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Original article

Recurrent respiratory infections in children: a study in clinical practice

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Summary. Recurrent respiratory infections (RRI) are very frequent in childhood. RRI are commonly associated with some co-morbidities and typical clinical features. This study aimed to test the hypothesis whether an ENT visit could identify predicting factors for IRR. Globally, 1,002 children (550 males, mean age 5.77 years) were consecutively visited at an ENT clinic. Clinical visit, nasal endoscopy, and skin prick test were performed in all patients. RRI were present in 633 (63.5%) children. Some parameters were predicting factor for RRI: male gender (OR=1.68), tonsil and adenoid volume, even if partially for some volume grading. On the other hand, familiar atopy (OR=0.68), acute otitis media (OR=0.29), and certain tonsil and adenoid size (OR range 0.68-0-47) seemed to be protecting factor for RRI. This real-life study showed that during an ENT visit it is possible to identify some predictive factors involved in RRI: some seem to be protective, whereas other seem to be predisposing. (www.actabiomedica.it)

Key words: ENT visit, Recurrent respiratory infections, familiar atopy, tonsil, adenoid, otitis, children

Introduction

Children with recurrent respiratory infections (RRI) represent a daily challenge for the otolaryngologist and the paediatrician in clinical practice. The diagnosis of RRI is usually performed according to the following criteria: i) >6 RI per year; ii) >1 RI per month involving upper airways from September to April; iii) >3 RI involving lower airways (1). RRI have a relevant impact on pharmaco-economy and cause a relevant burden for both the family and the society.

It has been postulated that many factors may be involved in promoting and/or causing RRI, including age (for a relative immaturity of the immune system), early attending at nursery school, air and home pollution, passive tobacco smoking, low socio-economic level, and atopy (2). Moreover, it has been hypothesized that allergy may play a particular role in promoting the RI recurrence as the immune response is impaired in allergic subjects and allergic inflammation favours infections. Actually, allergic subjects have a defect of the type 1 immune response that is appointed to hinder infections producing anti-infective cytokines, namely IFN-γ. In fact, allergic children are prone to have more numerous and severe infections than normal subjects (3). Moreover, allergic subjects present typically minimal persistent inflammation, i.e. mucosal inflammatory cell infiltrate closely associated to allergen exposure (4). This event may account to sustained susceptibility to infections because of impaired type 1 response, increased ICAM-1 expression (the main rhinovirus receptor) on epithelial cells, and local inflammation that represents a *pabulum* for pathogens (5). In addition, viral infections may increase the probability of contracting frequent RI because of the high number of circulating viruses and the numerous sub-types (6). Viral infections are pre-

dominant, but bacterial super-infections may frequently appear. Consequently, there is an overuse/misuse of antibiotics that in turn induces antibiotic resistance (7, 8). Moreover, biofilm causes frequent antibiotic unsuccess and 25-45% of children with severe RRI need surgical intervention (9, 10).

On the other hand, there is no available biomarker able to identify children at risk of RRI. Therefore, we tested the hypothesis whether an ENT visit could provide useful information able to identify some risk factor involved in RRI. The aim of this study was to identify the effect of demographic and clinical factors, such as, age, gender, type of birth and feeding, passive smoking, familiar atopy, co-morbidities (including allergic rhinitis, acute otitis media, respiratory sleep disorders), and endoscopic findings (i.e. tonsil volume, adenoid volume, turbinate size, pale nasal mucosa, and pathological discharges) on RRI in a large group of children visited in a real-life setting, such as an ENT clinic.

Methods

Patients: 1,002 children (550 males, mean age 5.77±1.84 years), complaining upper airway symptoms, were consecutively referring to the ENT Unit of the Casa di Cura Villa Montallegro (Genoa, Italy) during the 2015-2017 years. 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, familiar atopy, passive smoking, documented diagnosis of: 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 (11,12).

Tonsils volume assessment: Tonsils volume was classified according to validated criteria (13) 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 (14). 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 maker for turbinate hypertrophy as previously validated (11,15).

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 (16). The allergen panel consisted of the following: house-dust mites (*Der-*

matophagoides 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 are 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 RRI. The odd ratios associated with RRI 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 RRI was the dependent variable. Multivariate analysis was performed using again the Logistic Regression model and the model selection was done by the Akaike an Information Criterion. Differences, with a p-value less than 0.05, were selected as significant and data were acquired and analysed in R v3.5.1 software environment.

Results

A total of 1,002 (550 males) children were enrolled in this study. The demographic and clinical characteristics of the study children are summarized in Table 1. About the primary outcome, 633 (63.5%) children suffered from RRI, whereas 364 (36.5%) children had no RRI. In addition, the mean age was 5.77 years (SD=1.84); only 77 children had premature birth. The majority of children (N=638) received breastfeeding until 6 months, 127 had breastfeeding until 12 months, while 236 received artificial feeding. The other variables are reported analytically in the Table 1.

Descriptive statistics of demographic and clinical factors, after stratification for the presence or absence of RRI, are reported in Table 2. The age means in the two RRI sub-groups groups were quite similar, also after stratifying in pre-schoolers and school aged children, as well as the number of children with premature birth. Type and duration of feeding and passive smoking were similar in the two sub-groups. Equally, allergic rhinitis, respiratory sleep disorders, inferior and middle turbinate contact, pale nasal mucosa, and pathological discharge were similar in the two RRI subgroups. However, the gender significantly affected RRI as there was a significant predominance of males in the RRI sub-group: 380 (69.6%) out of 546 males showed RRI, whereas 251 (55.9%) out of 449 females had RRI. Familiar atopy was more prevalent in children without RRI: 39.34% vs 29.04%. Acute otitis media was more common in children without RRI (53.59% vs 29.11%). The largest tonsil volume was associated with RRI as well as adenoid volume. Consequently, the univariate logistic regression analysis (Table 2), using the complete set of data, demonstrated a significant association among gender, familiar atopy, acute otitis media, tonsil and adenoid volume, and RRI (p-values<0.05).

The multivariate analysis (Table 3) confirmed a statistically significant effect of gender, familiar atopy, acute otitis media, tonsil and adenoid volume on RRI (p-values: 0.0006, 0.0368, <0.0001, <0.0001 and <0.0001, respectively). In particular, male gender had an OR of 1.68, familiar atopy had an OR of 0.68, past acute otitis media had an OR of 0.29 and current acute otitis media had an OR of 0.31. Tonsil and adenoid volume showed a non-linear distribution as reported in Table 3.

Discussion

Recurrent respiratory infections constitute a burdensome task for the doctors in clinical practice.

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
Recurrent Respiratory Infections	
No	364 (36.5%)
Yes	633 (63.5%)
Age	5.77 (1.84)
Preschoolers	491 (49%)
School aged	511 (51%)
Gender	
Female	452 (45%)
Male	550 (55%)
Premature Birth	
No	924 (92.3%)
Yes	77 (7.7%)
Feeding	
Artificial	236 (23.58%)
Breastfeeding 0 to 6 months	638 (63.74%)
Breastfeeding until 12 months	127 (12.69%)
Passive Smoking	
No	929 (92.71%)
Yes	73 (7.29%)
Familiar Atopy	
No	273 (27.33%)
Yes	726 (72.67%)
Allergic Rhinitis	
No	453 (45.44%)
Yes	544 (54.56%)
Acute Otitis Media	
No	695 (69.36%)
Yes	213 (21.26%)
Ongoing	94 (9.38%)

Characteristic	Overall
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 Nasal Mucosa	
No	683 (68.16%)
Yes	319 (31.84%)
Pathological Discharge	
No	487 (48.6%)
Yes	515 (51.4%)

Moreover, RRI account for the first reason of antibiotic prescription (17), and RRI in childhood cause frequent school absence and consequently parents' work days loss. Therefore, contrasting RRI represents a crucial and compelling challenge in medical practice (18). However, the exact pathogenic mechanisms involved in the recurrence of RI are still unclear as well as there is no reliable biomarker able to identify predisposed children.

On the basis of this background, we aimed to test the hypothesis that some parameters linked to RRI could be verifiable during an ENT visit. The present outcomes showed that male gender was associated with RRI and represented a significant risk factor for them. On the contrary, familiar atopy and acute otitis media were protective factors for RRI. This finding could be explained by the greater use of anti-inflammatory drugs

Table 2. Contingency table and summary 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	
	Recurrent Respiratory Infections			
	No *364* *(36.5%)*	**Yes** *633* *(63.5%)*	**OR (95%C.I.)**	**p-value**
Age	5.82 (1.85)	5.76 (1.84)	0.98 (0.92 : 1.05)	0.9999
Pre-schoolers	147 (32.59%)	329 (60.48%)	1	
School aged	215 (39.52%)	298 (61.19%)		
Gender *				0.0001
Female	198 (44.1%)	251 (55.9%)	1	
Male	166 (30.4%)	380 (69.6%)	1.81 (1.39 : 2.35)	
Premature Birth				0.9999
No	337 (36.67%)	582 (63.33%)	1	
Yes	26 (33.77%)	51 (66.23%)	1.14 (0.7 : 1.88)	
Feeding				0.0567
Artificial	99 (42.13%)	136 (57.87%)	1	
Breastfeeding 0 to 6 months	207 (32.65%)	427 (67.35%)	1.5 (1.1 : 2.04)	
Breastfeeding until 12 months	57 (44.88%)	70 (55.12%)	0.89 (0.58 : 1.38)	
Passive Smoking				0.9999
No	335 (36.26%)	589 (63.74%)	1	
Yes	29 (39.73%)	44 (60.27%)	0.86 (0.53 : 1.42)	
Familiar Atopy *				0.0334
No	79 (29.04%)	193 (70.96%)	1	
Yes	284 (39.34%)	438 (60.66%)	0.63 (0.47 : 0.85)	
Allergic Rhinitis				0.3288
No	147 (32.59%)	304 (67.41%)	1	
Yes	215 (39.52%)	329 (60.48%)	0.74 (0.57 : 0.96)	
Acute Otitis Media *				<0.0001
No	202 (29.11%)	492 (70.89%)	1	
Yes	112 (53.59%)	97 (46.41%)	0.36 (0.26 : 0.49)	
Ongoing	50 (53.19%)	44 (46.81%)	0.36 (0.23 : 0.56)	
Respiratory Sleep Disorder				0.1028
No	113 (43.8%)	145 (56.2%)	1	
Snoring	196 (35.44%)	357 (64.56%)	1.42 (1.05 : 1.92)	
Sleep Apnoea	55 (29.73%)	130 (70.27%)	1.84 (1.24 : 2.76)	
Tonsil Volume *				<0.0001
1	141 (60.52%)	92 (39.48%)	1	
2	123 (39.81%)	186 (60.19%)	3.95 (2.88 : 5.49)	
3	66 (22.53%)	227 (77.47%)	0.69 (0.52 : 0.93)	
4	33 (20.62%)	127 (79.38%)	0.86 (0.66 : 1.11)	

(continued on next page)

Table 2 ***(continued)*****.** Contingency table and summary 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	
	Recurrent Respiratory Infections			
	No *364* *(36.5%)*	**Yes** *633* *(63.5%)*	**OR (95%C.I.)**	**p-value**
Adenoid volume *				<0.0001
1	123 (33.24%)	247 (66.76%)	1	
2	118 (54.38%)	99 (45.62%)	1.42 (1.09 : 1.85)	
3	64 (30.33%)	147 (69.67%)	1.59 (1.21 : 2.09)	
4	58 (29.29%)	140 (70.71%)	0.53 (0.4 : 0.7)	
Inferior Turbinate Contact				0.9999
No	110 (32.84%)	225 (67.16%)	1	
Yes	252 (38.3%)	406 (61.7%)	0.79 (0.6 : 1.04)	
Middle Turbinate Contact				0.1094
No	151 (32.13%)	319 (67.87%)	1	
Yes	212 (40.38%)	313 (59.62%)	0.7 (0.54 : 0.91)	
Pale Nasal Mucosa				0.3880
No	233 (34.16%)	449 (65.84%)	1	
Yes	131 (41.59%)	184 (58.41%)	0.73 (0.55 : 0.96)	
Pathological Discharge				0.9999
No	166 (34.37%)	317 (65.63%)	1	
Yes	198 (38.52%)	316 (61.48%)	0.84 (0.65 : 1.08)	

and antibiotics in children with otitis and allergic disorders (closely associated with familiar atopy). In addition, allergic rhinitis was not associated with RRI.

The same consideration has to be taken about tonsil and adenoid volume. Actually, the current study was conducted in a real-life setting such as an ENT clinic. All children were currently treated by their pediatricians who sent them to the otolaryngologist for a consultation. In this regard, children with the largest tonsil and/or adenoid volume were currently treated with more aggressive therapy than children with smaller tonsil and/or adenoid. Instead, children with intermediate tonsil/adenoid volume were treated less aggressively and consequently showed a higher predisposition for RRI.

Therefore, these results evaluated altogether suggest that it is possible to identify some parameters associated with RRI during an ENT visit, such as in clinical practice.

However, present study has some limitations: i) the cross-sectional design; ii) the selected population; and iii) the absence of data concerning the past use of medications. Therefore, further studies should be performed to address these issues. On the other hand, 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 occur in daily practice.

Conclusions

This real-life study showed that during an ENT visit it is possible to identify some factors that may be involved in predicting RRI, including male gender and with careful caution tonsil and adenoid volume.

Table 3. Multivariate analysis, the predictor effects on the Recurrent Respiratory Infections (N=988). 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)	2.63 (2.44 : 5.47)	<0.0001
Gender		0.0006
Female	1	
Male	1.68 (1.25 : 2.27)	
Familiar Atopy		0.0364
No	1	
Yes	0.68 (0.47 : 0.98)	
Acute Otitis Media		<0.0001
No	1	
Yes	0.29 (0.2 : 0.42)	
Ongoing	0.31 (0.19 : 0.52)	
Tonsil volume		<0.0001
1	1	
2	4.52 (3.02 : 6.86)	
3	0.61 (0.44 : 0.85)	
4	1.08 (0.81 : 1.44)	
Adenoid volume		<0.0001
1	1	
2	0.68 (0.46 : 0.99)	
3	1.96 (1.43 : 2.7)	
4	0.47 (0.34 : 0.64)	

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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