservative treatments [49]. Kuki et al. studied 181patients with PPP who answered questionnaires and showed that 54(45 %) out of 119 patients undergoing tonsillectomy and 21(34 %) out of 62 patients undergoing treatments other than tonsillectomy had disappearance of the skin lesions [46]. Kataura et al. reported that 54 % and 88 % of 211 patients with PPP experienced disappearance and improvement of PPP eruption more than 3 months follow up after tonsillectomy, respectively [3]. Yamakita et al. [47] conducted a randomized prospective comparison study and showed that the improvement rate and cure rate were significantly higher in tonsillectomy group ($n = 26$) than that in non-tonsillectomy group ($n = 37$) at 18 months follow up period (improvement rate 85% vs. 35 %, $p < 0.01$; cure rate 46% vs. 15 %, $p < 0.01$). Recently, Takahara et al. prospectively evaluated the outcome of tonsillectomy using subjective self-assessment in 138 patients and objective PPP area and severity index (PPPASI) scoring [50] in 80 patients with PPP. Results indicated that 60(44 %) and 106 (77 %) patients experienced disappearance and improvement of the PPP eruption by subjective evaluation, respectively, and that 42(53 %) and 57(71 %) patients experienced this after PPPASI evaluation, respectively, after a median 12 months follow up period [4].

3.1.2. Indication of tonsillectomy

Clinical factors affecting a favorable skin condition after tonsillectomy, comprising a shorter period between onset of PPP and tonsillectomy [45], age 61 years and older [49], history of tonsilitis [46], intercurrent PAO [4], and smoking cessation after tonsillectomy [4] were reported. However, for clinical use as an indicator of tonsillectomy, a more detailed exploration is required. Therefore, at present, the responsible otolaryngologist should recommend tonsillectomy because of its high efficacy.

3.2. Adult IgA nephropathy (IgAN)

Primary immunoglobulin A nephropathy (IgAN) is a common type of glomerulonephritis worldwide. The reported incidence of IgAN was reported to be 4.2 per 100,000 in Japan, and range from 0.39 to 1.4 per 100,000 in the United States [51]. The disease was previously considered non-severe. However, the long-term renal prognosis is poor, with approximately 40 % of IgAN patients developing renal failure within 20 years of diagnosis [52]. Tonsillectomy is commonly used to treat IgAN either alone or in combination with steroid pulse therapy (TSP). The effect of tonsillectomy on IgAN has been extensively studied, and there are numerous reports on this topic. Hotta et al. demonstrated that clinical remission, defined as the disappearance of proteinuria and hematuria, could serve as a surrogate marker for future renal preservation [5]. Table 2 summarizes the efficacy of tonsillectomy for IgA nephropathy [5-7,53-65]. The therapeutic efficacy of tonsillectomy for IgAN was first evaluated in Asia and Europe during the 1990s. Since Hotta et al. reported the therapeutic efficacy of TSP in Japan in 2001 [5], numerous studies have been conducted on TSP. We divided these articles into two categories in terms of treatment, tonsillectomy alone and TSP, and divided each category into two chapters in terms of treatment outcomes: clinical remission and prevention of end-stage kidney disease (ESKD).

3.2.1. Tonsillectomy monotherapy

3.2.1.1. Studies focusing of clinical remission as treatment outcome.

Regarding the efficacy of tonsillectomy monotherapy for IgA nephropathy, a randomized controlled trial conducted in China showed that patients who underwent tonsillectomy had significantly higher rates of proteinuria or hematuria disappearance than those who did not undergo tonsillectomy [61]. In three observational studies from Japan and China, the tonsillectomy group showed higher rates of clinical remission than the non-tonsillectomy group [55,56,60]. In these studies, Chen et al. reported that in a long-term follow up period of an average of 11 years, the clinical remission rate was significantly higher in the tonsillectomy group (46% vs. 28 %) [56]. Moreover, Maeda et al. reported that tonsillectomy was an independent factor inducing clinical remission in a multivariate analysis that included sex, age, clinical presentation, and renal histology [60].

3.2.1.2. Studies focusing of the prevention of ESKD as treatment outcome.

Five observational studies conducted in Japan showed that tonsillectomy significantly suppressed the progression to ESKD compared with conventional treatments [54,55,60,64,65]. Akagi et al. conducted a study of 41 patients in the tonsillectomy group and 30 patients in the non-tonsillectomy group and reported a higher renal survival rate (95% vs. 73 %, $p < 0.05$) in the tonsillectomy group than the non-tonsillectomy group [54]. Matsumoto et al. evaluated the efficacy of tonsillectomy using the log-rank test and reported that patients undergoing tonsillectomy ($n = 87$) became more resistant to ESKD than those receiving treatments other than tonsillectomy ($n = 120$) [64]. Hirano et al. selected 153 patients as the tonsillectomy and non-tonsillectomy groups, each without differences in patient background between the two groups from the 1065 patients enrolled in a multicenter cohort study, and showed that a more than 1.5-fold increase in serum creatinine level was less frequently observed in the tonsillectomy group [65]. In a study conducted by Chen et al., trend difference was observed in renal survival rates between the tonsillectomy and non-tonsillectomy groups (96 % and 88 %, respectively) over 10 years of follow up using log-rank test ($p = 0.059$) [56]. On the other hand, a European multicenter study (VALIGA cohort) with a composite endpoint of 50 % reduction in eGFR

Table 2
Outcome of tonsillectomy and/or steroid pulse therapy for an adult patient with IgA nephropathy.

Author	Year	Treatment	Number of patients	Age	Male: female	Observation period; months (median)	Clinical remisson	Renal survival	Note
Hotta [5]	2001	TSP	191	33.5 ± 12.1		82.3 ± 38.2	114 (59.7 %)*		Tonsillectomy was an independent factor for an achievement of clinical remission (CR). The patients in CR spent their lives without renal dysfunction, indicating that CR was useful as a surrogate marker for renal survial.
		SP	34	36.9 ± 13.6			12 (35.3 %)		
Sato [53]	2003	TSP	30	46.3 ± 10.7	20:10	12–137 (70.3)		26 (86.7 %)*	The patients enrolled in this study have severe renal dysfunction showing as serum Cr>1.5 mg/dl.
		Steroid	25	47.5 ± 13.9	20:5			11 (44.0 %)	
		Other	15	45.3 ± 13.7	11:4			4 (26.7 %)	No difference in renal survial rate among the grpups was observed in the patinets with serum Cr from 2 to 2.5 mg/dl.
Akagi [54]	2004	Tonsillectomy	41	8–58 (29.78)	19:22	120–262 (158.9)	10 (24 %)	39 (95 %)*	Efficay of tonsillectomy changed in proportion to degree of pathological severity on preopretative renal tissues.
		Non-tonsillectomy	30	12–50 (33.0)	13:17	120–206 (151.1)	4 (13 %)	22(73 %)	
Komatsu [55]	2005	Tonsillectomy ± steroid	104	31.4 ± 13.5	112:125	69.5 ± 50.5	33 (31.7 %)*	95(91.3 %)	Steroid therapy was performed in 28% of the patinets undergoing tonsillectomy, and 37% of the other patinets. Tonsillectomy significantly contributed to renal survival by log-rank tests, univariate and multivariate analyses.
		Non-tonsillectomy ± steroid	103			56.7 ± 40.5	22 (16.5 %)	112(84.2 %)	
Chen [56]	2007	Tonsillectomy ± steroid	54	24.7 ± 9.08		139.8 ± 49.7	25 (46 %)**	52(96 %)	Tonsillectomy have a predilection to induce favorable outcome for renal survival in log-rank test ($p = 0.059$).
		Non-tonsillectomy ± steroid	58	29.8 ± 9.87		120.7 ± 49.6	16 (28 %)	51(88 %)	
Miyazaki [57]	2007	TSP	75	34.4 ± 11.8	43:58	60	52 (69 %)**		Remission rate is higher in mild cases on the severity classification by proteinuria and serum Cr level.
		SP	18				7(39 %)		
		Others (3 of tonsillectomy)	8				3(38 %)		
Komatsu [58]	2008	TSP	35	30.9 ± 12.3	11:24	49.3 ± 15.6	19 (54 %)**	35(100 %)	Non-randomized controlled trials. Renal death was defined as a condition that serum Cr levels were more than double during the treatment .Inhibition of mesangial proliferation on renal tissues was observed only in the patients received TSP.
		SP	20	27.0 ± 10.7	10:10	62.4 ± 27.0	5(25 %)	19(95 %)	
Kawaguchi [59]	2010	TSP	240	31±12.8	112:128	24	174 (72.5 %)*		In the TSP group, the probability of clinical remission was significantly higher in the petinets with mild histologic changes on renal tissues.
		Tonsillectomy	67	34.1 ± 13.6	32:35		23(34.3 %)		
		SP	23	46.4 ± 15.2	12:11		9(39.1 %)		
		Others	58	43.5 ± 13.6	21:37		10(17.2 %)		
Maeda [60]	2012	Tonsillectomy ± steroid	70	25.2–36.7 (31.0)	19:31	(84)	34.2/year*	Decreased renal function 0.5/year*	Decreased renal function was defined as a condition that eGFR falls below 30 % of normal value. Steroid therapy was performed in 71% of the patients with tonsillectomy, and 15% of the patients without tonsillectomy. An incidence of the events per year were estimated by log-rank test.
		Non-tonsillectomy ± steroid	130	23.0–48.5 (32.1)	48:82		9.3/year	Decreased renal function 4.8/year	
Kawamura [6]	2014	TSP	33	36±13	17:16	12	47 %		Randomized controlled trials. Clinical remission rates are estimated from table5 in the report. The disappearance rate of proteinuria was significantly higher in the TSP group.
		Pulse	39	40±13	18:21		29 %		
Yang [61]	2016	Tonsillectomy + trypterygium glycosides	49	28.78±7.08	22:27	(48)	H 45 (91.8 %)* P 47 (95.9 %)*		Randomized controlled trials. Clinical remission is unknown because the disappearance rate of hematuria and proteinuria are shown separately.
		Tripterygium glycosides	49	31.28 ±10.64	23:26		H 23 (46.9 %) P 25 (51.0 %)		
Feehally [62]	2016	Tonsillectomy	41	34.9 ± 16.0	21:20	23–77 (39) Total 61 cases		38(93 %)	Renal death was defind as initiation of dialysis or less than 50 % of pretreatment eGFR. From 61 patients in tonsillectomy group and 988 in non-tonsillectomy group, each 41 patients were selected for a nested case control study. 17 of the 61 patients underwent tonsillectomy after the diagnosis of IgA nephropathy.
		Non-tonsillectomy	41	36.1 ± 17.9	21:20	28–93 (54) Total 988 cases		33(80 %)	
Hoshino [63]	2016	TSP	209	36.4 ± 11.7	110:99	84.0 ± 52.8		99.3/96.3/86.3/86.3 %**	The renal survial rates are shown at 5/10/15/20 years after treatment, respectively. TSP significantly contributed to renal survival compared to other treatment in Kaplan-Meier analysis. In the subgroup analysis, TSP significantly contributed to renal survival in subgroup consisting of the patients with proteinuria of 1 g or more per day and CKD grade 1–2.
		SP	103	46.2 ± 18.3	49:54	79.2 ± 64.8		90.6/85.7/85.7/85.7 %	
		Steroid	300	40.6 ± 15.7	166:134	124.8 ± 87.6		89.8/79.7/71.3/65.3 %	
		Renin-angiotensin system inhibitor	515	48.8 ± 14.4	313:202	96.0 ± 76.8		93.1/84.8/73.6/69.1 %	
Komatsu [7]	2016	TSP	46	32.1 ± 12.9	15:31	52.1 ± 27	33 (71.7 %)**	0 (0 %)	Renal death was defined as a condition such as an initiation of dialysis or more than double from pretreatment serum Cr levels. TSP was an independent prognostic factor for clinical remission.
		Steroid	9	34.0 ± 13.6	5:04	63.5 ± 45.7	4 (44.4 %)	0 (0 %)	

(*continued on next page*)

Table 2 (*continued*)

Author	Year	Treatment	Number of patients	Age	Male: female	Observation period; months (median)	Clinical remisson	Renal survival	Note
		Others (7 of tonsillectomy)	24	38.6 ± 17.4	11:13	61.9 ± 37.4	10 (41.7 %)	1 (4.2 %)	
Matsumoto [64]	2018	Tonsillectomy	37	24–37 (26)	8:29	45–134 (72)		37 (100 %)**	From 87 petients with tonsillectomy and 120 patinets without tonsillectomy, 37 and 57 patinets were selected for mild cohort analysis, respectively.
		Non-tonsillectomy	57	24–42 (30)	25:27	39–242 (109)		50(88 %)	
		Tonsillectomy ± steroid	153	24–46 (31)	66:87			146 (95 %)*	Renal death was defined as a condition such as an initiation of dialysis or elevation of 1.5 times and more serum Cr levels during the treatment .
		Non-tonsillectomy ±	153	23–44 (30)	50:83			133 (87 %)	
Hirano [65]	2019	steroid				22.8–102 (70) (in all 1065 cases)			Steroids were administered to 65 % of the patinets in tonsillectomy group and 63 % of the patinets in non-tonsillectomy group. Renal survival rates are significantly higher in tonsillectomy group by log-rank test.

* $p < 0.01$,. ** $p < 0.05$, Clinical remission: Disappearance of hematuria and proteinuria, TSP: tonsillectomy and Steroid pulse therapy, SP: Steroid pulse therapy, H: hematuria, P: proteinuria.

or ESKD concluded that tonsillectomy had no discernible therapeutic benefit in patients with IgAN [62]. This was a nested case-control study of 1147 patients, including 61 patients in the tonsillectomy group and 988 in the non-tonsillectomy group. In the tonsillectomy group, 44 (71 %) patients underwent tonsillectomy during childhood prior to the diagnosis with IgAN. Forty-one patients from each group were selected to eliminate background bias, and comparison of the groups showed no significant difference in the frequency of patients in the endpoint state ($p = 0.105$). Seventeen patients who underwent tonsillectomy after diagnosis did not develop ESKD.

3.2.2. *Tonsillectomy combined with steroid pulse therapy (TSP)*

3.2.2.1. Studies focusing of clinical remission as treatment outcome. A randomized controlled trial has been conducted in Japan [6]. This study included 33 patients who received TSP and 39 patients who received steroid therapy alone. The clinical remission rates at one year after the treatment were estimated to be 47 % and 29 % in the TSP group and steroid therapy group from figure 5 in this report, respectively. Although the difference was not statistically significant, the urinary protein disappearance rate was significantly higher in the TSP group and tonsillectomy was an independent disappearance factor by a multivariate analysis (odds ratio 2.98, 95 % confidence interval 1.01–2.83, $p = 0.049$). A non-randomized prospective study was conducted in Japan [58]. After 4.5 years of treatment, the clinical remission rates were 54 % and 25 % in TSP group ($n = 35$) and in steroid therapy groups ($n = 20$), respectively, and the difference between the two groups was significant. Furthermore, four observational studies from Japan indicated higher urinary remission rates after TSP than after conventional treatments [5,7,57,59]. However, the conventional treatment, content of steroid pulse therapy in TSP, and the definition of clinical remission differed in each report.

3.2.2.2. Studies focusing of the prevention of ESKD as treatment outcome. No prospective studies, including randomized controlled trials, have been conducted. Sato et al. conducted a retrospective cohort study in which they followed 70 patients with serum creatinine levels of 1.5 mg/dl or higher for 5.9 years, including 30 patients undergoing TSP [53]. TSP significantly reduced progression to ESKD compared with steroid pulse therapy and other treatment modalities and was more effective in patients with creatinine levels ranging from 1.5 to 2.0 mg/dl. Hoshino et al. conducted a retrospective cohort study in which they monitored 1127 patients, including 209 with TSP, over a mean period of 8.3 years. The log-rank test demonstrated that TSP considerably reduced the risk of progression to ESKD compared to steroid pulse therapy, oral steroids, and renin-angiotensin system (RAS) blockade in all patients [63]. Furthermore, a subgroup analysis showed that the reduction of risk was more apparent in patients with CKD stages G1–2 and urinary protein levels ≥1 g/gCr, but there was no advantage of TSP compared to steroid pulse therapy in other conditions.

3.2.3. *Indications for tonsillectomy*

Currently, there are no indication criteria for tonsillectomy in patients with IgAN. Nevertheless, most reports on this topic indicate that tonsillectomy is likely to positively affect the prognosis of IgA nephropathy. Notably, a randomized controlled trial was conducted in Japan [6]. While a trial report only showed alterations in urinary findings for the initial year following treatment, subsequent long-term observational results are eagerly anticipated. Thus, tonsillectomy may improve the prognosis of IgAN. Therefore, our otolaryngologist should recommend tonsillectomy to referred patients after presenting information on the efficacy of tonsillectomy and the potential hazards of the surgical procedure.

3.3. Pediatric IgA nephropathy

In Japan, the early detection of IgAN in children is facilitated through school physical examinations, allowing clinical trials to be conducted on patients with early onset disease [66,67]. As far as the prognosis of pediatric IgAN in Japan, 57 % of patients show normalized urinary findings, 9 % progress to renal failure, and 34 % experience persistent hematuria and proteinuria at 15 years after onset, suggesting relatively unfavorable prognosis [66-68]. Recently, the "Practice Guidelines for Pediatric IgA Nephropathy 2020″ by the Japanese Society of Pediatric Nephrology were updated [69]. According to the guidelines, drug therapy is recommended as the standard treatment for pediatric IgAN, and tonsillectomy is the treatment option for severe cases.

3.3.1. Tonsillectomy (with steroid pulse therapy) for pediatric IgA nephropathy

Tonsillectomy can be performed alone or in combination with steroid pulse therapy (TPS) in pediatric patients with IgAN. Representative reports are summarized in Table 3 [70-75]. Kawasaki et al. collected data from 32 pediatric patients diagnosed with severe IgAN pathologically showing diffuse mesangial proliferation and divided the patients into two groups: 16 patients with TSP and anticoagulant or antiplatelet drug treatment (TSP group) and 16 patients receiving multidrug therapy (MDT), such as corticosteroids, immunosuppressive agents, anticoagulants, and antiplatelet drugs (MDT group) [70]. After a 3-year follow up, 12 patients (75 %) in the TPS group and 9 patients (56 %) in the MDT group showed disappearance of hematuria and proteinuria (clinical remission: CR). Renal pathology in both groups showed improvement in the activity index (AI) without worsening of the chronicity index (CI). Moreover, it should be noted that over 50 % of patients in MDT group experienced an exacerbation of urinary findings due to upper airway inflammation including tonsillitis, whereas this was not observed in the TPS group. Kawasaki et al. continue the work and retrospectively compared 44 and 17 patients who received MDT and TPS, respectively. Both the MDT and TPS groups showed high rates of CR, preservation of renal function, and histological improvement in renal tissues during the long-term follow up period of 7–11 years. Moreover, five patients in the MDT group received TPS because of deterioration of renal function [75].

Because MDT is supposed to be conducted for patients in line with the guidelines, TPS is used for patients who are not cured by MDT. Kawasaki et al. administered TPS to 11 patients who failed to achieve CR following a two-year course of MDT [71]. Accordingly, seven patients achieved CR during an average 24.7 months of postoperative observation period. Moreover, urinary abnormalities such as hematuria and proteinuria improved in the remaining four patients. Kawasaki et al. compared 18 patients undergoing initial TPS with 15 patients undergoing TPS after MDT over a median observation period of 8 years [74]. The results demonstrated a significant improvement in urinary abnormalities, preservation of serum creatinine levels, and reduction in pathological renal glomerular crescent formation after tonsillectomy, with no significant differences between the two groups.

3.3.2. Indication of tonsillectomy (with steroid pulse therapy) for pediatric IgA nephropathy

According to the aforementioned results, tonsillectomy (combined with steroid pulse therapy) induces favorable outcomes in pediatric patients with IgAN and MDT. In accordance with the Guidelines for Pediatric IgA Nephropathy 2020, tonsillectomy is suggested as a potential treatment option for patients with IgAN refractory to MDT or those with IgAN and recurrent tonsillitis. With an understanding of the guidelines, our otolaryngologists should recommend tonsillectomy to patients referred by a pediatric doctor.

3.4. Recurrent IgAN after kidney transplantation

Recurrent IgAN after kidney transplantation is common and has been reported in 20–40 % of the patients [76]. There have been several reports on tonsillectomy (with steroid pulse therapy) for recurrent IgAN.

3.4.1. Tonsillectomy (with steroid pulse therapy) for recurrent IgAN after kidney transplantation

The main reports describing the treatment outcomes of tonsillectomy and/or steroid pulse therapy for recurrent IgA nephropathy (IgAN) after kidney transplantation are summarized in Table 4 [77-83]. Most reports have shown that tonsillectomy improves hematuria and/or proteinuria, suggesting the suppression of nephropathy progression. Hotta et al. followed 15 patients who underwent tonsillectomy and/or steroid pulse therapy for 12 months after tonsillectomy and showed that hematuria disappeared in five of six appropriate patients and that severe proteinuria decreased in all three patients [79]. Moreover, 10 patients showed an improvement in the histological damage of recurrent IgAN on repeat graft biopsy after tonsillectomy [79]. Regarding comparison between tonsillectomy and conservative treatments, Kennoki et al. compared 16 and 12 patients with and without tonsillectomy, respectively, and showed that improvement of proteinuria was observed in tonsillectomy group, but not in non-tonsillectomy group [77]. Moreover, Tanaka showed that three of nine patients who received conservative treatments for recurrent IgAN required subsequent dialysis, but 14 patients undergoing additional tonsillectomy avoided dialysis [82]. However, the follow up periods after tonsillectomy in these reports, in addition to the report by Doi et al. [83], were not sufficient to conclude that tonsillectomy is effective in preventing transplanted kidney death. Because the therapeutic modality was limited to recurrent IgAN, our otolaryngologist recommended tonsillectomy to the referred patients after explaining the treatment outcome and operative risk.

3.4.2. Preventive tonsillectomy

Preventive tonsillectomy was defined as the operation around kidney transplantation to prevent IgAN recurrence. Sato et al. compared 28 patients who underwent preventive tonsillectomy with 50 patients who did not undergo tonsillectomy and found no significant difference in the recurrence rate between the groups [80]. However, Nagai et al. reported no pathological or clinical recurrence in 39 patients who underwent preventive tonsillectomy during a maximum 5 year follow up [81]. Because 20–40 % of the recurrence rate was shown in previous reports [76], the preventive tonsillectomy might induce favorable outcomes. At present, we cannot conclude the significance of preventive tonsillectomy because of a lack of sufficient information. Our otolaryngologist decided on the indications for preventive tonsillectomy on a case-by-case basis through discussion among the patients and the principal doctor. Perioperative management of preventive tonsillectomy, especially pre-transplant tonsillectomy, is generally difficult, and tonsillectomy should be conducted in hospitals where acute-phase transplantation rejection can be managed.

3.5. Sternoclavicular hyperostosis (SCCH), palmoplantar pustulotic arthroosteitis (PAO), and acne-pustulosis-hyperostosis-osteitis syndrome (SAPHO)

Aseptically thickened bone lesions in the sternoclavicular joint are referred to as sternoclavicular hyperostosis (SCCH). Sonozaki et al. [17] reported 53 patients with SCCH complicated by palmoplantar pustulosis (PPP) and named SCCH with PPP palmoplantar pustulotic arthroosteitis (PAO). In 1987, Chamot and Kahn [84] reported 85 cases of osteoarticular hyperostosis, including SCCH with or without acne or PPP. These conditions were defined as syndromes, acne, pustulosis, hyperostosis (and). Currently, “S” shows synovitis, and

Table 3
Outcome of tonsillectomy and/or steroid pulse therapy for a child patient with IgA nephropathy.

Author	Year	Treatment	Number of patients	Age (median) Sex (M:F)	Posttreatment observation period; months (median)	Clinical remisson	Renal pathological findings	Note
Kawasaki [67]	2006	TSP +anticoagulant +antiplatelet	16 (Severe cases)	13.0 ± 2.0 9:7	36.1 ± 7.9	12 (75 %)	AI improved and CI sustained in both groups.	Prospective study. No patient in both group showed an exacerbation of renal function after treatment. More than 50% of the patients in multidrug therapy group experienced worsening of hematuria and/or proteinuria with tonsillitis.
		MDS	16 (Severe cases)	11.3 ± 3.0 8:8	37.6 ± 8.5	9 (56 %)		
Kawasaki [68]	2009	TSP +anticoagulant +antiplatelet	11 (MDT-resistant cases)	11.7 ± 2.0 7:4	Avarage 24.7	7 (64 %)	6 patients received renal biopsies after tonsillectomy. AI was improved in all cases. CI improved in 4 cases.	Immunosuppressive drugs were not used in MDT. Renal function was preserved after treatment in all cases.
Nishi [69]	2012	Tosillectomy	25	14.3 ± 5.6 13:12	(24.7)	10 (40 %)	19 patients received renal biopsies after tonsillectomy. AI was significantly improved in the patients recevied early tonsillectomy	Tonsillectomy whthin 3 years after diagnosis showed better outcome in urinary findings and histological activity.
Kawasaki [71]	2017	TSP	18	11.6 ± 2.5 10:8	106.8 ± 30	17 (94 %)	Depletions of IgA/C3 deposition and fibrosis/crescent formation were detected in both groups. (Oxford classification)	In 11 of 13 patients in MDS group, immunosuppressant was not used. Renal function was preserved after treatment in all patients belonging both groups.
		MDT failure →TSP+anticoagulant and antiplatelet	15	11.7 ± 2.0 11:4	98.4 ± 49.2	13 (87 %)		
Yamada [70]	2018	TSP	54 Severe cases 24 Moderate cases 30	4.8–17.9 (12.2) 32:22	24–120 (60)	Disapperance of H 47 (87 %) Disapperance of P 54 (100 %)		Disapperance of P was less frequently observed in severe cases. Renal function was preserved after treatment in all patients.
Kawasaki [72]	2018	TSP	17	11–13 (12) 10:7	85.2–134.4 (120)	15 (88 %)	Depletions of fibrosis/crescent formation in renal glomerulus were detected in both groups. (Oxford classification)	No patient in both group showed an exacerbation of renal function after treatment. 5 patients in MDS group showed exacerbation of H and/or P, and underwent TSP.
		MDS	44	10–14 (12) 28:26	98.4–135.6 (110.4)	30 (68 %)		

TSP: tonsillectomy and Steroid pulse therapy, MDT: Multidrug therapy, SP: Steroid pulse therapy, AI: Activity index, CI: Chronicity index, H: Hematuria, P: Proteinuria.

synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is more popular to indicate the disease condition [20]. Therefore, SCCH and PAO are associated with the SAPHO syndrome.

3.5.1. Effects of tonsillectomy

There are many case reports showing improvement or disappearance of arthralgia caused by SCCH, PAO, or SAPHO after tonsillectomy; however, studies involving more than 10 patients are limited [3,4]. Kataura et al. [3] reported 89 patients with SCCH or PAO who were followed up for > 3 months after tonsillectomy. As a result, the improvement and disappearance of arthralgia was seen in 72 (81 %) and 46 (52 %) patients, respectively. Takahara et al. [4] evaluated an arthralgia in 50 patients with PAO after tonsillectomy and showed that 43 (86 %) and 36 (72 %) patients realized the improvement and disappearance of arthralgia, respectively. On the basis of these reports, the efficacy of tonsillectomy in treating arthralgia is thought to be high.

Regarding onset time of tonsillectomy effect, Kaplan–Meier analysis revealed that the disappearance could be seen in 68 % of the patients at 6 months and in 78 % at 12 months after tonsillectomy. Subsequently, the disappearance rate plateau [4]. In other words, the onset can be realized relatively early and is expected to last for approximately 12 months after tonsillectomy. Therefore, at least 1-year follow up is necessary after tonsillectomy to evaluate its effectiveness.

3.5.2. Indications for tonsillectomy

Based on these findings, tonsillectomy can be indicated for patients with arthralgia caused by SCCH, PAO, or SAPHO. Presently, there are no reports suggesting the clinical factors indicative of tonsillectomy. Therefore, our otolaryngologist recommended that all patients with diseases be referred to a rheumatologist.

3.6. PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a broadly defined autoinflammatory disease with periodic fever sometimes accompanied by aphthous stomatitis, pharyngitis, and cervical adenitis; however, its pathogenesis has not been fully elucidated. This phenomenon was first reported by Marshall et al. in 1989 [85]. Subsequently, diagnostic criteria were proposed by Thomas et al. [86] and further developed, including adult-onset cases, by Padeh et al. [87]. PFAPA syndrome is the most common periodic fever syndrome, with a prevalence of approximately 1 in 5000 children. The long-term prognosis is generally good and spontaneous remission can be expected. However, frequent high fevers are physically and psychologically stressful for affected infants and parents. Therefore, active treatments, including surgery, are often required for patients experiencing severe stress. The first-line treatment is medication, including corticosteroids, leukotriene antagonists, colchicine, and cimetidine. Corticosteroids were used as antifebrile agents for high fever, whereas others were used to prevent periodic fever. However, steroids are reported to have the risk of shortening the duration between fever attacks [88].

3.6.1. Effect of tonsillectomy

Table 5 summarizes the main studies investigating the effects of tonsillectomy in patients with PFAPA syndrome [13,14,89-95]. Three randomized controlled trials (RCT) revealed that the number of fever attacks was significantly reduced in the tonsillectomy group compared to the wait-and-see group [13,14,95].

However, a small number of cases and short-term observations were noted in the first two reports of the Cochrane Database of Systematic Reviews [96]. Reports other than the RCT targeted a relatively large number of patients. For instance, Yıldız et al. reported that 313(95 %) of 328 patients with PFAPA syndrome experienced a cessation of the fever attack after tonsillectomy [94]. In contrast, Vigo et al. observed 41 patients undergoing tonsillectomy and 234 patients undergoing conservative treatment over 4 years and showed no difference in the frequency of fever attacks between the two groups [91]. However, this study had some limitations, including the lack of a randomized controlled trial, uncertain indications for tonsillectomy, and an unclear follow up period after tonsillectomy. With regard to additional adenoidectomy, because tonsillectomy alone induces a comparably high disappearance rate of fever attacks [13,95], sufficient effects may be expected with tonsillectomy alone.

3.6.2. Indications for tonsillectomy and level of evidence

Owing to the impact of the treatment outcomes mentioned above, tonsillectomy should be recommended for patients referred by a pediatric doctor for PFAPA syndrome. Importantly, otolaryngologists should bear in mind that these patients may blend into a group of patients with suspected recurrent tonsillitis. Therefore, patients, especially children,

Table 4
Outcome of tonsillectomy and/or steroid pulse therapy for a patient with recurrent IgAN after kidney transplantation.

Author	Year	Treatment	Number of patients	Posttreatment observation period; months (median)	Outcome	Number of patients undergoing dialysis	Note
Kennnoki [77]	2009	Tonsillectomy	16	(62.1)*	Improvement of proteinuria	0	About 17 observation months after tonsillectomy.
		Others	12	(59.8)*	No change of proteinuria	0	*Total observation months after recurrence
Koshino [78]	2013	Tonsillectomy	7	>36(6 patients)	3 (43 %) CR	2*	*2 patients showed severe renal histology.
Hotta [79]	2013	TSP	8	12	5(63 %) Histological improvement	0	All 15 patients received a repeat graft biopsy at 23.8 ± 15.8 months.
		Tonsillectomy	7		5(71 %) Histological improvement	0	
Sato [80]	2014	PT	28	(26.4)	4 (14 %) Recurrence	0	7 patients underwent tonsillectomy before renal dysfunction.
		Others	50	(45.6)	8 (16 %) Recurrence	0	Recurrence was diagnosed by renal histology.
Nagai [81]	2016	PT	25	>24	No recurrence	0	Recurrence was diagnosed by urinaly findings.
Tanaka [82]	2017	Tonsillectomy	14	(about 52)	8 (57 %) Improvement of proteinuria	0	Improvement is defined as under 0.3 g/day of proteinuria.
		Others	9		Not listed	3	
Doi [83]	2020	TSP	3	120	2 (66 %) CR	0	Long obeservation period.
		Tonsillectomy	1		CR	0	

TSP: tonsillectomy and Steroid pulse therapy, PT: preventive tonsillectomy, CR: Clinical remission (disapperarnce of hematuria and proteinuria).

Table 5
Outcome of tonsillectomy for a patient with periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome.

Author	Year	Number of patients	Age (median)	Male: female	Treatment	Follow up period months (median)	Number of cases with disappeared symptom
Renko M [13]	2007	14	1.5–14 (4.2)	8:6	Tonsillectomy	6	14 (100 %)*
		12	1.5–7.2 (4)	8:4	Wait-and-see	6	6 (50 %)
Licameli G [89]	2008	27	2–18	13:14	Tonsillectomy ± adenoidectomy	8–41	26(96 %)
Garavello W [14]	2009	19	3–13 (5.4)	9:10	Adenotonsillectomy	18	12(63 %)*
		20	2–12 (4.9)	13:7	Wait-and-see	18	1(5 %)
Licameli G [90]	2012	102	1.5–14.9 (4.8)	75:49[#]	Adenotonsillectomy	6–77 (43)	99 (97 %)
Vigo G [91]	2014	41	1.6–13.1 (5.3)[$]	23:18	Tonsillectomy	20–149 (69)[&]	27 (66 %)
		234	(3.1)[$]	139:95	Medication	12–201 (52)[&]	147 (63 %)
Lantto U [92]	2016	58	1.3–8.8 (3.3)	38:20	Tonsillectomy ± adenoidectomy	35–239 (107)	56(97 %)
Erdogan F [93]	2016	75	(4.4)[##]	49:26	Tonsillectomy ± adenoidectomy	(24)	74(99 %)*
		30	(4.9)[##]	17:13	Steroid	(24)	17 (57 %)
Yıldız M [94]	2021	328	(1.5)[#]	146:182[$]	Tonsillectomy ± adenoidectomy	>12	313 (95.4 %)
Lantto U [95]	2024	8	(3.8)[##]	10:6	Tonsillectomy	9	7 (88 %)
		8	(3.0)[##]		Wait-and-see		2 (25 %)

* Statistical significance. [#] Value in mother population. [$] Estimated value. [&] Period between first and last visit. [##] Age at onset.

with a periodicity of fever in the group, should be referred to the pediatrics department if they do not undergo an examination by a pediatric doctor.

Hara et al. [97] investigated the clinical factors affecting the effectiveness of tonsillectomy and concluded that headache and late onset were factors predicting the positive effects of tonsillectomy. These factors may be helpful in the decision-making process for tonsillectomy.

3.7. IgA vasculitis

IgA vasculitis, also called Henoch-Schönlein purpura, is a systemic allergic vasculitis that causes symptoms such as purpura, arthritis, abdominal pain, and nephritis. The age at which the disease is most likely to occur is approximately 6 years, and it is more common in boys. Although the prognosis is generally good, some patients with nephritis develop end-stage renal failure. IgA vasculitis shows IgA deposition in the glomeruli and exacerbation of upper respiratory tract inflammation, such as IgA nephropathy, suggesting that a common immune abnormality is involved.

Several reports on the efficacy of tonsillectomy for IgA vasculitis have been published [10,11,98,99], and, especially, Yan et al. [11] reported a randomized clinical trial in patients with IgA vasculitis associated with chronic tonsillitis, defined as recurrent fever with sore throat, irregular surface of the palatoglossal tonsils, and enlarged crypts. They compared two groups: a non-surgery group consisting of patients medicated with antimicrobials and antihistamines, and a surgery group of patients undergoing tonsillectomy. Accordingly, both groups showed improvement in the four main symptoms of skin rash, hematuria, proteinuria, and abdominal pain at the end; however, the surgery group had significantly earlier improvement of the symptoms than the non-surgery group. Other reports are observational studies without a target for comparison, but all reported postoperative cure or symptom remission, suggesting that tonsillectomy is highly effective.

Concomitant purpura nephritis is critical for long-term disease prognosis. Tonsillectomy reportedly disperses and preserves abnormal urinary findings and deteriorates renal function caused by purpura nephritis, respectively [10,98,99]. In addition, Inoue et al. [10] reported a positive correlation between the period from diagnosis to tonsillectomy and the disappearance of abnormal urinary findings. Therefore, early tonsillectomy is recommended for the patients with IgA vasculitis, especially for the patients who are refractory to conservative treatment or have purpura nephritis.

3.8. Plaque psoriasis, Guttate psoriasis

Plaque psoriasis is an inflammatory keratosis of unknown origin characterized by well-demarcated erythema and silvery-white scales on the extensor sides of the extremities. The disease is intractable to conservative treatment, with frequent remission and exacerbation. Guttate psoriasis is a type of psoriasis and characterized by erythema accompanied by relatively small scales after upper airway infection (UAI) caused by hemolytic streptococci and so on. Although the disease is generally curable, there have been some cases of repeated recurrence and chronic progression, followed by plaque psoriasis. The occurrence and exacerbation of these skin diseases are sometimes observed after UAI, and the efficacy of tonsillectomy has been indicated as a TFD [3].

Several studies have examined the effects of tonsillectomy on patients with psoriasis. Nyfors et al. [8] conducted a questionnaire survey of 74 patients with plaque psoriasis who underwent tonsillectomy because of resistance to dermatological treatment. They reported that 29 (39 %) and 24 (32 %) patients realized an improvement and disappearance of the skin eruptions, respectively. Kataura et al. [3] reported that 49 % of 35 patients with plaque psoriasis showed improvement in skin eruption more than 3 months after tonsillectomy, and the effect was more significant in younger women. Thorleifsdottir et al. [9,100] conducted randomized controlled trials in this field; 29 patients with plaque psoriasis exacerbated by the sore throat were divided into 15 patients who underwent tonsillectomy and 14 patients who received nonsurgical management. As a result, skin eruption itself and interference in patients' daily lives due to skin eruptions improved more in the tonsillectomy group than in the non-tonsillectomy group.

To date, no definitive indicators of tonsillectomy have been identified. However, younger age [3], female sex [3,100], and an exacerbation of the eruption at the UAI [9,100] may be candidates for this indicator. In addition, these three factors have been reported to correlate with each other [101]. Based on these results, tonsillectomy should be proposed with a discussion of the surgical risks and outcomes with the patient and responsible doctor.

3.9. Reactive arthritis, rheumatoid arthritis

Arthritis associated with tonsillitis caused by bacterial infection is known as reactive arthritis and is considered a TFDs. In most cases, the serum rheumatoid factor is negative, and asymmetric arthritis occurs in

the legs, knees, and other parts of the body after tonsillitis. Kobayashi et al. [12,102] reported that all eight patients with reactive arthritis resistant to antimicrobial therapy underwent tonsillectomy and were cured. Regarding of rheumatoid arthritis, Kataura et al. [3] reported that tonsillectomy was performed in 18 patients with rheumatoid arthritis, and 66.7 % of them showed improvement of the symptoms such as joint pain.

Although only a few retrospective observational studies have reported both reactive and rheumatoid arthritis, they all demonstrated the efficacy of tonsillectomy. In both diseases, tonsillectomy is likely to be effective and should be considered a treatment option.

3.10. Other tonsillar focal disease

Other than the major TFDs as described above, some patients with Behcet's disease, erythema nodosum, and tonsillar febricula were reported to experience improvement of the original findings and symptoms after tonsillectomy.

3.10.1. Behçet's disease

Behçet's disease is a rare disorder caused by recurrent systemic vasculitis and is characterized by symptoms such as mouth aphthas, eye inflammation, skin rashes, and genital ulcers. The disease is reportedly related to tonsillitis at onset and exacerbation [103,104], and is suggested to be caused by hypersensitivity to streptococcal antigens by fundamental investigation [105]. Therefore, this disease may be included in TFDs. Nanke et al. reported a patient with Behçet's disease who experienced a good clinical course after tonsillectomy [106].

3.10.2. Erythema nodosum

Erythema nodosum is a skin condition characterized by red nodules typically appearing on the lower extremities. The essence of the disease is a cutaneous reaction that may be associated with a wide variety of disorders, including infections, autoimmune disorders, pregnancy, and malignancies [107]. Streptococcal pharyngitis is a major background disease [108] and tonsillectomy has a favorable effect on the clinical course of patients [109]

3.10.3. Tonsillar febricula

Primary unknown low-grade fever is sometimes caused by smoldering infection of the palatine tonsils [107]. This condition was named as tonsillar febricula [110], and may be diagnosed by tonsillar annulation tests. In this case, tonsillectomy was reportedly beneficial for the disappearance of fever [107].

4. Conclusion

We present the background, diagnosis, and outcome of tonsillectomy for TFD as a guide for clinical management. The only treatment performed by otolaryngologists is tonsillectomy, which is routinely performed by general otolaryngology departments. Patients with TFD are mostly referred by dermatologists, nephrologists, and rheumatologists who anticipate the therapeutic effects of tonsillectomy. In the TFD described in this manuscript, otolaryngologists should thoroughly explain the therapeutic effects and actively recommend surgery.

Disclosure state

This study was conducted as part of the Committee of the Guidance of Clinical Management for Patients with TFDs, funded by the Japan Society of Stomato-pharyngology. The society is an independent academic organization that receives no sponsorship or funding from specific organizations or businesses. Furthermore, the society did not receive any funding for the present study from the companies.

Author contributions

All authors meet the ICMJE authorship criteria. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

None of the authors has any financial support or other benefits from commercial sources for the work, nor any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

Acknowledgment

We would like to thank Editage (www.editage.jp) for the English language editing.

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