



Diagnostic challenges of adult asthma

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Purpose of review

Bronchial asthma is a common disorder that affects about 300 million people worldwide. Its signs and symptoms however, can be present in other pulmonary and/or airway diseases and therefore a careful workup of patients with respiratory symptoms that might be due to asthma is required to a) keep a broad differential diagnosis, especially in cases that do not respond well to standard antiasthmatic therapy and b) attempt to subphenotype patients within the syndrome of asthma to diagnose e.g. precipitating factors, inflammatory subtypes and comorbidities.

Recent findings

The syndrome of asthma contains a number of different phenotypes that offer the possibility of personalized medicine based on the respective asthma phenotype. There are attempts to combine asthma and COPD in newly postulated overlap syndromes which this review discourages to do but instead, based on new and old information concerning asthma phenotyping, suggests to rule in comorbidities and rule out a number of other diseases that can mimic asthma clinically.

Summary

Bronchial asthma, although one of the most common respiratory diseases, can be mimicked by a number of other pulmonary and airway diseases, and especially patients with so called severe or treatment refractory asthma should receive a detailed diagnostic workup with a rather broad differential diagnosis.

Keywords

allergic, aspergillosis, aspirin, asthma, chronic obstructive pulmonary disease, differential diagnosis, intrinsic, occupational

INTRODUCTION

Asthma is one of the most common chronic diseases and among the two most frequent pulmonary diseases in the world [1]. Typical symptoms include shortness of breath, wheezing, chest tightness, and coughing either spontaneously or in response to airway irritants such as smoke, perfume, odors temperature changes, fog, etc. or, in the case of allergic asthma in response to inhalation of specific allergens to which the individual has been sensitized [2]. Many if not most patients have perennial, persistent symptoms. However, seasonal increases in symptoms are also common. Most patients, especially if untreated, report a characteristic circadian variation of signs and symptoms with a peak of airflow compromise during the early morning hours [3]. Not all of these symptoms are necessarily present in one patient, especially in patients with either mild or longstanding disease (Table 1).

However, many other pulmonary diseases can cause similar symptoms and there is a great need not to misdiagnose other airway or lung diseases with persistent and/or partially reversible airflow obstruction as asthma. The challenge to diagnose asthma

correctly on the one hand and not to miss other diagnosis on the other has been intensified in recent years because of an increasingly permissive definition of 'asthma' in national and international guidelines. Although eosinophils and mast cells were mentioned as predominant cells in asthma in the guidelines of 1991 [4], the latest definition only emphasizes the 'excessive' variability in lung function and airflow limitation [5], which, however, is not limited to asthma but can also be seen in chronic obstructive pulmonary disease (COPD) and other pulmonary diseases. Furthermore, in unexperienced hands asthma can also be falsely

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Curr Opin Pulm Med 2016, 22:38–45

DOI:10.1097/MCP.0000000000000232

KEY POINTS

- Asthma is a frequent disorder. It can be differentiated into several phenotypes with therapeutic consequences.
- In addition, asthma can be mimicked by a number of other pulmonary and/or airway diseases and has a broader differential diagnosis than commonly anticipated.
- Careful diagnostic workup and a high level of suspicion that pathogenic mechanisms of another origin might be present if patients do not respond to usual antiasthmatic treatment should be employed, especially in so called 'complicated' or 'treatment refractory' cases.

diagnosed based on 'excessive' variability in lung function because of suboptimal cooperation during pulmonary function tests.

CLINICAL PHENOTYPES

Allergic asthma

Allergic asthma is the classic 'model' disease of asthma. Atopic sensitizations and allergies are common especially among younger patients who often suffer from concomitant upper airway diseases such as allergic rhinitis [6], rhinoconjunctivitis, or other atopic manifestations such as atopic dermatitis [7]. In this group, a positive family history for atopic sensitizations and/or atopic dermatitis, rhinitis, allergic asthma are common whereas nasal polyps or hyperplastic sinus diseases are less frequently present.

Atopic sensitization can be elucidated by careful history with an emphasis on allergen-induced symptoms. This can be confirmed using skin-prick-tests, and measurements of total and specific IgE concentrations [8]. There is controversy about the usefulness of measuring total IgE levels because of its relatively low sensitivity and specificity to demonstrate clinically relevant atopic disease [9]. Although

guidelines do not advocate its use, it can provide additional diagnostic certainty in selected cases.

Occupational asthma

It is estimated that one out of 10 patients with adult-onset asthma might in fact be suffering from asthma related to inhaled stimuli at the workplace. This is of great epidemiologic but even more individual importance as occupational asthma could on the one hand be prevented and on the other hand can bear substantial consequences on an individual's occupational career.

Although an increasing number of occupational exposures can in fact cause asthma, such as bakers' asthma, a large percentage of patients with asthma suffer a loss of asthma control or even asthma attacks at work because of exposure against non-specific stimuli that trigger bronchial obstruction because of the increased bronchial hyperresponsiveness. This form of deterioration of asthma control has been labeled work-related asthma. Asthma caused by occupational exposures might be less common. However, both work-related asthma and asthma caused by occupational exposures are underdiagnosed and place a large burden on those affected. Occupational asthma can be identified by thorough history-taking, allergen skin-prick test, and specific IgE-measurement (if available) and/or pulmonary function measurements at the workplace or specific inhaled provocation tests with the suspected agents [10].

Intrinsic asthma

In addition to atopic asthma, there is a peculiar subgroup of usually older patients with intrinsic asthma. Occasionally, they are termed 'adult-onset' or 'nonallergic' asthma but neither of these are useful. In patients with intrinsic asthma atopic, IgE-mediated, type-1-sensitizations cannot be demonstrated. Therefore, the term intrinsic asthma appears more appropriate for this subpopulation with asthma. Their total IgE levels are typically

Table 1. Signs and symptoms suggestive of asthma

Episodic wheezing and/or coughing with symptom free periods

Nocturnal/early morning increase in symptoms

Airflow obstruction with wheezing in response to nonspecific airway irritants such as odors, fog, temperature changes, smoke, perfumes, etc. because of bronchial hyperresponsiveness

Exercise induced bronchoconstriction during or after exercise

Other atopic manifestations such as atopic eczema, allergic rhinitis, etc.

Seasonal variation in symptoms (depending on the individual spectrum of sensitization)

Deterioration of symptoms during respiratory tract infections

low and there is no specific IgE present to common aeroallergens [11]. Occasionally, specific IgE-concentrations to rare allergens can be found but their clinical relevance remains highly questionable. Patients with intrinsic asthma usually have a more intense eosinophilic inflammation and require higher doses of inhaled and/or systemic glucocorticosteroids to control their inflammation [12]. Nasal polyps and chronic sinusitis with polyposis are common in this group and patients with intrinsic asthma [13] are more likely to develop aspirin sensitivity leading to aspirin-exacerbated respiratory disease (AERD; Table 2) [11,13].

Both allergic and intrinsic asthma have in common that elevated numbers of eosinophils can be found in peripheral blood, sputum, bronchial biopsies, and bronchoalveolar lavage [14]. Sputum eosinophils have been advocated as diagnostic tools since the 1950s [15] and peripheral blood eosinophils have been emphasized as biomarkers of asthma since the 1970s [16]. They are not only diagnostic for asthma but predict response to treatment and can serve as markers of a deterioration in asthma control [16]. This knowledge was maintained until 1992 when the first definition of asthma according to the Global Initiative for Asthma still suggested that eosinophils and mast cells play a role in the pathogenesis of this disease.

In addition, since then this definition has been 'watered down' with subsequent definitions to include neutrophils, macrophages, and many other

cells. The downside to this broader definition is the fact that many more diseases with a clearly distinct pathogenesis from asthma can fall under this definition which would, according to this definition, also include diseases such as COPD, hypersensitivity pneumonitis, bronchiolitis, sarcoidosis, and many other, less well-defined diseases.

Asthmatic eosinophilia can be obscured by corticosteroid treatment [16]. Thus, in cases of insufficient treatment response to inhaled and/or systemic corticosteroids despite prolonged therapy, a trial of steroid withdrawal should be performed under close supervision and is useful to demonstrate whether eosinophils reappear in peripheral blood (or sputum) or not. In cases in which steroid withdrawal is not accompanied by an increase in peripheral blood eosinophilia the certainty of the diagnosis of asthma should be challenged and alternative diagnosis investigated.

'Miscellaneous' asthma

As mentioned above, in recent years, the 'label' of asthma has become very broad and there has been a trend to discuss asthma rather as a syndrome than a disease. This has been partly because of the fact that many conditions with signs and symptoms only fairly reminiscent of asthma received an asthma 'label'. This included patients with partially reversible airflow obstruction irrespective of their inflammatory phenotype which was defined by

Table 2. Differential diagnosis between allergic and intrinsic asthma (modified after [10])

	Allergic asthma	Intrinsic asthma
Onset	Before age 30	After age 40
Family history	+	–
Other atopic manifestations	+	–
Seasonal symptoms	Based on sensitization	–
Perennial symptoms	Based on sensitization	+
Asthma attacks	+	+ / – (persistent symptoms)
Skin-prick tests	+	–
Total IgE	Elevated	Normal
Specific IgE	Detectable	–
Eosinophilia	+	++
Sputum-eosinophilia	+	++
Chronic sinusitis	–	++
Nasal/sinus polyps	–	++
Aspirin-induced asthma	Rarely	+
Response to therapy	+	(–)
Steroid-free intervals	+	–
Systemic steroids required	Occasionally	Frequently

sputum cytology as 'neutrophilic' [17] or even 'paucigranulocytic' [18]. These phenotypes have been predominantly defined by sputum analysis in small numbers of patients and have rarely been followed longitudinally. Furthermore, in some of the studies with repeated analyses the inflammatory phenotypes have not been stable [19,20]. Although any asthma with an increase in eosinophils in blood or sputum usually responds to treatment with inhaled and/or systemic corticosteroids, the response in 'noneosinophilic' asthma is considerably weaker [21], suggesting that other pathogenetic mechanisms than those characteristic for asthma might be present. Thus, in any asthma-like syndrome without eosinophilia the differential diagnosis needs to be broadened to other, nonasthmatic diseases such as those mentioned below.

This includes patients with severe asthma-like symptoms and a massive obesity which have also been defined as 'asthmatics' despite their lack of response to antiasthmatic, antiinflammatory therapy which usually does no good but causes severe side effects [22].

So-called 'cluster analyses' of patients with 'severe' asthma have also suggested different 'phenotypes' [23–25]. But 'phenotypes' are highly dependent on the population in which they are investigated and included in such analyses (if nonasthmatic patients would be included they would form a separate cluster). Other investigations in patients which had been clinically diagnosed as severe, treatment-resistant asthma found completely different diagnoses when analyzed by open lung biopsy [26]. Granulomatous diseases of different etiology, (chronic) aspiration, bronchiolitis, and inflammatory autoimmune disease can thus be mistaken for 'asthma' because of their signs and symptoms even by physicians highly experienced in diagnosing and treating asthma.

Exercise-induced bronchoconstriction/ exercise-induced asthma

Many patients with asthma, provided they can and do exercise strongly enough, suffer from exercise-induced bronchoconstriction (EIB) [27]. This usually occurs after a period of submaximal exercise for a few minutes and not immediately at the start of the exercise. EIB is not a disease entity. It can occur in any asthma, provided that the exercise is long and strenuous enough. It is therefore especially prevalent in children and less commonly reported by adults who are more likely to avoid precipitating exercises. Exercise-associated hyperventilation with respective osmotic changes in the epithelial lining fluid of the bronchi has been implicated in the

pathogenesis of EIB. Thus, EIB most likely reflects the individual degree of airway hyperresponsiveness and can therefore be used as a classic indirect challenge model. In the differential diagnosis of exercise related dyspnea the onset of EIB usually occurs a few minutes after the start of a submaximal exercise and can still increase in intensity even after stopping exercise, which is less typically the case with other forms of exercise-related dyspnea such as in congestive heart failure or COPD. Repeated exercise challenges and subsequent pauses can result in a refractory period where exercise is better tolerated [28,29]. Prophylactic long-term treatment of exercise-induced asthma includes baseline antiasthmatic treatment including inhaled corticosteroids but acute attacks can be prevented by inhaling short-acting β_2 -agonists immediately prior to exercise or using leukotriene-receptor antagonists such as montelukast, which should be taken approximately 60 min before exercise.

Aspirin-exacerbated respiratory disease

A subgroup of patients with asthma develops intolerance to nonsteroidal anti-inflammatory drugs such as acetylsalicylic acid and other substances that inhibit cyclooxygenase 1. This was formerly named 'aspirin-induced' or 'aspirin-intolerant' asthma. The molecular mechanisms underlying this intolerance are incompletely understood and cannot be attributed to a change in prostaglandin metabolism alone. Patients with AERD usually have a history of severe asthma and/or nasal/sinus-polypsis [30]. Most patients with AERD are of the intrinsic phenotype and have elevated blood and tissue eosinophilia. Diagnosis of AERD is only possible with appropriate inhaled or oral challenge tests. Careful administration of increasing doses of aspirin can lead to desactivation and restoration of the tolerance toward aspirin [30]. In addition, there is evidence that daily administration of greater than 300 mg of aspirin in such desactivated patients will lead to an improvement in nasal symptoms and an improved asthma control [31].

ASTHMA MIMICKERS

Vocal cord dysfunction syndrome

Signs and symptoms of the vocal cord dysfunction syndrome (VCD) and other dysfunctional breathing disorders can mimic asthma. They are often coexistent with bronchial asthma, which can influence diagnostic accuracy. In VCD, patients have a paradoxical, mostly inspiratory incomplete closure of the vocal cords which often occurs paroxysmally

and can mimick severe asthma attacks and precipitate high-dose antiasthmatic therapy with its respective side-effects but no therapeutic improvement. The procedure of choice is endoscopic visualization of the dysfunctional movements of the vocal cords. Treatment of the underlying disorders such as gastroesophageal reflux, postnasal drip but also speech therapy and biofeedback can improve this syndrome [32].

Viral-induced wheezing versus childhood asthma

Many children suffer from airflow obstruction and clinical symptoms similar to asthma during viral infections [33]. This can be caused by respiratory syncytial virus, adenoviruses, and others, which cause respiratory bronchiolitis that is often indistinguishable from childhood asthma. Therefore, the differential diagnosis between virus-induced wheezing and symptomatic childhood asthma can be challenging, especially in small children. Frequent episodes of virus-induced wheezing in (small) children should prompt the diagnosis of persistent asthma and a trial of antiasthmatic therapy.

Allergic bronchopulmonary aspergillosis

A subgroup of patients with allergic asthma and sensitization to *Aspergillus fumigatus* (or occasionally other fungi) develop recurrent pulmonary infiltrates, bronchiectasis, and eventually upper lobe predominant fibrotic changes, mucus plugging, and highly elevated total IgE levels. Specific IgE antibodies and precipitating IgG antibodies against *A. fumigatus* are present. In patients from western Europe, rAsp 2-specific and rAsp 4-specific IgE antibodies appear to be specific for allergic bronchopulmonary aspergillosis (ABPA). The diagnosis is made on clinical (asthma, positive skin-prick test to *A. fumigatus*, recurrent pulmonary infiltrates), radiological (bronchiectasis, mucus plugging, pulmonary infiltrates, and fibrotic changes), and laboratory (highly elevated total IgE, elevated specific IgE against *A. fumigatus* and rAsp 2, rAsp4, and rAsp6, elevated blood and sputum eosinophilia, presence of *A. fumigatus* hyphae in the sputum) parameters [34]. Any patient with asthma with any of those features should be evaluated for ABPA. Pulmonary function including gas exchange can be severely impaired in patients with ABPA. There is no specific diagnostic pattern of pulmonary function changes in ABPA, which interindividually span the whole range from basically normal to severely obstructive and restrictive lung function pattern. ABPA is underdiagnosed and in some patients it

requires years before a correct diagnosis is made. Therefore, a high level of suspicion should be maintained in patients with asthma and recurrent pulmonary infiltrates in the presence of an elevated eosinophil count.

Chronic obstructive pulmonary disease

The most frequent challenge in the differential diagnosis of obstructive airway diseases is to distinguish between asthma and COPD especially in atopic patients with a longstanding smoking history. Traditionally, COPD-caused airflow obstruction has been considered as irreversible in response to bronchodilators but this concept has recently been challenged since some patients with a physician diagnosed COPD (assuming that the diagnosis is indeed correct and no asthma patients were included) can have considerable improvements in FEV1 in response to high doses of bronchodilators.

In central and Western Europe patients with COPD usually have a longstanding smoking history of generally greater than 20 pack years and suffer from other smoking-induced comorbidities, which are different to those of asthma and include ischemic cardiovascular disease, osteoporosis, lung cancer, and others.

Asthma-COPD-overlap-syndrome

In recent years it has been recognized that there is a substantial proportion of patients with asthma who despite of this condition have a longstanding and clinically relevant smoking history. Not unexpectedly such patients who are exposed to the consequences of two different types of airway inflammation are more likely to present with symptomatic airway diseases earlier than patients with only COPD due to smoking and it has been suggested that their exacerbations might be more severe and more frequent than those in patients with COPD only [35]. These patients have traditionally been excluded from therapeutic trials in asthma and much of treatment approaches used in these patients have been based on 'logical' extensions of results obtained in trials with nonsmoking asthmatics. Recently, there has been an attempt to classify these patients with a new label, so-called Asthma-COPD-overlap-syndrome (ACOS). However, it has been correctly questioned whether a new label for these patients who are more likely to have two different underlying pathological process in their lungs and airways (and not newly composed pathologic entity) is indeed helpful [36]. Careful dissection of the relative importance of the contributing diseases asthma and COPD and

analysis of the appropriate interventions might do this co-occurrence of two pathologic processes in one patient more justice than providing a new, unnecessary label. Irrespective of these critical remarks (which would include the suggestion not to use the label ACOS), there is a need to study the therapeutic requirements and options for this particular patient population which, in general, is less responsive to conventional anti-inflammatory asthma therapy than nonsmoking asthmatics.

Sarcoidosis

Patients with pulmonary sarcoidosis can develop obstructive airway disease which does not respond to bronchodilator therapy. Although most lung function patterns are restrictive sarcoid granulomas develop along the bronchovascular bundles and can therefore impair peripheral airflow [35]. Symptoms can include cough and dyspnea [35], which can occasionally be mistaken for asthma but responds only poorly to bronchodilator treatment. Systemic corticosteroids can improve the airflow impairment but usually to a lesser degree than observed in asthma. In contrast to asthma, there is neither diurnal nor seasonal variation in symptoms and wheezing on auscultation is rare.

Hypersensitivity pneumonitis

Classically, acute exposure to high doses of antigen in patients with hypersensitivity pneumonitis causes a restrictive lung function pattern together with fever and malaise. However, patients with chronic hypersensitivity pneumonitis may report similar symptoms of cough and breathlessness on exertion together with fixed airflow obstruction [37] like patients with chronic persistent asthma. A combined restrictive/obstructive lung function pattern can be observed by spirometry and/or body plethysmography [37]. Purely obstructive changes in pulmonary function with hyperinflation and reduced expiratory flows can be characteristic features of chronic hypersensitivity pneumonitis and can be mistaken for asthma or COPD [37]. Inspiratory crackles may be present and there is no relevant bronchodilation or improvement in hyperinflation following the inhalation of bronchodilators. A detailed history about previous exposure, frequently at the workplace, may help to elucidate the relevant antigens. In chronic hypersensitivity pneumonitis, high-resolution computed tomography scans can be mistaken for bullous lung disease and/or emphysematous changes [38] such as those observed in severe COPD.

Small airway disease (bronchiolitis)

Respiratory bronchiolitis can be because of several pathogenic mechanisms and may mimic bronchial asthma. It is observed following pulmonary or bone marrow transplantation but also in patients with chronic gastroesophageal reflux and following respiratory tract infections [39].

APPROACH TO DIFFERENTIATING ASTHMA PHENOTYPES

Sputum cytology

Although sputum analysis have been advocated to identify specific asthmatic phenotypes, the scientific basis for these definitions on sputum analysis rest on studies from selected populations. In addition, there is evidence that sputum-derived inflammatory phenotypes are not stable and might change considerably over time in children and adults [20,21]. In addition, sputum cytology has been shown to be less useful to predict the response to anti-IL-5 treatment in patients with eosinophilic asthma [40] compared with peripheral blood eosinophilia. In view of the relatively complex procedures to gather and process sputum samples in patients with asthma, which is regularly performed only in a few centers internationally, its use cannot be generally recommended in the differential diagnosis of asthma. However, in general, sputum samples, if available, that show increased percentages of eosinophils are indicative of a treatment response to inhaled and/or systemic corticosteroids. Sputum neutrophilia, however, has a much broader differential diagnosis and might either reflect a concurrent pulmonary infection, indicate nonresponsiveness to glucocorticosteroids or even a disease entity distinct from bronchial asthma such as bronchiectasis [41].

Additional procedures

In patients with suspected asthma, at the first consultation a normal chest X-ray should be taken to rule out parenchymal diseases, tumors, pneumothorax, and other pulmonary and/or thoracic conditions that can mimic asthma.

Second, in any patients with a diagnosis of asthma and a reduced FEV1 who do not respond to standard antiasthmatic inhalation therapy with bronchodilators and inhaled corticosteroids additional investigations such as high-resolution CT [42] (to rule out bronchiectasis, parenchymal lesions, or parenchymal disease and or bronchiolitis, etc.) should be considered.

Eosinophils, as mentioned above, are being rediscovered as a cytologic hallmark of asthma while other markers of a TH2-signature such as periostin are being explored.

Elevated concentrations in exhaled nitric oxide (FENO) can be correlated with eosinophilic inflammation of the airways but FENO is also produced by airway epithelium and can be used as a marker of endobronchial inflammation to guide therapy [43]. Very low levels of FENO are associated with ciliary dyskinesia and may be helpful in the differential diagnosis.

CONCLUSION

Asthma is a common disease but a number of pulmonary diseases, some of which are summarized above, can display features of asthma. Clinically, there is a strong suspicion that in recent years the diagnosis of asthma has been applied frequently and indiscriminately. A high level of suspicion should be entertained when making or maintaining the diagnosis of asthma in patients without eosinophilia (in the absence of corticosteroids) or who do not respond adequately to appropriate antiasthmatic, anti-inflammatory treatment. In cases in which there is no normalization of pulmonary function (FEV1) despite such treatment, the differential diagnosis should be broadened and additional diagnostic investigations including high-resolution computed tomography, bronchoscopy with bronchoalveolar lavage, and even open lung biopsy should be considered to improve diagnostic accuracy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

J.C. Virchow has lectured for and received honoraria from: Allergopharma, ALK, Asche-Chiesi, AstraZeneca, Avontec, Bayer, Bencard, Berlin-Chemie, Bionorica, Boehringer-Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, Kyorin, Leti, MEDA, Merck/MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, Takeda, TEVA, UCB/Schwarz-Pharma, Zydus/Cadila; has participated in advisory boards for ALK, Asche-Chiesi, Avontec, Berlin-Chemie, Boehringer-Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, MSD/Merck, Mundipharma, Novartis, Revotar, Sandoz-Hexal, UCB/Schwarz-Pharma, Takeda; and has received grants from Deutsche Forschungsgemeinschaft, Land Mecklenburg-Vorpommern, GSK, MSD.

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- of special interest
- of outstanding interest

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