

# Association of allergy, asthma and IgE sensitisation to adenoidectomy and infections in children\*

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## SUMMARY

**Objective:** To find out whether previous adenoidectomy is associated with asthma, allergic symptoms or allergen-specific IgE antibodies.

**Recruitment and methods:** We recruited 213 paediatric patients admitted for elective tonsillectomy and 155 paediatric controls. Using a structured questionnaire, we recorded their respiratory symptoms, allergies, bronchial asthma and environmental factors. Serum IgE antibodies against respiratory allergens were screened. Patients were divided into those previously adenoidectomised ( $n=100$ ) or not adenoidectomised ( $n=113$ ).

**Results:** Any allergy ( $p = 0.007$ ) and non-antibiotic allergy diagnosed by a doctor ( $p = 0.015$ ), and asthma ( $p = 0.015$ ) were more common among adenoidectomised than non-adenoidectomised children under the age of seven. Between ages 7 and 11, neither any kind of allergy nor asthma were associated with earlier adenoidectomy. In the oldest age group (12 to 17), only antibiotic allergy was more common in adenoidectomised children. Recurrent otitis media ( $p < 0.001$ ) and recurrent sinusitis ( $p = 0.007$ ) were more common in adenoidectomised children. After controlling for recurrent respiratory infections, doctor-diagnosed allergy remained significantly associated with adenoidectomy in the youngest age group. Prevalence of specific IgE did not differ between the patient groups, or between school-aged patients and controls.

**Conclusions:** Our results suggest that hypersensitivity disorders and infections may share aetiological factors. However, as adenoidectomised children of any age did not have higher levels of specific IgE, it seems possible that allergy is either clinically over-diagnosed or insufficiently detected by serology among young adenoidectomised children.

**Key words:** allergy, asthma, IgE, adenoid, infection

## INTRODUCTION

Respiratory allergy and adenotonsillar diseases are major health problems in children and strongly impact their quality of life. How they correlate with each other is largely unknown<sup>(1)</sup>. Relationships between allergy and adenotonsillar disease are especially interesting as the adenoid tissue is suggested to influence both the development of allergy and respiratory infections<sup>(2,3)</sup>.

The development of atopic diseases is determined by both genetic and environmental factors. The hygiene hypothesis states that an absence of infections in early childhood promotes Th2 type responses, which later in life manifest as allergy<sup>(4)</sup>. However, this hypothesis has been challenged with several

opposing observations. Otitis media with effusion is independently associated with IgE-mediated sensitisation and allergic respiratory symptoms<sup>(5)</sup>. The association between viral infections and bronchial asthma is firmly established<sup>(6)</sup>. Thus, infections that affect apoptosis of Th2 cell clones could skew immunologic reactions towards the development of allergy<sup>(7)</sup>. Consequently, the cause of the "allergy epidemic" could actually be recurrent viral infections, or they both might simply share common predisposing factors<sup>(7)</sup>.

Upper respiratory infections, especially of viral origin induce and exacerbate allergic symptoms and asthma<sup>(8-10)</sup>. As an example, asthmatics with IgE-mediated hypersensitivity have an impaired early apoptosis of rhinovirus infected cells resulting

in more severe respiratory disease and wheezing<sup>(9)</sup>. Allergic children have an increased incidence of upper respiratory infections, again suggesting that allergy and recurrent viral infections may share common pathogenetic mechanisms<sup>(11-13)</sup>.

Adenoid tissue belongs to the mucosa-associated lymphoid tissue in the Waldeyer's ring and protects against inhaled and swallowed foreign material. Adenoidectomy and adenotonsillectomy are the most common paediatric operations. Indications for these operations are somewhat age-dependent, infectious disorders becoming more prominent towards puberty<sup>(14)</sup>. Recently, immunologic consequences of surgery to Waldeyer's ring and its possible associations with allergic disorders have been studied in numerous prospective and retrospective studies with somewhat contradictory results<sup>(6, 15-18)</sup>. No apparent disturbance of the immune system has been found. In fact in a recent longitudinal birth cohort study from the Netherlands adenoidectomy or tonsillectomy in childhood did not result in a higher frequency of atopy in early adulthood<sup>(19)</sup>. Still, in another paediatric Norwegian population-based study, presence of atopy was associated with earlier upper respiratory tract surgery even after adjustments for infections<sup>(20)</sup>.

The aim of the present study was to find out whether previous adenoidectomy or recurrent infections are associated with bronchial asthma, allergic symptoms or to specific IgE antibodies against respiratory allergens later in life.

## MATERIALS AND METHODS

### *Study subjects*

We recruited, between November 2002 and February 2004, 213 consecutive voluntary children scheduled for (adeno)tonsillectomy performed in the Department of Otorhinolaryngology, Helsinki University Central Hospital. For enrolment, children had to be without acute respiratory symptoms at the time of the operation. Inclusion criteria and indications for tonsillectomy were: recurrent episodes of pharyngeal infection ( $\geq 6$  / year or  $\geq 3$  / year for 2 consecutive years, and at least one positive culture for *Streptococcus pyogenes*) with symptom-free intervals, or a clinical diagnosis of either chronic tonsillitis (prolonged pharyngeal infection despite antibiotic treatment) without symptom-free intervals or tonsillar hyperplasia (enlarged tonsils with symptoms such as sleep disturbed breathing, habitual snoring or swallowing problems).

During April 2004, we recruited 163 randomly selected controls aged 7 to 17 years from the elementary and junior high schools in the suburban community of Vihti. During randomisation, the pupils were given an ordinal number according to an alphabetical list of their family names. Thereafter, first an initial number was selected from a table of random figures and then every 10th pupil from each class level was chosen. Exclusion criterion was refusal at any stage. Only one child from each family was included.

### *Questionnaires and samples*

The patients or guardians filled out a structured questionnaire with questions on recurrent upper respiratory infections, recurrent otitis media ( $\geq 4$  episodes) or recurrent sinusitis ( $\geq 4$  episodes), chronic rhinitis (runny nose or crusting of the nose), snoring, diagnosis of allergy made by a physician, smoking at home, recurrent tonsillitis in contacts, day care, school attendance and bronchial asthma diagnosed by a doctor. Serum samples were taken during the procedure and stored at  $-70^{\circ}\text{C}$ . Control children did not fill out the questionnaire, only serum samples were collected and stored at  $-70^{\circ}\text{C}$ .

The study protocol was approved by the local ethics committee, and an informed written consent was obtained from all patients and controls or their guardians.

### *IgE Measurements*

Serum samples were screened with Phadiatop<sup>®</sup> (Pharmacia Diagnostics AB, Uppsala, Sweden) laboratory kit. Positive samples were further analysed for specific IgE against the following common respiratory allergens: birch, house dust mite (*Dermatophagoides pteronyssimus*), cat, dog, horse, timothy grass, mugwort and mold (*Alternaria alternata*) using Pharmacia CAP System<sup>™</sup> (Pharmacia Diagnostics AB, Uppsala, Sweden)<sup>(21)</sup>. A value of 0.35 kU/l or more of specific serum IgE was considered positive.

### *Statistical analysis*

Statistical analysis was performed using SPSS 12.0.1. (SPSS Inc., Chicago, IL, USA) and Statsdirect statistical softwares (version 2.3.5, Statsdirect, Cheshire, UK). Chi-square and Fisher's exact tests were used for the comparison of categorical data. In all cases a  $p < 0.05$  was considered significant. To clarify the influence of the different factors to clinical allergy symptoms or asthma, a forward stepwise logistical regression analysis was made. The compulsory school age in Finland is 7 years. For some statistical analysis, the children were divided into three age groups: 2 to 6 years, 7 to 11 years, and 12 to 17 years of age.

## RESULTS

### *Characteristics of patients and controls*

Comparison of demographic factors of the operated children and results of the questionnaire as divided by the history of previous adenoidectomy are shown in Table 1.

Adenoidectomy had previously been performed to 100 (47%), of whom 41 (19%) had undergone the procedure before the age of three (age data missing in 14 patients). Six patients had undergone adenoidectomy twice. Median age at the time of the first adenoidectomy was 3.0 years (age range 1-9). Of the 155 control children (age range 7.5-17.3 years, median 13.7), 78 (50%) were males.

Indication for surgery was recurrent tonsillitis in 58 (27%), chronic tonsillitis in 56 (26%) and tonsillar hyperplasia in 190

(89%). There were on average 1.4 indications per operation. The primary indication for tonsillectomy was infections in 95 (45%) of all patients and in 75 (65%) of patients over seven years. Indications for tonsillectomy were age dependent: tonsillar infections were the primary indication in 20% in children < 7 years, 46% in children between 7 and 11 and 85% in children  $\geq$  12 years ( $p < 0.0001$ , Chi-square test).

Previous respiratory infections reported are shown in Table 1. Perioperative otitis media was found in 32 (15%) patients and strongly associated with previous adenoidectomy ( $p < 0.0001$ , Chi-square test). Tympanostomy was performed during the procedure to 20 (9%) patients.

#### Doctor-diagnosed allergy

Doctor-diagnosed allergies were found in 51 (24%) of patients (Table 2). The diagnostic method had been skin prick testing in 33 (72%), serum IgE against allergens in two (4%). A clinical diagnosis alone had been given to 14 (27%) children, five (10%) with hypersensitivity symptoms from respiratory allergens, four (8%) from food allergens and five (10%) to antibiotics only. Two guardians recalled their child of having doctor-diagnosed allergy (one allergic to animals and dust, one to pollen and foods) but did not recall the diagnostic method. In patients with previous adenoidectomy 32% and in patients without previous adenoidectomy 17% had doctor diagnosed allergy ( $p = 0.010$  for difference, Chi-square test)(Figure 1a). However, in analysis of different types of allergy only allergy to antibiotics was significantly more common ( $p = 0.019$ , Chi-square test) in adenoidectomised children.

#### Doctor-diagnosed asthma

Bronchial asthma had been diagnosed by a doctor in 24 (11%) of

operated children. In 17 (71% of asthmatics) patients, diagnosis of asthma had been verified by pulmonary function testing in a hospital. In addition, peak expiratory flow follow up at home was the diagnostic method used in three patients. In one case the guardian did not recall the diagnostic method applied. The diagnosis of bronchial asthma was based on symptoms alone in the remaining three patients (two with regular medication, one with no medication). Asthmatics (median age 6.4 years, median time from diagnosis 3.0 years) had on average 1.6 different drugs against bronchial asthma, but on average only one was in regular use. The diagnosis of bronchial asthma was more common in adenoidectomised (17%) than non-adenoidectomised (6%) children ( $p = 0.016$ , Chi-square test) (Figure 1b).

#### IgE sensitisation

Positive result in the used screening test was found in 51 (24%) patients and 57 (37%) controls. Of these patients 48 (23% of all) had raised levels of specific IgE against at least one examined respiratory allergen, compared with 57 (37%) controls. Only 8 (17%) allergic patients were monosensitised (five to birch, one to timothy, one to dog and one to cat). Of the allergic controls 15 (26%) were monosensitised (three to birch, four to timothy, three to cat and five to house dust mite). Of the 38 patients with a doctor-diagnosed allergy to respiratory allergens, specific IgE was found in 29 (76%), 27 (71%) were multisensitised. Of the 175 patients without a diagnosis of allergy to respiratory allergens 17 (10%) had specific IgE against at least one tested allergens, 8 (5%) were multisensitised.

Out of 24 asthmatic patients, 17 (71%) had been diagnosed with allergy: 16 to respiratory allergens, six to foods and two to antibiotics. Specific IgE was found in 13 (54%) of asthmatics, of whom 11 (45%) were multisensitised. Twelve (75%) of those 16

Table 1. Characteristics of all study patients in groups by previous adenoidectomy.

	All tonsillectomised children n (%)	Previous adenoidectomy n (%)	No previous adenoidectomy n (%)	p1
No of patients	213	100	113	
Median age				
(range) $\square$	7.6			
(2.0-16.9)	8.1			
(2.0-16.6)	7.1			
(2.0-16.9)	0.8252			
Males	105 (49%)	56 (56%)	49 (43%)	0.0653
Recurrent URI $\ddagger$ *	103 (48%)	55 (55%)	48 (42%)	0.0683
Recurrent OME* (>3)	122 (57%)	75 (75%)	47 (42%)	<0.00013
Sinusitis*	47 (22%)	32 (32%)	15 (13%)	0.0013
Recurrent sinusitis (>3)	10 (5%)	9 (9%)	1 (1%)	0.0073
Chronic rhinitis*	67 (31%)	40 (40%)	27 (24%)	0.0113
Snoring*	172 (81%)	82 (82%)	90 (80%)	0.6643
Smoking at home	71 (33%)	38 (38%)	33 (29%)	0.1743
Day care	78 (37%)	36 (36%)	42 (37%)	0.8593

$\square$  Years,  $\ddagger$  URI=upper respiratory infections, # OME= otitis media with effusion, > 3 episodes of otitis/sinusitis verified by doctor, \*considered by guardian, 1 P-values between adenoidectomy+ and adenoidectomy- groups, 2 Mann-Whitney U test, 3 Chi-square test.

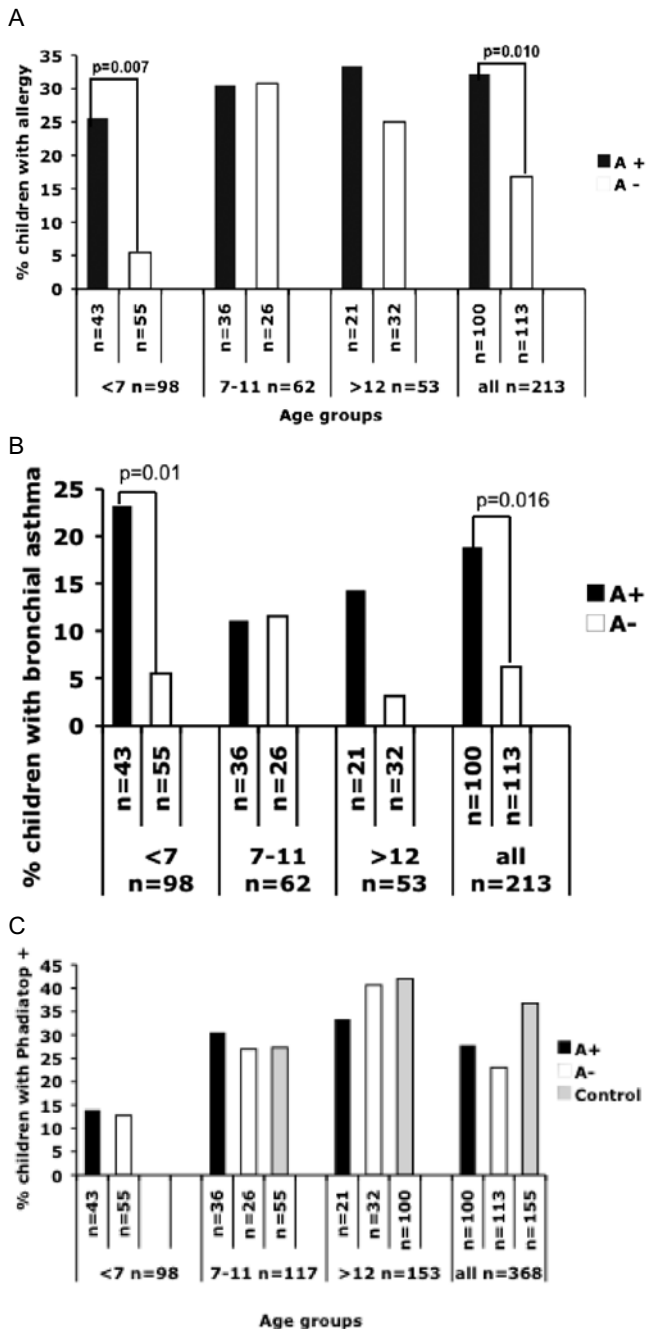


Figure 1A-C. The prevalence of a) doctor-diagnosed allergy, b) in study subgroups. Chi-square test. A= previous adenoidectomy.

asthmatics previously diagnosed with allergy to respiratory allergens had specific IgE against the tested respiratory allergens, 11 (69%) against several of them.

There was no statistically significant difference in positive results for specific IgE to respiratory allergens between adenoidectomised children 25 (25%) and non-adenoidectomised children 26 (23%) (Figure 1c).

#### Influence of age

No associations between previous adenoidectomy and doctor-diagnosed allergy or asthma were significant in ages 7 to 11

and 12 to 17 years (Figure 1 a-b). However, in the youngest age group, aged 2 to 6 years, doctor diagnosed allergy (any kind,  $p = 0.007$ ), doctor diagnosed non-antibiotic allergy ( $p = 0.015$ , Fisher's exact test) and asthma ( $p = 0.015$ , Fisher's exact test) were significantly more common in adenoidectomised children than in non-adenoidectomised children. IgE test results were not associated significantly with previous adenoidectomy in any age group (Figure 1c).

Positive IgE results were more uncommon in ages 2 to 6 years than older ages (Figure 1c). Since in addition to this all the controls were older than 6 years, we compared only patients aged 7 to 17 years to controls (Table 3). No significant differences were found in IgE results between patients and controls.

#### Logistic regression analysis

In children under seven years of age, doctor-diagnosed non-antibiotic allergy was significantly associated with reported recurrent upper respiratory infections (odds ratio [OR] 3.7; 95% confidence interval [95%CI] 1.0-13.6;  $p = 0.046$ ) and previous adenoidectomy (OR 4.8; 95%CI 1.2-19.3;  $p = 0.027$ ). In children between 7 and 11 years of age, doctor-diagnosed allergy was associated only with recurrent respiratory infections (OR 4.5; 95%CI 1.4-14.3;  $p = 0.011$ ). In children older than 11 years, doctor-diagnosed allergy was associated with recurrent otitis media (OR 4.4; 95%CI 1.4-21.7;  $p = 0.025$ ). Since the associations between doctor-diagnosed asthma and predisposing factors were related to infections in age groups, the age groups were pooled for further logistic regression analysis. Of the predisposing factors only recurrent otitis media then remained significantly associated (OR 9.9; 95%CI 2.3-43.2;  $p = 0.020$ ) with doctor-diagnosed asthma. Raised specific IgE levels were not associated with any of the predisposing factors tested.

#### DISCUSSION

In children coming for tonsillectomy, we found that diagnosed allergy and asthma were more common in children who had undergone adenoidectomy. Age-specific analyses, however, showed that these associations only prevailed among children younger than seven years of age. In logistic regression analysis, the strongest predictors of doctor-diagnosed allergy in children younger than seven years of age were recurrent respiratory infections and adenoidectomy. In children between seven and 11 years of age, recurrent respiratory infections, and in children older than 12, four or more diagnosed episodes of otitis media were significantly associated with the diagnosis of allergy. Recurrent otitis media ( $\geq 4$  episodes) was the strongest predictor of bronchial asthma in all age groups. However, when specific IgE antibodies against respiratory allergens were used for more objective assessment, no association was found. Also, no differences in the frequency of allergen specific IgE antibodies were noted between school-aged (7-17 years) patients and controls.

The frequency of allergen-specific IgE antibodies in tonsillecto-

Table 2. Reported allergic diseases of all study patients in groups by previous adenoidectomy.

	All tonsillectomised children n (%)	Previous adenoidectomy n (%)	No previous adenoidectomy n (%)	p1
No of patients	213	100	113	
Doctor-diagnosed allergy	51 (24%)	32 (32%)	19 (17%)	0.010
Respiratory allergy	38 (18%)	23 (23%)	15 (13%)	0.064
Food allergy	18 (8%)	9 (9%)	9 (8%)	0.786
Antibiotic allergy	21 (10%)	15 (15%)	6 (5%)	0.019
Doctor-diagnosed allergy (not to antibiotics)	46 (22%)	27 (27%)	19 (17%)	0.071
Asthma	24 (11%)	17 (17%)	7 (6%)	0.016

IP-values between adenoidectomy+ and adenoidectomy- groups, Chi-square test.

my patients closely corroborates the findings of an earlier study, where the frequency was at the same level both in children with severe adenotonsillar disease and in age-matched controls<sup>(15)</sup>. In our study, IgE-mediated hypersensitivity occurred independently of the indication to operate.

Interestingly, hypersensitivity without demonstrable allergen-specific IgE antibodies in the serum appeared to be more common in tonsillectomy patients with previous recurrent respiratory infections or otitis media. This may be a result of several factors. Some of these patients might have become falsely diagnosed as having no atopy, since skin prick testing was not performed. Prolonged infectious respiratory symptoms can falsely be interpreted as allergy. It is known, in accordance with our findings, that allergen specific IgE may be negative in the serum even with positive skin prick results.

Symptomatic hypersensitivity may be triggered from a silent predisposition to it by specific or recurrent infections. Possibly predisposition to infection is a result or comorbid with the tendency towards later development of allergy or non-IgE-mediated forms of hypersensitivity symptoms<sup>(22)</sup>. Possibly, allergen-specific IgE in the serum is not the optimal way to assess all clinically relevant forms of sensitisation that cause symptoms. It is known, in accordance with our findings; that the sensitivity of allergen specific IgE antibodies in the detection of hay fever is less than 80%<sup>(23,24)</sup>.

As a limitation of this study, data on previous allergies and asthma were retrospectively, although systematically collected. However, allergies and asthma diagnosed by a doctor, including the test methods applied, were specifically asked for. Only two guardians were unable to recall the testing method for allergy and one for asthma. Allergy to antibiotics was more common in children with previous adenoidectomy and recurrent infections. This is probably a result of repeated antibiotic treatments. That doctor-diagnosed allergy was more common in adenoidectomised children in the youngest age group stayed significant even when patients with doctor-diagnosed antibiotic allergies alone were excluded. In school-aged children, no statistical dif-

Table 3. Frequency of specific IgE against respiratory allergens in patients aged 7 to 17 years and controls.

	Patients 7-17 years (n=115)	Controls (n=155)	p <sup>1</sup>
Phadiatop screen	38 (33%)	57 (37%)	0.526
House dust mite	11 (10%)	21 (14%)	0.317
Cat	22 (21%)	31 (20%)	0.859
Horse	11 (10%)	14 (9%)	0.881
Dog	30 (26%)	28 (18%)	0.113
Timothy	19 (16%)	31(20%)	0.467
Mold	3 (3%)	4 (3%)	>0.999
Birch	25 (22%)	33 (21%)	0.929
Mugwort	15 (8%)	16 (10%)	0.488

<sup>1</sup> Chi-square test.

ference was seen when antibiotic allergies were excluded. It is possible that adenoidectomy is performed more readily to children with chronic rhinitis, both of allergic and non-allergic origin. The proportion of objectively assessed, sensitized children rose steadily with age and reached internationally reported levels in teenaged children (40%) in both patients and control children<sup>(25)</sup>.

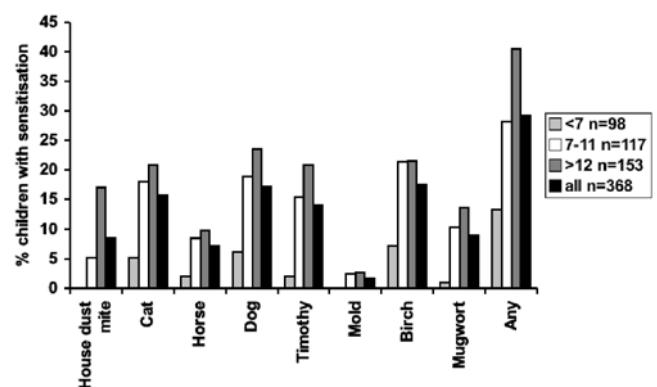


Figure 2. IgE sensitisation to respiratory allergens in different age groups.

Doctor-diagnosed asthma was also reported more often in children with previous adenoidectomy. In logistic regression analysis, this was associated with recurrent otitis media. Polymorphisms in loci encoding surfactant protein A, a component of the innate immunity response, have recently been suggested as a cause for this association between otitis media and bronchial asthma<sup>(26)</sup>.

The most important finding of the present study was a clear difference between symptomatic hypersensitivity or bronchial asthma compared with the presence of allergen-specific IgE to respiratory allergens in the serum, especially in children under 7 years of age. The hypersensitivity was associated with recurrent upper respiratory infections. Hypothetically, development of allergic symptoms may need a combination of inherited tendency to develop IgE antibodies together with infections caused by specific pathogens or recurrent infections. There may be other unknown factors that could predict development of symptomatic allergy.

We found that hypersensitivity disorders and upper respiratory infections commonly affect the same individuals. Our study suggests that symptomatic hypersensitivity and infections may not only share similar symptoms but even the same aetiological factors. Clinical allergy and asthma were significantly more common in children who had undergone adenoidectomy and were prone to upper respiratory infections especially in children under 7 years. By objectively measuring serum IgE for respiratory allergens we could find no differences.

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