ELSEVIER

International Journal of Pediatric Otorhinolaryngology
66 (2002) 251–257

INTERNATIONAL JOURNAL OF Pediatric Oto Rhino Laryngology

www.elsevier.com/locate/ijporl

Is immune system influenced by adenotonsillectomy in children?

Aykut İkincioğulları [a], Figen Doğu [b,*], Aydan ikincioğulları [b], Yonca Eğin [b], Emel Babacan [b]

[a] *1.ENT Department of Ankara Numune Research and Training Hospital, Ankara, Turkey*
[b] *Department of Pediatric Immunology and Allergy, Ankara University, School of Medicine, Ankara, Turkey*

Received 2 May 2002; received in revised form 22 July 2002; accepted 23 July 2002

Abstract

Objective: Tonsils and adenoids are lymphoid tissues that are located in the pharynx and play an important role against invading antigens of the upper respiratory tract. The present study analyses serum immunoglobulin levels and peripheral blood (PB) lymphocyte subsets in children, 24–48 h prior to and 4–6 weeks after adenotonsillectomy, in order to determine early effects of adenotonsillectomy on the immune system. *Methods:* The study population consists of 15 children (aged 4–10 years) who underwent adenotonsillectomy because of adenoidal hypertrophy and chronic tonsillitis and 15 age-matched healthy children without a history of adenotonsillectomy. Serum IgG, IgA and IgM levels were measured by nephelometry. PB lymphocyte subsets were analysed by using monoclonal antibodies and flow cytometry. *Results:* 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 adenotonsillectomy, despite ongoing B lymphocyte activation, CD8+ T lymphocyte levels increased and B cell levels returned to normal. A slight decrease in serum IgG, IgA and IgM levels was detected in the post-operative period compared to prior levels. *Conclusion:* Adenotonsillectomy performed in children leads to alterations that may reflect a compensatory response of the developing immune system after the removal of the lymphoid tissue in the setting of chronic antigenic stimulation. However, these changes do not cause significant immune deficiency.

Keywords: Adenotonsillectomy; Immune system; Children; Immunoglobulin; Lymphocyte subsets

1. Introduction

Human palatine tonsils and the adenoids are the largest components of Waldeyer's ring. They are located at the entrance of the respiratory and

* Corresponding author. Present address: Sancak Mah, 219.sok, 8/12, Yıldız, Ankara 06100, Turkey. Fax: +90-312-362-0581
E-mail address: esin.figen@veezy.com (F. Doğu).

0165-5876/02/$ - see front matter © 2002 Elsevier Science Ireland Ltd. All rights reserved.
PII: S0165-5876(02)00249-5

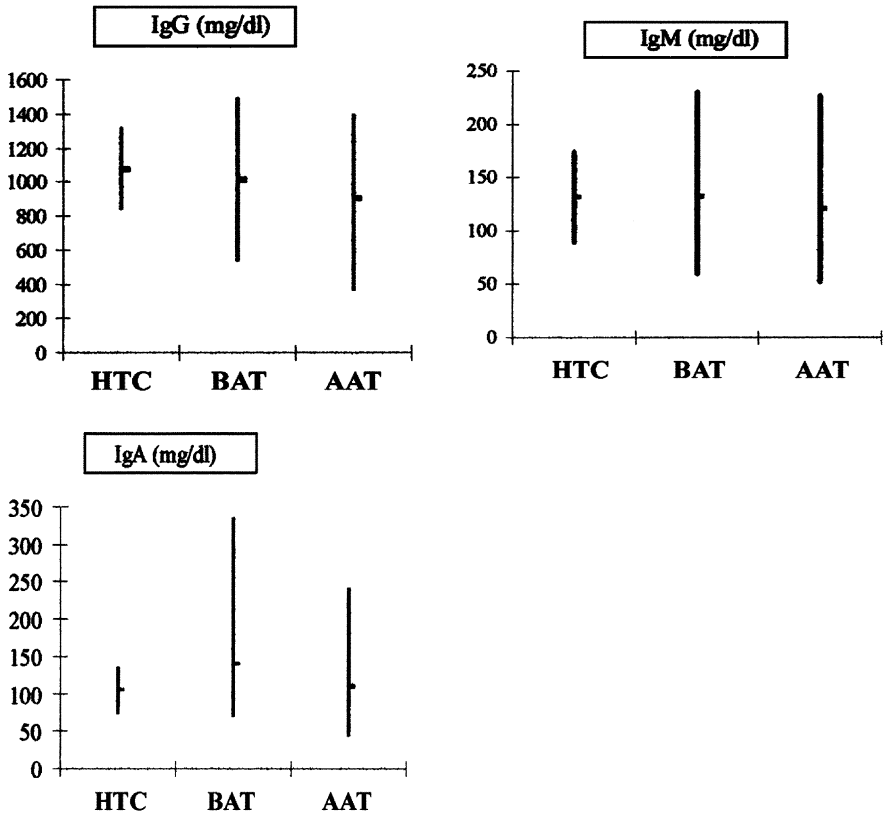

Fig. 1. Serum IgG, IgA and IgM levels of healthy Turkish children and patients before and after adenotonsillectomy. HTC: Healthy Turkish Children. BAT: Before Adenotonsillectomy. AAT: After Adenotonsillectomy.

alimentary tracts and represent the first site of contact with a variety of microorganisms and other antigenic substances present in food and inhaled air [1]. The growing understanding in recent years of the immunologic functions of both tonsils and adenoids has led to arguments against adenotonsillectomy. Much of the controversy has focused on the benefits of extirpating chronically inflamed tissues versus the possible harm which tonsillectomy may produce by eliminating an important local source of mucosal defence in the host [2] and has led to a reconsideration of the indications for the procedure. In the present study, in order to determine the early effects of adenotonsillectomy on humoral and cellular immune systems, serum immunoglobulin levels and peripheral blood (PB) lymphocyte subsets were analysed in children prior to and after adenotonsillectomy.

2. Material and methods

This study was conducted on 15 children aged 4–10 years (median 6.5 years) undergoing surgery because of adenoid hypertrophy and chronic tonsillitis at 1.ENT Department of Ankara Numune Hospital. The indications for operation were (a) at least five repeated attacks of sore throat in the last 2 years and (b) mouth breathing and snoring. Sleep apnea was diagnosed in five of the fifteen children. All subjects were normal in growth. None of the patients had a family history

Table 1
PB lymphocyte subsets and activation markers in healthy children and in patients before and after surgery

%	Control (n=15)	BAT (n=15)	AAT (n=15)
CD 3+	69.39 ± 1.39	66.54 ± 1.66	69.65 ± 1.83
		p<0.05	
CD 4+	41.71 ± 1.20	37.67 ± 1.79	39.09 ± 2.17
CD 8+	28.76 ± 1.22	28.36 ± 1.22	29.76 ± 1.44
CD 56+	14.63 ± 1.40	13.13 ± 1.10	12.23 ±1.40
CD 19+	16.93 ± 0.86	21.54 ±1.47	17.63 ± 1.17
	p<0.01		p<0.05
CD3+CD25+	0.37 ± 0.06	0.77 ± 0.19	0.53 ± 0.06
CD4+CD25+	0.57 ±0.10	0.95 ± 0.25	0.59 ± 0.09
CD8+CD25+	0.09 ± 0.02	0.13 ± 0.04	0.22 ± 0.04
		p<0.01	
CD56+CD25+	0.13 ± 0.02	0.31 ± 0.08	0.23 ± 0.05
	p<0.05		
CD19+CD23+	0.14 ± 0.03	0.40 ± 0.09	0.41 ± 0.07
	p<0.01		
	p<0.001		

BAT: Before adenotonsillectomy

AAT: After adenotonsillectomy

of immunodeficiency or atopic disease. Fifteen control cases were selected among children of the same age (4–10 years, median 7 years) with no history of adenotonsillectomy or symptoms indicating need for the operation. An informed consent was obtained from the parents both of patients and controls.

Immunological studies were carried out in the Pediatric Immunology–Allergy Research Laboratory of Ankara University. Venous blood samples were taken from the patients 24–48 h prior to and 4–6 weeks after the surgery. Serum IgG, IgA and IgM levels were measured by using the liquid phase immunoprecipitation method (Turbox TM, immunoglobulin G, A, M, Orion Diagnostica, Finland) and compared to age-matched serum immunoglobulin reference ranges of Turkish children [3]. Total lymphocyte counts were calculated

Table 2
Results of patients ≤6 years before and after surgery

	≤6 Years ($n=6$)	
	Before surgery	After surgery
CD 3+ (%)	66.13±2.10	70.27±2.05
CD 4+ (%)	35.83±2.34	36.87±2.86
CD 8+ (%)	29.34±1.51	31.73±1.85*
CD 56+ (%)	13.02±1.70	12.29±1.71
CD 19+ (%)	21.68±1.73	16.02±1.12**
CD 3+CD 25+ (%)	0.37±0.07	0.60±0.06*
CD 4+CD 25+ (%)	0.44±0.04	0.70±0.12
CD 8+CD 25+ (%)	0.08±0.03	0.21±0.02**
CD 56+CD 25+ (%)	0.18±0.05	0.29±0.08
CD 19+CD 23+ (%)	0.29±0.13	0.52±0.06
IgG (g/l)	10.87±1.06	9.87±0.89
IgA (g/l)	1.10±0.09	1.02±0.20
IgM (g/l)	1.30±0.18	1.27±0.14

* $P<0.05$.
** $P<0.01$.

according to the formula:

TLC : % lymphocyte × WBC count/100

PB lymphocyte subsets and activation markers were determined by using CD3–FITC/CD 25–PE, CD 4–FITC/CD 25–PE, CD 8–FITC/CD 25–PE, CD 25–FITC/CD 56–PE, CD 23–FITC/CD 19–PE monoclonal antibodies (Immunotech, Marseille, France) and flow cytometry (Coulter-EPICS-XL-MCL).

2.1. Statistical analysis

For statistical analysis, student's t-test and paired t-test were used, P-values <0.05 were regarded as significant.

3. Results

The serum IgG, A and M levels of the patients (prior to and after the surgery) and controls are shown in Fig. 1. A marked increase in serum IgA levels was detected in patients with adenoid hypertrophy and chronic tonsillitis as compared to the healthy children. Serum IgG, A and M levels were slightly decreased, but still in the normal range, in the post-operative period compared to prior levels.

PB lymphocyte subsets and activation markers of patients and controls are shown in Table 1. CD3+, CD4+, CD8+ T lymphocyte and CD56+ natural killer cell levels did not show any differences between the study groups. But, the activated (CD3+CD25+, CD4+CD25+, CD8+CD25+) T cell levels of the patients were found to be slightly elevated in the pre-operative period compared to controls ($P>0.05$). After surgery, the higher CD3+CD25+ and CD4+CD25+ cell levels showed a slight decrease, but activated CD8+CD25+ T lymphocyte levels continued their rise and the difference reached a significant level compared to healthy children ($P<0.01$).

Prior to surgery, children with chronic tonsillitis had increased levels of CD19+ B lymphocytes compared to healthy controls. However, CD19+ B lymphocyte levels decreased to the normal range after surgery. The percentage of B lymphocytes bearing CD23 (CD19+CD23+) was found to be significantly ($P<0.01$) higher in patients before

Table 3
Results of patients ≥7 years before and after surgery

	≥7 Years ($n=9$)	
	Before AT	After AT
CD 3+ (%)	67.15±2.93	68.72±3.62
CD 4+ (%)	40.42±2.62	42.42±3.09
CD 8+ (%)	26.88±2.04	26.80±1.82
CD 56+ (%)	13.30±1.23	12.13±2.61
CD 19+ (%)	21.33±2.82	20.05±2.14
CD 3+CD 25+ (%)	1.38±0.36	0.43±0.09
CD 4+CD 25+ (%)	1.70±0.49	0.43±0.10
CD 8+CD 25+ (%)	0.22±0.07	0.23±0.09
CD 56+CD 25+ (%)	0.52±0.16	0.13±0.03
CD 19+CD 23+ (%)	0.57±0.08	0.23±0.11
IgG (g/l)	9.38±1.25	7.92±1.36
IgA (g/l)	1.80±0.41	1.20±0.27
IgM (g/l)	1.35±0.29	1.12±0.26

Table 4
The effects of adenotonsillectomy on humoral and cellular immunity (literature review and the results of the present study)

	Number of subjects evaluated		Age range (years)	Time after surgery	Immunological studies	
	BAT	AAT			Serum immunoglobulins	Cellular immunity
Gogoi D, 1979 [5]	80	10	5–14	3 months	No significant change was detected	Positivity rate to PPd, Candida and DNCB increased after surgery
Cantani A, 1986 [2]	65	65	2–11	1–4 months	Decreased after surgery SIgA decreased after surgery	ND
Bussi M, 1991 [6]	40	40	3–30	3 months	ND	Increased CD3+, CD4+, CD8+ and B cells, increased HLA-DR and CD25 expression
Friday GA, 1992 [7]	268	152	1.5–16	7–30 months	Decreased IgG levels after surgery tend to occur more commonly in surgery group	ND
Moreno PM, 1992 [8]	22	22	5–10	1 month	ND	Decreased lymphoproliferative response to PHA, PWM, ConA
Bock A, 1994 [9]		160	4–8	0.5–11 years	Decreased IgA	Increased CD21+, CD4+, CD4+DR4 cell numbers
Redondo F, 2000 [10]	117	117		1–6 months	Slight but not significant decrease in IgG	ND
İkincioğulları A, 2002	15	15	4–10	1–1.5 month	Slight but not significant decrease	Increased CD3+, CD8+C25+, CD19+CD23+ and decreased CD19+ cell numbers

BAT: Before adenotonsillectomy, AAT: after adenotonsillectomy, ND: not determined.

surgery and remained the same ($P < 0.01$) early after surgery as well.

To investigate the influence of surgery on the immune system of patients of different age, we divided the patients into two groups—those ≤ 6 years and those ≥ 7 years. In patients ≤ 6 years, in the post-operative period there was an increase in total T lymphocyte numbers due to a rise in CD8+ T lymphocytes. Activated T and B lymphocyte levels were also elevated. However, B lymphocytes were decreased and returned to normal compared to prior levels. In patients ≥ 7 years, activation of T and B lymphocytes declined after surgery. The immunological profiles of these two groups are shown in Tables 2 and 3.

4. Discussion

Although adenotonsillectomy is a common surgical procedure, its possible immunological sequelae have not been fully investigated. The question of whether removal of tonsils and adenoids compromises the protection of the upper respiratory tract resulting in immunodeficiency continues to be the subject of debate [4].

A number of researchers have found decreased immunoglobulin levels after adenotonsillectomy while others have failed to find significant changes. The effects of adenotonsillectomy on the cellular immunity of children have not been investigated extensively (Table 4: The effects of adenotonsillectomy on humoral and cellular immunity. Literature review and the results of the present study) [2,5–10].

In the present study, serum immunoglobulin levels decreased slightly in the post-operative period compared to prior levels, but were still within the normal range. This slight decrease in immunoglobulin levels may be attributed to the reduction in the antigenic load or to the removal of antibody-producing tissue. However, there is no associated humoral immunodeficiency state.

In our study, one of the striking findings was the in vivo immune activation detected in children with chronic tonsillitis before adenotonsillectomy. This probably reflects the immune response of the host against the various antigenic stimuli triggering the chronic tonsillitis. Cellular immunity changes detected in the PB of patients after adenotonsillectomy may be attributed to a modulating effect on systemic immunity of the tonsils. Alterations in cellular immunity following surgery are aimed at stabilising the activation caused by chronic tonsillitis and adenoid hypertrophy. Therefore, there is no indication that surgery hinders the development of systemic immunity to cause immunodeficiency.

In the light of our results, we speculate that following adenotonsillectomy the immune system response is age dependent, which could be a reflection of immune maturation. In patients ≤ 6 years, the most prominent findings detected after surgery are a decline in B lymphocyte counts and the elevation of CD3+, CD8+ cells together with T and B lymphocyte activation. The increased T and B lymphocyte activation may be interpreted as a struggle of the immune system to compensate for the decrease in B lymphocyte counts. However, in patients ≥ 7 years, T and B lymphocyte activation declined after surgery. So, adenotonsillectomy in patients over 6 years appears to eliminate the immune activation caused by the chronic antigenic stimuli.

The results of this study reveal the need for further investigations to determine whether the immune system maintains its normal status in the long-term in the post-operative period and whether the age of the patient influences the immune alterations detected after surgery.

References

[1] W.J. Richtsmeier, A.H. Shikhani, The physiology and immunology of the pharyngeal lymphoid tissue, Otolaryngol. Clin. North Am. 20 (2) (1987) 219–228.

[2] A. Cantani, P. Bellioni, F. Salvinelli, L. Businco, Serum immunoglobulins and secretory IgA deficiency in tonsillectomized children, Ann. Allergy 57 (1986) 413–416.

[3] İ. Tezcan, A.İ. Berkel, F. Ersoy, Ö. Sanal, Sağlıklı Türk çocukları ve erişkinlerde turbidometrik yöntemle bakılan serum immunoglobulin düzeyleri, Çocuk Sağlığı ve Hastalıkları Dergisi 39 (1996) 649–656.

[4] P.N. Boyaka, P.F. Wright, M. Marinaro, H. Kiyono, J.E. Johnson, R.A. Gonzales, et al., Human nasopharyngeal associated lymphoreticular tissues. Functional analysis of subepithelial and intraepithelial B and T cells from

adenoids and tonsils, Am. J. Pathol. 157 (6) (2000) 2023–2035.
[5] D. Gogoi, O.P. Gupta, M.K. Agarwal, R.M. Gupta, Immunological evaluation of children undergoing tonsillectomy, J. Otolaryngol. 8 (6) (1979) 508–514.
[6] M. Bussi, M.T. Carlevato, E. Galeazzi, B. Morra, Immunological investigations on tonsillar and peripheral blood lymphocytes after adenotonsillectomy. Possible suggestions for phenotypical and functional differences, Acta Otolaryngol. 111 (2) (1991) 379–383.
[7] G.A. Friday, J.L. Paradise, B.S. Rabin, D.K. Colborn, F.H. Taylor, Serum immunoglobulin changes in relation to tonsil and adenoid surgery, Ann. Allergy 69 (3) (1992) 225–230.
[8] P.M. Moreno, M. Sanchez, M. Sainz, F. Gutierrez, Changes in immunological response in tonsillectomised children II: Decreased cellular response, Clin. Otolaryngol. 17 (5) (1992) 380–382.
[9] A. Bock, W. Popp, K. Herkner, Tonsillectomy and the immune system: a long term follow up comparison between tonsillectomized and nontonsillectomized children, Eur. Arch. Otorhinolaryngol. 251 (7) (1994) 423–427.
[10] F. Redondo, F. Ventura, D. Guerrero Gilabert, P. Reina Garcia, D. Lopez Aguada, Serum immunoglobuline levels in tonsillectomized patients: an unsolved mystery, Acta Otorhinolaryngol. Esp. 51 (5) (2000) 403–406.