Kidney Medicine Original Research

Tonsillectomy Monotherapy for IgA Nephropathy: A Case Series

Hirokazu Marumoto, Nobuo Tsuboi, Tetsuya Kawamura, and Takashi Yokoo

Rationale & Objective: Studies of immunoglobulin A nephropathy (IgAN) have suggested the therapeutic benefit of simultaneously adding tonsillectomy to corticosteroid therapy. However, the efficacy of tonsillectomy monotherapy in the absence of simultaneous use of corticosteroids is unclear.

Study Design: Patients with IgAN treated with tonsillectomy monotherapy were analyzed retrospectively. Clinical parameters, including kidney function slope, were compared before and after tonsillectomy.

Setting & Participants: Patients with biopsy-proven IgAN who received tonsillectomy monotherapy at our hospital between 2007 and 2018.

Results: 20 Japanese patients with IgAN were included in this study (mean follow-up period, 135 months from initial biopsy diagnosis to tonsillectomy). All patients had been treated with renin-angiotensin-aldosterone system inhibitors. 17 patients had a history of induction therapy with corticosteroids. Mean time to tonsillectomy from termination of corticosteroid therapy was 84 months. Hematuria, proteinuria, and clinical remission were achieved in 13 of 17 (76%), 10 of 17 (59%), and 8 of 20 (40%) patients at medians of 3.0, 6.0, and 13.5 months, respectively, after tonsillectomy. The slope of the estimated glomerular filtration rate (eGFR) increased significantly during the 81-month observation period, including the periods before and after tonsillectomy (−2.59 vs 1.05 mL/min/1.73 m^2 per year; $P < 0.001$). The effect on eGFR slope was consistent in 11 patients with reduced GFR (eGFR < 60 mL/min/1.73 m^2) at the time of tonsillectomy (−3.07 vs −0.39 mL/min/1.73 m^2 per year; $P < 0.001$).

Limitations: Small sample size. Lack of a control (no-tonsillectomy) group due to the difficulty of setting the baseline time point (which corresponded to tonsillectomy in our sample). Potential exclusion of patients with the most severe disease who are likely to receive corticosteroids. Lack of generalizability to patients in other countries.

Conclusions: Tonsillectomy monotherapy may prevent kidney function decline in some patients with IgAN with kidney disease that has been progressive despite long-term application of conventional therapies.

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Immunoglobulin A (IgA) nephropathy (IgAN) is the most common form of primary glomerulonephritis and the major cause of end-stage kidney disease worldwide.[1] Treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors or corticosteroids can prevent the progression of reduced glomerular filtration rate (GFR).[2–4] However, these evidence-based therapies fail in a considerable proportion of patients with IgAN diagnosed; disease typically progresses to end-stage kidney disease in 30% to 40% of patients.[5–7] The predictors of worse kidney outcomes in patients with IgAN receiving established therapies include reduced GFR at the time of diagnosis and heavy proteinuria at the time of diagnosis or during follow-up.[8–11]

Recent studies have revealed a crucial role of mucosal immunity, including aberrantly glycosylated IgA produced by tonsillar lymphocytes, in the pathogenesis of IgAN.[12–14] Previous studies have demonstrated the therapeutic benefit of adding tonsillectomy to corticosteroid therapy relative to corticosteroid monotherapy in patients with IgAN.[15–17] Recent meta-analyses and a large-scale retrospective cohort study have shown that the effect of tonsillectomy on IgAN is statistically independent of that of corticosteroids.[18–20] However, to date, few studies have focused on the effect of tonsillectomy monotherapy; that is, not in combination with corticosteroids.[21,22] In addition, the effect of tonsillectomy monotherapy performed soon after the initial biopsy diagnosis was analyzed in most previous studies; few of these studies included patients with a long-term history of conventional therapy before tonsillectomy.

We analyzed the long-term clinical courses of patients with IgAN who received tonsillectomy monotherapy. All patients showed persistent urinalysis abnormalities and/or established reduced GFR (estimated GFR [eGFR] < 60 mL/min/1.73 m^2) despite long-term treatment of IgAN.

METHODS

Patient Selection

This study included adult patients with biopsy-proven IgAN who received tonsillectomy monotherapy (without simultaneous use of corticosteroids) at our hospital between 2007 and 2018. Indications for tonsillectomy were: (1) clinically apparent habitual tonsillitis and/or (2) subclinical chronic tonsillitis based on laryngoscopy findings by otolaryngologists. The patient selection process is shown in Figure 1. Criteria for inclusion were persistent

PLAIN-LANGUAGE SUMMARY

Immunoglobulin A nephropathy (IgAN) is a major cause of end-stage kidney disease worldwide. The underlying cause of IgAN remains largely unknown, but basic studies have suggested the involvement of mucosal immunity of palatine tonsils. Tonsillectomy has been performed for the treatment of IgAN for many years, but its effectiveness remains unclear. This is probably because tonsillectomy for IgAN is often performed with concurrent steroid therapy. This study compared urinalysis abnormalities (hematuria and proteinuria) and speed of glomerular filtration rate (GFR) decline (estimated GFR [eGFR] slope) before and after tonsillectomy monotherapy in patients with IgAN. Both urinalysis abnormalities and eGFR slope were improved by tonsillectomy. This new finding suggests that tonsillectomy is an effective and promising treatment option for patients with IgAN.

urinary abnormalities (urinary protein excretion [UPE] ≥ 0.5 g/d or red blood cell [RBC] count in urinary sediment ≥ 5/high-power field [HPF]) despite 2 or more years' follow-up with conventional therapies and 1 or more year of observation before and after tonsillectomy.

Definitive diagnoses of IgAN were based on typical kidney histopathologic features of focal or diffuse mesangial proliferative glomerulonephritis, observed by using light microscopy. Glomerular IgA deposition was confirmed by immunohistochemistry or immunofluorescence, and the presence of dense deposits in the corresponding mesangial and paramesangial areas of glomeruli was detected by using electron microscopy. Kidney transplant recipients and patients with other systemic diseases associated with glomerular IgA deposition, including IgA vasculitis, liver cirrhosis, systemic lupus erythematosus, and lymphoproliferative diseases, were excluded. Patients with a history of corticosteroid therapy were not excluded. However, patients who terminated corticosteroid therapy less than 1 year before tonsillectomy and those treated with immunosuppressive agents including corticosteroids after tonsillectomy were excluded.

Consent was obtained by opting out for individual participants. All participants read and reviewed the presented documentation in the hospital and were provided the opportunity to ask questions and discuss the study. This study was approved by the Ethics Review Board of Jikei University School of Medicine (31-163 [9662]).

Definitions

Hypertension was defined as systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or use of antihypertensive medications. Patients prescribed RAAS inhibitors for renoprotection despite having normal blood pressure were not regarded as having hypertension. Treatment with RAAS inhibitors was defined as use of an angiotensin-converting enzyme inhibitor or angiotensin type 1 receptor blocker. Immunosuppressive induction therapy was defined as use of any immunosuppressive agent, including corticosteroids, within 1 year after the initial diagnostic kidney biopsy, irrespective of duration or dose. eGFR was calculated from serum creatinine (Scr) level using a modified equation for Japanese individuals: $eGFR = 194 \times age^{-0.287} \times Scr^{-1.094}$ (× 0.739 if female).[23] Reduced GFR was defined as eGFR < 60 mL/min/1.73 m^2. Creatinine clearance rate was measured using Scr and urine creatinine concentrations in a 24-hour urine collection. UPE, urinary sodium excretion, and estimated protein intake were measured in a 24-hour urine collection. RBC count in urinary sediment was graded as follows: 0, <5 RBC/HPF; 1, 5 to 9 RBC/HPF; 2, 10 to 19 RBC/HPF; 3, 20 to 49 RBC/HPF; 4, 50 to 99 RBC/HPF; and 5, >99 RBC/HPF. Remission of urinary abnormalities was defined as reported previously, using data from 3 consecutive visits at 3-month or longer intervals.[24] Hematuria remission was defined as RBC count in urinary sediment of <5 RBC/HPF. Proteinuria remission was defined as UPE < 0.3 g/d. Clinical remission was defined as remission of both hematuria and proteinuria. Patients in remission according to urinalysis findings at the time of tonsillectomy were excluded from the analysis of remission status after tonsillectomy. To evaluate hematuria, proteinuria, and other laboratory parameters, we used median or mean values determined at follow-up visits during the same

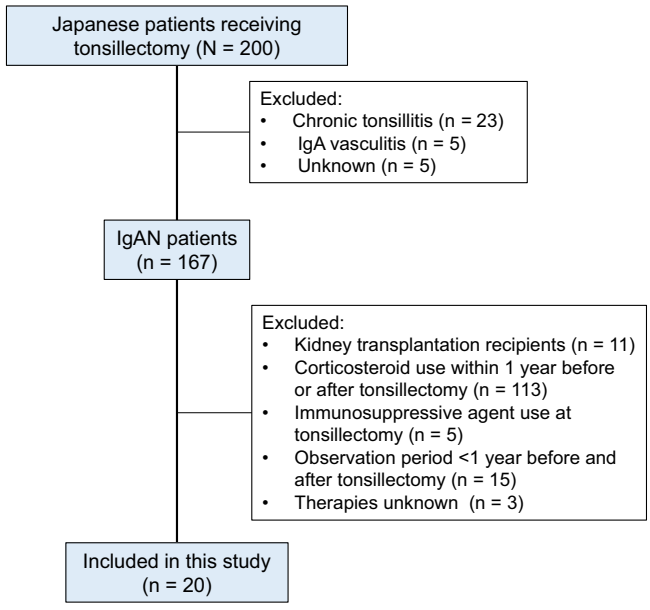

Figure 1. Patient selection. Abbreviations: IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy.

Table 1. Clinical and laboratory findings at tonsillectomy

Characteristics (n = 20)	All (n = 20)	eGFR ≥ 60 (n = 9)	eGFR < 60 (n = 11)
Clinical findings			
Men	13 (65%)	7 (78%)	6 (55%)
BMI, kg/m^2	21.3 ± 2.8	20.6 ± 2.9	21.7 ± 2.8
Hypertension	1 (5%)	0 (0%)	1 (9%)
Age at biopsy diagnosis, y	31.1 ± 12.6	23.8 ± 10.6	37.1 ± 11.9
Age at tonsillectomy, y	42.2 ± 11.4	34.4 ± 7.7	48.6 ± 10.0
Observation period from diagnosis to tonsillectomy, mo	134.7 ± 61.9	129.4 ± 62.2	139.0 ± 64.4
Observation period before and after tonsillectomy, mo	40.5 ± 13.5	41.3 ± 16.3	39.8 ± 11.5
Antiplatelet use	10 (50%)	6 (67%)	4 (36%)
RAAS inhibitor use	20 (100%)	9 (100%)	11 (100%)
– ACE inhibitor	0 (0%)	0 (0%)	0 (0%)
– ARB	20 (100%)	9 (100%)	11 (100%)
History of corticosteroid therapy	17 (85%)	7 (78%)	10 (91%)
History of corticosteroid pulse therapy	6 (30%)	1 (17%)	5 (50%)
Period from termination of corticosteroid therapy to tonsillectomy, mo	84.3 ± 55.5	69.2 ± 39.1	93.3 ± 63.6
Laboratory findings			
Serum creatinine, mg/dL	1.18 ± 0.40	0.91 ± 0.22	1.39 ± 0.40
eGFR, mL/min/1.73 m^2	57.9 ± 23.8	78.0 ± 19.5	41.6 ± 10.6
CL_{cr}, mL/min/1.73 m^2	80.9 ± 25.2	93.8 ± 26.3	70.3 ± 19.4
Serum IgA, mg/dL	260 ± 60.8	329 ± 100	282 ± 111
Serum IgA/C3 ratio	3.1 ± 1.0	3.3 ± 0.4	3.3 ± 1.6
Serum albumin, g/dL	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4
LDL cholesterol, mg/dL	106 ± 33.5	104 ± 38.2	107 ± 32.7
HDL cholesterol, mg/dL	78 ± 27	74 ± 29	81 ± 28
Serum uric acid, mg/dL	6.1 ± 1.3	5.2 ± 0.75	6.6 ± 1.2
UPE, mg/d	468 [288-532]	515 [345-552]	440 [282-521]
Urinary RBC counts, 0/1/2/3/4/5 grade	8/4/1/3/4/0	1/2/0/2/4/0	7/2/1/1/0/0
Japanese Clinical Grade[a] (C-grade I/II/III)	4/5/11	4/5/0	0/0/11

Note: Data for categorical variables expressed as number (percent); data for continuous variables expressed as mean ± standard deviation or median [interquartile range]. Conversion factors for units; serum creatinine in mg/dL to μmol/L, ×88.4; cholesterol in mg/dL to mmol/L, ×0.02586.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin type 1 receptor blocker; BMI, body mass index; CL_{cr}, creatinine clearance; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IgA, immunoglobulin A; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system; RBC, red blood cell; UPE, urinary protein excretion.
[a]Japanese Clinical Grade classification: C-grade I, UPE < 0.5 g/d and eGFR ≥ 60 mL/min/1.73 m^2; C-grade II, UPE ≥ 0.5 g/d and eGFR ≥ 60 mL/min/1.73 m^2; C-grade III, eGFR < 60 mL/min/1.73 m^2.[39]

observation periods before and after tonsillectomy (Fig S1). eGFR slope (ΔeGFR) was defined as rate of change in eGFR at follow-up visits, calculated using a linear regression model and the least-squares principle (Fig S2).

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR). Nonparametric continuous variables were compared using Mann-Whitney U test. We used Wilcoxon signed rank test to compare data obtained before and after tonsillectomy. Categorical variables are presented as percentage and were compared using χ^2 test. Log-rank test was performed to evaluate remission status of the urinalysis findings. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (R Foundation for Statistical Computing, version 2.4.0).[25]

RESULTS

Clinical Characteristics at Tonsillectomy

Clinical characteristics of patients at the time of tonsillectomy are shown in Table 1. The sample comprised 20 patients; men predominated, and mean age was 42 years. All patients had recurrent or persistent urinary abnormalities and/or reduced GFR at the time of tonsillectomy. Urinalysis showed that median grade of the RBC count in urinary sediment was 1.0 (IQR, 0.0-3.0) and median UPE was 468 (IQR, 288-532) mg/d. The mean follow-up period from initial biopsy diagnosis to tonsillectomy was 135 months. All 20 patients had been treated with RAAS inhibitors. Seventeen patients had a history of induction therapy with corticosteroids; the time from the termination of corticosteroid therapy to tonsillectomy was 84

Table 2. Clinical Characteristics

Case No.	Sex	Age, y	eGFR, mL/min/1.73 m²	Urinary RBC count, grade[a]	UPE, mg/d	Past Corticosteroid Use	Past Pulse Dose Corticosteroid Use	Antiplatelets	RAAS Inhibitors	Diagnosis to Tonsillectomy, mo	Interval From Last Corticosteroids, mo	Observations Before and After Tonsillectomy, mo
At Tonsillectomy						**Medications**				**Durations**		
eGFR≥60mL/min/1.73m² at Tonsillectomy												
1	M	40s	71	1	520	+	−	Dipyridamole	Telmisartan	223	240	54
2	M	30s	62	0	552	+	−	Dilazep	Losartan	174	98	48
3	M	40s	71	1	195	−	−	Dilazep	Losartan	66	NA	33
4	M	30s	82	3	385	−	−	—	Losartan	158	NA	30
5	M	40s	66	4	345	+	−	Dilazep	Losartan	90	83	57
6	F	20s	103	3	515	+	−	Dipyridamole	Losartan	183	120	63
7	M	40s	70	4	836	+	+	—	Losartan	37	29	45
8	F	20s	117	4	288	+	−	Dipyridamole	Losartan	85	20	30
9	M	30s	60	4	633	+	−	—	Losartan	149	65	12
Cases 1-9		34.4 ± 7.7	78.0 ± 19.5	3.0 [1.0-4.0]	515 [345-552]	7 (77%)	1 (11%)	6 (67%)	9 (100%)	129 ± 62	70 ± 77	41.3 ± 16.3
eGFR<60mL/min/1.73m² at Tonsillectomy												
10	F	50s	28	1	900	+	−	—	Losartan	191	165	42
11	F	40s	43	0	216	+	−	—	Losartan	193	151	54
12	F	40s	44	2	288	+	+	Dilazep	Losartan	219	200	60
13	F	40s	44	0	496	+	+	—	Olmesartan	120	83	39
14	M	50s	39	0	525	+	+	Dilazep	Losartan	70	64	45
15	M	40s	29	0	352	+	−	Dipyridamole	Valsartan	142	29	45
16	M	30s	53	0	113	−	−	—	Candesartan	34	NA	30
17	F	40s	54	1	440	+	−	—	Losartan	179	126	30
18	M	50s	57	3	2543	+	−	—	Olmesartan	131	12	42
19	M	50s	41	0	276	+	+	—	Losartan	200	63	21
20	M	70s	26	0	516	+	+	Dipyridamole	Losartan	50	40	30
Cases 10-20		48.6 ± 10.0	41.6 ± 10.6	0.0 [0.0-1.0]	440 [282-521]	10 (91%)	5 (45%)	4 (36%)	11 (100%)	139 ± 64	86 ± 71	39.8 ± 11.5

Note: Data for categorical variables are expressed as number (percent); data for continuous variables are expressed as mean ± standard deviation or median [interquartile range].
Abbreviations: eGFR, estimated glomerular filtration rate; F, female; HPF, high-power field; M, male; NA, not available; RAAS, renin-angiotensin-aldosterone system; RBC, red blood cell; UPE, urinary protein excretion.
[a]Grades of RBC counts in urinary sediment are: 0, <5 RBC/HPF; 1, 5 to 9 RBC/HPF; 2, 10 to 19 RBC/HPF; 3, 20 to 49 RBC/HPF; 4, 50 to 99 RBC/HPF; and 5, >99 RBC/HPF.

Table 3. Time-Averaged Laboratory Values Before and After Tonsillectomy

	Urinary RBC Count,[a] grade		UPE,[b] mg/d			Serum IgA,[b,c] mg/dL		
Case No.	Before	After	Before	After	% Change	Before	After	% Change
eGFR≥60mL/min/1.73m² at Tonsillectomy								
1	1	0	655	190	−71.0	268	266	−0.7
2	3	0	486	93	−80.8	251	188	−25.1
3	1	0	323	312	−3.6	NA	NA	NA
4	1.5	0	577	117	−79.7	248	214	−13.9
5	4	3	500	306	−38.7	217	207	−4.8
6	3	1	598	913	52.5	309	216	−30.0
7	3	3	484	304	−37.1	232	233	0.8
8	1	0	328	95	−70.9	193	159	−17.2
9	4	2	1233	543	−55.9	393	270	−31.5
eGFR<60mL/min/1.73m² at Tonsillectomy								
10	0	0	628	539	−14.2	288	297	3.1
11	2	0	781	533	−31.8	266	256	−3.9
12	0.5	0	324	265	−18.2	340	290	−14.6
13	0	0	791	173	−78.1	331	NA	NA
14	1	0	475	304	−36.0	383	356	−6.8
15	1	0	1,446	330	−77.2	358	340	−4.9
16	1	0	473	547	15.8	NA	NA	NA
17	1	1	1,409	243	−82.8	NA	NA	NA
18	1	0	1,530	956	−37.5	348	343	−1.5
19	0	0	645	992	53.8	NA	NA	NA
20	0	0	666	884	32.6	NA	NA	NA
Case No.	**Before**	**After**	**Before**	**After**	***P***	**Before**	**After**	***P***
Cases 1-20	1.0	0.0	718	432	0.01[d]	295	260	0.003[d]
Cases 1-9	3.0	0.0	576	319	0.04[d]	264	219	0.02[d]
Cases 10-20	1.0	0.0	833	524	0.10	331	314	0.09

Note: Before and after indicates mean or median values before and after tonsillectomy, respectively. Percentage change was defined as follows:

$$\frac{(\text{Time-averaged value after tonsillectomy}) - (\text{Time-averaged value before tonsillectomy})}{(\text{Time-averaged value before tonsillectomy})} \times 100\ (\%).$$

Grades of RBC counts in urinary sediment are: 0, <5 RBC/HPF; 1, 5 to 9 RBC/HPF; 2, 10 to 19 RBC/HPF; 3, 20 to 49 RBC/HPF; 4, 50 to 99 RBC/HPF; and 5, 99 RBC/HPF.
Abbreviations: eGFR, estimated glomerular filtration rate; HPF, high-power field; IgA, immunoglobulin A; NA, not available; RBC, red blood cell; UPE, urinary protein excretion.
[a]Median value.
[b]Mean value.
[c]Values for serum IgA levels were missing for 6 patients and analyses were performed in 14 patients.
[d]Statistically significant.

months. No patient received an immunosuppressant other than corticosteroids.

Clinical characteristics of 9 patients with preserved kidney function (eGFR ≥ 60 mL/min/1.73 m^2) and 11 patients with reduced kidney function (eGFR < 60 mL/min/1.73 m^2) at the time of tonsillectomy are shown in Table 2.

Laboratory Findings Before and After Tonsillectomy

Time-averaged values for laboratory findings obtained before and after tonsillectomy are provided in Table 3. Fourteen (70%) and 16 (80%) of the 20 patients showed reductions in hematuria and proteinuria, respectively. Twelve of 14 (86%) patients showed decreases in serum IgA levels. Overall, the grade of the RBC count in urinary sediment, UPE, and serum IgA level decreased significantly after tonsillectomy relative to pretonsillectomy values; no such difference in mean urinary sodium excretion or estimated protein intake values was observed.

Achievement of Urinalysis Remission After Tonsillectomy

Patients' remission status after tonsillectomy according to urinalysis findings is shown in Figure 2. Hematuria, proteinuria, and clinical remission occurred in 13 of 17 (76%), 10 of 18 (57%), and 8 of 20 (40%) patients at a median of 3.0, 6.0, and 13.5 months, respectively, after tonsillectomy.

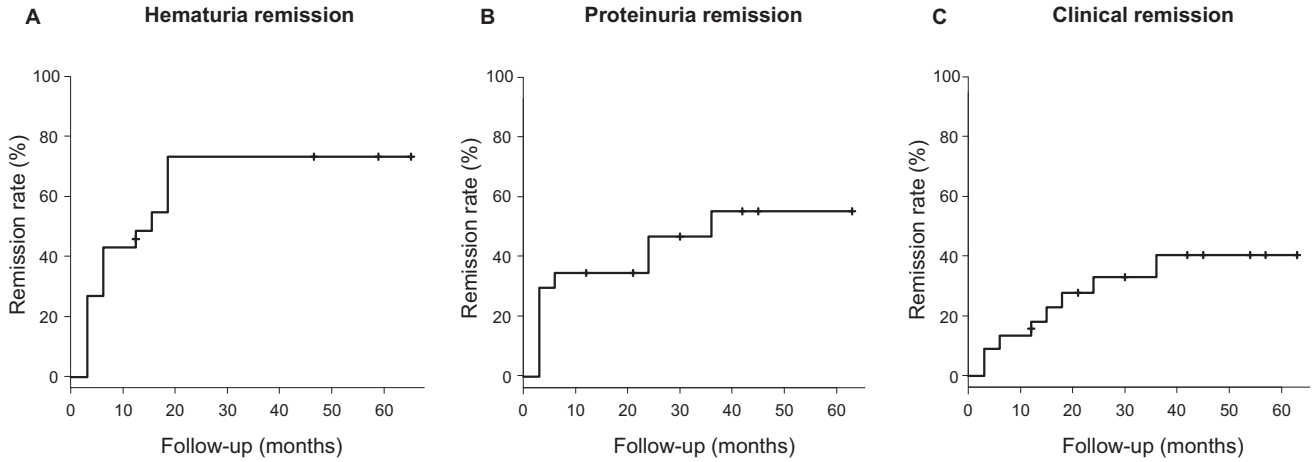

Figure 2. Remission status according to urinalysis findings after tonsillectomy. (A) Hematuria remission, (B) proteinuria remission, and (C) clinical remission after tonsillectomy were analyzed using log-rank test. Abbreviation: eGFR, estimated glomerular filtration rate.

Changes in Kidney Function Slope After Tonsillectomy

Compared with the pretonsillectomy value, ΔeGFR after tonsillectomy was significantly greater (−2.59 vs 1.05 mL/min/1.73 m^2 per year; $P < 0.001$; Fig 3). This increase in ΔeGFR was significant in the 11 patients with reduced GFR (eGFR < 60 mL/min/1.73 m^2) at the time of tonsillectomy (−3.07 vs −0.39 mL/min/1.73 m^2 per year; $P < 0.001$).

DISCUSSION

Among 20 patients with IgAN and an incomplete response to conventional therapy, tonsillectomy was associated with improvements in hematuria, proteinuria, and eGFR decline. For this retrospective case series, we recruited 20 patients with biopsy-proven IgAN who underwent tonsillectomy without simultaneous use of corticosteroids and analyzed their clinical courses before and after tonsillectomy. All patients showed recurrent or persistent hematuria/proteinuria and/or concomitant GFR decline despite receiving conventional therapies for many years. Compared with pretonsillectomy, time-averaged values for hematuria grade, proteinuria, and ΔeGFR were significantly improved after tonsillectomy. The results suggest that tonsillectomy is beneficial in patients whose disease is resistant to conventional therapies. In addition, the results are consistent with

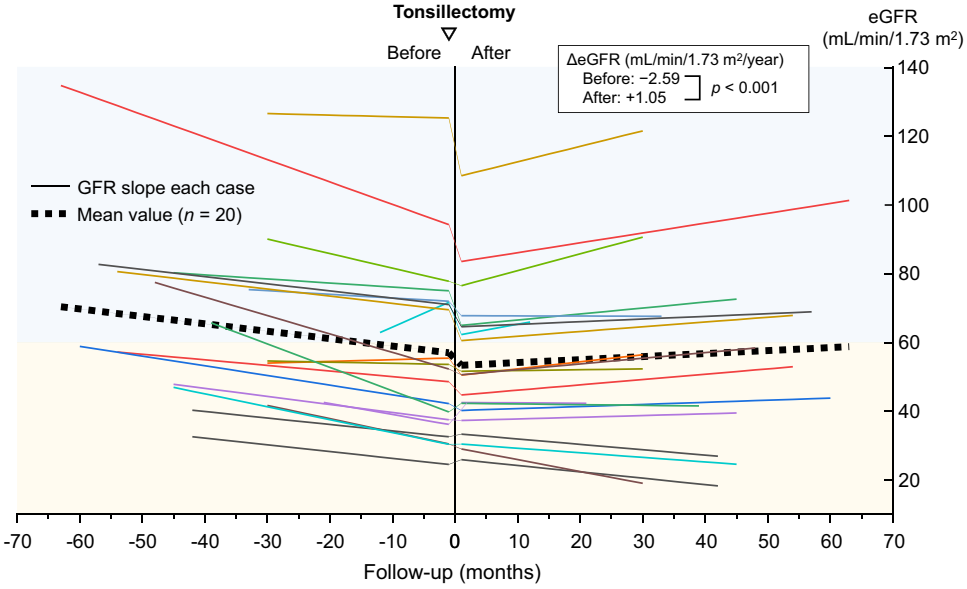

Figure 3. Slopes of eGFR before and after tonsillectomy. Estimated glomerular filtration rate (eGFR) slopes (ΔeGFRs) were calculated before and after tonsillectomy using a linear regression model. The same color in the left and right panels indicates the same patient, and the black dashed line indicates the mean value for all patients.

previous reports that attenuation of the decline in kidney function in IgAN is associated closely with the remission or regression of hematuria/proteinuria.[26–28]

Since the first case was reported in the 1980s, much knowledge has accumulated on the effect of tonsillectomy in patients with IgAN.[29,30] The cellular and molecular mechanisms underlying the effects of tonsillectomy on urinary abnormalities and associated kidney function decline are under investigation. Recent studies have revealed that aberrantly glycosylated IgA and mucosal immunity are involved in the pathogenesis of IgAN.[12,13] The IgA produced by tonsillar lymphocytes has the same aberrant glycosylation pattern as IgA deposits on glomeruli.[14] Hotta et al[31] demonstrated that IgA identified in initial diagnostic biopsies was no longer present in serial kidney biopsies performed after tonsillectomy plus corticosteroid pulse therapy. These findings suggest that tonsillar lymphocytes produce aberrantly glycosylated IgA, which is associated with the pathogenesis of glomerulonephritis. Interestingly, the resected tonsils of all 20 patients in the present study were diagnosed histopathologically with chronic tonsillitis. However, only a minority of the patients showed clinically identifiable features of recurrent tonsillitis, consistent with a recent report that tonsil size does not correlate with disease severity or the therapeutic effect of tonsillectomy in patients with IgAN.[32]

The strengths of this study include the long-term observation of patients with slowly progressive reduction in GFR before tonsillectomy, which enabled comparison of the clinical courses before and after tonsillectomy. Consistent with previous reports, beneficial effects of tonsillectomy on urinary abnormalities and GFR decline were observed in patients with and without reduced GFR at the time of tonsillectomy.[33,34] Of note, remission rates for urinary abnormalities and improvement in ΔeGFR were greater in patients with preserved GFR. In this study, the difference in ΔeGFR before and after tonsillectomy correlated positively with eGFR at the time of tonsillectomy (Fig S3). More patients with preserved GFR at the time of tonsillectomy achieved proteinuria remission than those with reduction in GFR at the time of tonsillectomy (Fig S4). Thus, tonsillectomy may provide greater benefit to patients with preserved GFR.

In this study, remission or regression of urinary abnormalities after tonsillectomy occurred without the use of additional immunosuppressive agents, including corticosteroids. Interestingly, most patients showed regression of ΔeGFR after tonsillectomy relative to the pretonsillectomy value; the mechanisms underlying this regression are unclear. Most previous studies of tonsillectomy in patients with IgAN involved combination therapy with corticosteroids; thus, the effect of tonsillectomy might have been masked by the immunosuppressive effect of corticosteroids. In this respect, our observations likely reflect the effect of tonsillectomy on chronic IgAN. Thus, tonsillectomy monotherapy may be an option for patients with IgAN who are at greater risk for adverse effects of corticosteroids, particularly those treated previously with corticosteroids.[35–37] The advantages of tonsillectomy monotherapy are reductions in lifetime recurrence risk and adverse effects of corticosteroids.[38] A prospective controlled trial of tonsillectomy with and without corticosteroid therapy is required to evaluate this hypothesis.

This study has several limitations. First, we could not include a control (no-tonsillectomy) group due to the difficulty setting the baseline time point (which corresponded to tonsillectomy in our sample). The improvements in urinary abnormalities may have reflected natural remission or disease burn-out during the follow-up period in some patients. Second, inclusion of a small number of patients and lack of patients who did not achieve the kidney outcome may have introduced bias. Third, kidney histopathologic parameters were difficult to analyze due to the intervals between biopsy diagnosis and tonsillectomy (Table S1). Finally, the retrospective design may have resulted in selection bias. Patients with rapid deterioration in kidney function and those with severe proteinuria would be preferentially given corticosteroid therapy and might not have been included in the study population.

In conclusion, tonsillectomy monotherapy may improve urinary abnormalities and slow kidney function decline in some patients with IgAN who may be resistant to conventional therapies and could therefore be an effective therapy for such patients. Further studies will provide additional insight on treatments suitable for patients with IgAN at risk for both progression to end-stage kidney disease and the adverse effects of corticosteroids.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Study design 1.

Figure S2: Study design 2.

Figure S3: Correlation of eGFR at tonsillectomy with the difference between pre- and post-tonsillectomy eGFR slopes.

Figure S4: Remission status according to urinalysis findings after tonsillectomy of patients with preserved and reduced kidney function at tonsillectomy.

Table S1: Pathologic findings in initial diagnostic kidney biopsy.

ARTICLE INFORMATION

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