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Allergic rhinitis causes loss of smell in children: The OLFAPEDRIAL study

Authors:

Cristobal Langdon^{1,9}

José María Guilemany^{1,9}

Meritxell Valls¹

Isam Alobid^{1,9}

Joan Bartra^{2,10}

Ignacio Dávila³

Alfonso del Cuvillo⁴

Marta Ferrer^{5,10}

Ignacio Jáuregui⁶

Javier Montoro⁷

Joaquín Sastre⁸

Antonio Valero^{2,9}

Joaquim Mullol^{1,9}

Affiliations:

1) Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia, Hospital Clínic, IDIBAPS. Barcelona, Catalonia, Spain.

2) Unitat d'Al·lèrgia, Servei de Pneumologia i Al·lèrgia Respiratòria, Hospital Clínic. IDIBAPS. Universitat de Barcelona. Barcelona, Catalonia, Spain.

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- 3) Servicio de Inmunoalergia, Complejo Asistencial Universitario de Salamanca. IBSAL. Salamanca, Spain.
- 4) Unidad de Rinitis y Asma. UGC ORL. Hospital de Jerez. Cádiz, Spain.
- 5) Departamento de Alergología e Inmunología Clínica, Clínica Universidad de Navarra Navarra, Pamplona, Spain.
- 6) Servicio de Alergología, Hospital de Basurto. Bilbao, Spain.
- 7) Hospital Universitario Arnau de Vilanova. Facultad de Medicina. Universidad Católica de Valencia “San Vicente Mártir”. Valencia, Spain.
- 8) Servicio de Alergia, Fundación Jiménez Díaz. Madrid, Spain.
- 9) Centro de Investigación Biomédica en Red en Enfermedades Respiratorias (CIBERES). Barcelona.
- 10) Red de Investigación de Reacciones Adversas a Alergenos y Fármacos, RIRAAF, Spain.

Corresponding address:

Joaquim Mullol, MD, PhD

Rhinology Unit & Smell Clinic

Department of Otorhinolaryngology

Hospital Clínic i Universitari

c/ Villarroel 170, Barcelona 08036,

Catalonia, Spain

Tel: + 34 932 279 872

FAX: + 34 932 279 813

jmullol@clinic.ub.es

Short title: Loss of smell in children with allergic rhinitis.

ABSTRACT

Background: The objective of the OLFAPEDRIAL study was to assess the olfactory dysfunction in allergic paediatric population, which has been scarcely studied. **Methods:** Observational, cross-sectional, and multicentre study evaluated the sense of smell in

untreated allergic rhinitis (AR) paediatric patients aged 6-12 yrs. **Results:** Forty-four percent (551 out of 1260) of children with AR reported smell dysfunction, with both loss of smell frequency (52.1%, $p < 0.001$) and intensity (0.75 ± 0.84 , $p < 0.0001$) being more frequent in patients with persistent than intermittent AR (38.0% and 0.51 ± 0.73 , respectively). In addition, both loss of smell frequency and intensity increased according to disease severity (m-ARIA classification) but always being significantly higher in persistent ($p < 0.0001$) than in intermittent AR. **Conclusions:** children with allergic rhinitis present a mild-moderate loss of smell which frequency and intensity is clearly related to the disease duration and severity. The loss of smell can be considered, as in adults, a clinical marker of disease severity.

Keywords: allergic rhinitis, ARIA, olfaction, loss of smell.

INTRODUCTION

Allergic rhinitis (AR) has an estimated worldwide prevalence between 10% and 25% (1), and is one of the most common chronic diseases in childhood with a prevalence reaching up to 40% in some regions (2). The International Study of Asthma and Allergies showed that 8.3% of children between 6 and 7 year olds from Western Europe had allergic rhinitis, compared with 8.8% in North America and 13.1% in South America (3).

It is proven that AR has a significant impact on paediatric patients' quality of life (QoL) affecting school, home, leisure activities and children cognitive performance (4). The AR in Schoolchildren Consensus Group found that this condition impaired school performance (5). A study of 23 children with allergic rhinitis and 69 controls found significantly lower health related QoL (assessed using the child health questionnaire) in children with AR compared with healthy controls (6). However, QoL can be improved with treatment (7).

Studies that assess the olfactory dysfunction in paediatric population are scarce, even though several potential aetiologies of olfactory dysfunction (e.g. AR, head trauma, enlarged adenoids) are common among children. There is evidence that olfactory function and discrimination are linked to learning (8), and smell disorders could be an important handicap in children's development. Up to 23% of patients with AR suffer from smell disturbances (9, 10). Several studies have addressed smell disorders in seasonal and persistent AR (11, 12) but none of them have studied the potential alteration of olfaction in paediatric patients with AR.

The aim of this study was to assess the impact of AR on the sense of smell in children, as well as to characterize it on the basis of ARIA (Allergic Rhinitis and its Impact on Asthma) duration and severity criteria.

MATERIAL AND METHODS

Study design and patients. A total of 271 centres and 334 investigators (from Allergy, Otorhinolaryngology and Paediatrics' centres) participated in this epidemiological, multicentre, cross-sectional population-based registry. Patients' recruitment was based on the following inclusion criteria: (i) age between 6-12 years old, (ii) confirmed diagnosis of AR made by an allergist, (iii) a parental informed written consent, and (iv) children should have not received any treatment for their AR during at least the two weeks preceding inclusion. Patients were considered suffering from AR if they had (i) suggestive symptoms of rhinoconjunctivitis within the precedent year or more, and (ii) at least one positive skin prick-test and/or serum specific IgE to an aeroallergen clinically relevant. Children were enrolled between May and July 2008, and were recruited from all regions of Spain to avoid any geographic influence. The Ethics Committee of the Hospital Clínic of Barcelona (Spain) approved the study.

Study outcomes. Demographic data (age, gender, height and weight), place of residence and household characteristics, as well as allergen sensitization profile, were obtained. The presence of comorbidities including asthma, atopic dermatitis, rhinosinusitis, otitis media with effusion and adenoid hypertrophy was also evaluated (13). The diagnosis of rhinosinusitis was based on symptomatology without ENT examination or radiology, as settle by the EPOS 2012 (14) guidelines for epidemiological studies.

Duration of disease was classified according to ARIA guidelines (15). Severity of the disease was assessed by the four ARIA items (sleep, daily activities/sport, work/school performance and troublesome symptoms) to classify paediatric patients in the two original levels (o-ARIA) of disease severity (16): mild (no affected items), moderate/severe (one or more affected items); as well as distinguishing between moderate (one to three affected items) and severe (four affected items), using the modified (m-ARIA) classification (17).

In order to associate the smell disorder with AR we performed the analysis of subjective loss of smell using a 4-point scale from 0 to 3 (0, no symptoms; 1, mild; 2, moderate; 3, severe). Children were asked to rate their sense of smell during the last 7 days.

Statistical methods. A descriptive analysis of the studied population -in terms of demographic characteristics and distribution of patients according to o-ARIA and m-ARIA classifications was performed. Statistical analysis included a comparison between different degrees of severity according to ARIA classification and loss of smell. Statistical analysis was carried out by Infocienzia Clinical Research, S.L. (Barcelona, Spain), using SAS (Statistical Analysis System, Chicago, IL, USA) software, version 9.1.3. The number of valid cases (N) was used in all tables, as well as in calculating percentages or any other statistical consideration.

Comparisons were made using the appropriate tests (Chi-squared, Mann-Whitney, or Kruskal-Wallis) in each case for all comparisons, a p-value of 0.05 was considered of statistical signification.

RESULTS

Demographic characteristics. Socio-demographic and clinical characteristics are summarized in table 1. A total of 1,260 children (41.3% female) were included in the study with a mean age of 9.05 years old. Almost 60% of patients had intermittent AR and 90% suffered from moderate/severe AR. The most frequent forms of AR were moderate/severe intermittent (52.1%) followed by moderate/severe persistent (37.6%). Regarding comorbidities, 49.5% of the children had asthma and 40% atopic dermatitis. As for the skin prick test, 53.5% were positive to pollens and 43.5% to house dust mites, as previously reported (15).

Olfaction and AR duration. Almost 44% (551 out of 1,260) of children had smell dysfunction. The prevalence of smell disorders increased depending on duration of AR (Fig 1A), 38% of patients with intermittent AR (IAR) and 52.1% of patients with persistent AR (PER). The intensity of the loss of smell, accordingly to the 4-point scale, also showed a relationship with the duration of AR (Fig 1B).

Olfaction and AR severity. A more severe disease was associated with a higher severity of smell dysfunction ($p<0.001$), 7.9% of children with mild disease, 41.3% of those with moderate disease, and 63.2% with severe disease having smell loss. This difference was maintained when comparing persistent and intermittent AR (Fig 1A). Globally the intensity of smell loss for mild (0.10 ± 0.33), moderate (0.56 ± 0.76), and severe (0.90 ± 0.81) AR was associated with the severity of disease, and this was observed in both IAR and PER (Fig 1B). We found a positive correlation between loss of smell and severity of IAR ($r=0.26$, $p<0.0001$) and PER (0.20 , $p<0.0001$).

DISCUSSION

The present study is the first to describe the presence of olfactory dysfunction in children with AR using the ARIA classification. The main findings of the study were: 1) allergic rhinitis caused a moderate impact on the sense of smell in children; and 2) the prevalence of olfactory dysfunction was higher in persistent than in intermittent allergic rhinitis, and loss of smell was linked to the severity of disease, particularly in persistent AR.

AR has been associated with loss of smell in adults in about 50% of the patients (9, 12, 18, 19). The pathogenesis of olfactory dysfunction in AR seems to be the result of two potential causes: obstruction and inflammation. The blockage of odour particles to reach the olfactory neuroepithelium may partly explain the loss of smell in AR (20). Regarding inflammation, patients with AR have shown a close correlation between the loss of smell and inflammatory markers such as eosinophilic cationic protein (ECP) (21) and the blood eosinophil concentration (10). In fact, intranasal steroid treatments are efficient in improving the smell disorder in AR patients (19).

The PEDRIAL study validated the ARIA classification in children through surveys on patients consulting for AR in clinical practice (16). It showed that allergen-based classification and ARIA classification of AR are different in children from 6- to 12-yr old. Furthermore, Montoro et al. (17) reported that m-ARIA classification could discriminate between moderate and severe AR in a large population of untreated paediatric patients. Using these classifications we show that in children with AR the sense of smell correlates with the severity of disease. Patients with severe disease reported a worse smell score compared to moderate patients using the m-ARIA classification, while those with PER reported a higher score than those with IAR. As reported previously, we observed a high prevalence of rhinosinusitis and this was associated with severity but not duration of disease (13). However the diagnosis of rhinosinusitis was made based on clinical symptoms but not on EPOS criteria nor in CT scan

or nasal endoscopy (and without differentiating between acute and chronic), and the latter challenges to draw conclusion regarding the implications of rhinosinusitis over smell loss in AR.

A limitation of the study was that olfactory function was not measured with an objective test. Tests available for evaluating olfactory function in children are scarce and may not be suitable for very young children. Young children are less likely to be familiar with several of the odour stimuli used (e.g., gasoline, smoke, pineapple) and also have limited ability to read labels, from which they must select the option that best represents the odour. This raises the question of whether the test is actually measuring olfactory ability in young children or whether cognitive or language confounds are responsible for their relatively poor performance. Dalton et al.(22) observed in their cross-sectional cohort study that children as young as 3 years of age can perform olfactory testing as they were perfectly capable of understanding the instruction and question of the tests. Nevertheless, we used the Likert scoring system to assess the olfactory function in a high number of patients from 6- to 12-yr old showing a good correlation with ARIA severity classification. Future studies are needed to investigate in depth the impact of allergic rhinitis on the sense of smell in paediatric population with specific and validated olfactory tests of the olfactory dysfunction regarding detection, recognition and identification of odours.

In conclusion children with allergic rhinitis present a moderate loss of smell with a higher smell impairment related to the duration of symptoms and disease severity. In consequence, the loss of smell should always be investigated in children with allergic rhinitis to mainly define the severity of disease.

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Table 1. Characteristics of the cohort study population of children with allergic rhinitis (n = 1260).

Social-demographical characteristics	Values
Age, years (mean $\pm$ SD)	9.05 $\pm$ 1.93
Gender: female, N (%)	541 (41.3)
AR clinical characteristics	
Time since AR diagnosis, years (mean $\pm$ SD)	2.54 $\pm$ 2.38
Duration of AR (according to ARIA), %	
<i>Persistent</i>	40.5
<i>Intermittent</i>	59.5
Severity of AR, %	
o-ARIA	
<i>Mild</i>	10.3
<i>moderate/severe</i>	89.7
m-ARIA	
<i>Mild</i>	10.3
<i>Moderate</i>	59.2
<i>Severe</i>	30.5
Olfactory dysfunction, %	
<i>Total AR</i>	44.0
<i>IAR</i>	38.0
<i>PER</i>	52.1

AR comorbidities, %	
<i>Asthma</i>	49.5
<i>Atopic dermatitis</i>	40.0
<i>Rhinosinusitis</i>	26.1
<i>Sero-mucous OM</i>	23.8
<i>Adenoid hypertrophy</i>	17.3
Skin prick test positivity, %	
<i>Pollens (cypress, olive three, parietaria, grass)</i>	53.5
<i>House dust mites</i>	43.5
<i>Animal dander (cat or dog)</i>	14.2
<i>Mould</i>	7.2

AR, allergic rhinitis; IAR, intermittent AR; INS, intranasal corticosteroids; m-ARIA, modified ARIA severity classification; o-ARIA, original ARIA severity classification; OM, otitis media; PER, persistent AR; SD, standard deviation.

Figure 1. Impact of duration and severity of allergic rhinitis (AR) on the loss of smell. A) Frequency of smell dysfunction in AR patients and according to m-ARIA severity classification; children with higher degrees of severity reported a more frequent smell dysfunction, this being always higher ($p<0.001$) in persistent than in intermittent AR, either in mild, moderate, or severe disease. B) Intensity of loss of smell in AR patients and according to m-ARIA severity classification; children with higher degrees of severity reported higher intensity in loss of smell, this being always higher ($p<0.01$ to $p<0.0001$) in persistent than in intermittent AR, either in mild, moderate, or severe disease.

