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ORIGINAL ARTICLE

Bronchial hyperresponsiveness and asthma in the paediatric population

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Abstract
Objective: To determine whether the intensity of bronchial hyperresponsiveness (BHR) is correlated to other clinical data such as patient age at the onset of asthma, the serum IgE levels and familial genetic susceptibility, with the purpose of establishing a prognosis or phenotype.
Material and methods: BHR was evaluated using the methacholine provocation test, with the patients divided into six groups according to the amount of methacholine needed to obtain PD20. A total of 138 children and adolescents up to age 18 years (94 males and 44 females) were included. Most had a clinical diagnosis of asthma, while tracheobronchitis or rhinitis was diagnosed among the least reactive subjects. The patients were divided into subjects with a family history of atopic disease (84 cases) and those without such a history (54 cases). In this latter case we discuss possible causes of BHR or dyspnoea triggering factors.
Results: There were no significant differences in patient age at onset or in serum IgE among the patients with different intensities of BHR, or between those with a family history of atopic disease and those without.
Conclusions: No differences were found among the groups. It is therefore concluded that the intensity of BHR is not a valid parameter for establishing a prognosis or phenotype, although it can be used to assess the severity of asthma.

Asthma is a heterogeneous disease with a variety of underlying causes in which bronchial hyperresponsiveness (BHR) is a constant and essential pathogenic element, although the mechanism triggering HBR can differ in each case, as in asthma induced by exercise or by aspirin.[1] However, allergy is the most frequent cause of asthma and initially manifesting in childhood, genetics is known to play a key role – particularly in relation to the existence of BHR and atopic predisposition or susceptibility.[2] Nevertheless, in early childhood, BHR may develop as a consequence of repeated viral infections. In other cases, including children and adolescents, BHR can appear later in life, as also occurs in professional asthma, as a consequence of exposure

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Table 1 Patient characteristics.

Methacholine PD20 (μg)	Patients with atopic relatives			Patients without atopic relatives		
	No. patients	Age at onset (yr) Mean (range)	Mean IgE (KU/l)	No. patients	Age at onset (yr) Mean (range)	Mean IgE (KU/l)
<500	12	4.7 (<1–13)	439	13	3.2 (<1–6)	512
501–1000	16	4.5 (<1–14)	512	14	4.9 (<1–12)	471
1001–1500	10	4.4 (<1–9)	373	7	5.4 (2–10)	559
1501–2000	10	7.7 (3–18)	299	1	3 (3–3)	512
>2000 Asthma	16	4.7 (<1–14)	745	14	4.9 (<1–14)	237
>2000 Tracheobronchitis/ rhinitis	20	5.4 (<1–10)	293	5	9(4–15)	280
Total	84	5.2	443	54	5.0	428

to certain environmental factors (tobacco smoke, different irritants, allergens) which initially produce bronchial inflammation and subsequently BHR secondary to vagal stimulation.

Based on the review of a group of patients with established BHR, most of whom were diagnosed with asthma, while others were diagnosed with tracheobronchitis or rhinitis, the present study was carried out with the main purpose of examining the different factors that participate in the onset of asthma in paediatric patients (including adolescents), taking into account both genetic susceptibility and possible exogenous elements, in an attempt to determine whether the intensity of BHR has prognostic or phenotyping applications.

Materials and methods

Patients

In a total of 138 patients (94 males and 44 females, aged between 8 and 18 years) visiting the clinic with respiratory symptoms, in most cases with suspected asthma (cough, acute dyspnoeic episodes, wheezing and/or frequent or sporadic mild dyspnoea, predominantly at night, and signs of rhinitis), methacholine provocation testing was performed to evaluate the presence of bronchial hyperresponsiveness (BHR). In addition, in all cases we demonstrated allergic sensitisation based on skin tests and total and specific serum IgE.

In order to determine whether the intensity of BHR may be of use in establishing a prognosis or phenotype, the patients were divided into six groups according to the amount of methacholine needed to obtain PD20. Those requiring over 2000 g, without reaching PD20 in most cases, were divided into two groups: one in which the clinical diagnosis was asthma, and another in which the dominant symptoms were cough and sometimes wheezing or noisy breathing, but without dyspnoeic episodes. These latter patients were finally generically classified as presenting tracheobronchitis, without discarding the possibility of eosinophilic bronchitis in some of them.[3,4] Symptoms of rhinitis were dominant in some of these patients. In turn, two groups (patients with and without a family history of atopy) were established in order to evaluate the influence of familial susceptibility to atopic disease. In those patients without familial susceptibility, we evaluated the possible existence of exogenous symptom-triggering factors. Likewise, in all groups we recorded patient age at the onset of the process and the total serum IgE values. Table 1 presents all these data.

Methacholine provocation test

Methacholine testing was carried out using an abbreviated method in which the aerosol is inhaled during inspiration, allowing quantification of the administered methacholine dose from a single concentration of the drug.[5,6] The patients were asymptomatic at the time of provocation with methacholine, without taking bronchodilator or anti-inflammatory medication for at least two days before the test, and with respiratory function in the normal range (with FEV1% >70). The 1/100 dilution of methacholine (Provocholine®, Roche) was prepared with physiological saline solution, yielding a concentration of 10 mg/ml. Spirometry was carried out with the Vicatest Spimco (Mijnhardt, The Netherlands) before testing and two minutes after each of the inhalations (Mediprom FDC 88 dosimeter, Paris, France). After fitting to the nebuliser (De Vilbiss 5610 D) by means of a mouthpiece, the patient was instructed to breathe normally, followed by maximum inspiration (1–2 s) after forced expiration. This was followed by three seconds of apnoea and then gentle expiration.[1,4] The decrease in FEV1 was estimated from the FEV1 value recorded after inhalation of the saline solution with which the test was started. In the first inhalation we administered 100 μg (0.5 μmol) of methacholine, followed by the repeated administration of 200 μg (cumulative dose: 300 μg, 500 μg, 700 μg, 900 μg, etc.). The test ended when FEV1 dropped approximately 20% (PD20) – the value being calculated posteriorly from the dose–response curve. Administration was suspended if the mentioned decrease was not reached with the maximum cumulative dose of 2100 μg.

Results

Methacholine test. BHR was corroborated in all patients (whether with or without a family history of atopic

Table 2 Family antecedents of atopic disease.

Methacholine PD20 (μg)	No. patients	Only father	Only mother	Both parents	Other relatives (uncles/aunts, grand parents)
<500	12	1	6	0	8
501–1000	16	5	2	3	12
1001–1500	10	3	4	1	5
1501–2000	10	0	5	1	8
>2000 Asthma	16	2	5	1	9
>2000 Tracheobronchitis/ rhinitis	20	4	6	0	14
Total	84	15	28	6	56

disease) in which PD20 was reached with methacholine doses of under 2000 μg. In those requiring larger doses, the diagnosis of asthma was confirmed in both groups (16 and 14 patients, respectively), while in those subjects where the dominant diagnosis was tracheobronchitis and/or rhinitis, a clear difference was observed between those with (20 cases: 23.8% of the 84 patients) and without family antecedents (five cases: 9.2% of the 54 patients) (Table 1).

Family history. Of the total 138 patients, 84 (60.86%) had relatives with allergic disease – mostly asthma and/or rhinitis, but also other processes such as eczema, or food or drug allergies. In the remaining 54 patients (39.13%), the relatives reported no allergic problems. The incidence of allergic disease in the parents was similar in the six groups, while allergy in other relatives (uncles/aunts, grandparents) was somewhat more prevalent in group 2 (12 atopic subjects) and in group 6 (14 atopic subjects) (Table 2).

Age at onset. In most of the patients the symptoms originally manifested in early childhood (up to six years of age). In 13 of the patients with a family history of atopic disease, symptoms onset was in the first year of life, while in 47 cases symptoms onset was between 2 and 6 years of age, and in 24 it was after this age. Among the patients without a family history of atopic disease, symptoms onset was in the first year of life in nine cases, between 1 and 6 years in 32 patients, and after this age in 13 cases (Table 3). On examining the mean age at symptoms onset in each group, from the first year of life to after the age of six years, no differences were found between the patients with (5.2 years) and without atopic relatives (5.0 years) (Table 1).

Total serum IgE: assessment of atopy. Globally, the serum IgE levels were elevated in all groups. Referring to the patients with or without atopic relatives, clear differences were observed in the mean values in groups 3 and 5. Group 4, involving a single patient without a family history of atopic disease, was not considered. Despite these differences, the mean values were globally similar in both groups: 443 KU/l in those with atopic relatives versus 428 KU/l in those without atopic relatives (Table 1).

Discussion

Bronchial hyperresponsiveness constitutes the pathogenic basis of dyspnoeic crises. Inflammation, as a consequence of such episodes, is responsible for the symptoms between crises, although inflammation may also induce hyperresponsiveness. Undoubtedly, genetic susceptibility is fundamental in most patients in which asthma develops at an early age.[7] Several mutations in chromosome 5q31-q33 give rise to blocking of the bronchial smooth muscle β2-adrenergic receptors, which receive adrenergic stimuli.[8] More recently, protocadherin-1 (PCDH1) has been identified in this same gene. This molecule could alter the integrity of the bronchial epithelium, which acts as the first line of defence against inhaled substances, thereby contributing to the development of BHR.[9,10] A different mechanism of action applies to the mast cells found in the bronchial smooth muscle of asthmatic patients, in contrast to patients with eosinophilic bronchitis. The mediators released by these cells as a result of the allergic reaction (histamine, prostaglandin D, cysteinyl–leukotrienes)

Table 3 Age at symptoms onset.

Methacholine PD20 (μg)	Patients with atopic relatives				Patients without atopic relatives			
	No. patients	Age at onset			No. patients	Age at onset		
		1st yr	2–6 yrs	>6 yrs		1st yr	2–6 yrs	>6 yrs
<500	12	3	5	4	13	4	9	0
501–1000	16	4	9	3	14	2	9	3
1001–1500	10	1	7	2	7	0	4	3
1501–2000	10	0	5	5	1		1	
>2000 Asthma	16	2	10	4	14	3	7	4
>2000 Tracheobronchitis/ rhinitis	20	3	11	6	5	0	2	3
Total	84	13	47	24	54	9	32	13

Table 4 Triggering factors in patients without atopic relatives.

Methacholine PD20 (μg)	No. patients	Smoke	Exercise	Fungi	Polysensitisation	Not known
<500	13	3	7	1	2	3
501–1000	14	1	4	1	0	10
1001–1500	7	0	1	1	1	4
1501–2000	1	0	0	0	0	1
>2000 Asthma	14	0	0	1	3	10
>2000 Tracheobronchitis/ rhinitis	5	0	0	0	1	4
Total	54	4	12	4	7	32

directly induce contraction of the muscle, and thereby contribute to bronchial hyperresponsiveness.[11–13] The reason for dividing the patients into six groups was to determine whether the intensity of BHR is correlated to other parameters such as patient age at onset of the symptoms, the presence or absence of a family history of atopic disease, or the serum IgE levels, with a view to establishing whether BHR could serve as the basis for defining a prognosis or phenotype. As can be seen in Table 1, only group 6 showed a difference in patient age at onset (means of 5.4 and 9.0 years). This finding could be related to the final diagnosis, although assessment is restricted by the small number of patients without atopic antecedents. No significant differences were recorded in the other five groups; as a result, potential usefulness in establishing a prognosis is discarded.

In a previous study we examined the long-term conditions of asthmatic patients with different degrees of BHR. We interviewed 78 patients approximately 10 years after having been judged to have healed as a result of aetiopathogenic treatment (mean age 30 years). All claimed to be in good condition, despite differences in response to methacholine this showing that the intensity of BHR, even when persisting after disappearance of the symptoms, lacks prognostic value.[14]

In allergic asthma, a familial predisposition to atopic disease is a determinant factor in most cases. However, this antecedent was not demonstrated in 39.13% of our series of patients, and other inducers could intervene, such as environmental contaminants or irritants such as smoke (tobacco and others), industrial pollution (more common in occupational asthma), and an abundance of environmental allergens (pollen, fungi). However, in 32 of our 54 patients without a family history of atopy there were no known triggering factors; only in some cases were there references to smoke, fungi (Aspergillus) and polysensitisation – elements which were seen to be summed in some children. The physical exercise mentioned by some subjects can be regarded as common in many asthmatics, as a result of the diminished airflow caused by the inflammation (Table 4).

In those children who develop asthma in early childhood, BHR is very likely a consequence of viral infections, which are frequent especially in the first three years of life, favoured by the immature immune system of these patients. The repetition of viral infections, particularly when the intervals between episodes are brief, gives rise to bronchial epithelial damage, which in turn favours constrictive vagal stimulation as well as direct exposure to allergens.[15,16] Rhinovirus and respiratory syncytial virus (RSV) are more aggressive and are often responsible, but mention must also be made of other agents such as pneumovirus, influenza A and B, parainfluenza 1, 2 and 3, among others.[17] In our series, 22 of the children in the six groups developed asthma in the first three years of life (data not shown in the tables) – this suggests that repeated viral infections may have played an important role in the development of BHR.

The onset of asthma before five years of age could be influenced by another chromosomal variant, namely the ORMDL3 gene of chromosome 17q21. Different studies have related it to viral infections in this early stage of life, but possibly also due to tobacco smoke and domestic pets – with an apparent relation to BHR but not to atopy. The underlying mechanism of action has not been established, although a possible molecular mechanism has been suggested.[18–21] It is not possible to rule out the participation of this chromosome in asthma onset in our youngest patients, without a familial predisposition to atopic disease.

There is no doubt about allergen sensitisation in all of our patients, as evidenced by the prick test and specific IgE results in all cases. As can be seen in Table 1, there were no significant differences in the mean total serum IgE values in the six groups, and no differences between those with and without a family history of atopy. In accounting for sensitisation in the absence of such familial antecedents, mention must be made of the already commented exogenous factors, environmental pollutants, and allergen abundance in the environment of the patient.

In sum, genetic transmission is a key factor in most asthmatic patients in which the disease develops in infancy or adolescence, in the same way as in other atopic disorders. However, in a non-negligible percentage of cases neither the parents nor other close relatives (uncles/aunts, grandparents) reported having asthma or any other allergic disorder. As a result, initiation of the process must be attributed to other factors. There may have first been genetic mutations, but it is more likely that exogenous agents were responsible for symptoms onset. Repeated viral infections in very young children, and the pollutants commonly found in certain environments, can give rise to bronchial hyperresponsiveness secondary to epithelial damage, which facilitates allergen exposure – particularly when allergens are abundant in the environment or are particularly aggressive.

Ethical disclosures

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research

Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors have no conflict of interest to declare.

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