

Prevalence of Hyperventilation Syndrome in Patients Treated for Asthma in a Pulmonology Clinic

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OBJECTIVE: Although the presence of hyperventilation syndrome can affect the symptoms of patients with asthma, there is very little information available regarding its frequency in Spain. The aim of this study was to investigate the prevalence of hyperventilation syndrome in the asthmatic population treated as outpatients and establish its relationship with anxiety disorders.

PATIENTS AND METHOD: We studied 157 consecutive asthmatic patients (61 men and 96 women; mean [SD] age, 45 [17] years; forced expiratory volume in the first second, 84% [21%] of the predicted value) treated in our outpatients clinic. The patients had stable disease with varying degrees of severity. After collecting demographic data and medical histories, we asked the patients to complete the Spanish versions of the Anxiety Sensitivity Index, the Asthma Symptom Checklist, and the Nijmegen questionnaire; in the latter test, a score of 23 or over was considered diagnostic for hyperventilation syndrome. Finally, patients were evaluated to determine whether they had suffered from panic disorder in the last 6 months (according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders).

RESULTS: Hyperventilation syndrome was present in 57 asthmatic patients (36%) and panic disorder in 4 patients (2%). The majority of patients with hyperventilation syndrome were women (78% vs 51%; $P=.001$) and were older (49 vs 42; $P=.01$); they displayed more basal dyspnea (1.26 vs 0.89 on the Medical Research Council scale; $P=.01$), greater sensitivity to anxiety ($P=.001$), and went to the emergency room more often for exacerbations ($P=.002$). Patients with hyperventilation syndrome scored significantly higher on all subscales of the Asthma Symptoms Checklist. Finally, the variables introduced in the regression analysis (stepwise) to explain the score on the Nijmegen questionnaire ($r^2=0.57$) were basal dyspnea and sensitivity to anxiety.

CONCLUSIONS: Approximately one third of the asthmatic patients treated in a pulmonology clinic also present hyperventilation syndrome. This cannot be explained by comorbidity of asthma with panic disorder, and is only partly linked to the symptoms associated with hyperventilation that appear during an asthma attack.

Key words: Asthma. Hyperventilation syndrome. Prevalence. Anxiety.

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Prevalencia del síndrome de hiperventilación en pacientes tratados por asma en una consulta de neumología

OBJETIVO: Aunque la presencia del síndrome de hiperventilación (SH) puede influir en los síntomas de los pacientes con asma, existe escasa información acerca de su frecuencia en nuestro medio. Nuestro objetivo ha sido investigar la prevalencia de SH entre la población asmática controlada ambulatoriamente y establecer su relación con los trastornos de ansiedad.

PACIENTES Y MÉTODO: Con este propósito hemos estudiado a 157 asmáticos consecutivos (61 varones, 96 mujeres; edad media \pm desviación estándar de 45 ± 17 años; volumen espiratorio forzado en el primer segundo: $84 \pm 21\%$), controlados en nuestras consultas externas, en situación estable y con diferentes grados de gravedad. Tras recoger los datos demográficos y los relativos a su enfermedad, cumplimentaron las versiones españolas del Índice de Sensibilidad a la Ansiedad, el Listado de Síntomas durante un Ataque de Asma y el cuestionario Nijmegen; en este último, una puntuación de 23 o superior se consideró diagnóstica del SH. Finalmente, se valoró si habían presentado un trastorno de pánico en los 6 últimos meses (criterios de la cuarta edición del *Manual diagnóstico y estadístico de los trastornos mentales*).

RESULTADOS: Presentaron SH 57 asmáticos (36%) y trastorno de pánico, 4 (2%). Los pacientes con SH eran mayoritariamente mujeres (un 78 frente a un 51%; $p = 0,001$) y tenían más edad (49 frente a 42; $p = 0,01$), más disnea basal (1,26 en la escala del Medical Research Council frente a 0,89; $p = 0,01$), más sensibilidad a la ansiedad ($p = 0,001$) y acudían más veces a urgencias por agudizaciones ($p = 0,002$). Los pacientes con SH puntuaron significativamente más alto en todas las subescalas del Listado de Síntomas durante un Ataque de Asma. Por último, las variables introducidas en el análisis de regresión (pasos sucesivos) para explicar la puntuación en el cuestionario Nijmegen ($r^2 = 0,57$) fueron: disnea basal y sensibilidad a la ansiedad.

CONCLUSIONES: Aproximadamente un tercio de los asmáticos controlados en una consulta de neumología presentan además SH. Esto no puede explicarse por la comorbilidad asma-trastorno de pánico y tiene que ver sólo en parte con los síntomas relacionados con la hiperventilación que aparece durante un ataque de asma.

Palabras clave: Asma. Síndrome de hiperventilación. Prevalencia. Ansiedad.

Introduction

Hyperventilation syndrome is a poorly defined entity that is associated, at least in part, with anxiety disorders.¹ Symptoms of acute alveolar hyperventilation occur in association with respiratory alkalosis and a group of somatic manifestations that usually result in the patient presenting in an emergency department: dyspnea, palpitations, vertigo, tremor, paresthesia, precordial pain, restlessness, and syncope. However, patients sometimes present symptoms that are more subtle and difficult to identify; this group of symptoms is normally referred to as chronic alveolar hyperventilation (other authors prefer the terms dysfunctional breathing² or behavioral breathlessness³). The pathogenesis of this ventilatory disorder, which has a prevalence in the general population of 5% to 10%, is not fully understood. In contrast, the effects of hyperventilation/hypocapnia on the airways are known⁴; data from laboratory animals indicate that hyperventilation is independently able to generate inflammation of the airways and impair β_2 -adrenergic agonist-induced relaxation.⁵ What remains to be defined is the extent of comorbidity of hyperventilation syndrome with asthma and the resulting diagnostic and therapeutic implications.

Given that patients with asthma display higher levels of psychiatric morbidity than the general population,^{6,7} it is likely that the prevalence of hyperventilation syndrome will also be increased in this group. In a recently published study in which a postal survey was undertaken in a group of asthmatic patients treated in a primary care setting, 28% of patients who responded to the questionnaire were found to present hyperventilation syndrome.⁸ No data exists on the prevalence of the syndrome in Spain, and furthermore, there is very little information available regarding its influence on the progression of asthma. Consequently, we have undertaken a study to assess the prevalence of hyperventilation syndrome in an asthmatic population treated as outpatients in a pulmonology clinic in our setting. In addition, we have attempted to establish the relationship between this syndrome, anxiety disorders (specifically, panic attacks), and the symptoms reported by patients.

Patients and Methods

The study included 157 consecutive asthmatic patients attending the outpatient pulmonology clinic of Sagunto hospital. The inclusion criteria were as follows: *a*) diagnosis of asthma according to American Thoracic Society guidelines⁹; *b*) clinically stable, defined as the absence of clinical change or treatment alteration for a minimum of 4 weeks; *c*) presence of asthma for a minimum of 1 year; and *d*) age between 15 and 70 years. Exclusion criteria were lack of patient cooperation and impossibility of performing tests.

Patients were evaluated in a single visit. During this visit, an interview was undertaken in which demographic data were obtained (age, sex, tobacco consumption, and educational and socioeconomic level) along with information on asthma history: age of onset of the disease, use of medical services in the last year (visits to the emergency department and periods

spent in hospital), and maintenance treatment prescribed for asthma. Basal dyspnea was evaluated according to the modified Medical Research Council scale¹⁰ and forced expiratory volume in the first second (percentage of theoretical value) was determined by forced spirometry. Based on the information obtained, the severity of the disease was then categorized according to the criteria of the Spanish Guidelines for Asthma Management (GEMA,¹¹ the Spanish adaptation of the GINA—Global Initiative for Asthma—guidelines¹²): intermittent asthma and mild, moderate, or severe persistent asthma. Finally, patients were evaluated to determine whether they had suffered from panic disorder in the last 6 months (according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders¹³) and were asked to complete the Spanish versions of 3 self-completed questionnaires: the Nijmegen questionnaire,¹⁴ the Anxiety Sensitivity Index,¹⁵ and the Asthma Symptom Checklist.¹⁶

The Nijmegen questionnaire (translated and validated in a Spanish population by our research group; see Appendix) was used as part of the diagnosis of hyperventilation syndrome. The questionnaire contains 16 items rated on a scale of 0 to 4. A total score of 23 or more is considered diagnostic of chronic hyperventilation syndrome^{17,18} (sensitivity of 91% and specificity of 95%¹⁴).

The Asthma Symptom Checklist assesses the subjective experience of the patient during an asthma attack.¹⁹ It contains 36 items rated on a 5-step Likert scale (from never to always) and the items can be grouped into 5 subscales¹⁶: panic-fear, obstruction, irritability, fatigue, and hyperventilation.

Statistical Analysis

All variables were compared using analysis of variance in patients classified as presenting or not presenting hyperventilation syndrome. In addition, the Spearman's correlation coefficient was established between the study variables and the score on the Nijmegen questionnaire. Finally, variables showing a significant correlation were introduced into a stepwise multiple regression analysis.

Results

The 157 asthmatic patients that participated in the study (96 women and 61 men) had a mean (SD) age of 45 (17) years (range, 15 to 69 years). The mean number of years for which the disease had been diagnosed was 16 (13), with a range of 2 to 54 years, and the forced expiratory volume in the first second as a percentage of the predicted value showed a mean value of 84% (21%) with a range of 43% to 120%. The distribution of the patients according to asthma severity was as follows: 33 suffered from intermittent asthma (21%), 45 from mild persistent asthma (29%), 44 from moderate persistent asthma (28%), and 35 from severe persistent asthma (22%). The majority had never smoked (58%), but 23% were active smokers. Forty-eight percent of patients had received primary level education and 41% had received secondary level education (occupational training, high school diploma, or similar), while patients who had received university education or no schooling at all were in the minority. Socioeconomic level was self-assessed as average by 75% of the patients interviewed.

TABLE 1
Characteristics of Patients With and Without Hyperventilation Syndrome*

	With HS (n=57)	Without HS (n=100)	P
Age, years	49 (16)	42 (18)	.014
Sex			.001
Women	45	51	
Men	12	49	
Education			NS
No schooling	5	1	
Primary level education	28	48	
Secondary level education	20	44	
Higher level education	4	7	
Socioeconomic level			NS
Low	1	0	
Low average	10	7	
Average	39	79	
High average	7	14	
Maintenance treatment for asthma			NS
IC	8	13	
IC+β ₂	26	43	
IC+β ₂ +AL	13	17	
OC	1	0	
Age at onset of asthma, years	32.7 (16)	26 (16)	.025
Active smoking	9	27	NS
Attendance in emergency department in the last year	0.8 (1)	0.3 (0.7)	.002
Hospitalizations	0.23 (0.6)	0.06 (0.2)	.018
Basal dyspnea, MRC	1.3 (0.3)	0.9 (0.3)	.036
FEV ₁ basal, % of predicted value	83 (20)	84 (21)	NS
Asthma severity, GEMA criteria			NS
Intermittent	7	26	
Mild persistent	20	25	
Moderate persistent	18	26	
Severe persistent	12	23	
Anxiety Sensitivity Index	21.8 (10)	13.1 (7.7)	.0001
Panic attacks	3	1	NS

*Data are shown as the mean (SD) or number of cases. HS indicates hyperventilation syndrome; MRC, Medical Research Council; FEV₁, forced expiratory volume in the first second; GEMA, Spanish guidelines for asthma management; IC, inhaled corticosteroids; β₂, long-acting β₂ agonists; AL, antileukotrienes; OC, oral corticosteroids; NS, not significant.

Sixty-eight percent of the patients had not attended an emergency department for asthma in the preceding year and 91% had not been hospitalized during the same period. Only 4 patients (2.5%) had been treated in intensive care as a result of asthma. In terms of maintenance treatment for asthma, 44% were treated with a combination of inhaled steroids and long-acting β-agonists, and 19% with additional antileukotrienes, while 13% received only

TABLE 2
Patient Scores on the Subscales of the Asthma Symptom Checklist*

	With HS (n=57)	Without HS (n=100)	P
Panic-fear	27.38 (9.58)	20.2 (7.8)	.0001
Obstruction	47.7 (9)	39.9 (10)	.0001
Hyperventilation	18.5 (3.9)	11.8 (3.4)	.0001
Fatigue	28.4 (6.5)	21.1 (6.6)	.0001
Irritability	21.6 (6)	17.6 (5.4)	.0001

*Data are expressed as means (SD). HS indicates hyperventilation syndrome.

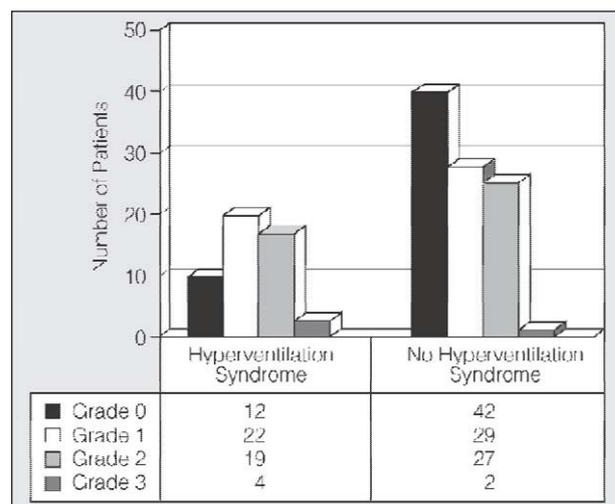


Figure. Basal dyspnea (Medical Research Council scale) in asthmatic patients with or without hyperventilation syndrome.

inhaled steroids, 2% only antileukotrienes, and 0.6% needed additional systemic corticosteroids.

The mean score on the Anxiety Sensitivity Index was 16 (9), with a range of 1 to 47, and 18 (8) on the Nijmegen questionnaire (range, 0-44). The scores on each of the subscales of the Asthma Symptom Checklist were as follows: a) panic-fear, 22 (9) with a range of 10 to 49; b) obstruction, 42 (10), with a range of 18 to 73; c) irritability, 19 (6), with a range of 7 to 33; d) fatigue, 23 (7), with a range of 9 to 45; and e) hyperventilation, 14 (4), with a range of 6 to 26.

Hyperventilation syndrome was presented by 57 asthmatic patients (36%) and panic disorder by 4 patients (2%). The characteristics of patients with or without hyperventilation syndrome are shown in Table 1. Basal dyspnea is shown graphically in both groups according to the Medical Research Council scale (Figure). The presentation of hyperventilation syndrome in asthmatic patients was more common in women, older patients, and patients who displayed greater anxiety, more basal dyspnea, and more frequent attendance at an emergency department and hospitalization due to asthma. Notably, there was no variation in the presence of hyperventilation syndrome according to asthma severity classification. Also, we found no statistically significant relationship between hyperventilation syndrome and treatment prescribed for asthma.

When the scores on each of the 5 subscales of the Asthma Symptom Checklist were analyzed separately, we found that patients with hyperventilation syndrome scored significantly higher on all of them, not only those related to hyperventilation symptoms (Table 2).

We also evaluated the score on each of the 16 items on the Nijmegen questionnaire in patients with and without hyperventilation syndrome (Table 3). Patients with hyperventilation syndrome scored significantly higher on all of them.

The scores of patients on the Nijmegen questionnaire showed significant correlations (Spearman correlation

TABLE 3
Patient Scores on the 16 Items of the Nijmegen Questionnaire*

Item	With HS (n=57)	Without HS (n=100)	P
1	1.9 (0.9)	0.7 (0.8)	.0001
2	2.4 (0.9)	1.3 (1)	.0001
3	1.4 (1)	0.4 (0.8)	.0001
4	1.4 (1)	0.4 (0.8)	.0001
5	0.8 (0.9)	0.2 (0.5)	.0001
6	1.6 (0.9)	0.9 (0.9)	.0001
7	1.8 (0.8)	1.1 (0.9)	.0001
8	1.9 (0.8)	0.7 (0.8)	.0001
9	1.6 (1)	0.8 (0.9)	.0001
10	2 (1)	1 (1)	.0001
11	2.4 (0.7)	1.5 (0.9)	.0001
12	1.6 (1)	0.5 (0.8)	.0001
13	0.9 (1)	0.3 (0.6)	.0001
14	1.9 (1.2)	0.9 (1)	.0001
15	1.5 (0.9)	0.8 (0.9)	.0001
16	2.2 (0.8)	1 (1)	.0001

*Data are expressed as means (SD). HS indicates hyperventilation syndrome.

TABLE 4
Spearman Correlation Coefficients Between the Study Variables and the Score on the Nijmegen Questionnaire*

	Correlation Coefficient	P
Age, years	0.27	.0001
Sex, women	0.27	.001
Education	-0.20	.009
Age at onset of asthma, years	-0.16	.043
Severity, GEMA	0.171	.032
Attendance in emergency department in the last year	0.204	.010
Hospitalizations	0.178	.025
Dyspnea, MRC	0.274	.001
Panic attacks, 6 months	0.167	.036
Anxiety Sensitivity Index	0.498	.0001
Asthma Symptom Checklist	0.497	.0001

*GEMA indicates the Spanish guidelines for asthma management; MRC, Medical Research Council.

coefficient) with the variables shown in Table 4. In the stepwise regression analysis performed with these variables, the score on the Nijmegen questionnaire was the dependent variable. The variables that were finally introduced into the regression model (corrected $r^2=0.57$) were as follows: sensitivity to anxiety (β coefficient=0.485; $P<.001$) and basal dyspnea (β coefficient=0.198; $P=.004$).

Discussion

The problem of the relationship between hyperventilation syndrome and asthma must be considered from 2 perspectives: *a*) that hyperventilation syndrome may be confused with asthma in a patient not suffering from respiratory disease, and *b*) that the 2 processes may coexist in the same individual. The present study is based on the second hypothesis, since the first requirement for inclusion of a patient in the study was that they met the criteria for diagnosis of asthma. Thus, in this study we observed comorbidity for the 2 conditions in 36% of a group of consecutive patients treated for asthma in a pulmonology clinic.

Although this percentage is slightly higher than that found by Thomas et al.,⁸ their study was undertaken in a group of asthmatic patients treated in a primary care facility and is biased by the fact that information was obtained via postal survey in their cross-sectional study, with the loss of patients that this procedure implies. However, previous studies in this area demonstrated the clear synergy between the 2 conditions.²⁰

Some authors argue that a high score on the Nijmegen questionnaire might be attributable to the individual experiencing panic attacks.²¹ Consequently, in this study we specifically evaluated the percentage of asthmatic patients who suffered these attacks. We only found 4 asthmatic patients who suffered panic attacks (prevalence of 2%); 3 of these patients had a score on the Nijmegen questionnaire that indicated hyperventilation syndrome and 1 did not (score of less than 23 points). No statistically significant effect was observed in relation to this variable, indicating that hyperventilation syndrome is not attributable to individuals experiencing panic attacks. In a previous study in which the same diagnostic criteria for anxiety and panic attack were used,²² the authors observed a higher prevalence of panic attacks in asthmatic patients (9.7%) than we found in the present study; nevertheless, data from the literature allows us to conclude that although in some patients there is overlap between hyperventilation syndrome and panic attacks, the prevalence of the 2 conditions is different.

To address whether high overall scores were the result of high scores in certain aspects, the scores for each item on the Nijmegen questionnaire were broken down (Table 3). Our data show that patients with hyperventilation syndrome score significantly higher on all items. When the same patients complete the Asthma Symptom Checklist, which gives a reflection of their subjective experience of an asthma attack, asthmatic patients with hyperventilation syndrome also obtain higher scores in all areas (not only those related specifically to symptoms that could coincide with the clinical presentation of acute hyperventilation). This indicates that asthmatic patients with hyperventilation syndrome experience all symptoms of asthma more acutely.

Univariate analysis showed that asthmatic patients with hyperventilation syndrome had the same degree of asthma severity, but that comorbidity is more common in women and in patients with higher basal dyspnea, more anxiety, and who attend the emergency department and are hospitalized more frequently due to asthma exacerbations. It is of particular interest that we did not find that these patients are prescribed more antiasthmatic medication. The more acutely experienced symptoms suffered by this group would logically lead to doctors prescribing higher doses or a larger number of bronchodilators and antiinflammatory drugs. Thomas et al.²³ recently published a study of asthmatic patients with hyperventilation syndrome who received breathing retraining (fundamentally diaphragmatic breathing) and showed that this procedure leads to a reduction in the score obtained on the Nijmegen questionnaire at 1-month and 6-month follow-up and to a

parallel improvement in quality of life; nevertheless, these changes do not lead to changes in the use of medication. Taken together with our results, these data indicate that asthmatic patients with hyperventilation syndrome suffer more discomfort and go to the emergency department more frequently, but that this does not necessarily translate into higher consumption of asthma medication at home.

Multivariate analysis revealed that hyperventilation syndrome is particularly associated with basal dyspnea and anxiety. Previous studies of dyspnea in asthmatic patients performed by our group^{24,25} showed that dyspnea (both basal and in response to acute obstruction) is related to emotional state, particularly to levels of anxiety. Consequently, the strong correlation between dyspnea, anxiety, and hyperventilation syndrome is not surprising. In conclusion, approximately one third of the asthmatic patients treated in our pulmonology clinic also suffer from hyperventilation syndrome. These patients suffer from anxiety, a high degree of basal dyspnea, and significant discomfort caused by their asthma, even though they do not necessarily suffer from more severe disease. It would be advisable to identify such patients in order to offer breathing retraining programs that would allow them to improve their quality of life. However, this issue still requires further investigation.

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APPENDIX

Spanish Version of the Nijmegen Questionnaire*

A continuación encontrará unas frases que describen una serie de sensaciones que podemos notar las personas. Lea cada frase atentamente y señale con un círculo la puntuación de 0 a 4 que mejor describa la frecuencia con que usted experimenta dichas sensaciones.					
	Nunca	Rara vez	Algunas veces	Casi siempre	Siempre
1. Dolor en el pecho	0	1	2	3	4
2. Sentirse tenso, en tensión	0	1	2	3	4
3. Visión borrosa	0	1	2	3	4
4. Vértigo	0	1	2	3	4
5. Confusión o sentir que las cosas que le rodean son irreales	0	1	2	3	4
6. Respiraciones profundas pero muy rápidas	0	1	2	3	4
7. Respiración entrecortada	0	1	2	3	4
8. Opresión en el pecho	0	1	2	3	4
9. Hinchazón o malestar en el estómago	0	1	2	3	4
10. Hormigueo en dedos y manos	0	1	2	3	4
11. Dificultad para respirar profundamente	0	1	2	3	4
12. Rigidez o calambres en dedos y manos	0	1	2	3	4
13. Tensión o tirantez alrededor de la boca	0	1	2	3	4
14. Manos o pies fríos	0	1	2	3	4
15. Palpitaciones	0	1	2	3	4
16. Ansiedad	0	1	2	3	4

*The questionnaire shown was translated by the authors from the English version¹⁴ and validated in Spanish subjects prior to use in this study.