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PRACA POGLĄDOWA/*REVIEW PAPER*

Asthma – its symptoms, risk factors, genetic predisposition, and diagnostics

Astma oskrzelowa – objawy, czynniki ryzyka, uwarunkowania genetyczne i diagnostyka

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ABSTRACT

Bronchial asthma is one of the most important diseases of our time in terms of its medical and social consequences. The view of asthma and its treatment is changing considerably. There are several very effective drugs available, the correct administration of which can have a highly beneficial effect on the disease. Asthma is a common chronic disease that affects people of all ages. It is a condition in which the airways narrow and swell and produce extra mucus. This can make it hard to breathe. Asthma can be triggered by allergies, exercise, cold air, emotional stress, or other factors. People with asthma may have shortness of breath, chest tightness, wheezing, and coughing. Asthma can be mild, moderate, or severe. It is a serious condition that can be deadly. There is no cure for asthma, but it can be controlled with medication. This review will discuss our perception of bronchial asthma based on theoretical characteristics such as its triggers, risk factors, symptoms, diagnostic tests, and genetic predisposition. This review will discuss our perception of bronchial asthma based on theoretical characteristics such as its triggers, risk factors, symptoms, diagnostic tests, and genetic predisposition.

KEY WORDS

asthma, symptoms and triggers, diagnosis, genetic predisposition.

ADDRESS FOR CORRESPONDENCE

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INTRODUCTION

Bronchial asthma is currently one of the most common chronic diseases of the respiratory system worldwide. The gradual but rapid decline in air quality is directly correlated with the increasing number of patients with asthma. The immune and respiratory systems regress to seemingly innocuous stimuli such as pollen, animal hair, dust, dust mites, or psychological stress. Subsequently, patients develop symptoms characteristic of bronchial

asthma: shortness of breath, wheezing, chest tightness, and coughing. The disease has an impact on the patient's psychological state, where in many cases it can be the cause of depression, anxiety, or a reduction in self-control. Bronchial asthma is a lifelong disease, but under the control of medical treatment, patients can live a good quality and fulfilling life. Treatment of bronchial asthma is a lifelong process, but the prognosis is excellent. It is very important that it is diagnosed early and that the subsequent treatment is set up correctly. Also, the use of medications should be regular and accompanied by the use of relaxants and oral corticosteroids during anxiety states.

EPIDEMIOLOGY

In 2019 there were 262 million people affected by asthma and 455,000 deaths caused. Studies have shown that asthma is significantly more prevalent in women (10.40%) than in men (6.20%), in persons living below the poverty line (11.80%), and in persons who identify as an ethnic or racial minority, particularly black (10.20%) and Puerto Rican Hispanic (14.90%). Geographic prevalence also ranges widely, from 4.90% to 12.70% by state [1, 2].

SYMPTOMS

Bronchial asthma is manifested by airflow limitations through the airways that are recurrent. These episodes are accompanied by chest tightness, a feeling of shortness of breath, coughing, and wheezing [3]. The cause of this disease is airway inflammation that persists even when the patient is not experiencing difficulties. Untreated allergies or non-allergic air pollutants can often contribute to the worsening of asthma. Difficulty in breathing is caused by muscle spasm in the breathing muscles. This is followed by swelling of the lining of the airways, and the production of thick mucus in the lungs, which is another cause of difficult breathing. The narrowing of the airway lumen causes audible wheezing in the lungs during inspiration and expiration [4].

Symptoms of bronchial asthma may manifest differently in each individual. Some patients experience symptoms during strenuous activity (exercise, running, hiking, etc.). Other patients experience symptoms constantly. The most common manifestations include shortness of breath, chest tightness or pain, wheezing when exhaling (especially in children), trouble sleeping caused by shortness of breath, coughing or wheezing, and coughing or wheezing attacks that are exacerbated by a respiratory virus such as a cold or the flu [5, 6].

PATHOPHYSIOLOGY

Asthma is a condition in which the patient is exposed to environmental allergens, and acute reversible airway inflammation occurs. At the beginning of this pathological process is the inhalation of an allergen or other irritant, which, due to bronchial hypersensitivity, leads to inflammation of the respiratory system and increased mucus production [5, 6].

According to the degree of severity, bronchial asthma is divided into 4 groups: intermittent, persistent mild, persistent moderate, and persistent severe asthma (Table 1). The severity of bronchial asthma is assessed according to the intensity and frequency of daytime and night-time symptoms, the intensity and frequency of exacerbations, the frequency of rescue medication use, the degree of lung function impairment, and the limitation of any activity [7].

We define intermittent asthma as a condition where daytime symptoms occur less than once a week, nighttime symptoms are present less than once a month, forced expiratory volume in 1 s (FEV1) or peak expiratory flow (PEF) values are above 80.00% of reference values, and variability is less than 20.00%. Seasonal asthma means that symptoms appear with seasonal occurrence of allergens, otherwise symptoms are minimal or ab-

TABLE 1. Determining the form of severity of bronchial asthma (source: Edited: Khajotia)

Asthma type		Symptoms and pulmonary function		
		Daily symptoms	Nocturnal symptoms	FEV1 and PEF
Intermittent		Rare, mild exacerbations, normal lung function between episodes	≤ 2 times per month	≥ 80.00% RH variability < 20.00%
Persisting	Light	> 1 time weekly, but not daily, normal lung function between episodes	> 2 times per month	≥ 80.00% RH variability < 20.00–30.00%
	Moderate	> 1 time per week	≥ 1 time per week	60.00–80.00% RH variability > 30.00%
	Serve	Daily symptoms, frequent exacerbations, limitation of physical activity	Frequent	≤ 60.00% RH variability > 30.00%

sent. The persistent mild form occurs when symptoms occur more frequently than once a week but not daily [8], FEV1 and PEF values are above 80.00% of reference values, and variability is between 20.00 and 30.00%. In persistent moderate asthma, symptoms are more frequent than once a week. Pulmonary function tests are between 60.00% and 80.00% of reference values, and the variability is more than 30.00%. The most severe stage is the persistent severe form, where the individual's physical activity is limited by symptoms, with more severe exacerbations occurring. Lung function test values are below 60.00% of reference values, and variability is greater than 30.00% [8, 9] (Table 2).

TABLE 2. Displaying the percentage of predicted FEV (source: Edited: Krajčovičová, 2017)

Estimated FEV1	Result
Over 80.00%	Normal
79.00–70.00%	Slightly normal
69.00–60.00%	Slightly abnormal
59.00–50.00%	Moderately to severely abnormal
49.00–35.00%	Severely abnormal
Lower 35.00%	Very severely abnormal

RISK FACTORS

Gender and population affiliation are other intrinsic factors for the development of asthma. Childhood asthma is more common in boys, due to narrower airways, increased bronchomotor tone, and higher IgE levels. The difference between the sexes disappears by the age of 10 years. During puberty and adulthood, females are more susceptible [10, 11]. There are clinical indicators showing that the female population has increased symptoms of bronchial asthma from puberty onwards compared to the male population. The role of sex hormones acting in the regulation of asthma after puberty has not been elucidated. In animals, oestrogen has been shown to increase and testosterone to decrease Th2-mediated airway inflammation. Similarly, studies have confirmed that IL-17A-mediated airway inflammation is increased in females compared to males [12].

Allergens are the most important sensitizing and provoking factor in the context of asthma. Mites, animal hair, and food allergens are perennial allergens. Pollen and mould spores belong to the group of seasonal allergens. Allergens of the genus *Alternaria* and *Cladosporium* have been implicated as risk factors for asthma in several studies [13]. Treatment aimed at controlling the allergen component depends on the interpretation of sensitization and includes education about the role of allergens in the disease and advice on how to avoid allergen exposure [14].

Multiple studies have suggested that low serum vitamin D levels (< 20 ng/ml) are associated with increased exacerbations, increased airway inflammation, reduced lung function, and poor prognosis in patients with asthma [15]. Research has shown that vitamin D deficiency may play a role in the severity of symptoms. Vitamin D and vitamin D receptor activation have immunomodulatory and anti-inflammatory properties. It has been hypothesized that through this receptor, vitamin D may inhibit the effects of both innate and adaptive immune responses through its effects on dendritic cells, macrophages, and T and B lymphocytes [16]. Vitamin D may also play a role in airway remodelling through modifications on epithelial cells and alveolar macrophages and by guiding the transcription of pro-inflammatory cytokines. In research in animal models of vitamin D deficiency, airway remodelling was noted, increased eosinophilia in bronchial lavage fluid and decreased regulatory T-cell numbers were present, nuclear factor-κB (NF-κB) expression was increased, and proinflammatory cytokine levels were elevated. There is a suggestion that similar mechanisms may underlie asthma in patients with vitamin D deficiency [17].

Respiratory infections in childhood may have an inhibitory effect on the development of asthma, but in later life they clearly act as triggers. The most common triggers are rhinoviruses (HRV), respiratory syncytial virus (RSV), parainfluenza, coronavirus, adenovirus, and others. Bacterial colonization of airway surfaces plays an important role in the defence mechanism, with host factors as well as infections contributing to the development and progression of asthma [18]. Viral respiratory tract infections are associated with nearly 80.00% of asthma exacerbation episodes [18, 19].

Air pollution factors include processes with the resulting release of sulphur dioxide, carbon monoxide, a similar spectrum of pollutants enriched in particulate matter, formaldehyde, isocyanates, and others. Overweight patients are more prone to asthma in polluted air. A recent study has shown a direct correlation between a higher incidence of asthma in children than in adolescents or adults [20]. A recently meta-analysis consisting of 41 publications demonstrated the importance of increased exposure to traffic-related air pollution (TRAP), especially its components PM2.5, PM10, NO2, and black carbon, in the development of asthma [21]. These results support studies looking for a link between direct exposure of children to indoor or outdoor air pollution and the occurrence of asthma in adulthood [22, 23].

Maternal smoking during pregnancy and childhood has been shown to increase the risk of wheezing and childhood asthma. More recent studies also suggest that paternal smoking during pregnancy may affect foetal lung

development and increase the risk of asthma in offspring. One study looked at children whose parents smoked during pregnancy and found that the risk of asthma increased if one or both parents smoked [24]. To the foetus, exposure to tobacco smoke, especially nicotine, causes a reduction in maximal expiratory flow and decreases lung compliance [25]. As a result of foetal exposure to tobacco smoke, there are changes in DNA methylation, changes in gene expression, and an increased propensity for T helper 2 (Th2) pathways. They are also thought to play a role in increased susceptibility to asthma [26].

Genetic predisposition is one of the intrinsic factors. The risk of asthma increases with its presence also in the parents, being highest in the presence of both parents. A multicomponent genetic transmission is involved in the transmission, and its structure has not been precisely elucidated. Asthma is conditioned by multiple genes that interact, with some having a protective effect, while others contribute to the pathogenesis of the disease. It is likely that each gene is influenced by the environment [27, 28]. The most extensively studied asthma susceptibility gene is located on chromosome 20p13. It is a highly polymorphic gene with 14119 bps, 22 exons, and 21 introns. Several studies have confirmed the association between this gene and asthma. ADAM 33 is a member of the family of protein A disintegrin and metalloproteinase 33 (ADAM33) was the first positionally cloned asthma susceptibility gene [28, 29]. According to the research conducted, the risk of asthma in children where one parent suffers from the disease is 25.00%, while in children where both parents suffer from the disease it is 50.00%. In studies conducted in twins, it has been shown that the prevalence of occurrence in an individual is higher if he/she has a genetic relative with the disease. Which implies that the prevalence of asthma is higher in identical twins than in dizygotic twins just in terms of genetic predisposition. It is not only genetic factors but also environmental factors that influence the prevalence of asthma [30, 31]. Filaggrin is designated as a protein that is associated with intermediate filaments and aggregates keratin filaments in the epidermis, thereby helping to maintain an effective skin barrier. This gene is localized to 1q21 and is most commonly associated with the skin disease ichthyosis vulgaris. It is first synthesized as a polyprotein precursor (profilaggrin) located in keratohyalin granules. It is later processed into individual filaggrin molecules. This protein is associated not only with ichthyosis vulgaris but also with asthma and in persons who have developed atopic dermatitis. As skin barrier dysfunction increases sensitization to allergens, thus leading to allergic reactions. This in turn causes increased levels of IgE, meaning that allergens are absorbed through the skin, which can lead to the development of other diseases such as asthma or hay fever [32–34]. From the emerging results, asthma is defined as a complex genetic disorder. Several genetic and environmental factors modulate the clinical expression of the disease and its associated phenotypes. In addition to environmental exposures, genetic factors have an important influence on the onset, severity, and treatment of asthma [35].

DIAGNOSTICS

The criteria for the diagnosis of bronchial asthma are based on the patient's medical history, physical examination, pulmonary function tests, and allergy testing. The rate of asthma increases as the number of symptoms increases. Symptoms are characterised by changing intensity and time of onset, worsening late at night or early in the morning. They are usually triggered by viral infection, exposure to allergens, exertion, weather changes, or inhalant irritants (cigarette smoke, smog, strong smells and odours) [3, 36]. Symptoms of bronchial asthma can be variable, which means that the physical examination of the respiratory tract may be normal. The likelihood of a finding is increased if the patient undergoes a physical examination in an impaired state [37]. Diagnosis of asthma involves a thorough history, physical examination, and objective assessment of lung function in persons ≥ 6 years of age (spirometry before and after bronchodilator therapy is preferred) to document variable expiratory flow limitation and confirm the diagnosis. Testing and assessment of markers of airway inflammation using bronchoprovocation may also be useful in the diagnosis of the disease, particularly when objective measures of lung function are normal despite the presence of asthma symptoms [38]. In a patient with typical respiratory symptoms, objective evidence of excessive variability in expiratory airflow limitation is essential to confirm a diagnosis of asthma. The greater the variations in lung function or the more times the excessive variations are seen, the more likely the diagnosis will be asthma. Spirometry is the preferred objective measure to assess airflow limitation and excessive variability in lung function; it is recommended for all patients older than 6 years who are able to undergo lung function testing [38, 39]. A pulmonary function test measures how an individual inhales or exhales air volume as a function of time. There are various types of spirometers based on whether the built-in physiological mechanics measure lung volume or airflow changes or both [40].

This testing focuses on 3 key elements:

1) How much air the lungs are able to hold;
2) The amount of air circulating in and out of the lungs when breathing in;
3) Determination of blood gases (oxygenated blood) [41, 42].

Before the spirometer examination, the patient is advised not to eat or smoke; the examination takes 20 min or less. This test can detect the lung problem and its severity, as well as the effectiveness of treatment [41, 42].

A graphical representation of a pulmonary function test is the spirometry curve, which plots the expiratory flow rate (or expiratory flow) against the volume of air exhaled (called the flow/volume curve). Each patient has a characteristic curve that provides a simple, highly accurate, and highly predictive "future" assessment of lung function compared to the normal curve. Spirometry in the normal range means that maximal expiration has been produced with maximal effort without difficulty. In mild lung obstruction, we may notice that the curve is not in sufficient flow, which means that the patient had minor complications during expiration. In obstructed lung, we observe a decrease in lung volume at expiration and a decrease in lung flow, which means that the patient did not or could not exert sufficient effort [43]. Spirometric norms vary depending on age, body height, body weight, population, and gender. The system calculates the predicted normal value based on pre-specified values (age, body weight, and body height). After the maximum breath, the test person exhales quickly and as much as he/she can. The observed test score is compared with the predicted normal. A spirometry result is considered normal if the score is 80.00% or more of the predicted value [44].

The following parameters are evaluated during spirometry testing:

- FVC – forced vital capacity – total exhaled lung volume,
- FEV1 – exhaled volume per unit time – the volume exhaled from the total volume per second,
- FEV1/FVC – Tiffeneau index – the amount of volume exhaled from the total volume per second,
- PEF – quantity of maximum exhaled air,
- FEF 25–75 – average flow during effortful expiration – indicators of small airway constriction [41].

If spirometry is normal but symptoms and clinical history are suggestive of asthma, measuring the airway response using direct airway exposure to inhaled bronchoconstrictor stimuli (e.g. methacholine or histamine) or indirect stimuli (e.g. mannitol or exercise) can help confirm the diagnosis of asthma [45]. At present, the diagnostic tests recommended in the national asthma guidelines predominantly interpret large airway pathophysiology and do not consider the small airways. This is probably due to the easy availability and the minimally invasive nature of large airway investigations. Small airways are defined as airways without cartilage and with a diameter < 2 mm [46].

CONCLUSIONS

Asthma is a lifelong disease, but with proper medical treatment a patient can live a full life. The disease has an increasing global prevalence, not only because of allergens but also because of pollution and air pollution. There are several types of tests for the diagnosis of asthma, but a pulmonary function test together with a correct and early diagnosis of symptoms is one of the most important tests that a patient with suspected asthma should undergo.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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