

Otitis Media in Infancy and the Development of Asthma and Atopic Disease

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Abstract Otitis media is a frequent respiratory infection of early childhood and it is important to fully understand the long-term complications and sequelae. Literature examining otitis media in early childhood and subsequent development of atopic disease is sparse despite there being vast literature on the association between respiratory infections and atopic disease. Current data support the hypothesis that otitis media infections in early life, especially frequent or severe infections, influence the developing immune system, resulting in increased risk for asthma. Recent findings have also reported an association between otitis media and eczema. Atopic children and those with a family history of atopy appear to be at greater risk. Future work should investigate the specific mechanisms involved. It is possible that vaccines and preventive strategies aimed at reducing the burden of otitis media could also reduce the burden of childhood asthma and atopic disease.

Keywords Otitis media · Asthma · Atopy · Atopic disease · Respiratory infection · Eczema · Hygiene hypothesis · Infancy

Introduction

Otitis media is a frequent respiratory infection of early childhood and one of the most common reasons children visit a physician or are prescribed antibiotics [1]. The economic burden attributed to otitis media is significant and improved understanding of long-term complications and sequelae is therefore important [2].

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Numerous studies have investigated the possible association between respiratory infections during early childhood and subsequent development of asthma [3•].

Unfortunately, there remains uncertainty due to the fact that current literature is split between supporting one of two theories: that early life infections are associated with the development of atopic disease; and the hygiene hypothesis, which states that infections in early life protect against allergic diseases. Although there is overwhelming evidence in support of the hygiene hypothesis, there is also evidence for the first hypothesis—even across studies that have examined the same infectious agent [4•].

Otitis media generally occurs when viral or bacterial pathogens colonize the middle ear cavity. The middle ear mucosa has the same immunological capabilities as the upper and lower respiratory airways, and the viruses responsible for the common cold (rhinovirus), bronchiolitis (respiratory syncytial virus) and influenza have been isolated in middle ear fluid [5, 6]. It is clear that viruses play a role in asthma etiology and exacerbation [7]. Previous research suggests that severe viral infections during infancy may predispose individuals to wheeze, asthma and allergic sensitization, while the results for mild respiratory infections have been inconsistent [8, 9]. Lower respiratory tract infections caused by respiratory syncytial virus have been consistently associated with early life wheeze and the development of asthma, and evidence is increasing to support a similar association for human rhinovirus [3•, 10]. Literature examining upper respiratory tract infections, specifically otitis media, has been lacking despite the presence of similar innate and adaptive immune responses throughout the upper and lower airways.

Recent Findings

We previously reported associations between physician-diagnosed otitis media during the first 2 years of life and

atopic disease in a population-based birth cohort of 1,690 German children [11•]. There were consistent positive associations between early life otitis media and school age asthma (Table 1) and late onset allergic eczema [OR 2.68 (95 % CI:1.35–5.33)]. Effect estimates increased when analyses were restricted to children with maternal atopic diseases: 5.50 (1.23–24.6) for asthma and 6.17 (2.06–18.5) for eczema for children with three or more episodes of otitis media during the first 2 years of life. There was no consistent association between early life otitis media and allergic rhinitis.

Eldeirawi and colleagues recently reported on a cross-sectional study of otitis media in infancy and development of childhood asthma [12•]. This study included 2,023 Mexican school children, and disease was ascertained by parental report of physician diagnosis. They found positive associations between otitis media during the first year of life and asthma at school age. Similar to our previous findings, the magnitude of the adjusted estimates increased with otitis media frequency, and results were statistically significant only for those children with more than three episodes of otitis media during infancy (Table 1).

Otitis media is multi-factorial, and there exist different sub-categories of disease. In acute otitis media, the infection often begins as an upper respiratory tract infection and then spreads through the eustachian tube(s). In otitis media with effusion, eustachian tube dysfunction leads to a build-up of fluid in the middle ear cavity. Otitis media with effusion often presents without signs of acute infection, suggesting that viral and bacterial pathogens may not be as important for this sub-entity. Atopy has been cited as an independent risk factor for otitis media with effusion, and chronic otitis

has been classified as an allergic disease in numerous studies [13•, 14, 15]. Atopic asthma and allergic rhinitis have also been identified as risk factors for recurrent otitis media in a cohort of 323 healthy children [16], but the findings were not consistent and may have been a result of confounding by atopy.

Discussion

The association with atopy may highlight a mechanism for the positive association between otitis media and asthma. Atopic children tend to suffer more frequent and prolonged bouts of respiratory tract infections, and the resulting inflammation of the respiratory mucosa and infiltration of immune cells could be a first step in asthma pathogenesis. Family history of atopy has been important in previous studies of infection and asthma. One study found significant associations between early life infections and persistent wheeze at school age only if children had at least one atopic parent [17]. A prospective birth cohort of children with parental atopy reported an association between febrile infections of the lower respiratory system and asthma at 10 years [RR 2.57 (95 % CI:1.33–4.98)]; particularly if the children were atopic prior to their second birthday [RR 4.92 (95 % CI:2.59–9.36)] [18•].

Associations between early life otitis media and asthma development have been reported previously [19–21]. However, the most interesting evidence linking early exposure to infectious diseases with programming of the developing immune system are our findings for atopic eczema [11•]. Unlike asthma and allergic rhinitis, eczema does not manifest in the respiratory system, and the association we reported between otitis media and atopic eczema supports the theory that early life infection influences the development of the immune system. This is supported by previous findings where children diagnosed with otitis media with effusion were found to have more atopic eczema [22], and a positive association between bronchitis and eczema was reported [23]. A more recent study found no relationship between respiratory infections during the first year of life and incidence of atopic eczema during the second year of life in a population-based cohort study of 370 German children, but it is possible that the follow-up period of this study was too short [24].

Inflammation of the upper airways, particularly the eustachian tubes, is part of the causal pathway by which otitis media occurs. A high correlation between symptom scores suggestive of otitis media with effusion and rhinitis has previously been noted in school entrant children [25, 26], but due to the paucity of literature available, it is not possible to draw conclusions about the association between otitis media and rhinitis at this time.

Table 1 Association between otitis media in infancy and asthma development during school age, as reported by Eldeirawi et al. [12•] and MacIntyre et al. [11•]

Otitis media during infancy ^a	Asthma during school-age ^b	
	Eldeirawi et al. [12•] aOR (95 % CI) ^c	MacIntyre et al. [11•] aOR (95 % CI) ^d
None	1.00	1.00
1–2 episodes	1.38 (0.82–2.33)	–
≥2 episodes	–	1.67 (0.48–5.87)
≥3 episodes	3.09 (1.62–5.86)	4.26 (1.34–13.6)

^a Infancy defined as the first year of life [12•] and as the first 2 years of life [11•]

^b Asthma diagnoses ascertained between 6 and 13 years [12•] and at 6 years [11•]. Children diagnosed with asthma during infancy were excluded from all analyses

^c Adjusted for age, sex, country, antibiotic use, regular doctor or clinic and family history of atopy

^d Adjusted for sex, older siblings, city, parental education, breastfeeding and daycare attendance

Antibiotic use during infancy has been examined as a possible risk factor for childhood asthma. A recent systematic review found that antibiotic use during infancy slightly increased the risk of asthma by age 18 years, and these results remained statistically significant after adjusting for respiratory infections [27]. However, other studies have reported that the effect of antibiotic use became non-significant after adjusting for respiratory infection (bronchitis, otitis media and pneumonia) [28], and reverse causation and confounding by indication have been cited as possible explanations for the association with antibiotic use [29]. Early life infections and school-age atopic disease were examined in our prospective birth cohort and febrile respiratory tract illnesses, not antibiotics, were found to be a predictor of asthma at school age [30]. Furthermore, Eldeirawi and colleagues [12••] adjusted for antibiotic use in their analysis of otitis media and asthma.

Reverse causation, for viral otitis media with effusion in particular, must be carefully considered when evaluating these studies, because allergic inflammation of the respiratory epithelium may predispose a child to respiratory infection. And, conversely, during viral infection of the upper respiratory tract, congestion and inflammation of the mucosa lining the eustachian tube and middle ear promote additional viral and bacterial infection by impairing eustachian tube function; and these same viruses may induce wheeze and asthmatic symptoms [31]. On a similar note, it is also possible that asthma increases the risk for otitis media, because chronic inflammation of the airways can impair mucociliary clearance thus making the host more susceptible to pathogens; increased mucus production, epithelium disruption, and alterations in innate or adaptive immune responses have also been cited as mechanisms [32]. Both the recent studies described above [11••, 12••] excluded children who had received asthma diagnoses during infancy.

The study of otitis media and allergic disease is complex, and future studies should aim to prospectively characterize the natural history of otitis and allergic symptoms and/or physician diagnoses throughout childhood, as well as include a standardized measure of atopy. Atopic eczema should be considered in addition to asthma. Longitudinal studies are best suited to address the limitations of previous studies, i.e. recall bias, detection bias, reverse causation, and confounding by indication.

Conclusions

Our understanding of the relationship between early life otitis media and incidence of atopic disease at school age is improving, but uncertainty remains surrounding the specific mechanisms involved. Current literature supports the hypothesis that otitis media infections in early life, especially frequent or severe infections, increase the risk of asthma and possibly

atopic eczema. There is currently no evidence for an association with allergic rhinitis. Atopic children and those with a family history of atopy are at greater risk. It is possible that vaccines and preventive strategies aimed at reducing the burden of otitis media could also reduce the burden of childhood asthma and atopic disease, and further research into this area is warranted.

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- Of importance
- Of major importance

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