Long-term effects of pediatric adenotonsillectomy on serum immunoglobulin levels: results of a randomized controlled trial

Emma H. van den Akker, MD, PhD*; Elisabeth A. M. Sanders, MD, PhD†; Birgit K. van Staaij, MD, PhD‡; Ger T. Rijkers, PhD†; Maroeska M. Rovers, PhD*†‡; Arno W. Hoes, MD, PhD‡; and Anne G. M. Schilder, MD, PhD*

Background: It remains controversial whether pediatric adenotonsillectomy ultimately results in decreased serum immunoglobulin levels and if so whether such a decrease is associated with increased susceptibility to upper respiratory tract infections (URIs).

Objective: To evaluate changes in serum immunoglobulin levels in relation to occurrence of URIs in children participating in a randomized controlled trial on the effectiveness of adenotonsillectomy.

Methods: 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 (WW). Serum samples were collected at baseline and at 1-year follow-up. Occurrence of throat infections and other URIs during first-year follow-up was recorded in a diary by the child's parents.

Results: Paired serum samples were available for 123 children (63 in the adenotonsillectomy group and 60 in the WW group). 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 WW group, but this difference disappeared in cases where children experienced frequent URIs. In general, no relation between immunoglobulin levels and the number of throat infections or URIs at 1-year follow-up was found.

Conclusions: Immunoglobulin levels of children undergoing adenotonsillectomy decreased from elevated to slightly elevated or reference values for age during 1-year follow-up irrespective of treatment (adenotonsillectomy or WW). IgA showed a greater decrease in the adenotonsillectomy group but rose to levels comparable with the WW group in cases of frequent URIs. This finding indicates that the remaining mucosa-associated lymphoid tissue can compensate for the loss of tonsil and adenoid tissue.

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INTRODUCTION

The tonsils and adenoid are part of the Waldeyer ring and are important elements in the defense against airborne and alimentary organisms. They play an important immune-inductive role as components of mucosa-associated lymphoid tissue (MALT).[1] Tonsils contain B cells that, in response to antigens, differentiate to plasma cells and generate polymeric IgA, resulting in systemic immunity and mucosal immunity.[2]

Adenotonsillectomy is one of the most frequently performed surgical procedures in children. Nevertheless, the ultimate effects of the procedure are still uncertain.[3–5] It has been hypothesized that the removal of the tonsils and adenoid in young children may cause a delay in development and a limited and less differentiated immune response.[1,6] This, in turn, might increase children's susceptibility to respiratory infections rather than lead to the intended decrease of infections by surgical removal of the infection focus. With respect to humoral immunity, several studies have reported a decrease in serum immunoglobulin levels after adenotonsillectomy.[7–15] The relevance of these findings is however questionable, since most of these studies did not include a randomly allocated nonsurgical control group and no associated occurrence of respiratory infections could be found.[7,9,11,12]

The present study aims to answer the following questions: (1) Do immunoglobulin levels change after adenotonsillectomy in children, and, if so, are these changes different from those in children managed nonsurgically for the same tonsillar complaints? (2) Are changes in serum immunoglobulin levels related to the occurrence of throat infections and other upper respiratory tract infections (URIs)? To answer these questions, we evaluated changes in immunoglobulin levels and the occurrence of URIs in a large population of children participating in a multicenter randomized controlled trial (RCT) on the effectiveness of adenotonsillectomy.

* Department of Otorhinolaryngology, Wilhelmina Children's Hospital/University Medical Center Utrecht, The Netherlands.
† Department of Pediatric Immunology, Wilhelmina Children's Hospital/University Medical Center Utrecht, The Netherlands.
‡ Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands.
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MATERIALS AND METHODS

Patients

The present study is part of an open, multicenter RCT on the effectiveness of adenotonsillectomy in children in The Netherlands.[16] Between March 2000 and August 2002, otorhinolaryngologic surgeons in 21 general hospitals and 3 academic centers in The Netherlands recruited participants and provided information for every child aged 2 to 8 years for whom adenotonsillectomy was indicated according to current medical practice. For this purpose, participating otorhinolaryngologic surgeons completed a questionnaire that asked what was most important in their decision to perform surgery: either recurrent throat infections (3 or more episodes per year) or other indications such as obstructive complaints or recurrent URIs.

Exclusion Criteria

Children with either (1) a history of 7 or more throat infections in the preceding year, 5 or more in each of the 2 preceding years, or 3 or more in each of the 3 preceding years[17] or (2) a high suggestion of obstructive sleep apnea syndrome (ie, Brouillette obstructive sleep apnea score of more than 3.5)[18] were excluded from this trial because consensus already exists as to the benefit of the procedure for these indications. Other exclusion criteria included Down syndrome, craniofacial malformation, and documented immunodeficiency other than IgA and IgG2 subclass deficiency.

Randomization

Children whose parents gave informed consent were randomly assigned to 1 of 2 trial arms: adenotonsillectomy within 6 weeks or a nonsurgical or watchful waiting (WW) strategy. For this purpose, computer-generated fixed blocks of 4 were used within hospitals. The study was undertaken in accordance with the European statement for good clinical practice, which includes the provisions of the declaration of Helsinki of 2000.[19] The medical ethics committees of all participating hospitals approved the study protocol.

Inclusion

At inclusion, disease-specific questionnaires were filled out, including information on number of throat infections and URIs in the year before trial entry, previous otorhinolaryngologic operations, and risk factors for URIs such as atopic symptoms and attendance at daycare. A venous serum sample for immunoglobulin evaluation was collected.

Follow-up

During the study, parents kept a diary of complaints of URIs in their child, such as sore throat, pain or difficulty swallowing, cough, rhinorrhea, earache, and otorrhea. The child's temperature was measured daily with a validated infrared tympanic membrane thermometer.[20] Both diary and thermometer data were collected by the study physician during the scheduled follow-up visits at 3, 6, 12, 18, and 24 months. At 12 months a second serum sample for immunoglobulin evaluation was collected.

Immunologic Measurements

Total serum immunoglobulin concentrations of IgM and IgA were determined by rate nephelometry. The IgG subclass concentrations were measured by radial immunodiffusion (Behring Werke, Mannheim, Germany, and Central Laboratory of the Red Cross Blood Transfusion Service, Amsterdam, The Netherlands). Serum immunoglobulin levels within the range of 2 SDs below or above the age-specific mean were considered normal.[21] Complete deficiency of IgA was defined as a serum level of 0.05 g/L or less. Complete deficiency of IgG2 was defined as a serum level of 0.02 g/L or less.

Subgroups

To address the question of whether children with few throat infections during follow-up differ immunologically from children with frequent throat infections, children were divided in 2 subgroups: 103 children with 0 or 1 throat infection during the first year of follow-up vs 20 children with 2 or more episodes. Similar subgroups were formed for children with 0 to 3 URIs (n = 105) vs 4 or more episodes (n = 18) during the first year of follow-up.

Throat infections were defined as sore throat and/or pain or difficulty swallowing combined with fever (temperature $\geq$38.0°C as measured by the infrared tympanic thermometer)[20] for at least 1 day. The URIs were defined as sore throat and/or pain or difficulty swallowing and/or cough and/or rhinorrhea and/or earache and/or otorrhea combined with fever (temperature $\geq$38.0°C as measured by the infrared tympanic thermometer) for at least 1 day. A throat infection or URI episode ended when patients were symptom free for at least 1 day. A new episode of throat infection or URI was registered after a minimum 7-day interval free of symptoms. Since age plays a role in susceptibility to infections, the children were divided into 2 age groups: 2 to 4 years and 4 to 8 years.

Statistical Analysis

Both χ^2 tests and *t* tests were used to evaluate possible differences in categorical and continuous characteristics, respectively, between the adenotonsillectomy and the WW group at baseline. Paired *t* tests were used to compare the immunoglobulin levels at baseline and 1 year. Fold decrease of immunoglobulins was calculated by dividing the mean immunoglobulin level at baseline by the mean level at 1 year. The *t* tests were used in subgroup analyses.

RESULTS

Patients

Between March 2000 and February 2003, 300 children participated in the trial. At baseline (T0), 218 venous serum samples were collected for immunologic evaluation; at 1-year follow-up (T12), 165 samples were collected. For 123 children, paired samples were available: 63 children in the adenotonsillectomy group and 60 children in the WW group. Patient characteristics did not differ between groups (eg,

mean ages at inclusion were 59 months [SD, 16.9 months] and 57 months [SD, 13.9 months], respectively) (Table 1).

Changes in Immunoglobulin Levels During Follow-up

Table 2 gives the changes in immunoglobulin levels from baseline to 1-year follow-up according to randomization and age group. In children aged 2 to 4 years, mean IgA and IgM levels decreased both in the adenotonsillectomy and WW group but remained elevated (ie, mean concentrations at 1-year follow-up were above 2 SDs of the age-related mean). In children aged 4 to 8 years, mean IgA and IgM levels decreased from elevated to values within the normal range. Mean IgG1 and IgG2 levels in both randomization groups, regardless of age, were within the reference range at baseline, and although they decreased during follow-up, the levels remained within the normal range for age. Differences between the adenotonsillectomy group and the WW group were only noted for IgA levels; mean serum IgA decreased more in children aged 4 to 8 years in the adenotonsillectomy group than in the WW group ($P = .01$). Overall, mean serum immunoglobulin levels at 1-year follow-up did not differ significantly between both randomization groups. None of the children developed hypogammaglobulinemia or IgA deficiency.

Fold decreases (T0/T12) of IgA, IgM, IgG1, and IgG2 levels are presented in Table 3. Fold decreases of IgA and IgG1 are more pronounced in the adenotonsillectomy group than the WW group: 1.30 vs 1.06 for IgA ($P < .001$) and 1.22 vs 1.10 for IgG1 ($P = .02$), respectively. For IgM and IgG2 the differences between both randomization groups are smaller and not statistically significant.

Association Between Immunoglobulin Levels at 1-Year Follow-up and Occurrence of Throat Infections and URIs

In the present study, no significant difference was found between children in the adenotonsillectomy and the WW groups in the mean number of throat infections and URIs in the first year of follow-up: 0.71 (SD, 0.87) vs 0.68 (SD, 0.93) throat infections and 1.73 (SD, 2.26) vs 1.92 (SD, 1.90) URIs, respectively. Children in the adenotonsillectomy group with 0 or 1 throat infection during the first year of follow-up had a lower serum IgA level at 1-year follow-up than children from the WW group with the same number of throat infections: 0.96 g/L (SD, 0.46 g/L) vs 1.18 g/L (SD, 0.56 g/L) ($P = .03$) (Table 4), whereas other immunoglobulin levels did not differ. In children with 2 or more throat infections during the first follow-up year, however, serum IgA levels at 1-year follow-up were the same for the adenotonsillectomy and WW groups: 1.02 g/L (SD, 0.53 g/L) vs 1.03 g/L (SD, 0.41 g/L) ($P = .97$). Again, serum IgG1, IgG2, and IgM levels at 1-year follow-up were not statistically different between the children in the 2 randomization groups. In Table 5 a similar analysis is given for the number of URIs categorized as 0 to 3 and 4 or more episodes during the first year of follow-up, with comparable findings.

DISCUSSION

In this large group of children who participated in an RCT comparing the effectiveness of adenotonsillectomy and a nonsurgical WW strategy, serum IgG1 and IgG2 levels decreased during the 1-year follow-up but remained within the reference ranges for age, irrespective of treatment (adenotonsillectomy vs WW). IgA and IgM levels in both randomization groups were above the reference range for age at baseline and decreased after 1-year follow-up but remained higher than 2 SDs above the mean value for age, irrespective of treatment. A greater decrease of serum IgA was observed in children aged 4 to 8 years in the adenotonsillectomy group compared with those of the same age in the WW group. For children with few throat infections (0 or 1 episode), we found significantly lower IgA levels in the adenotonsillectomy group, but as soon as children had experienced 2 or more throat infections, IgA levels became comparable in both randomization groups. In general, no relation was found between immunoglobulin levels and occurrence of throat infections and URIs during the first year of follow-up.

In a previous study (E. H. van den Akker, unpublished data, 2002), we showed serum IgG, IgM, and IgA levels in children with tonsillar disease, both recurrent tonsillitis and

Table 1. Demographic and Disease-Specific Characteristics of 123 Trial Participants, According to Treatment Group*

Characteristics	Adenotonsillectomy (n = 63)	WW (n = 60)
Male	38 (60)	32 (53)
Age, mean (SD), mo	59 (17)	57 (14)
No. of tonsillitis episodes in the year before the study, mean (SD)	2.69 (1.60)	2.70 (1.68)
Previous otorhinolaryngologic surgery		
Adenoidectomy	12 (19)	12 (20)
Tympanostomy tubes	4 (6)	6 (10)
Atopy†	32 (51)	32 (53)
Breastfed for more than 1 month	37 (60)	39 (65)
Daycare attendance (only for children <4 years)	14 (93) (n = 15)	16 (100) (n = 16)

Abbreviation: WW, watchful waiting.

* Data are presented as number (percentage) of patients unless indicated otherwise.

† Atopy is defined as having eczema, hay fever, recurrent wheezing, or asthma.

Table 2. Mean Serum Immunoglobulin Levels at Baseline (T0) and 1-Year (T12) Follow-up According to Treatment and Age Groups

Patient group	T0	T12	Difference (SD)	Paired *t* test	Reference range	*P* value for adenotonsillectomy vs WW at T12
Patients 2–4 years old in adenotonsillectomy group						
IgA, g/L	1.08	1.04	−0.04 (0.44)	0.72	0.31–0.87	.88
IgM, g/L	1.54	1.33	−0.21 (0.48)	0.11	0.56–1.22	.85
IgG1, g/L	8.42	7.35	−0.96 (2.09)	0.11	2.25–8.50	.61
IgG2, g/L	1.47	1.22	−0.21 (0.24)	0.005	0.50–2.80	.64
Patients 4–8 years old in adenotonsillectomy group						
IgA, g/L	1.24	0.94	−0.30 (0.35)	<0.001	0.48–1.22	.01
IgM, g/L	1.54	1.33	−0.20 (0.28)	<0.001	0.60–1.34	.30
IgG1, g/L	9.16	7.70	−1.48 (2.35)	<0.001	3.50–10.00	.42
IgG2, g/L	1.64	1.43	−0.19 (0.43)	0.005	0.50–3.50	.49
Patients 2–4 years in WW group						
IgA, g/L	0.96	1.08	0.11 (0.43)	0.31	0.31–0.87	
IgM, g/L	1.34	1.29	−0.05 (0.41)	0.63	0.56–1.22	
IgG1, g/L	8.04	7.60	−0.44 (1.54)	0.27	2.25–8.50	
IgG2, g/L	1.12	1.14	0.03 (0.37)	0.77	0.50–2.80	
Patients 4–8 years in WW group						
IgA, g/L	1.22	1.18	−0.05 (0.37)	0.43	0.48–1.22	
IgM, g/L	1.44	1.25	−0.19 (0.33)	<0.001	0.60–1.34	
IgG1, g/L	8.77	8.03	−0.79 (1.76)	0.005	3.50–10.00	
IgG2, g/L	1.62	1.50	−0.10 (0.47)	0.18	0.50–3.50	

Abbreviation: WW, watchful waiting.

Table 3. Fold Decrease of Mean Immunoglobulin Levels According to Treatment Group

Immunoglobulin	Fold decrease (T0/T12), mean (SD)		*P* value
	Tonsillectomy (n = 63)	WW (n = 60)	
IgA	1.30 (0.35)	1.06 (0.33)	<.001
IgM	1.16 (0.25)	1.16 (0.27)	.90
IgG1	1.22 (0.34)	1.10 (0.22)	.02
IgG2	1.17 (0.34)	1.10 (0.41)	.31

Abbreviations: T0, baseline; T12, 1-year follow-up; WW, watchful waiting.

tonsillar hypertrophy, to be above reference values for age, probably due to repeated antigenic stimulation. Similar results were obtained in other populations of children with tonsillar disease.[7,8,10,13,22] Regarding changes in pretonsillectomy and posttonsillectomy serum immunoglobulin levels in children with tonsillar disease, however, study results were inconsistent.[7–15,23,24] Some found only a decline in IgG levels after adenotonsillectomy,[8,9] whereas others only found low IgA levels[7,11,23,24] or a decline of all immunoglobulin levels.[10,12–15] In these studies, the magnitude of the decrease in immunoglobulin levels differed as well. A possible explanation for the different results of immunoglobulin changes after adenotonsillectomy is the moment of serum collection: samples taken within 1 to 4 months postoperatively show a larger decrease in immunoglobulin levels of most isotypes than samples collected after 1 year. Apparently, immunoglobulin levels tend to normalize over time.[15]

Table 4. Mean (SD) Immunoglobulin Levels at 1-Year Follow-up by Number of Throat Infections During the First Year of Follow-up According to Treatment Group

No. of throat infections	Adenotonsillectomy	WW	*P* value
0–1 Episode			
IgA, g/L	0.96 (0.46)	1.18 (0.56)	.03
IgM, g/L	1.35 (0.40)	1.30 (0.51)	.53
IgG1, g/L	7.83 (1.85)	7.97 (1.85)	.71
IgG2, g/L	1.39 (0.45)	1.44 (0.58)	.59
≥2 Episodes			
IgA, g/L	1.02 (0.53)	1.03 (0.41)	.97
IgM, g/L	1.20 (0.25)	1.09 (0.41)	.47
IgG1, g/L	6.32 (1.52)	7.69 (1.46)	.06
IgG2, g/L	1.31 (0.71)	1.24 (0.40)	.79

Abbreviation: WW, watchful waiting.

The only significant difference we found between both randomization groups was a greater decrease in IgA levels after 1 year in the adenotonsillectomy group than in the WW group, especially in children aged 4 to 8 years (Tables 2 and 3). It has been suggested that low IgA levels are associated with an increased susceptibility to URIs.[25,26] In our population, however, no associated occurrence of throat infections or URIs during follow-up was found. These results agree with those of others who found (transitory) serum IgA decreases after tonsillectomy but without an associated increase in respiratory infections.[7,11,13,23] Interestingly, we observed that this difference in IgA levels between the adenotonsillectomy and WW groups was confined to the children with few

Table 5. Mean (SD) Immunoglobulin Levels at 1-Year Follow-up by Number of URIs During Follow-up According to Treatment Group

No. of URIs	Adenotonsillectomy	WW	*P* value
0–3 Episodes			
IgA, g/L	0.95 (0.45)	1.18 (0.57)	.02
IgM, g/L	1.34 (0.39)	1.30 (0.50)	.69
IgG1, g/L	7.66 (1.92)	7.87 (1.71)	.57
IgG2, g/L	1.37 (0.45)	1.43 (0.57)	.54
≥4 Episodes			
IgA, g/L	1.14 (0.65)	1.05 (0.37)	.69
IgM, g/L	1.30 (0.25)	1.09 (0.45)	.32
IgG1, g/L	7.18 (1.39)	8.11 (2.08)	.34
IgG2, g/L	1.43 (0.67)	1.30 (0.49)	.70

Abbreviation: URIs, upper respiratory tract infections; WW, watchful waiting.

infections (0 or 1 throat infection and 0 to 3 URIs during follow-up) and thus not in children with 2 or more throat infections or 4 or more URIs. Apparently, in children who experience frequent URIs in the adenotonsillectomy group, the remaining MALT compensates for the loss of IgA production by the tonsil and adenoid, similar to children who were treated nonsurgically.

We compared our study to the study of Friday et al,[9] who studied immunoglobulin changes in children who participated in an RCT on the effectiveness of adenotonsillectomy. Friday et al found a significantly lower IgG level in the adenotonsillectomy group than in the WW group but no relation between immunoglobulin level changes and the occurrence of throat infections during follow-up. Thus, although some effect of adenotonsillectomy on the different isotype serum levels have been observed, one may conclude that it does not result in a higher susceptibility to respiratory infections.

To appreciate the results of this study, strengths and limitations should be considered. First, by excluding children with very frequent throat infections from our trial,[7] the relationship between these infections and serum immunoglobulin levels may be underestimated. Friday et al,[9] however, included children with very frequent recurrent throat infections and still found no association between immunoglobulin levels and number of throat infections.

Second, paired serum samples were available for only 123 (41%) of the 300 trial participants. The only significant differences between children included in the present study and the 177 other children in the trial were sex (male: 56.9% vs 43.8%, respectively; $P = .03$) and daycare attendance (96.8% vs 76.8%, respectively; $P = .02$). Subgroup analyses for sex and daycare attendance, however, showed no differences in immunoglobulin levels.

Third, we did not measure salivary IgA. Decreases in salivary IgA after adenotonsillectomy have been reported[27,28] and have been suggested to be correlated with the occurrence of URIs.[29] Nevertheless, several other studies have shown that after 1 month the salivary IgA levels were comparable to age-matched controls, suggesting that such decreases are transitory.[12,23]

The strength of our study is that our results are based on a large population of children who participated in an RCT in which throat infections and URIs have been carefully documented in diaries and fever associated with these infections has been measured objectively with a validated infrared tympanic membrane thermometer.[20] By including a randomly allocated nonsurgical comparison group, possible changes in immunoglobulin levels in the adenotonsillectomy group can be put in perspective. Since the study by Friday et al published in 1992,[9] this is the first prospective controlled study on immunoglobulin levels in association with occurrence of throat infections and URIs. The number of participants in our study was larger than in the previous one: 123 vs 75 children in the study by Friday et al.[9] We evaluated the relation of immunoglobulins to not only throat infections but also URIs, since currently used indications for adenotonsillectomy also include recurrent URIs.[30–33] However, no such relation was found.

In conclusion, immunoglobulin levels of children in whom adenotonsillectomy is indicated decreased to levels within or slightly above the reference range for age after 1-year follow-up irrespective of treatment (adenotonsillectomy or WW). This decline did not result in an increased susceptibility to throat infections or URIs. Most likely, the observed decrease is compatible with a natural reduction of antigenic stimulation with age. In children with persisting recurrent infections during follow-up, IgA levels are similar in children of the adenotonsillectomy and the WW group, indicating that the remaining MALT compensates for the loss of tonsil and adenoid tissue in children with frequent URIs.

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Requests for reprints should be addressed to:
Anne G. M. Schilder, MD, PhD
Wilhelmina Children's Hospital/University Medical Center Utrecht
Department of Otorhinolaryngology (KE 04.140.5)
PO Box 85090
3508 AB Utrecht, The Netherlands
E-mail: A.Schilder@umcutrecht.nl