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Asthma and asthma-like disorders

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Bronchial asthma is defined as a chronic inflammatory disease resulting in a reversible and variable bronchial obstruction. For the clinical diagnosis of the disease there are some key indicators but as there is no 'gold standard' a correct diagnosis will sometimes not be obtained. Examples are patients in a symptom-free stage, current medication interfering with the methods used, patients with asthma-like symptoms reporting lack of effect of bronchodilators and patients who are unable to perform a forced expiration in an airway function test. The prevalence of asthma is reported to be 5–10%. The prevalence of asthma-like symptoms may be double this.

The term 'asthma-like' has been used to an increasing extent during the last few years, which may indicate an increasing awareness of the fact that asthma-like symptoms are not always classical asthma. In this overview some disorders with asthma-like symptoms, especially in adults, are presented. The spectrum of differential diagnoses in a clinic may depend on which doctor/specialist the patient is consulting. In an asthma and allergy clinic it has been found that the most common differential diagnoses are chronic obstructive pulmonary disease (COPD), non-asthmatic cough and sensory hyper-reactivity (SHR), a disorder which is sometimes mixed up with asthma due to similar symptoms (heavy breathing, cough, increased secretion, difficulty in getting air etc.) and similar trigger factors (smoke, strong scents, exercise, cold air etc.). Recently it has been suggested that a capsaicin inhalation test may be an objective test for identifying patients with SHR. In asthma effective treatment is available today but in asthma-like disorders, such as SHR, no effective therapy is available, underlining the need of further research for understanding the pathophysiological mechanisms.

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Introduction

Bronchial asthma is a well-known disease, in international consensus reports (1–4) defined as a chronic inflammatory disease, in which eosinophils, mast cells and other cells and cellular elements play an important role. The inflammation causes airway hyper-responsiveness and is the reason for the appearance of variable and reversible airflow obstruction. However, although the role of inflammation is stressed there is still no easily available method for assessing the type and degree of airway inflammation (5). Methods aimed at reflecting airway inflammation such as assessments of cells and cell elements in induced sputum (6–8), inflammatory markers in the blood (9) and markers in exhaled air (10,11), have not yet been widely used.

There is also no 'gold standard' for the definition of clinical asthma but some key indicators are diagnostic (4). Major key indicators are an increase in forced expiratory volume in 1 sec (FEV_1)$\geq$12% or $\geq$200 ml after a bronchodilator, diurnal variation in peak expiratory flow (PEF) $\geq$20 % and a positive methacholine or histamine test. No single test is diagnostic and exclusion of other possible diagnoses is always needed. Furthermore, there are no airway symptoms that may, with certainty, be associated with asthma although wheezing, particularly in the early morning and after exposure to cold air and exercise, is a strong indicator. There is also a relatively weak correlation between the different diagnostic tests (12). The consequence is that the clinical diagnosis is dependent on what symptoms, diagnostic methods and normal limits have been selected.

Although it has been emphasized that making the correct diagnosis of asthma is extremely important (1,4), little attention has been paid to the fact that this is associated with considerable difficulty in many cases. Examples are patients with atypical airway symptoms, patients in a symptom-free stage, current medication interfering with the methods used, patients with asthma-like symptoms reporting lack of effect of bronchodilators, different responses in different asthma tests, no or slight response to oral steroid burst and patients who are unable to perform a forced expiration in airway function and methacholine tests. Treatment with anti-asthmatic drugs such as corticosteroids and β_2-agonists is a special problem, as these drugs may reduce or normalize diagnostic variables, such as symptoms, reversibility, variability and bronchial hyper-reactivity. The influence of asthma medication stresses the importance of making the diagnostic work, including adequate spirometry, before any medication is introduced.

The intensity of differential diagnostic work is dependent on the need for demarcation of other adjacent disorders. Such a separation and identification is an important issue,

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TABLE 1. Disorders including asthma-like symptoms

Chronic obstructive pulmonary disease (COPD)
Chronic bronchitis due to smoking
Chronic cough for other reasons
Hyperventilation
Mechanical obstruction of the airways
Congestive heart failure
Pulmonary embolism
Gastro-oesophageal reflux (GER)
Multiple chemical sensitivity (MCS)/idiopathic environmental illness (IEI)
Reactive airway dysfunction syndrome (RADS)
Sick building syndrome (SBS)
Vocal cord dysfunction
Sjogren's syndrome
Functional respiratory disorder/sensory hyper-reactivity

as patients presenting asthma-like symptoms may report symptoms as well as physical and social handicaps as severe as patients with classical asthma (13,14). Asthma is a respiratory disease that has been much in focus during the last few years. The consequence of this may be that other common but less well-known disorders are not sufficiently considered. The prevalence of asthma in several countries is found to be 5–10%, but the prevalence of asthma-like symptoms may be double this. Breathing troubles induced by trigger factors such as cold air, exercise and chemical irritants were present in 15–20% in an epidemiological study (to be published) and bronchial inflammation in biopsies not typical for asthma was found in about 10 % of the population (15). For these changes the term asthma-like inflammation has been suggested (15).

Asthma-like

The term 'asthma-like' has been used to an increasing extent during the last few years, which may indicate an increasing awareness of the fact that asthma-like symptoms are not always associated with asthma (reversible bronchial obstruction). In this overview a selected number of disorders that may be mixed up with asthma are presented. Of course, only disorders with given names are mentioned, there may be more, not yet identified. The presentation focuses on the differential diagnoses of asthma in adults, but asthma-like disorders have also been observed in children (14,16). Disorders including asthma-like symptoms are shown in Table 1.

Chronic obstructive pulmonary disease

One of the most common differential diagnoses of asthma is chronic obstructive pulmonary disease (COPD), often preceded by chronic bronchitis. The disease is characterized by a slowly progressive reduction of the pulmonary ventilation due to a combination of emphysema and bronchiolitis with obstruction of the small airways. The most important aetiological factor is tobacco smoking. The first symptom is usually an exercise-induced breathing complaint. COPD is distinguished from asthma by demonstration that the bronchial obstruction is not, or only slightly, reversible to steroids and bronchodilators.

Chronic cough

Cough, not due to smoking, with or without other asthma-like symptoms may have several different aetiologies, for example asthma, gastric-oesophageal reflux, post-nasal drip, pertussis, acetyl cholinesterase (ACE) inhibitor therapy and sensory hyper-reactivity (17), but in some cases cough is a single symptom not induced by any known trigger factor. Cough at night and cough associated with physical exercise may be indications of asthma. For the diagnosis of asthma tests such as reversibility to a bronchodilator, methacholine/histamine test and increased levels of exhaled nitric oxide (18) have to be positive. Reflex bronchoconstriction and cough may be induced by different sensory pathways (19).

Hyperventilation syndrome

The hyperventilation syndrome has been defined as a syndrome characterized by a variety of somatic symptoms induced by physiologically inappropriate hyperventilation and usually reproduced in whole or in part by voluntary hyperventilation (20). The symptoms are thought to be due to hyperventilation with subsequent hypocapné. Some of these, such as shortness of breath, accelerated/deepened breathing and feeling unable to breathe deeply are asthma-like with the risk that this condition is mixed up with asthma (21). Hyperventilation may also induce a bronchial constriction in susceptible individuals. For establishing the diagnosis two criteria have been proposed, symptoms reproduced by a hyperventilation test (22) and a slow recovery of CO_2 in blood or expired air after a hyperventilation test (21,22). The diagnostic criteria and the definition of the syndrome, however, are a matter of debate (23). One major problem is that many patients reporting acute airway symptoms associated with hyperventilation do not show any lowering of end-tidal CO_2. Another problem is that the specificity and sensitivity of the hyperventilation test are not high (24), indicating that the hyperventilation syndrome is not a well-defined clinical entity. It is more likely that hyperventilation, like cough, should only be considered as a symptom with different aetiological origins.

Reactive airway dysfunction syndrome (RADS)

RADS, the term coined in 1985, is an illness with asthma-like symptoms developing as the direct consequence of massive toxic inhalation exposure (25). The bronchial

histological changes show an increase of inflammatory cells although eosinophils and mast cells do not dominate. Not all experts are certain that this syndrome is a distinct clinical entity.

Multiple chemical sensitivity/ idiopathic environmental intolerance

Multiple chemical sensitivity (MCS), also called idiopathic environmental illness (IEI), (26) is defined as a disease acquired in relation to some environmental exposure leading to symptoms in more than one organ. The symptoms occur in response to chemical compounds at doses below those known to cause harmful effects in the general population. However, the disorder has not been well defined and there is not yet any objective test that can identify patients with this disorder (27). Common symptoms are headache, weakness, memory problems, inability to concentrate, throat soreness, abdominal pain and discomfort. In the airways the patients may suffer from nasal congestion and asthma-like symptoms such as cough and chest tightness. A number of theories have been put forward to address the cause of MCS/IEI and the mechanism by which diverse environmental exposures produce symptoms. Most studies to date have found an excess of current and past psychopathology. Controlled studies to verify the patient's reported increased sensitivity to specific environmental chemicals have to be carried out.

Sick building syndrome (SBS)

Sick building syndrome is a complex disease of skin and mucous membrane irritation caused mainly by inadequate air-handling systems in energy efficient buildings (28). The most common symptoms are dry skin in the face, irritation of the eyes and some airway symptoms like rhinitis, dry throat, hoarseness and cough (29). Unlike MCS/IEI these patients experience a limited range of symptoms associated with the affected building only.

Sjogren's syndrome

Sjogren's syndrome is a common systemic rheumatic disease. Pulmonary disease is prevalent including asthma-like symptoms like chronic cough and bronchial obstruction (30). Other manifestations are pulmonary lymphoma and interstitial lung disease.

Vocal cord dysfunction

Vocal cord dysfunction is characterized by episodic or acute attacks of breathing troubles similar to attacks of asthma. It is distinguished from asthma by the absence of ronchi over basal-dorsal lung areas and the presence of stridor over the larynx as well as visible abnormality of the vocal cords at inspection (31). Clinically, the effect of bronchodilators is slight or none.

'Ski asthma'

In elite cross-country skiers, asthma, asthma-like symptoms and bronchial hyper-responsiveness are more common compared to non-skiers and the general population (32). Strenuous exercise in cold air may be the most probable explanation for this disorder. The disorder has been called 'ski asthma', although typical asthmatic bronchial inflammation, such as increased counts of neutrophil and eosinophil cells and increased level of eosinophil cationic protein have not been detected. Biopsy sections from the bronchi have shown inflammation with aggregates of lymphoid cells (33) and after exposure to cold air an increase of the number of granulocytes and macrophages in the lower airways has been reported (34).

Sensory hyper-reactivity

A differential diagnosis of asthma called sensory hyperreactivity has recently been described (17). The disorder, earlier called functional breathing disorder (13,35), is a syndrome that has frequently been found among patients referred to a specialist clinic for investigation of suspected asthma (36). The clinical research was inspired by the fact that asthma in many cases was, and still is, mixed up with this asthma-like syndrome (37,38). The characteristics are airway symptoms and trigger factors known from the asthma literature, but in these cases not directly associated with reversible and variable bronchial obstruction (13,35,36,39,40). Furthermore, spirometry is sometimes difficult to obtain due to inability to perform an adequate forced expiration, which may incorrectly be interpreted as an indication of bronchoconstriction. The most common symptoms are heavy breathing, cough, increased secretion, difficulty in getting air and chest pressure/load (35,38). The symptoms are often induced by a trigger factor, the most common being irritants, such as smoke and strong scents, and physical exercise. Some symptoms earlier reported to indicate asthma, such as difficulty in breathing and breathlessness (4), may more likely be indicators of sensory hyper-reactivity. The symptoms are in some cases more dramatic than those of asthma and, unless critically examined and properly investigated with spirometry, the symptoms may be interpreted as severe asthma. This is of special importance as asthma and asthma-like symptoms may be present in the same individual.

In a recent re-evaluation of the diagnosis of asthma it was shown that the diagnosis could be verified in only two thirds of the patients (41), the most common diagnoses in non-verified cases being COPD and functional breathing disorder with symptoms seen in patients with sensory hyper-reactivity. Some of the asthma-like symptoms presented may be induced by hyperventilation (21), and the question is whether or not functional breathing disorder and sensory hyper-reactivity is part of the hyperventilation syndrome. However, in most patients with a sensory hyper-reactivity no changes in

endtidal-CO_2 at rest can be demonstrated and only a few patients react with a reduction of endtidal-CO_2 during exercise and provocation to perfume and capsaicin. Hyperventilation may therefore be considered as one of several asthma-like symptoms. The reported asthma-like disorder may be recognized by the pattern of symptoms in the absence of reversible bronchial obstruction and other known airway disease. In some patients non-respiratory symptoms, such as eye irritation, chest pain and tiredness have also been observed. However, the diagnosis of sensory hyper-reactivity has so far been limited to patients with asthma-like symptoms as mixing of asthma and asthma-like disorders is a clinical problem today. To identify sensory hyper-reactivity is possible in the majority of the patients referred for suspected asthma, but it needs experience and carefully performed airway function tests. Recently it has been shown that a capsaicin inhalation test can provoke these kinds of symptoms (17), suggesting that this test may be useful for objective identifcation of these patients. Capsaicin is a specific stimulus of sensory nerves and has earlier been used for assessing the tendency to cough (42). Our present theory is that asthma-like symptoms are provoked by a sensory nerve-mediated disturbance of the respiratory pattern. Studies aimed to block this kind of hyper-reactivity are in progress.

Trigger factors

Trigger factors are of special interest in differential diagnoses of asthma. The most generally reported trigger factors in asthma inducing acute breathing troubles are allergens, physical exercise, cold air, chemical irritants, mental stress, aspirin and respiratory viral infections. When symptom scores from chemical triggers, such as smoke, exhaust fumes and perfumes, are correlated with the response to methacholine, no correlation was found indicating different mechanisms of action. Only the symptom score from exercise and cold air were significantly correlated to the methacholine test (unpublished data). Furthermore, when symptom scores from strong scents were correlated with a methacholine test no significant correlations were found indicating that the methacholine test cannot be used for revealing an increased sensitivity to strong scents (43).

Treatment and management

For asthma effective medication is available, but in some cases of asthma-like disorders, particularly sensory hyper-reactivity, there is no effective medication. However, the majority of patients with an asthma-like disorder referred for investigation of suspected asthma have been prescribed some kind of asthma medication. It has also been observed that treatment compliance in asthma is low (44,45). One of the reasons may be lack of subjective effect. This may be interpreted as poor compliance in cases where a new evaluation may show that the diagnosis was not correct. An asthma-like disorder must always be considered in patients resistant to conventional therapy (37), particularly in steroid-insensitive asthma (46) as steroids are the most potent drugs in the treatment of asthma, and as up to 25 % of all patients with reported severe asthma may be steroid-insensitive (46). Because the clinical and social severity of the disease may be similar or worse in patients with asthma-like symptoms (13,14), it is of fundamental importance to identify and describe these disorders. This is a matter for research, especially initial clinical research, as symptoms and signs are difficult to study in the laboratory.

References

1. National Heart, Lung, and Blood Institute, National Institutes of Health. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. NHLBI/WHO workshop report. NIH publ. no 95-3659; January 1995.
2. British Thoracic Society, British Paediatric Association, Royal College of Physicians of London. The King's Fund Centre, National Asthma Campaign *et al.* Guidelines on the management of asthma. *Thorax* 1997; **52:** S1-S24.
3. British Asthma Guidelines Coordinating Committee. British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997; **52:** S1-S24.
4. National Institutes of Health, National Heart, Lung, and Blood Institute. Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 2. NIH publ. No. 98-4051; Reprinted April 1998.
5. Sterk PJ. Non-invasive monitoring of bronchial inflammation in asthma. *Schweiz Med Wochenschr* 1997; **127:** 1686–1692.
6. Sorva R, Metso T, Turpeinen M, Juntunen-Backman K, Bjorksten F, Haahtela T. Eosinophil cathionic protein in induced sputum as a marker of inflammation in asthmatic children. *Pediatr Allergy Immunol* 1997; **8:** 45–50.
7. Gibson PG. How to measure airway inflammation: induced sputum. *Can Respir J* 1998; **5:** (Suppl A): 22A–6A.
8. Hargreave FE. Induced sputum for the investigation of airway inflammation: Evidence for its clinical application. *Can Respir J* 1999; **6:** 169–174.
9. Wever AM, Wever-Hess J, Hermans J. The use of serum eosinophil cathionic protein (ECP) in the management of steroid therapy in chronic asthma. *Clin Exp Allergy* 1997; **27:** 519–529.
10. Kharitonov SA, Barnes PJ. Nitric oxide in exhaled air is a new marker of airway inflammation. *Monaldi Arch Chest Dis* 1996; **51:** 533–537.
11. van Rensen EL, Straathof KC, Veselic-Charvat MA, Zwinderman AH, Bel EH, Sterk PJ. Effect on inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma. *Thorax* 1999; **54:** 403–408.
12. Siersted HC, Mostgaard G, Hyldebrandt N, Hansen HS, Boldsen J, Oxhoj H. Interrelationships between diagnosed asthma, asthma-like symptoms, and abnormal airway behaviour in adolescence: the Odense Schoolchild Study. *Thorax* 1996; **51:** 503–509.

13. Ringsberg KC, Löwhagen O, Sivik T. Psychological differences between asthmatics and patients suffering from an asthma-like condition, functional breathing disorder: a comparison between the two groups concerning personality, psychosocial and somatic parameters. *Integr Physiol Behav Sci* 1993; **28:** 358–367.
14. Maier WC, Arrighi HM, Morray B, Llewllyn C, Redding GJ. The impact of asthma and asthma-like illness in Seattle school children. *J Clin Epidemiol* 1998; **51:** 557–568.
15. Haahtela T. Asthma-like inflammation—a new term is needed. *Nord Med* 1997; **112:** 110–111.
16. Remes ST, Korppi M, Remes K. Outcome of children with respiratory symptoms without objective evidence of asthma: a two-year, prospective, follow-up study. *Acta Paediatr* 1998; **87:** 165–168.
17. Millqvist E, Bende M, Lowhagen O. Sensory hyperreactivity—a possible mechanism underlying cough and asthma-like symptoms. *Allergy* 1998; **53:** 1208–1212.
18. Chatkin JM, Ansarin K, Silkoff PE, *et al.* Exhaled nitric oxide as a noninvasive assessment of chronic cough. *Am J Respir Crit Care Med* 1999; **159:** 1810–1813.
19. Choudry NB, Fuller RW, Andersson N, Karlsson JA. Separation of cough and reflex bronchoconstriction by inhaled local anaesthetics. *Eur Respir J* 1990; **3:** 579–583.
20. Lewis RA, Howell JBL. Definition of hyperventilation syndrome. *Bull Eur Physiopathol Respir* 1986; **22:** 201–205.
21. Ringsberg K, Akerlind I. Presence of hyperventilation in patients with asthma-like symptoms but negative asthma test responses: provocation with voluntary hyperventilation and mental stress. *J Allergy Clin Immunol* 1999; **103:** 601–608.
22. Hardonk HJ, Beumer HM. Hyperventilation syndrome. In: Vinken P, Bruyn G, ed. *Handbook of Clinical Neurology*. New York. North-Holland 1979; **38:** 309–360.
23. Bass C. Hyperventilation syndrome: a chimera? *J Psychosom Res* 1997; **42:** 421–426.
24. Hornsveld H, Garssen B, The low specificity of the hyperventilation provocation test. *J Psychosom Res* 1996; **41:** 435–449.
25. Alberts WM, Brooks SM. Reactive airways dysfunction syndrome. *Curr Opin Pulm Med.* 1996; **2:** 104–110.
26. Position paper, AAAAI Board of Directors. Idiopathic environmental intolerance. *J Allergy Clin Immunol* 1999; **103:** 36–40.
27. Graveling RA, Pilkington A, George JPK, Butler MP, Tannahill SN. A review of multiple chemical sensitivity. *Occup Environ Med* 1999; **56:** 73–85.
28. Redlich CA, Sparer J, Cullen MR. Sick-building syndrome. *Lancet* 1997; **349:** 1013–1016.
29. Bjornsson E, Janson C, Norback D, Boman G. Symptoms related to the sick building syndrome in a general population sample: associations with atopy, bronchial hyper-responsiveness and anxiety. *Int J Tuberc Lung* Dis 1998; **2:** 1023–1028.
30. Papiris SA, Maniati M, Constantopoulos SH, Roussos C, Moutsopoulos HM, Skopouli FN. Lung involvement in primary Sjogren's syndrome is mainly related to the small airway disease. *Ann Rheum Dis* 1999; **58:** 61–64.
31. Butani L, O'Connell EJ. Functional respiratory disorders. *Ann Allergy Asthma Immunol* 1997; **79:** 91–101.
32. Larsson K, Ohlsen P, Larsson L, Malmberg P, Rydstrom PO, Ulriksen H. High prevalence of asthma in cross country skiers. *BMJ* 1993; **307:** 1326–1329.
33. Sue-Chu M, Larsson L, Moen T, Rennard SI, Bjermer L. Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without "ski asthma". *Eur Respir J* 1999; **13:** 626–632.
34. Larsson K, Tornling G, Gavhed D, Muller-Suur C, Palmberg L. Inhalation of cold air increases the number of inflammatory cells in the lungs in healthy subjects. *Eur Respir J* 1998; **12:** 825–830.
35. Lowhagen O. Functional respiratory disorders as significant differential diagnosis in asthma. *Lakartidningen* 1989; **86:** 57–59.
36. Lowhagen O, Balder B. Histamine and methacholine tests in cases of hyperreactive bronchi—a 10-year experience. *Lakartidningen* 1990; **87:** 3413–3418.
37. Lowhagen O, Ellbjar S, Jorgensen N, Toss L. Severe asthma was found to be an asthma-like condition. Consider reduced doses of cortisone. *Lakartidningen* 1996; **93:** 3711–3713.
38. Lowhagen O, Ellbjar S, Jorgensen N. Asthma or asthma-like condition ? *Nord Med* 1997; **112:** 119–121.
39. Ringsberg KC, Wetterqvist H, Lowhagen O, Sivik T. Physical capacity and dyspnea in patients with asthma-like symptoms but negative asthma tests. *Allergy* 1997; **52:** 532–540.
40. Millqvist E, Lowhagen O. Placebo-controlled challenges with perfume in patients with asthma-like symptoms. *Allergy* 1996; **51:** 434–439.
41. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? *Family Practice* 1999; **16:** 112–116.
42. Midgren B, Hansson L, Karlsson JA, Simonsson BG, Persson CGA. Capsaicin-induced cough in humans. *Am Rev Respir Dis* 1992; **146:** 347–351.
43. Millqvist E, Lowhagen O. Methacholine provocations do not reveal sensitivity to strong scents. *Ann Allergy* 1998; **80:** 381–384.
44. Mawhinney H, Spector SL, Heitjan D, Kinsman RA, Dirks JF, Pines I. As-needed medication use in asthma usage patterns and patient characteristics. *J Asthma* 1993; **30:** 61–71.
45. Schmier JK, Leidy NK. The complexity of treatment adherence in adults with asthma: challenges and opportunities. *J Asthma* 1998; **35:** 455–472.
46. Chan MTS, Leung DYM, Szefler SJ, Spahn JD. Difficult-to-control asthma: Clinical characteristics of steroid-insensitive asthma. *J Allergy Clin Immunol* 1998; **101:** 594–601.