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(Adeno)tonsillectomy: what is the impact on the immune system?

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Abstract. *Objectives*: The effect of (adeno)tonsillectomy (ATE) on the immune system is still a point of discussion. In this study, we investigate the local and systemic immunological consequences of removing (adeno)tonsillar tissue, based on changes in immunoglobulin (Ig) levels, T and B lymphocyte counts, and frequency of pre- and post-operative upper airway infections.

Methodology: We performed a literature review and included six studies examining short-term effects (≤1 year post-operative) and six studies examining long-term effects (≥1 year post-operative) of ATE on humoral and cellular immunity. The use of medication, frequency of visits to the doctor, cost-effectiveness of the procedure, and quality of life pre- and post-operatively were also used as outcome parameters for long-term effects.

Results: In the short term, only one study showed a significant post-operative decrease in IgA, IgM, and IgG levels, as well as cytotoxic T-lymphocyte count. Two studies noted both a significant decrease in IgG levels and a significant increase in T helper cells. No significant change in Ig levels or lymphocyte counts were observed after ATE in the long term.

Conclusion: There is no evidence that ATE compromises the immune system in either the short or long term. Physicians and researchers agree that ATE is an effective treatment for recurrent adenotonsillitis that improves quality of life and reduces the frequency of upper airway infections. However, additional long-term and large-scale studies are needed.

Introduction

Waldeyer's ring, known to be important in both local and systemic immunity, consists of lymphoid tissue situated in the nasopharynx and oropharynx and comprises the palatine, lingual and tubal tonsils, the adenoid, and the tubopharyngical strands. Mucosa associated lymphoid tissue (MALT) at Waldeyer's ring is called nasal-associated lymphoid tissue (NALT) and provides local mucosal immunity primarily via IgA-secreting plasma cells.[2-4] Secretory IgA (sIgA) is abundantly present on mucosal surfaces and stimulates the phagocytosis of bacterial surface antigens and viruses,[5] while epithelial M cells with microvilli transport antigens to the underlying lymphoid follicles.[1] Naive T lymphocytes enter the interfollicular area of the secondary lymphoid organs (SLO) and scan the surface of dendritic cells for their specific antigen, leading to T cell retention and activation if successful.[3,4,6] These naive immune cells are generated in the primary lymphoid organ and become activated in the germinal centers (GC) of the SLO after encountering antigens.[2] B cells also differentiate into either plasmablasts or memory B cells in the GC,[4,6] and plasmablasts terminate differentiation into plasma cells after leaving the GC.[6] While tonsillar plasma produces all immunoglobulin classes, IgG and IgA are the main export products in tonsillitis, and T follicular helper cells (TFH cells) are primarily responsible for B cell help during a GC response.[7] TFH cells stimulate B cell selection and affinity maturation by the action of mediators including cytokines (IFNg, IL-4, IL-21) and PD-1 (Programmed cell death protein 1).[7,8] T follicular regulatory cells (TFR cells) inhibit the

GC reaction by controlling the initiation, size and output of the immune response,[8] and are therefore thought to prevent exaggerated immune responses and autoimmunity. The acute phase of tonsillitis is marked by a higher production of IgM than IgG, while[9] chronically infected tonsils seem to produce higher levels of Igs, especially IgG.[9,10] Although ATE is one of the most commonly performed surgical procedures in children, the impact on the immune system of these patients remains widely debated.[11,12] ATE is done for recurrent acute or chronic tonsillitis or upper airway obstruction due to adenotonsillar hyperthophy.[13,14]

Patients with recurrent tonsillar inflammation demonstrate tonsillar plasma cells with reduced expression of J-chains which may affect the action of sIgA.[3] Chronic stimulation also leads to reduction of the tonsillar immunocompetency and acceleration of the involution of the tonsils, with a diminished differentiation of B cells to plasma cells, which is normally an age-related process.[3] Cytotoxic T cells proliferate in infected patients, which leads to a reversal of the CD4+/CD8+ ratio and an early local suppression of the generation of Igs which later becomes systemic.[5] Large numbers of cytokines activate fibroblasts and endothelial cells, resulting in the growth of immunologically silent fibrotic tissue that substitutes for immunologically active tissue.[15]

Tonsils vulnerable to the accumulation of micro-organisms such as bacteria and viruses. Beta-haemolytic streptococci are one of the most frequent causative agents of bacterial tonsillitis, next to H. influenza, S. pyogenes and S. aureus, while viral tonsillitis can be caused by the influenza virus and the Epstein-Barr virus (EBV).[16] EBV first infects Waldeyer's ring and then the entire body through circulating memory B cells.[17]

This review provides an overview of the current literature of the impact of (adeno)tonsillectomy (ATE) on local and systemic immunity, from the points of view of both an immunologist and a clinician.

Materials and methods

We searched the PubMed and Cochrane Library databases from 2014 to 2016 for studies reporting the effect of ATE on the local and systemic immune system and did duplicate study selection and data extraction. We used the following search strategy: "(tonsillectomy [Title/Abstract]) AND immunology [Title/Abstract]" or other key-word combinations with Waldeyer's ring, immunoglobulins, or lymphocytes. We limited all searches to English language articles published between January 1999 and December 2016. Studies were included if they examined the short-term and/or long-term effects of ATE on humoral (Ig) and/or cellular (lymphocytes) immunity and on local and/or systemic immunity. We limited the number of studies to 6 articles about short-term effects and 6 articles about long-term effects. Articles were excluded based on date of publication and usage of parameters that did not fit our predetermined parameters and objectives. The short-term effects (≤1 year post-operative) are defined as the change of Ig levels and lymphocyte counts shortly after surgery. In each of the six studies, a comparison was made between patients who underwent ATE because of obstructive hypertrophied tonsils/adenoid and/or recurrent tonsillitis (patient group) and healthy individuals (control group). Long-term effects (≥1 year post-operative) were evaluated by observing immunological and clinical parameters. Two studies examined the change in Ig levels and lymphocyte counts at least one year after surgery, while four studies used the use of antibiotics or respiratory medication, the frequency of visits to the doctor, the cost-effectiveness of the procedure, and the quality of life pre- and post-operatively as outcome parameters.

Results

Short term impact on immune system

One month after surgery, Zielnik-Jurkiewicz *et al*. reported a significant decrease in Igs (IgA, IgM, IgG) and cytotoxic T lymphocytes in the patient group compared with the control group. Both levels increased to values similar to those observed in the control group six months after surgery. The patient group showed significantly increased values of all the Igs and cytotoxic T lymphocytes pre-operatively.[18] Ikinciogullari *et al*. (2002) saw a slight but not significant decrease in Igs in the patient group after ATE, compared to pre-operative values. Cytotoxic T lymphocytes were increased and B cells were returning to normal six to eight weeks post-operatively. Children with recurrent tonsillitis showed increased levels of B

Table 1

Summary of 7 studies, representing short- and long-term effects of ATE on humoral (Ig) and/or cellular (lymphocytes) immunity

short		Zielnik-Jurkiewicz[18]	Ikinciogullari[19]	Kaygusuz[10,23]		Faramarzi[11]	Nasrin[9]	Santos[12]	
		short	short	long	short	short	short	long	
Ig	A	↓↓	↓	≈		↑ → ↓		≈	↓↓
	M	↓↓	↓	≈		≈		≈	
	G	↓↓	↓	≈		≈	↓↓		↓↓
T-lymph	Th		↑	↑↑	↑↑	↓		↑↑	↑
	Tcyt	↓↓	↓	≈	↓↓	↓		↓	↑
B-lymph					↓↓	≈			

↓↓: significant decrease
↓: no significant decrease
↑↑: significant increase
↑: no significant increase
≈: almost no change
↑ → ↓: increase 2 weeks post-operatively, decrease 8 weeks post-operatively

lymphocytes and increased B lymphocyte activation pre-operatively, compared to healthy controls.[19] Kaygusuz *et al*. (2003) saw no differences in Ig levels in patients compared with controls. T helper cells showed a significant rise to control levels, but cytotoxic T lymphocyte levels showed no difference pre- and post-operatively. Pre-operative levels were higher for IgA, IgM, IgG, and cytotoxic T lymphocytes, but were lower for T helper cells in patients compared to healthy controls.[10] Faramarzi *et al.* (2006) showed that serum IgA levels were significantly higher two weeks after the procedure compared to pre-operative values. Changes in IgG, IgM, and B lymphocyte counts were not significant, and IgA levels dropped to pre-operative values eight weeks later. Pre-operative T lymphocyte counts were normal, with a modest decrease after 2 weeks followed by a rise after 8 weeks.[11] Nasrin *et al.* (2012) observed higher IgG levels and lower IgA and IgM levels before surgery in the patient group relative to controls, but changes in IgG, IgM and IgA levels were not significant one month after surgery. Three months later, only IgG was significantly lower than pre-operative or control values.[9] Santos *et al*. (2013) indicated that T helper lymphocyte count was significantly increased post-operatively (1 to 2 months post-surgery), but cytotoxic T lymphocytes showed a slightly reduced count that was still within the normal range. Serum levels of IgA, IgM and IgG didn't show significant alterations when compared with the pre-surgical values.[12] In summary, only one study showed a significant decrease in IgA, IgM, IgG levels, and cytotoxic T-lymphocyte count after ATE, and two studies noted a significant decrease in IgG levels and a significant increase in T helper cells after surgery.

Long term impact on immune system

Kaygusuz *et al*. extended their 2003 short-term follow up study and published long-term outcomes in 2009. In that study they concluded that there were no significant differences between the short- and long-term values of IgA, IgG, and IgM, but levels of T helper cells and B lymphocytes showed an increase when compared to the short-term values.[23] In 2013 Santos *et al.* also performed a long-term follow-up of patients that underwent adenotonsillectomy one year before. IgA and IgG levels showed a significant reduction at this long-term follow-up, but remained within a normal range. They also reported that no subjects had altered Ig or lymphocyte levels. T helper cells and cytotoxic T cells increased on the long run, but were not high enough to be significant.[12]

Table 1 summarizes the seven studies discussed above and the post-operative changes in IgA, M, and G, T-helper cells, cytotoxic T-cells (T-lymphocytes) and B-lymphocytes after ATE.

In the following four studies, the use of antibiotics or respiratory medication, the frequency of visits to the doctor, the cost-effectiveness of the procedure, and the quality of life pre- and post-

operatively were observed as outcome parameters. In 2010, Lemkens *et al.* showed an average drop from four boxes of antibiotics a year to just one box a year after the operation. The average number of visits to pediatricians was also reduced, from seven in one year to four.[20] Piessens *et al.* (2012) performed a similar study, comparing the median use of respiratory medication in children of 0-15 years old one year before and one year after ATE. They reported a drastic reduction of medication use one year post-operatively in the group that had used respiratory medication at least once in the preceding year, and saw a reduction from 3.2 boxes in the year before to 1.6 boxes in the year after surgery.[14] Chang *et al.* (2014) studied the cost-effectiveness of the procedure and concluded that it was cost-effective. They attributed the reduction in cost primarily to a reduced number of doctor visits and less frequent antibiotic use.[21] Goldstein *et al*. (2008) evaluated quality of life (QoL) in children who underwent ATE and found that their subjects demonstrated significant improvements in many of their parameters, including breathing, infection, and cost of health care utilization.[22]

Effect on the remaining components of Waldeyer's ring

Emerick *et al.* (2006) examined tubal tonsil hypertrophy (TTH), which commonly occurs in patients after adenoidectomy. At an average of 4 years after the procedure, these patients showed recurrent symptoms of nasal obstruction, obstructive sleep disorder, rhinosinusitis, recurrent otitis media, and otitis media with effusion, and they concluded that TTH was a significant cause of recurrent symptoms after removal of the adenoid.[24] Whether the enlargement of the lingual tonsil is a compensation for the removal of the palatine tonsils and/or a consequence of chronic infections in this lymphoid region remains an unanswered question in patients with lingual tonsil hypertrophy (LTH).

Involution of the secondary lymphoid organs

Primary follicles are already present in human tonsils at 16 weeks of gestation,[13] but formation of active GC does not occur until birth, indicating the need for exposure to antigens.[6,13] This lymphoid tissue proliferation induces the growth of the tonsil. Tonsil size peaks in children between four and eight years of age, coinciding with the period in which the tonsils are immunologically most active (between the ages of four to ten years), and involution begins during the second decade of life. Around puberty, fibrous tissue proliferates in and around the capsule, fatty degeneration sets in, and the epithelium becomes less multi-layered.[13] In some cases, atrophy of the tonsils occurs, showing only one to two lymphoid follicles with no distinctive GC. Age-related changes in the proportions of different lymphocyte populations in tonsils and adenoids have been observed.[25] The normal distribution of lymphocytes includes 60% B lymphocytes and 40% T lymphocytes. The number of T cells increases and the amount of B cells decreases with age,[25] and the number of CD8+ T cells decreases, while the number of CD4+ T cells increases with age.[25] Linterman *et al*. recently described a more extensive hypothesis.[8] They state that there is a decrease in the size and quality of the GC response with age in human tonsils, which is related to the involution of the organs.[8] The formation and function of TFH cells, germinal B cells, and TFR cells (the key cellular regulators of the GC response) all change with age, which influences the GC. Reduction of TFH function and a reduction in the sensitivity of B-cells to TFH causes a reduction in proliferation, class switching, and affinity maturation of B-cells with age in GC.[8] An age-related increase of the amount of TFR cells could rule out the GC response.[8]

Discussion

This review gives an overview of what is known and studied by immunologists and clinicians concerning the impact of ATE on immunity. Controversy remains as to whether removing the tonsillar tissue results in the removal of an important immunological barrier. Many studies examining the short-term effects of the surgical procedure reported pre-operative increases in Ig levels and increased or divergent T helper and cytotoxic T cell counts.[9,10,18,19] This is plausible, since ATE is performed as a treatment for recurrent tonsillitis, a state of chronic inflammation characterized by elevated immunological parameters. The immunological parameters didn't always show this uniformity after ATE. These results should be interpreted with caution, due to the small number of patients and control groups and less significant results. Two additional studies described increased

cellular immunity after ATE, we specifically refer to the significant increase in T helper cells seen post-operatively by Santos *et al*.[12] and Kaygusuz *et al.*[10] There were also differences in humoral immunity between studies, but most studies reported a decrease in Ig levels after surgery, followed by a notable recovery to normal values during the course of several months.[10,11,18] Possible explanations for this post-operative reduction include a reduction in production due to surgical stress, a reduction in Ig-producing tissue, and/or a reduction in antigen load, an opinion shared by other authors.[9,10,12,19]

Some studies analyzing post-operative immunological parameters during a longer period of time (1 to about 5 years after the surgery), reported changes in Ig levels, although it was always within the normal range,[12,23] indicating that removing Ig-producing tissue does not seem to lead to a significant reduction in Ig levels. It is plausible that other lymphoid tissue in Waldeyer's ring compensates for the production of Ig. The fact that hypertrophy of these structures can occur after ATE supports this hypothesis.[24] No notable alterations in cellular immunity were reported, although some studies suggested that lymphocyte counts were slightly elevated.[12,23]

Various studies used the frequency of upper airway infections after the procedure as an indication of the effectiveness of the treatment, and these studies all agreed that ATE reduces the frequency of upper airway infections. The use of antibiotics or respiratory medication, frequency of visits to the doctor, cost-effectiveness of the procedure, and quality of life pre- and post-operatively were all used as outcome parameters.[14,20,21,22] However, these studies were mostly conducted in small groups, typically including fewer than fifty people, and long-term follow-up studies performed after more than one year are scarce.

Some studies also question the importance of age at the time of surgery. Does the ring still exert an important immunological function in old age or is its activity only temporary and relevant at a young age? An age limit for the removal of tonsils could be established if this were known. According to a study by Linterman *et al*., memory T cells in the elderly show increased expression of pro-apoptotic factors and decreased expression of anti-apoptotic factors, causing them to enter apoptosis much earlier.[8] Another factor is the increased number of CD28-negative T cells with age. CD28 is essential for the function of memory T cells,[8] thus the number of memory cells which have the capacity to mount a secondary GC response also decrease with age, causing the immunological memory to correspondingly decrease (immunosenescence).[8] Taking these facts into consideration it is not certain whether the removal of parts of Waldeyer's ring remains without consequences, but if Waldeyer's ring only plays a role in the development of immunity in childhood, its components will not have a major function at the time of involution. There is an age at which a person has encountered practically all the antigens in its environment and the formation of a vast collection of memory (B- and T) cells has occurred, in agreement with a possible decreased function of Waldeyer's ring with age, related to its involution.

Finally, some articles wonder whether infected tonsils still have a normal function. In case of recurrent tonsillitis, it is the case that Waldeyer's ring is a source of infection rather than a source of immunological protection against infection.

Conclusion

The strategic location of Waldeyer's ring and its capability to capture passing antigens shows direct immunological relevance. Waldeyer's ring is important in both local and systemic immunity. There is no conclusive evidence that ATE compromises either the local or systemic immune system. There are no significant changes in Ig levels and lymphocyte counts after ATE, in either the short or long term. Physicians and researchers appear to agree that ATE improves quality of life and reduces the frequency of upper airway infections.

We conclude that ATE is a good treatment for recurrent adenotonsillitis. However, we suggest the need for more long-term and large-scale studies to confirm this conclusion.

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