Early Stage Impacts of Adenoidectomy With/Without Tonsillectomy on Immune Functions of Children Aged Less Than Three Years

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Objective: To evaluate the early stage effects of adenoidectomy with/without tonsillectomy on immune functions in children aged <3 years.

Methods: Twenty-four children aged <3 years underwent adenoidectomy with/without tonsillectomy were included. The levels of IgG, IgA, IgM, C3, and C4 were measured for humoral immunity, and the levels of CD3⁺, CD4⁺, CD8⁺, CD19⁺, CD56⁺, CD3⁺CD4⁺CD8⁺, and CD3⁺CD4⁺CD8⁺ T cells were measured for cellular immunity before and 2 weeks after the operation.

Results: The postoperative levels of IgA, IgG, IgM, C3, and C4 were significantly increased compared with the preoperative levels ($P < 0.05$). The levels of CD3⁺, CD4⁺, CD8⁺, CD56⁺, CD3⁺CD4⁺CD8⁺, and CD3⁺CD4⁺CD8⁺ T cells were increased, while the level of CD19⁺ was decreased in postoperative period compared with preoperative period. Compared with those in the control group, the preoperative levels of IgA, IgG, and CD3⁺CD4⁺CD8⁺ T cells were significantly increased ($P < 0.05$), while the levels of IgM, C3, C4 and CD3⁺, CD4⁺, CD8⁺, CD56⁺, and CD3⁺CD4⁺CD8⁺ T cells were not significantly changed. The postoperative levels of IgA, IgG, C3, C4, CD3⁺CD4⁺CD8⁺, and CD3⁺CD4⁺CD8⁺ T cells were significantly increased ($P < 0.05$), while the levels of IgM, CD3⁺, CD4⁺, CD8⁺, and CD56⁺ T cells were not significantly changed compared with those in the control group.

Conclusion: Adenoidectomy with/without tonsillectomy could stimulate the immune responses, which could avoid significant immune deficiency in a short period of time in children aged <3 years.

Keywords: adenoidectomy, tonsillectomy, humoral immunity, cellular immunity

Introduction

HUMAN ADENOIDS AND TONSILS are the Waldeyer's ring most important structures¹⁻³ and are secondary lymphoid organs, part of the mucosa-associated lymphoid tissue.^{4,5} They are considered as the host's first line of defense against respiratory infections due to their location at the entrance of the respiratory and digestive systems.^{5,6} They are exposed to a wide number and variety of microbes, environmental pollutants, and food antigens and involved in both local immunity and immune surveillance for the development of immune defense mechanisms. Some studies have reported that atopy and passive smoke may significantly affect immune responses, mainly in children.^{7,8}

The human immune responses are divided into 2 types: (1) humoral immune response, which is dependent on B cells, plasma cells, and antibodies and (2) cellular immune

response, which is dependent on T cells and cytokines. Adenoids and tonsils are known to be immunologically reactive lymphoid organs, which manifest specific antibodies and B and T cell activity in response to a variety of antigens through carrying out the functions of humoral and cellular immunity.^{9,10}

Leukocyte in the surface secretion of adenoids can produce and secrete immunoglobulin (IgA, IgG, and IgM), that plays an important role in antigen phagocytosis. The surface secretion of adenoids contains a large number of activated T cells, which participate in the cellular immunity. The tonsils B and T lymphocytes, particularly the tonsils B lymphocytes, play a dual role both in humoral immunity and cellular immunity. To a certain extent, the serum levels of IgA, IgG, IgM, C3, and C4 can reflect the humoral immune status. Furthermore, when immune function decreased, it is usually manifested a decline of CD4⁺ T cells, an increase of CD8⁺ T cells, or a decline of CD4⁺/CD8⁺.⁴

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Adenoid hypertrophy can result in various symptoms, such as mouth breathing, nasal obstruction, speech abnormalities, and snoring.⁵ Furthermore, tonsillar diseases are among the most commonly encountered health-related problems in children.⁴ Previously, some studies have shown that adenoidectomy with or without tonsillectomy as the most frequently performed surgical procedures in children, could improve sleep and life quality, produce clearer and better phonation, achieve more significant growth and weight, resolve nocturnal enuresis, behavior, and neurocognitive disorders.^{4,11–15} However, the possible effects of adenoidectomy with or without tonsillectomy on the patients' immunological integrity remain controversial.⁴

Because of the incomplete development of the systemic immune organs in childhood, the tonsil and adenoid immune activities are more important in children than in adults.¹⁴ Previously, some studies had reported the effect of adenoidectomy/tonsillectomy on immunity of children.^{4,5,9,10,16} However, those studies mainly focused on the immunity impacts of adenotonsillectomy/tonsillectomy on the children, whose mean age is >3 years. The purpose of this study was to investigate the possible early stage impacts of adenoidectomy with/without tonsillectomy on the cellular and humoral immunity of children aged <3 years.

Patients and Methods

Patients

This study has been approved by the Ethical Committee of Children's Hospital of Hebei Province (No. 2016015). Written informed consent was obtained from the parents or guardians of the patients. The present study was performed on 24 children (<3 years old, 5 girls and 19 boys aged 1.17–2.92 years, and mean age 2.40 ± 0.41 years), who underwent elective adenoidectomy with/without tonsillectomy, at the ENT clinic of our hospital from November 2016 to August 2017.

The indications for adenoidectomy with/without tonsillectomy were as follows: upper airway obstruction resulting from the hypertrophy of adenoids with/without hypertrophy of tonsils and presence of the main obstructive symptoms, such as snore buccal respiration and short of breath. Patients with personal or family history of immune deficiency, or disease related to the immune etiology, were excluded.

All patients received general anesthesia that was induced through sufentanil (0.5 mg/kg) and midazolam (0.05 mg/kg), and maintained through remifentanyl (0.5 mg/kg/min). The surgical procedure was performed in classical style. All the surgeries were conducted by a same surgeon. Under general anesthesia, palatine tonsils mucosa was removed with a sickle knife, then the tonsils was fully peeled off and removed. The adenoids were excised with a microdebrider under indirect laryngoscopy.

The control group comprised 24 children (<3 years old, 6 girls and 18 boys, aged 1.42–2.92 years, and mean age 2.50 ± 0.41 years) without history of recurrent upper tract infections and hypertrophy of tonsils and adenoids. Among the 24 children, 6 cases were ear mass, 5 cases were neck mass, 3 cases were accessory auricles, and 10 cases were preauricular fistula. All the blood samples of the control group were extracted before operation.

Immunologic analysis

Blood samples were taken 24–48 h before adenoidectomy with/without tonsillectomy (preoperative) and 2 weeks after surgery (postoperative). A volume of 4 mL of venous blood was obtained. Following examinations were carried out for all children: serum levels of IgA, IgG, and IgM; complements C3 and C4; and percentage of CD3⁺ (T helper), CD4⁺, CD8⁺ (T cytotoxic), CD19⁺, CD56⁺, CD3⁺ CD4⁺ CD8⁺, and CD3⁺ CD4⁺ CD8⁺ T cells.

The serum levels of IgA, IgG, and IgM and complements C3 and C4 were determined by a standard turbidometric technique, using automatic biochemical analyzer (DXC 600; Beckman Coulter, Inc.). Lymphocyte subpopulations (CD3⁺, CD4⁺, CD8⁺, CD19⁺, CD56⁺, CD3⁺CD4⁺CD8⁺, and CD3⁺CD4⁺CD8⁺ T cell) levels were determined by flow cytometry (Cytomics FC-500; Beckman Coulter, Inc.).

Statistical analysis

All statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). Student's *t*-test for unpaired data was used to compare the results between the study group and the control groups. The comparison of preoperative and postoperative values was performed by Student's *t*-test. Values are given as means $\pm$ standard deviation. A *P* value of <0.05 was considered as significantly different.

Results

Serum levels of IgA, IgG, and IgM and complements C3 and C4

Table 1 shows the data obtained from the analysis of IgA, IgG, IgM, C3, and C4 values of the study group, before and after adenoidectomy with/without tonsillectomy, and those of the control group. There were statistically significant differences between preoperative and postoperative values of IgA, IgG, IgM, C3, and C4, which increased after surgery (2 weeks after adenoidectomy with/without tonsillectomy, *P* < 0.05). It was observed that the mean preoperative value of IgA was significantly higher than that in the control group (*P* < 0.05).

However, no significant difference was observed regarding the mean preoperative values of IgG and IgM and C3 and C4 before surgery compared with those in the control group (*P* > 0.05). After adenoidectomy with/without tonsillectomy, significant differences were observed between the levels of immunoglobulins (IgA, IgG, and IgM) and complements (C3 and C4) when compared with those of the control group, which increased after surgery (*P* < 0.05).

Cellular immune analysis in children

Table 2 shows the results obtained from the analysis of T lymphocytes in patients of the study group before and after adenoidectomy with/without tonsillectomy and those of the control group. Two weeks after adenoidectomy with/without tonsillectomy, we observed a slight decrease in mean value of CD19⁺ and slight increase in the mean values of CD3⁺, CD4⁺, CD8⁺, CD56⁺, CD3⁺CD4⁺CD8⁺, and CD3⁺CD4⁺CD8⁺ relative to the preoperative values, but all had no statistically significant difference (*P* > 0.05). Compared with those of the control group, the preoperative and postoperative mean value

TABLE 1. HUMORAL IMMUNE PARAMETERS IN CHILDREN, BEFORE AND AFTER SURGERY (2 WEEKS AFTER SURGERY)

Parameters	Preoperative (n = 24)	Postoperative (n=24)	Controls (n=24)	P value ^a	P value ^b	P value ^c
IgA	0.73 ± 0.32	0.88 ± 0.35	0.44 ± 0.31	0.009*	0.014*	<0.01
IgG	6.97 ± 2.17	8.06 ± 1.49	5.92 ± 1.61	0.024*	0.148	<0.01
IgM	1.03 ± 0.50	1.34 ± 0.12	0.91 ± 0.27	<0.01	0.353	0.021*
C3	1.05 ± 0.11	1.23 ± 0.14	1.08 ± 0.26	<0.01	0.730	<0.01
C4	0.17 ± 0.05	0.27 ± 0.14	0.15 ± 0.06	0.003*	0.290	<0.01

Values are given as mean ± SD.

^aComparison of preoperative with postoperative (paired Student's *t*-test).

^bComparison of preoperative values with controls (unpaired Student's *t*-test).

^cComparison of postoperative with controls (unpaired Student's *t*-test).

**P* < 0.05.

SD, standard deviation.

of CD3⁺CD4⁺CD8⁺ T lymphocytes was significantly higher (*P* < 0.05) and other T lymphocytes had no significant difference (*P* > 0.05).

Discussion

Hypertrophy of the adenoids and palatine tonsils is the second most common cause of upper respiratory tract obstruction and, consequently, sleep disorders, snoring, shortness of breath, and mouth breathing in children.¹⁷ Delayed diagnosis and treatment may result in serious consequences such as behavior alterations, low growth and lack of concentration, mastication, and swallowing disorder.⁵ Previously, the studies have described the benefits of adenoidectomy for children with sleep-related breathing disorders.^{12,18} Although adenoidectomy is a common surgical procedure,^{11,19} the possible immunological sequelae have not been fully investigated. Thus, the resection of adenoids and tonsils whether or how affect immune system remains a controversy.

Previously, some studies have reported the effect of adenotonsillectomy/tonsillectomy on immunity of children. Böck et al.²⁰ found that 160 children (6.6 ± 2.1 years) with tonsil adenoidal hypertrophy have significantly higher levels of CD21⁺ and CD4⁺ and lower levels of IgA after surgery compared with the preoperative levels. Ikinogullari et al.¹ reported that 15 children (4–10 years) had no significant alteration in serum IgG, IgA, and IgM levels, while CD19⁺ decreased and CD3⁺ and CD8⁺ increased at 1–1.5 months follow-up, when compared with preoperative levels.

Kaygusuz et al.^{10,16} reported that 1 month after tonsillectomy, the levels of IgA, IgG, and IgM were significantly

decreased compared with the control group, the numbers of CD8⁺, CD16⁺, CD25⁺, and CD65⁺ were significantly increased, and the numbers of CD4⁺ and CD19⁺ cells were significantly decreased compared with the control group. While 54 months after surgery, all those returned to normal as the control group. Amoros Sebastia et al.² presented a prospective study with 89 healthy children aged 4–10 years, measuring serum levels of IgG, IgA, and IgM before surgery and 1 and 4 months after adenoidectomy and/or tonsillectomy. They found that serum IgG levels dropped after surgery, but partially restored to normal 4 months later. IgA dropped less significantly and IgM did not change its levels.

None of the studied immunoglobulins dropped below the normal serum levels. Faramarzi et al.⁴ reported about 102 children (2–15 years) who underwent adenotonsillectomy. They found that the serum level of IgA increased a few weeks after surgery. There was no statistically significant difference in terms of the IgM and IgG levels and B lymphocyte count before and after surgery. However, there was a slight decrease in the T lymphocyte count in the early stage of postoperation, which returned to normal after 8 weeks. Nasrin et al.²¹ reported that in children aged >18 years, the level of IgG was slightly decreased, and the levels of IgM and IgA were increased 1 month after tonsillectomy compared with the preoperative values, although not statistically significant.

Santos et al.⁵ reported a prospective study of 29 children (mean age 4.5 years) with adenotonsillar hypertrophy who underwent adenotonsillectomy. The result showed that TCD4⁺ cell counts were significantly increased shortly after surgery. IgA and IgG values were significantly reduced in

TABLE 2. CELLULAR IMMUNE PARAMETERS IN CHILDREN, BEFORE AND AFTER SURGERY (2 WEEKS AFTER SURGERY)

Parameters	Preoperative (n=24)	Postoperative (n=24)	Controls (n=24)	P value ^a	P value ^b	P value ^c
CD3 ⁺	66.36 ± 5.52	68.06 ± 7.24	67.11 ± 8.14	0.115	0.747	0.723
CD4 ⁺	36.23 ± 6.91	36.32 ± 8.18	39.49 ± 6.26	0.959	0.178	0.246
CD8 ⁺	22.71 ± 4.67	24.38 ± 8.80	22.45 ± 5.63	0.222	0.883	0.494
CD19 ⁺	23.74 ± 6.47	22.32 ± 8.54	21.71 ± 7.45	0.387	0.404	0.834
CD56 ⁺	5.97 ± 2.94	6.56 ± 2.92	7.98 ± 4.34	0.380	0.108	0.255
CD4/CD8	1.69 ± 0.59	1.72 ± 0.71	1.88 ± 0.60	0.800	0.386	0.524
CD3 ⁺ CD4 ⁺ CD8 ⁺	7.33 ± 3.47	7.59 ± 3.62	4.98 ± 1.57	0.616	0.033*	0.023*
CD3 ⁺ CD4 ⁺ CD8 ⁺	0.11 ± 0.11	0.13 ± 0.17	0.18 ± 0.19	0.512	0.129	0.398

Values are given as mean ± SD.

^aComparison of preoperative with postoperative (paired Student's *t*-test).

^bComparison of preoperative values with controls (unpaired Student's *t*-test).

^cComparison of postoperative with controls (unpaired Student's *t*-test).

**P* < 0.05.

the long run, but were all within their normal ranges for patients at this age stage. Therefore, the current evidences failed to demonstrate whether removing the adenoids and tonsils could lead to compromised immunity.^{11,22}

During the last 3 decades, there have been many reports about the immune impacts of adenotonsillectomy/tonsillectomy on pediatric patients.^{11,12} As the above previous study reported, the serum levels and lymphocyte subpopulations levels mostly returned to the normal as the control group in the long-term follow-up.^{2,10,16} In addition, Rusetskii et al. reported that the application of adenoidectomy based on the proper medical indications has no adverse effects on the children's health conditions and the mechanisms of immune protection.²³

However, no relevant research has been conducted to investigate the effect of adenoidectomy with/without tonsillectomy simply on children aged <3 years. Therefore, in children of this age, whether adenoidectomy would reduce the children's immune function has attracted a great deal of attention from parents and the clinicians. In this study, we focused primarily on a special group of children who were <3 years old who underwent adenoidectomy with/without tonsillectomy and evaluated the serum levels and lymphocyte subpopulations levels of early stage.

We found that the levels of IgA, IgG, IgM, C3, and C4 were considerably increased after adenoidectomy with/without tonsillectomy. We also found that the level of CD19⁺ was decreased in the postoperative period although not significant. The ratio of CD4⁺/CD8⁺ and the levels of other T lymphocytes (CD3⁺, CD4⁺, CD8⁺, CD56⁺, CD3⁺CD4⁺CD8⁻, and CD3⁺CD4⁺CD8⁺) was slightly higher with no significance. These might be explained as immune response produced by B cells and T cells and activated by surgical stimulation of adenoidectomy and/or tonsillectomy and stimulation of antigens that accessed to the nasal cavity and mouth. This immune response resulted in the increase of serum levels of IgA, IgG, IgM, C3, and C4 and most T lymphocytes.

Compared with preoperative level, B cell reaction increased more obviously and had statistical significance. The T lymphocytes reaction was mild and not statistically significant compared with preoperative level. The results suggest that humoral immunity might be the main immune response in nasopharynx and oropharynx. In addition, we found that the preoperative level of IgA before surgery was significantly higher than that in the control group ($P < 0.05$), and the postoperative level of IgA was significantly higher than that of the preoperative value. These findings demonstrated the importance of IgA in the immune response of nasopharynx and oropharynx.

Several limitations of this study should be pointed out. First, this is a small sample size and single-center study. Second, the follow-up time was short because of the poor compliance of patients. We should prolong the follow-up time to determine whether the immune system can maintain its normal status in the long-term after surgery. Further large-size and multicenter studies are needed to confirm our conclusion. Despite these limitations, our results demonstrate that adenoidectomy with/without tonsillectomy could stimulate the immune response, which could avoid significant immune deficiency in a short period of time in children aged <3 years.

Author Disclosure Statement

No competing financial interests exist.

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