

Adenoidectomy during early life and the risk of asthma

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The objective of the study was to evaluate the risk of asthma in children who had undergone an adenoidectomy, an operation frequently performed on children with glue ear or recurrent otitis media. Two surveys were carried out, a nation-wide questionnaire returned by 483 individuals (survey A) and a survey of hospital discharge records involving 1616 children who had undergone an adenoidectomy and 161 control children who had undergone probing of the nasolacrimal duct due to congenital obstruction (survey B). The questionnaire (survey A) showed that an adenoidectomy before the age of 4 years was associated with asthma (OR 3.19, 95% CI 1.25; 8.13) and with allergy to animal dust (OR 2.50, 95% CI 1.27; 4.95). In survey B, asthma diagnosis was retrieved from the national asthma register. It showed also that adenoidectomy at an early age was associated with an increased risk of asthma (OR 6.74, 95% CI 2.99; 15.2). There was an association between asthma and adenoidectomy, even before adenoidectomy had actually been performed. The risk of asthma was highest among children who had had adenoidectomy because of recurrent otitis media. The observed association between an adenoidectomy and asthma may be explained by an underlying factor predisposing to both recurrent otitis media and asthma.

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Repeated runny nose (1) and exposure to a farming environment during early life (2) have been proposed to have an inverse association with asthma, a disease associated with atopy and a Th2-type immune response (3). This has been attributed to exposure to endotoxin and other microbial compounds that regulate the production of interferon- γ and interleukin-12 that select against T-helper 2 (Th2) cells and thereby counteract allergic sensitization (4). Thus, moderate exposure to microbes during early life may protect against asthma. However, lower respiratory tract infections (1), infections caused by respiratory syncytial virus (5) and measles (6) during early childhood are associated with an increased risk of asthma. This implies that the location or the type of respiratory tract infection are important factors that are associated with the onset of asthma.

Adenoidectomy is frequently performed on children who suffer from recurrent otitis media or from otitis media with effusion (OME, glue ear), which represents a cohort of children who are exposed to recurrent respiratory infections. To assess the frequency of asthma among children who have undergone adenoidectomy, two separate surveys were carried out: a questionnaire, which enabled a nation-wide assessment on the association between asthma and adenoidectomy, and a survey of hospital discharge records.

Patients and methods

Subjects of the questionnaire survey (survey A)

A questionnaire was sent in 1998 to 819 Finnish individuals. They had been selected on the basis

of sex and date of birth from the Finnish National Population Registry, serving as a control cohort in a study of 819 Finnish children with type 1 diabetes (7). This group was a random representative of Finnish children except for sex distribution (370 females, 449 males). Altogether 483 (59%) of the 819 forms were returned. The mean age of the responders was 18.3 years (range 10.7–27.5); 243 were female and 240 were male. The questionnaire was designed to evaluate the frequency of childhood infections and allergy. It did not give the impression that the role of adenoidectomy in the development of asthma would be specifically probed. Also data on education, occupation, eye diseases, kidney diseases, tonsillectomy, and other airway diseases were collected. The following questions on an adenoidectomy, airway disease, and allergy were asked. (1) Have your adenoids been removed (adenoidectomy)? (2) If an adenoidectomy was performed, at what age? (3) Have you been diagnosed as having asthma by a physician? (4) Have you had episodes of wheezing accompanied by difficulty in breathing? (5) Have you been diagnosed as having any allergy to the following airborne allergens? (a) Pollen? (b) Animal dust (dog, cat, horse, etc.)? (6) If you have an allergy to airborne allergens, how have you reacted? (a) With nasal symptoms? (b) With eye symptoms? (c) With bronchial symptoms (wheezing)? The questions were followed by multiple choice answer fields including *no*, *yes*, and *do not know* choices in applicable places. The questionnaire included a schematic figure with explanatory text showing the anatomical location of the adenoids and tonsils to help the respondent understand the questions concerning adenoidectomy.

Subjects of the survey of hospital discharge and asthma medication records (survey B)

Hospital discharge records of the Eye and Ear Hospital, Helsinki University Central Hospital were reviewed in order to look for children who had undergone adenoidectomy (1616 children). Children who had undergone probing of the nasolacrimal duct due to congenital obstruction served as controls (161 children). Children who were born after 1st January 1992 and were operated before 1st January 2000 were included in the analysis (1001 male, 776 female children). Asthma diagnosis among these children was retrieved from the nation-wide register of the Social Insurance Institution of Finland of individuals eligible for reimbursement of the costs of drugs used for treatment of asthma. The data of

asthma diagnosis were available in this register since January 1st 1992, i.e. for all children included in the analysis starting from their birth. Children who were entitled to the reimbursement by the Social Insurance Institution should have experienced at least two or three wheezy attacks with a good response to inhaled bronchodilators as confirmed by a pediatrician to justify the asthma diagnosis. Children older than 4 years were entitled to the reimbursement even after a single episode of wheezing if bronchial hyperactivity was confirmed by spirometry with or without an exercise test. The end-point of the follow-up was 23rd December 2000. The mean age at the end of the follow-up was 6.2 years (range 2.1–9.0 years). The indication for an adenoidectomy in our hospital is almost exclusively related to recurrent otitis media or to glue ear especially in children less than 4 years of age (8). Diagnosis of glue ear among children who had undergone adenoidectomy was retrieved from the hospital discharge records as identified by the ICD-9 or ICD-10 codes (3812A or H65.3, respectively).

Statistical analysis

Multivariate logistic regression analysis was applied in the questionnaire survey (survey A) to test the risk of asthma and atopy as adjusted by sex and age. The risk of asthma in the survey of patient records (survey B) was estimated using the Cox proportional hazards method as adjusted by sex and age.

The Ethical Review Committees of the Helsinki University Central Hospital and the Social Insurance Institution of Finland approved the survey of the patient records. The Ethical Review Committee of the Finnish National Health Institute approved the questionnaire survey.

Results

The questionnaire survey (survey A) revealed an association between adenoidectomy before the age of 4 years and asthma (odds ratio 3.19, 95% CI 1.25; 8.13, $p = 0.015$, Table 1). There was also an association between adenoidectomy at an early age and wheezy bronchitis (odds ratio 2.68, 95% CI 1.36; 5.25, $p = 0.004$), allergy to animal dust (odds ratio 2.50, 95% CI 1.27; 4.95, $p = 0.008$), and bronchial symptoms to respiratory allergens (odds ratio 3.25, 95% CI 1.31; 8.08, $p = 0.011$, Table 1).

The analysis of the hospital discharge records and the national registry for asthma medication (survey B) also revealed that adenoidectomy was

Table 1. Frequency of respiratory tract diseases and allergy by adenoidectomy status among individuals as assessed by the questionnaire

	No. adenoidectomy	Adenoidectomy before the age of four	Odds ratio (95% CI)
Asthma	5.8% (359)*	15% (47)	3.19 (1.25; 8.13)†
Wheezy bronchitis	17.0% (347)	34% (47)	2.68 (1.36; 5.25)‡
Allergy to respiratory allergens			
Pollen	24.7% (344)	29% (45)	1.24 (0.62; 2.48)
Animal dust	19.9% (341)	36% (44)	2.50 (1.27; 4.95)‡
Type of symptoms to respiratory allergens			
Conjunctival	56.5% (161)	58% (31)	1.05 (0.48; 2.30)
Nasal	63.0% (162)	66% (32)	1.14 (0.51; 2.54)
Bronchial	14.7% (150)	36% (28)	3.25 (1.31; 8.08)†

*Number of individuals of which information was available.

† $p < 0.05$.

‡ $p < 0.01$.

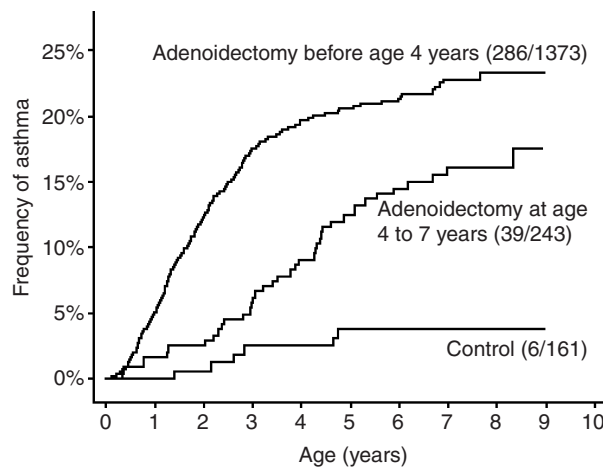


Fig. 1. Cumulative frequency of asthma by age. The results of Kaplan-Meier life table analysis are presented for children who had an adenoidectomy before the age of 4 years, between ages 4–7 years, and in children who underwent probing of the nasolacrimal duct (Control). The numbers of children with asthma and the total number of children in each group are given in parenthesis.

associated with an increased risk of childhood asthma (Fig. 1). The odds ratio of asthma risk exceeded 6 when adenoidectomy was performed before the age of 4 years (odds ratio 6.74, 95% CI 2.99; 15.2, $p < 0.001$, Fig. 1). When adenoidectomy was performed between ages 4–7 years, the odds ratio of asthma risk was 4.36 (95% CI 1.85; 10.4, $p < 0.001$, Fig. 1). Adenoidectomy was associated with an asthma diagnosis among children free from asthma at the time of adenoidectomy (odds ratio 3.61, 95% CI 1.47; 8.8, $p = 0.004$), as well as among children who had asthma already at the time of an adenoidectomy (odds ratio 7.99, 95% CI 1.11; 57.4, $p = 0.039$).

Table 2. Risk of asthma among children who had undergone an adenoidectomy by the middle ear status

	Frequency of asthma (n*)	Risk of asthma OR (95% CI)
Glue ear	12.9% (498)	3.27 (1.39; 7.63)†
Recurrent otitis media	23.4% (1118)	7.52 (3.34; 16.9)‡

The reference was 161 children who had probing of the nasolacrimal duct due to congenital obstruction.

*Number of children.

† $p < 0.01$.

‡ $p < 0.001$.

Children who did not have middle ear effusion at the time of adenoidectomy had a higher risk of asthma (OR 7.52) than children who suffered from glue ear (OR 3.27, Table 2). The risk of asthma was almost twice the risk among children who suffered from recurrent otitis media than among children who had glue ear (OR 1.91, 95% CI 1.45; 2.51).

Discussion

The questionnaire showed a strong association between adenoidectomy at early age and asthma. The frequency of asthma was evaluated by the question 'Have you been diagnosed as having asthma by a physician?' which presumably results in a rather specific and sensitive diagnosis of asthma because self-reported physician-diagnosed asthma has been shown to correlate well with objective findings of asthma diagnosis (9, 10). Although the data obtained by the questionnaire may be somewhat inaccurate, it is feasible that false-positive statements of a history of an adenoidectomy may be relatively rare. Nevertheless, the strong association between asthma and adenoidectomy was confirmed by the survey of patient records, which provided an evaluation based on objective criteria.

The questionnaire also revealed an association between allergic symptoms to animal dust and adenoidectomy. However, the history of atopic symptoms is prone to a bias as self-reported atopic symptoms may not always have a good correlation with objective findings of atopy such as skin prick tests, serum allergen specific or total IgE (9). This bias in the self-reported atopic symptoms in the present survey was minimized by asking the participants whether they had 'ever been diagnosed as having an allergy' to animal dust or pollen. It has previously been reported that persistent IgE-mediated hypersensitivity reactions occur in children up to 7 years of age who have had severe respiratory syncytial virus

infections during infancy (11). Respiratory syncytial virus has also been found to cause otitis media (12). Therefore, it is possible that the apparently increased risk of allergic symptoms to animal dust observed in children who have undergone adenoidectomy may be related to exposure to respiratory tract infections preceding adenoidectomy.

The finding in the survey of patient records that the risk of asthma was increased even before adenoidectomy was actually performed supports the notion that respiratory tract infections, not adenoidectomy per se, is associated with the increased frequency of asthma. Further, adenoidectomy performed because of recurrent otitis media was associated with a higher risk of asthma than adenoidectomy performed because of glue ear, a persistent but sometimes indolent inflammation of the middle ear (13). This is in line with the assumption that repeated infections of the respiratory tract may be associated with asthma.

It is possible that in addition to environmental factors, such as exposure to recurrent upper respiratory tract infections, the genetic composition may also contribute to the association between asthma and otitis media. In a recent survey of 209 children aged 3–8 years with chronic or recurrent otitis media with effusion, it was found that the frequency of asthma, nasal eosinophilia, and positive skin prick tests had increased (14). Among these children even the frequency of a positive family history of atopic disorders was high suggesting that the genetic background may predispose to both atopic disorders and to chronic otitis media. Even further, it is possible that atopic reactions may directly predispose to otitis media.

Our finding on the association between asthma and adenoidectomy is compatible with the study by Bager et al. (6) who found an increased risk of atopy in women who had measles during the first year of life or with increasing exposure to measles, rubella, varicella, and mumps during the first 2 years of life. Apparently these individuals had experienced frequent respiratory tract infections very early in life and thus resemble the children who had undergone adenoidectomy at an early age in the present survey. It has also been found that rhinovirus infections, which are among the most common upper respiratory tract infections, exacerbate symptoms of asthma (15). It is thus feasible that recurrent infections might provoke asthma symptoms in a child with subclinical bronchial hyperreactivity and thereby increase the risk of fully developed asthma.

Our results and those of Bager et al. (6) are surprising in light of the findings on reduced frequency of asthma among children with a frequent runny nose during early life (1) and the observations of an inverse association between risk of atopy and family size (16–18), which have been interpreted that exposure to microbes would not increase, but on the contrary, decrease the risk of atopy. The apparent discrepancy may be explained in part by the magnitude of exposure. Although moderate microbial exposure might be protective, excessively frequent upper respiratory tract infections may increase the risk of asthma.

Why then, would an excessive microbial exposure be harmful but a moderate be protective? During evolution humans may have adapted to an environment where young children are exposed to microbes constantly to a limited extent. This environment is presumably very different from the modern urban environment, which at one extreme may result in quite infrequent exposure to microbes, or on the other extreme, an environment with frequent indoor contacts over-exposing the growing child to recurrent respiratory tract infections.

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References

- ILLI S, VON MUTIUS E, LAU S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001; 322: 390–5.
- RIEDLER J, BRAUN-FAHRLANDER C, EDER W, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001; 358: 1129–33.
- UMETSU D, MCINTIRE J, AKBARI O, MACAUBAS C, DEKRUYFF R. Asthma: an epidemic of dysregulated immunity. *Nature Immunol* 2002; 3: 715–20.
- VON MUTIUS E, BRAUN-FAHRLANDER C, SCHIERL R, et al. Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; 30: 1230–4.
- STEIN RT, SHERRILL D, MORGAN WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; 354: 541–5.
- BAGER P, WESTERGAARD T, ROSTGAARD K, HJALGRIM H, MELBYE M. Age at childhood infections and risk of atopy. *Thorax* 2002; 57: 379–82.
- TUOMILEHTO J, LOUNAMAA R, TUOMILEHTO-WOLF E, et al. Epidemiology of childhood diabetes mellitus in Finland-background of a nationwide study of type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1992; 35: 70–6.

8. MATTILA PS, TAHKOKALLIO O, TARKKANEN J, PITKÄNIEMI J, KARVONEN M, TUOMILEHTO J. Causes of tonsillar disease and frequency of tonsillectomy operations. *Arch Otolaryngol Head Neck Surg* 2001; 127: 37–44.
9. KAUPPI P, LAITINEN LA, LAITINEN H, KERE J, LAITINEN T. Verification of self-reported asthma and allergy in subjects and their family members volunteering for gene mapping studies. *Resp Med* 1998; 92: 1281–8.
10. BARNES KC, FREIDHOFF LR, HOROWITZ EM, et al. Physician-derived asthma diagnoses made on the basis of questionnaire data are in good agreement with interview-based diagnoses and are not affected by objective tests. *J Allergy Clin Immun* 1999; 104: 791–6.
11. SIGURS N, BJARNASON R, SIGURBERGSSON F, KJELLMAN B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; 161: 1501–7.
12. HEIKKINEN T, THINT M, CHONMAITREE T. Prevalence of various respiratory viruses in the middle ear during acute otitis media. *New Eng J Med* 1999; 340: 260–4.
13. PARADISE JL. Treatment guidelines for otitis media. The need for breadth and flexibility. *Pediatr Infect Dis J* 1995; 14: 429–35.
14. ALLES R, PARIKH A, HAWK L, DARBY Y, ROMERO JN, SCADDING G. The prevalence of atopic disorders in children with chronic otitis media with effusion. *Pediatr Allergy Immunol* 2001; 12: 102–6.
15. FOLKERTS G, NIJKAMP F. Virus-induced airway hyper-responsiveness and asthma. *Am J Respir Crit Care* 1998; 157: 1708–20.
16. STRACHAN DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299: 1259–60.
17. STRACHAN DP. Family size, infection, and atopy: the first decade of the 'hygiene hypothesis'. *Thorax* 2000; 55 (Suppl. 1): S2–10.
18. BODNER C, GODDEN D, SEATON A. Family size, childhood infections, and atopic infections. The Aberdeen WHEASE Group. *Thorax* 1998; 53: 28–32.