

Role of tonsillectomy in the management of IgA nephropathy

Mohamed Abd Allah Salama and Wagdy Z. El Badramany

From ENT and nephrology departments

Al Azhar University

Abstract:

Background :The tonsils represent a site of local immunity where immunoglobulin-bearing cells are capable of producing IgA. The tonsils have been considered the foci of abnormal IgA production in IgAN, thus, a relationship is suggested between the tonsillar immune response and the pathogenesis of IgAN. IgAN, then, is considered a tonsillar focal infection.

Patients and methods :This study was done on 15 patients their ages ranged between 15 and 35 (10 males and 5 females). All patients were already diagnosed by renal biopsy-proven IgA nephropathy by the nephrologists and under medical treatment by conventional steroid. The diagnosis of IgA nephropathy was based on histologic assessment of percutaneous renal biopsy tissue. The main problem in all patients is that development of gross haematuria, deterioration of urinary findings and deterioration of the general condition of the patient after any acute attack of upper respiratory tract infection especially acute tonsillitis. Tonsillectomy was done after one month from controlling the acute infection. Postoperative follow up for all patients was done at 1st, 3rd, 6th, 12th month by clinical examination and laboratory investigations

Results :The gross haematuria was completely stopped in all patients after tonsillectomy except two patients one of them was complicated by hypertension and the other one was complicated by nephritic syndrome. Also there was marked reduction in proteinuria, microscopic haematuria, marked reduction in the serum IgA concentration, urinary abnormalities disappeared and also improvement of renal function for the patients with serum creatinin less than 2mg/dl while in the two patients with serum creatinin more than 2mg/dL there was no much improvement after tonsillectomy with more deterioration of renal function of both patients with the development of chronic renal failure in the patient with nephritic syndrome 9 month postoperative

Conclusion :Tonsillectomy is effective in improving renal function ,urinary symptoms, gross haematuria and decreasing the level of IgA in patients with IgAN if it is done in mild to moderate cases with serum creatinin less than 2mg/dL while has no much efficacy on moderate to severe cases with serum creatinin more than 2mg/dL or complicated cases.

Key words :IgA nephropathy; tonsillectomy; Immunoglobulins; hematuria.

Aim of the work: to evaluate the role of tonsillectomy on renal functional decline in immunoglobulin A (IgA) nephropathy

Introduction:

Immunoglobulin A nephropathy (IgAN, also known as Berger's disease), is defined immunohistologically by the presence of mesangial deposits of IGA in renal biopsy tissue in the absence of a systemic disease. IGA nephropathy with mesangial IgA-IgG deposits was first reported by *Berger and Hinglais in 1968* and described by *Berger and English in 1969*. The tonsils represent a site of local immunity where immunoglobulin-bearing cells are capable of producing IgA. In the tonsils of IgAN patients demonstrating tonsillitis, the numbers of IgA-positive plasma cells increase (*Bene et al., 1983*) IgA-positive cells accumulate in the

subepithelial sinusoids (*Terasawa, et al., 1991*), IgA1-positive cells enter the germinal centre (*Kusakari et al., 1991*) and the production of polymeric IgA increases (*Egido et al., 1984*). In addition, several clinical studies have demonstrated that the clinical manifestations of IgAN improved after tonsillectomy in IgAN patients (*Sanai and Kudoh, 1996*). Several reports have shown that the level of serum IgA decreased in IgAN patients after tonsillectomy (*Masuda et al., 1988*).

The tonsils have been considered the foci of abnormal IgA production in IgAN (*Sugiyama and Masuda, 1985*); thus, a relationship is suggested between the

tonsillar immune response and the pathogenesis of IgAN (*Tokuda et al., 1996*). IgAN, then, is considered a tonsillar focal infection (*Iino et al., 1993*). However, several clinical studies have also reported patients who failed to improve after tonsillectomy (*Tomioka, et al., 1996*). In such cases, the mechanism of IgA production is still unclear; it may be that the tonsils have no relation to the pathogenesis of IgAN, and the foci of abnormal IgA production may be elsewhere. The findings from these reports suggest that not all IgAN is related to the tonsils.

Studies for more than 30 years demonstrated that primary IgAN is an immune complex—mediated glomerulonephritis defined immunohistologically by the presence of glomerular IgA deposits (*EMANCIPATOR, 1994*).

IgAN is now generally known to be the most common form of primary glomerulonephritis throughout the world (*D'AMICO, 1987*).

Although primary IgAN was considered a benign condition for many years, it is now clear that a large number of cases eventually progress to renal failure (*D'AMICO et al., 1987*). Indeed, IgAN is the main cause of end-stage renal disease (ESRD) in patients with primary glomerular disease who requires renal replacement therapy (*BRIGANTI et al., 2001*). However, the cause of primary IgAN, source of IgA deposited in glomeruli and the mechanism underlying mesangial IgA deposition in IgAN, is unclear and there is no effective treatment available for patients with IgAN (*DONADIO and GRANDE, 2002*).

Both IgA produced by tonsil cells and IgA deposited in glomerular mesangium with IgAN are mainly J chain-positive polymeric IgA (*HARPER and FEEHALLY, 1993*).

Suzuki et al., (1994) reported that the antigen and antibodies of outer membranes of *Haemophilus parainfluenzae*, a common bacterium on the tonsils, were present in glomerular mesangium and sera of IgAN, respectively, suggesting that *H. parainfluenza* infection may have a role in the etiology of IgAN. *Rekola et al., (1985)* reported that 38 of 187 IgAN

patients had possible acute glomerulonephritis at the onset of their disease. Antistreptococcal antibodies increased in forty-three percent of the patients. Thirty-three percent of the patients had different groups of beta-hemolytic streptococci isolated from their throats. This result indicates a possible role of beta-hemolytic streptococci, a most common bacterium in tonsils or throat, in the pathogenesis of some IgAN cases.

There is an adult case report in which granular depositions of adeno- and herpes simplex viral antigens were detected in the glomerular mesangial areas in IgAN patients associated with episodes of recurrent tonsillitis and in the tonsillar epithelial cells by *H. parainfluenza* immunofluorescence (*Tomino et al., 1987*).

The IgA deposited in glomerular mesangium in patients with IgAN appears to be exclusively of the IgA1 subclass-34 and IgA produced by tonsillar lymphocytes in patients with IgAN is mainly polymeric IgA1, about half of patients with IgAN their serum IgA levels increase-35 and tonsillectomy decrease the levels of serum IgA, suggesting there is any relationship between tonsils and IgAN. Recently, we demonstrated that the tonsillectomy has a favorable effect on long-term renal survival in patients with IgAN (*Xie et al., 2003*).

IgAN can occur at any age but most commonly has its clinical onset in the second and third decades of life. It is more common in males than females, and its highest prevalence is in Asia, which is thought to be partly attributable to the increased use of renal biopsy in countries such as Japan. Patients with IgAN frequently present initially with macroscopic hematuria (tea-colored urine) after upper respiratory infections, including tonsillitis. This presentation is more common in patients younger than 40 years, while older patients may present with abnormal sediment in the urine and proteinuria without symptoms (*Donadio and Grande, 2002*). Appropriate communication between nephrologists and otolaryngologists is crucial to ensure timely evaluation of these patients of IgAN (*Kodama and Suzuki, 2007*).

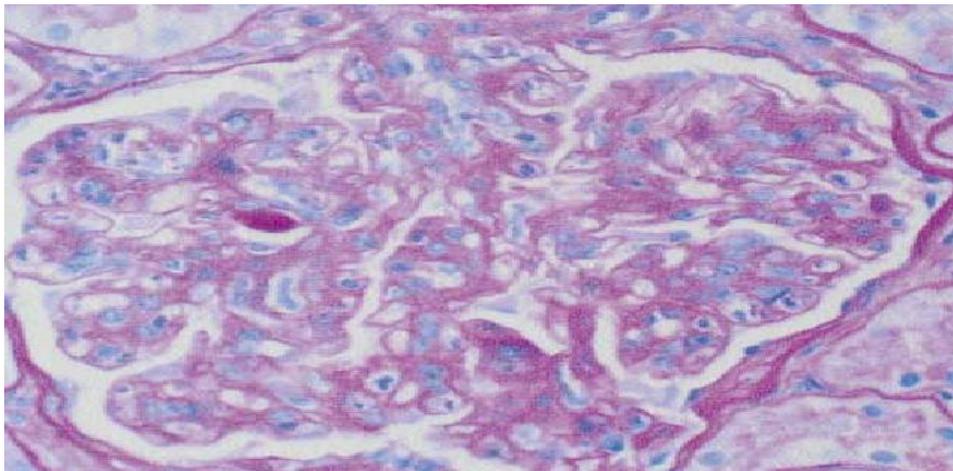
Patients and methods:

Patient Selection

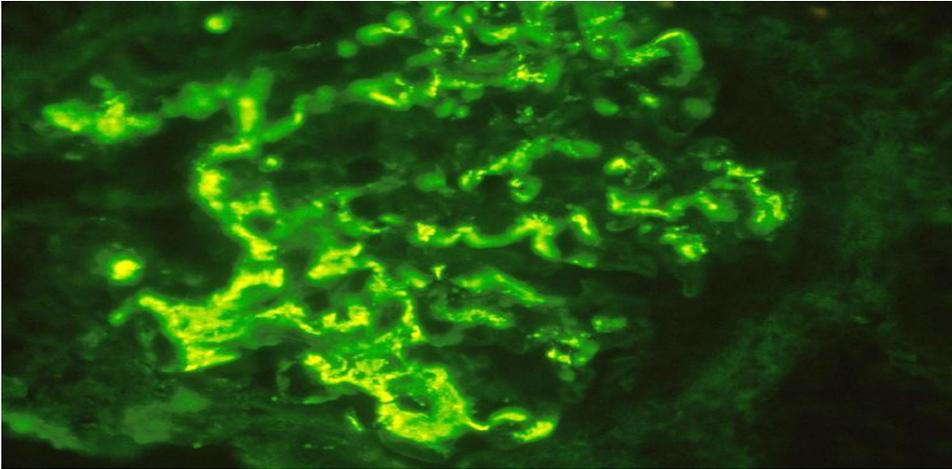
15 patients were selected in this study between the age of 15 and 35 (10 males and 5 females)

All patients was already diagnosed by renal biopsy-proven IgA nephropathy by the nephrologists(Fig 1 and 2) and under medical treatment by conventional steroid and supportive therapy at a baseline .The diagnosis of IgA nephropathy was based on histologic assessment of Percutaneous renal biopsy tissue. creatinine levels of 1.5 to 2 mg/dL except in two patient only the serum creatinine was more than 2mg/dl

and one of the two patients was had hypertension while the other one was complicated by nephritic syndrome but the main problem in all patients is that development of gross haematuria, deterioration of urinary findings and deterioration of the general condition of the patient after any acute attack of upper respiratory tract infection specially acute tonsillitis so these patients were referred to our E.N.T clinic to control and managing the acute infection and prepare them for tonsillectomy which was done after one month from controlling the acute infection.



Fig(1): light microscopy (~400) demonstrates expansion mesangial reions, with cells and matrix (periodic acid-Schiff stain) .



Fig(2):Immunofluorescence microscopy demonstrating large mesangial immunoglobulin A (IgA) deposits diagnostic of IgA nephropathy.

Postoperative follow up for all patients was done at 1st, 3rd, 6th, 12th month by clinical examination and laboratory investigations in the form of :

- Complete urine analysis(Urinalysis)
- BUN and serum creatinine levels
- Renal function tests, A 24-hour urine collection: This is used is to estimate creatinine clearance (CrCl) and protein excretion.
- serum immunoglobulin A (IgA) concentration

Normal ranges : normal range ; [serum creatinine 0.2-1.4mg/dl , urine protein is <150mg/24hour in adult, IGA 40-400 mg/dl & 0.4-4.00 g/l SI Units]

Results:

The gross haematuria which was follows any attack of upper respiratory tract infection was completely stopped in all patients used in the present study after tonsillectomy except the two patients that one of them was complicated by hypertension and the other one was complicated by nephritic syndrome. Also there was marked reduction in proteinuria , microscopic haematuria ,marked reduction in the serum

immunoglobulin A (IgA) concentration ,urinary abnormalities disappeared and also improvement of renal function for the patients with serum creatinin less than 2mg/dl while in the two patients with serum creatinin more than 2mg/dL there was no much improvement after tonsillectomy with more deterioration of renal function of both patients with the development of chronic renal failure in the patient with nephritic syndrom 9 month postoperative. Table :(1)

Patient.NO	Age (yr)	sex	Pre-operative presentation					The last post operative presentation at the end of follow up period				
			Gross hematuria	urinalysis	Serum creat. mg/dl	Urine protein g/24h	IGA conc mg/dl	Gross hematuria	Urine analysis	Serum creatinine mg/dl	Urine protein g/24h	IGA conc.
1-	15	F	+ve	RBC casts	0.9	1.5 g/24h	600	-ve		1.2	0.5g/24h	400
2-	18	F	+ve	RBC casts	1.3	2 g/24h	550	-ve		1.1	1.0 g/24h	350
3-	27	M	+ve	Pus cells	2	2.3 g/24h	455	-ve		2.0	2.0 g/24h	325
4-	30	M	+ve	RBCs	1.8	2.5 g/24h	540	-ve		1.7	2 g/24h	350
5-	19	F	+ve	RBC casts	0.5	3 g/24h	580	-ve		1	2.5 g/24h	390
6-	24	M	+ve	Pus cells bacteria	1.4	200mg/24h	500	-ve		1.2	150mg/24h	350
7-	27	M	+ve	hyaline cast	1.6	1.7 g/24h	660	-ve		1.6	1.5 g/24h	500
8-	30	F	+ve	Pus cells	1.2	2.2 g/24h	680	-ve		1.5	2 g/24h	550
9-	28	M	+ve	RBC casts	1.1	1.9 g/24h	690	-ve		1.2	1.6 g/24h	460
10-	35	F	+ve	RBC casts	3.1	5 g/24h	1000	+ve	RBC casts	3	4.3 g/24h	890
11-	33	M	+ve	RBC casts	3	3.5 g/24h	960	+ve	RBC casts	2.9	4 g/24h	860
12-	17	M	+ve	RBC casts	1.8	1.6 g/24h	620	-ve		1.6	1.8 g/24h	500
13-	26	M	+ve	leucocytes	2	3 g/24h	700	-ve		2	2 g/24h	540
14-	22	M	+ve	RBCs	1.4	2.3 g/24h	510	-ve		1.3	.9 g/24h	370
15-	18	M	+ve	RBC casts	1.3	2 g/24h	480	-ve		1.4	1.4 g/24h	330

Discussion:

Bene et al., (1993) followed up the evolution of urinary protein and serum creatinine in 34 patients with IgAN, and *Barta et al (1996)* followed up 35 IgAN patients after tonsillectomy. The urinary protein and microhematuria decreased significantly from 6 months after tonsillectomy than that before operation, and no significant variation was observed in the levels of creatininemia. Furthermore, tonsillectomy stopped gross hematuria in more than two thirds of patients. *Tamura et al (1993)* reported that 46% IgAN patients with chronic tonsillitis showed distinct improvement in urinary findings after the tonsillectomy. And these results agree with our results in the present study.

Akagi et al., (1999) followed up 24 patients with IgAN for more than 2 years after tonsillectomy. Remission of proteinuria was observed in 41.7% of the patients 6 months after surgery and in 50.0% 2 years after surgery. The clinical remission rate of urinary finding and the stable renal function rate in tonsillectomy patients with IgAN were significantly higher than that in nontonsillectomy patients (*Kosaka 1998*). And these results also agree with our results in the present study.

Studies demonstrated that tonsillectomy decreased the levels of serum IgA and salivary secretory IgA, especially in children, several months or years after operation (*Cantani et al., 1986*). However, these changes do not cause significant immune deficiency and are clinically insignificant. Moreover, these alterations do not increase incidence of immunomodulated diseases, such as infections of the upper respiratory tract (*Bock et al., 1994*).

Tonsillectomy decreased significantly the IgA levels compared with preoperation, but there is no significant difference compared with normal nonoperative controls (*Jung et al., 1996*)

Recent study demonstrated children with chronic tonsillitis have increased levels of CD19⁺ B lymphocytes compared to healthy controls in the pre-operative period. The percentage of B lymphocytes

bearing CD23 was found to be significantly higher in patients, most likely representing in vivo B lymphocyte activation due to chronic antigenic stimulation. After the tonsillectomy, despite ongoing B lymphocyte activation, CD8⁺ T lymphocyte levels increased and B cell levels returned to normal (*Ikinciogullari et al., 2002*)

Nephrologically, indications for tonsillectomy are to date still unclear. In fact, many factors have effect on the efficacy of tonsillectomy in patients with IgAN, such as urinary finding and grades of renal damage. In general, the efficacy of tonsillectomy in patients with hematuria type IgAN, especially presenting hematuria after tonsil infection, is good (*Zhou et al., 1993*). We have showed that with a mild renal damage condition, in which the amount of urine protein excretion was less than 1.0 g/24 hours and global glomerular sclerosis less than 25%, none of 26 patients with tonsillectomy needed dialysis, whereas five (13.2%) of 38 patients without tonsillectomy required dialysis.. The percentage entering dialysis in the tonsillectomy patients with moderate renal damage, such as urinary protein was more than 1.0 g/24 hours, but global glomerular sclerosis was less than 25% of total, was less than half of that in the nontonsillectomy patients (*Xie et al., 2003*). On the other hand, the patients with a marked renal damage, in whom both the amount of urine protein excretion was more than 1.0 g/24 hours and global glomerular sclerosis was more than 25% of total or crescent formation was more than 25% of total might develop renal failure even if tonsillectomy was performed, that is, tonsillectomy is mainly indicated for patients with mild or moderate IgAN (*Hattori, 1998*)

Komatsu et al., (2005) examined renal outcomes in 237 patients with IgA nephropathy (aged 31 ± 14 years, mean ± SD) who had been followed-up for at least 6 months (follow-up periods, 62.3 ± 45.5 months). On univariate analysis, tonsillectomy was the only significant treatment that contributes to the maintenance of normal renal function. In addition, urinary abnormalities

disappeared at a significantly higher frequency when patients were treated by tonsillectomy. However, the severity of baseline renal disease was not equivalent in all groups and the protective effect of tonsillectomy was eliminated after adjusting for other baseline variables.

Xie *et al.*, (2003) retrospectively reviewed data from over 15 years in 118 patients with idiopathic IgA nephropathy, including 48 patients who had undergone tonsillectomy and 70 who had not. After adjusting for baseline risk factors, only five (10.4%) of patients (n = 48) who had undergone tonsillectomy entered dialysis, whereas 18 (25.7%) of 70 patients who had not undergone tonsillectomy required dialysis (P = 0.04). Cox regression analysis showed that the relative risk for terminal renal failure in patients following tonsillectomy was lower compared to control patients (hazard ratio 0.22, 95% CI: 0.06–0.76, P = 0.0164).

Akagi *et al.*, (2004) performed a 10-year retrospective case-control study of 71

patients with IgA nephropathy to evaluate the long-term effects and prognostic factors associated with tonsillectomy. A total of 41 patients who had undergone tonsillectomy were compared with 30 patients who had not. After over 12 years of follow-up, the clinical remission rate was 24% in the tonsillectomy group and 13.3% in those not receiving tonsillectomy. Similarly, renal survival was higher in patients who had undergone tonsillectomy.

Conclusion:

These results suggest that tonsillectomy is effective in improving renal function, urinary symptoms, gross haematuria and decreasing the level of IgA in patients with IgAN if it is done in mild to moderate cases with serum creatinin less than 2mg/dL while has no much efficacy on moderate to severe cases with serum creatinin more than 2mg/dL or complicated cases.

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دور استئصال اللوزتين في مناجزة الاعتلال الكلوي الناتج عن العلوبلين المناعي (أ)

محمد عبد الله سلامة و وجدي البدرماني

قد أجريت هذه الدراسة على خمسة عشر مريضاً تتراوح أعمارهم ما بين الخامسة عشر والخامسة والثلاثين (10 ذكور و 5 إناث). وقد تم تشخيص الخمسة عشر مريضاً على أنهم مرضى الاعتلال الكلوي الناتج عن العلوبلين (أ) بأخذ عينة من الكلى عبر الجلد وامريض خاضع للعلاج الطبي تحت إشراف طبيب الكلى. وكانت المشكلة الكبرى في كل المرضى هي نشوء بيلة دموية واضحة وتدهور في نتائج تحاليل البول وتدهور في الحالة العامة لكل مريض بعد كل نوبة التهابات حادة في المجرى التنفسي العلوي خاصة التهاب اللوزتين. وقد أجريت عملية استئصال اللوزتين بعد شهر من علاج الالتهابات وقد تمت متابعة كل المرضى بعد شهر ، ثلاثة ، ستة ، اثني عشر شهراً بالفحص الإكلينيكي والأبحاث المعملية فكانت نتيجة المتابعة كالآتي:

- توقف البيلة الدموية تماماً بعد استئصال اللوزتين في كل المرضى ما عدا اثنين من المرضى حدثت لهم مضاعفات فالأول أصيب بارتفاع ضغط الدم والآخر أصيب بمتلازمة الالتهاب الكلوي.
- حدوث انخفاض ملحوظ في البيلة البروتينية والبيلة الدموية المجهرية واختفاء تغيرات البول الأخرى.
- انخفاض ملحوظ في تركيز علوبلين (أ) بمصل الدم.
- تحسن وظائف الكلى بمستوى كرياتينين أقل من 2 مجم/ديسي ليتر بينما ظل الكرياتينين أكثر من 2 مجم/ديسي ليتر في اثنين من المرضى.
- عدم وجود تحسن ملحوظ بعد استئصال اللوزتين و تدهور وظائف الكلى مع حدوث فشل كلوي مزمن بعد العملية بتسعة شهور.