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Asthma and rhinoconjunctivitis comorbidity: United airway disease or inherited target organs?

Garcia-Marcos L, Ruiz TR, Garcia-Hernandez G, Suarez-Varela MM, Valverde-Molina J, Sanchez-Solis M. Asthma and rhinoconjunctivitis comorbidity: United airway disease or inherited target organs? Pediatr Allergy Immunol 2009.

The idea of a united airway disease for asthma and rhinoconjunctivitis is supported by clinical and epidemiological data. However, many asthmatics do not have rhinoconjunctivitis and vice versa. The aim of this study was to investigate if the family history of a specific organ involvement is associated with the implication of the same organ in the allergic child. According to the organ involvement in either or both parents, the family history of 739 children who were skin prick positive to either *Dermatophagoides pteronyssinus* or *D. farinae* or both was defined as: asthma and rhinoconjunctivitis positive; asthma and rhinoconjunctivitis negative; asthma negative and rhinoconjunctivitis positive; and asthma positive and rhinoconjunctivitis negative. Asthma and rhinoconjunctivitis in the children were defined according to the International Study of Asthma and Allergies in Childhood questionnaire. Associations between each type of family history and the presence of asthma and/or rhinoconjunctivitis in the children were calculated and adjusted for usual confounders. Adjusted odds ratio of children having asthma, when family history included asthma, was 2.48 (1.38–4.45) when it also included rhinoconjunctivitis; and 2.13 (1.12–4.05) when it did not. However, family history of rhinoconjunctivitis was not associated with asthma in the child. Conversely, the odds ratio of children having rhinoconjunctivitis when family history included rhinoconjunctivitis was 1.84 (1.05–3.21) when it also included asthma; and 1.89 (1.23–2.89) when it did not. Family history of asthma was not associated with rhinoconjunctivitis in the child. In a population of children sensitized to mites, the organ or organs (nose and/or lung) which are implicated in parents tend to be also involved in their children.

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There is a growing body of evidence that links rhinoconjunctivitis with asthma to the extent that it has been considered a 'united airway disease' by some authors (1). The evidence of a link between the two diseases is not new and comes from the epidemiological field (those individuals with rhinoconjunctivitis are at greater risk of suffering from asthma) in both adults (2–4) and children (5); as well as from the clinical field (treatment of rhinoconjunctivitis improves asthma control) again in both adults (6) and children (7). Additionally, patients who have seasonal or perennial rhinoconjunctivitis also tend to have bronchial hyper-responsiveness (8) without asthma symptoms (9) and the presence of rhinoconjunctivitis can precede the onset of asthma (10). Furthermore, treating seasonal rhinoconjunctivitis in children without asthma with immunotherapy protects from the development of asthma as

shown in the Preventive Allergy Treatment (PAT) study (11, 12).

However, a large survey (13) carried out some time ago in Germany among 9- to 11-yr-old children showed that family history (at least one parent) of asthma was a risk factor for this condition in the offspring, while a family history of allergic rhinitis was not. Conversely, a family history of allergic rhinitis was a risk factor for both asthma and rhinitis in the child. That study, based only on symptom questionnaires on a general population, could not correct for atopy in the child, thus not allowing disentangling the confounding effect that atopy may have had on the inheritance of asthma and/or rhinitis. Additionally, earlier reports of the International Study of Asthma and Allergies in Childhood (ISAAC) study on the global prevalence of asthma and rhinitis show that although the prevalences of these conditions were correlated, the association was not particularly strong and there were numerous centers which had high prevalence for asthma, but not for rhinitis and vice versa (5).

A survey among young adults specifically focused on the prevalence and risk factors of asthma and rhinoconjunctivitis comorbidity showed that asthma-like symptoms can be found in only 50% of patients with allergic rhinoconjunctivitis and according to the analysis of risk factors, asthma without rhinoconjunctivitis was a different entity from asthma-rhinoconjunctivitis comorbidity (14). The main limitation of that study is that definitions were based on questions and not on objective allergy tests. More recently, in a group of perfectly characterized adult patients with allergic (prick test) rhinoconjunctivitis, it has been shown that the presence of asthma was less than 50%, and that rhinoconjunctivitis severity – according to the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative – did not correlate with the presence of asthma (15). Additionally, the results of the Manchester Asthma and Allergy Study have demonstrated that in 5-yr-old children, there is no association between the presence of rhinoconjunctivitis (either allergic or non-allergic) and wheezing severity, increased airway reactivity, or reduced lung function. Furthermore, only 40% of the children with rhinoconjunctivitis symptoms (with independence of being allergic or not) suffered from wheezing (16). Those results have led some authors to hypothesize that although coexistent, the two diseases are less related at these ages than afterwards (17).

From the aforementioned studies and from morphogenesis of the nasal cavity and of the lungs occurring totally separately, it may be hypothesized that – although related through the immunological system – the nose and the bronchial system might not be so united and that the organ itself can play an important role in the presentation of symptoms. The aim of the present study was to show to what extent the parental history of rhinoconjunctivitis and/or asthma determines the presence of the same disease(s) in a group of school children all of whom were sensitized to mites.

Methods

Study population

The sample of this study consisted of a subgroup of children who were part of the total population of school children 9–12 yr old included in the ISAAC phase II in Spain (see Appendix for the members of the ISAAC phase II group). The details of the protocol of this phase of ISAAC have been published elsewhere (18). Information about the specific number of children, participation rate, prick test procedure, and validation of the questionnaire in Spanish has been published previously (19). This study was approved by the ethics committee of the '12 de Octubre' hospital for all Spanish centers.

The subgroup of children included in the present analysis (n = 736) consists of all children who had a positive skin prick test to *Dermatophagoides pteronyssinus* and/or to *D. farinae*, and whose parents had completed the questionnaire. A positive skin prick test was considered when the wheal diameter measured 3 mm or more after subtraction of the control value (histamine). Additionally, the mean wheal diameter was measured as $[(D + d)/2]$, where '*D*' is the maximum diameter and '*d*' is the perpendicular one.

Definition of variables

The main outcome variables were asthma and/or rhinoconjunctivitis in the children and asthma and/or rhinoconjunctivitis in the family history. Asthma in children was defined as a positive answer to the question: 'Has your child had wheezing or whistling in the chest during the last 12 months?', while rhinoconjunctivitis was defined as a positive answer to both the following questions: 'In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?'.

A parental history of asthma or rhinoconjunctivitis was considered according to the answer to the questions 'Has the child's mother had any of the following diseases? Asthma (yes/no); hay fever or allergic rhinoconjunctivitis (yes/no); and 'Has the child's father had any of the following diseases? Asthma (yes/no); hay fever or allergic rhinoconjunctivitis (yes/no). When the mother or the father answered affirmatively to asthma, the parental history was considered positive to asthma; similarly, when the mother or the father answered affirmatively to hay fever or allergic rhinoconjunctivitis, the parental history was considered positive to rhinoconjunctivitis. Therefore, the four possible types of parental history were: asthma and rhinoconjunctivitis positive; asthma and rhinoconjunctivitis negative; asthma positive and rhinoconjunctivitis negative; and asthma negative and rhinoconjunctivitis positive.

Statistical analysis

The proportion of children with asthma (with or without rhinoconjunctivitis) or with rhinoconjunctivitis (with or without asthma) was calculated for the different types of parental history, i.e., asthma only, rhinoconjunctivitis only, both diseases, and none of them. Proportions were compared in two 4×2 contingency tables (one for asthma and another one for rhinoconjunctivitis) and associations in each of the eight cells were evaluated according to the standardized residuals corrected for the number of rows and columns total. A residual was considered statistically significant ($p < 0.05$) when its value was ≥ 1.96. The positive or negative sign of the residual indicated the existence of a positive or negative association. The Pearson's chi-square was also estimated for the two tables. Both residuals and chi-square were calculated by the SPSS v15 software package (SPSS Inc., Chicago, IL, USA).

To have an estimate of the robustness of the univariate associations, we also performed a multivariate analysis. This analysis was carried out by two different logistic regressions (one for asthma and another one for rhinoconjunctivitis, both in children as dependent variables), which – apart from the type of parental history as independent variable – included confounders which could be related to asthma or rhinitis prevalence: gender; birth weight < 2000 g; having older or younger siblings; smoking at home; mold stains on the household walls; living in a rural area (as opposed to urban) and having a cat or a dog during the first year of life. Logistic regressions were carried out using the Intercooled Stata v7.0 statistical software (Stata Corp., College Station, TX, USA).

Results

Among the 736 children (57.2% males, age 10.3 ± 0.71 yr) all of whom had a positive skin prick test to either *Dermatophagoides pteronyssinus* or *D. farinae*, 176 had asthma (23.9%) with or without rhinoconjunctivitis and 263 had rhinoconjunctivitis (35.7%) with or without asthma. Most children did not have any parental history of asthma or rhinoconjunctivitis (67.8%); only rhinoconjunctivitis was found in 16.2%, while only asthma was described in 7.2%. Both diseases were found in 8.8% of those parental histories (Table 1).

There was a statistically significant association between a parental history of asthma and the child suffering from this disease. Similarly, there was a statistically significant association between a parental history of rhinoconjunctivitis and the offspring suffering from rhinoconjunctivitis. These associations were disease-specific. When the parental history included rhinoconjunctivitis but not asthma, the children tended to suffer only from rhinoconjunctivitis. Similarly, when the parental history included asthma but not rhinoconjunctivitis, the children tended to suffer only from asthma. When the parental history included both diseases, the children tended to suffer from asthma and rhinoconjunctivitis (Table 2). The Pearson's chi-square for the contingency table type of parental history $\times$ asthma was 10.8

Table 1. Demographic characteristics of the children included in the study (all of them showing sensitization to mites) (n = 736)

	n	(%)
Mean age (yr)	10.3 ± 0.71	
Male gender	421	57.2
Child symptoms		
Asthma	176	23.9
Rhinoconjunctivitis	263	35.7
Family history		
$Asthma^{-}Rhinoconjunctivitis^{-}$	499	67.8
$Asthma^{+}Rhinoconjunctivitis^{+}$	65	8.8
$Asthma^{+}Rhinoconjunctivitis^{-}$	53	7.2
$Asthma^{-}Rhinoconjunctivitis^{+}$	119	16.2
Risk factors		
Birth weight <2000 g	20	2.8
Older siblings	374	50.8
Younger siblings	336	45.7
Smoker at home	386	54.8
Mold stains on household walls	22	3.1
Rural area	74	10.1
Dog at home during fist year of child's life	91	12.4
Cat at home during first year of child's life	30	4.1

Table 2. Proportion of children suffering from asthma or rhinoconjunctivitis symptoms according to their parental history

		Asthma symptoms in child		Rhinoconjunctivitis symptoms in child	
Parental history	n	n (%)	Residual*	n (%)	Residual*
Asthma$^-$Rinoconjunctivitis$^-$	499	106 (21.2)	−2.5	160 (32.1)	−3.0
Asthma$^+$Rinoconjunctivitis$^+$	65	23 (35.5)	+2.3	29 (44.6)	+1.6
Asthma$^+$Rinoconjunctivitis$^-$	53	19 (35.8)	+2.1	16 (30.2)	−0.9
Asthma$^-$Rinoconjunctivitis$^+$	119	28 (23.5)	−0.1	58 (48.7)	+3.2

*Standardized residuals corrected for rows and columns totals: values ≥1.96 indicate statistical significant association ($p < 0.05$); the sign shows if the association is positive or negative.

($p = 0.013$), while that for rhinoconjunctivitis was 14.6 ($p = 0.002$).

In the multivariate logistic regression, the same trend of an association of a specific parental history with a specific disease in the children was observed. Male gender and birth weight <2000 g were independent risk factors for asthma, whilst having a dog during the first year of the child's life was a risk factor for rhinoconjunctivitis. Female gender showed a trend to be an independent risk factor for rhinoconjunctivitis (Table 3).

The mean wheal diameter (mm) to mites in the skin prick test of children according to the different types of parental history was: 4.94 ± 2.35 (asthma and rhinoconjunctivitis positive); 4.96 ± 2.32 (asthma and rhinoconjunctivitis negative); 4.87 ± 2.32 (asthma positive and rhinoconjunctivitis negative); and 5.24 ± 2.62 (asthma negative and rhinoconjunctivitis positive).

Discussion

There is a generalized opinion of a close connection between the upper and the lower airway disease in allergic individuals, based upon epidemiological (individuals with rhinoconjunctivitis are at greater risk of suffering from asthma, and vice versa) and clinical (treating rhinoconjunctivitis may improve asthma control) data (6, 7). This connection has led some authors to use the term 'united', 'coexistent', 'integrated' or 'one' airway to refer to the rhinoconjunctivitis and asthma comorbidity (2–5, 11, 12).

The paradigm of the 'united airway disease' seems to be mainly related to the 'allergic airway disease' and, in fact, the main connection between the nose and the bronchial system has been hypothesized to be the bone marrow, i.e., the immunological competent cells and their mediators. This has been explained recently in a review by Rimmer and Ruhno (20) who proposed that localized inflammation (bronchial system or nose) leads to a systemic response in which mediators – mainly interleukin-5 – (21), provoke the release of progenitor cells by bone marrow, which are subsequently recruited to other tissue sites (nose or bronchial system).

Due to this paradigm of 'united airway disease' being based on the 'allergic airway disease,' we decided to study a group of children who were all sensitized to dust mites. We chose dust mites because they are the main perennial allergens in our region, allowing for the allergen charge being more uniform among the children. The fact that all of them were sensitized permits controlling for the confounding association between asthma/rhinitis and atopy.

Table 3. Multivariate analysis (logistic regression) assessing the associations between the different types of parental history and the organ involved in the child (controlled for all the variables in the table)

	Asthma symptoms in child			Rhinoconjunctivitis symptoms in child		
	aOR	95% CI	p	aOR	95% CI	p
Parental history						
Asthma$^-$Rhinoconjunctivitis$^-$	1	–	–	1	–	–
Asthma$^+$Rhinoconjunctivitis$^+$	2.48	1.38–4.45	0.002	1.84	1.05–3.21	0.03
Asthma$^+$Rhinoconjunctivitis$^-$	2.13	1.12–4.05	0.02	0.89	0.46–1.71	0.7
Asthma$^-$Rhinoconjunctivitis$^+$	1.11	0.67–1.85	0.7	1.89	1.23–2.89	0.003
Male Gender	1.58	1.08–2.31	0.02	0.75	0.54–1.04	0.09
Birthweight <2000 g	2.63	0.99–6.95	0.05	1.71	0.66–4.40	0.2
Older siblings	1.20	0.77–1.86	0.4	1.09	0.74–1.61	0.7
Younger siblings	1.01	0.65–1.59	0.9	1.39	0.94–2.06	0.1
Smoker at home	1.13	0.77–1.64	0.5	0.97	0.69–1.34	0.8
Mold stains on household walls	2.30	0.93–5.67	0.07	1.50	0.62–3.67	0.3
Rural area	0.87	0.46–1.61	0.6	0.63	0.35–1.11	0.1
Dog at home during first year of child's life	1.43	0.83–2.47	0.2	1.64	0.99–2.70	0.05
Cat at home during first year of child's life	1.00	0.40–2.50	1.0	0.65	0.27–1.55	0.3

aOR, adjusted odds ratio.

Apart from this immunological connection, there are several physical mechanisms that could help explain the link between the upper and the lower airway: breathing through the mouth (when there is a nasal obstruction) could indeed have deleterious effects on the lower airway, including a decrease in the ability to avoid allergens reaching the lower airway. Other mechanisms, such as the so-called naso-bronchial reflex whose existence has been challenged (22) post-nasal dripping and the antiviral, bacteriostatic, bronchodilator nitric oxide concentrations – which are much higher in the nose than in the lower airway (23) – are probably less involved in the maintenance of chronic conditions such as asthma.

In spite of the evidence supporting the link between the nose and the bronchial system, it is also obvious that not all individuals with rhinoconjunctivitis have asthma or vice versa. This lack of connection might be more apparent among the children, especially among the youngest (17). In a group of pre-school children 5 yr old, Marinho et al. (16) have shown that among those having rhinoconjunctivitis symptoms, less than half of them also had asthma symptoms. Furthermore, rhinoconjunctivitis was not associated with wheeze severity, increased airway reactivity or decreased lung function. Similarly, the results of a major Brazilian survey showed that only 45% of schoolchildren (6–7 yr old) and 37% of adolescents (14–15 yr old) with rhinoconjunctivitis described asthma symptoms (24). Unfortunately, neither of the studies indicated how many children with rhinoconjunctivitis showed allergy in an objective test. However, a very recent study in more than one thousand adults diagnosed of allergic (skin prick test positive) rhinoconjunctivitis showed that according to ARIA classification (mild intermittent, moderate–severe intermittent, mild persistent, and moderate–severe persistent), the corresponding asthma prevalence was only: 48%, 50%, 37%, and 47% (15), respectively.

If the PAT study (11, 12) is interpreted in a negative way, less than 50% of new asthma cases in children with rhinoconjunctivitis could be prevented by immunotherapy. Unfortunately, this study did not adjust for family history, so we cannot know if 'responders' tended to have a family history of rhinoconjunctivitis while 'non-responders' tended to have it of asthma. In summary, although the connection is very plausible, using terms such as 'united' or 'one' preceding 'airway' is probably not totally accurate.

To the best of our knowledge, only one previous study has addressed the issue of an independent inheritance of asthma and rhinitis. The study by Dold et al. (13) in a very numerous German population of 9- to 11-yr-old children showed that parental history (at least one parent) of asthma was a risk factor for this condition in the offspring, while a parental history of allergic rhinitis was not. Conversely, a parental history of allergic rhinitis was a risk factor for both asthma and rhinitis in the child. According to the authors, this one-sided direction (asthma in a parent is a risk factor for rhinitis) might support the hypothesis that rhinitis is a mild form of asthma. However, this study was performed in a general population of children and did not correct for the presence of atopy in children. Consequently, it is difficult to know if what is inherited is just atopy or the specific disease (asthma or rhinitis). In fact, the idea of rhinitis being a mild form of asthma could be explained by both diseases sharing the common risk factor of atopy. On the other hand, at the age of 9–11 yr, there is an important number of children with asthma symptoms who do show atopy (19), a fact that could further confound the findings of the German results.

The present results show that when there is a parental history of asthma, children are predisposed to suffer from this condition. Similarly, when there is a parental history of rhinoconjunctivitis, children are prone to suffer from rhinoconjunctivitis (and not from asthma, in contrast with the German study) (13). When parents show both diseases, children also tend to show the two diseases. It is important to bear in mind that all the children in the study showed sensitization to mites and consequently, all of them might eventually have their nose-bronchial system connection ongoing. The age range of the children in the study is narrow enough to think that the disease progression is not an important factor in this case. Furthermore, the age did not show a great influence in the multivariate analysis. Other known risk factors of asthma did not alter the associations of the type of parental history with the condition shown in the child.

The main limitation of this study comes from the fact that the duration and intensity of the contact with mites was not measured. It could be argued that higher the allergenic load in time and concentration, the more probable the two diseases appear due to a higher challenge to the immunological system and the subsequent greater inflammatory response. However, the skin reaction was comparable between the children

with different types of parental history and this could be an indirect marker that the challenge might have been similar.

The present study – which was controlled for atopy in the children, as all of them showed this condition – challenges the hypothesis that the relationship between the upper and the lower airway is only explained by their immunological or physical connection and supports the idea that on top of this, there are two different organs that may have genetic pre-disposition to exhibit a certain type of inflammation under specific circumstances and to respond to that inflammation in a different way.

Appendix: The ISAAC phase II group in Spain

Cartagena: L Garcia-Marcos, A Martinez-Torres, JJ Guillen-Perez, A Piñana Lopez, S Castejon Robles, C Gimenez Marzo, MJ Celdran Rosell. **Almería**: J Batlles-Garrido, T Rubi-Ruiz, A Bonillo Perales, MM Sanchez Gutierrez, B Chamizo Moreno, J Momblan de Cabo, R Jimenez Liria, J Aguirre Rodriguez, A Losilla Maldonado, M Torres Daza. **Valencia**: M Morales Suarez-Varela, A Llopis Gonzalez, A Escribano Montaner, MJ Vila Lopez, A Albero Cortes, P Olmo Saez, M Gracia Antequera, M Tallon Guerola, A Regueira Armero. **Madrid**: G Garcia-Hernandez, A Martinez Gimeno, C Luna Paredes, AL Moro Rodriguez, I Gonzalez Gil.

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