

# Short- and long-term impacts of adenoidectomy with/without tonsillectomy on immune function of young children <3 years of age

## A cohort study

Yuyan Yan, MD\*, Yingluan Song, MD, Yingying Liu, MD, Jinzhu Su, MD, Li Cui, MD, Juan Wang, MD, Jiangqiao Geng, MD, Xiaofeng Liu, MD, Yanan Shi, MD, Shan Quan, MD, Aiping Hang, MD, Lujie Zuo, MD

### Abstract

To investigate the short- and long-term impacts of adenoidectomy with/without tonsillectomy on the immune functions of young children < 3 years of age.

This longitudinal prospective study included 40 pediatric patients (age <3 y) undergoing adenoidectomy with/without tonsillectomy for snoring and sleep apnea. Serum immunoglobulin IgA, IgG, IgM, complement C3, and C4 levels were measured for the status of humoral immunity; CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, and CD3+CD4+CD8+ T cells were measured for the status of cellular immunity. Blood samples were taken at 3 time points: before surgery, 1 month after surgery (short-term), and 3 months after surgery (long-term). All patients were assessed for short-term outcome at 1-month postoperation, but only 30 patients were followed at 3 months after surgery. The incidence of recurrent respiratory tract infections and other immune-related conditions were recorded at each follow-up.

The levels of IgA significantly decreased from the preoperative level at 1-month follow-up ( $P < .05$ ), but still within normal range. No significant changes were found in the levels of IgA, IgG, IgM, C3, C4, CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, and CD3+CD4+CD8+ T cell at 3-month follow-up in comparison with preoperative levels. There was also no episode of recurrent respiratory tract infection and other immune-deficiency conditions.

Adenoidectomy with/without tonsillectomy may result in a reduction in individual antibodies in children <3 years of age, but did not show negative impacts on their immune functions. Also, the surgery does not lead to the increased risk of upper respiratory tract infection in these children.

**Abbreviations:** CD = cluster of differentiation, GCs = germinal centers, Ig = immune globulin, SD = standard deviation, SPSS = statistic package for social science, US = United States.

**Keywords:** adenoidectomy, immune functions, tonsillectomy, young children

## 1. Introduction

Adenoids and tonsils are important organs of human immune system that protect the body from pathogens invading the upper

respiratory tract,<sup>[1]</sup> especially in young children. As the largest components of Waldeyer ring,<sup>[2-4]</sup> they are secondary lymphoid organs, and part of the mucosa-associated lymphoid tissue.<sup>[5,6]</sup>

Adenoids and tonsils play an important role in both humoral and cellular immunity.<sup>[7,8]</sup> They consist of 4 specialized lymphoid compartments participating in the immune function of the organs, namely the reticular crypt epithelium, the extrafollicular area, the mantle zones of lymphoid follicles, and the follicular germinal centers (GCs).<sup>[9,10]</sup> Leukocytes in the surface secretion of adenoids can secrete immunoglobulin IgA, IgG, and IgM, which are essential in antigen phagocytosis. The surface secretion of adenoids also contains a large number of activated T cells, which participate in the cellular immunity. The tonsils contain both B and T lymphocytes, involved in both humoral and cellular immunity.

Hypertrophy of adenoid and tonsil could cause sleep snoring, mouth breathing, apnea, restlessness, anorexia, and other diseases, seriously affecting the growth, development, and quality of life in children. Many studies have shown that adenoidectomy with/without tonsillectomy could effectively improve the upper airway obstruction in pediatric patients and lead to improved sleep quality, better growth, and weight gain, resolution of nocturnal enuresis and behavior and neurocognitive disorders, and subsequently improved quality of life.<sup>[11-15]</sup> To date, adenotonsillectomy has been commonly performed in

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Department of Otolaryngology, Head and Neck Surgery, Children's Hospital of Hebei Province Affiliated to Hebei Medical University, Shijiazhuang city, Hebei Province, China.

\* Correspondence: Yuyan Yan, Department of Otolaryngology, Head and Neck Surgery, Children's Hospital of Hebei Province Affiliated to Hebei Medical University, 133# Jianhuanan Street, 050030 Shijiazhuang city, Hebei Province, China (e-mail: yyy20181979@sina.com).

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children.<sup>[16,17]</sup> The available evidence suggests that adenotonsillectomy is effective for sleep-disordered breathing and severe recurrent throat infections.<sup>[18–21]</sup> But given the important role of adenoids and tonsils in human immune system, whether adenotonsillectomy could exert negative effects on children's immune function is still controversial. In 2003, Kaygusuz et al<sup>[8]</sup> reported that humoral and cellular immunity of patients undergoing tonsillectomy was decreased in the early period and came back to normal later. In 2006, Faramarzi et al<sup>[5]</sup> reported that 2 weeks after adenotonsillectomy, the serum IgA level was increased, while the T lymphocyte count was decreased when compared with baseline, but both measurements returned to the normal levels 8 months after the surgery. Most of these studies reported no obvious effect on the children's immune function and risk of immune deficiency disorders. The age of study population in these researches ranged from 1.5 to 18-years old. Till now, there is no research only focused on young children <3 years old with regards to the effects of adenotonsillectomy.

In recent years, due to environmental pollution and increased incidence of allergic reactions, more and more young children (<3-years old) suffer from sleep apnea-related to adenoid or tonsillar hypertrophy. 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. The purpose of this study is to investigate the short- and long-term impacts of adenoidectomy with/without tonsillectomy on immune functions of young children <3 years of age.

## 2. Materials and methods

### 2.1. Patients population

The study was approved by the Ethical Committee of the Children's hospital of Hebei Province in China. The parents or guardians of the subjects were informed about the purpose and design of this study and the possible risks associated with participating in the study, and signed an Informed Consent form prior to enrollment.

This cohort study took the preoperative immune status of children as the control group, and their postoperative immune status as the case group. The inclusion criteria were: children (<3 years age); need to undertake adenoidectomy with/without tonsillectomy due to the hypertrophy of adenoids and/or tonsils that caused the upper airway obstruction. The main symptoms included snore, buccal respiration, and apnea; no immune deficiency or related diseases. The exclusion criteria were: patients who have personal and family history of immune deficiency or diseases with known immune-related etiology and who have signs/symptoms of upper respiratory tract infection.

The surgical procedure was performed using classical approach. Children lied on the back, under general anesthesia the mouth was opened using mouth opener to adequately expose the tonsils. The procedure of a Coblation tonsillectomy was followed and the palatal pharyngeal arch mucosa was cut open using low temperature plasma. After the tonsil capsule was exposed, the cryogenic plasma knife was used to remove the tonsils and stanch the bleeding. Similarly, adenoidectomy was performed by pulling up the soft palate, exposing the adenoids, and resecting the hypertrophic adenoids using low-temperature plasma to clear the posterior nostril.

### 2.2. Specimen collection

Blood samples were collected at 3 time points: 24 to 48 hours prior to adenoidectomy with/without tonsillectomy (preoperative), 1 month after surgery, 3 months after surgery. Approximately 4 mL of venous blood was drawn each time to examine the status of humoral immunity: serum levels of immunoglobulins A, G, and M (IgA, IgG, IgM) and complements C3 and C4; and cellular immunity: percentage of CD3+ (T helper), CD4+, CD8+ (T cytotoxic), CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, and CD3+CD4+CD8+ T cells.

### 2.3. Experimental method

The serum levels of IgA, IgG, IgM, C3, and C4 were determined using the standard turbidimetric technique with Automatic biochemical analyzer (Beckman Coulter Inc, Brea, CA, DXC600). Lymphocyte subtypes (CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, and CD3+CD4+CD8+ T cell) were measured by flow cytometry using Flow cytometer (Beckman Coulter Inc, Brea, CA, CYTOMICS FC 500). The tests of humoral immunity and cytokines were performed at the Clinical Laboratory and the Children's hospital of Hebei Province. The specific methods are as follows: humoral immunity was tested using the Automatic biochemical analyzer (Beckman Coulter Inc, Brea, CA, DXC600). The results were obtained in 2 hours. The peripheral blood T lymphocyte subsets were detected using the Flow cytometer of Beckman Company and its matching lymphocyte subsets detection kit. The procedure was as follows: 100  $\mu$ L peripheral venous blood with EDTA anticoagulant was added into 2 tubes respectively. Antibodies for CD45+CD4+CD8+CD3+ (Beckman Coulter Inc, Brea, CA) and CD45+CD19+CD56+CD3+ (Beckman Coulter Inc, Brea, CA) were added into the 2 tubes respectively, followed by gentle mix and darkroom incubation. Hemolysin (Beckman Coulter Inc, Brea, CA) was then added to lyse red blood cells, followed by gentle mix and incubation again in the darkroom. After centrifugation and washing, results of peripheral blood T lymphocyte subsets, B lymphocytes, and NK cells were analyzed using flow cytometer (Beckman Coulter Inc, Brea, CA, CYTOMICS FC 500).

At each follow-up, the information of recurrent respiratory tract infections and immune deficiency conditions were also collected.

### 2.4. Statistical analysis

SPSS version 16.0 (Chicago, IL) was used for the statistical analysis. Continuous data were summarized as mean  $\pm$  SD. The comparison between pre- and postoperative measurements was performed using paired Student *t* test. *P* < .05 was defined to statistically significant.

## 3. Results

A total of 40 patients (18 girls and 22 boys, age ranged from 1 year 3 months to 2 years 11 months, with a mean of  $2.3 \pm 0.4$  years) from the Otolaryngology Department of Children's hospital of Hebei Province were enrolled into the study. The study period was from November 2016 through August 2018. Three months after operation, 10 children were lost from the follow-up and 30 were followed for the long-term outcome (12

**Table 1**  
**Humoral and cellular immunity markers in children before the surgery (baseline) and 1 mo after surgery (n=40).**

Parameters	Before surgery	1 mo after surgery	P value
IgA	0.78 ± 0.51	0.65 ± 0.39	.023
IgG	7.70 ± 1.70	7.26 ± 1.47	.082
IgM	0.97 ± 0.46	1.01 ± 0.47	.304
C3	1.18 ± 0.20	1.19 ± 0.16	.751
C4	0.24 ± 0.12	0.23 ± 0.08	.361
CD3+	66.40 ± 6.9	67.40 ± 6.52	.279
CD4+	35.06 ± 6.83	35.40 ± 7.52	.721
CD8+	24.22 ± 5.18	24.63 ± 5.10	.447
CD19+	21.34 ± 5.77	21.37 ± 5.15	.97
CD56+	7.43 ± 4.04	7.27 ± 3.50	.837
CD4/CD8	1.52 ± 0.50	1.53 ± 0.53	.855
CD3+CD4-CD8-	7.04 ± 3.06	7.35 ± 3.2	.329
CD3+CD4+CD8+	0.10 ± 0.09	0.14 ± 0.10	.053

CD = cluster of differentiation.  
 Values are summarized as mean ± standard deviation.  
 P < .05 (Student t test for paired samples): comparison between baseline and 1 mo after surgery.

girls and 18 boys, age from 1 year 8 months to 2 years 11 months, mean age 2.3 ± 0.5 years).

Table 1 shows the data of IgA, IgG, IgM, C3, C4, and CD3+ (T helper cells), CD4+, CD8+ (cytotoxic T cells), CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, CD3+CD4+CD8+ T cells counts, at baseline and 1 month after the surgery. IgA level was significantly decreased 1 month after the surgery, when compared with the preoperative level (P < .05), while still in normal range (0.21–1.45 g/L). The results of other immunoglobulins (IgG, IgM), complements (C3, C4), and CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, CD3+CD4+CD8+ T cells showed no significant changes from baseline.

Table 2 shows the results of IgA, IgG, IgM, C3, C4, and CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, CD3+CD4+CD8+ T cells counts, at baseline and 3 months after the surgery. There were no significant differences for any humoral and cellular immunity markers. In addition, there was no recurrent respiratory tract infection and immune deficiency condition reported from these patients during the entire follow-up.

**Table 2**  
**Humoral and cellular immunity markers in children before the surgery (baseline) and 3 mo after surgery (n=30).**

Parameters	Before surgery	3 mo after surgery	P value
IgA	0.71 ± 0.13	0.63 ± 0.16	.210
IgG	7.27 ± 2.00	6.48 ± 1.23	.196
IgM	1.09 ± 0.64	1.04 ± 0.65	.338
C3	1.15 ± 0.21	1.14 ± 0.18	.858
C4	0.22 ± 0.12	0.21 ± 0.10	.808
CD3+	66.11 ± 7.91	64.99 ± 8.43	.345
CD4+	34.04 ± 8.16	35.25 ± 7.86	.268
CD8+	24.15 ± 3.53	22.39 ± 3.28	.069
CD19+	22.20 ± 6.76	23.32 ± 6.36	.543
CD56+	7.09 ± 3.99	7.01 ± 4.22	.947
CD4/CD8	1.44 ± 0.37	1.57 ± 0.37	.152
CD3+CD4-CD8-	7.82 ± 4.07	7.2 ± 2.87	.512
CD3+CD4+CD8+	0.15 ± 0.08	0.12 ± 0.12	.496

Ig = immune globulin, CD = cluster of differentiation.  
 Values are summarized as mean ± standard deviation.  
 P value (Student t test for paired samples): comparison between baseline and 3 mo after surgery.

#### 4. Discussion

In this study, we observed that serum IgA level was affected the most after adenoidectomy with/without tonsillectomy in the short term, showing a significant reduction from the baseline 1 month after the surgery, while other humoral and cellular immunity markers did not show significant changes. However, 3 months after the surgery, all humoral and cellular immunity markers, including IgA, showed no significant differences from the preoperative levels. Also, despite the reduction at 1-month postoperative follow-up, serum IgA level was still in normal range, and there was no recurrent respiratory tract infection and immune deficiency condition reported during the follow-up. These results suggested that humoral immunity may be the main immune response at nasopharynx and oropharynx, and IgA may be the most important marker of adenoid and tonsil in the immune response of nasopharynx and oropharynx.

Adenoids and tonsils are important immune organs. Located at the entrance of the upper respiratory and gastrointestinal tract, they play a key role in initiating both humoral and cellular immunity against various pathogens that enter the body through mouth and nose. Some literatures reported that tonsils contain B cells which, in response to antigens, can develop into plasma cells and generate polymeric IgA, resulting in systemic immunity and mucosal immunity.<sup>[10]</sup> Researches also reported that adenoidal lymphocytes can synthesize Ig spontaneously in culture without the presence of any mitogens and antigens and contribute directly to regional surface protection by providing local SIgA. SIgA may then participate in the local immune response and play an important role in upper respiratory tract immunological defense mechanisms. First, SIgA may prevent pathogen adhesion to the mucosal epithelia, thereby blocking dissemination and further infection. Second, IgA can bind to newly synthesized viral proteins within the epithelial cells to prevent viral assembly. Third, SIgA may block some antigens, preventing an increased antigen uptake in the nasal epithelium and subsequent allergic reaction.<sup>[22]</sup> Therefore, IgA is an important immune factor in adenoids and tonsils. Our results again demonstrated the importance of IgA in the immune function of adenoids and tonsils, which may be the reason why adenoidectomy with/without tonsillectomy resulted in a short-term decrease in serum IgA level. However, due to the body's compensatory function, this did not lead to reduced immune function or deficiency in young children <3 years of age, and IgA titer is still within the normal range. Moreover, it was restored to the preoperative level in 3 months after the surgery. The other immune factors of adenoid and tonsil are relatively limited and did not show significant change after the surgery, no matter at 1 or 3-month follow-up.

A few researches on immune impact of adenotonsillectomy in children have been reported. Böck et al<sup>[23]</sup> reported that the levels of IgA were decreased about 6.6 ± 2.1 years after tonsillectomy, while CD21+ and CD4+ levels were increased from preoperative levels, through researching on hundreds of children 4 to 8 years age. Ikinçiogullari et al<sup>[2]</sup> studied 15 children aged 4 to 10 years old, following for 1 to 1.5 months, and found no significant alteration in serum IgG, IgA, and IgM levels, while CD19+ decreased and CD3+, CD8+ levels significantly increased from the preoperative levels. Kaygusuz et al<sup>[8]</sup> indicated that 1 month after tonsillectomy, the level of CD4+ was significantly increased while the level of CD25+ was reduced, and immunoglobulins as well as C3 and C4 were decreased after tonsillectomy. Amorós Sebastiá et al<sup>[4]</sup> studied 5 to 9 years old children and found that

serum IgG levels dropped after adenoidectomy, but partially only recovered 4 months later. IgA dropped less significantly and IgM did not change. No immunoglobulins studies dropped below the normal level. Faramarzi et al<sup>[5]</sup> reported that the serum IgA level rise few weeks after the surgery in children of 2 to 15 years old, and no significant changes were found for IgM, IgG, and lymphocyte counts after adenotonsillectomy. Kaygusuz et al<sup>[24]</sup> also found that tonsillectomy did not compromise the immune function in 20 children aged 2 to 15 years old. Nasrin et al<sup>[25]</sup> indicated that 1 month after tonsillectomy, the level of IgG was slightly decreased and IgM and IgA were increased compared with preoperative level but there was no significant difference. Santos et al<sup>[6]</sup> found that adenotonsillectomy does not pose negative short-term (1–2 months after surgery) or long-term (12–14 months after surgery) impacts on the cellular and humoral immunity of children submitted to the procedure. Some studies demonstrated that tonsillectomy decreased the levels of serum IgA, especially in children, several months or years after operation, but do not cause significant immune deficiency and increase incidence of immunomodulated diseases, such as infections of the upper respiratory tract.<sup>[26]</sup> It can be seen from these study results that there is no uniform research program and route about the effect of adenoidectomy and tonsillectomy on immunity in children. The number of subjects, selection criteria (age of subjects, etc) and follow-up period varied. Although the immune factors studied are similar, the results are inconsistent. In the end, current evidences fail to show that the removal of the adenoids and tonsils could lead to compromised immunity.<sup>[19,27]</sup>

Although many papers have been published within the last 3 decades on the immune impacts of adenotonsillectomy in pediatric patients, and some of the previously reported subjects involved infants, no research has been reported that focus on young children <3 years of age, a special age group. This is the largest difference between this study and previous reports. Children's immune system is gradually developing with age, the immune factors and their functions in the body's immune response also change over time. No studies can confirm that age has no effect on these study results. So, we cannot infer the effect of adenoidectomy with/without tonsillectomy on the immune function of this special group of children simply from these studies. Due to their young age, whether adenoidectomy with/without tonsillectomy can reduce their immune function, or even result in immunodeficiency, has been the focused interest of their parents and treating clinicians. Especially, because of the environmental pollution or other influencing factors, more and more children are suffering from the conditions that require adenoidectomy with/without tonsillectomy, it becomes urgent to understand the effect of this surgery on the immune function of these young children.

Here, we focused our study on young children < 3 years of age. Because adenoids and tonsils play an important role in both humoral immunity and cellular immunity, considering factors reported in previous researches, our study included IgA, IgG, IgM, C3, C4 as humoral immune factors and CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, CD56+, CD3+CD4-CD8-, and CD3+CD4+CD8+ T cells as cellular immune factors. The immune factors measured in this study are more comprehensive than previous studies. To understand the short and long impacts of adenoidectomy with/without tonsillectomy on young children (<3 years), consistent with the literature, we chose 1 month after surgery to assess the short-term impact, and 3 months after surgery as the long impact.

The limitations of this study are relatively limited number of subjects and length of follow-up. This research mainly focused on young children <3 years of age, an understudied population with regards to the effect of adenotonsillectomy. Due to various reasons, the incidence of sleep snoring and apnea in children due to adenoid and tonsil hypertrophy is on the rise. Adenoidectomy and tonsillectomy are the most effective approaches to relieve their symptoms. But whether the surgery will have a negative impact on their immune function is of a great concern of clinicians and their families. This study provides further information to dispel the scruple, help promote the adoption of clinical surgery, and provide a reference for further research in the future.

In conclusion, adenoidectomy with/without tonsillectomy could 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.

### Author contributions

**Conceptualization:** Yuyan Yan, Jinzhu Su.

**Data curation:** Yuyan Yan.

**Formal analysis:** Yuyan Yan.

**Investigation:** Yuyan Yan, Yingying Liu, Li Cui, Jiangqiao Geng, Xiaofeng Liu, Yanan Shi, Shan Quan, Aiping Hang, Lujie Zuo.

**Methodology:** Yuyan Yan.

**Project administration:** Yuyan Yan.

**Resources:** Yuyan Yan, Yingluan Song.

**Software:** Yuyan Yan, Juan Wang.

**Supervision:** Yingluan Song.

**Validation:** Yingluan Song.

**Writing – original draft:** Yuyan Yan.

**Writing – review & editing:** Yuyan Yan.

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