Risk Factors for Recurrent Acute Otitis Media and Chronic Otitis Media with Effusion in Childhood

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José Faibes Lubianca Neto and Tania Sih

Host-associated Risk Factors for RAOM

Allergy

Although there is epidemiologic, mechanical, and therapeutic evidence showing that allergic rhinitis contributes to the pathogenesis of otitis media, there are still many controversies about its influence as a risk factor. Kraemer et al. [1], in a case-control study, compared the prevalence of atopic symptoms in 76 cases submitted to tympanotomy for the placement of ventilation tubes with 76 controls paired by age, sex, and season of the year on admission to have general pediatric surgery performed. The cases presented with approximately four times more complaints of atopic symptoms. Through a cohort of 707 children with recurrent acute otitis media (RAOM), Pukander and Karma [2] found more persistent middle-ear effusion (MEE) for 2 months or longer in children with atopic manifestations than in those that were non-allergic. Bernstein et al. [3] followed up 77 children who had RAOM with chronic MEE, and who had at least one ventilation tube placement performed. There was increased IgE in the MEE in 14 out of 32 children with allergic rhinitis, compared with 2 out of 45 children considered to be nonallergic. In an interesting German cohort study through the first two years of life, children diagnosed with otitis media during infancy were at greater risk for developing late-onset allergic eczema and asthma during school age, and associations were stronger for frequent otitis media [4].

On the other hand, there are also well-delineated articles on allergic rhinitis, which have not been able to demonstrate association with RAOM [5−7]. Interestingly, contributing to this discordance, there are two meta-analyses of risk factors for RAOM with conflicting results. Whereas Uhary et al. [8] did not find significance of the association of atopy and RAOM, Zhang et al. [9] have shown a significant pooled odds ratio of 1.36 (confidence interval, CI 1.13–1.64).

Craniofacial Abnormalities

There is higher incidence of otitis media in children with uncorrected cleft palate than in normal children, mainly when considering those aged up to 2 years [10]. When, however, the cleft is corrected, RAOM is reduced [11], possibly because

J. F. L. Neto (✉)
Department of Otolaryngology and Pediatric Otorhinolaryngology, Santo Antônio Children's Hospital, Rua Dona Laura, 320/9th floor, Porto Alegre, RS 90430-090, Brazil
e-mail: Lubianca@otorrinospoa.com.br

Department of Clinical Surgery, Medical School of Federal University of Health Sciences, Porto Alegre, RS, Brazil

T. Sih
Department of Pediatric Otolaryngology, Medical School University of São Paulo, 306 Mato Grosso St. suite 1510, São Paulo, SP 01239-040, Brazil
e-mail: tsih@amcham.com.br

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it allows improved Eustachian tube function [12]. In a retrospective cohort, Boston et al. [13] demonstrated that the presence of craniofacial deformities increased the chance of the child requiring multiple interventions for ventilation tube placements. Otitis media is also more prevalent in children with craniofacial abnormalities and Down's syndrome.

Gastroesophageal Reflux (GER)

Much of the evidence about the association of Gastroesophageal reflux (GER) and RAOM is of level III or IV, and comes from reports on cases or series of patients and from studies in animals. In 2001, four cases were reported of adults with chronic otitis media that was difficult to resolve and who, after diagnosis of GER, had been confirmed by pHmetry and endoscopy, started treatment with omeprazole and had their conditions resolved. One of these patients restarted bilateral otorrhea after suspension of the drug and had the situation controlled again with the reintroduction of omeprazole [14].

After 2002, several studies were carried out. A randomized clinical trial in rats showed that infusion of hydrochloric acid/pepsin solution in the rhinopharynx was capable of causing dysfunction in the pressure regulation and mucociliary depuration of the middle ear, contrasting to the effects of a saline infusion in the region [15]. Rosmanic et al. [16], by means of pHmetry, demonstrated pathologic GER in 55.6% of children with RAOM or chronic suppurative otitis media (COME), and as a result recommended double channel pHmetry in children who did not respond to conventional otitis media treatments. Tasker et al. [17] measured the pepsin concentration in MEE samples, and showed that 83% of them contained pepsin/pepsinogen at a concentration over 1000 times higher in relation to the serum concentration, concluding that gastric juice reflux may be the major cause of MEE in children. The same group of authors in a more sophisticated study reproduced their previous results and concluded that "it is almost certain that pepsin in MEE comes from acid content reflux and that there may therefore, be a role for anti-reflux therapy in the treatment of COME" [18]. This enthusiasm was not confirmed in the conclusions of other publications, as the study of Antonelli et al. [19], for example, who measured the total pepsinogen concentration in 26 acute otorrhea samples after ventilation tube placement and found pepsinogen in some cases, but at low concentrations, lower than normal serum levels. By other means, Pitkaranta et al. [20] also did not find evidence of the association of MEE and GER. Analyzing the presence of *Helicobacter pylori* through serological tests to detect antigens and through adenoids and MEE cultures, they found only 20% of the serological tests positive, and in none of the cases was there growth of the germ in adenoid or middle-ear cultures.

In a recent systematic review dealing only with the association between otitis media and gastroesophageal reflux, Miura et al. [21] concluded that "the prevalence of GER in children with COME/RAOM may be higher than the overall prevalence for children. Presence of pepsin/pepsinogen in MEE could be related to physiologic reflux. A cause-effect relationship between pepsin/pepsinogen in MEE and otitis media is unclear. Anti-reflux therapy of otitis media cannot be endorsed based on the existing research."

Adenoids

Those that defend the association between adenoid tissue hyperplasia and RAOM or COME base it on three different types of evidence. There are those that prefer articles pointing out great correlation (approximately 70%) between the rhinopharyngeal bacteria and those cultivated in the MEE in acute episodes [22] or those that point towards a larger number of colony counts in adenoid cultures coming from cases operated on for RAOM as compared with those operated on for obstruction [23]. The theory that adenoids functioning as a bacterial reservoir is more accepted currently than the theory of mechanical obstruction of the tube by adenoidal growth, a fact rarely proved in clinical practice [23]. Notably, randomized clinical trials have demonstrated

a positive effect of adenoidectomy on reducing various end points related to otitis media [24–27].

However, there are well-delineated and well-conducted randomized clinical trials with conflicting results, demonstrating that adenoidectomy alone or associated with ventilation tube placement does not play a role in the prophylaxis of RAOM in children younger than 2 years [28, 29] at least at the first ventilation tube placement [27].

A recent meta-analysis of risk factors for RAOM [9] analyzed the potential role of large adenoids as a risk factor for RAOM. The meta-analysis examined two factors that may be linked to the presence of large adenoids-chronic nasal obstruction and snoring. Whereas results did not show any association of chronic nasal obstruction with RAOM, it showed that persistent snoring almost doubled the frequency of RAOM (OR 1.96; CI 1.78–2.16).

In conclusion, it would appear that original investigations dealing with adenoid hyperplasia and risk of RAOM or COME are lacking, and that the level of existing evidence is primarily based on expert opinion (level of evidence V) or indirect end points. The evidence comes from studies that assess the effect of adenoidectomy on events related to otitis media. It would seem that adenoidectomy is more efficient in the treatment of COME than in RAOM, and the majority of authors agree that adenoidectomy must be performed, irrespective of the size of the adenoids [30], at least when the second ventilation tube placement is performed (level of evidence I).

Genetic Susceptibility

There is anatomic, physiologic, and epidemiologic evidence showing a genetic predisposition to RAOM. In a huge prevalence study in Greenland, the positive parental history for RAOM was one of the two factors that remained a significant predictor of RAOM after the logistic regression was performed [31]. In the meta-analysis of Uhari et al. [8], positive history of acute otitis media (AOM) in any other member of the family, increased the risk for AOM in a child by 2.63 times (CI 1.86–3.72). A marker of genetic inheritance, the HLA-A2 antigen, was found more frequently and the HLA-A3 less frequently in children with RAOM than in healthy children [32, 33].

The strongest evidence of a genetic susceptibility to RAOM was shown in studies evolving twins and triplets. There are two retrospective studies. The first one, with 2750 Norwegian twin pairs, has estimated the heritability in 74% in girls and 45% in boys [34]. In the second study, with a sample of 1373 twin pairs, the estimated heritability in the ages of 2, 3, and 4 years to RAOM was, in the average, 0.57 [35]. In the prospective twins and triplets Pittsburgh study, where monthly monitoring of the middle ear was done, the estimated heritability of otitis media at the 2-year end point was 0.79 in girls and 0.64 in boys [36]. Of the original 140 pairs of twins and triplets with determined zigosity, 114 were followed up to the age of 3 and the 83 pairs followed up to the age of 5. The correlation between twins for the proportion of time with MEE was significantly higher in the monozygotic (0.65–0.77) than in the dizygotic (0.31–0.39) twins for each year until the third year. Later, it decreased, a result explained by the decrease in the incidence of otitis media in the older children. The estimates of discordance for three or more episodes of MEE in monozygotic and dizygotic twins followed up to the 5 years was 0.02 and 0.40, respectively ($p = 0.07$). The estimated heritability of the proportion of time with MEE in the first 5 years of life was 72% ($p < 0.001$). The correspondent estimative for boys and girls separately was 0.66 and 0.75, respectively. The results of the 5-year study still continue to support a strong genetic component to otitis media [37].

Another approach to get clues to the genetic susceptibility to RAOM is the linkage studies searching for candidates genes that predisposes to RAOM in the whole genome. As otitis media is a multifactorial disease in humans, it is not probable that one unique gene is the cause of otitis media. Linkage studies have already shown that there are some hotspots in the genome for RAOM. The first linkage study was performed by Daly et al. [38] that provided evidence of linkage of COME and RAOM to 10q26.3 and to 19q13.43. Another study was conducted at

Pittsburgh on a population of full siblings, two or more, who had a history of tympanostomy tube insertion due to a significant history of otitis media, their parent(s) and other full sibling(s) with no history of tympanostomy tube insertion. The study did not provide evidence for linkage in the previously reported regions. Most significant linkage peak was on chromosome 17q12, that include AP2B1, CCL5, and a cluster of other CCl genes, and in 10q22.3, STFPA2 [39].

The genetic predisposition to otitis media is only starting to be discovered. Potential therapeutic targets are the genes regulating mucin expression, mucus production, and host response to bacteria in the middle ear (Li et al. 2013). The identification of the susceptibility genes to otitis media could improve the knowledge of the otitis media physiopathology and provide development of molecular diagnostic methods that could be used to establish the risk for otitis media of a specific child and perhaps modify the follow-up and the treatment according to this established risk.

Environmental Risk Factors for RAOM

Upper Respiratory Tract Infections (URTI)

Both epidemiologic evidence and clinical experience strongly suggest that otitis media is frequently a complication of URTI. The incidence of COME is greater during autumn and winter months, and less in summer in both hemispheres [40, 41], parallel to the incidence of AOM [42, 43], and URTI [40, 41]. URTI increases the incidence of AOM. In a meta-analysis by Zhang et al. [9], pooled analyses showed that URTI increase the risk of otitis media almost sevenfold (OR 6.59; 95% CI 3.13–13.89). Revai et al. [44] evaluated 623 URTI episodes in 112 children (6–35 months of age) and found an AOM associated incidence of 30%. In another prospective cohort [4] of 294 healthy children (6 month to 3 years of age), the overall incidence of OM complicating URTI was 61%, including 37% AOM and 24% COME. Having had recurrent URTI in the past 12 months was one of the variables in the multivariable model that increased the risk of RAOM in a 2010 study [45]. This evidence supports the assumption that URTI plays an important role in the etiology of otitis media (level of evidence II), and prevention of viruses may decrease the incidence of RAOM.

Studies that have tried to isolate MEE virus in children have indeed demonstrated both viral antigens and even live viruses in MEE [46–48]. Among the various mechanisms by which URTI may predispose patients to RAOM and COME, are inflammation and harm to the mucocilliary movement of the epithelium that lines the auditory tube, which has been demonstrated both experimentally [49] and clinically [50]. Viral URTI promotes the replication of the bacterial infection and increases inflammation in the nasopharynx and ET.

Day-care Center Attendance

Day-care center attendance has been considered a major risk factor for developing RAOM for a long time. Alho et al. [51] examined questionnaires that were sent to 2512 randomly selected Finnish children's parents and also reviewed their clinical record cards and found an estimated relative risk of 2.06 (95% CI 1.81–2.34) for development of AOM in children that frequented day-care centers when compared with care in their own homes. It was also demonstrated that children in day-care centers are more prone to needing ventilation tube insertion than children cared for at home. In another analysis, the risk found for COME was 2.56 (95% CI 1.17–5.57) [52].

It would appear that the setting of where the child is cared for influences this association. It has been shown that susceptibility to AOM diminished in a group of children who are cared for in family homes, in comparison with day-care center attendance [5, 6]. The prevalence of negative pressure in the middle ear and type B tympanograms, indicative of MEE, are greater in children cared for in day-care centers with many others; intermediate in children cared for

in family homes with fewer "companions" and less still in children cared for at home [52, 53]. In the meta-analysis of Uhari et al. [8], the risk of AOM also increased with child care outside the home (RR 2.45; 95% CI 1.51–3.98) and although on a lower scale, also with care in family homes (RR 1.59; 95% CI 1.19–2.13). It is postulated that the risk is proportional to the number of "companions" the children are in contact with [5, 6]. Large group child care centers increase otitis media incidence and were defined as those in which professional educators provided care for up to 10 groups of 8–12 children in the same setting [54]. A possible mechanism is related to the greater number of URTI presented by children that are exposed to many other children [55]. In conclusion, there would appear that there is little doubt here, day-care center attendance is a risk factor for RAOM and COME (level of evidence II). Alho et al. [56] in a hypothetical cohort estimated that if 825 children were transferred from day-care centers to home care and followed up for 2 years, approximately two out of five affected would escape RAOM.

Family Size (Siblings)

Greater incidence of AOM and COME is described in children belonging to big families (especially if many of them are under 5 years of age) [10, 57]. History of RAOM in siblings is considered to be a risk factor [5, 58]. Birth order was also associated with the rate of otitis media episodes and with the percentage of time with MEE, with the first child having the lower rates in the first 2 years of life than the others with older siblings [58]. The chance of RAOM increases 4.18 times (95% CI 2.74–6.36) in the younger generation among siblings [59]. Also, having more than one sibling was found to be significantly related to early onset of otitis media [60].

The findings of the studies dealing with this risk factor, however, are not unanimous. A population study by Vinther et al. [61] did not demonstrate that family size was a risk factor for otitis media. The same was seen in the classical cohort study by Teele et al. [62]. It is very difficult to separate the influence of genetics from care in day-care centers and the socioeconomic level itself (families with lower purchasing power tend to be larger) from the exclusive effect of the number of siblings as a risk factor. In the meta-analysis of Uhari et al. [8], which pooled the results of two previous conflicting studies [5, 62], an increase of 92% in the incidence of otitis media if there is at least one sibling was shown (RR 1.92; 95% CI 1.29–2.85).

Passive Smoking

It is one of the most studied risk factors for RAOM. From 1978 to 1985, only case-control and cross-sectional studies with some methodological limitations were published, followed by well-designed cohorts later in 1985 and meta-analysis in 1996. The first class of studies were more controversial, showing positive [1, 63–65] and negative [61, 66–69] associations between otitis media (AOM, COME) and second-hand smoke exposure.

The first prospective cohort study of Iversen et al. [70] studying 337 children recruited in day-care centers, showed smoking as a risk for COME, with the additional finding that the risk associated with passive smoking increased with age. Zielhius et al. [70] followed up a cohort of 1463 children and found a relative risk for COME of 1.07 (95% CI 0.90–1.26) in children exposed to passive smoking. In 1993, follow up of 698 children demonstrated that the presence of smokers and greater numbers of cigarette packs smoked daily in the house increased time with MEE [71]. Ey et al. [72] prospectively analyzed 1013 children from birth to 1 year old, demonstrating that mothers' heavy smoking (20 or more cigarettes/day) was a significant risk factor for RAOM, with a relative risk of 1.78 (95% CI 1.01–3.11) in multivariate analysis. In another prospective cohort involving 918 children, it was demonstrated that children whose mothers smoked 20 or more cigarettes a day were at significantly increased risk of having four or more episodes of AOM (RR 1.8; 95% CI 1.1–3.0) and of having the first episode of AOM much earlier (RR 1.3;

95% CI 1.0–1.8). The risk of RAOM increased parallel to the number of cigarettes smoked [73]. In another prospective cohort study, children who underwent insertion of tympanostomy tubes were followed up for 12 months. Maternal smoking increased the risk for RAOM (OR 4.15; CI 1.45–11.9) after insertion of ventilation tubes [74].

There are at least four studies that measured objectively the exposure to tobacco smoking through a nicotine metabolite (cotinine) in saliva and urine. In 1987, Etzel [75] conducted a retrospective cohort of 9 years with 132 day-care children. He measured exposure to passive smoking through salivary cotinine concentration. The incidence density rate of MEE was 1.39 (95% CI 1.15–1.69) and 1.38 (95% CI 1.21–1.56) in the first year and in the first 3 years of life, respectively. However, the significance disappeared with the introduction of other variables in the logistic regression. In 1989, Strachan et al. [66] did not find association between salivary cotinine and otitis media. In 1999, Daly et al. [6] were unable to demonstrate association between the early onset of AOM and the rate of cotinine–creatinine in urine. In 2001, Ilicali et al. [76] found that around 74% of the children in the "case" group required surgical intervention by RAOM or COME and 55% in the "control" group were exposed to passive smoking ($p = 0.046$).

At least three meta-analyses studied the association of passive smoking with RAOM and COME. The first was done by Uhari et al. [8], demonstrating a significant increase of 66% (RR 1.66; 95% CI 1.33–2.06). Strachan and Cook [63] demonstrated estimated relative risks, if at least one of the parents smoked, of 1.48 (95% CI 1.08–2.04) for RAOM, of 1.38 (95% CI 1.23–1.55) for MEE, and of 1.21 (95% CI 0.95–1.53) for COME. Finally, Zhang et al. [9] calculated a risk of 1.92 (95% CI 1.29–2.85) for RAOM.

In conclusion, although some authors have declared the relationship between RAOM and COME with passive smoking as firm [77], others are against such affirmation [78]. It may be said that passive smoking does not increase the chance of nonrecurrent AOM (level of evidence IV). With regard to RAOM and COME, passive smoking is a probable risk factor (level of evidence II).

Breast-feeding

The majority of researchers believe that breast-feeding protects against otitis media. In a prospective cohort of Saarinen et al. [78], children that were breast-fed up to 6 months of age did not have any episodes of AOM, whereas 10% of those that started with cows' milk before they were 2 months old presented with such episodes in this period. At the end of the first year, the incidence of two or more episodes of otitis was 6% in the first and 19% in the second group. From the end of the first up to the third year, four or more episodes of otitis occurred in 6% of breast-fed children, compared with 26% of those artificially fed. Although there were many subjects lost to follow-up in the study, it was shown that prolonged breast-feeding (6 months or longer) protects the child against RAOM up to the third year of life. The group that used cows' milk had the first AOM episode much earlier.

The retrospective study of Cunningham et al. comprising 503 patients, found 3.7 and 9.1 episodes per 1000 patients/week for the breast-fed and artificially fed groups, respectively. In this study, with adequate control of confounding factors, significant difference was shown (total number of episodes—23 vs. 182) [79]. Case-control studies also showed a significantly lower number of episodes of otitis in the first 2 years in breast-fed children in comparison with those that were fed with cows' milk (0.3 episodes (9/30) compared with the 2.9 (86/30) episodes) [80]. Stahlberg et al. [7], in a case-control study with 115 children "prone to otitis," hospitalized to have adenoidectomy performed, demonstrated association between the duration of breast-feeding and age of introduction to cows' milk with RAOM. Duncan et al. [81] followed up 1013 nursing infants for 1 year and demonstrated that those that were exclusively breast-fed for 4 months or longer, had half the number of AOM episodes, compared with non-breast-fed infants, and 50% less otitis than those that were breast-fed for less than 4 months. A cohort of 306 children followed up for the first 2 years demonstrated that between 6 and 12 months of age, the cumulative incidence of first episodes increased from

25 to 51% in exclusively breast-fed infants and from 54 to 76% in nursing infants fed on formulas since birth. The peak of AOM incidence and MEE was inversely related to the breast-feeding rates beyond 3 months of age. There was double the risk for the first episode of AOM in nursing infants exclusively fed on formulas, compared with nursing infants exclusively breast-fed for 6 months during the same period of life [82]. Mandel et al. [83] followed up 148 children, aged 1.0–8.6 years, and showed that the lack of breast-feeding was one of the significant predictors of otitis media with effusion (OME) and AOM incidence. However, there are some studies that have not found a protective effect of breast-feeding in the risk of otitis media [84, 85].

One of the mechanisms involved in the association between breast-feeding and otitis media is "positional otitis media," according to which, children breast-fed in a unsuitable position (lying down) are at greater risk for otitis media [81, 86]. A cohort with 698 children followed up from birth to 2 years of age demonstrated that the supine breast-feeding position was associated with earlier onset of COME [71].

In conclusion, the majority of the studies, corroborated by findings of meta-analysis showing that children breast-fed for at least 3 months reduced the risk of AOM by 13% (RR 0.87; 95% CI 0.79–0.95) by Uhari et al. [8], demonstrated that breast-feeding has a protective effect against middle-ear disease (level of evidence II). However, there is controversy with respect to the optimal duration of breast-feeding required for protection. A study that focused on the duration of the protection given by breast-feeding after it ceases demonstrated that the risk of AOM is significantly reduced for up to 4 months after it stops. Approximately 12 months after breast-feeding has stopped, the risk is virtually the same among those that were or were not breast-fed [87].

Use of Pacifier

Niemela et al. [88], in a sample of 938 children, demonstrated that those that used pacifiers had a greater risk of presenting with RAOM than those who did not use them. Following 845 day-care children prospectively, Niemela et al. [89, 90] found that the use of a pacifier increased the annual incidence of AOM and was responsible for up to 25% of the episodes of the disease. Warren et al. [91] demonstrated that pacifier sucking was significantly associated with otitis media from the 6th to the 9th month and presented a strong trend towards statistical significance in the period from 9 to 12 months ($p = 0.56$). Lastly, in the meta-analysis of Uhari et al. [8], the use of a pacifier increased the risk for AOM by 25% (estimated RR 1.24; 95% CI 1.06–1.46) (level of evidence II).

Through an open randomized clinical trial, 14 baby welfare clinics were paired in accordance with the number of children and social class of the parents they served. One clinic in each pair was randomly allocated for intervention, while the other served as control. Intervention consisted of a leaflet explaining the deleterious effects of pacifier use and gave instructions for restricting it (basically to use the pacifier only at the time of going to sleep). A total of 272 children under 18 months of age were recruited from the intervention clinics and 212 from control clinics. After intervention, there was a 21% decrease in continuous pacifier use from 7 to 18 months of age ($p = 0.0001$), and the occurrence of AOM was 29% lower among children from the intervention clinics. The children that did not use the pacifier continually in any of the clinics had 33% fewer episodes of AOM than the children that used them.

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