European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 08, Issue 04, 2021

Short Term Impact of Adenotonsillectomy on Humoral Immunity in Children

Ezzat Ahmed Merwad [1], Kolaj Kattel [2], Adly Ahmed tantawy [1], Mohamed Hussam El-Din Mourad [3], Amany Abdelaziz Hasan [4], Mohamed Mahmoud Al-dahshan [5]

[1]Otolaryngology, Head and Neck Surgery Department, Faculty of Medicine, Zagazig University, Egypt.
[2]Otolaryngology, Head and Neck Surgery Department, Nobel Medical College Teaching Hospital, Nepal.
[3]Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt.
[4]Microbiology and Immunology Department, Faculty of Medicine, Helwan University, Egypt.
[5]Otolaryngology, Head and Neck Surgery Department, Hearing and Speech Institute, Giza, Egypt.

Corresponding author: **Ezzat Ahmed Merwad**, Email: eamerwad@medicine.zu.edu.eg

Received: 18-12-2020, **Revised:** 26-1-2021, **Accepted:** 15-2-2021, **e-Published:** 28-2-2021

ABSTRACT

The adenoids and tonsils are thought to be an essential part of the immune system protecting against pathogens invading the upper respiratory tract. They are immunologically reactive lymphoid organs which manifest specific antibodies along with B and T cells activity in response to variety of antigens. This study aimed to observe the changes in humoral immunity in children with chronic adeno-tonsillitis and/or hypertrophy of adenoids and tonsils before and after adeno-tonsillectomy. Patients and methods: This study included 50 children who were classified according to presence or absence of chronic adeno-tonsillitis and/or hypertrophy of adenoids and tonsils into two main groups; Group A (operative) including 25 children that have chronic adeno-tonsillitis and/or hypertrophy of adenoids and tonsils who underwent adenotonsillectomy, Group B (control) including 25 healthy children, to compare their serum immunoglobulins levels with Group A. All children were subjected to full history, clinical examination, routine investigations and measurements of serum immunoglobulins (IgA, IgG and IgM). Two samples of blood were taken, one before adenotonsillectomy and one after three months from Group A, while a single blood sample was taken from Group B Results: There was a statistically significant difference pre-operatively between Group A and Group B with regard to serum levels of IgA, IgG and IgM (P<0.05) with higher level in Group A compared with Group B. There was marked decrease in serum levels of immunoglobulins in Group A post-operative than in pre-operative, while a statistically non-significant difference between Group A post-operative and Group B with regard to serum levels of IgA, IgG and IgM was seen. Conclusion: After adenotonsillectomy, the humoral immunity parameters were found reduced but overall impact on the status of humoral immunity was not significantly changed.

Keywords: Tonsils, IgA, IgG, IgM, and Adenotonsillectomy.

Introduction

Adenoids and tonsils, the largest component of Waldeyer's ring are thought to be an essential part of the body protecting against pathogens invading the upper respiratory tract. Human adenoids and tonsils are known to be immunologically reactive lymphoid organs which manifest specific antibodies, B and T cells activity in response to variety of antigens carrying out the functions of humoral and cellular immunity.[1] Four specialized lymphoid compartments constitute the immune function of adenoid and tonsil, namely the reticular crypt epithelium, the

extrafollicular area, the mantle zones of lymphoid follicles and the follicular germinal centers.[2] The histological structure of the adenoids and tonsils is closely related to immunologic function. It appears that the 10–30 crypt-like invaginations in the adenoids and tonsils that are lined by squamous epithelium serve as a complex system and access route for both inhaled and ingested antigens due to presence of M cells, antigen presenting cells and micropores that deliver the antigen to the active lymphoid cells underlying the tonsillar epithelium.[3]

It is well known that inflamed human adenoids and tonsils have many surface crypts showing characteristic lymphoepithelial symbiosis, which play an important role in immune response. The crypt epithelia are rich in blood vessels which could be the source of various kinds of immune responses.[4] The human immune responses are divided into humoral immune response, which is dependent on B cells, plasma cells and antibodies, and cellular immune response which is dependent on T cells and cytokines. The lymphocytes are most important cells in the immune system and a common lymphoid precursor cell in the bone marrow, from where they will migrate to the peripheral lymphatic tissues.[5] T lymphocytes need a period of maturation in the thymus, where they express their T-cell receptor and other surface markers of differentiation. The B lymphocytes, develop fully in the bone marrow and migrate directly to the peripheral tissues. When B lymphocytes are stimulated by antigen, they multiply and are transformed into plasma cells, which commence synthesis of antibody against the antigen.[6]

The pathogenesis of infectious disease in adenoids and tonsils most likely has its basis in their anatomic location and their inherent function as organs of immunity, processing infectious material and then becoming, paradoxically, a focus of infection.[7] The adenoids and tonsils are unique in that they are involved in both local immunity and immune surveillance for development of body's immunologic defense resulting in the production of local antibody, shift of B and T cell ratios, and according to some a change in serum immunoglobulin levels, which then return to normal after adenotonsillectomy. There were observed increases of serum levels of immunoglobulins A and G in patients with hypertrophy of adenoids and/or tonsils.[8, 9, 10]

Knowledge gathered on Waldeyer's ring physiology and evidences on the contributions it makes to immune local and systemic response have been the topic of controversy, in particular due to the injudicious manner in which adenotonsillectomy procedures have been carried out along the years. Thus, further research is required to analyze the possible immune adverse impact consequent to the procedure.[11]So far, the best treatment is still surgery. Because of the unique development state of these children, whether adenotonsillectomy can reduce the function of their immune system has been the interest of many clinicians and researchers.[1]

Therefore, the aim of the current work is to observe the changes in humoral immunity in children with chronic adeno-tonsillitis and/or hypertrophy of adenoids and tonsils before and after adeno-tonsillotomy through estimation of the levels of serum immunoglobulins (IgA, IgG and IgM) in diseased children and compare them to healthy ones.

Patients and Methods

This study was conducted in the Otorhinolaryngology, Head and Neck surgery Department, Zagazig University Hospitals, Egypt, after taking approval from the institutional review board.

Written informed consent was taken from the parents and an assent was taken from the children where possible. The study included a total number of 50 children; they were divided into two main equal groups of 25 children each.

Inclusion Criteria:

- Group A: Children between the age of 4-12 years undergoing adenotonsillectomy for chronic adeno-tonsillitis and/or adeno-tonsillar hypertrophy.
- Group B: Age matched healthy children without a prior history of adeno-tonsillitis or adeno-tonsillar hypertrophy.

Exclusion criteria:

Unmatched age, medically unfit for surgery, personal or family history of immune deficiency or disease with known immune-related etiology and upper respiratory tract infection within the previous 6 weeks.

Study design:

Group A (Operative) included 25 children who underwent adenotonsillectomy for chronic adeno-tonsillitis and/or adeno-tonsillar hypertrophy. 8 males and 17 females with mean age 6.32 ± 2.47.

Group B (Control) included 25 age matched healthy children (healthy state proved by history and clinical examination) .13 males and 12 females with mean age 6.2 ± 2.04.

All children were subjected to detailed history, clinical examination, routine investigations and measurements of serum immunoglobulins (IgA, IgG and IgM). Two samples of blood were taken, one before adenotonsillectomy and one after three months from Group A. Only one sample of blood was taken from Group B to be compared with that of Group A.

Immunologic analysis:

Serum was separated and kept at -20°C until the immunoglobulins were analyzed. Analysis was done using BN Prospec nephelometry from Siemens diagnostic. Proteins contained in human body fluids form immune complexes in an immunochemical reaction with specific antibodies, these complexes scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result was evaluated by comparison with a standard of known concentration.

Ethical approval:

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Written informed consent was obtained from all participants and the study was accepted by the research ethical committee of Faculty of Medicine, Zagazig University.

Surgical procedure:

A standard anesthetic protocol was applied to all patients in Group A, who underwent adenotonsillectomy, with orotracheal intubation. The usual physiological parameters (respiratory rate, pulse, blood pressure, and temperature) were monitored throughout the surgery. Standard surgical technique was used. The cold dissection technique for tonsillectomy and curettage technique for adenoidectomy were performed by otolaryngology residents under the supervision of the attending surgeon.

Statistical analysis:

All data were analyzed using SPSS 15.0 for windows (SPSS Inc., Chicago, IL, USA) &MedCalc 13 for windows (MedCalc Software bvba). Quantitative variables were expressed as the mean ± SD and qualitative variables as absolute frequencies. Kolmogorov-Smirnov test and independent Student t-test, Mann-Whitney U (MW) test, Paired t test, Chi-square ($\chi 2$) test and Wilcoxon Signed Ranks (WSR) test were used to compare data between the studied groups. Pearson's correlation was done between immunoglobulin level and selected study parameters. Spearman's rank correlation coefficient was calculated. $P < 0.05$ was considered statistically significant (S), $p < 0.005$ was considered statistically highly significant (HS), and $p > 0.05$ was considered statistically non-significant (NS).

Results

There was a significant difference between groups A (pre-operative) and group B in regard to serum levels of IgA, IgG and IgM. A higher levels of serum IgA, IgG and IgM with high statistical significance (P<0.05) was found in Group A (pre-operative) compared with Group B (**Table 1).**

When comparing between the Group A pre- and post-operative arms, there was highly significant (P<0.005) decrease in serum IgA, IgG, IgM level post-operatively than pre-operatively **(Table 2).**

When comparing immunoglobulin levels between Group A (post-operative) and Group B, no statistically significant difference was found between the two groups (P> 0.05) **(Table 3).**

Table (1): Comparison of immunoglobulin level of Group A (pre- operative) with Group B

	Group A Pre-operative (n=25)	**Group B Control group (n=25)**	**t**	**p**
IgA				
Mean ± SD	**1.85 ± 0.44**	**1.48 ± 0.22**	**3.734**	**0.001 (HS)**
Median (Range)	**1.81 (1.04 – 2.77)**	**1.5 (1 – 2.2)**		
IgG				
Mean ± SD	**11.35 ± 0.91**	**10.76 ± 0.67**	**2.566**	**0.013 (S)**
Median (Range)	**11.54 (9.36 – 12.9)**	**10.68 (9.45 – 12.2)**		
IgM				
Mean ± SD	**1.35 ± 0.21**	**1.11 ± 0.15**	**4.618**	**<0.001 (HS)**
Median (Range)	**1.37 (1 – 1.88)**	**1.06 (0.88 – 1.5)**		

t: independent Student t-test; p< 0.05 is significant ; S: significant; Hs: highly significant

Table (2): Comparison between pre & post operative immunoglobulin level in Group A (n=25)

	Group A Preoperative (n=25)	Group A Postoperative (n=25)	Test	p
IgA			**Paired t**	
Mean ± SD	**1.85 ± 0.44**	**1.51 ± 0.41**	**7.297**	**<0.001**
Median (Range)	**1.81 (1.04 – 2.77)**	**1.47 (1 – 2.4)**		**(HS)**
IgG			**Paired t**	
Mean ± SD	**11.35 ± 0.91**	**10.32 ± 0.91**	**10.277**	**<0.001**
Median (Range)	**11.54 (9.36 – 12.9)**	**10.55 (7.92 – 12)**		**(HS)**
IgM			**WSR**	
Mean ± SD	**1.35 ± 0.21**	**1.14 ± 0.17**	**-4.286**	**<0.001**
Median (Range)	**1.37 (1 – 1.88)**	**1.12 (0.88 – 1.5)**		**(HS)**

Paired t: Paired t test for dependent samples, P<0.05 is significant, WSR: Wilcoxon Signed Ranks test; HS: highly significant

Table (3): Comparison between Group A (post-operative) & Group B immunoglobulin level (n=25)

	Group A Post-operative (n=25)	Group B Control group (n=25)	Test	p
IgA			**t**	
Mean ± SD	1.51 ± 0.41	1.48 ± 0.22	0.273	0.786
Median (Range)	1.47 (1 – 2.4)	1.5 (1 – 2.2)		(NS)
IgG			**t**	
Mean ± SD	10.32 ± 0.91	10.76 ± 0.67	-1.931	0.059
Median (Range)	10.55 (7.92 – 12)	10.68 (9.45 – 12.2)		(NS)
IgM			**MW**	
Mean ± SD	1.14 ± 0.17	1.11 ± 0.15	290.000	0.662
Median (Range)	1.12 (0.88 – 1.5)	1.06 (0.88 – 1.5)		(NS)

t: independent student t-test; MW: Mann Whitney U test; P< 0.05 is significant; NS: non-significant.

Discussion

The tonsils and adenoids are part of the mucosa-associated lymphoid tissue, with roles in both humoral and cellular immunity. The humoral immunity is activated when B lymphocytes are stimulated by antigens, they proliferate and evolve into plasma cells, resisting the antigen and producing antibodies. Tonsils and adenoids can secrete, IgA, IgG, and IgM and cytokines.[12]

It is known that the concentration of lymphocytes in tonsils of children is more than those in adults. Also, higher levels of immunoglobulins in the pre-tonsillectomy period are due to constant antigenic stimulus from infected tonsils.[13]

Adenoidectomy with/without tonsillectomy may reduce serum IgA levels in young children <3 years of age in a short time after the surgery, but this tends to be short lived and generally does not lead to increased risk of infection or immune-deficiency disorders in young children (age<3 years). This finding indicates that the remaining mucosa-associated lymphoid tissue can compensate for the

loss of adenoid and tonsil tissue. IgA may be the most important immune factor in adenoids and tonsils.[1]

Our study was conducted in the department of Otorhinolaryngology, Head and Neck surgery, Zagazig University Hospitals on 25 children diagnosed with chronic adeno-tonsillitis and/or hypertrophy of adenoids and tonsils Group A (operative) who underwent adenotonsillectomy and control Group B including 25 healthy children , to compare their serum immunoglobulin levels with Group A. The aim of the current study was to observe the changes in humoral immunity in children with chronic adeno-tonsillitis and/or hypertrophy of adenoids and tonsils before and after adeno-tonsillotomy.

In our study, the serum levels of IgA, IgG and IgM decreased considerably after adenotonsillectomy. This decrease maybe explained due to the recovery of infected tissue and disappearance of continuous antigenic stimulus. We consider that, before adeno-tonsillectomy, the activation of the classical complement pathway was the result of the increase in microorganism in the infected tonsils and adenoid, leading to continuous antigenic stimulus which in turn led to formation of antigen-antibody complex in the immune system. Upon removal of the tonsils and adenoid the antigenic stimulus was eliminated, that led to decrease in the immunoglobulins post-operatively.

These results are in agreement with **Zielnik-Jurkiewicz et al.**[14] who observed a significant higher serum levels of immunoglobulin A, G and M in patients with hypertrophy of adenoids and tonsils compared with those of the control group before operation. One month after adenotonsillectomy the serum levels of immunoglobulins significantly decreased to the level seen in the control group.

Also, **Baradaranfar et al.**[15] reported that the mean preoperative level of serum IgA, IgM and IgG were significantly higher in patients with chronic adeno-tonsillitis than in control group; the values of which dropped significantly after adenotonsillectomy, the post-operative values being comparable with those of the control group.

Similar to our results, **Santos et al.**[11] showed that there is a significant decrease in serum immunoglobulins level in children after adenotonsillectomy but within normal range when compared to the control group. Thus, they documented that the adenotonsillectomy pediatric patients enrolled in the study did not present short or long-term adverse impacts upon their cellular or humoral immunity.

Our results are also consistent with **Kaygusuz et al.**[16] who found statistically significant differences between pre- and post-operative values of IgG, IgA, IgM, C3 and C4, which decreased after surgery ($P<0.05$). However, the post-operative levels were comparable with those of the control group even after 1 month. On long term follow up (4-6yrs) post tonsillectomy **Radman et al.**[17] found that the mean serum levels of IgM, IgA, and IgG in the case group were significantly ($P < 0.0001$) lower than the control group.

There is a common belief especially among the parents that adenotonsillectomy impairs the immunity for the rest of life. But our study showed that the immunity was not significantly affected 3 months after adenotonsillectomy and their related immunity parameters did not significantly differ from age-matched healthy controls. More studies are needed using a larger number of patients with

long term follow up to assess the long-term impaction. Also study of other aspects of immunity like cellular immunity and the impact of adenotonsillectomy on it is needed.

Conclusion:

After adenotonsillectomy, the humoral parameters were found reduced but overall impact on the status of humoral immunity was not significantly changed. Our results indicate that adenotonsillectomy does not significantly impair immune function. Serum marker levels, albeit reduced, were kept within normal range. This is highly relevant in respect to the realm of clinical practice, as this finding becomes an important tool in advising patient family members and informing other assisting physicians over the actual impact of surgery.

Conflict of interest: The authors declare no conflict of interest.
Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Author contribution: Authors contributed equally in the study.

References:

1- **Yan, Y., Song, Y., Liu, Y., Su, J., Cui, L., Wang, J., ... & Zuo, L. (2019)**. Short-and long-term impacts of adenoidectomy with/without tonsillectomy on immune function of young children< 3 years of age: a cohort study. *Medicine*, *98*(19).
2- **Brandtzaeg, P. (2003, November)**. Immunology of tonsils and adenoids: everything the ENT surgeon needs to know. In *International Congress Series* (Vol. 1254, pp. 89-99). Elsevier.
3- **Bailey, B. J., Johnson, J. T., & Newlands, S. D. (4th Eds.),(2006)**. *Head & neck surgery--otolaryngology* (Vol. 1). Lippincott Williams & Wilkins.
4- **Dhingra, P. L., & Dhingra, S. (2013)**. *Diseases of Ear, Nose and Throat-E-Book*. Elsevier Health Sciences, Tonsillectomy 382-385.
5- **Abbas, A. K., Lichtman, A. H., & Pillai, S. (2010)**. Properties and overview of immune responses. *Cellular and Molecular Immunology. 6th ed. Philadelphia, USA: Saunders Elsevier*, 1-18.
6- **Huether, S. E., McCance, K. L., & Parkinson, C. F. (2011)**. *Study guide for understanding pathophysiology-E-book*. Elsevier Health Sciences.
7- **Wang, B., Tang, X., Xu, J., & Yao, H. (2012)**. Differential expression of Immunoglobulin A in the adenoids of children with and without exudative otitis media. *International journal of pediatric otorhinolaryngology*, *76*(5), 728-730.
8- **Burton, M. J., Glasziou, P. P., Chong, L. Y., & Venekamp, R. P. (2014)**. Tonsillectomy or adenotonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. *Cochrane Database of Systematic Reviews*, (11).

9- **Nasrin, M., Miah, M. R. A., Datta, P. G., Saleh, A. A., Anwar, S., & Saha, K. L. (2012).** Effect of tonsillectomy on humoral immunity. *Bangladesh Medical Research Council Bulletin*, *38*(2), 59-61.

10- **Bitar, M. A., Dowli, A., & Mourad, M. (2015).** The effect of tonsillectomy on the immune system: A systematic review and meta-analysis. *International journal of pediatric otorhinolaryngology*, *79*(8), 1184-1191.

11- **Santos, F. P., Weber, R., Fortes, B. C., & Pignatari, S. S. N. (2013).** Short and long term impact of adenotonsillectomy on the immune system. *Brazilian journal of otorhinolaryngology*, *79*(1), 28-34.

12- **Dai, Z. Y., Huang, D. Y., & Zhou, C. Y. (2014)**. Effects of partial tonsillectomy on the immune functions of children with obstructive sleep apnea-hypopnea syndrome at early stage. *Genet Mol Res*, *13*(2), 3895-902.

13- **Lopez-Gonzalez, M. A., Sanchez, B., Mata, F., & Delgado, F. (1998)**. Tonsillar lymphocyte subsets in recurrent acute tonsillitis and tonsillar hypertrophy. *International journal of pediatric otorhinolaryngology*, *43*(1), 33-39.

14- **Zielnik-Jurkiewicz, B., & Jurkiewicz, D. (2002)**. Implication of immunological abnormalities after adenotonsillotomy. *International journal of pediatric otorhinolaryngology*, *64*(2), 127-132.

15- **Baradaranfar, M. H., Dodangeh, F., & Atar, S. T. Z. M. (2007)**. Humoral and cellular immunity parameters in children before and after adenotonsillectomy. *Acta Medica Iranica*, 345-350.

16- **Kaygusuz, I., Gödekmerdan, A., Karlidağ, T., Keleş, E., Yalçin, Ş., Aral, I., & Yildiz, M. (2003)**. Early stage impacts of tonsillectomy on immune functions of children. *International journal of pediatric otorhinolaryngology*, *67*(12), 1311-1315.

17- **Radman, M., Ferdousi, A., Khorramdelazad, H., & Jalali, P. (2020)**. Long-term impacts of tonsillectomy on children's immune functions. *Journal of Family Medicine and Primary Care*, *9*(3), 1483.