INVESTIGATION OF BRONCHIAL HYPER-REACTIVITY. ECRHS II TEST QUESTIONNAIRE VERSUS HISTAMINE PD20 FEV1

ANDREEA-IULIA SOCACIU[1], ARMAND GABRIEL RÂJNOVEANU[2], ARISTOTEL COCÂRLĂ[3], SORANA DANIELA BOLBOACĂ[4]

[1,2,3,4]*"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca*

Keywords: *Bronchial hyperreactivity (BHR), FEVI test, ECRHS II questionnaire*

Abstract: *Bronchial hyperreactivity (BHR), common in asthma occurs in other diseases such as chronic airway obstruction. Our aim is the validation of the ECRHS II questionnaire (The European Community Respiratory Survey II) in detecting BHR. Methodology: ECRHS II questionnaire was applied on a group of 278 patients with respiratory symptoms, without asthma and was correlated with: smoking index, allergy tests and nonspecific bronchial challenge test with histamine (PD20 FEV1). Results: The PD20 FEV1 test was positive in 85.2% of subjects, the most common symptoms were: wheezing (48% in positive and 15% in negative subjects, with a statistically significant difference), morning chest tightness and sudden shortness of breath. There was no relation between PD20 FEV1 test and atopic status or smoking index. Conclusions: Subjects with wheezing, chest tightness or attacks of shortness of breath after a strenuous effort have BHR with high probability. The combination of the three symptoms certifies BHR's presence.*

Cuvinte cheie: *hiperreactivitate bronşică, test PD20 VEMS, chestionar ECRHS II*

Rezumat: *Hiperreactivitatea bronşică (HRB), comună astmului bronşic, apare şi în alte patologii precum obstrucţia cronică a căilor aeriene. Scopul studiului este validarea chestionarului ECRHS II (The European Community Respiratory Survey II) în depistarea HRB. Metodologie: Pe un lot de 278 pacienţi cu simptome respiratorii, fără astm bronşic, s-a aplicat chestionarul ECRHS II corelându-se cu: indicele de fumat, teste alergologice şi testul de provocare bronşică nespecifică cu histamină (PD20 VEMS). Rezultate: Testul PD20 VEMS a fost pozitiv la 85,2% dintre subiecţi, cele mai frecvente simptome fiind: wheezing (48% între subiecţii pozitivi şi 15% între cei negativi, diferenţă statistic semnificativă), senzaţia de constricţie toracică matinală şi dispneea instalată brusc. Nu s-a constatat o relaţie între testul PD20 VEMS şi starea atopică sau indicele de fumat. Concluzii: Subiecţii cu wheezing, senzaţie de constricţie toracică sau atac de dispnee după un efort epuizant prezintă cu probabilitate crescută HRB. Asocierea celor trei simptome certifică prezenţa HRB.*

INTRODUCTION

Bronchial hyperreactivity (BHR) is a pathological condition defined as an abnormality of the airways that leads to a rapid and excessive narrowing consecutive to the action of nonspecific stimuli.(1) The pathophysiological alterations are the expression of airway inflammation and imply, at the same time, a bronchial remodelling process.(2)

BHR is a key phenomenon of asthma but it is not specific: it can be present in chronic rhinitis (3), upper respiratory tract infections (4) and even in asymptomatic subjects with normal respiratory function.(5)

Of particular significance is the presence of BHR in chronic airway obstruction. In communities exposed to occupational risk factors for lung disease, potentially causing BHR, knowing this anomaly is of particular importance for developing and implementing preventive conservation programmes for the ventilatory function. Because many of the employees working in these conditions accept with difficulty or do not accept at all a bronchial challenge test using pharmacological agents representing the "gold standard" of the confirmation of BHR, applying symptoms questionnaires would be an acceptable alternative.

PURPOSE

The purpose of this study is the validation of the ECRHS II questionnaire (The European Community Respiratory Health Survey II) (6) for the BHR, regarding the relation between symptoms collected by this method and the histamine challenge testing.

METHODS

The study group includes 278 subjects, of which 194 women and 83 men, who were admitted at the Occupational Health Clinic in Cluj Napoca for the evaluation of respiratory symptoms. This batch is selected, meaning that we included only subjects who were not diagnosed with asthma until admission to the clinic, the main exclusion criterion being item Q14 of the ECRHS II questionnaire.

Also, we excluded from the study batch subjects with arterial hypertension, ischemic heart disease, those who had a FEV1 value for basal ventilatory functional exploration less than 70% of the prediction value and those who presented upper respiratory tract infections in the last 4 weeks.

The questionnaire was applied partially by resident physicians in occupational medicine going through the items

[1]Corresponding author: Andreea-Iulia Socaciu, Str. Ioan Budai Deleanu, Nr. 28, Cluj Napoca, România, E-mail: medisyn@yahoo.com, Tel: +40752 55576,
Article received on 07.11.2012 and accepted for publication on 07.01.2013
ACTA MEDICA TRANSILVANICA March 2013;2(1):234-237

Q1-14 for the recording of symptoms and Q74-75 to assess smoking.

After the questionnaire was conducted, an inhaled histamine test was performed, observing the cumulative dose that causes a 20% fall in FEV1 (PD20 FEV1). The histamine administration was performed with an APS Jaeger (Germany) equipped with an electric valve system that allows the aerosol administration only in the inhalation phase. We made sure that in the last 3 days preceding the test, the subjects did not use medication such as: bronchodilators, anticholinergics, antihistamines or corticosteroids.

At first, we measured the basal ventilatory parameters, and then, using dosimeters, the subjects received a phosphate buffer solution, followed by the reassessment of ventilatory parameters. If the buffer solution administration produced no more than a 8-10% decrease in FEV1, we switched to histamine aerosol administration by a dosimetric method recommended by Yan, Salome and Woolcock (7) considering the probative PD20 FEV1 value for the BHR smaller than 7.8 µmol.

The identification of atopic subjects was performed by using skin prick tests to habitual pneumoalergens, provided by the Stallergenes SA (Anthony, France) company: artemisia vulgaris, betulacee, mixture of 5 grasses, Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria and Aspergillus mix. Two control witnesses were used: the positive - histamine and the negative - serum phenol 1%. The test was considered positive if 15 minutes after the application there was a papula at least 3 mm in diameter with erythema and pruritus for one or more allergens.

Smoking index was calculated as: (*number of cigarettes per day)* x (*number of years the subject smoked)* / 20.

Statistical analysis: qualitative variables were summarized as percentages, with 95% confidence interval. Confidence intervals were determined by an exact method of calculation.(8) The confidence intervals calculated by the 2 × 2 contingency table for the diagnostic test parameters (sensitivity, specificity) were determined with the Wilson method without continuity correction.(9) Chi-square test was applied to identify independence in 2 × 2 contingency table. The comparison of two proportions was performed by applying the proportions Z test.

The quantitative variables were summarized as means and standard deviations for normally distributed variables, respectively median, 25% and 75% percentiles for variables that did not follow a normal distribution. The comparison of independent samples was done by applying the Student-t Test when variables followed a normal distribution, respectively, Mann-Whitney test for variables that did not follow a normal distribution.

Statistical tests were applied to a significance level of 5%, p-value <0.05 was considered statistically significant. Data processing was performed with SPSS v16. Graphic representations were made with Microsoft Excel.

RESULTS

The mean age of the entire study batch of 278 subjects at 42 years old was not statistically significant between groups PD20 FEV1(+) and PD20 FEV1 (-) (p=0,08).

PD20 FEV1 test was positive in 85.2% of subjects, of which 70.1% women and 29.9% men. There were no statistically significant frequency differences found by gender (p = 0.79).

The most common symptom was wheezing (item Q1) with a prevalence of 48% in the PD20 FEV1(+) group and 15% in the PD20 FEV1(-) group. The absence of wheezing occurred in about half of the subjects with BHR and in a large proportion (85%) of those without BHR. The difference of frequency for wheezing, between the two groups, was statistically significant (p<0,01). Sensation of shortness of breath associated with wheezing (item Q1.1) was recorded in 16 subjects, belonging exclusively to the PD20 FEV1(+) lot. Outside “colds”, most subjects described the presence of wheezing episodically (item Q1.2).

Another symptom with a different and statistically significant prevalence was the morning chest tightness, present in 65 subjects from the PD20 FEV1(+) group and only in 3 subjects for the negative group (item Q2). Proportionally and statistically significant, dyspnea at rest was encountered more frequently in the PD20 FEV1(-) group (item Q3). In contrast, sudden dyspnea with short and rapid ventilatory incursions after an exhausting effort has occurred mostly in the PD20 FEV1(+) group (41% and 29%, respectively) but the difference in prevalence did not reach a threshold of statistical significance (item Q4). In the last 12 months, no subject was woken up by an attack of dyspnea (item Q5) and very few were woken up because of coughing (item Q6).

The presence of cough in winter on mornings (item Q7), or during the day or night (item Q8) was virtually identical in the two groups with and without a demonstrated BHR.

The presence of cough in most days during three successive months each year (Q8.1) was present in 22% of the whole batch in the last 12 months, without statistically significant difference between PD20 FEV1(+) and (-) groups.

The presence of morning sputum during winter (item Q9) day or night (item Q10) was declared by a relatively large number of respondents with significant difference between the two histamine challenge groups. Even fewer (15%) recognized these symptoms as lasting at least 3 successive months each year (item Q10.1). They met the diagnostic criteria of chronic bronchitis that occurs with similar frequency in both PD20 FEV1(+) and PD20 FEV1(-) groups. The question regarding the presence of respiratory disorders (item Q11) was not clear enough for many respondents, the answer being cleared after consulting the doctor, and those who gave a positive answer were a small number of subjects.

None of the subjects showed any walking disabilities: locomotor, heart or lung related (item Q12). A frequency of about 10% was observed for mild dyspnea (item Q12.1). There was not any positive response regarding a possible relation of respiratory symptoms and menstrual cycle (item Q13). For the item Q14 all the responses were negative, meaning that the subjects were never diagnosed or treated for asthma. In fact, the Q14 was one of the exclusion criteria for the establishment of the study batch.

According to the responses for the ECRHS II questionnaire, the most common symptoms associated with BHR were, in order, wheezing, dyspnea attack installed after an exhausting effort and morning chest tightness.

The statistical calculation revealed that these symptoms are specific for the BHR, while their sensitivity is low (tables no. 1,2,3).

Table no. 1. The statistical analysis and performance for the item Q1

Q1	PD_{20}+	PD_{20}-	Total
yes	114	6	120
no	123	35	158
Total	**237**	**41**	**278**

Sensitivity:	0.4810	CI: 0.4182 to 0.5444
Specificity:	0.8537	CI: 0.7156 to 0.9312
Positive likelihood ratio:	3.287	CI: 1.551 to 6.966
Negative likelihood ratio:	0.608	CI: 0.51 to 0.725
Diagnostic odds ratio:	5.407	CI: 2.192 to 13.334

Table no. 2. The statistical analysis and performance for the item Q2

Q2	PD_{20}+	PD_{20}-	Total
yes	62	3	65
no	175	38	213
Total	**237**	**41**	**278**

Sensitivity:	0.2616	CI: 0.2098 to 0.321
Specificity:	0.9268	CI: 0.8057 to 0.9748
Positive likelihood ratio:	3.575	CI: 1.178 to 10.851
Negative likelihood ratio:	0.797	CI: 0.71 to 0.893
Diagnostic odds ratio:	0.223	CI: 0.066 to 0.748

Table no. 3. The statistical analysis and the test performance for the item Q4

Q4	PD_{20}+	PD_{20}-	Total
yes	98	12	110
no	139	29	168
Total	**237**	**41**	**278**

Sensitivity:	0.4135	CI: 0.3527 to 0.4771
Specificity:	0.7073	CI: 0.5552 to 0.8239
Positive likelihood ratio:	1.413	CI: 0.857 to 2.328
Negative likelihood ratio:	0.829	CI: 0.663 to 1.037
Diagnostic odds ratio:	1.704	CI: 0.829 to 3.503

The frequency analysis of PD20 FEV1(+) for the most common symptoms (Q1, Q2, Q4) showed a prevalence of BHR of 89% in those who experienced sudden dyspnea after an exhausting effort, of 95.3% in those with a sense of chest pressure and of 95% in those with wheezing. The association between items Q1 and Q2 involved positive responses in 97%, between Q1 and Q4 in 98.5% and between Q2 and Q4 in 100%.

We have studied the relation between symptom scores and PD20 FEV1 value as a quantitative relationship, by applying the Kolmogorov-Smirnov test and the Anderson-Darling test, for a significance level of 5%. This did not confirm a linearity relation between the two variables. No significant differences were found between the intensity of the response to histamine and the practice of smoking.

Regarding the relationship between atopic status and PD20 FEV1 test results, there was no statistically significant relationship.

DISCUSSIONS

Various randomized population studies evaluated the BHR frequency between 10.3% and 24.5%.(10) Our observed frequency was very large (86%). This can be explained by the fact that the group was selected based on the presence of respiratory symptoms. These turned out to be wheezing, shortness of breath characterized by short and rapid ventilatory incursions occurring after a strenuous physical exertion and morning chest tightness. Their association increases the chance for the presence of BHR, the probability being close to certainty. The essential symptom proved to be wheezing, observed also in other studies that confirmed a clear relation between BHR and wheezing.(11) If this symptom was associated with difficulty in breathing, the PD20 FEV1 test was constantly positive.

The ECRHS II questionnaire is a good tool with which you can select the BHR suggestive symptoms before the onset of a functional ventilatory decline. Its application is easy, all the subjects were cooperating although some of them deemed extra explanations. The ECRHS II questionnaire is very complex, but for our goal it was enough covering the items 1-14 and 74-75.

Although the involvement of smoking in the installation and worsening of BHR is known (12.13), we have found no significant differences in the prevalence of symptoms

depending on smoking status and no relation between the intensity of the response to histamine and the smoking index.

According to literature data, atopy implies a higher frequency of BHR (14), something that our study did not confirm. The frequency of our positive PD20 histamine cases is approximately equal in atopic and nonatopic subjects. At least in part, this discrepancy is explained by the fact that much of the intended subjects of this study were occupationally exposed to respiratory irritants, causing chronic neurogenic inflammation leading to disturbances in the balance between inhibitory nonadrenergic and excitatory noncolinergic system.(15)

CONCLUSIONS

The patients who presented themselves for admission for one of these symptoms: wheezing, chest tightness or attacks of shortness of breath after a strenuous effort have bronchial hyperreactivity syndrome with high probability, but the association of the three confirms with certainty the presence of BHR.

REFERENCES

1. Woolcock AJ. Asthma. In: Murray JF, Nadel JA, Eds. Textbook of Respiratory Medicine, 2nd. Edn. Philadelphia: WB Saunders Company; 1994. p. 1283.
2. Riemersmaa R, Dirkje P, Kerstjensb H, et al. Development of a questionnaire for the assessment of bronchial hyperresponsiveness. Primare Care Resp J. 2009;18(4);287-293.
3. Cockroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy. 1977;7:235-243.
4. Empey DW, Laitinen LA, Jacobs L, et al. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Am Rev Respir Dis. 1976;113:131-139.
5. Rhodes BJ, Weiller JM, Donelly AL, et al. Young asymptomatic nonatopic adults have a high prevalence of methacholine airway responsiveness regardless of smoking history. Am Rev Respir Dis. 1986;133(part 2):A176.
6. Burney PGJ, C. Luczynska, S. Chinn, D. Jarvis. The European Community Respiratory Health Survey. Eur Respir J; 1997. p. 954-960.
7. Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. Thorax. 1983;38:760-765.
8. Jäntschi L, Bolboacă SD. Exact probabilities and confidence limits for binomial samples: Applied to the difference between two proportions. 2010;10:865-878.
9. Newcombe RG. Two-sided confidence intervals for the single proportion: Comparison of seven methods. Statistics in Medicine. 1998;17:857-872.
10. Trigg CJ, Bennet JB, Tooley M, et al. A general practice based survey of bronchial hyperresponsiveness and its relation to symptoms, sex, age, atopy and smoking. Thorax. 1990;45:866-872.
11. Woolcock AJ, Peat JK, Salome CM, et al. Prevalence of bronchial hyperresponsiveness and asthma in a rural adult population. Thorax. 1987;42:361-368.
12. Gerbase MW, Schindler C, Zellweger JP, et al. Respiratory effects of environmental tobacco exposure are enhanced by bronchial hyperreactivity. Am J Respir Crit Care Med. 2006;174(10):1125-1131.
13. Chinn S, Jarvis DR, Luczynska CM, Ackermann-Liebrich U, et al. An increase in bronchial responsiveness is associated with continuing or restarting smoking. Am J Respir Crit Care Med. 2005;172(8):956-961.
14. Cockroft D, Murdock K, Berscheid B. Relationship between atopy and bronchial responsiveness to histamine in a random population. Ann. Allergy. 1984;53:26-29.
15. Vogelzang PF, van der Gulden JW, Folgering H, Heederik D, et al. Longitudinal changes in bronchial responsiveness associated with swine confinement dust exposure. Chest. 2000;117(5):1488-1495.