Risk factors for recurrent acute otitis media: a real-life clinical experience

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Acute otitis media (AOM) is the most common bacterial infection in children. Some children with AOM tend to be otitis-prone, such as frequent recurrence of AOM (RAOM). Possible RAOM risk factors are widely debated. The current study was performed in a real-life setting, such as an otorhinolaryngologic (ORL) clinic, to identify predictive factors, including clinical data and endoscopic findings, for RAOM in children. In this study, 1,002 children (550 males, 452 females, mean age 5.77 ± 1.84 years) complaining of upper airway symptoms were consecutively visited. Detailed clinical history and nasal endoscopy were performed. Throughout the ORL visit, it was possible to define some factors involved in the recurrence of AOM, including female gender, artificial feeding, tonsillar and adenoid hypertrophy. Adenoid and tonsillar hypertrophy, female gender, and artificial are factors significantly associated with RAOM. Therefore, reducing adenoid and tonsil size, also using topical corticosteroids or glycyrrhizin, could be a reasonable strategy to potentially reduce adenoid and tonsil size. The current study suggests that also in a primary care setting, it is possible to achieve meaningful information that is relevant in clinical practice.

Acute otitis media (AOM) is an ear disease defined by acute infection signs or symptoms [1]. AOM is the most common bacterial infection in children [2-6]. Consequently, AOM is the most common reason for antibiotic prescription in the pediatric age [7,8]. Almost all children experience at least one episode of AOM during childhood. Therefore, the burden of AOM is relevant concerning the direct (healthcare expense) and indirect cost (loss of school and workdays) and the impact on the quality of life of children and their parents. Moreover, antibiotic overuse is the leading cause of the increase of multidrug-resistant microbes and the occurrence of adverse reactions [9,10]. For these reasons, several guidelines on AOM management were performed to optimize therapy [2-4].

Notably, some children with AOM tend to be otitis-prone, such as frequent recurrence of AOM (RAOM). International guidelines on AOM management define RAOM as when at least three episodes occur in the preceding six months or at least four episodes in the preceding year [3-6]. So, the identification of factors involved in the recurrence may have a beneficial interest. In particular, allergy is still a controversial and debated risk factor for RAOM. Therefore, the current study was performed in a real-life setting, such as an otorhinolaryngologic (ORL) clinic, to identify predictive factors, including clinical data, allergy, and endoscopic findings, for RAOM in children.

Keywords: recurrent acute otitis media; tonsils, real-life, predictive factors, children

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MATERIALS AND METHODS

Patients

1,002 children (550 males, 452 females, mean age 5.77 ± 1.84 years), complaining of upper airway symptoms, were consecutively referring to an ORL clinic during 2015-2018. They were consecutively enrolled in the study. Inclusion criteria were: age between 3 and 10 years and complaints of upper airways. Exclusion criteria were: current disorder(s) and treatment(s) able to interfere with the findings. The study was approved by the local Review Board and informed the parents obtained written consent.

All children were evaluated by detailed medical history (concerning RAOM, premature birth, feeding type (breastfeeding or artificial), familiar atopy, passive smoking, wheezing, recurrent respiratory infections); clinical visit; nasal endoscopy (assessing turbinate, tonsillar, and adenoid hypertrophy); and skin prick test.

Tonsil hypertrophy was defined according to Friedman's classification [11]. Adenoid hypertrophy was defined according to Parikh's classification [12]. Turbinate Hypertrophy was considered as previously described and validated [13].

Skin Prick Test was performed, as stated by the European Academy of Allergy and Clinical Immunology [14].

Statistical analysis

Continuous variables were expressed as means with standard deviations (S.D.) and categorical variables as the number of subjects and percentage values. The univariate Logistic Regression models were performed to screen the effect of clinical and demographic variables on the RAOM. The odds ratios associated with RAOM were calculated with their 95% confidence interval for each factor from the Logistic model. The Likelihood Ratio (L.R.) test was used as a statistical significance test, and the estimated p-values were adjusted for multiple comparisons by the Bonferroni correction method. The covariates with a p-value <0.05 were then selected for the multivariate analysis, where the RAOM was the dependent variable. Possible multicollinearity was assayed using Intraclass Correlation Coefficient (ICC), and the variables with an ICC >0.5 were considered associated. Multivariate analysis was performed using the Logistic Regression model again, and the model selection was made by the Akaike an Information Criterion. Moreover, multiplicative interaction terms were used to test whether the feeding type was different according to the risk factors.

The multivariate model performance was assayed using K-fold cross-validation. In particular, the dataset was split into a training set (95% of the data) and a test set (5% of the data) randomly for k different times and then the percentage of total items classified correctly, false positive and false negative rate were estimated using a confusion matrix.

Stratified analysis was then performed based on that variable using the Penalised Logistic Model for the results suggestive of an interaction with the feeding type factor (p-value <0.05).

Differences with a p-value less than 0.05 were selected as significant, and data were acquired and analyzed in the R v3.5.3 software environment [15].

RESULTS

A total of 1002 (550 males) children were consecutively visited and included in this study. The demographic and clinical characteristics of the study participants are summarised in Table I. Briefly, the mean age was 5.77 years (SD=1.84). The majority of children (N=765) received breastfeeding, while 236 received artificial feeding time. About the primary outcome, 210 (20.96%) children had RAOM, while 792 (79.04%) had no RAOM, so children were subdivided into two groups: with and without RAOM.

Descriptive statistics of demographic and clinical factors in comparison to RAOM are reported in Table II. The mean age of children in the two groups was quite similar (5.84 and 5.52 years, respectively). In patients without RAOM, artificial feeding time was received by 169 (71.61%) children, while 623 (81.44%) children received breastfeeding. Instead, in children with RAOM, 67 (28.39%) and 142 (18.56%) had artificial feeding and breastfeeding, respectively.

The univariate logistic regression analysis (Table II), using the complete set of data, demonstrated a significant association among gender, feeding type, wheezing, recurrent respiratory infections, turbinate hypertrophy, tonsillar hypertrophy, adenoid hypertrophy, and RAOM (p<0.05).

The multivariate analysis (Table III) confirmed

Table I. *Demographic and clinical characteristics of study participants (n= 1002). The results are expressed as mean with standard deviation or number of subjects with the percentage*

Characteristic	Overall
Recurrent Acute Otitis Media	
Absence	792 (79.04%)
Presence	210 (20.96%)
Age (years)	5.77 (1.84)
Gender	
Female	450 (45%)
Male	550 (55%)
Prematurity	
No	924 (92.31%)
Yes	77 (7.69%)
Feeding type	
Artificial	236 (23.58%)
Breastfeeding	765 (76.42%)
Passive Smoking	
No	929 (92.71%)
Yes	73 (7.29%)
Family Atopy	
No	273 (27.33%)
Yes	726 (72.67%)
Allergic rhinitis	
No	453 (45.44%)
Yes	544 (54.56%)
Wheezing	
No	872 (87.11%)
Yes	129 (12.89%)
Recurrent respiratory infections	
No	364 (36.51%)
Yes	633 (63.49%)
Turbinate Hypertrophy	
No	288 (28.74%)
Yes	714 (71.26%)
Tonsillar Hypertrophy	
No	233 (23.3%)
Yes	767 (76.7%)
Adenoid Hypertrophy	
No	370 (36.96%)
Yes	631 (63.04%)

a statistically significant effect of gender, feeding type, recurrent respiratory infections, tonsillar hypertrophy, and adenoid hypertrophy on RAOM (p: 0.0004, 0.0117, <0.0001<0.0001, and 0.0313, respectively).

Children with tonsillar hypertrophy had a chance three times more likely to have RAOM than children without tonsillar hypertrophy, maintaining constant the other covariates (OR = 2.97). Consistently, children with adenoid hypertrophy had a chance of having MAOR about 1.4 times more likely than children without adenoid hypertrophy, maintaining constant the other covariates (OR = 1.36).

Finally, the multivariate model performance showed an excellent model average accuracy (accuracy = 0.81). All the accuracy scores are greater than 0.66, and they ranged from 0.66 to 0.96. Moreover, low false positive and negative rates were 0.01 and 0.18, respectively.

DISCUSSION

RAOM represents an intriguing challenge in the clinical practice for both the pediatrician and the ORL specialist. The AOM diagnosis requires adequate procedure and precise differential diagnosis, mainly concerning OME. There is current debate concerning the identification of risk factors associated with RAOM. Allergy is a controversial candidate. Moreover, AOM therapy is controversial as many guidelines suggest watchful waiting for mild-moderate episodes in children > 2 years. The prevention of RAOM is overwhelmingly desirable, even though it is debated. At present, there is no convincing evidence of preventing RAOM by the proposed treatments, both conventional and not (2-6). Therefore, as there is no effective preventing and effective preventive treatment for RAOM, knowing predictive factors for RAOM could be fruitful from a pragmatic point of view.

Therefore, this real-life study aimed to evaluate whether some clinical data and/or endoscopic findings may be predictive markers of Recurrent Acute Otitis Media (RAOM) in children during an ORL visit. In other words, the current study would identify easy and straightforward factors that could be achieved during an ORL consultation.

The data analysis allowed us to define some variables to predict RAOM in children with upper respiratory complaints. In particular, adenoid and tonsillar hypertrophy were relevant risk factors for RAOM. Consistently female gender and artificial feeding were associated with RAOM. On the other hand, male gender, breastfeeding, and recurrent respiratory infections were protective factors for RAOM.

These outcomes confirm partially known mechanisms involved in RAOM, even though they reinforce the value of a thorough ORL visit, including endoscopy. In particular, anatomic and mechanic features play a relevant pathogenic role in favoring the recurrence of AOM. Tuba compression/obstruction is a crucial factor in promoting infections in the middle ear. Also, adenoids and tonsils are a reservoir for pathogens; enlargement increases the odds of re-infection (16).

Table II. *Contingency tables and summary output of the univariate analysis. Characteristic: variable taken into account; OR (95% CI): Odd Ratios with 95% Confidence Interval; p-value: Likelihood Ratio p-value. *Variables entering in the multivariate analysis (see the text for abbreviations and further details).*

Characteristic	Descriptive statistic		Univariate analysis	
	Recurrent Acute Otitis Media			
	Absence *792 (79.04%)*	Presence *210 (20.96%)*	OR (95% C.I.)	p-value
Age	5.84 (1.87)	5.52 (1.69)	0.93 (0.85 : 1.01)	0.9407
Gender *				0.0037
Female	333 (74%)	117 (26%)	1	
Male	457 (83.09%)	93 (16.91%)	0.56 (0.41 : 0.77)	
Prematurity				0.8649
No	736 (79.65%)	188 (20.35%)	1	
Yes	56 (72.73%)	21 (27.27%)	1.66 (0.95 : 2.78)	
Feeding type *				0.0070
Artificial	169 (71.61%)	67 (28.39%)	1	
Breastfeeding	623 (81.44%)	142 (18.56%)	0.54 (0.39 : 0.77)	
Passive Smoking				0.9999
No	739 (79.55%)	190 (20.45%)	1	
Yes	53 (72.6%)	20 (27.4%)	1.51 (0.85 : 2.58)	
Family Atopy				0.8737
No	207 (75.82%)	66 (24.18%)	1	
Yes	583 (80.3%)	143 (19.7%)	0.73 (0.53 : 1.03)	
Wheezing *				0.0492
No	676 (77.52%)	196 (22.48%)	1	
Yes	115 (89.15%)	14 (10.85%)	0.46 (0.25 : 0.79)	
Allergic rhinitis				0.1039
No	341 (75.28%)	112 (24.72%)	1	
Yes	451 (82.9%)	93 (17.1%)	0.66 (0.48 : 1.01)	
Recurrent respiratory infections *				<0.0001
No	254 (69.78%)	110 (30.22%)		
Yes	538 (84.99%)	95 (15.01%)	0.42 (0.3 : 0.57)	
Turbinate Hypertrophy *				0.0058
No	207 (71.88%)	81 (28.12%)	1	
Yes	585 (81.93%)	129 (18.07%)	0.56 (0.4 : 0.77)	
Tonsillar Hypertrophy *				<0.0001
No	213 (91.42%)	20 (8.58%)	1	
Yes	579 (75.49%)	188 (24.51%)	2.32 (1.67 : 3.34)	
Adenoid Hypertrophy *				<0.0001
No	325 (87.84%)	45 (12.16%)	1	
Yes	466 (73.85%)	165 (26.15%)	1.84 (1.44 : 2.4)	

Interestingly, recurrent respiratory infections seem to be negatively associated with RAOM. This finding confirms the dichotomy between respiratory and ear infective recurrence as it is a common experience to observe children with RAOM without recurrent respiratory infections, such as RAOM is a separate issue. Also, recurrent respiratory infections often are treated, if not overtreated, with antibiotics and immunomodulators so that RAOM could be diminished (17).

Breastfeeding is an essential protective measure to promote the global well-being of the child and immune system maturation (18). Male gender may be another protective factor, probably for hormonal influence on the immune response (19). Finally, an allergy could represent a protective factor for adenoidal hypertrophy; consequently, it might represent a factor not associated with RAOM (20).

On the other hand, the current study has some limitations, including the cross-sectional design,

Table III. *Multivariate analysis, the predictor effects on the Recurrent Acute Otitis Media (N=986). Results are expressed as odds ratio (OR) with a 95% confidence interval (95%CI); p-value: Likelihood Ratio p-value.*

Characteristic	Multivariate analysis	
	OR (95%C.I.)	p-value
(Intercept)	0.52 (0.35 - 0.77)	0.0013
Gender		0.0004
Female	1	
Male	0.55 (0.39 - 0.77)	
Feeding type		0.0117
Artificial	1	
Breastfeeding	0.62 (0.43 - 0.9)	
Recurrent respiratory infections		<0.0001
No	1	
Yes	0.33 (0.24 - 0.47)	
Tonsillar Hypertrophy		<0.0001
No	1	
Yes	2.97 (2.05 - 4.45)	
Adenoid Hypertrophy		0.0313
No	1	
Yes	1.36 (1.03 - 1.81)	

the lack of biomarkers measurement able to identify specific pathogenic mechanisms. However, the study's strength is the high number of enrolled children and the real-life setting, so the outcomes may mirror what happens in daily clinical practice.

CONCLUSIONS

The current study showed that adenoid and tonsillar hypertrophies were a significant risk factor for RAOM and female gender and artificial feeding. Therefore, reducing adenoid and tonsil size, also using topical corticosteroids or glycyrrhizin, could be a reasonable strategy to potentially reduce adenoid and tonsil size. This study also demonstrated that, during an ORL visit, it was possible to define some factors involved in the recurrence of AOM.

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