Can an otorhinolaryngological visit induce the suspect of allergic rhinitis in children?

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Abstract

Allergic rhinitis (AR) is very frequent in childhood. AR is commonly associated with some co-morbidities and typical clinical features. This study aimed to test the hypothesis whether an otorhinolaryngological (ORL) visit could induce the suspect of AR.

Globally, 1,002 children (550 males, mean age 5.77 years) were consecutively visited at an ORL clinic. Clinical visit, nasal endoscopy, and skin prick test were performed in all patients. In particular, history investigated atopic familiarity, birth, feeding type, passive smoking, comorbidities, including asthma, respiratory infections, otitis media, respiratory sleep disorder. Endoscopy assessed the tonsil and adenoid volume, turbinate contacts, mucosal color, and nasal discharge. Univariate and multivariate analysis were performed.

The study showed that 547 (54.6%) children had AR. Some parameters were predicting factor for suspecting AR: middle turbinate contact (OR=9.27), familial atopy (OR=6.24), pale nasal mucosa (OR=4.95), large adenoid volume (OR=3.02 for score 4), and asthma co-morbidity (OR=2.95).

In conclusion this real-life study showed that during an ORL visit it is possible to suspect AR in children with turbinate hypertrophy, familial atopy, nasal pale mucosa, adenoid enlargement, and asthma comorbidity.

Key words: Otorhinolaryngological visit, allergic rhinitis, familial atopy, endoscopy, children.

Introduction

Allergic rhinitis (AR) is the most common immune-mediated disorder in childhood as it may affect up to 40% of children (1). AR is frequently associated with relevant comorbidities, including other allergies, rhinosinusitis, recurrent respiratory infections, otitis, adenoid hypertrophy (AH) and tonsillar hypertrophy (TH), as recently reported by several recent studies (2-6). Moreover, the possible correlation between AR and AH-TH has been investigated by some studies which reported a positive association between the two disorders (7-11). Familiar atopy is also common in AR children.

Actually, the otorhinolaryngology (ORL) specialist visits children with nasal symptoms daily. The desire of every doctor is to diagnose a disease already at the time of the visit thanks to the personal background, experience, and practice and possibly with the instruments present in the clinic. Therefore, predictive diagnostic information could be very fruitful in clinical practice. In this regard, to observe a pale mucosa in the nasal cavity has been traditionally considered a sign suggesting allergic rhinitis by most ORL specialists for a long time until today (12,13). However, it has been evidenced that turbinate hypertrophy is a sign with higher predictive reliability to suspect allergic rhinitis during an ORL visit both in children and adults (14,15). Consequently, nasal obstruction may be a trustworthy symptom able to suggest the presence of allergy. Consistently, it has been reported that also bronchial airflow limitation, documented by a simple spirometry, may be able to suspect allergy (16,17). Furthermore, it has to be highlighted that to define a diagnostic marker there is the need to fulfill a series of pragmatic requirements as recently pointed out (18).

On the basis of this background, we tested the hypothesis that the ORL visit could suggest the suspect of allergic rhinitis. Therefore, this real-life study aimed to evaluate whether some clinical data and endoscopic findings may be predictive factors of allergic rhinitis in children during an ORL visit.

Materials and Methods

Patients: 1,002 children (550 males, 452 females, mean age 5.77 ± 1.84 years), complaining upper airway symptoms, were consecutively referring to the ORL Unit of the Casa di Cura Villa Montallegro (Genoa, Italy) during the period 2015-2017. They were consecutively enrolled into the study. Inclusion criteria were: i) age between 3 and 10 years; ii) to have complaints of upper airways (i.e. nasal obstruction, rhinorrhea, otalgia, sore throat, cough, snoring). Exclusion criteria were: i) a craniofacial syndrome, ii) recent facial trauma, and iii) current treatment able to interfere with the findings. The study was approved by the local Review Board and an informed written consent was obtained by the parents.

Study design: All children were evaluated by clinical visit, nasal endoscopy, and skin prick test.

Clinical visit: included detailed medical history, concerning premature birth, feeding type (breastfeeding or artificial), familiar atopy, passive smoking, documented diagnosis of: asthma, recurrent respiratory infections, recurrent acute otitis media, otitis media with effusion, and respiratory sleep disorders.

Endoscopy: was performed with a pediatric rigid endoscope diameter 2.7 mm with 30° angle of vision (Karl Storz cod 7207 ba) with a 300-W cold light source (Storz Xenon Nova, cod. 20134001, and a light cable of 1.8 mm length. Endoscopy was video recorded by a micro-camera connected to digital recorder set (Karl Storz Tele Pack, cod. 20043002-020). A flexible endoscope (3 mm diameter) was used in restless children and in those with narrow nasal fossa due to anatomical abnormalities. The child lied supine with his-her head bent by about 45°. Some cotton wool soaked with anesthetic solution (ossibuprocaine 1%) was placed into the nose for 5 minutes. The complete description of the procedure was previously described in detail (11,14,19). In particular, pale nasal mucosa was defined by a lighter color than the close mucosal tissues (depending on the edema of the turbinate); it was defined as present or absent (20). Nasal discharge is defined by a draining into the nasal cavity that may have different appearance: clear and watery typically in allergic subjects and purulent in infective disorders; it was defined as present or absent (15).

Tonsils volume assessment

Tonsils volume was classified according to validated criteria (21) as follows: grade 1: tonsils in the tonsillar fossa barely seen behind the anterior pillar; grade 2: tonsils visible behind the anterior pillar; grade 3: tonsils

extended three quarters of the way to med-line; grade 4: tonsils completely obstructing the airway (also known as kissing tonsils).

Adenoids volume assessment

The patients were evaluated by nasal endoscopy for adenoid hypertrophy. The adenoids were graded in according to Parikh's classification that was created based on the anatomical relationships between the adenoid tissue and the following structures: vomer, soft palate, and torus tubarius (22). The grading is based on the relationship of the adenoids to adjacent structures when the patient is at rest (i.e. when the soft palate is not elevated). Specifically: grade 1 adenoids are non-obstructive and do not contact any of the previously mentioned anatomic subsites; subsequently, grade 2,3 and 4 adenoids contact the torus tubarius, vomer, and soft plate (at rest) respectively.

Turbinate Hypertrophy

The contact of turbinate was considered as surrogate marker for turbinate hypertrophy, as previously described and validated (14,15).

Skin Prick Test

Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens by performing a skin-prick test. It was performed as stated by the European Academy of Allergy and Clinical Immunology (23). The allergen panel consisted of the following: house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cats, dogs, grasses mix, *Compositae* mix, *P. judaica*, birch, hazel trees, olive trees, cypress, *Alternaria tenuis, Cladosporium,* and Aspergilli mix. The concentration of allergen extracts was 100 immune reactivity/mL (Stallergenes-Greer Italia, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as positive control and the glycerol-buffer diluent of the allergen preparations was used as negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets. The skin reaction was recorded after 15 minutes by evaluating the skin response in comparison with the wheal given by the positive and the negative control. A wheal diameter of at least 3 mm was considered as a positive reaction.

The AR diagnosis was made if nasal symptom history was consistent with sensitization, such as the demonstration of symptom occurrence after exposure to the sensitizing allergen.

Statistical analysis

Continuous variables were given as means with standard deviations (SD) and categorical variables as number of subjects and percentage values. The univariate Logistic Regression models were performed to screen the effect of the clinical and demographic variables on the AR diagnosis.

The odd ratios associated with AR were calculated with their 95% confidence interval for each factor from the Logistic model. The Likelihood Ratio (LR) test was used as a test of statistical significance and the estimated p-values were adjusted for multiple comparisons by the Bonferroni correction method.

Those covariates with a p-value <0.05 were then selected for the multivariate analysis, where the AR was the dependent variable. Possible multicollinearity was assayed using Intraclass Correlation Coefficient (ICC) and those variables with an ICC more than 0.5 were considered associated. Multivariate analysis was performed using again the Logistic Regression model and the model selection was done by the Akaike an Information Criterion. The sensitivity and specificity of the model were evaluated using confusion matrix (a tabular representation of Actual *versus* Predicted values). Moreover, multiplicative interaction terms were used to test whether the feeding type was different according to the risk factors. For those results suggestive of an interaction with the feeding type factor (p-value <0.05), a stratified analysis was then performed based on that variable using Penalized Logistic Model. Differences, with a p-value less than 0.05, were selected as significant and data were acquired and analyzed in R v3.5.1 software environment.

Results

A total of 1002 (550 males) children was enrolled in this study. The demographic and clinical characteristics of the study participants are summarized in Table 1. About the primary outcome, 547 (54.6%) children had AR. The mean age was 5.77 years (SD=1.84); 77 (7.7%) children were born prematurely; the majority of children (76.4% N=765) received breastfeeding, while 236 (23.6%) received artificial feeding. Passive smoking was present in 73 (7.3%) cases, 726 (72.7%) children had familial atopy. About comorbidity, asthma was documented in 129 (12.9%) children, recurrent respiratory infections in 633 (63.5%), recurrent acute otitis media in 187 (18.7%), otitis media with effusion in 213 (21.3%), and a respiratory sleep disorder was present in 739 (73.9%) children. About endoscopic findings, only 233 (23.3%) children had a tonsil volume of grade 1; 370 (37%) children had adenoid volume of grade 1, 661(66.3%) had the inferior turbinate contact and 528 (52.8%) had middle turbinate contact, 319 (31.8%) children showed a pale mucosa, and 515 (51.4%) had nasal discharge.

Descriptive statistics of demographic and clinical factors according to AR diagnosis are reported in Table 2. The percentages of males and females in AR groups were quite similar (range: 44.22% to 55.78%), whereas there was a significant difference about the age: allergic children were older than non-allergic children ($p<0.0001$). There were significant differences between the subgroups regarding: feeding, passive smoking, familial atopy, asthma comorbidity, respiratory sleep disorders, tonsil and adenoid volume, turbinate contact, pale mucosa, and nasal discharge. The univariate logistic regression analysis (Table 2), using the complete set of data, demonstrated a significant association among feeding, passive smoking, familial atopy, asthma, respiratory sleep disorder, tonsil volume, adenoid volume, inferior and middle turbinate contact, pale mucosa and AR (p-values<0.05). Multicollinearity presence was observed between inferior and middle turbinate contact: ICC (95%C.I.) = 0.51 (0.46 : 0.55). Due to this result, the inferior turbinate contact was not included in the multivariate analysis.

The multivariate analysis (Table 3) confirmed a statistically significant effect of feeding, familial atopy, asthma, adenoid volume, middle turbinate contact, and pale mucosa on AR (p-values<0.0001). In particular, an increased probability of having AR was shown for the asthma co-morbidity (OR; 95%C.I.) = 2.95 (1.37 -

6.65), the middle turbinate contact (OR; 95%C.I.) = 9.27 (6.05 - 14.43), and the pale mucosa (OR; 95%C.I.) = 4.95 (3.05 - 8.26). As regard multiplicative interaction term, the effect of feeding on AR was significantly different according to the familial atopy presence/absence (p-value for the interaction term = 0.0302). The sensitivity and specificity of the model were 88.08% and 90.07%, respectively.

The subsequent stratification analysis (Table 4) showed that the breastfeeding was associated with increased risk of having AR, only in children with familial atopy (OR; 95%C.I.) = 2.98 (1.75 - 5.10).

Discussion

Upper airways symptoms are very common in pediatric population. In particular, allergic rhinitis is frequent in children affecting up to 40% of the general population. Allergic rhinitis may be frequently associated with several co-morbidities, including respiratory infections and asthma, and familiar atopy (24).

The present study was based on a real-life setting, such as the studied cohort was constituted of children complaining upper airways symptoms and visited at an ENT office, undergoing nasal endoscopy.

The main outcome was the ability to identify some clinical parameters that could induce the suspect of AR during an ORL visit. In particular, five parameters could predict AR: middle turbinate contact (OR= 9.27), familial atopy (OR= 6.24), pale mucosa (OR= 4.95), adenoid hypertrophy (OR= 3.02 for the volume 4), and asthma comorbidity (OR= 2.95).

The current study demonstrated that middle turbinate contact was the main predictor factor for AR; the turbinate contact depends essentially on the hypertrophy of the turbinate. This outcome confirmed previous studies that reported consistently a significant association between this sign and AR diagnosis (14,15,20). So, this endoscopic finding may be reasonably considered as a surrogate marker for turbinate hypertrophy (18).

The familial atopy represents another relevant predictive factor for having AR; this finding was expected and was consistent with the literature evidence as recently reported in an International Consensus on AR (25). The genetic background of allergy is well known as allergy is widespread in allergic families (26). In this regard, breastfeeding is strongly recommended, as necessary for the healthy growth of infants (27) particularly in children with high risk for atopy. However, a real protective role in preventing allergic disorders is not clear. Indeed, there are conflicting results about the prevention of allergy as provided by different meta-analysis and reviews (28-32). Consistently, the current study showed that breastfeeding was not significantly associated with AR even though breastfeeding combined with atopic familiarity may predict AR. This finding should be considered cautiously as the predictivity is closely dependent on the genetic predisposition.

Nasal pale mucosa also significantly predicted AR diagnosis. Pale mucosa depends on tissue edema consequent to allergic inflammation. Notably, we found conflicting results in a previous study that reported no predictive role of this endoscopic sign (14). The possible explanation could be related to the smaller sample

analyzed in the previous study. Similarly, we reported previously an inverse relationship between adenoid hypertrophy and AR (11). Probably, the limited sample size could account for the negative result. However, the present study showed the AR predictivity of adenoid hypertrophy, namely with an impressive size-dependent progression. Moreover, the current outcome is consistent with a previous study that showed a positive association between adenoid hypertrophy and AR (33).

Asthma comorbidity was another predictive factor for AR. Association with asthma is well known in patients with allergic rhinitis (34) and underlines the close relationship between upper and lower airways, successfully defined by the term "allergic march", such as the progression from the nose to the bronchi of the allergic reaction (35).

The current study identified a series of clinical parameters with increased odds for having AR. Therefore, it demonstrated that it is conceivably possible to characterize some predictive factors for AR diagnosis during an ENT visit. However, AR diagnosis should be based on other criteria, including documented sensitization, such as IgE production, and proved consistency between exposure to sensitizing allergen and immediate symptom occurrence. This study once more confirms that obtaining an adequate history and a thorough clinical examination are most important for suspecting AR.

The main limitations of the present study are: i) the cross-sectional design; ii) the selected population; iii) the lack of standardized score for some endoscopic signs, and iv) the absence of immunological investigation, able to clarify the pathogenic mechanisms. Therefore, further studies should be performed to address these issues.

However, the strength of this study is the large number of children, the careful work-up, and the real-life setting, so the outcomes may mirror what could occur in daily practice.

Conclusions

This real-life study showed that during an ORL visit it is possible to suspect AR in children with turbinate hypertrophy, familial atopy, nasal pale mucosa, adenoid enlargement, and asthma comorbidity.

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Table 1: **Demographic and clinical characteristics of study participants (n= 1002). The results are expressed as mean with standard deviation or as number of subjects with percentage.**

Characteristic	Overall
Allergic Rhinitis	
No	455 (45.4%)
Yes	547 (54.6%)
Age (years)	5.77 (1.84)
Gender	
Female	452 (45%)
Male	550 (55%)
Premature birth	
No	924 (92.31%)
Yes	77 (7.69%)
Feeding	
Artificial	236 (23.58%)
Breastfeeding	765 (76.42%)
Passive Smoking	
No	929 (92.71%)
Yes	73 (7.29%)
Familiar Atopy	
No	273 (27.33%)
Yes	726 (72.67%)
Asthma	
No	872 (87.11%)
Yes	129 (12.89%)
Recurrent respiratory infections	
No	364 (36.51%)
Yes	633 (63.49%)
Recurrent Acute Otitis Media	
No	792 (79.04%)
Yes	187 (18.66%)
Ongoing	23 (2.3%)
Otitis Media with Effusion	
No	695 (69.36%)
Yes	213 (21.26%)
Ongoing	94 (9.38%)
Respiratory Sleep Disorder	
No	262 (26.17%)
Snoring	553 (55.24%)
Sleep Apnoea	186 (18.58%)
Tonsil Volume	
1	233 (23.3%)
2	310 (31%)
3	294 (29.4%)
4	163 (16.3%)
Adenoid Volume	
1	370 (36.96%)

2	218 (21.78%)
3	215 (21.48%)
4	198 (19.78%)
Inferior Turbinate Contact	
No	336 (33.7%)
Yes	661 (66.3%)
Middle Turbinate Contact	
No	472 (47.2%)
Yes	528 (52.8%)
Pale Mucosa	
No	683 (68.16%)
Yes	319 (31.84%)
Nasal Discharge	
No	487 (48.6%)
Yes	515 (51.4%)

Table 2: Contingency tables and Output of the univariate analysis. Characteristic: variable taken into account in the analysis; 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	
	Allergic Rhinitis		OR (95%C.I.)	p-value
	No *455 (45.4%)*	**Yes** *547 (54.6%)*		
Age	5.46 (1.85)	6.05 (1.8)	1.2 (1.12 : 1.29)	<0.0001
Gender				0.9999
Female	211 (47.11%)	239 (52.89%)	1	
Male	241 (44.22%)	304 (55.78%)	1.12 (0.87 : 1.44)	
Premature Birth				0.5325
No	408 (44.4%)	511 (55.6%)	1	
Yes	44 (57.14%)	33 (42.86%)	0.6 (0.37 : 0.96)	
Feeding *				<0.0001
Artificial	143 (60.59%)	93 (39.41%)	1	
Breastfeeding	309 (40.66%)	451 (59.34%)	2.24 (1.67 : 3.03)	
Passive Smoking *				<0.0001
No	396 (42.86%)	528 (57.14%)	1	
Yes	57 (78.08%)	16 (21.92%)	0.21 (0.12 : 0.36)	
Familiar Atopy *				<0.0001
No	237 (86.81%)	36 (13.19%)	1	
Yes	215 (29.82%)	506 (70.18%)	15.49 (10.67 : 23.09)	
Asthma *				<0.0001
No	429 (49.48%)	438 (50.52%)	1	
Yes	23 (17.83%)	106 (82.17%)	4.51 (2.87 : 7.39)	
Recurrent respiratory infections				0.3993
No	147 (40.61%)	215 (59.39%)	1	
Yes	304 (48.03%)	329 (51.97%)	0.74 (0.57 : 0.96)	
Recurrent Acute Otitis Media				0.2076
No	341 (43.06%)	451 (56.94%)	1	
Yes	99 (54.4%)	83 (45.6%)	0.63 (0.46 : 0.88)	
Ongoing	13 (56.52%)	10 (43.48%)	0.58 (0.25 : 1.34)	
Otitis Media with Effusion				0.4498
No	304 (43.74%)	391 (56.26%)	1	
Yes	94 (45.19%)	114 (54.81%)	0.94 (0.69 : 1.29)	
Ongoing	55 (58.51%)	39 (41.49%)	0.55 (0.35 : 0.85)	
Respiratory Sleep Disorder *				<0.0001
No	99 (38.52%)	158 (61.48%)	1	
Snoring	226 (40.87%)	327 (59.13%)	0.91 (0.67 : 1.23)	
Sleep Apnoea	127 (68.28%)	59 (31.72%)	0.29 (0.19 : 0.43)	
Tonsil Volume *				<0.0001
1	39 (16.74%)	194 (83.26%)	1	

2	127 (40.97%)	183 (59.03%)	0.17 (0.12 : 0.23)	
3	176 (59.86%)	118 (40.14%)	1.52 (1.14 : 2.04)	
4	109 (68.99%)	49 (31.01%)	0.98 (0.77 : 1.25)	
Adenoid volume *				<0.0001
1	57 (15.41%)	313 (84.59%)	1	
2	80 (36.7%)	138 (63.3%)	0.1 (0.07 : 0.13)	
3	164 (78.1%)	46 (21.9%)	1.88 (1.39 : 2.55)	
4	151 (76.26%)	47 (23.74%)	1.78 (1.32 : 2.42)	
Inferior Turbinate Contact *				<0.0001
No	305 (90.77%)	31 (9.23%)	1	
Yes	144 (21.95%)	512 (78.05%)	34.98 (23.48 : 53.77)	
Middle Turbinate Contact *				<0.0001
No	368 (77.97%)	104 (22.03%)	1	
Yes	85 (16.25%)	438 (83.75%)	18.23 (13.33 : 25.21)	
Pale Mucosa *				<0.0001
No	384 (56.22%)	299 (43.78%)	1	
Yes	69 (21.97%)	245 (78.03%)	4.56 (3.37 : 6.23)	
Nasal Discharge *				<0.0001
No	328 (68.05%)	154 (31.95%)	1	
Yes	125 (24.27%)	390 (75.73%)	6.65 (5.05 : 8.8)	

Table 3: Multivariate analysis, the predictor effects on AR. Results are expressed as odds ratio (OR) with 95% confidence interval (95%CI); p-value: Likelihood Ratio p-value.

Characteristic	Multivariate analysis	
	OR (95%C.I.)	**p-value**
(Intercept)	0.02 (0.01 - 0.06)	
Feeding		<0.0001
Artificial	1	
Breastfeeding	0.75 (0.26 - 2.26)	
Familiar Atopy		<0.0001
No	1	
Yes	6.24 (2.29 - 18.3)	
Asthma		<0.0001
No	1	
Yes	2.95 (1.37 - 6.65)	
Adenoid volume		<0.0001
1	1	
2	0.15 (0.1 - 0.23)	
3	2.88 (1.87 - 4.48)	
4	3.02 (1.94 - 4.78)	
Middle Turbinate Contact*		<0.0001
No	1	
Yes	9.27 (6.05 - 14.43)	
Pale Mucosa		<0.0001
No	1	
Yes	4.95 (3.05 - 8.26)	
Familiar Atopy * Feeding		0.0302
Familiar Atopy (No): Artificial	1	
Familiar Atopy (Yes): Breastfeeding	3.91 (1.14 - 12.95)	

Table 4: Stratification analysis for Familiar Atopy presence/absence on the risk of AR. Results are expressed as odds ratio (OR) with 95% confidence interval (95%CI), keeping constant Asthma, Adenoid Volume, Middle Turbinate Contact and Pale Mucosa.

	Familiar Atopy					
	No			**Yes**		
Characteristic	**Descriptive Statistics**		**OR (95%C.I.)**	**Descriptive Statistics**		**OR (95%C.I.)**
(Intercept)			0.03 (0.01 - 0.10)			0.15 (0.09 - 0.25)
Feeding						
Artificial	42 (80.77%)	10 (19.23%)	1	97 (54.8%)	80 (45.2%)	1
Breastfeeding	189 (88.32%)	25 (11.68%)	0.99 (0.32 - 3.17)	115 (21.42%)	422 (78.58%)	2.98 (1.75 - 5.10)