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Original article

IgE sensitization, respiratory allergy symptoms, and heritability independently increase the risk of otitis media with effusion

Background and aims: Epidemiological evidence examining the role of atopy and/or allergy in the pathogenesis of otitis media with effusion (OME) is inconclusive. The aim of this study was to assess any increased risk for OME attributable to allergy-related factors, in a well-characterized population using a case-control design and multivariate analysis.

Subjects and methods: Eighty-eight 1–7-year-old children with OME, diagnosed by clinical and tympanometric evaluation and 80 matched controls were enrolled. A standardized questionnaire was completed, in order to assess factors related to OME and allergy-related symptoms and diagnoses using strict clinical definitions. Specific IgE was measured by skin-prick tests and/or CAP-FEIA.

Results: The patient and control groups were well matched. Factors conferring increased risk for OME in the univariate analysis included IgE sensitization, dyspnea, wheezing, asthma, paroxysmal sneezing, rhinitis, eczema, 'any allergic disease,' family history of otitis media, and family history of allergy. After multivariate analysis IgE sensitization, wheezing, nasal obstruction, family history of otitis, and child-care attendance remained as independent risk factors for development of OME.

Conclusion: IgE sensitization and respiratory allergy symptoms are independent risk factors for the development of OME, suggesting that both immunological and mechanical pathways may contribute to the development of the disease. Otitis heritability provides additional risk, as well as frequent exposure to viral upper respiratory tract infections in children attending daycare. Treatment and/or prevention of OME using anti-allergic medications should be further examined.

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Key words: allergic rhinitis; asthma; atopy; multivariate analysis; otitis media with effusion.

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Otitis media with effusion (OME) involves the accumulation of middle ear effusion (MEE) behind an intact tympanic membrane (TM) without signs or symptoms of acute infection. Otitis media with effusion is affecting up to 80% of preschool children at some time (1) and is the commonest cause of hearing loss in children in developed countries (2), potentially leading to language deficits (3). Therefore, effective prevention and treatment is considered imperative. However, current management options have been relatively suboptimal (3), leading many researchers during the last decades to attempt clarifying its unclear pathophysiology.

The possibility that allergy contributes to OME has been extensively discussed, but not conclusively ascertained (3–6). Analyses of the effusion content have consistently revealed significantly elevated levels of allergy-related mediators (IL-4, IL-5, IL-6, RANTES, ECP, tryptase, IgE), as well as differences between atopic and nonatopic patients with OME (7–10). However, epidemiological studies on OME have been controversial in this respect, showing increased (11, 12), or not affected (13, 14) prevalence of atopy and/or allergic diseases in OME patients. It has also been uncertain whether IgE sensitization *per se*, or clinical allergic disease(s) associated with mechanical eustachian tube (ET) dysfunction are involved in any reported associations (15–17). Factors that may explain this confusion include discrepancies in the definition of allergy, atopy, and IgE sensitization among different studies, nonhomogeneous patient populations, noncontrolled study designs, and lack of power.

We hypothesized that IgE sensitization, allergic diseases or both predispose to the development of OME. The aim of this study was to assess any increased risk for OME attributable to the above factors, in a well-characterized population using a case-control design and multivariate analysis.

Subjects and methods

Subjects

Between October 2002 and May 2004, 88 OME patients (56 males; age range: 1–6.7 years, mean: 4.5 years), and 80 controls (53 males; age range: 1.3–6.7 years, mean: 4.4 years), attending at the ENT department of P. & A. Kyriakou Children's Hospital, were enrolled. Informed consent was obtained from parents and the study was approved by the hospital's Ethics Committee.

Otitis media with effusion was diagnosed by a specialist based on clinical symptoms (hearing loss, otalgia, or irritability, 'plugged' feeling or 'popping' in their ears, speech, or behavioral disorders, tinnitus, vertigo), otoscopy and tympanometry after removal of wax from the ears. Children included in the study had type B or C tympanograms, with symptom duration of >1 month or a history of recurrent OME. Control subjects were enrolled from children attending the same department for reasons other than OME, mostly adenoidal or tonsilar hypertrophy and rhinosinusitis, had no history of OME, no frequent (>2 per year) episodes of otitis media (OM), no otoscopic findings of OM and type-A tympanogram.

Children with the following conditions were excluded from the study: acute OM, perforations of the TM, craniofacial abnormalities, sensoneural hearing loss, chronic underlying diseases or under chronic pharmaceutical management (except asthma and anti-asthmatic medication). Those with underage mothers and those whose parents/guardians were unable or unwilling to cooperate for the study were also excluded.

Study design

After enrolment, a standardized questionnaire was completed by the study physician (FMC). The questionnaire included information regarding date of examination, age, gender, country of birth, race, insurance, parental age, educational level, area of residence, number of siblings, exposure to tobacco smoke, daycare attendance, history of breast feeding, bottle feeding in supine position, birth weight, and gestational age, previous adenoidectomy, previous episodes of OM, family history of allergy, and OM. Lifetime prevalence of allergy-related diagnoses (asthma, eczema, rhinitis, conjunctivitis, urticaria, anaphylaxis, and food hypersensitivity) was assessed using strict clinical definitions (18–20).

The questionnaire was followed by clinical examination and performance of skin-prick tests (SPT) and/or CAP-FEIA to seven locally relevant allergens (grass mix, weed mix, dust mite mix, olive, cat, alternaria, and egg white), using the appropriate positive and negative controls. SPT wheals ≥3 mm in diameter and greater than the negative control were considered positive. CAP-FEIA ≥class 2 was considered positive. A blood sample was also obtained in which eosinophil counts and total IgE were assessed.

Statistical analysis

A power calculation was performed, based on the assumption that the proportion of controls that are exposed to the primary risk factor (IgE sensitization) was estimated at 20% and that the minimum odds ratio (OR) that we wished to detect was 3. For a two-sided test at the 5% level of significance and power 80%, 160 subjects needed to enter the study. Presuming a 3% withdrawal, 165 patients were planned to enter the study.

Statistical analysis was performed using SPSS 11.5.1 (SPSS Inc., Chicago, IL). The Mann–Whitney *U*-test and the Fisher's exact test were used for the comparison of continuous and categorical data, respectively. In all cases a $P < 0.05$ (two tailed) was considered significant.

The crude effect of various risk factors on OME development was assessed by univariate logistic regression. Subsequently, multivariate logistic regression was performed with a backward selection procedure, and removal criterion $P > 0.10$. The associations were measured and reported by OR and their corresponding 95% confidence intervals (CIs).

In addition to unique variables, the following composite variables were also analyzed: 'IgE-mediated allergic rhinitis,' 'IgE-mediated asthma,' and 'IgE-mediated eczema' defined as a history of the respective diseases combined with IgE sensitization, 'any allergic disease,' defined as a positive clinical history of asthma, rhinitis, eczema, or any combination of these, and 'atopy,' defined as the presence of 'any allergic disease,' as above, combined with IgE sensitization. Anaphylaxis, and food or drug reactions were not included in composite variables due to small number of cases and low reliability of clinical definitions (21, 22).

Results

Study population characteristics and assessment of confounders

The patient and control groups were comparable in respect to all demographic parameters and exposures to most risk factors for OME (23, 24), as shown in Table 1. All children were properly vaccinated according to their age. Cases had increased percentage of daycare attendance ($P = 0.02$).

Assessment of risk factors for OME development

Twenty-eight children (32%) with OME were sensitized to at least one allergen in comparison to 12 (15%) from the control group (OR = 2.64, 95% CI: 1.22–5.65,

Table 1. Demographic characteristics and otitis media with effusion (OME) predisposing factors in children with OME and controls

Factor	Cases	Controls	*P*
Gender (male) (%)	56 (64)	52 (65)	0.85
Age (years)	4.6 (1–7)	4.6 (1–7)	0.62
Daycare attendance (%)	77 (87.5)	58 (73)	0.02
Siblings (number)	0.9 (0–3)	0.8 (0–4)	0.23
Congregation at home (persons/room)	1.1 (0.5–4)	1.1 (0.4–5)	0.97
Birthplace (Greece) (%)	84 (95.5)	76 (95)	1.0
Paternal education [higher or further (%)]	35 (40)	23 (29.5)	0.15
Maternal education [higher or further (%)]	36 (41)	31 (40)	0.88
Residence (urban) (%)	55 (62.5)	48 (60)	0.74
Exposure to tobacco smoke (%)	32 (37)	32 (41)	0.58
Gestational exposure to tobacco smoke (%)	9 (10)	8 (10)	0.94
Prematurity (<36 weeks) (%)	3 (3)	6 (7.5)	0.31
VLBW (%)	1 (1)	2 (2.5)	0.60
Breast feeding (%)	63 (73)	62 (78.5)	0.43
Exclusive breast feeding for ≥4 months (%)	29 (35)	27 (34)	1.0
Bottle feeding in supine position (%)	28 (33)	24 (30)	0.76
Adenoidal hypertrophy (%)	59 (68)	54 (67.5)	0.97
History of adenoidectomy (%)	6 (7)	5 (6)	0.88

Numbers are mean (range) for continuous variable and number (percentage) for categorical variables.

Table 2. Univariate logistic regression analysis of risk factors for OME

	Cases *n* (%)	Controls *n* (%)	OR (*P*)	95% CI
IgE sensitization	28 (32)	12 (15)	2.64 (0.01)	1.24–5.65
Any allergic disease	53 (60)	34 (42.5)	2.05 (0.02)	1.11–3.79
IgE-mediated allergic disease (atopy)	21 (24)	6 (7.5)	3.87 (0.01)	1.47–10.15
Dyspnea	26 (29.5)	13 (16)	2.16 (0.04)	1.02–4.58
Wheezing	25 (28)	5 (6)	5.95 (0.001)	2.15–16.46
Recurrent cough	45 (51)	35 (44)	1.35 (0.34)	0.73–2.47
Asthma	29 (33)	14 (17.5)	2.32 (0.02)	1.12–4.79
IgE-mediated asthma	11 (12.5)	3 (4)	3.67 (0.05)	0.98–13.66
Rhinitis	37 (42)	22 (27.5)	1.91 (0.05)	1–3.66
Nasal obstruction	80 (91)	67 (84)	1.94 (0.17)	0.76–4.96
Rhinorrhea	56 (64)	41 (51)	1.67 (0.11)	0.89–3.07
Paroxysmal sneezing/ nasal itching	35 (40)	20 (25)	1.98 (0.04)	1.02–3.84
IgE-mediated allergic rhinitis	16 (18)	4 (5)	4.22 (0.01)	1.35–13.23
Conjuctivitis	5 (4.5)	6 (7.5)	0.73 (0.37)	0.37–1.44
Eczema	13 (15)	3 (4)	4.45 (0.02)	1.22–16.24
IgE-mediated eczema	7 (8)	0 (0)	* (0.01)	*
Food reactions	9 (10)	3 (4)	2.92 (0.12)	0.76–11.18
Drug reactions	12 (14)	8 (10)	1.4 (0.49)	0.54–3.63
Urticaria	24 (27)	16 (20)	1.5 (0.27)	0.73–3.09
Anaphylaxis	1 (1)	0 (0)	* (1.0)	*
Elevated eosinophil count (>4%)	20 (27)	19 (32)	0.78 (0.52)	0.37–1.65
Increased total IgE†	24 (52)	17 (39.5)	1.67 (0.23)	0.72–3.87
Family history of OM	31 (36)	11 (14)	3.48 (0.002)	1.6–7.56
Family history of allergy	51 (59)	36 (45)	1.78 (0.07)	0.96–3.29

*OR, 95% CI cannot be calculated because of 0 control.
†Cut-off values were according to age of the child.
OR, odds ratio; CI, confidence interval; OM, otitis media.

$P = 0.01$) (Table 2). There were no differences between groups in the proportion assessed by SPT (59/80, 60/88 in controls and cases, respectively), or CAP (21/80, 28/88 in controls and cases, respectively). In addition, dyspnea, wheezing, asthma, paroxysmal sneezing, rhinitis, eczema, and 'any allergic disease,' were also significant risk factors for the development of OME in the univariate analysis. Odds ratios were always higher when IgE-mediated allergic diseases were analyzed (Table 2). Finally, a positive family history of OME increased the risk of OME in the offspring by more than threefold ($P = 0.002$), while a marginally increased risk was also conferred by family history of allergy (Table 2).

In order to examine the relative importance of IgE sensitization, symptom, and heritability components on the risk for OME, multivariate logistic regression analysis was performed. The fitted model included: IgE sensitization, recurrent cough, wheezing, dyspnea, nasal obstruction, rhinorrhoea, paroxysmal sneezing/nasal itching, eczema, family history of allergy, family history of OM, gender, age, daycare, and adenoidal hypetrophy. After multivariate analysis, IgE sensitization, wheezing, and family history of OM remained as independent risk factors, while nasal obstruction and child care attendance were marginally significant (Table 3).

Table 3. Multivariate logistic regression analysis

	OR	95% CI	*P*
IgE-sensitization	2.52	1.06–5.99	0.04
Wheezing	8.17	2.68–24.92	<0.001
Nasal obstruction	2.84	0.96–8.36	0.06
Family history of OM	4.39	1.86–10.37	0.001
Daycare attendance	2.29	0.92–5.75	0.08

Estimated ORs and 95% CIs for the effect of IgE sensitization, wheezing, nasal obstruction, family history of otitis and daycare attendance on the risk of OME. The remaining parameters included in the model were not significant.
OM, otitis media.

Discussion

To our knowledge, this is the first study to describe concurrent and independent associations of OME with IgE sensitization, allergy-related symptoms and otitis heritability, conclusively confirming previously suggested relationships between allergic disease and OME.

A number of studies have attempted in the past to assess possible links between IgE-mediated allergy and OME (11, 12, 14, 16, 25–27). However, in none of these studies there was an adjustment for the effects of possible confounders and none made an attempt to differentiate between the components of atopic disease: IgE sensitization, symptoms, and heritability.

A high incidence of atopic disease among children with OME was initially reported in 1983 (11). An association between OME and IgE sensitization was described a decade later (12). However, in other similar studies the results were conflicting (13, 14). These discrepancies may be attributed to study design, including diagnostic criteria for allergy and differing populations.

Such potential problems were taken into account in the design of the present study. The population sample was restricted to the sensitive age range of 1–7 years; cases and controls were well matched; adenoidal hypertrophy, a factor associated with OME and possibly with allergy (24, 28), was also matched between the groups. Among exposure parameters, only daycare attendance was found to be more common in children with OME, remaining marginally significant after being included in the multivariate model. This is most probably related to increased frequency of viral respiratory infections, which are also the main triggers of rhinitis and acute asthma exacerbations (29).

The most important finding of this study is the demonstration of independent risk components associated with OME. It is not surprising that symptoms of respiratory allergy were independent risk factors for OME, while eczema was not. Several epidemiological studies, as also this one, have documented associations

between OME and allergic rhinitis (14–16). Experimental studies have shown a transient tubal dysfunction, evoked by nasal allergic reactions in sensitized animal models or patients with allergic rhinitis, without however resulting in MEE or histological change in the tympanic cavity (15, 17). On the other hand, anti-genic challenge into the tympanic cavity results in mucosal changes and mucociliary clearance impairment (17). Middle ear effusion can be produced after transtympanic injection of ovalbumin in sensitized rats, reduced after pretreatment with diphenhydramine (30). These observations suggested that allergic rhinitis-associated mechanical ET dysfunction might not be sufficient for the accumulation of MEE.

This is also supported by our finding that history of wheezing was in this study the strongest factor associated with OME development, independent of IgE sensitization and rhinitis. A mechanical effect of wheezing on ET function could be proposed as an explanation, however, this is not very likely, as wheezing in this age group is usually intermittent and of short duration. It is possible that additional mechanisms, such as epithelial dysfunction or defective responses to viral infections (31, 32) observed in asthmatic individuals, may also affect the middle ear, although these hypotheses require further evaluation.

In this respect, it is also interesting to note that associations with OME were stronger when IgE-mediated diagnoses were analyzed. The fact that IgE sensitization is independently associated with OME shows that immunological parameters, unrelated to mechanical obstruction, are associated with the disease: this supports previous suggestions that the middle ear may serve as a target organ for allergic reactions (33) and/or that the consequences of atopy, related to defective reactions to external stimuli, may also affect the middle ear.

Consequently, an augmented inflammatory response in the middle ear mucosa and a disruptive effusion clearance may act together for the development of OME.

An association of food allergy with OME has been reported in the past (25). This was not confirmed in our study, however, the etiology of reported food reactions was not properly evaluated in this study; it is well documented that only a small proportion of reported food reactions are true food allergy, or even hypersensitivity reactions (21).

A heritable predisposition for OME was also observed, as increased risk by both family history of OM and family history of allergy, of which the former was stronger and remained significant in the multivariate analysis. This is in agreement with previous epidemiological reports (34, 35), and it may represent additional factors, such as, e.g. anatomical variability, however, it may certainly be a composition of several heritability predispositions, including susceptibility to viral infection and/or allergic disease.

The main limitation of this study is the fact that it did not include objective measures for allergic disease diagnosis. However, objective measures of asthma and rhinitis at this age group are rather cumbersome and not completely reliable, while objective assessment of food and drug allergy requires double-blind challenges, which were out of the scope of this study. An objective measure (tympanogram) was used for the diagnosis of OME.

In conclusion, our results demonstrate that OME is independently associated with IgE sensitization, symptoms of respiratory allergy, and otitis heritability. Additionally, they are suggestive of an interaction of allergy and viral infections in the upper airways, leading to an increased risk of MEE development. Among the above factors, symptoms of respiratory allergy are the most straightforward targets for possible intervention; the effectiveness of relevant medications in preventing and/or treating OME should now be scrutinized.

References

1. Zielhuis GA, Rach GH, Van Den Broek P. The occurrence of otitis media with effusion in Dutch pre-school children. Clin Otolaryngol 1990;**15**:147–153.
2. Klein JO. The burden of otitis media. Vaccine 2000;**19**(Suppl. 1):S2–S8.
3. Rosenfeld RM, Culpepper L, Doyle KJ, Grundfast KM, Hoberman A, Kenna MA et al. Clinical practice guideline: otitis media with effusion. Otolaryngol Head Neck Surg 2004;**130**(Suppl. 5): S95–S118.
4. Fireman P. Otitis media and eustachian tube dysfunction: connection to allergic rhinitis. J Allergy Clin Immunol 1997;**99**:S787–S797.
5. Skoner DP. Complications of allergic rhinitis. J Allergy Clin Immunol 2000;**105**:S605–S609.
6. Lack G. Pediatric allergic rhinitis and comorbid disorders. J Allergy Clin Immunol 2001;**108**(Suppl. 1):S9–S15.
7. Smirnova MG, Birchall JP, Pearson JP. The immunoregulatory and allergy-associated cytokines in the aetiology of the otitis media with effusion. Mediators Inflamm 2004;**13**:75–88.
8. Jang CH, Kim YH. Demonstration of RANTES and eosinophilic cataionic protein in otitis media with effusion with allergy. Int J Pediatr Otorhinolaryngol 2003;**67**:531–533.
9. Hurst DS, Weekley M, Ramanarayanan MP. Evidence of possible localized specific immunoglobulin E production in middle ear fluid as demonstrated by ELISA testing. Otolaryngol Head Neck Surg 1999;**121**:224–230.
10. Hurst DS, Venge P. Evidence of eosinophil, neutrophil, and mast-cell mediators in the effusion of OME patients with and without atopy. Allergy 2000;**55**:435–441.
11. Borge P. Atopy and secretory otitis media. Immunological studies and responses to topical corticosteroid therapy. J Laryngol Otol 1983;**97**:117–129.

12. Corey JP, Adham RE, Abbass AH, Seligman I. The role of IgE-mediated hypersensitivity in otitis media with effusion. Am J Otolaryngol 1994;**15**:138–144.
13. Saim A, Saim L, Saim S, Ruszymah BH, Sani A. Prevalence of otitis media with effusion amongst pre-school children in Malaysia. Int J Pediatr Otorhinolaryngol 1997;**41**:21–28.
14. Caffarelli C, Savini E, Giordano S, Gianlupi G, Cavagni G. Atopy in children with otitis media with effusion. Clin Exp Allergy 1998;**28**:591–596.
15. Mogi G, Tomonaga K, Watanabe T, Chaen T. The role of type I allergy in secretory otitis media and mast cells in the middle ear mucosa. Acta Otolaryngol Suppl 1992;**493**:155–163.
16. Mion O, De Mello Jr JF, Lessa MM, Goto EY, Miniti A. The role of rhinitis in chronic otitis media. Otolaryngol Head Neck Surg 2003;**128**:27–31.
17. Tomonaga K, Chaen T, Kurono Y, Mogi G. Type I allergic reactions of the middle ear and eustachian tube: an experimental study. Auris Nasus Larynx 1990;**17**:121–131.
18. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the world allergy organization, October 2003. J Allergy Clin Immunol 2004;**113**: 832–836.
19. Bachert C, Van Cauwenberge P. The Who Aria (allergic rhinitis and its impact on asthma) initiative. Chem Immunol Allergy 2003;**82**:119–126.
20. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ et al. The U.K. working party's diagnostic criteria for atopic dermatitis. I. derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol 1994;**131**:383–396.
21. Ortolani C, Bruijnzeel-Koomen C, Bengtsson U, Bindslev-Jensen C, Bjorksten B, Host A et al. Controversial aspects of adverse reactions to food. European Academy of Allergology and Clinical Immunology (EAACI) Reactions to Food Subcommittee. Allergy 1999;**54**:27–45.
22. Demoly P, Bousquet J. Drug allergy diagnosis work up. Allergy 2002; **57**(Suppl. 72):37–40.
23. Daly KA, Hunter LL, Giebink GS. Chronic otitis media with effusion. Pediatr Rev 1999;**20**:85–93.
24. van Cauwenberge PB, Bellussi L, Maw AR, Paradise JL, Solow B. The adenoid as a key factor in upper airway infections. Int J Pediatr Otorhinolaryngol 1995;**32**(Suppl.):S71–S80.
25. Aydogan B, Kiroglu M, Altintas D, Yilmaz M, Yorgancilar E, Tuncer U. The role of food allergy in otitis media with effusion. Otolaryngol Head Neck Surg 2004;**130**:747–750.
26. Irander K, Borres MP, Bjorksten B. Middle ear diseases in relation to atopy and nasal metachromatic cells in infancy. Int J Pediatr Otorhinolaryngol 1993;**26**:1–9.
27. Bernstein JM, Lee J, Conboy K, Ellis E, LI P. The role of IgE mediated hypersensitivity in recurrent otitis media with effusion. Am J Otol 1983;**5**:66–69.
28. Fokkens WJ, Vinke JG, De Jong SS, Bogaert DP, Kleinjan A, Eichhorn E. Differences in cellular infiltrates in the adenoid of allergic children compared with age- and gender-matched controls. Clin Exp Allergy 1998;**28**:187–195.
29. Papadopoulos NGPS, Manoussakis E, Saxoni-Papageorgiou P. The role of respiratory viruses in the origin and exacerbations of asthma. Curr Opin Allergy Clin Immunol 2003;**3**:39–44.
30. Labadie RF, Jewett BS, Hart CF, Prazma J, Pillsbury HC III. Allergy increases susceptibility to otitis media with effusion in a rat model. Second place–resident clinical science award 1998. Otolaryngol Head Neck Surg 1999;**121**:687–692.
31. Holgate ST. Asthma and allergy–disorders of civilization? QJM 1998;**91**: 171–184.
32. Papadopoulos NG, Stanciu LA, Papi A, Holgate ST, Johnston SL. A defective type 1 response to rhinovirus in atopic asthma. Thorax 2002;**57**:328–332.
33. Ogra PL. Mucosal immune response in the ear, nose and throat. Pediatr Infect Dis J 2000;**19**(Suppl. 5):S4–S8.
34. Daly KA, Rich SS, Levine S, Margolis RH, Le CT, Lindgren B et al. The family study of otitis media: design and disease and risk factor profiles. Genet Epidemiol 1996;**13**:451–468.
35. Casselbrant ML, Redfern MS, Furman JM, Fall PA, Mandel EM. Visual-induced postural sway in children with and without otitis media. Ann Otol Rhinol Laryngol 1998;**107**:401–405.