

Non respiratory symptoms in asthma as possible predictors of exacerbations

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Clinical Implications

- In patients with ascertained bronchial asthma, the occurrence of nonrespiratory symptoms before attacks is common (63.27%).
- An early recognition of nonrespiratory symptoms could be useful to predict a possible worsening of bronchial obstruction.

TO THE EDITOR:

International Guidelines on Asthma Management (GINA) provide detailed information on the diagnosis and management of asthma and its exacerbations. However, these recommendations focus mainly on respiratory symptoms (RS) or possible comorbidities. The occurrence and role of nonrespiratory symptoms (n-RS) before or during worsening of asthma is poorly known, and very few data on this aspect are reported in the literature.^{1,2} Consequently, this “classic” view of asthma diagnosis, based only on RS, implies that airway obstruction is virtually disconnected from other organs or systems. Conversely, it has been widely recognized that, at least in part, airways homeostasis is under the control of both the sympathetic and parasympathetic systems. The autonomic nervous system also plays an important role in controlling the function of other organs. We hypothesize that a sympathetic/parasympathetic imbalance in the airways could be associated with other n-RS.

The aim of this study was to quantify the occurrence and type of n-RS and to evaluate whether these could represent a predictive sign of asthma worsening. Twenty-three allergy units uniformly distributed over the Italian territory were involved in this cross-sectional study. Each center recorded the data of at

TABLE I. Distribution of n-RS (%) in 510 patients, according to asthma severity*

nRS	Moderate or severe persistent asthma	Intermittent or mild persistent asthma	All patients
Anxiety	34	37	36
Headache	28	23	26
Abdominal pain	1	3	2
Weakness	13	4	9
Depression	5	0	3
Impaired sleep	4	8	7
Nicturia	7	0	5
Chest pain	11	7	9
Excitement	13	6	10
Nonlocalized pain	4	4	4
Hunger	3	4	3
Lack of appetite	5	5	5
Fever	1	3	2
Nausea	1	5	4
Urticaria	3	0	2
Palpitation	28	23	26
Heartburn	11	7	10
Generalized itching	22	30	25
Reflux	9	10	10
Flushing	2	3	2
Yawning	9	7	7
Dry mouth	11	11	11
Drowsiness	9	4	5
Daze	10	5	7
Sweating	13	16	14
Tremor	8	9	9
Dizziness	6	11	8

*ANOVA between subjects with intermittent/mild persistent and moderate/severe persistent asthma with at least 1 n-RS (F = 36.5; P < .001).

least 20 consecutive outpatients referred for ascertained bronchial asthma. The data were collected from January 1 to June 30, 2013. All centers followed the same diagnostic protocol and recorded the results in a previously agreed form. This form reported some essential information such as demographic data, family history of atopy/asthma, presence of allergic sensitization, asthma diagnosis according to GINA criteria, and a list of n-RS containing 27 items (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In the presence of any n-RS, patients were asked to quantify the time interval until the worsening of asthma (<3 hours, between 3 and 6 hours, >6 hours, or undefined time). Patients whose n-RS were induced by specific clinical conditions (that could be identified as known comorbidities) or by other reasons, such as fever during viral/bacterial infections, gastrointestinal pain from gastroesophageal reflux disease or food allergy, and palpitations from β_2 agonists' adverse effects, were not included.

A total of 806 patients with asthma were included. Five hundred and ten patients (63.3%) reported at least 1 n-RS that appeared before an asthma attack. These subjects had a mean age

of 36.2 years (range, 8–75 years) and 278 (54.50%) of them were female (for details, see Table E1 in this article's Online Repository at www.jaci-inpractice.org). According to GINA guidelines, 304 (59.60%) and 206 (40.39%) patients were diagnosed with persistent moderate/severe and intermittent/persistent mild asthma, respectively. Statistical analysis was carried out by ANOVA. Percentages of n-RS reported by patients with asthma are presented in Table I. Anxiety (36%), headache (26%), palpitations (26%), and itching (25%) were the most common n-RS, whereas sweating, dry mouth, reflux, heartburn, excitement, and sleep disorders accounted for 10% to 14% of n-RS. All the remaining n-RS listed had percentages ranging from 2% to 9%. n-RS were significantly more frequent in patients suffering from persistent moderate/severe asthma than in those with intermittent/persistent mild asthma ($F = 36.53$; $P < .001$). Most patients (43.5%) reported an interval of less than 3 hours between the appearance of n-RS and the onset of an asthma attack ($P < .001$), 23.9% reported an interval of 3 to 6 hours, 12.9% reported n-RS more than 6 hours before their attack, and 6.7% were unable to quantify the interval. A lower percentage of patients with asthma (18.0%, 6.3%, 5.9%, and 0.4 %) reported more than 2 n-RS at intervals of less than 3 hours, between 3 and 6 hours, more than 6 hours, and undefined hours, respectively.

The results of our study show that the regular appearance of n-RS before a worsening of respiratory conditions is a frequent event in patients with asthma (63.27%), especially in those with persistent moderate/severe asthma. Behavioral symptoms such as anxiety and, to a lesser extent, excitement or depression represented the most common n-RS. This confirms the possible role of these risk factors in the development and triggering of an asthma attack.^{3,4} Studies have shown that psychological stress may enhance bronchial hyperactivity through several mechanisms such as mast cell activation and mediator release, inflammation, and in balance of the autonomic system. A significant relationship was found between psychosocial stress and stimulation of the cholinergic system.⁵ As a consequence, it is likely that some symptoms induced by cholinergic hyperactivity/hyperactivation (eg, dry mouth, sweating, and heartburn) could be present together with parasympathetic-associated RS such as bronchial obstruction.⁶ An example of this association might be the presence of gastrointestinal symptoms (not related to food allergy) in some patients with asthma.⁷ An association of increased bronchial obstruction and abdominal pain before defecation has also been described.⁸ The association between headache and atopic disorders has been recently highlighted, and our findings seem to confirm this relationship.⁹ Palpitationlike symptoms (that may be psychogenic, cardiologic, or associated to β_2 agonists) remain difficult to explain, whereas itching, as a prodromal symptom of asthma, has already been described but without a plausible explanation. In some patients, drowsiness also may precede asthma attacks. This finding is supported by studies showing the importance of sleep-related disorders or sleep impairment.¹⁰

Our study provides evidence of the remarkably frequent occurrence of various n-RS before asthma exacerbations. A strict temporal relationship between the onset of n-RS and the onset of a clinically relevant worsening of bronchial obstruction (within 3 hours in most cases) was seen. These data suggest that n-RS, especially those related to a possible imbalance of the autonomic system with a cholinergic prevalence, might be predictive of a short-term worsening of asthma. Recently, Newton et al¹¹

showed that some n-RS are associated with the loss of asthma control in children. In this study, questionnaires were filled out by the caregivers. They found that irritability, anxiety, tension, and sleep impairment are the most common n-RS in children. These findings are similar to what we found in adults in our study.

Some limitations of this study should be acknowledged. Although a detailed assessment of history and clinical documentation was performed, we cannot exclude the possibility that n-RS may be occurring frequently in patients when they are not having an asthma attack. Likewise, although we tried to exclude patients whose n-RS were due to comorbidities or due to β_2 agonists, we cannot be sure that the n-RS seen in our study were not related to other conditions or medications. Finally, a possible limitation is the inability of patients to exactly define the time elapsed between n-RS and asthma attacks, although fewer than 7% of the patients were not able to make such an estimate, at least within the parameters provided.

In an era in which advanced diagnostic procedures (computerized spirometry, nitric oxide measurement, *in vitro* specific IgE evaluation, molecular-based diagnosis) play an important role in asthma, we believe that physicians managing patients with asthma, and patients themselves, should be informed on the possible relevance of these strictly “clinical” signs. These n-RS could be added to the GINA recommendations to help clinicians in predicting a possible worsening of bronchial obstruction. This could then potentially lead to more timely therapeutic interventions, and avoidance of emergency department visits.

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QUESTIONNAIRE ON THE OCCURRENCE OF NON-RESPIRATORY SYMPTOMS BEFORE AN ASTHMA ATTACK IN PATIENTS SUFFERING FROM BRONCHIAL ASTHMA.				
CENTRE :				Sheet n° ...
Patient's initials :	Year :	SEX : M ☐ F ☐	Family history of allergy : Yes ☐ No ☐	
Date of birth :				
Clinical symptoms (°): Rhinitis ☐ Bronchial asthma ☐ (°) Also associated Conjunctivitis ☐ Others		Respiratory symptoms usually predictive of an asthma attack. Cough ☐ Whizzing ☐ Breathlessness ☐ Chest tightness ☐ Hair hunger ☐		
Presence of pets at home: Yes ☐ No ☐		Therapeutic options usually used None ☐ Broncodilators long-acting ☐ Broncodilators short-acting ☐ Inhalant steroids ☐ Associations steroids-broncodilat. ☐ Anti-leukotrienes ☐		
Diagnosis of asthma according to GINA criteria		Intermittent ☐ Persistent ☐ Slight ☐ Moderate ☐ Severe ☐		
Presence of positive in vitro/ in vivo tests for inhalant allergens : ☐ Yes ☐ No				
Age of onset of respiratory symptoms:		Tobacco smoke : Yes ☐ No ☐ Previous ☐ Passive exposure ? ☐		
Previous allergen immunotherapy : Yes ☐ No ☐				
Eventual notes: 		Non- respiratory symptoms before an asthma attack. Yes No		

	< 3 h	3- 6 h	> 6 h	?
Cutaneous symptoms:				
Flushing	☐	☐	☐	☐
Itch	☐	☐	☐	☐
Urticaria	☐	☐	☐	☐
Psychic symptoms :				
Anxiety	☐	☐	☐	☐
Depression	☐	☐	☐	☐
Excitation	☐	☐	☐	☐
Neurological symptoms:				
Dizziness	☐	☐	☐	☐
Daze	☐	☐	☐	☐
Tremors	☐	☐	☐	☐
Yawnings	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Sleep disorders	☐	☐	☐	☐
Gastrointestinal symptoms:				
Nausea	☐	☐	☐	☐
Abdominal colic	☐	☐	☐	☐
Hunger	☐	☐	☐	☐
Heartburn	☐	☐	☐	☐
Reflux	☐	☐	☐	☐
Lack of appetite	☐	☐	☐	☐

Non-respiratory symptoms

Time interval between the onset of non-respiratory symptoms and asthma attack

	< 3 h	3- 6 h	> 6 h	?
Urinary tract symptoms :				
Frequent micturition	☐	☐	☐	☐
Cardiologic symptoms :				
Palpitations	☐	☐	☐	☐
Chest pain	☐	☐	☐	☐
General symptoms :				
Hyperthermia	☐	☐	☐	☐
Pains	☐	☐	☐	☐
Sweating	☐	☐	☐	☐
Dryness of mouth	☐	☐	☐	☐
Weakness	☐	☐	☐	☐
Other symptoms :				
.....				

FIGURE E1. The questionnaire sheet used in the survey.

TABLE E1. Characteristics of the patients with and without n-RS
(N = 806)

Characteristic	With n-RS	Without n-RS
N (%)	510 (63.3)	296 (36.7)
Age range (y)		
0-20	84 (16)	33 (11)
21-40	172 (34)	82 (28)
41-60	208 (41)	127 (43)
>60	46 (9)	54 (18)
Sex: male/female	222/286	140/156
Family history of atopy*	300 (59)	160 (54)
Intermittent/mild persistent asthma	206 (40)	194 (66)
Moderate/severe persistent asthma	304 (60)	102 (34)
Pets at home	118 (23)	54 (18)
Allergic sensitization†	408 (80)	204 (69)
Age of onset of asthma (y)		
0-20	300 (59)	150 (51)
21-40	130 (25)	90 (30)
41-60	72 (14)	54 (18)
>60	8 (2)	2 (1)
Smoking habit		
Never	340 (67)	184 (62)
Actual	100 (20)	37 (12)
Past	54 (10)	58 (20)
Passive smoke	16 (3)	17 (6)
Previous immunotherapy	234 (46)	48 (16)

Values represent n (%) unless otherwise indicated.

*At least 1 parent with history of asthma/allergic rhinitis/atopic dermatitis/food allergy.

†At least 1 positivity at standard skin prick test.

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