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Validating childhood symptoms with physician-diagnosed allergic rhinitis

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ABSTRACT

Background: Multiple population-based and high-risk cohort studies use parental questionnaire responses to define allergic rhinitis (AR) in children. Individual questionnaire items have not been validated by comparison with physician-diagnosed AR (PDAR).
Objective: To identify routine clinical questions that best agree with a physician diagnosis of AR and can be used for early case identification.
Methods: Children participating in a longitudinal birth cohort study were evaluated at ages 1 through 4 and at age 7 ($n = 531$) using questionnaires, physical examinations, and skin prick tests (SPT) with 15 aeroallergens (AG). Parents answered 3 stem questions pertaining to their child, including presence of nasal symptoms absent a cold/flu (ISAAC-validated question), presence of hayfever, and ocular itch. Substem questions were answered with details regarding seasonality, nasal triggers, and ocular seasonality. A global assessment of allergic diseases, including AR, was performed by a specialty-trained clinician. Percent agreement, sensitivity, specificity, and positive predictive values were assessed for individual stem and substem questions.
Results: Positive response to having hayfever and presence of ocular symptoms had the highest specificity (84% and 69%, respectively) and the highest percent agreement (74% and 68%) with PDAR. Identification of triggers for nasal and ocular symptoms had the highest sensitivity (89%). Positive predictive values ranged from 31 to 39%. Combining 2 responses with highest agreement increased specificity for PDAR to 91%.
Conclusion: Responses to hayfever and ocular symptoms had better specificity and percent agreement with PDAR than the ISAAC-validated questionnaire item. Combining 2 rhinitis questions sharply increases specificity and may improve diagnostic accuracy of clinical questions.

Introduction

Case definitions for allergic rhinitis (AR) are not well standardized or validated in epidemiological studies or clinical practice. The most widely used questionnaire items in epidemiological studies of AR are adapted from the International Study of Asthma and Allergies in Childhood (ISAAC).[1] The validation process for the ISAAC items has not been rigorous; at best ISAAC AR-specific questions have been validated by comparison with aeroallergen sensitization only, without considering physician diagnosis or clinical history.[2] The ISAAC item of "presence of nasal symptoms in the absence of a cold" with or without sensitization to aeroallergens is routinely used as a case definition for AR. Without clinical correlation, misclassification of patient phenotypes is likely.[3–8] Without validated questions to identify patients with AR, comparing different epidemiologic studies is difficult or impossible because of inconsistent definitions for AR.[9–15]

Individual questionnaire items have not been compared in a birth cohort prospectively with clinician-diagnosed AR that accounts for both aeroallergen sensitization and a clinical history. Thus, the study purpose was to determine the efficiency of standardized rhinitis questionnaire items for identifying children with physician-diagnosed AR.

Methods

The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) is an ongoing well-described birth cohort of high-risk atopic infants.[16] Newborns were identified between 2001 and 2003 from birth certificate records and were eligible to enroll if living less than 400 m or more than 1,500 m from the nearest interstate or highway. Parents of these newborns were screened with an allergy symptom questionnaire and with questions adapted from ISAAC.[16] If the parents answered affirmative to any symptoms, the infant

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Table 1
Rhinitis-specific questionnaire items from the year seven visit of the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) Cohort[a]

	n with outcome/ Total *n* analyzed	%
Q1. In the past 12 months, has your child ever had a problem with sneezing, or a runny, or a blocked nose when he she did NOT have the cold or flu?	234/531	44%
Q1a. If YES, is the child's nose problem worse during any of these times compared with the rest of the year? (March to mid May, mid May to June, mid August to September, October to February, or none)	189/234	81%
Q1b. If YES, has this nose problem been accompanied by itchy–watery eyes?	156/234	67%
Q1c. If YES, does this nose and eye problem occur when your child is in the same room with a cat, dog, disturbance of house dust, or when outdoors near freshly cut grass?	129/156	83%
Q2. In the past 12 months, has your child had "hayfever"?	107/531	20%
Q3. In the past 12 months, have you noticed your child itching or scratching his or her eyes when he or she is in the same room with a cat, dog, or disturbance of house dust, or when outdoors near freshly cut grass?	200/531	38%
Q3a. If YES, is the child's itching/scratching of the eyes worse during any of these times compared with the rest of the year? (March to mid May, mid May to June, mid August to September, October to February, or none)	140/200	70%

[a]Questions Q1, Q2, and Q3 are stem questions.

underwent skin prick testing to a panel of 15 aeroallergens that included white oak, elm, maple mix, eastern red cedar, fescue and timothy grasses, short ragweed, four mold allergens (*Alternaria alternata*, *Aspergillus fumigatus*, *Penicillium* species mix, and *Cladosporium* species), cat, dog, house dust mite mix (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), and German cockroach (ALK-Abelló). Enrolled infants (n = 762) had at least one parent with both positive symptoms and at least one positive skin prick test (SPT). Parents answered a detailed symptom questionnaire, and infants received a physical examination and SPTs to the same panel of 15 aeroallergens on an annual basis at ages 1, 2, 3, 4, and again at age 7. A positive SPT was defined as a wheal at least 3 mm larger than the negative saline control.

Rhinitis-specific questionnaire items consisted of 3 stem questions and 4 sub-questions that were contingent on responses to the stem questions (Table 1). Multiple responses were possible for each child. A specialty-trained clinician made a global assessment of allergic rhinitis based on clinical history, physical examination, and skin test results. Assessment was performed by different individuals, and the clinician was blinded to questionnaire responses. Parents signed an informed consent, which was approved by the University of Cincinnati Institutional Review Board.

Sensitivity (positive response to questionnaire item given positive diagnosis), specificity (negative response given a negative diagnosis), positive predictive values (positive response given positive diagnosis divided by all positive responses), and percent agreement were calculated, comparing questionnaire items with a gold standard of physician-diagnosed AR (PDAR). Percent agreement, or test efficiency, was calculated as follows: (true positives + true negatives)/all responses. Because substem question responses were contingent on stem question responses, the total number of responses decreased for all substem questions.

Preliminary analyses showed age 7 to be optimal for the outcome of AR, as PDAR at earlier ages was recognized with low frequencies ($n \leq 20$ for ages younger than 7). Meaningful analyses were not possible with such small numbers; thus, only data from age 7 were analyzed for this study. Children assessed at age 7 also had a more mature and recognizable phenotype of AR compared with children younger than age 7. All procedures were performed using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Seven hundred sixty-two children were enrolled during their first year of life. Of these, 531 children had complete physical examinations, skin testing, and questionnaires through age 7 and were evaluated. Of 531 children, 21% were African-American. One hundred thirteen (21%) children had the outcome of PDAR at age 7. Prevalence of ocular symptoms ranged from 25 to 38% (data not shown). As shown in Figure 1, the stem questionnaire item showing best agreement or test efficiency with PDAR was response to hayfever (Q2) at 74%, when compared with ocular itch (Q3) and nasal symptoms (Q1) (68% and 63%, respectively). Specificity followed a similar pattern, in which hayfever (Q2) had the highest specificity of 84% compared with ocular itch (Q3) and nasal symptoms (Q1) (69%, and 62%, respectively). Conversely, ocular itch (Q3) and nasal symptoms (Q1) had similar sensitivities (64% and 67%), whereas hayfever (Q2) had the lowest sensitivity (35%). When stem questions with the highest percent agreement were combined (hayfever, Q2, and ocular itch, Q3), specificity increased to 91% (data not shown).

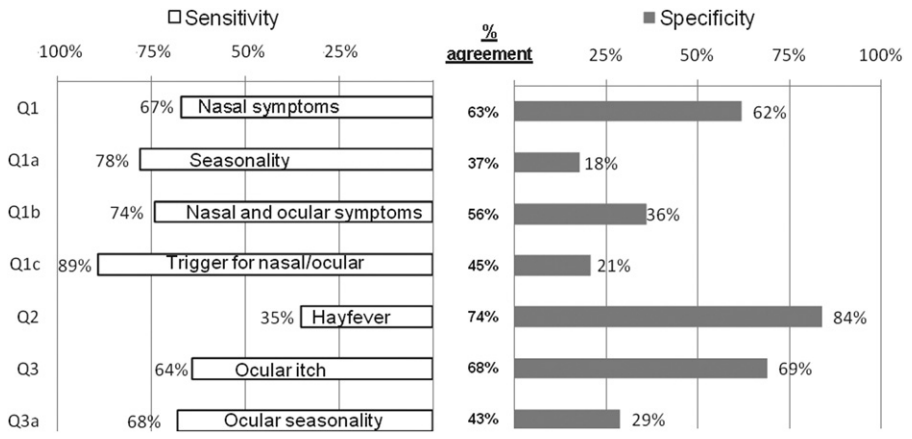

Fig. 1. Percent agreement (*vertical axis*), sensitivity (*open bars*), and specificity (*shaded bars*) of individual questionnaire items compared with physician-diagnosed allergic rhinitis (PDAR).

Subquestions for nasal symptoms (Q1) did not improve the parameters of percent agreement or specificity (Fig 1). Asking additional questions about seasonality (Q1a), presence of ocular symptoms (Q1b), or triggers for nasal/ocular symptoms (Q1c) resulted in lower percent agreements with PDAR of 37%, 56%, and 45%, respectively. Specificity also did not improve. Ocular itch (Q3) had only 1 subquestion asking about seasonality of ocular symptoms (Q3a). This subquestion (Q3a) also resulted in lower percent agreement (43%) and specificity (29%). Sensitivity, however, improved for each subquestion (Fig. 1). In particular, if positive for nasal symptoms (Q1), identification of triggers (ie, cat, dog, disturbance of house dust, or outdoors near freshly cut grass) for nasal and ocular symptoms (Q1c) had the highest sensitivity (89%).

Positive predictive values for stem questions ranged from 31 to 39%. The highest positive predictive value comparing stem questions with PDAR was hayfever (Q2, 39%, data not shown).

Discussion

The stem questions with the best percent agreement with PDAR were those asking about hayfever (Q2) and ocular itch (Q3) in the presence of animals, dust, or fresh cut grass. We were surprised that the widely used ISAAC questionnaire item (nasal symptoms over the past 12 months in the absence of a cold or flu, Q1) did not have the highest percent agreement with PDAR (Fig 1). The same stem questions on hayfever (Q2) and ocular itch (Q3) had the best percent agreement and the highest specificities (Fig 1), and both were again better than the ISAAC questionnaire item (nasal symptoms, Q1). Highly specific questions will correctly identify the "true negatives," or those who answered negatively given absence of AR as determined by the clinician. When we combined the 2 stem questions with the best percent agreement and best specificity (ocular itch, Q3, and hayfever, Q2), our specificity for AR increased to 91%. The superior performance of questions regarding hayfever (Q2) and ocular itch (Q3) over nasal symptoms alone (ISAAC-validated, Q1) suggests the latter does not address specific features of AR as reported by the layperson (ie, parent respondents).

The substem questions increased sensitivity in every case, most notably when parents were asked about triggers for nasal and ocular symptoms (Q1c, 89%). These findings can be interpreted to mean that in the CCAAPS cohort, parents whose child has been diagnosed with AR will have a positive "test" or will answer "yes" that they have triggers for nasal and ocular symptoms 89% of the time (the true positives). Specificity did not increase for the substem questions (Fig 1). Notably, up to 38% of the children reported ocular symptoms, underscoring the importance of querying school-age children about symptoms other than nasal congestion.

This study is novel in its validation methods because the gold standard of physician-diagnosed allergic rhinitis (PDAR) is used, rather than aeroallergen sensitization by SPT alone as previously reported.[2] When nasal challenges have been used to define disease, the specificity of positive clinical history combined with positive skin test in identifying patients with AR approaches 100%, whereas specificity of SPT in isolation ranges from 70 to 97%.[17] Although nasal and natural challenges correlate well with PDAR, these may be impractical for use in large epidemiological studies.[18–20] Investigators conducting large epidemiologic studies and using standardized questionnaire items to define clinical outcomes should strongly consider how laypersons may interpret symptoms and the somewhat awkward phrasing of the ISAAC question "without a cold." We have shown that the best performing questions are not necessarily those that have been widely used in epidemiological studies.[5,21] Parental understanding or ability to accurately perceive the child's symptoms as allergic may not be captured by asking about nasal symptoms alone.

This study also compares performance of specific questionnaire items. An alternative approach using a scoring system for AR (score for AR, SFAR) has been proposed, combining a composite score of multiple questions, including nasal symptoms, eye symptoms, seasonal increase in symptoms, skin test results, and previous diagnoses of AR. A study testing SFAR identified a numerical cutoff total score that was highly predictive of a physician's diagnosis of AR.[22,23] The patients recruited for those analyses, however, already had preexisting nasal symptoms or asthma and thus represented a selected population, as opposed to our cohort, a prospective birth cohort who did not have a priori atopic disease.

Recently the Rhinitis Control Assessment Test (RCAT) was validated as a tool compared with physician assessment of control of AR.[24] The population studied in the RCAT validation differed from our cohort, as the CCAAPS children did not have established atopic disease, although they were an at-risk population. The RCAT patients were more mature (at least 12 years old) than the CCAAPS cohort, and all patients in RCAT had a preexisting history of AR. The intent of our study differed from that of the RCAT validation because we did not aim to validate a clinician's assessment of symptom control in patients with known AR; rather, the purpose of this study was to determine which questionnaire items best predicted AR in at-risk children. The RCAT is likely to be more useful once a diagnosis has been made to assess control, but not in aiding clinicians to identify high-risk children.

Up to 80% of cases of AR develop before age 20, placing the responsibility for diagnosis and management often on the pediatrician. Recent estimates, however, show that fewer than half of pediatricians are familiar with professional guidelines for diagnosis and treatment of AR.[25,26] Questionnaire items in this study with high specificity (ie, presence of hay fever or ocular triggers) could aid general clinicians in early identification of children with AR. This finding may be particularly important in high-risk atopic children with pollinosis, for whom early treatment with pollen immunotherapy can modify risk for development of allergic asthma.[27,28] This benefit can persist for up to 7 years after completion of immunotherapy.[29]

Age 7 was chosen for this study because older children have a more recognizable phenotype of AR that is less likely to be confounded by viral upper respiratory infections as in younger children. In our cohort, a maximum of 20 children at each annual visit from ages 1 through 4 were identified by clinicians as having AR, and meaningful analyses were not possible. Even in a high-risk cohort such as CCAAPS, that clinicians did not identify AR in substantial numbers until age 7 is surprising. Further studies are required to validate these questionnaire items in younger children.

We chose to use the outcome of PDAR rather than sensitization alone. We recognize that for large epidemiologic studies standardized outcomes such as sensitization and positive questionnaire responses are required so that comparisons can be made between populations. The prevalence of sensitization alone has wide variability, depending on the study population examined. A retrospective database review of 1,394 specialty-referred patients (up to 21 years old) indicated that the prevalence of sensitization to any aeroallergen was 26.5% for children younger than 2 years of age, and peaked at 81.2% between the ages of 10 and 12.[30] Similarly, in a select group of children aged 0 to 2 years old, the prevalence of any aeroallergen sensitization was 28%.[31] When examined in regression models, increasing age is significantly associated with aeroallergen sensitization in a general population, supporting the findings of these studies.[32] In our cohort, previous authors have also demonstrated an increasing trend in aeroallergen sensitization from age 1 (18%) to age 2 (36.3%).[16] We argue that isolated positive skin tests in the absence of clinically relevant symptoms may not be the optimal outcome. When 10-year-old children known to be persistently sensitized to any aeroallergen were queried on the presence of rhinitis symptoms, only 13% also reported persistent

rhinitis symptoms.[33] Sensitization thus trends upward as age increases, but it may not equate with clinically relevant disease.

In conclusion, we have presented evidence demonstrating variable performance of rhinitis questionnaire items relative to clinicians' diagnoses of AR based on their global assessments combined with SPT results. Incorporation of questions such as hayfever and ocular itch should be considered for case definitions and identification of AR.

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