

REVIEW ARTICLE

Diagnosis of asthma – new theories

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Introduction: Recent studies have shown a remarkably high frequency of poorly controlled asthma. Several reasons for this treatment failure have been discussed, however, the basic question of whether the diagnosis is always correct has not been considered. Follow-up studies have shown that in many patients asthma cannot be verified despite ongoing symptoms. Mechanisms other than bronchial obstruction may therefore be responsible. The current definition of asthma may also include symptoms that are related to mechanisms other than bronchial obstruction, the clinical hallmark of asthma. **Aim:** Based on a review of the four cornerstones of asthma – inflammation, hyperresponsiveness, bronchial obstruction and symptoms – the aim was to present some new aspects and suggestions related to the diagnosis of adult non-allergic asthma. **Conclusion:** Recent studies have indicated that “classic” asthma may sometimes be confused with asthma-like disorders such as airway sensory hyperreactivity, small airways disease, dysfunctional breathing, non-obstructive dyspnea, hyperventilation and vocal cord dysfunction. This confusion may be one explanation for the high proportion of misdiagnosis and treatment failure. The current diagnosis, focusing on bronchial obstruction, may be too “narrow”. As there may be common mechanisms a broadening to include also non-obstructive disorders, forming an asthma syndrome, is suggested. Such broadening requires additional diagnostic steps, such as qualitative studies with analysis of reported symptoms, non-effort demanding methods for determining lung function, capsaicin test for revealing airway sensory hyperreactivity, careful evaluation of the therapeutic as well as diagnostic effect of corticosteroids and testing of suggested theories.

Keywords

Diagnostics, epidemiology, exercise induced, management/control, mechanisms

History

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Introduction

The current definition of asthma originates from the early 1990s and includes airway inflammation, hyperresponsiveness, reversible bronchial obstruction and airway symptoms [1–3]. At the first international asthma symposium, the CIBA Guest Symposium 1959 [4], asthma was defined as an intermittent or reversible airways obstruction. In 1962 the American Thoracic Society added and emphasized the increased excitability [5] of the airways and in 1975 the World Health Organization [6] added and stressed the variable bronchial obstruction. The new component of inflammation was added around 1990 based on observations in a limited number of patients [7–11]. Despite the advent of new diagnostic tools diagnosis is still based on the existence of a variable and reversible airway obstruction.

The treatment of asthma has improved during the last decades, and the mortality rate has drastically dropped. However, despite the availability of effective treatment,

studies in recent years have shown a remarkably high ratio of poorly controlled asthma [12–26]. Although asthma is due to airway inflammation some patients do not respond to anti-inflammatory therapy [27–35]. Different causes of this treatment failure have been discussed and different terms have been suggested for the phenomenon: severe asthma, steroid-resistant asthma and problematic and refractory asthma [27–29,31,32,34–55].

Follow-up studies have shown that physician-diagnosed asthma cannot be verified in up to one-third of patients investigated [56–60]. As many of these non-asthma patients still have symptoms other non-obstructive mechanisms must exist [60]. The high proportion of treatment failure and misdiagnosis may justify the testing of new theories. A key question is whether the diagnosis is always correct, for example, are asthma-like disorders sometimes mixed up with “classic” asthma [60–62]. If the diagnosis is not right, the medication will not be right.

Aim

Based on a critical review of the four cornerstones in asthma – inflammation, hyperresponsiveness, bronchial obstruction and symptoms – the aim was to present some new aspects and suggestions for the diagnosis of asthma.

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Asthma as an inflammatory disease

Inflammation was added as a component of the asthma definition around 1990 [8–10]. It was primarily based on studies of autopsy material and mucosal lavage and biopsy sample material taken by bronchoscopy [8]. In the International Consensus Report on Diagnosis and Management of Asthma 1992 the support for the incorporating inflammation in the definition was based on eight references including a limited number of patients [8]. On the basis of these results an operational definition of asthma as a chronic inflammatory disorder was stated [8,63]. As this statement has contained only a few hints of exceptions [35] the definition should obviously cover all types of asthma. The scientific accuracy of an extrapolation from a small number of selected patients to millions of asthmatic individuals worldwide has not been questioned in subsequent consensus reports [1–3].

Many studies have subsequently shown the presence of airway inflammation. The strongest indications may be the positive effect of anti-inflammatory drugs, such as corticosteroids, which are used worldwide. The original definition of asthma as an inflammatory disease is cited in the majority of later asthma articles [1–3]. However, later studies have also shown that anti-inflammatory therapy can sometimes fail and that inflammatory markers may not be effective in guiding therapy [64]. Furthermore, the airway inflammation is not defined, and methods for measuring the degree of inflammation are not completely reliable or easily available.

Theory 1: Airway inflammation is the most important component of asthma but represent only one of several endotypes within the asthma syndrome.

Hyperresponsiveness a typical feature of asthma

Airway hyperresponsiveness (AHR) expressed as bronchial constriction to a defined number of stimuli is a typical feature of asthma [2,65,66]. The stimuli are divided into direct stimuli, such as methacholine and histamine (acting directly on the airway smooth muscles) and indirect, such as hypertonic saline, adenosine monophosphate and mannitol [65–67].

The methods have been extensively used in the diagnosis of asthma and in different kinds of clinical studies. A positive test provides support for the presence of asthma, while a negative test is an even stronger support for the finding of non-asthma (high negative predictive value) [65,66]. The mechanism of AHR is not yet clear, and there is only a weak association with markers of inflammation, asthma trigger factors and symptoms [65,67]. However, it has been shown that there is a connection with the asthmatic disease as an AHR test (methacholine) may be used to guide treatment for reducing exacerbations and decline in lung function [66]. That a component of asthma is related to “the whole” but not to “the parts”, however, seems contradictory and needs further examination.

Although a negative test may exclude asthma it does not exclude other disorders. It has repeatedly been shown that AHR tests may be negative despite ongoing asthma-like symptoms [58,59,68,69]. This may be explained by the presence of non-obstructive mechanisms. From studies on

methacholine-induced bronchial obstruction it is known that the degree of the bronchial obstruction is not correlated with the subjective sensitivity to chemical irritants such as smoke and scents. This indicates the presence of at least one additional mechanism besides the bronchial constriction [70,71]. Asthma-like symptoms induced by non-allergic trigger factors are common and may be interpreted as asthma symptoms (bronchial obstruction) [60]. According to the literature such symptoms may be associated with hyperventilation, panic attack, vocal cord dysfunction, post-nasal drip, reflux, anxiety/depression [1], non-obstructive dyspnea [60] or airway sensory hyperreactivity [72]. In sensory hyperreactivity (hypersensitivity to scents and positive capsaicin test) it has been clearly shown that asthma-like symptoms may occur without a concomitant bronchial obstruction [73].

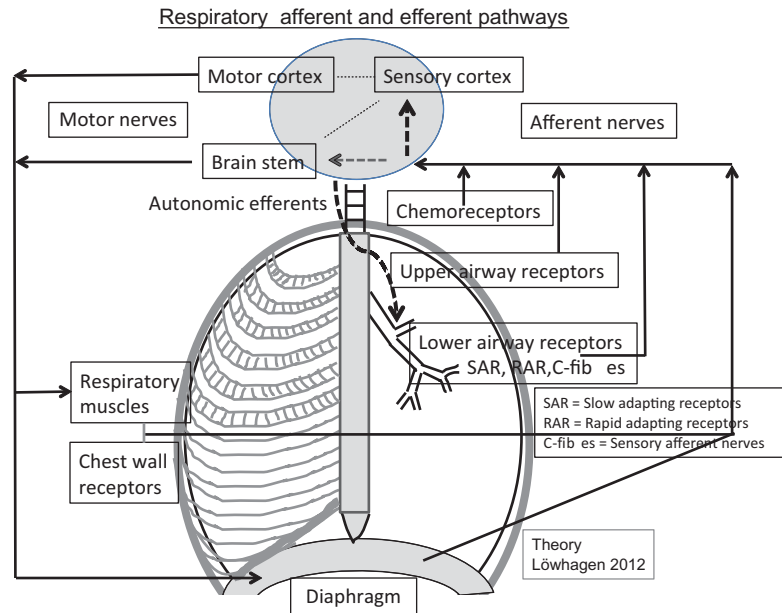
A major problem in the discussion of AHR, as well as the diagnosis of asthma, is the fact that incorrect diagnosis has been found in a remarkably high proportion of patients investigated. In one study the asthma diagnosis could be confirmed in only 66% of the patients [56]. In another confirmatory study of 304 adult patients with a physician-diagnosed asthma, 27% had a negative methacholine test, indicating non-asthma. However, of these non-asthma patients the majority still had symptoms such as cough, dyspnea, chest tightness or wheeze [59] indicating other underlying mechanisms besides the bronchial obstruction. In a cohort of 420 patients investigated for suspected asthma a similar proportion (25%) had a negative methacholine challenge despite ongoing asthma-like symptoms [68]. In a confirmatory study of physician-diagnosed asthma in obese and non-obese patients, it was found that the asthma diagnosis could not be verified in about a third of the cases, the same for obese and non-obese. However, the majority of these non-asthma patients (75%) still had symptoms such as wheeze and dyspnea [58]. This was not commented on in the article. As long as there are ongoing airway symptoms it is, of course, as important to investigate and treat test-negative patients as it is to treat test-positive ones. All patients should have treatment, including information, but only asthma patients should have asthma medication. For other patients other treatment may be tested, however, research to find new therapies are neglected.

Theory 2: The observations that hyperresponsiveness inhalation tests may be negative despite ongoing asthma-like symptoms indicate the presence of mechanisms other than bronchial obstruction. Research and clinical investigations should include these additional mechanisms.

Exercise-induced asthma

AHR also includes the bronchospastic reaction triggered by physical exertion. Different methods, such as ergometer cycling, running on a treadmill and free running have been applied and standardized [74–76]. The commonly used term exercise-induced asthma (EIA) is inappropriate as exercise induces bronchial constriction, not asthma. A more logical term is exercise-induced bronchospasm (EIB) [76]. Usually a reduction in FEV₁ from a baseline of $\geq 10\%$ is considered as a positive test. The exercise tests are of great diagnostic value,

Figure 1. The figure shows a possible view of the neurophysiological respiratory pathways (afferents to the right, efferents to the left) that may give rise to respiratory sensations when afferent signals become conscious in the sensory cortex. Besides obstruction in larger and smaller airways, stimulation of chemoreceptors and receptors in the upper and lower airways, chest wall and respiratory muscles may result in dyspnea.



as they imitate the situation in real life. For elite athletes, the tests are of particular importance due to the need for certification of contestants. A diagnostic problem, however, is that the relationship between a positive test and a physician-diagnosed asthma [65,74] or a history of exercise-induced symptoms is usually weak [74,75,77–80].

In studies of exercise-induced bronchoconstriction the degree of bronchial obstruction is regularly recorded, most often as a fall in FEV₁, but only rarely are the triggered symptoms recorded [76,81–85]. This means that a test could be negative despite the fact that severe breathing difficulties have been induced. Most often the diagnosis is one-sided focused on the detection and rejection of bronchospasm. The few more open studies that have been performed have shown that hyperventilation and non-obstructive dyspnea can be induced [81–84]. One possible mechanism is activation of the airways receptors, as different trigger factors can trigger asthma-like symptoms without inducing bronchospasm [86] (Figure 1).

Theory 3: The most important issue for the moment is to emphasize the importance of assessing exercise-induced symptoms and signs. Because only a small percentage of the large number of individuals with exercise-induced complaints are positive in exercise tests and the triggered symptoms are most often neglected, the real cause of the problems may remain unsolved in many cases.

Reversible and variable bronchial obstruction

According to the first international consensus report in 1959, the CIBA Guest Symposium [4], the diagnosis of asthma should be based on reversible bronchial obstruction. In fact, this rule has been followed ever since. The advent of new diagnostic methods has not affected this main rule. The degree of bronchial obstruction is most often measured as decreases in FEV₁, FVC and PEF. These methods are practical but have drawbacks. Clinical experience has shown

that one disadvantage is the requirement of full participation of the patient. Some patients have difficulty in making powerful expirations with the consequence that the values may be too low with the risk of being interpreted as bronchospasm.

Theory 4: The high rate of misdiagnosed asthma may sometimes be due to a lack of proper use of pulmonary tests or the patient's inability to make adequate forced expirations. Less effort dependent tests would provide more reliable results.

Theory 5: In epidemiological studies, the diagnosis is often based on questionnaires (not on pulmonary tests) including different symptoms, most often called “physician-diagnosed asthma”. As there are no typical symptoms this can make the diagnosis uncertain [87–92].

Reversible bronchial obstruction is the main clinical feature of asthma. However, non-obstructive mechanisms may also be relevant in both asthma and asthma-like disorders. These may be non-reversible dyspnea induced by activation of the airway receptors [60,93–95], small airways disease [96,97], airway sensory hyper-reactivity [72], dysfunctional breathing [98,99], hyperventilation [100,101], disturbances of the breathing pattern and disturbances of the chest mobility [60,102].

Symptoms

The medical history, especially the degree and frequency of symptoms, is the starting point in most diagnostic processes. In international guidelines the asthma symptoms listed are episodic breathlessness, wheeze, cough, tightness of the chest and shortness of breath [1,61]. A key question is how these symptoms are related to reversible and variable bronchial obstruction, the cardinal sign of asthma. For example, how is breathlessness related to bronchial obstruction? The literature is unclear on this point, and in fact, it seems that some asthma symptoms in the international guidelines are

not evidence-based. Factor analysis on questionnaire data in an epidemiological study showed that “episodic breathlessness”, the first mentioned asthma symptom in the Global Initiative for Asthma [1], as well as “shortness of breath” was not related to asthma (reversible bronchial obstruction) [103].

In a study by Ringsberg et al. [104] comparing one group with well-defined reversible bronchial obstruction and one group with asthma-like symptoms (no airway obstruction and no airway hyperresponsiveness), it was found that the patients described most trigger factors and symptoms in a similar way. Of 14 lower airway symptoms, five were significantly different: “difficulty in getting air”, “difficulty in taking deep breaths”, “wheezing”, “hissing” and “feeling of sore throat”. All symptoms, except wheezing and hissing, were significantly more common in the asthma-like group indicating the presence of a non-obstructive mechanism [104].

Asthma-like symptoms are common in patients with a physician-diagnosed asthma. Thomas et al. found asthma-like symptoms, called dysfunctional breathing, in 35% of women and 20% of men with a physician-diagnosed asthma [98,105]. The symptoms were assessed with the Nijmegen questionnaire, usually used for identifying individuals with hyperventilation syndrome. This study indicates that non-obstructive symptoms are common even in patients with an established asthma diagnosis. Asthma-like symptoms like cough and breathing troubles are also characteristic of airway sensory hyperreactivity (SHR), another asthma-like, non-obstructive disorder [73]. The prevalence of SHR in the general population is estimated to be about 6%, which could be compared with an asthma prevalence of about 8% in the same area [106]. In an investigation of recent-onset of airway symptoms in primary care, it was found that asthma-like non-obstructive disorders were as common as asthma (diagnosed according to internationally recognized criteria). The symptoms were also similar [107].

Theory 6: The importance of evidence-based medical knowledge is always emphasized. However, asthma symptoms in international guidelines seem not to be evidence-based, although wheeze and cough may be exceptions. Breathlessness and shortness of breath may not primarily be associated with bronchial obstruction [108].

Dyspnea

Studies of dyspnea may contribute to the understanding of asthma symptoms. Instead of symptoms, the term *dyspnea* (Greek for difficult breathing) is usually used in pulmonary, cardiovascular, neuromuscular, and other diseases related to the respiration. The current theory of dyspnea is that it arises as a result of a mismatch between incoming signals from peripheral receptors and outgoing signals from the respiratory center to the respiratory muscles (motor command) [95]. Studies of dyspnea have shown that healthy individuals as well as patients are able to distinguish different types of dyspnea. The most studied so-called descriptors are air hunger, chest tightness and sensation of work/effort [95,109,110]. The respiratory center receives projections from a variety of receptors, central and peripheral chemoreceptors, receptors in the airways, chest joints, tendons and

respiratory muscles. When propagated to the sensory area of the cortex, the mismatch is felt as dyspnea of varying type and degree. The qualitatively different types/sensations may be explained by different pathophysiological mechanisms [95]. Of special diagnostic interest is the observation that symptoms like air hunger, chest tightness and difficulty taking deep breaths may occur independent of bronchial obstruction [109,111].

Theory 7: The explanation for non-obstructive symptoms may be a stimulation of “hypersensitive” airway receptors [93,95,109]. Other mechanisms may be hyperinflation, increased work of breathing, disturbances of the breathing pattern, and reduction of the mobility of the chest [102,112].

Theory 8: Figure 1 shows a view of possible neurophysiological respiratory pathways (afferents to the right, efferents to the left) that may give rise to respiratory sensations when afferent signals become conscious in the sensory cortex. Besides obstruction in larger and smaller airways, stimulation of chemoreceptors and receptors in the upper and lower airways, chest wall and respiratory muscles may result in dyspnea or asthma-like symptoms.

Conclusion

Poor clinical control of asthma and high frequency of misdiagnosis have been revealed. Some symptoms described in the current definition of asthma may reflect mechanisms other than bronchial constriction, the main clinical criterion of asthma. Several recent studies have indicated that “classic” asthma may sometimes be confused with asthma-like disorders. Common but still unrecognized underlying mechanisms may be an explanation. In fact, these mechanisms may belong to the same clinical syndrome. The current discussion of severe asthma, steroid-resistant asthma, problematic asthma, refractory asthma and so forth is important. However, of more primary importance is the discussion of the diagnosis of asthma from a broader perspective.

The main hypothesis in this presentation is that the current diagnosis in international guidelines [1–3] is too “narrow” and that a broadening must include also non-obstructive disorders. Therefore, in addition to the term “asthma” the term “asthma syndrome” might cover this wider perspective. The exploration of new therapies will certainly require good knowledge of all mechanisms within the asthma syndrome.

Proposed actions

Detailed proposals for action are beyond the scope of this presentation. However, the following initial steps would be required.

- (1) Qualitative patient studies with analysis of the symptoms (descriptors) that patients are reporting. Those symptoms that are associated with bronchial obstruction and those that are not should be identified. Only the patient can recognize symptoms and describe them. For example, it is extremely rare that a patient complains of dyspnea, an expression “invented” by physicians. The patients use their own words. The clinicians and researchers have to “translate” these expressions into pathophysiological mechanisms.

- (2) In spirometry, for example, measuring FEV₁, the forced expiration does not just reflect a bronchial obstruction, but also the ability of muscle coordination and the power of the expiration. This method should therefore be supplemented by non-effort-demanding methods, such as impulse oscillometry [113,114], interrupter technique (Rint) [115,116] and body plethysmography [115], especially if the expiration curves are irregular and the predicted values are low. At low values bronchodilators should always be applied in order to verify a possible reversibility. The presence of a small airways disease should be considered and at normal values and concurrent asthma-like symptoms an asthma-like disorder, such as non-obstructive dyspnea or airway sensory hyperreactivity should be suspected.
- (3) In patients sensitive to irritants, such as scents and smelling agents a capsaicin inhalation test may reveal an airway sensory hyperreactivity, which is usually not associated with bronchial obstruction but with cough and other asthma-like symptoms.
- (4) Short-term treatment with corticosteroids can be useful both from a diagnostic and therapeutic point of view. However, the effect must be carefully evaluated within 1–2 months. A lack of effect may be an indication of an asthma-like disorder.
- (5) Finally, clinical testing of the above-mentioned theories is proposed.

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Declaration of interest

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