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Title: Detection of Local Allergic Rhinitis in children with chronic, difficult-to-treat, non-allergic rhinitis using Multiple Nasal Provocation Tests

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Running title: Pediatric Local Allergic Rhinitis

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Title: Detection of Local Allergic Rhinitis in children with chronic, difficult-to-treat, non-allergic rhinitis using Multiple Nasal Provocation Tests

Abstract:

Background: There is little evidence on the incidence and characteristics of local allergic rhinitis (LAR) in children. Most studies have included subjects with perennial rhinitis only and results are based on the investigation of no more than three allergens per study. Our aim was to determine the proportion of children with LAR amongst children with chronic, difficult to treat, perennial or seasonal, rhinitis but no evidence of sensitization to aeroallergens, or other alternative diagnosis.

Methods: We performed multiple nasal provocation tests (M-NPT) with four locally relevant aeroallergens (P. pratense, O. europea, A. alternata, D. pteronyssinus) in children with absence of aeroallergen-sensitization, seen during a calendar year in a specialized rhinitis clinic. We additionally performed single NPT to children with allergic rhinitis (AR; positive control group). The result of the NPT was based on symptoms and acoustic rhinometry. Identification of nasal hyper-reactivity (NHR) triggers was through a questionnaire.

Results: LAR was confirmed in 29.2% (7/24) of the negative SPT/blood testing population. All but one of the children reacted to one allergen and one to two. All AR-children had positive single NPT with results similar to the LAR. There were no differences in age at examination and rhinitis onset, gender distribution, family atopy, and past or current environment of residency while the prevalence of reported NHR-triggers was comparable amongst the three groups.

Conclusion: This is the first pediatric study where the seasonal or perennial rhinitis population was thoroughly tested for LAR against four aeroallergens. LAR is present in a considerable proportion of children with chronic, difficult to treat, rhinitis and no sensitization to aeroallergens and therefore, the performance of NPT should be strongly considered in these cases. There were no distinct clinical characteristics between LAR, AR and non-allergic rhinitis in children.

Keywords: rhinitis, local allergic rhinitis, LAR, rhinitis phenotypes, pediatric rhinitis, non-allergic rhinitis, nasal hyperreactivity, nasal provocation test, multiple nasal provocation test, allergic rhinitis

Abbreviations:
AR: allergic rhinitis
LAR: local allergic rhinitis
NAR: non allergic rhinitis
NHR: nasal hyperreactivity

NPT: nasal provocation test
M-NPT: multiple nasal provocation test
IR: idiopathic rhinitis
sIgE: serum allergen-specific IgE
SPT: skin prick test

Introduction:

Non-infectious rhinitis is traditionally classified into allergic (AR) and non-allergic (NAR) (1-3) based on the clinical history and evidence of systemic IgE production to relevant inhalant allergens. NAR is a heterogeneous group of nasal conditions, some of which are associated with a particular trigger or cause (e.g. drug-induced, hormonal), although in the majority of patients with NAR, the cause is unknown and the term idiopathic rhinitis (IR) has been used to categorize these patients. Although NAR in adolescent/adult rhinitis populations is common at >25% (4), its prevalence in childhood has not been well established (4).

Development of symptoms upon exposure to non-specific triggers (temperature/humidity changes, strong odors/fragrances etc) is known as nasal hyper-reactivity (NHR) (5) which is the key characteristic of patients with IR but a clinical feature of AR too (6). Given the fact that the majority of the NAR and AR patients develop NHR (7), the presence of NHR does not discriminate between NAR and AR (2). Nevertheless, in the era of precision medicine, grouping based on distinct clinical patterns, known as phenotyping (2), is a priority. For rhinitis (sub)phenotype-characterization, various clinical criteria can be used including age of onset, severity, symptom pattern/frequency, triggers etc.

Another form of rhinitis, local allergic rhinitis (LAR), is a new AR phenotype that has perplexed further the rhinitis classification. Indeed, LAR is defined by a history of perennial or seasonal rhinitis symptoms, the absence of systemic atopy [identified by skin prick test (SPT) and/or serum allergen-specific IgE (sIgE)] and a positive specific nasal provocation test (NPT) (8-12). In a recent review (13), LAR prevalence in 17 adult studies ranged from 7.4% (14) to 69.6% (15) of the NAR participants, with some of the studies having thoroughly investigated patients for nasal reactivity to four common respiratory allergens. Only a few pediatric LAR studies have been conducted (16-22), most of them have investigated children with perennial symptoms only while only two have had children challenged with three aeroallergens each (18, 19). Similar to adults (13), the reported prevalence ranged from 3.7% (17) to 66.6% (19). Acknowledging these gaps in knowledge, the aim of our study was to determine the proportion of children with LAR amongst children with chronic, difficult to treat, perennial or seasonal, rhinitis symptoms but no evidence of sensitization to respiratory allergens, or other alternative diagnosis, by performing NPTs to four common aeroallergens. Our secondary objective was to elucidate whether LAR children have any distinct clinical features including NHR triggers as opposed to non-LAR NAR children.

Methodology:

Study population and design

The study population derived from the children seen within one calendar year (October 2016 to September 2017) in the joint allergy-ENT outpatient clinic of a tertiary pediatric hospital in Athens. This is an outpatient clinic established to mainly address the needs of children less than 18 years old with severe chronic rhinitis symptoms referred by pediatricians, pediatric allergists or ENT doctors.

The focus of our study was on children with negative skin and blood sIgE testing who further fulfilled the following inclusion criteria: A) age > 6 years at examination, B) rhinitis symptoms over the last 12 months at least, C) absence of nasal anatomical abnormalities that could justify the rhinitis symptoms. Eligible children were prospectively recruited with the aim to undergo multiple NPT (M-NPT) to investigate the existence of LAR to common aeroallergens in Greece. During the outpatient clinic consultation, the rhinitis symptoms as well as their duration, triggers and impact on quality of life were recorded along with any other atopic comorbidities (current and/or past) and family history of atopy. All children received an anterior rhinoscopy and SPT (house dust mites, molds, grasses, weeds, trees, animal dander). Blood specific IgEs (ImmunoCapPhadia, positive cutoff value at>0.35 kU/L) to Dermatophagoides pteronyssinus, Alternaria alternata, Olea europea and Phleum pratense were obtained and children were booked to return for an M-NPT. All children with a positive M-NPT were invited for a confirmative single NPT to the eliciting allergen(s). For every child with a positive M-NPT, we additionally performed a single NPT to a main sensitizing allergen of a randomly picked AR child representing the positive control group. Teenage patients and all carers provided informed written consent. The study was approved by the hospital Ethics Committee.

NAR specific causes and NHR triggers:

We additionally sought to identify triggers related to specific NAR-sub-phenotypes (drug-induced, hormonal, gustatory) that may be relevant in childhood, through a doctor-administered questionnaire. We also addressed questions in relation to a number of non-specific environmental stimuli (cigarette smoke, temperature/humidity changes, strong odours/fragrances, and other irritants) in order to investigate for NHR.

M-NPT

M-NPT were performed according to the protocol developed by Rondon et al (23) outside of the olive and grass pollen season (typically May to July for Greece) and at days the patients were asymptomatic (or with mild symptoms if patients with perennial symptoms(24)). In short, four prevalent aeroallergens were applied every 15 minutes with an established order depending on the length of symptoms the children/carers reported, as follows:

1. perennial rhinitis: P. pratense, O. europea, A. alternata, and D. pteronyssinus;
2. seasonal rhinitis: A. alternata, D. pteronyssinus, O. europea, and P. pratense.

This order ensured that the most likely to be involved allergen(s) was(were) tested last during the M-NPT allowing the exclusion of as many aeroallergens as possible before a positive response would occur in that visit. We decided to use the four allergens Rondon et al had proposed as we had identified them as very common sensitizing allergens in children through the participation of our Allergy Department in the Global Allergy and Asthma European Network (GA^2LEN) Skin Test Study (25). According to this study, in children seen previously in our Allergy Department grasses and olive were the most common seasonal outdoor sensitizing inhalant allergens at 49.5% and 35% sensitization rates respectively while D. pteronyssinus and Alternaria were the most prevalent perennial allergens (of different genus) at 32.7% and 23.8% respectively.

The result of each NPT was assessed based on A) subjective (total of five - nasal obstruction, rhinorrhea, pruritus, sneezing, and ocular symptoms - 100mm visual analogue scale (VAS) scores, and B) objective parameters (nasal patency assessed by means of acoustic rhinometry with the use of an A1 Acoustic Rhinometer (GM Instruments LTD, Kilwinning, UK)). For the latter, the parameter used was the volume of the nasal cavity from 2 to 5 cm (VOL 2-5cm), which is the volume of the nasal cavity suggested by the Standardization Committee on Acoustic Rhinometry for the purpose of estimating mucosal changes (26). Symptoms were recorded and acoustic rhinometry was performed before the application of the normal saline and henceforth 15 minutes from the administration of the normal saline and each allergen. The test was considered positive when there was an increase of >30% in the total VAS score together with a decrease of >30% in VOL 2-5 cm from at least one (the most affected) nasal cavity. Both values were compared to the corresponding post normal saline values. Children were given another M-NPT no earlier than 7 days from the positive M-NPT (23) while the confirmative single NPT took place after at least 3 weeks.

NPTs were unilateral with 0.07ml (equivalent to 1 puff) of normal saline or the challenge solution [volume recommended by the manufacturer (LETI)] sprayed through a nasal dosing pump pointed towards the middle/inferior turbinate at 15-minute intervals. NPT details and exclusion criteria complied with international guidelines (24). Four initially freeze-dried and then reconstituted allergen solutions of D. pteronyssinus (100HEP/ml), A. alternata (30HEP/ml), O. europea (30HEP/ml), and P. pratense (30HEP/ml) were used. Children were asked to remain for >1 hour after the application of the last allergen so that their symptoms could be monitored. Families were requested to report back in case of symptoms developing after leaving the allergy service.

Data analysis

Quantitative variables (age, age of onset, and mean duration of symptoms) were compared among groups using Wilcoxon's rank-sum test (in case of 2 groups) or Kruskal-Wallis test (in case of 3 groups) due to lack of normality for the aforesaid variables (as obtained by utilizing the Shapiro-Wilk test for composite normality). Qualitative variables (all others) were compared among groups using Pearson's chi-squared test of independence. Statistical significance was taken when $p<0.05$. Statistical analysis was held with R, the language for statistical computing (version 3.5.0), with the assistance of RStudio (version 1.1.383).

Results:

Eighty-six children were examined for the first time in the joint allergy-ENT clinic within the defined time frame. Sixty-two (72.1%) had positive SPT with the majority (38.7%) found sensitized to both perennial and seasonal allergens (35.5% to seasonal, 25.8% to perennial). Children with positive as opposed to those with negative SPT had earlier onset of their rhinitis symptoms (at 5.9 ±2.9 SD versus 7.5±4.2 SD years respectively) and were seen at a younger age (9.4 ±3.4 SD versus 10.6 ±3.4 SD respectively) without however these differences reaching statistical significance. Gender distribution between these two groups did not differ either.

Results from the M-NPT and control AR NPT:

All children with negative SPT (n=24) fulfilled the inclusion criteria and upon receipt of their negative blood sIgE results were invited to come back for an M-NPT. None of the participants reacted to normal saline. Seven children [29.2% of the negative-SPT population/8.1% of the whole study population (Figure 1)] were diagnosed with LAR based on positive M-NPT with six of them reacting to a single allergen (two to A. alternata, two to P. pratense, one to O. europea and one to D. pteronyssinus) and one of them to two (D. pteronyssinus and A. alternata) (Table 1). All reactions took place no later than 15 minutes from the application of the eliciting allergen. More specifically, five children reacted after the application of the 1st or the 2nd or the 3rd allergen and returned back no earlier than 7 days for an M-NPT to three allergens (all but the eliciting) which in all cases were negative (Table 1). Two children reacted after the application of the 4th allergen receiving the diagnosis of LAR in one visit each (Table 1). In all seven children, the mean reduction in VOL 2-5cm of one nostril was 41.6% (9.6SD), which was accompanied by a 722% (555.3SD) mean increase in the total VAS. Two out of the seven children accepted to return for a confirmation single NPT to the allergen they had reacted to (O. europea, A. alternata) and both had a positive outcome during their single NPT too (Table 1).

Furthermore, two out of the 24 children had >30% reduction in VOL 2-5 cm but presented/reported no accompanying symptoms and therefore, the outcome of their M-NPT was determined as negative and they were classified as non-LAR NAR. There were no reports that any of the 17 non-LAR NAR subjects developed symptoms (late phase reactions) after leaving the allergy service.

Out of the 62 children with positive SPT, seven were randomly selected and undertook a single NPT to a major sensitizing allergen on the basis of their SPT results and relevant rhinitis symptoms. They all had positive NPT defined by a 44.9% (14.2SD) mean decrease in VOL 2-5cm and a 434% (243.4SD) mean VAS increase (Table 1). VAS increase ($p=0.42$) and VOL 2-5cm decrease ($p=0.9$) were comparable between the LAR and AR-control groups. On the contrary, there was a statistically significant decrease in VOL 2-5cm ($p<0.001$) and VAS increase ($p<0.001$) when comparing the LAR, AR and non-LAR NAR NPT results.

Overall, there were no bronchial symptoms or in general symptoms not involving the nose or the eyes taking place during any of the NPT of the three groups. None of the families reported that a participant experienced a late phase reaction after leaving the study center.

Absence of remarkable nasal anatomical abnormalities in the LAR, non-LAR NAR and AR children:

None of the children had signs of infectious rhinitis or significant relevant nasal anatomical abnormality at the time of their recruitment while 3/7, 6/17 and 3/7 in the LAR, non-LAR NAR and AR group respectively had no pathological findings (data not shown). A mildly inflamed mucosa was the most common finding in all groups.

Clinical characteristics of LAR, non-LAR NAR and AR children:

Children with a positive M-NPT were evaluated at a mean age of 11.4 years (3.6SD) and had an onset of rhinitis symptoms at 7 (4.3 SD) years (Table 2). There were no differences in gender distribution, family atopy, past or current environment (urban or rural) of residency either. Atopic dermatitis (71.4%) and asthma (41.2%) were the most frequent current and/or past comorbidities in the LAR and non-LAR NAR subjects respectively as opposed to conjunctivitis (42.9%) in the AR group. Notably, atopic dermatitis appeared to be a particularly common comorbidity in LAR when compared to the other two groups (p=0.06).

In all groups, the majority of children had persistent moderate/severe rhinitis according to the ARIA classification (1) and reported symptoms of similar duration over the last calendar year (Table 3). Nasal blockage was the main nasal symptom in 71.4%, 58.8% and 57.1% of the LAR, non-LAR NAR and AR children respectively with the majority of carers mentioning the children were sleeping with their mouth open. Postnasal drip was not infrequent (28.6% in LAR, 41.2% in non-LAR NAR and 28.6% in AR) while hyposmia was absent in the LAR group only.

Specific and Non-specific Triggers of Rhinitis Symptoms in LAR, non-LAR NAR and AR children:

Overall, the prevalence of reported specific causes or non-specific-NHR triggers in the three groups was comparable (Online Repository Table 1).

No children had known hormonal disorder or rhinitis reactions following aspirin/NSAIDs or any other medication use. One child from each group had rhinitis symptoms related to prolonged nasal decongestant use while two in the LAR and one in the non-LAR NAR had symptoms upon spicy food consumption.

With regards to non-specific NHR triggers, there were proportionately more children in the LAR (n=6/7, 85.7%) as well as the AR (n=5/7, 71.4%) versus the non-LAR NAR group (n=8/17, 47.1%) reacting to at least one trigger (p=0.17).

Discussion:

Although Huggins and Brostoff first detected sIgE to D. pteronyssinus in the nasal secretions of individuals with negative SPT results and absence of serum sIgE in 1975 (27), LAR is still not widely accepted as an entity and reports on its prevalence vary. Most LAR studies have taken place with adults and only a few with children. Additionally, most pediatric studies were on perennial rhinitis and in general, have investigated no more than three allergens each, while the results are highly variable. Furthermore, there is limited information on whether LAR patients have distinct clinical features that could potentially support the clinician to suspect the existence of LAR as opposed to NAR.

In this study, we demonstrated the presence of LAR in almost one third (29.2%, n=7/24) of our population that included children with chronic, problematic, seasonal or perennial, rhinitis, negative allergy investigations for numerous respiratory allergens and absence of relevant nasal anatomical abnormalities. This LAR proportion is comparable to the 25% reported by the only pediatric study (18) that investigated children with seasonal or perennial rhinitis (NPT performed with D. pteronyssinus, D. farinae, grass mix). Meanwhile, LAR prevalence in studies with children with perennial symptoms ranged from 3.7% (17) to 66.6% (19) versus 44.4% (21) to 60.3% (20) reported in children with seasonal symptoms. In our study, 6/7 LAR children were mono-sensitized and one was co-sensitized to the two perennial allergens checked. Of the three pediatric studies that did NPT to more than one aeroallergen, Duman et al (18) reported just monosensitised (n=7), Zicari et al (19) one dual-sensitized (1 out of 12 LAR) in contrast to Krajewska et al (20) who reported that nearly 40% of the seasonal LAR children were dual-sensitized (21 out of 53 LAR).

We did not identify any particular clinical characteristics of the LAR-children; there were no differences in terms of gender distribution, age of rhinitis onset, rhinitis duration, severity or impact on quality of life (Table 2 and 3), which enhances what, has been reported in the literature (18, 21, 22). Nasal blockage was the predominant symptom in all groups with the majority of children reported to be sleeping with an open mouth. We found that atopic dermatitis was the most common (71.4%) comorbidity in the LAR children as opposed to conjunctivitis (95%) reported by Blanca et al (21). On the contrary, asthma was most common (41.2%) in our non-LAR NAR children in agreement with Blanca et al. Notably, atopic dermatitis, considered as the start of the atopic march, was a particularly common comorbidity in the LAR children when compared to the other two groups which supports the notion that LAR may be a precursor of AR.

We additionally looked for the presence of NAR specific causes and NHR non-specific triggers through the history of symptoms and reported comparable prevalence of these between the groups (Online Repository Table 1). Interestingly though, a higher proportion of children in the LAR (85.7%) group reported symptoms to at least one non-specific NHR trigger as opposed to the AR (71.4%) and non-LAR NAR (47.1%) group without this being statistically significant. It has been already reported that NHR cannot discriminate between NAR and AR (7) and our results extend this observation in LAR. These results indicate that it may be difficult for a clinician to distinguish the LAR children based on the clinical history alone. This

supports the need for NPT, preferably to more than one aeroallergens, to be performed in children with chronic rhinitis and no evidence of sensitization to inhalant allergens.

There are some limitations to our study, mostly related to the relatively small number of patients included, which may explain the lack of statistically significant differences between the groups. The study population derived from a clinic meant to evaluate children with uncontrolled rhinitis and LAR proportion may have been different if more children with mild intermittent rhinitis were involved. We did not perform non-specific NPT (e.g. dry cold air) to verify NHR. Although we checked participants against four common aeroallergens in Greece we cannot exclude that there may be other relevant aeroallergens involved in LAR. Lastly, we did not investigate for local production of allergy inflammatory mediators or sIgE.

To the best of our knowledge, this is the first published pediatric LAR study where participants were thoroughly challenged against four (2 seasonal and 2 perennial) common aeroallergens in particular through the use of the standardized M-NPT protocol (23), while we addressed the presence of NHR as an additional way to potentially set a differential diagnosis. Study strengths also include rhinitis comprehensive evaluation; SPT to numerous inhalant allergens and not just the four checked at M-NPT and anterior rhinoscopy to exclude the presence of significant nasal anatomical abnormalities that could justify the rhinitis symptoms. Additionally, we included a positive control group (AR) whose NPT results were comparable to the positive M-NPT and used strict NPT positivity criteria comprising of both subjective and objective criteria.

In conclusion, in this study we demonstrated that approximately one third of the children that would have been given the diagnosis of NAR were proven to be suffering with LAR (Figure 1). Therefore, LAR seems to affect a considerable proportion of this population (children with chronic, problematic, seasonal or perennial, rhinitis) and the performance of NPT should be strongly considered pending that there is trained staff to execute them. In the era of precision medicine, it is possible that children diagnosed with LAR may benefit from allergen immunotherapy that needs to be further evaluated.

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Authorship – Contributions:

OT conceived and designed the study, performed nasal provocation tests, selected and interpreted the study data and drafted the manuscript; MK and IM performed nasal provocations tests; JL performed the statistical analysis of the data; ET, PM, ND provided input in the conception and design of the study-protocol; NGP conceived and designed the

study, interpreted the study data, reviewed intermediate drafts of the manuscript. All authors have critically revised the manuscript and have given final approval of the version submitted.

Conflict of interest declaration:
The authors declare no conflict of interest relevant to the submitted work

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Patient	VOL 0-5 cm (%)	VOL 2-5 cm (%)	VOL 0-3 cm (%)	VAS (%)	Positive after application of	Duration of symptoms during the last 12 months	Specific months symptoms occurred the last 12 months	Number of M-NPT visits needed
Positive M-NPT (LAR, N=7)								
1	26	30	22	350	A. alternata	2	August - September	2
2	51	56	45	1600	D. pteronyssinus	10	August - June	1
3	41	46	28	500	P. pratense	3	February - April	1
4	39	44	28	138	P. pratense	6	March – May & September - October	2
5	41	45	37	800	O. europea	2	April - May	2
6	29	30	32	228	A. alternata	12	All year	2
7a	43	49	28	1500	A. alternata	10	September - June	2
7b	29	33	30	660	D. pteronyssinus			
Mean (SD)	37.4 (8.6)	41.6 (9.6)	31.3 (6.98)	722 (555.3)		6.4 (4.2)		
Confirmative Single NPT of positive M-NPT								
5	40	47	32	850	O. europea	2	April - May	N/A
6	35	35	37	400	A. alternata	12	All year	N/A
Mean (SD)	37.5 (3.5)	41 (8.5)	34.5 (3.5)	625 (318.2)				
AR Single NPT (N=7)								
8	42	45	29	500	D. pteronyssinus	11	January–July & September-October	N/A
9	26	30	19	600	P. pratense	5	April–June & September-October	N/A
10	51	56	45	850	D. pteronyssinus	5	April–June & September-October	N/A
11	27	31	20	200	O. europea	4	March-June	N/A

12	63	70	50	400	A. alternata	5	March-June & October	N/A
13	39	44	28	138	D. pteronyssinus	4	November-February	N/A
14	24	38	12	350	P. pratense	9	September-May	N/A
Mean (SD)	38.9 (14.5)	44.9(14.2)	29 (14)	434 (243.4)		6.1 (2.7)		
Negative M-NPT (non-LAR NAR, N=17)								
Mean (SD)	3.4 (13.2)	3.4 (16.3)	2.7 (12)	0.28 (0.37)	N/A	6.2 (2.4)	N/A	1 (0)

Table 1: Objective and subjective parameter results of all study nasal provocations tests and related clinical details

Table presents the decrease in volume (VOL) 0-5cm, 2-5cm and 0-3cm of one nostril and the corresponding accompanying increase in the total visual analogue scales (VAS) as well as the eliciting allergen, duration and seasonality of symptoms in the i) seven children that had positive multiple nasal provocation tests (M-NPT) [diagnosed with local allergic rhinitis (LAR)]; one child had two positive provocation tests (7a & 7b), ii) seven allergic rhinitis (AR) children (positive control group) that all had positive NPT, and iii) 17 children that had negative M-NPT (only mean (SD) values shown). A nasal provocation test was considered positive when there was an increase of 30% or greater in the total VAS score together with a decrease of 30% or greater in VOL 2-5 cm from at least one nasal cavity (the most affected); both values were compared to the corresponding post normal-saline values.

	AR (N=7)	LAR (N=7)	non-LAR NAR (N=17)	p-value
Demographics:				
Age (years) at examination				0.43[a]
mean (SD)	12.4 (3.2)	11.4 (3.6)	10.3 (3.4)	
range	7 - 17	7 - 16	6 - 16	
median	12	11	10	
Age (years) at rhinitis onset				0.91[a]
mean (SD)	8 (4.3)	7 (4.3)	7.7 (4.3)	
range	2 - 14	2 - 14	1 - 14	
median	7	5.5	7.5	
Gender				0.55[b]
male, n (%)	5 (71.4)	4 (57.1)	8 (47.1)	
Brought up in urban				0.17[b]
yes, n (%)	7 (100)	6 (85.7)	17 (100)	
Current residency in urban				0.17[b]
yes, n (%)	7 (100)	6 (85.7)	17 (100)	
Atopy of close family member				0.50[b]
yes, n (%)	2 (28.6)	4 (57.1)	6 (35.3)	
Comorbidities:				
Conjunctivitis				0.43[b]
yes, n (%)	3 (42.9)	2 (28.6)	3 (17.6)	
Asthma Symptoms				0.41[b]
yes, n (%)	1 (14.3)	3 (42.9)	7 (41.2)	
Atopic Dermatitis				0.06[b]
yes, n (%)	1 (14.3)	5 (71.4)	5 (29.4)	
Food allergy				0.55[b]
yes, n (%)	0 (0)	1 (14.3)	1 (5.9)	

Table 2: Demographics and Comorbidities of children diagnosed with AR, LAR or non-LAR NAR

Table presents data on demographics and comorbidities of seven randomly selected children with allergic rhinitis (AR) and of all children with negative skin prick test results (n=24). Data of the latter are divided into those diagnosed with local allergic rhinitis (LAR) versus those diagnosed with non-local non-allergic rhinitis (non-LAR NAR) following a multiple specific nasal allergen challenge with 4 common inhalant allergens in Greece. P-values were extracted using [a] Kruskal-Wallis test, [b] Pearson's chi-squared test of independence.

	AR (N=7)	LAR (N=7)	non-LAR NAR (N=17)	p-value
Symptom Duration (months) the last 12 months				0.99[a]
mean (SD)	6.1 (2.7)	6.4 (4.2)	6.2 (2.4)	
range	4 - 11	2 - 12	3 - 12	
median	5	6	6	
ARIA classification				1[b]
intermittent mild, n (%)	0 (0)	0 (0)	0 (0)	
intermittent moderate/severe, n (%)	1 (14.3)	0 (0)	2 (11.8)	
persistent mild, n (%)	0 (0)	1 (14.3)	1 (5.9)	
persistent moderate/severe, n (%)	6 (85.7)	6 (85.7)	14 (82.4)	
Main nasal Symptom				0.51[b]
blockage, n (%)	4 (57.1)	5 (71.4)	10 (58.8)	
blockage & rhinorrhea, n (%)	2 (28.6)	2 (28.6)	3 (17.6)	
rhinorrhea, n (%)	0 (0)	0 (0)	3 (17.6)	
pruritus, n (%)	0 (0)	0 (0)	1 (5.9)	
sneezing, n (%)	1 (14.3)	0 (0)	0 (0)	
Postnasal drip				0.77[b]
yes, n (%)	2 (28.6)	2 (28.6)	7 (41.2)	
Sleep with open mouth				0.20[b]
yes, n (%)	4 (57.1)	6 (85.7)	15 (88.2)	
Snoring				0.38[b]
yes, n (%)	3 (42.9)	2 (28.6)	10 (58.8)	
Hyposmia				0.06[b]
yes, n (%)	4 (57.1)	0 (0)	7 (41.2)	

Table 3: Rhinitis-related symptoms of children diagnosed with AR, LAR or non-LAR NAR

Table presents details on rhinitis-related symptoms of seven randomly selected children with allergic rhinitis (AR) and of all children with negative skin prick test results (N=24). Data of the latter are divided into those diagnosed with local allergic rhinitis (LAR) versus those diagnosed with non-local non-allergic rhinitis (non-LAR NAR) following a multiple specific nasal allergen challenge with 4 common inhalant allergens in Greece. P-values were extracted using [a] Kruskal-Wallis test, [b] Pearson's chi-squared test of independence.

Figure 1: Precise Diagnosis of Rhinitis Phenotypes based on M-NPT

Left figure shows the diagnosis the study population (n=86) received based on their skin prick test (SPT) and sIgE results. Right figure shows the diagnosis the study population received following multiple nasal provocation test (M-NPT) in addition to SPT/sIgE results.
AR: allergic rhinitis; LAR: local allergic rhinitis; NAR; non-allergic rhinitis