Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Local allergic rhinitis in children: A systematic review

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Received 12 December 2021; Accepted 29 December 2021
Available online 1 March 2022

KEYWORDS
adolescent;
child;
phenotype;
prevalence;
rhinitis

Abstract
Background: Local allergic rhinitis (LAR) is a well-defined and reported phenotype in adults, but data is scarce for children and adolescents, and it is probably an undiagnosed and highly underestimated condition in childhood.
Objectives: The objectives of this systematic review were to identify original observational studies published on LAR in children and adolescents and to describe the prevalence and characteristics of this phenotype in the pediatric age group.
Methods: A systematic search was performed in PubMed and EMBASE databases. The search was limited to publications on humans, written in English, published between January 1, 2000 and September 20, 2021. Participants had to be under 18 years old and with a diagnosis of LAR confirmed by nasal allergen provocation test (NAPT).
Results: Ten articles were identified. Despite the wide variability of protocols, prevalence rates ranged from 3.7 to 83.3% among children previously diagnosed as having nonallergic rhinitis, being markedly lower in Eastern countries (3.7–16.6%) when compared to Western countries (22.3–83.3%). To date, no relevant clinical characteristics capable of differentiating LAR patients from other childhood rhinitis phenotypes have been identified.
Conclusions: LAR is an allergic rhinitis phenotype also found in children. Population and regional differences and differences in NAPT protocols may explain the heterogeneity in LAR prevalence rates observed in different parts of the world. In addition to clarifying this large discrepancy, longitudinal studies are also needed to assess the clinical characteristics of the LAR phenotype in the pediatric age group, and its stability into adulthood must be confirmed.

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https://doi.org/10.15586/aei.v50i2.560

Introduction

Allergic rhinitis (AR) is one of the most prevalent chronic diseases in the world, affecting approximately 40% of people from different age groups. Between 5 and 25% of children has rhinitis symptoms,[1] which induce negative impacts on sleep, mood, social functioning, school performance, and high direct and indirect economic costs.[2]

Local allergic rhinitis (LAR) is a phenotype that is clinically very similar to classic AR, but it presents a nasal Th2 allergic inflammatory response, with no systemic allergic sensitization identified by the standard methods used *in vivo* (skin prick tests [SPTs]) or *in vitro* (quantification of specific serum IgE [sIgE]).[3] Its diagnosis is established by monitoring local responses during a nasal allergen provocation test (NAPT)[4] to the relevant allergens in each region.

In adults, LAR is a well-defined and reported phenotype, predominantly affecting young, well-nourished, nonsmoking women with a family history of atopy. LAR symptoms are persistent and are often associated with allergic conjunctivitis and asthma.[5] Approximately 36% of patients with LAR report its onset in childhood and persistence and worsening of rhinitis symptoms throughout life, considering it a stable rhinitis phenotype and not an early stage of classic AR.[6] The identification of LAR and its consequent distinction from nonallergic rhinitis (NAR) have potential benefits for patients, such as the possibility of treating it with specific immunotherapy and implementing care to reduce environmental exposure to the identified allergens.

There is little information available about LAR in the pediatric age group, even data on prevalence and clinical characteristics. There is a clear need to learn more about this phenotype of rhinitis in the pediatric age group, to identify and institute early treatment in patients, which can provide a consequent improvement in quality of life and reduce burden of the disease.

Objectives

This systematic review aimed to identify and summarize information from original observational studies published on LAR in children and adolescents.

Materials and Methods

Eligibility criteria

For this review, a search for relevant articles was performed in PubMed and EMBASE databases on September 20, 2021. The search was limited to publications on humans, written in English, published between January 1, 2000 and September 20, 2021, using the following keywords for parameters: Local Allergic Rhinitis AND Children OR Adolescents; OR articles that contained Local Allergic Rhinitis in the title. We also performed an active manual search of the study references included in the review to identify additional studies with possible relevance (Figure 1).

A predefined list of inclusion and exclusion criteria (Table 1) was used to evaluate potentially relevant titles and summaries. After the search was completed, the articles were excluded from the analysis for multiple reasons: duplicate articles, study population with no differentiation between adults and children, full articles written in a language other than English, and conference summaries. Two researchers (FTM and TRTG) selected the articles independently, and if there was a difference of opinion, a third party (GFW) was brought in to break the tie.

Data were evaluated following PRISMA's (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[7] Following the eligibility criteria, 396 titles and summaries were obtained, and one article[8] was found in an active search among the bibliographic references. After removing 13 duplicate articles, 384 titles and summaries were analyzed, and 336 were excluded based on the above exclusion and inclusion criteria. After thoroughly reading all 48 articles, 38 additional articles were excluded from the review. We tried unsuccessfully to contact four authors who presented data from children and adolescents but did not have a clear separation from adults. Therefore, they were excluded from the review.

Results

A total of 10 publications were selected, and a summary of their main findings is presented in Table 2.

Fuiano et al.[8] evaluated the local production of nasal-specific IgE (nsIgE) for *Alternaria* in children with clinical symptoms of rhinitis. A single-allergen NAPT (S-NAPT) was performed with *Alternaria* at concentrations of 0.2, 0.5, 0.8, and 2.8 IR, and the test was only monitored subjectively (Nasal Symptoms Questionnaire).

Buntarickpornpan et al.[9] performed an S-NAPT with *Dermatophagoides pteronyssinus* (DP) in children diagnosed with NAR (determined by negative systemic sensitization tests) between May 2014 and April 2015. A NAPT was performed with increasing concentrations of 200, 600, and 2000 AU/mL, subjectively monitored by a Symptom Questionnaire (Lebel Questionnaire), Visual Analog Scale (VAS) and objectively monitored by Acoustic Rhinometry (AcRh) (positivity parameter: >25% drop in the minimum cross-sectional area [MCA]) and peak nasal inspiratory flow (PNIF) (positivity parameter: >40% drop). After evaluating the 54 patients, only 2 (3.7%) were positive for NAPT with DP, with no change in levels of nasal tryptase or nsIgE for DP (<0.01 mcg/L), before and after NAPT.[9]

Krajewska-Wojtys et al.[10] performed the NAPT with multiple allergens (M-NAPT) using extracts with 5000 SBE/mL in 2-week intervals. The NAPT was monitored subjectively by VAS (positivity parameter: ≥30% increase of the total score) and objectively by AcRh (positivity parameter: ≥30% drop in nasal cavity volume between 2 and 6 cm [V2-6]). The authors found positive NAPT in 53/101 (52.5%) patients, 17 (16.8%) of them to *Phleum pratense*, 6 (5.9%) to *Artemisia*, and 9 (8.9%) to birch. Twenty-one patients (20.8%) had positive NAPT to the three allergens. Unlike Buntarickpornpan et al.,[9] they showed an increase in nsIgE only for *P. pratense* after 6 hours of NAPT.

Duman et al.[11] performed an M-NAPT with increasing concentrations of 0.1, 1, 10, and 100 IR/mL, and a 1-week interval between the different allergens. The

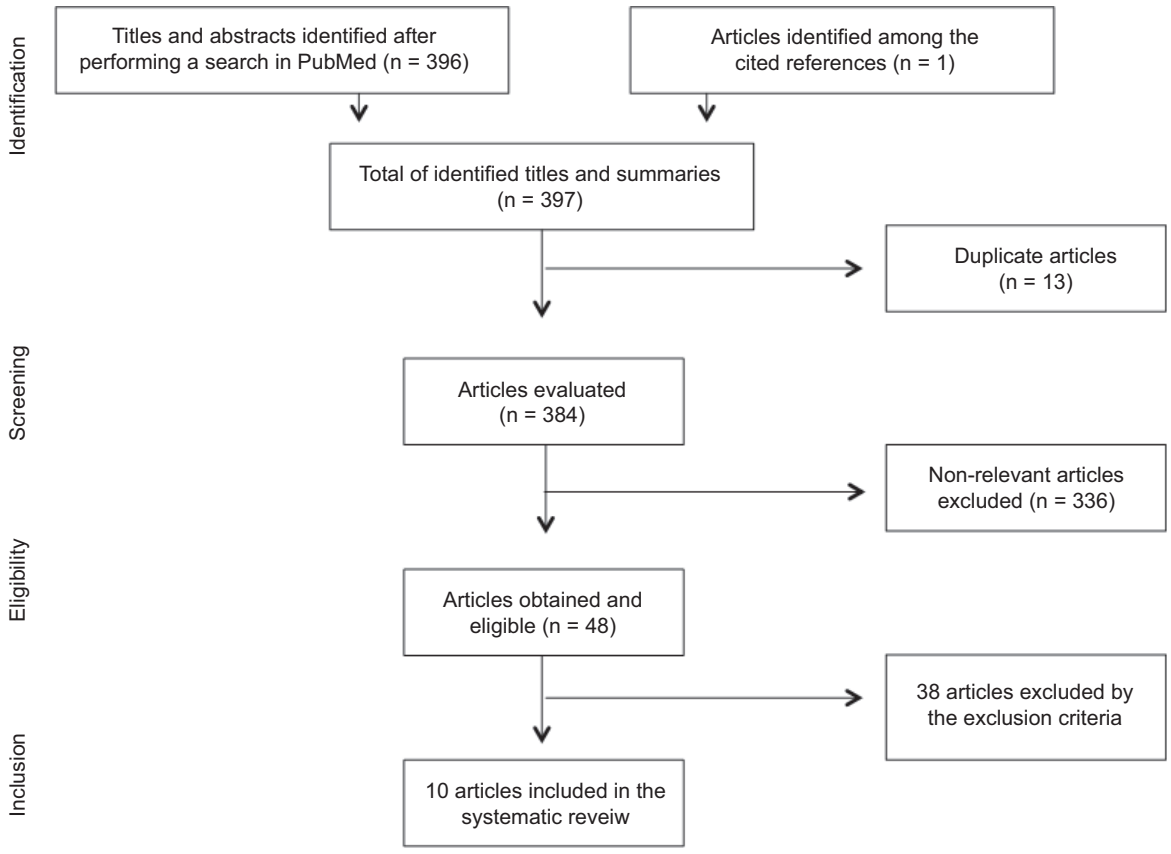

Figure 1 Flowchart of information obtained in the different phases of the systematic review.

Table 1 Inclusion and exclusion criteria for selecting eligible articles.

Domain	Inclusion criteria	Exclusion criteria
Participants	Participants mandatorily under 18 years old; the minimum age limited by the objective methods used for diagnosing LAR, carrying out the NAPT.	Studies with no age differentiation between adults and children, presence of significant anatomical defects of the upper respiratory tract (septum deviation, adenoid hypertrophy, nasal polyposis).
Intervention	Mandatory NAPT to determine LAR, which may be associated with dosage of other nasal markers, such as cytokines or nasal-specific IgE (nsIgE)	No NAPT performed, regardless of other collected markers.
Outcome	Quantification of patients identified as having LAR exclusively in the pediatric age group	Noninclusion of relevant outcome or nonquantification of patients diagnosed with LAR
Type of study	Quantitative, observational, or intervention studies	Review articles and qualitative studies
Type of publication	Original peer-reviewed published articles	Conference summaries, case report

LAR: Local allergic rhinitis; NAPT: Nasal allergen provocation test; nsIgE: Nasal-specific IgE

NAPTs were monitored subjectively by VAS and Total Nasal Symptom Score (TNSS) and objectively by Active Anterior Rhinomanometry (AAR) (positivity parameter: >40% drop in nasal flow at 150 Pascals (Pa) or >20% drop in the nasal flow associated with >2 difference in TNSS). At the end of the evaluation, 7/28 (25%) of the patients were diagnosed with LAR, and two children were positive to the grass mix, three to DP, and two to *Dermatophagoides farinae* (DF). There was no change in the quantification of eosinophils in nasal secretion.

Zicari et al.[12] performed an M-NAPT with 100 AU of each allergen (50 AU per nostril) and an interval longer than 2 days between provocations. The tests were subjectively monitored by a symptom questionnaire (NOSE score)[13] and objectively by AAR (positivity parameter: >50% drop in nasal flow at 150 Pa). At the end of the assessment, 12/18 (66.7%) were positive to at least one NAPT: six (33.3%) were positive to house dust mite, five (27.8%) were positive to grass pollen mix, and one (5.6%) was positive to both allergens. The authors also reported an increase

Table 2 Summary of the main findings of the articles selected for the systematic review.

First Author, Study location	Year of publication (recruitment period)	Age (Average age)	Total number of participants (patients with rhinitis with no systemic sensitization)	NAPT type	Prevalence of LAR (%)
Fuiano et al.,[8] Italy	2012	50–216 months (137 ± 43.2 months)	56 (36)	S-NAPT (*Alternaria*)	30/36 (83.3%)
Buntarickpornpan et al.,[9] Thailand	2016 (May 2014–April 2015)	8–18 years (11.1 ± 2.1 years)	54 (54)	S-NAPT (DP)	2/54 (3.7%)
Krajewska-Wojtys et al.,[10] Poland	2016	12–18 years (15.4 ± 3.8 years)	101 (101)	M-NAPT (*Phleum pratense, Artemisia,* and birch)	53/101 (52.5%)
Duman et al.,[11] Turkey	2016	5–16 years (10.0 ± 2.9 years)	58 (28)	M-NAPT (grass pollen mix, DP, and DF)	7/28 (25%)
Zicari et al.,[12] Italy	2016	6–12 years (8.33 ± 1.71 years)	18 (18)	M-NAPT (dust mite and grass pollen)	12/18 (66.7%)
Ha et al.,[14] Korea	2017 (May 2011–Jun 2012)	1–18 years (5.9 ± 3.3 years)	145 (64)	S-NAPT (Der p1)	5/64 (7.8%)
Tao et al.,[16] China	2018 (Mar 2016–Mar 2017)	< 14 years	40 (6)	M-NAPT (weed pollen mix, house dust mite mix, and mold mix)	1/6 (16.6%)
Bozek et al.,[17] Poland	2019	5–18 years	293 (152)	M-NAPT (DP, *P. pratense, Artemisia*, birch and cat)	34/152 (22.3%)
Tsilochristou et al.,[18] Greece	2019 (Oct 2016–Sep 2017)	6–18 years	86 (24)	M-NAPT (*P. pratense, Olea europaea, Alternaria Alternata,* and DP)	7/24 (29.2%)
Prieto et al.,[20] Spain	2021 (Jan 17–Dec 19)	5–18 years (15.1 ± 2.2 years)	173 (74)	M-NAPT (grass-mix pollen, *O. europaea, A. alternata, P. judaica*, DP)	43/74 (58.11%)

DF: *Dermatophagoides farinae*; DP: *Dermatophagoides pteronyssinus*; M-NAPT: Nasal allergen provocation test with multiple allergens; S-NAPT: Single-allergen nasal allergen provocation test

in interleukin-5, Thymic stromal lymphopoietin (TSLP; 33% of the children with positive NAPT), and nsIgE for allergens tested after the NAPT, but it must be noted that the author used 0.1 kU/L as the cutoff value to consider the nsIgE positive. Otherwise, the author justifies that this difference could be explained by considering that the samples were 50% more concentrated than the original volume.

Ha et al.[14] performed S-NAPTs with 0.4 and 4 µg/mL of freshly reconstituted freeze-dried DP between May 2011 and June 2012, monitored only subjectively by VAS and Total Symptom Score. They used the within-subject standard deviation (SDw) as a positivity parameter, calculated by dividing the difference of the symptom scores between the initial value and the value after saline challenge by the square root of 2.[15] An SD index value >2 SDs was categorized as positive.

Tao et al.[16] performed M-NAPTs between March 2016 and March 2017 using the following concentrations: house dust mite mix, 22 mg/mL; weed pollen mix, 50 mg/mL; and mold mix, 40 mg/mL, with unspecified intervals between NAPTs. Nasal provocations were monitored subjectively by VAS and objectively by AAR, using as a positive parameter: an increase of >30% in the total VAS, accompanied with an increase of >100% in total airway resistance at 150 Pa, or an increase of >15% in the eosinophil ratio in the nasal secretion smear. The study included adults and children, but only patients under 14 years old (n = 40) were analyzed for this systematic review.

Bozek et al.[17] performed M-NAPTs with 5000 SBE/mL extracts in 2-week intervals. The NAPT was monitored subjectively by VAS (positivity parameter: ≥30% increase) and objectively by AcRh (positivity parameter: ≥30% drop in V2-6). The study included adults and children, but only patients under 18 years old with positive NAPTs (n = 293) were analyzed for this systematic review. Despite the NAPTs being divided by age group, the clinical characteristics

were not separated in the same way, and it is not possible to extract data to clinically categorize children with LAR. In adults, unlike Rondon et al.,[5] they noted that the typical characteristics of patients with LAR in this group were as follows: older men with more perennial types of symptoms who are monosensitized, mainly to DP.

Tsilochristou et al.[18] performed M-NAPTs between October 2016 and September 2017, with doses of *P. pratense*, *Olea europaea, Alternaria alternata* (all 30 HEP/mL), and DP (100 HEP/mL) on the same day per the protocol developed by Rondon et al.,[19] with a preestablished order depending on the length of symptoms reported. Children were given another M-NAPT no earlier than 7 days from the positive M-NAPT, and the confirmative single NAPT took place after at least 3 weeks. The M-NAPT was monitored subjectively by VAS (positivity parameter: ≥30% increase) and objectively by AcRh (positivity parameter: ≥30% drop in V2-5).

Prieto et al.[20] performed M-NAPTs with grass-mix pollen, *O. europaea, A. alternata, Parietaria judaica* (all 30 HEP/mL), and DP (100 HEP/mL). Individuals exposed to pets were also provoked with cat and dog allergens (both 30 HEP/mL). Four increasing concentrations (1/100, 1/10, 1/2, and undiluted) were used for each allergen. The NAPT was monitored subjectively by VAS (positivity parameter: ≥30% increase) and objectively by AcRh, using as a parameter for positivity: a drop ≥30% in V2-6 (patients ≥160 cm tall) or V2-4 (patients <160 cm tall). The authors found that DP was the leading elicitor of LAR.

Only four authors assessed the clinical characteristics of children diagnosed with LAR (Table 3). Duman et al.[11] found that patients with LAR had disease durations of 3.9 ± 2.0 years: 5/7 patients (71.4%) were male, 2/7 (28.6%) had asthma, and 4/7 (57.1%) had moderate-to-severe persistent rhinitis, but none of these characteristics were significantly different from those manifested by the group diagnosed with NAR. Ha et al.[14] observed that among patients with LAR, 4/5 patients (80%) were male, 1/5 (20%) had asthma, and there was also no significant difference between the LAR, AR, and NAR groups. Tsilochristou et al.[18] also did not observe differences regarding gender (57.1% male), family atopy (57.1%), place of residence (urban or rural), or comorbidities such as atopic dermatitis (71.4%) and asthma (42.9%). Prieto et al.,[20] unlike the other authors, found 29/43 female patients (67.4%) and identified some characteristics with significant differences between the LAR and NAR groups. In children with LAR, they observed higher frequency of family history of atopy (OR: 4.13; 95%CI: 1.53–11.12), greater coexistence with allergic conjunctivitis (OR: 5.24; 95%CI: 1.85–14.84), greater presence of moderate-to-severe rhinitis (OR: 7.96; 95%CI: 2.75–23.04), nasal itching (OR: 4.40; 95%CI: 1.60–12.01), sneezing (OR: 4.01; 95%CI: 1.47–10.99), symptoms triggered by house dust and vegetation, and a trend toward clinical worsening over time. On the other hand, milder symptoms elicited by irritant smells and nasal obstruction were more common among those with NAR. However, these characteristics did not differentiate LAR patients from AR patients.

Table 3 Leading clinical characteristics described associated with local allergic rhinitis in the articles selected for systematic review.

Author	Clinical characteristics
Duman et al.[11]	Rhinitis duration 3.9 ± 2.0 years 71.4% male gender 28.6% asthma 57.1% Moderate-to-severe rhinitis
Ha et al.[13]	80% male gender 20% asthma
Tsilochristou et al.[16]	57.1% male gender 57.1% family atopy 71.4% atopic dermatitis 42.9% asthma
Prieto et al.[17]	32.6% male gender Family atopy Allergic conjunctivitis Moderate-to-severe rhinitis Itching Sneezing Symptoms triggered by house dust and vegetation and a trend toward clinical worsening over time.

Discussion

We observed a vast variation in the LAR diagnosis rates (3.7–83.3%) in children and adolescents previously classified as having NAR. These are markedly lower in Eastern countries (3.7–16.6%) when compared to Western countries (22.3–83.3%). Differences in populations and regions, the relevance of seasonal allergens, and the pattern of sensitization and differences in the local prevalence of allergic sensitization may justify the differences obtained between studies on children.

Despite LAR being a well-established phenotype of AR in adulthood, there are few studies that assess its prevalence, specifically in the pediatric age group. This lack of data is partly due to the difficulty in diagnosing children (technical difficulty in performing NAPTs in the pediatric age group, lack of technical knowledge, availability of equipment or resources, and time consumption) and partly also due to the lack of clinical interest in performing the complete differentiation between this rhinitis phenotype and NAR, which has a lower prevalence in children. Furthermore, everyday drug treatment is often carried out empirically regardless of the rhinitis phenotype. However, in adults, the identification of LAR and its consequent distinction from NAR have potential benefits for patients, such as the possibility of treating it with specific immunotherapy and implementing care to reduce environmental exposure to the identified allergens. Clinical trials with immunotherapy for children with LAR have not yet been performed. Once they emerge, we will be able to assess whether children will also benefit from this treatment.

The allergen choice to the NAPT from every publication in this study was specifically based on the etiological relevance of AR at the study site, and when seasonal allergens

were used, NAPTs were performed at times of the year not known for pollination, decreasing the chance of interference with nasal patency. Thus, choosing to perform an S-NAPT or M-NAPT was closely interlinked with the presence of seasonal and/or perennial AR in each region.

Although the choice of allergens was justified by local characteristics, the NAPTs showed a clear lack of standardization in many aspects, making it difficult to compare authors from different locations in the world. Among the factors evaluated were as follows: concentrations of allergen extracts presented differently (AU/mL, IR, SBE/mL, HEP/mL), variable instillation protocols (dosage, concentrations, and intervals between M-NAPTs), and standardization was lacking in the forms of subjective and objective monitoring. Objective monitoring is essential in performing and interpreting NAPTs and can be performed in many ways. For example, when AcRh is chosen, factors such as which parameter should be used (MCA or nasal volume) and which cutoff points should be used to consider a positive NAPT must be defined. The cutoff points defined to consider NAPT positivity also varied when the PNIF or AAR was used. Even after the EAACI position paper on the standardization of nasal allergen challenges[21] (Table 4) was published in 2018, we verified that the articles maintain heterogeneity in presenting results.

Two articles (Fuiano et al.[8] and Ha et al.[14]) only monitored the NAPT subjectively, using questionnaires. There was no objective monitoring, as currently proposed by the EAACI position paper on the standardization of nasal allergen challenges.[21] This fact justifies the inclusion of younger children in these studies because the objective NAPT monitoring methods are usually technically difficult to be employed in preschool children (AcRh, PNIF, and AAR). Fuiano et al.[8] are also not clear on whether the NAPT protocol with *Alternaria* was previously validated or performed on control patients or patients without AR, ensuring that the extracts used do not cause irritation.

The relevance of cytokines in nasal secretion is another point that should be clarified in LAR in children and adolescents. Th2 nasal cytokine measurements were performed among the selected studies, such as IL-5 (12), TSLP,[12] tryptase,[9,16] nsIgE,[8-10,12,16,17] and nasal eosinophils,[11,12,16] demonstrating heterogeneous results in patients with LAR. Although these tests are less invasive, the NAPT remains the gold standard for diagnosing LAR.

Particular attention should be paid to nsIgE values. Rondon et al.[22] reported that sIgE levels in nasal lavage have high specificity but low sensitivity (up to 40%), possibly associated with two factors. The first is related to the small amounts of nsIgE found in patients with LAR, and it is likely that this occurs due to local extravasation through the nasal mucosa once the local synthesis of IgE has not been demonstrated.[23] The second, by the possible dilution effect related to the nasal lavage method of Naclerio et al.,[24] used to detect nsIgE in some studies. In this systematic review, some authors performed the nasal lavage method of Naclerio et al.[24] (Buntarickpornpan e tal.,[9] Krajewska et al.,[10] Zicari et al.[12]), others used a sinus pack placed in the nasal common meatus to absorb nasal secretions (Tao et al.[16]) or the detection of IgE antibody *in situ* on nasal mucosa method used by Marcucci and Sensi[25] (Fuiano et al.).

The LAR phenotype in adults appears to be associated with young, well-nourished, nonsmoking women with a family history of atopy, persistent perennial rhinitis, and frequently associated with conjunctivitis and asthma.[5] The clinical characteristics in the pediatric age group, although described in some studies, are still unclear, and it is not possible to clinically differentiate them from other rhinitis phenotypes (AR and NAR).

Summary of evidence

The 10 articles included in this systematic review had a large variation in LAR diagnosis rates (3.7–83.3%) in children and adolescents that were previously categorized as affected by NAR, with markedly lower rates in Eastern countries (3.7–16.6%) when compared Western countries (22.3–83.3%). To date, no relevant clinical characteristics capable of differentiating LAR patients from other childhood rhinitis phenotypes have been identified.

Table 4 Recommendations of parameters to be used to consider a specific nasal provocation test as positive.

Method	Clearly positive	Moderately positive
Subjective measures		
Visual Analog Scale (VAS)	Symptoms ≥ 55 mm	Symptoms ≥ 23 mm
Lebel score	Increase ≥ 5 points	Increase ≥ 3 points
Linder Score	Increase ≥ 5 points	Increase ≥ 3 points
Total Nasal Symptom Score (TNSS)	Increase ≥ 5 points	Increase ≥ 3 points
Objective measures		
Peak nasal inspiratory flow (PNIF)	Flow decrease of ≥ 40%	Flow decrease of ≥ 20%
Active anterior rhinomanometry (AAR)	Flow decrease of ≥ 40% at 150 Pa	Flow decrease of ≥ 20% at 150 Pa
Acoustic rhinometry (AcRh)	MCA-2 decrease of ≥_40%	Decrease in sum of 2-6 cm^2 ≥ 27% bilaterally
4-phase rhinomanometry (4PR)	≥ 40% increase in logarithmic (lg) effective resistance	≥ 20% increase in logarithmic (lg) effective resistance

Adapted from the Augé et al. EAACI position paper on the standardization of nasal allergen challenges.[21]

Limitations

There are several limitations to our findings. First, the small number of articles published exclusively on the pediatric age group and the small number of participants in each article demonstrate the difficulty of measuring the prevalence and characteristics of LAR in children and adolescents around the world. Second, the lack of NAPT standardization and LAR diagnosis make comparisons between studies difficult, even when the allergens used are similar. Third, having only cross-sectional studies on children does not allow us to evaluate the stability of LAR as a phenotype until adulthood. This data is significant once it is known that the prevalence of positive SPT results and rhinitis increases with age[26] and that 36% of adults with LAR report the onset of rhinitis during childhood.[27]

Conclusions

As observed in adults, we can state that LAR is also a phenotype described and found in the pediatric age group. Additional studies from different parts of the world are necessary to clarify LAR prevalence, clinical characteristics, and stability in children. Furthermore, future publications may investigate the large discrepancy between the rates obtained in Eastern and Western countries and prove the efficiency of immunotherapy in the childhood rhinitis phenotype. Standardizing NAPTs is essential to allow better comparisons among studies. Several aspects of the NAPTs should be standardized, such as defining the best parameters to be used in NAPTs objective monitoring methods on children, and appropriate concentrations to be used and intervals in cases of M-NAPTs. Furthermore, standardizing the technique for measuring nsIgE and other nasal cytokines, and using the basophil activation test (BAT), could make data collection more manageable, more consistent, and clear, favorable to carrying out more studies on this age group. Longitudinal studies are needed to assess the LAR phenotype stability during childhood through adulthood.

Funding

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brazil).

Fundação de apoio à Pesquisa do Estado de São Paulo (FAPESP): Grant 2017/03075-2.

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