The Atopy Index Inventory: a brief and simple tool to identify atopic patients

Federica Di Berardino[1]*, Diego Zanetti [1], Daniele Monzani [2], Bruno Rossaro [3], Giovanna Cantarella [4], Philippe Dejonckere [5], Lorenzo Pignataro [4]

[1] Audiology Unit, Department of Specialistic Surgical Sciences, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; DISCCO (Department of Clinical Sciences and Community Health), University of Milan, Milan, Italy

[2] ENT Department, University Hospital Policlinico di Modena, Italy

[3] DeFENS (Department of Food, Enviromental and Nutritional Sciences), University of Milan, Milan, Italy.

[4] ENT Unit, Department of Biomedical, Surgical and Dental Sciences, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; DISCCO (Department of Clinical Sciences and Community Health), University of Milan, Milan, Italy

[5] ORL-Phoniatrics, Utrecht University, A.Z.U. F.02.504, GA Utrecht, Netherlands.

Short title: The Atopy Index Inventory

*Corresponding Author

Federica Di Berardino - Audiology Unit, Dept. of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - Università degli Studi di Milano
Via Pace 9 - 20122 Milan (ITALY) Tel. +39 02 5503.3922 Fax +39 02 50320754
[federica.diberardino@unimi.it]

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Abstract

Introduction. Atopy and ear, nose and throat (ENT) diseases are frequently associated; however, no clinical tool has been proposed so far to discriminate which patients could be atopic and therefore deserving of a further immunoallergological evaluation. **Objective.** The aim of this study was to assess and validate a set of dichotomous responses suitable for predicting the presence of atopy in adults' patients. **Methods.** An 11-item questionnaire called "atopy index inventory (AII), composed by four questions regarding the clinical history for allergic disease and seven questions evaluating the presence of the most frequent clinical signs affecting allergic patients, was developed and administered to 226 adult subjects (124 atopic subjects and 102 healthy, not atopic subjects). The atopic condition was proved by an immunoallergological evaluation according to the diagnostic criteria of the EAACI guidelines. Internal consistency and clinical validity were tested. **Results.** In healthy subjects, the first 4 variables of the AII returned a 100% correct response (all answered "no") and were defined as "decisive" responses. In the logistic regression analysis, when decisive items were negative, the atopic condition was confirmed when answering "yes" to at least 3 "probability" items (cut-off = 2.69). The difference of AII scores between allergic and healthy group was significant using the Mann-Whitney U test ($p < 0.0001$). Sensitivity and specificity of the AII were 0.97 and 0.91, respectively, with a true predictive value of 0.92 and a false predictive value of 0.97. The ROC curve showed an area of 0.94, with an odds ratio of 0.88 [interval of confidence (95%): 0.87–0.97, p=0.0001]. Internal consistency by the Cronbach alpha coefficient was 0.88. **Conclusion.** The AII has proved to be a brief, simple and sufficiently accurate tool for screening ENT patients in search of atopic individuals and allow their clinical management.

INTRODUCTION

Atopy is a polygenic disorder characterized by the expression of certain allergic hypersensitivity reactions, mediated by IgE, to the exposure to allergens. As a consequence, atopy produces allergy with the typical symptoms of asthma, rhino conjunctivitis, or eczema. Atopy has been associated with several ear, nose and throat (ENT) disorders, such as otitis media with effusion [1-4], adenoid hypertrophy [5-7], rhinitis and sinusitis [8-9], Ménière's disease [10-12] and Reinke's edema [13]. When a patient is referred for one of these common diseases, the ENT specialists usually address the existence of an allergic substrate by means of a direct, time-consuming interview or empiric treatments [14]. If an allergic condition is only marginally suspected, the patient is then frequently referred for immunoallergological evaluation.

Various clinical measures of allergy (e.g., skin-prick test positivity, elevated total IgE, and specific IgE titer) and questionnaires have been assessed in a number of studies, but none of these tools have been studied to screen for an atopic condition [15, 16]. In particular, the questionnaires on atopy [17-22] are aimed at monitoring clinical symptoms, determining the clinical evolution of allergic sensitization, or quantifying the effects of therapy or changes in the quality of life but none of the questionnaires are targeted for screening purposes. Furthermore, it is widely acknowledged that the diagnosis of atopy is not very straightforward [23, 24] due to its polygenic nature and because an increase of total and specific IgE is not a necessary landmark for identifying atopic individuals [23]. In fact, the correlation between skin tests and in vitro tests for specific IgE is not always very strong since mucosal and skin IgE may be different from blood IgE [24 - 27]. Moreover, currently available allergenic extracts manufactured by different companies for allergy testing are very heterogeneous [28, 29], and some allergens, such as storage mites (glycyphagidae and acaridae), although considered important, are not always included in the testing batteries [30].

The aim of this study was to assess and validate a questionnaire to identify patients requiring further allergological evaluation. For this purpose, we developed and assessed AII that could be easily and rapidly administered that could expedite the assessment of potentially atopic patients in an ENT

clinical setting and define which patients should be referred for further investigation of a possible allergic condition since it may have practical implications for treatment.

MATERIALS AND METHODS

Validation of the AII

Item generations were founded: a) on the international literature review through Medline database; b) on the most commonly reported symptoms related to atopy [15-22] and c) on the most commonly routine questions posed in clinical practice. The resulting screening questionnaire denominated the Atopy Index Inventory (AII) included 11 items aimed at identifying the allergic condition. (Table 1)

The statistical analysis of this study consisted of two separate phases: scale development and then reliability and validity analysis.

According to the STARD guidelines, we tested the AII on 226 consecutive subjects attending our outpatient clinic between 2012 and 2015, at the time of their first referral visit for audiological evaluation. Patients were administered the AII as part of the clinical assessment, and no other questions concerning the possibility of "atopy" were asked. The ENT specialists filled out the AII. All 226 subjects were then referred for immunoallergological evaluation. All were tested with skin tests using a standardized method: 1) prick tests for the most common inhalants, cow milk proteins, ovoalbumin, and water extract from wheat flour and 2) prick tests for tomato, potato, apple, and carrots (fresh foods). Histamine was used as a positive control and extract diluent as a negative control. Patients with negative prick tests were further investigated by an intradermal test with a Dermatophagoides mixture. Subsequently, the 226 patients were classified by the immunologists into two subgroups according to the immunoallergological results into the "atopic group" and "control group" according to the EAACI guidelines [19].

Atopic group

This group included 124 individuals, 76 females (age range 4–79 years, mean 36.8 ± 19.11) and 48 males (age range 6–70 years, mean 32.7 ±18.97). According to the EAACI guidelines [19], this group included those patients with a positive skin test to at least one of the allergens tested and/or positive on an intradermal test (wheal > 5 mm) and/or elevated total IgE > 260 U.I./ml and/or specific IgE > 0.70 KU/l, allergic rhinopathy according to The International Consensus statement on Allergy and Rhinology: Allergic Rhinitis [31] and/or treated with immunotherapy with success.

Control group

This group comprised 102 individuals: 61 females (age range: 19–74 years, mean 36.0±14.3) and 41 males (age range 19–74 years, mean 38.8 ±17.6). The "control group" was constituted by all (non-atopic) patients who tested negative on all the previously reported parameters at the immunoallergological evaluation.

The participation in the study for both groups was voluntary, and subjects were not compensated. Patients signed a written informed consent for the publication of the results. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki of 1975, as revised in 2008; all the procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and have been approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy (n.2174- 2016). This study also complies with the Standards for Reporting of Diagnostic Accuracy Studies [32]. Informed consent was obtained from all individual participants included in the study. Patients' anonymity has been guaranteed.

Statistical analysis

Data were collected in an Excel datasheet, imported and analyzed by means of the R-program for statistical computing (R core team, 2015) using the package MASS to carry out logistic regression, and the packages ROCR and AUC to estimate and plot different performance measures, such as optimum cut-off, accuracy, sensitivity and specificity, odds, true and false predictive value (TPV and FPV, respectively) and interval of confidence (IC). The internal consistency of the 11 tests was assessed using the Cronbach alpha coefficient by the package PSY. (CRAN, R core team, 2015) The presence of ceiling and floor effects was evaluated on the basis of the percentage of patients with the maximum or minimum AII score and was considered present if this was the case in 15% or more of the patients [33]. The Kaiser-Meyer Olkin (KMO) measure of sampling adequacy and the Bartlett Test of Sphericity (BTS) were conducted on the data prior to factor extraction to ensure that the characteristics of the data set were suitable for the exploratory factor analysis (EFA) to be conducted. For the EFA, the number of factors to extract was determined by the scree plot and Kaiser's criterion of unity (i.e., Eigen values > 1). Principal component analysis with Varimax rotation was used to maximize the amount of variance explained by the instrument items. Spearman's rank correlation was used for evaluating the relationship among the 11 items. The fitted values of the responses obtained from the logistic regression were the starting point to estimate the probabilities to assign a subject to a group. Since individual items differed in their association with "atopy", each item was weighted by its odds ratio in favor of "atopy". The fitted values obtained with logistic regression were turned into a binary class decision by choosing a cut-off using the package ROCR. The presence of a normal distribution was assessed by a Shapiro-Wilks normality test; a goodness-of-fit test was used to verify the Poisson distribution. A Wilcoxon Mann-Whitney nonparametric test was used to test significant differences between the two groups ($p< 0.05$).

RESULTS

The Cronbach alpha coefficient was 0.8 [interval of confidence (95%): 0.86–0.90], indicating a high intrinsic reliability of the AII's items. The adequacy of the sample was confirmed by KMO sampling adequacy analysis, yielding an index of 0.889. The Bartlett measure of sampling adequacy (anti-image correlation matrix) for the 11 items of the AII was highly significant ($\chi^2 = 1065.3$, df = 55, $p < 0.0001$), indicating that the data satisfied the psychometric criteria for the factor analysis to be performed based on data distribution characteristics. Ceiling and floor effects were absent. Exploratory factor analysis showed a high interrelationship among all the AII items, showing that all eleven items have to be included in the instrument. The AII scores between atopic and control group were significantly different ($p < 0.0001$).

The first 4 items of the AII gave a 100% correct response ("no") in healthy subjects (control group), so these four items were confirmed as "decisive" responses ("s"). (Table 2) The ROC curve was calculated including the entire group of allergic and nonallergic subjects. Results showed an odds ratio of 0.88 with an area under the curve (AUC) value of 0.94, and suggested that a cutoff score of 2.69 was able to accurately identify atopic subjects with a sensitivity value of 0.97 and specificity of 0.91. TPV was 0.92, and FPV 0.97. [interval of confidence (95%): 0.87–0.97, p=0.0001] (Figure 1)

Using an Excel datasheet, it was possible to fit a formula in which each of the responses obtained from the newly tested subjects (potentially "atopic" or "healthy") could be singularly multiplied by the regression coefficients, including the intercept. In this proposed formula, the discriminating threshold value became: $Y = \ln (p /(1 - p) = -0.348$, where $Y > 0.348$ identifies the TRUE condition ("atopic").

The scores have also been recalculated as weighted means, adding the first 4 AII items and weighting all 11 AII items with their accuracy, as reported in Table 2. Logistic regression was carried out with the 7 "probability" items to obtain the regression coefficients and their significance as shown in Table 3. Age and sex did not significantly contribute to any reduction of residual deviance.

A threshold could be established by plotting the Poisson distributions of the responses of atopic and healthy individuals (Figure 2). The crossing of the two plots was confirmed at a value of 2.69, which was selected as the cut-off point, providing a 94% probability of correctly identifying a patient with an “atopic” condition.

DISCUSSION

The impact of atopy on several ENT disorders has not been fully clarified so far, and therefore an easy and rapid inventory that could expedite the assessment of potentially allergic patients and reduce the referral rate to immuno-allergologists is highly desirable.

The results showed strong internal consistency and clinical and external validity. Summarizing the results of the statistical analysis, we can conclude that an "atopic condition" was confirmed if the answer was "yes" to at least one of the "decisive" questions (s) or to at least three "probability" questions (r), with high sensitivity and specificity (0.97 and 0.91, respectively), a true predictive value of 0.92 and a false predictive value of 0.97. The Cronbach alpha coefficient of 0.88 is generally considered ''good'' and greater than 0.9 ''excellent,'' whereas a value greater than 0.7 is often considered satisfactory. In the present study, the first 4 AII items were able to give a satisfactory test, while the inclusion of at least one of the other 7 AII items were able to give a good test, even if the inclusion of all the 11 variables gave a result near to excellent (alpha = 0.88).

The strength of this study relies on the unequivocal identification of atopic subjects based on the logistic regression analysis [19]. Furthermore, as far as we know, no other comparable questionnaires are available to act as a "gold standard" to validate the AII. The inventory AII, in fact, differs significantly from the other existing tools as AII is designed to screen for possibly atopic subjects, while the commonly used questionnaires only allow the quantification of the severity of symptoms and monitoring of therapy effects.

Conversely, a limitation of this study is that, with atopy, it is almost impossible to select a control group of unquestionably non-atopic individuals [15] since it is widely accepted that the diagnosis of atopy is complex and it is only confirmed by the expression of atopic symptoms, which might occur later on at any age [23].

The validation analysis allowed us to keep all 11 items, resulting in a questionnaire that could be applied rapidly enough to use for screening. In fact, the data showed that eliminating the questions

(r6, r7) with the lowest accuracy did not provide enough evidence of differences in the results, while causing a significant reduction in sensitivity. We also observed that the item s1 ("Do you think you suffer from an allergy or have you received medical treatments for allergies?) had 100% specificity but provided 28% of the false negative results when asked alone. Even combining the 2 items with the highest accuracy (s1, r1) resulted in the index not being accurate enough.

Interestingly, the occlusal condition (r1) gave the highest accuracy, odds ratio and logistic coefficients. While not directly correlated to allergic diseases, the position of the teeth was able to identify the "atopic" patients in 96% of cases. The relationship between atopy and teeth position might be explained by the chronic oral breathing in the atopic subjects since a low position of the tongue and narrowing of the palate have been found to be associated with protrusion of the upper incisors [33-36].

As highlighted in the European Academy of Allergy and Clinical Immunology (EAACI) position paper for Rhinology in 2011 [19], "*the patients' history is vital in understanding and diagnosing the problem. In rhinitis and rhinosinusitis an accurate history is usually more important than any other investigation.*"

Our data confirm that atopic patients are easily identifiable when they express the classic symptoms of allergic sensitization (the "decisive" questions of the AII) but they may be underdiagnosed when their symptoms are related to minimal persistent inflammation of the upper airways due to sensitization to aero-allergens, which is investigated by the "probability" items. To our knowledge, the AII is the first reliable and simple tool designed specifically for the initial identification of the condition of "atopy" also in such patients accessing the ENT clinic.

Based on the promising results of this study it would be useful and interesting to test the AII in other clinical settings or in more extensive ENT fields, in order to select those who should be referred to an immunologist or should be provided an initial symptoms-relieving therapy.

Statements

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Statement of Ethics The participation in the study for both groups was voluntary, and subjects were not compensated. Patients signed a written informed consent for the publication of the results. The work was carried out in accordance with the Declaration of Helsinki of 1975, as revised in 2008; all the procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and have been approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy (July 2016). Informed written consent was obtained from all individual participants included in the study.

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FIGURE LEGENDS

Figure 1. ROC curve

Figure 2. Plot of the responses calculated by multiplying the binary responses of the 11 variables by their accuracies; separated histograms and fitted poisson distributions are plotted (red: “atopic” and green: healthy “control” group)