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NEPHROLOGY - ORIGINAL PAPER

Effect of tonsillectomy and its timing on renal outcomes in Caucasian IgA nephropathy patients

Tibor Kovács · Tibor Vas · Csaba P. Kövesdy · Péter Degrell · Györgyi Nagy · Zsuzsanna Rékási · István Wittmann · Judit Nagy

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Abstract
Purpose The role of tonsillectomy in the treatment of IgA nephropathy in Caucasian patients is controversial.
Methods A retrospective cohort study was conducted in 264 patients with biopsy-proven primary IgA nephropathy to examine the association between tonsillectomy and long-term renal survival, defined as the incidence of estimated glomerular filtration rates (eGFRs) of $\leq$30 ml/min/1.73 m^2 or end-stage renal disease (the composite of initiation of dialysis treatment or renal transplantation). The association of tonsillectomy with renal end-points was examined using the Kaplan–Meier method and Cox models.
Results One-hundred and sixty-six patients did not undergo tonsillectomy (Group I, follow-up 130 $\pm$ 101 months) and 98 patients underwent tonsillectomy (Group II, follow-up 170 $\pm$ 124 months). The mean renal survival time was significantly longer for both end-points between those patients who underwent tonsillectomy (Group II) versus patients without tonsillectomy (Group I) ($p < 0.001$ and $p = 0.005$). The mean renal survival time was significantly longer for both end-points between those patients who had macrohaematuric episodes versus patients who had no macrohaematuric episodes ($p = 0.035$ and $p = 0.019$). Tonsillectomy, baseline eGFR and 24-h proteinuria were independent risk factors for both renal end-points.
Conclusion Tonsillectomy may delay the progression of IgA nephropathy mainly in IgA nephropathy patients with macrohaematuria. Prospective investigation of the protective role of tonsillectomy in Caucasian patients is needed.

Keywords IgA nephropathy · Progression of IgA nephropathy · Tonsillectomy

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis and is an important cause of end-stage renal disease (ESRD) worldwide [1–3]. Long-term observations in many countries have shown that IgAN causes ESRD in as many as 40 % of patients within 20 years after diagnosis [4, 5]. The most common clinical presentation in adults is microhaematuria with variable degrees of proteinuria. However, mainly in children or in young adults, IgAN often presents with recurrent episodes of macrohaematuria associated coincidentally or immediately with upper respiratory tract infections, particularly tonsillitises.

Pathologically, IgAN is characterised by the glomerular deposition of polymeric IgA1 mainly in the mesangium. In patients with IgAN, circulating as well as glomerular IgA1 molecules have an aberrant structure of O-glycans [6–8]. The excess amounts of this

Tibor Kovács and Tibor Vas have contributed equally to this work.

T. Kovács · T. Vas · P. Degrell · I. Wittmann · J. Nagy (✉)
2nd Department of Internal Medicine and Nephrological Center, Clinical Center, University of Pécs, Pacsirta Str. 1, Pecs 7624, Hungary
e-mail: judit.nagy@aok.pte.hu

C. P. Kövesdy
University of Tennessee Health Science Center and Memphis VA Medical Center, Memphis, TN, USA

G. Nagy
Department of Otolaryngology, Clinical Center, University of Pécs, Pecs, Hungary

Z. Rékási
Department of Laboratory Medicine, Clinical Center, University of Pécs, Pecs, Hungary

undergalactosylated IgA1 appear to be the trigger for generation of glycan-specific IgA and IgG autoantibodies, resulting in the formation of circulating IgA immune complexes. These immune complexes may accumulate in the mesangium with activation of the mesangial cells, proliferation of the extracellular matrix and release of cytokines and chemokines that can initiate and perpetuate glomerular injury [9–12]. In addition, altered glycosylation leads to a decrease in the clearance of IgA1 molecules by the liver [13].

The frequent association of acute tonsillitis with episodes of macrohaematuria in IgAN leads to the hypothesis that the underglycosylated IgA1 may be produced in the tonsils and tonsillectomy could be a treatment option of IgAN.

Tonsillectomy is a commonly used treatment in Japanese IgAN patients usually in combination with steroids [14]. A recent meta-analysis from Japan suggested a benefit from tonsillectomy combined with oral or pulse steroid treatment [15], while this was not supported by studies in Caucasian patients [16, 17]. Ieiri et al. with the analysis of 830 Japanese IgAN patients concluded that the shorter duration of IgAN in patients treated by tonsillectomy and steroid treatment was associated with a much better clinical outcome [18]. In a recent retrospective study with long-term follow-up from Japan, tonsillectomy was associated with a favourable renal outcome of IgAN in terms of clinical remission and delayed renal deterioration even in patients not treated with steroids [19]. There are no data about the impact of tonsillectomy on the *development of IgAN*.

Our group has previously published data about tonsillar abnormalities in IgAN and about the effect of tonsillectomy on the clinical course of a small number of patients with this condition [20–23], but the information about the clinical impact of tonsillectomy in Caucasian patients remains scarce. We hypothesised that tonsillectomy has a beneficial effect on the clinical course of established IgAN in Caucasian patients. We thus examined the association of tonsillectomy performed at various time points relative to the course of IgAN with renal outcomes in a moderately large population of patients with IgAN who were followed over several decades at our Institution.

Patients and methods

This retrospective cohort study included 264 patients who were diagnosed with IgAN by renal biopsy at the Nephrological Center, Clinical Center, University of Pécs between 1970 and 2005 and who had normal or mild-to-moderately decreased renal function (CKD Stage 1–3 [24]) at the time of diagnosis. The patients were followed up at 3- to 6-month intervals by the same two nephrologists, TK and JN. Patients with rapidly progressive crescentic glomerulonephritis, and patients with secondary IgAN due to systemic diseases, including Schönlein–Henoch purpura, liver disease or other pre-existing conditions were excluded from analyses.

Data collection

Clinical and laboratory data were collected on all participants at the time of diagnosis and at each follow-up visit. Blood was collected by venipuncture after an overnight fast of at least 10 h at all follow-up examinations. The Department of Laboratory Medicine, Clinical Center, University of Pécs measured all serum chemistry levels in fresh samples with commercially available reagents. Twenty-four hour urine collection was performed on three consecutive days for the examination of proteinuria. The glomerular filtration rate (eGFR; ml/min/1.73 m^2) was estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [25]. Blood pressure was measured using a mercury sphygmomanometer in a sitting position after a few minutes of rest. Treatments with corticosteroids, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor-blocking agents (ARB), and statins were also recorded.

Definition of progression of IgAN

The selected end-points of renal outcome were the first occurrence of a decrease in eGFR to <30 ml/min/1.73 m^2 [number of events: 64 (24.2 %)] or reaching end-stage renal disease (ESRD) (defined as the composite of the initiation of dialysis treatment or renal transplantation, number of events: 43 (16.3 %).

Timing of tonsillectomy

Of the 264 patients, 98 underwent tonsillectomy; 68 of them were tonsillectomised as a treatment for IgAN and 30 of them were tonsillectomised >3 years before the diagnosis of IgAN (mainly in childhood). Three patients were excluded from analyses because they underwent tonsillectomy more than 3 years after the diagnosis of IgAN.

Indication for tonsillectomy

In the group of patients who were operated on due to their renal disease tonsillectomies were done on the basis of a consultation with otolaryngologists. In these patients the indication for tonsillectomy was the presence of chronic, recurrent tonsillitis with or without episodes of macrohaematuria. The diagnostic criteria for chronic tonsillitis were past episodes of habitual sore throat and tonsillar

Table 1 Baseline characteristics of IgAN patients treated without (Group I) or with tonsillectomy (Group II) at the time of diagnosis (renal biopsy) (mean ± SD)

	Group I. Patient without tonsillectomy ($n = 166$)	Group II. Patients with tonsillectomy ($n = 98$)	p
Age (years)	38.0 ± 13.9	30.2 ± 10.1	<0.001
Sex (M/F)	121 (73 %)/45 (27 %)	73 (75 %)/25 (25 %)	NS
Follow-up (months)	133 ± 102	171 ± 124	=0.012
Renal function			
eGFR (ml/min/1.73 m^2)	98.2 ± 32.9	108.1 ± 28.0	=0.01
Clinical parameters			
Hypertension (Y/N)	124 (75 %)/42 (25 %)	57 (58 %)/41 (42 %)	=0.006
Systolic BP (mmHg)	134 ± 17	129 ± 14	=0.015
Diastolic BP (mmHg)	85 ± 12	83 ± 8	NS
Proteinuria (g/24 h)	1.30 ± 1.68	0.88 ± 0.94	NS
Macroscopic haematuria (Y/N)	42 (25 %)/124 (75 %)	50 (51 %)/48 (49 %)	<0.001
Drugs			
ACEI/ARB (Y/N)	66 (40 %)/100 (60 %)	21 (21 %)/77 (79 %)	=0.003
Statin (Y/N)	22 (13 %)/144 (87 %)	4 (4 %)/94 (96 %)	=0.018
Steroid (Y/N)	20 (12 %)/146 (88 %)	6 (6 %)/92 (94 %)	NS

hypertrophy, and the presence of infectious tonsils with enlarged lacunae and/or pus plugs. We have no information about the indication of tonsillectomy in patients who were tonsillectomised before the diagnosis of their renal disease.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviations (SD) and were compared by using Student's t tests or analysis of variance (ANOVA). Variables with skewed distribution were compared with the Mann–Whitney U test or nonparametric Kruskal–Wallis test and categorical variables were expressed as percentage and compared by the Chi-squared test. The mean renal survival time until the selected end-points was calculated using the Kaplan–Meier method [26]. Differences between the calculated mean renal survival times were compared using the log-rank test. The effect of confounders was assessed by Cox regression analysis.

Confounders were established a priori based on theoretical considerations.

We constructed three multivariable models with sequential adjustment for the following variables: in model 1 age and gender, in model 2 systolic and diastolic blood pressure, eGFR, 24-h proteinuria and macrohaematuria in addition to model 1 variables; in model 3 ACEi/ARB, statin and steroid therapy in addition to model 2 variables. A p value of <0.05 was considered statistically significant. Data analysis was performed using the SPSS software programme version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Effect of tonsillectomy

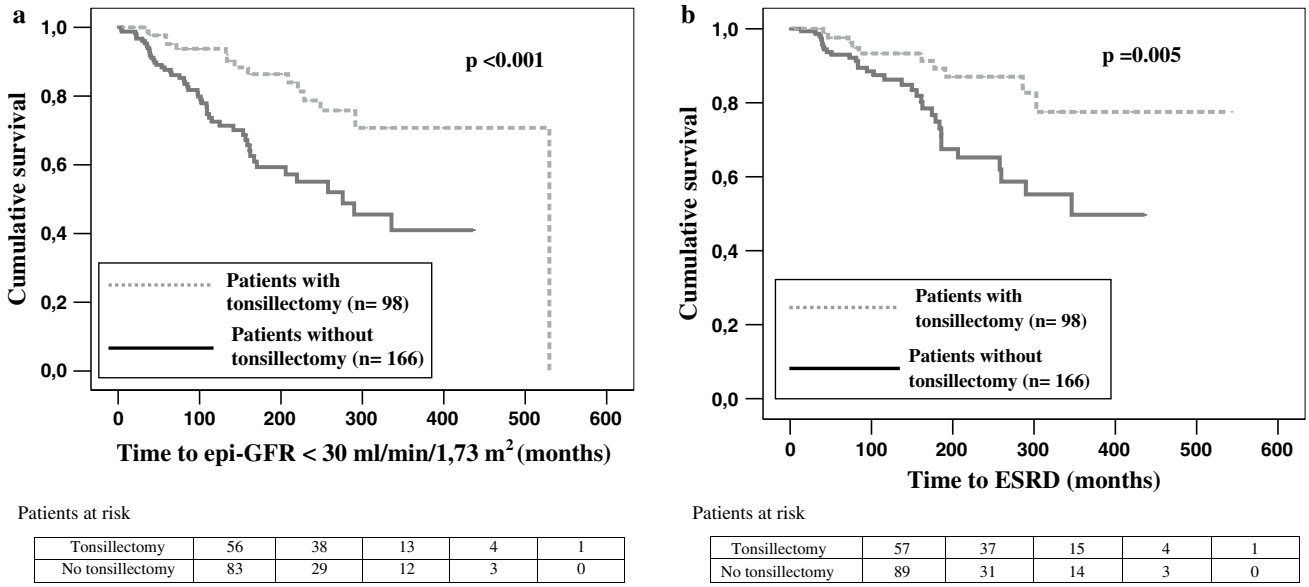
Baseline characteristic of patients without ($n = 166$, Group I) and with tonsillectomy ($n = 98$, Group II) at the time of the renal biopsy are summarised in Table 1. Tonsillectomised patients (group II) were significantly younger, had longer time of follow-up, more macrohaematuria episodes, better renal function, less hypertension and they were treated less frequently with ACEi/ARB and statins. There was no significant difference between the two groups in 24-h proteinuria and steroid treatment.

On the basis of the Kaplan–Meier analyses, the renal survival was significantly better in the tonsillectomised group for both end-points (Fig. 1a, b).

Timing of tonsillectomy

Patients with tonsillectomy before the diagnosis of IgAN ($n = 30$) were significantly older, their eGFR was lower, they had less macrohaematuria, more hypertension and they were treated more frequently with ACEi/ARB and statin than patients with tonsillectomy due to the diagnosis of IgAN ($n = 68$). There was no significant difference between the two groups in their sex, follow-up time, 24-h proteinuria, or steroid treatment.

The renal survival was significantly better in patients with tonsillectomy due to the diagnosis of IgAN versus patients without tonsillectomy at both end-points ($p = 0.001$, $p = 0.008$). Tonsillectomy in patients due to the



Patients at risk

Tonsillectomy	56	38	13	4	1
No tonsillectomy	83	29	12	3	0

Patients at risk

Tonsillectomy	57	37	15	4	1
No tonsillectomy	89	31	14	3	0

Fig. 1 Time to reach the different end-points in IgAN patients with and without tonsillectomy. **a** Time to reach eGFR <30 ml/min/1.73 m^2 (months). **b** Time to reach ESRD (months)

Table 2 Baseline characteristics of IgAN patients grouped on the basis of occurrence of macrohaematuria at the time of diagnosis (renal biopsy) (mean ± SD)

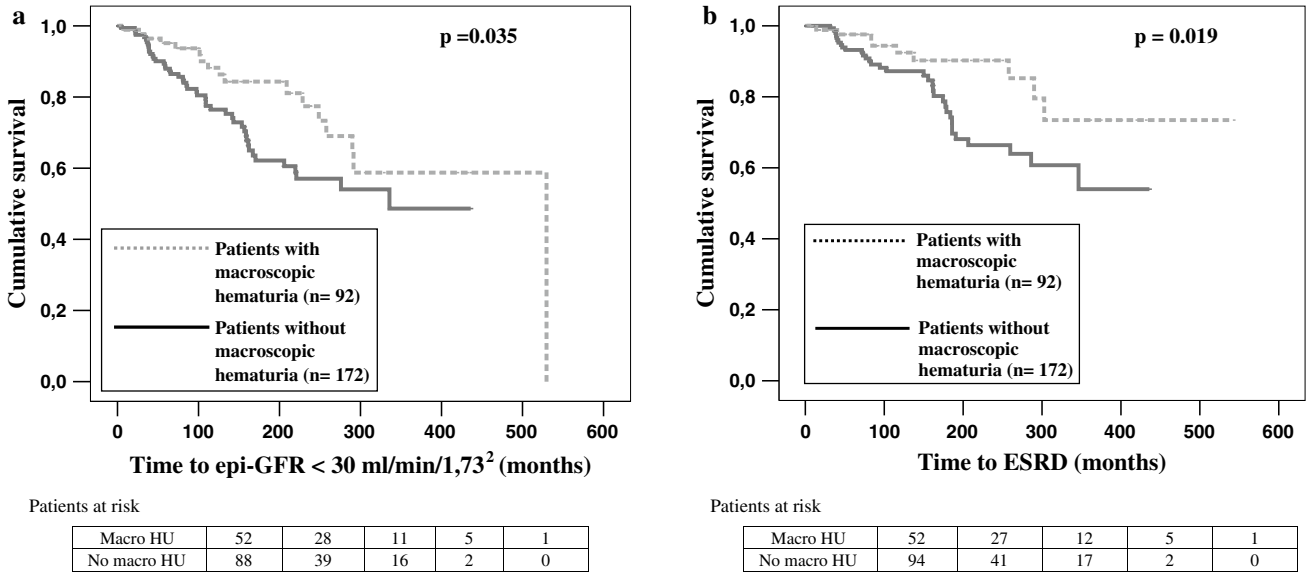
	Group I. Patients with macroscopic haematuria ($n = 92$)	Group II. Patients without macroscopic haematuria ($n = 172$)	p
Age (years)	30.8 ± 11.57	37.47 ± 13.56	<0.001
Sex (M/F)	62 (67 %)/30 (33 %)	132 (77 %)/40 (23 %)	NS
Follow-up (months)	159.48 ± 125.77	140.82 ± 104.73	NS
Renal function			
eGFR(ml/min/1.73 m^2)	108.21 ± 31.03	98.61 ± 31.42	=0.018
Clinical parameters			
Hypertension (Y/N)	57 (62 %)/35 (38 %)	124 (72 %)/48 (28 %)	NS
Systolic BP (mmHg)	128 ± 16	134 ± 17	=0.034
Diastolic BP (mmHg)	83 ± 10	85 ± 11	NS
Proteinuria (g/24 h)	0.89 ± 1.07	1.28 ± 1.62	=0.016
Drugs			
ACEI/ARB (Y/N)	31 (34 %)/61 (66 %)	56 (33 %)/116 (67 %)	NS
Statin (Y/N)	4 (4 %)/88 (96 %)	22 (13 %)/150 (87 %)	=0.030
Steroid (Y/N)	6 (7 %)/86 (93 %)	20 (12 %)/152 (88 %)	NS

diagnosis of IgAN was independently associated with lower risk of the ESRD in both Groups ($p = 0.011$, $p = 0.008$).

Macrohaematuria and tonsillectomy

On the basis of the clinical observation that macrohaematuric patients with IgAN have a more benign outcome (except in rapidly progressive crescentic IgAN, but these patients were not included in our study), we divided our patients into two groups on the basis of presence or absence of macrohaematuria independently from tonsillectomy. Characteristic features of patients in the two groups are summarised in Table 2. There was no significant difference in the follow-up time of the two groups. Macrohaematuric patients were younger, their renal function (eGFR) was better and their proteinuria was <1 g/24 h.

In the Kaplan–Meier analysis, the renal survival was significantly better in the macrohaematuric patients versus patients without macrohaematuric events for both end-points (Fig. 2).



Patients at risk

Macro HU	52	28	11	5	1
No macro HU	88	39	16	2	0

Patients at risk

Macro HU	52	27	12	5	1
No macro HU	94	41	17	2	0

Fig. 2 Time to reach the different end-points in IgAN patients with and without macrohaematuria. **a** Time to reach eGFR <30 ml/min/1.73 m^2 (months). **b** Time to reach ESRD (months)

Discussion

In this single-center retrospective cohort study, 264 adult biopsy-proven IgAN patients with long follow-up were analysed for the long-term effect of tonsillectomy on the outcome of IgAN. In tonsillectomised patients, the mean renal survival time was significantly longer than in non-tonsillectomised patients for both end-points (Table 3).

On the basis of the recently published nationwide survey of Matsuzaki et al. [14], tonsillectomy is the major therapeutic approach for adult IgAN patients in Japan with or without steroid treatment. There is much less information from other countries. We summarised all of the publications about the efficacy of tonsillectomy on the outcome of IgAN patients in Table 4. All of them were retrospective cohort studies from Japan except one from China, one from Germany and one from Italy [17–19, 27–38]. The majority of these comprehensive studies examining patients from Asia described favourable effect of tonsillectomy on the outcome of IgAN (9 out of 15). Another 4 studies have found at least significant effect of tonsillectomy on remission or relapse rates of IgAN.

Two studies examined Caucasian patients. Rasche et al. [17] examined 16 tonsillectomised and 39 non-tonsillectomised IgAN patients. The mean observation time of the patients after renal biopsy was 3.4 ± 4 years (mean ± SD). On the basis of their analysis, tonsillectomy did not reduce the risk of developing renal failure or did not prevent a progressive course of IgAN. Piccoli et al. [18] examined 15 tonsillectomised and 46 non-tonsillectomised IgAN patients. As a control they examined 121 patients with mesangioproliferative glomerulonephritis free of IgA deposits, no data were provided about the follow-up time of the IgAN patients. They concluded that tonsillectomy had no influence on the progression of IgAN. The larger retrospective study we report here suggests that tonsillectomy may be beneficial not only in Asians, but also in European IgAN patients. Differences in the results of the previous two European studies and our study could be explained by the larger sample size, and the significantly longer follow-up in our study (mean 147 ± 112 months). On the basis of the current literature, at least 8–15 years of follow-up is needed to determine the effectiveness of tonsillectomy in IgAN [27].

Timing of tonsillectomy

The association between tonsillectomy long before the diagnosis of IgAN and the long-term outcome of IgAN has not previously been discussed in the literature. Two recent reviews [12, 39] suggested that IgAN can exist in three clinical forms, namely

1. *covert or lanthanic cases* in which no clinical signs or laboratory alterations suggesting IgAN exist, but renal biopsies detect the typical IgA deposition in the mesangium (prescribed in "zero-time" renal biopsies of transplanted kidneys or in post-mortem examination of the kidneys of apparently normal individuals dying suddenly of accidents),
2. *asymptomatic cases* in which routine or screening examinations discover urine abnormalities, typically

Table 3 Multivariable-adjusted hazard ratio for the end-points in IgAN patients with tonsillectomy

	End-points			
	GFR <30 ml/min/1.73 m^2 HR (95 % CI)	*p*=	ESRD HR (95 % CI)	*p*=
Model 1				
Tonsillectomy (IgAN)	0.402 (0.217–0.742)	0.004	0.356 (0.172–0.736)	0.005
Age (year)	1.019 (0.999–1.040)	0.057	0.992 (0.967–1.018)	0.554
Gender (M/F)	0.724 (0.400–1.313)	0.288	0.566 (0.262–1.221)	0.146
Model 2				
Tonsillectomy (IgAN)	0.397 (0.210–0.750)	0.004	0.333 (0.154–0.718)	0.005
Age (year)	0.986 (0.961–1.012)	0.291	0.947 (0.915–0.980)	0.002
Gender (M/F)	0.849 (0.463–1.556)	0.596	0.640 (0.292–1.403)	0.265
BP (syst., mmHg)	1.001 (0.974–1.028)	0.969	1.021 (0.990–1.054)	0.187
BP (diast., mmHg)	1.010 (0.971–1.051)	0.611	0.975 (0.931–1.021)	0.274
eGFR (ml/min/1.73 m^2)	0.979 (0.969–0.988)	0.000	0.977 (0.966–0.988)	0.000
Proteinuria (g/24 h)	1.132 (1.982–1.303)	0.087	1.151 (0.998–1.328)	0.054
Macrohaematuria (Y/N)	0.770 (0.425–1.393)	0.387	0.524 (0.243–1.128)	0.098
Model 3				
Tonsillectomy (IgAN)	0.433 (0.226–0.831)	0.012	0.317 (0.143–0.702)	0.005
Age (year)	0.982 (0.956–1.008)	0.181	0.942 (0.909–0.975)	0.001
Gender (M/F)	0.873 (0.476–1.600)	0.660	0.651 (0.297–1.426)	0.284
BP (syst., mmHg)	1.002 (0.974–1.030)	0.912	1.024 (0.991–1.057)	0.151
BP (diast., mmHg)	1.005 (0.965–1.046)	0.812	0.967 (0.922–1.015)	0.175
eGFR (ml/min/1.73 m^2)	0.980 (0.970–0.990)	0.000	0.974 (0.961–0.986)	0.000
Proteinuria (g/24 h)	1.162 (1.001–1.349)	0.048	1.148 (0.982–1.342)	0.082
Macrohaematuria (Y/N)	0.633 (0.346–1.157)	0.137	0.482 (0.224–1.035)	0.061
ACEi/ARB(Y/N)	2.509 (1.332–4.729)	0.004	1.546 (0.673–3.549)	0.304
Statin (Y/N)	0.676 (0.273–1.674)	0.398	0.274 (0.058–1.303)	0.104
Steroid (Y/N)	0.641 (0.310–2.058)	0.579	1.247 (0.456–3.410)	0.666

Table 4 Efficacy of tonsillectomy on the outcome of IgA nephropathy patients

Study	Country	Follow-up (months)	Treatment	*n*	Efficacy of Tx on outcome
Hotta et al. [27]	Japan	82.3	Tx + steroid versus steroid	329	Benefit
Akagi et al. [28]	Japan	>151	Tx + steroid versus steroid	71	Benefit
Chen et al. [29]	China	130	Tx + steroid versus steroid	112	No benefit but higher remission rate
Miyazki et al. [30]	Japan	60	Tx + steroid versus steroid	101	Benefit
Komatsu et al. [31]	Japan	60	Tx + steroid versus steroid	55	Benefit
Ohya et al. [32]	Japan	70	Tx + steroid versus steroid	62	No benefit but reduction in relapse rate
Ochi et al. [33]	Japan	54	Tx + steroid versus steroid	41	No benefit but higher remission rate
Sato et al. [34]	Japan	70.3	Tx + steroid versus general ± steroid	70	Benefit
Maeda et al. [19]	Japan	60	Tx + steroid versus general ± Steroid	200	Benefit in outcome, remission
Komatsu et al. [35]	Japan	84	Tx + steroid versus general ± steroid	46	Benefit in outcome, remission
Rasche et al. [17]	Germany	41	Tx ± ISU versus general ± ISU	55	No benefit
Xie et al. [36]	Japan	193	Tx ± steroid ± ISU versus general ± steroid ± ISU	118	Benefit
Nishi et al. [37]	Japan	>191	Tx ± steroid ± ISU versus general ± steroid ± ISU	120	Benefit
Piccoli et al. [18]	Italy	ND	Tx versus non-Tx	61	No benefit
Nakagawa et al. [38]	Japan	48	Tx versus Tx + steroid	40	Tx + steroid is better

microscopic haematuria with or without mild proteinuria,

3. *symptomatic cases* in which patients recognise an abnormality, typically an event of macrohaematuria.

The rationale for tonsillectomy is the possible reduction of a source of undergalactosylated IgA1 to prevent its deposition in the mesangium [40]. However, the effect of tonsillectomy in inducing a significant decrease in cellular and humoral immune response generally lasts about 6 months in healthy subjects, although other investigations found a longer duration of immunosuppression [41]. Furthermore, tonsils are only the most accessible but not the largest part of the gut-associated lymphoid tissue (GALT), which is also well represented in the intestinal submucosal lymphoid cells; for this reason, it has been thought that it is unlikely that tonsillectomy can decrease the formation of undergalactosylated IgA1 in the IgAN patients for a prolonged time [41], and hence, it is possible that IgAN could develop in a patient who was previously tonsillectomised. However, it is described after tonsillectomy that serum IgA levels remain significantly decreased in IgAN patients for several years compared to the unchanged levels seen in IgAN patients without tonsillectomy [42].

Another relevant question is the relationship of the macrohaematuric clinical picture with tonsillectomy. We observed a significantly better survival in patients who had both macrohaematuric episodes and tonsillectomy, but the number of the cases in the groups was not enough for a further statistical analysis. Several studies have shown that most patients with macrohaematuric events (if the rapidly progressive, crescentic IgAN cases are excluded) have a good prognosis. This may represent 'lead time bias'—cases being diagnosed earlier because of the macrohaematuria or it is possible that cases with macrohaematuria have a milder phenotype of glomerular injury.

It could be argued that in these mild early phases of IgAN, tonsillectomy may be more effective [18, 19, 36]. Early diagnosis can also be facilitated by screening programmes for renal diseases as it is currently done in Japan.

Our study has several limitations. We studied Caucasian patients from a single institution; hence, our results may not apply to patients of other race or ethnicity or from other countries. We performed a retrospective analysis of data collected for clinical purposes; therefore, we can only establish associations but cannot prove that the better outcomes were indeed caused by tonsillectomy. Although ours is the largest study of tonsillectomy yet reported in Caucasians, our study size may not have been sufficient to detect other weaker associations.

We conclude that tonsillectomy may improve the long-term outcome in IgAN especially in those who have chronic pathologic alterations in their tonsils, those with macrohaematuric events and those whose kidney function is preserved (GFR >60 ml/min/1.73 m^2) at the time of the renal biopsy. Prospective investigation of the protective role of tonsillectomy in Caucasian patients is needed.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Schena FP, Pesce F (2009) Epidemiology and ancestral difference. In: Lai KN (ed) Recent advances in IgA nephropathy. World Scientific Publishing Co., New Jersey, pp 9–20
2. Feehally J, Floege J (2010) IgA nephropathy and Henoch-Schönlein nephritis. In: Floege J, Johnson RJ, Feehally F (eds) Comprehensive clinical nephrology, 4th edn. Elsevier, Amsterdam, pp 270–281
3. Wyatt RJ, Julian BA (2013) IgA nephropathy. N Engl J Med 368:2402–2414
4. Berthoux FC, Mohey H, Afiani A (2008) Natural history of primary IgA nephropathy. Semin Nephrol 28:4–9
5. D'Amico G, Imbasciati E, Barbiano DI et al (1985) Idiopathic IgA mesangial nephropathy. Clinical and histological study of 374 patients. Medicine (Baltimore) 64:49–60
6. Suzuki H, Kiryluk K, Novak J et al (2011) The pathophysiology of IgA nephropathy. J Am Soc Nephrol 22:1795–1803
7. Boyd JK, Cheung CK, Molyneux K et al (2012) An update on the pathogenesis and treatment of IgA nephropathy. Kidney Int 81:833–843
8. Lai KN (2012) Pathogenesis of IgA nephropathy. Nat Rev Nephrol 8:275–283
9. Barrat J, Feehally J (2011) Primary IgA nephropathy: new insight into pathogenesis. Semin Nephrol 31:349–360
10. Floege J (2011) The pathogenesis of IgA nephropathy: What is new and how does it change therapeutic approaches? Am J Kidney Dis 58:992–1004
11. Hiki Y, Ito A, Yamamoto Y et al (2011) IgA nephropathy and aberrant glycosylation of tonsillar, serum and glomerular IgA1. Adv Otorhinolaryngol 72:68–70
12. Glassock RJ (2011) The pathogenesis of IgA nephropathy. Curr Opin Nephrol Hypertens 20:153–160
13. Rifai A, Fadden K, Morrison SL et al (2000) The N- glycans determine the differential blood clearance and hepatic uptake of human immunologlobulin (Ig)A1 and IgA2 isotypes. J Exp Med 191:2171–2181
14. Matsuzaki K, Suzuki Y, Nakata J et al (2013) Nationwide survey on current treatments for IgA nephropathy in Japan.Clin Exp Nephrol. doi:10.1007/s10157-013-0779-7
15. Wang Y, Chen J, Wang Y et al (2011) A meta-analysis of the clinical remission rate and long-term efficacy of tonsillectomy in patients with IgA nephropathy. Nephrol Dial Transplant 26:1923–1931

16. Rasche FM, Schwarz A, Keller F (1999) Tonsillectomy does not prevent a progressive course in IgA nephropathy. Clin Nephrol 51:4147–4152
17. Piccoli A, Codognoto M, Tabbi MG et al (2010) Influence of tonsillectomy on the progression of mesangioproliferative glomerulonephritis. Nephrol Dial Transplant 25:2583–2589
18. Ieiri N, Hotta O, Sato T, Taguma Y (2012) Significance of the duration of nephropathy for achieving clinical remission in patients with IgA nephropathy treated by tonsillectomy and steroid pulse therapy. Clin Exp Nephrol 16:122–129
19. Maeda I, Hayashi T, Sato KK et al (2012) Tonsillectomy has beneficial effects on remission and progression of IgA nephropathy independent of steroid therapy. Nephrol Dial Transplant 27:2806–2813
20. Nagy J, Brandtzaeg P (1988) Tonsillar distribution of IgA, IgG immunocytes and IgA subclasses in IgA nephropathy. Contrib Nephrol 67:107–110
21. Nagy J, Brandtzaeg P (1988) Tonsillar distribution of IgA and IgG immunocytes and production of IgA subclasses and J chain in tonsillitis vary with the presence or absence of IgA nephropathy. Scand J Immunol 27:393–399
22. Barta J, Kovács T, Fazekas A et al (1996) Does tonsillectomy cause any change in long-term course of IgA nephropathy? (In Hungarian with English abstract). Orv Hetil 137:2903–2906
23. Kovács T, Vas T, Barta J et al (2002) Tonsillectomy and the progression of IgA nephropathy. (In Hungarian with English abstract). Hyperton Nephrol 6:228–231
24. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 39(suppl 1):S1–S266
25. Levey AS, Stevens LA, Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
26. Kaplan EL, Meier P (1958) Nonparametric estimation for incomplete observation. J Am Stat Assoc 53:116–122
27. Hotta O, Miyazaki M, Furuta T et al (2001) Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis 38:736–743
28. Akagi H, Kosaka M, Hattori K et al (2004) Long-term results of tonsillectomy as a treatment for IgA nephropathy. Acta Otolaryngol Suppl 555:38–42
29. Chen Y, Tang Z et al (2007) Long-term efficacy of tonsillectomy in Chinese patients with IgA nephropathy. Am J Nephrol 27:170–175
30. Miyazaki M, Hotta O, Komatsuda A et al (2007) Japanese Multicenter Study Group on treatment of IgA nephropathy (JST-IgAN). A multicenter prospective cohort study of tonsillectomy and steroid pulse therapy in Japanese patients with IgA nephropathy: a 5-year report. Contrib Nephrol 157:94–98
31. Komatsu H, Fujimoto S, Hara S et al (2008) Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. Clin J Am Soc Nephrol 3:1301–1307
32. Ohya M, Otani H, Minami Y et al (2013) Tonsillectomy with steroid pulse therapy has more effect on the relapse rate than steroid pulse monotherapy in IgA nephropathy patients. Clin Nephrol 80:47–52
33. Ochi A, Moriyama T, Takei T et al (2013) Comparison between steroid pulse therapy alone and in combination with tonsillectomy for IgA nephropathy. Int Urol Nephrol 45:469–476
34. Sato M, Hotta O, Tomioka S et al (2003) Cohort study of advanced IgA nephropathy: efficacy and limitations of corticosteroids with tonsillectomy. Nephron Clin Pract 93:c137–c145
35. Komatsu H, Fujimoto S, Kikuchi M et al (2012) Tonsillectomy delays progression of advanced IgA nephropathy to end-stage kidney disease. Ren Fail 34:448–453
36. Xie Y, Chen X, Nishi S et al (2004) Relationship between tonsils and IgA nephropathy as well as indications of tonsillectomy. Kidney Int 65:1135–1144
37. Nishi S, Xie Y, Ueno M et al (2004) A clinicopathological study on the long-term efficacy of tonsillectomy in patients with IgA nephropathy. Acta Otolaryngol Suppl 555:49–53
38. Nakagawa N, Kabara M, Matsuki M et al (2012) Retrospective comparison of the efficacy of tonsillectomy with and without steroid-pulse therapy in IgA nephropathy patients. Intern Med 51:1323–1328
39. Coppo R, Feehally J, Glassock JR (2010) IgA nephropathy at two score and one. Kidney Int 77:181–186
40. Ponticelli C (2012) Tonsillectomy and IgA nephritis. Nephrol Dial Transplant 27:2610–2613
41. Coppo R (2010) Can a dysregulated mucosal immune system in IgA nephropathy be controlled by tonsillectomy? Nephrol Dial Transplant 25:2395–2397
42. Bene MC, Faure GC, Harault de Ligny B et al (2004) Clinical involvement of the tonsillar immune system in IgA nephropathy. Acta Otolaryngol Suppl 555:10–14