Impact of Adenotonsillectomy on the Immune System

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Waldeyer’s ring is formed by the nasopharyngeal tonsils (adenoids) located superiorly in the midline of the posterior nasopharyngeal wall; the tubal tonsil are localized in the submucous layer of the nasopharynx, posterior to the pharyngeal ostium of the eustachian tube; the palatine tonsils are located between the anterior and posterior tonsillar pillars at the lateral opening of the oropharynx; the lingual tonsils are located in the posterior third of the tongue; and for the submucosal collections of lymphoid tissue scattered in the mucosa of the pharynx behind the posterior tonsillar pilar and posterior wall of the pharynx.¹ (Figure 1)

Figure 1. Waldeyer’s ring is formed by the nasopharyngeal tonsils (adenoids), tubal tonsils, palatine tonsils, lingual tonsils, and the submucosal collection of lymphoid tissue scattered in the mucosa of the pharynx.

The tonsils and adenoids are considered as secondary lymphoid organs, part of the mucosa-associated lymphoid tissue (MALT), which present immune activity mainly between four and ten years of age.² The palatine tonsils contain B lymphocytes (50%-65%), T lymphocytes (40%) and mast cells (3%). The tonsils have several unique characteristics: 1.- they are not fully encapsulated, 2.- they do not possess afferent lymphatics; 3.- they are lymphoreticular structures, and also lymphoepithelial organs; (4) the tonsillar epithelium provides a protective surface
that covers, invaginates and lines the tonsil crypts; 5) the adenoids are lined mainly with a ciliated respiratory epithelium and the palatine tonsils are lined with stratified squamous nonkeratinized or parakeratinized epithelium; 6) the tubal tonsils are covered mainly with a ciliated respiratory epithelium.\(^1\) (Figure 2)

The adenoids and tonsils are strategically located to serve as secondary lymphoid organs, initiating immune responses against antigens entering the body through the mouth or nose. The greatest immunological activity of the tonsils occurs between the ages of 3 and 10 years.\(^3\) The tonsils are most active during this period of childhood and later presents age-dependent involution.\(^4\) The tonsils and adenoids contain four specialized lymphoid compartments participating in the immune functions of these organs:\(^5,6\)

1. the reticular crypt epithelium, which contains a system of 10 to 30 tonsillar crypts; 2. the extra follicular area, where the dendrite cells and macrophages process antigens; 3. the mantle zone of lymphoid follicles with an outer ring of small lymphocytes surrounding a germinal center; and 4. the follicular germinal centers, where B-cells stimulated by T helper cells and cytokines proliferate and turns into mast cells that produce immunoglobulins. Primary follicles are present in human tonsils as early as at 16 weeks of gestation\(^5,6\).

The tonsillar crypts are blind, often branched invaginations of the epithelium into the submucosal lymphoid tissue, which considerably increase the epithelium surface area for direct antigenic stimulation. In healthy tonsils the openings of the crypts are fissure-like, and the walls of the crypt are in apposition.\(^1\) The epithelium of the tonsils is cryptic and reticulated and contains M-cells, numerous lymphocytes, macrophages and dendritic cells, and may contain a few granulocytes.\(^5\) These cells take up antigens and transport them to the extrafollicular region or the lymphoid follicles. In the extrafollicular region interdigitating dendritic cells and macrophages process the antigens and present them to helper T lymphocytes. These lymphocytes stimulate proliferation of follicular B lymphocytes and their development into either antibody-expressing B memory cells, capable of migration to the nasopharynx and other sites or plasma cells that produce antibodies and release them into the lumen of the crypt.\(^5\) During chronic infection the surface epithelium can become ulcerated and the surface and crypt epithelium is infiltrated by neutrophilic granulocytes producing a cryptitis with crypt abscesses.

The tonsils protect the access of both respiratory and alimentary tract and their main function is to discriminate between potentially infectious pathogens and innocuous airborne and food antigens.\(^7,8,9\) They are the first site of contact with a variety of microorganisms and other antigenic substances present in food...
and inhaled air, and as secondary lymphatic organs the tonsils process antigens. Small amounts of antigens are transported through the reticular cell epithelium by M cells and antigen-presenting cells.

The Waldeyer’s ring plays an important immune-inductive role as components of mucosa-associated lymphoid tissue (MALT). The tonsils contain B cells that in response to antigens differentiate to plasma cells and generate polymeric IgA, resulting in systemic immunity and mucosal immunity. IgG, IgA and IgM are detectable in the secretory material from the pharynx and in the pharyngeal roof tissue as early as week five of gestation. The tonsils produce immunoglobulins from the fetal stage, although they do not acquire important levels until birth.

While all five immunoglobulin isotypes are produced in the palatine tonsils, IgA is the most important product of the tonsillar immune system. In its dimeric form IgA may attach to the transmembrane secretory component to form secretory IgA, a critical component of the mucosal immune system of the upper airway. Although the secretory component is produced only in the extratonsillar epithelium, the tonsils do produce immunocytes bearing the J chain carbohydrate. This component is necessary for binding of IgA monomers to each other and to the secretory component and is an important product of B-cell activity in the follicles of the tonsil. The tonsil of a child has a greater concentration of lymphocytes than adults and the helper and cytotoxic T lymphocytes are increased in sick tonsils and the higher levels of immunoglobulins in the pretonsillectomy period is due to constant antigenic stimulus from infected tonsils.

Widespread tonsillectomy was common during the first 6 decades of the last century, when focal infection was implicated as the cause of many of the diseases of childhood. The immunological impact of tonsillectomy in children has long been a source of debate among Otolaryngologists, Pediatricians, Infectologists, Immunologists and Family Doctors. In several countries of Latin-America some physicians and parents are afraid of tonsillectomy, because they are concerned that the removal of palatine and pharyngeal tonsils may result in impaired immunity, and in consequence the patients will suffer recurrent throat infections. Others are afraid that the surgery may cause sterility, obesity and permanent voice changes.

Currently the two most common indications for tonsillectomy are recurrent throat infections and sleep related breathing disorders. Other indications for surgery are orthodontic concerns, tonsiloliths, halitosis, and chronic tonsillitis. Tonsillectomy is the second most common ambulatory surgical procedure performed on children in the United States. Pediatric and adolescent adenotonsillectomy rates vary considerably in different countries, most probably as a result of continuing differences in attitudes towards the indication for adenotonsillectomy and antibiotic therapy.

Reports from 1978 to 1986 showed that the rate of tonsillectomy for treatment of throat infections declined; however, the frequency of sleep related breathing disorders as the primary indication for the procedure increased. A recent study reported that the overall incidence rates of tonsillectomy have significantly increased in the past 35 years, with sleep related breathing disorders being the primary indication for surgery.
Tonsillectomy is a surgical procedure with an associated significant morbidity. A common complication of tonsillectomy is bleeding during or after the surgery.\textsuperscript{17} Mortality rates for tonsillectomy have been estimated at between 1 in 16,000 to 1 in 35,000, based on data from the 1970s.\textsuperscript{22} There is a medical controversy in regard to possible side effects related with the removal of chronically infected tonsils and/or hypertrophied tonsils and the possible effects caused by the elimination of the host Waldeyer’s ring defense barrier.

**Impact of adenoidectomy, tonsillectomy and adenotonsillectomy on immunity**

With chronic or recurrent tonsillitis, the controlled process of antigen transport and presentation is altered due to shedding of the M cells from the tonsillar epithelium,\textsuperscript{5} and in consequence the direct influx of antigens disproportionately expands the population of mature B-cell clones and fewer early memory B cells go on to become J-chain-positive IgA immunocytes. If the tonsillar lymphocytes are overworked by persistent antigenic stimulation they may be incapable of responding to other antigens, and the tonsils are unable to function properly in local protection and reinforcement of the secretory immune system.\textsuperscript{17}

In 1954, the Journal of Public Health reported that “Absence of the tonsils put the person at increased risk of bulbar or bulbospinal polio. Of 85 patients who developed bulbar polio, 85.9\% had had a tonsillectomy. The rate of bulbar polio in those who still had their tonsils was 14.1\%. Out of 39 patients with bulbar paralysis, 35 had undergone tonsillectomy a proportion of 90\%. Of these 35 tonsillectomized patients with bulbar paralysis, only four had undergone tonsillectomy in the twelve months, and only one in the two months, prior to the onset of poliomyelitis”.\textsuperscript{24} In the same year Anderson and Rondeau in 1954 published a paper based upon epidemiological histories of 2,669 cases of poliomyelitis during the epidemic of 1946. For all age groups, 71.4 per cent of 535 bulbar cases gave a history of tonsillectomy at some previous time up to many years, as compared with 28.2 per cent of 936 severe spinal; 36.2 per cent of 908 mild spinal, 34.8 per cent of 299 nonparalytic cases. The results of these studies shows that a history of tonsillectomy is two to three times more frequent in patients with bulbar poliomyelitis than it is with patients having spinal or nonparalytic poliomyelitis.\textsuperscript{25}

Several reports in the 1940s suggested that tonsillectomy predisposed to polio and should be avoided in the summer polio season. Ogra\textsuperscript{27} showed that the mucosal antibody response to polio vaccine in nasopharyngeal secretions was markedly blunted after tonsillectomy/adenoidectomy compared with the response before surgery, and in 1971 he showed that combined tonsillectomy and adenoidectomy in children reduced the level of IgA antibody to poliovirus three- to four-fold in their nasopharyngeal secretions and delayed or canceled their local immune response to subsequent live oral polio vaccine.

An increase in Hodgkin’s lymphoma in tonsillectomized children in New York was reported in 1971.\textsuperscript{28} However, Langman and Kaplan\textsuperscript{29} reviewed the evidence associating tonsillectomy and Hodgkin’s lymphoma, and reported that Hodgkin’s lymphoma and tonsillectomy may share certain epidemiologic features, such as higher socioeconomic status, but there is no evidence that tonsillectomy causes
Hodgkin’s lymphoma. Scadding\textsuperscript{30} considers that the association of tonsillectomy and Hodgkin’s lymphoma could be more related to chronic tonsillitis, than to tonsillectomy. Vestergaard\textsuperscript{31} found that tonsillectomy was associated with a significantly increased risk of Hodgkin’s lymphoma among persons who were younger than 15 years, whereas persons aged 15 years or older had a significantly increased Hodgkin’s lymphoma risk at 1-4 years after tonsillitis. As tonsillitis most often precedes tonsillectomy it cannot be ruled out that severe tonsillitis, rather than removal of the tonsils, could be associated with increased Hodgkin’s lymphoma risk.\textsuperscript{31}

Several studies attribute alterations of immunoglobulin concentrations in serum following tonsillectomy. Veltri \textit{et al.}\textsuperscript{34} reported statistically significant decreases, though within normal range, in IgG levels, whereas IgA, IgM, and IgD remained unaltered. Lal \textit{et al.}\textsuperscript{32} also found reduced IgG levels, although not lower than controls ($p<0.01$). Kerr \textit{et al.}\textsuperscript{35} performed measurements of serum immunoglobulin levels in 96 children undergoing tonsillectomy for recurrent sore throats. They found levels of IgA, IgM and IgG similar to those in healthy children, and $7-29\%$ of the children had ‘low’ IgA serum levels. Jeschke and Stroder\textsuperscript{36} performed tonsillectomy in children and found that their serum IgG and salivary IgA levels decreased for up to 3 years. D’Amelio \textit{et al.}\textsuperscript{37} observed no salivary IgA reduction, but decreased serum IgA, in previously tonsillectomized adults (16-24 years old).

Prusek \textit{et al.}\textsuperscript{38} found normal values of T and B lymphocytes in children 4-10 months after tonsillectomy for chronic tonsillitis. Lal \textit{et al.}\textsuperscript{32} reported that the mean pre-operative level of serum IgG and IgA were significantly higher in patients with chronic tonsillitis than in the control group; the values dropped significantly 1 month after tonsillectomy and the post-operative values were comparable to those of the control group. Cantani \textit{et al.}\textsuperscript{39} found that salivary IgA as well as serum IgA were significantly reduced 4 months after adenotonsillectomy in children. Sainz \textit{et al.}\textsuperscript{40} measured the levels of IgG, IgM and IgA in patients with chronic tonsillitis and reported that increased pre-operative immunoglobulin levels were significantly decreased after surgery and there were no change in the levels of serum complement fractions C3 and C4 before and after tonsillectomy.

Friday \textit{et al.}\textsuperscript{41} in 268 children age 1-16 years evaluated before and after tonsillectomy, adenoidectomy or adenotonsillectomy the serum levels of IgA, IgG and IgM. They found a significantly lower IgG level in the adenotonsillectomy group than in the control group, but no relation between immunoglobulin level changes and the occurrence of throat infections during a follow-up of 16-30 months.

Various investigators have reported high serum levels of IgG and IgA in patients with chronic tonsillitis. Sennaroglu \textit{et al.}\textsuperscript{42} reported that tonsillectomy improves the abnormal neutrophil chemotaxis and has a positive effect on the immune system of patients with chronic tonsillitis. El-Ashmawy \textit{et al.}\textsuperscript{43} reported that the levels of IgG and IgA in serums of patients with chronic tonsillitis were increased, while IgM levels were not significantly altered, and that 2 months after tonsillectomy, these high levels of serum IgG and IgA were significantly reduced. Kaygusuz \textit{et al.}\textsuperscript{44} showed that IgA, IgG and IgM levels, complement fractions
(C3, C4), cytotoxic T lymphocytes and activated B lymphocytes are increased in patients with chronic tonsillitis as a response to chronic bacterial stimulus. Tonsillectomy restores these parameters by removal of bacterial stimulus without negatively affecting the patient’s immune functions.

Popp et al.\textsuperscript{45} reported that removal of the tonsils did not inhibit the development of the immune system in 160 children 0.5-11 years after tonsillectomy, were compared with 302 age-matched non-tonsillectomized children. In tonsillectomized children the incidence of infections of the upper respiratory tract was not increased compared to the control group. The immunoglobulin levels were within the normal range, however the IgA levels in the tonsillectomized children became lower while IgM and IgG did not change significantly. Zielnik-Jurkiewicz et al.\textsuperscript{46} observed statistically significant higher serum levels of IgA, IgM and IgA 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.

Van den Akker et al.\textsuperscript{47} in a total of 300 children aged 2 to 8 years, with symptoms of recurrent throat infections or tonsillar hypertrophy, were randomly assigned to either adenotonsillectomy or watchful waiting. Serum samples were collected at baseline and at 1-year follow-up. IgG1 and IgG2 levels decreased but remained within the reference range for age in both study arms. IgM and IgA levels decreased as well but remained elevated. The IgA level in the adenotonsillectomy group decreased in significantly greater degree compared with the watchful waiting group, but this difference disappeared in cases where children experienced frequent upper respiratory tract infections. In general, no relation between immunoglobulin levels and the number of throat infections or upper respiratory tract infections at 1-year follow-up was found. This finding indicates that the remaining mucosa-associated lymphoid tissue can compensate for the loss of tonsil and adenoid tissue.

Amintehran et al\textsuperscript{48} in 25 children booked for adenotonsillectomy did not find a significant difference in the pre and postoperative values of serum IgM IgA, IgG and IgA. There was a small postoperative elevation of IgG subclasses (IgG1, IgG2, IgG3 and IgG4). Santos et al \textsuperscript{49} studied the short and long-term impact of tonsillectomy upon the cellular and humoral immunity of children. This longitudinal prospective study included 29 children referred to adenotonsillectomy for adenotonsillar hypertrophy. Serum IgA, IgM, and IgG and lymphocyte counts were analyzed at three points in time: before surgery, 1-2 months after surgery, and 12-14 months after surgery. TCD4+ cell counts were significantly increased shortly after surgery, and IgA and IgG values were significantly reduced in the long run, but were within normal ranges for this age group.

Bitar et al\textsuperscript{50} in a review paper of the articles published between the years 1971 and 2009, and the author’s unpublished data of 2010, included a total of 1665 patients, with their age ranging from 1.5 years to 30 years. Twenty one studies that included 943 patients found that adenotonsillectomy does not have a negative effect on the immune system, while six studies that included 722 patients showed that adenotonsillectomy has a negative effect on the immune system. All the studies that showed a negative effect on the immune system were conducted prior to 1997.
Conclusion

The majority of the early studies did not evaluate the immune system preoperatively and did not include a nonsurgical control group. The majority reported a decrease secretory IgA, IgG and IgM after adenotonsillectomy. More recent publications reported transient reduced antibody production, though within normal range, and without an increment of upper airway infections. There are no studies to date that demonstrate a significant clinical impact of tonsillectomy on the immune system.

References


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