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Diagnosis of Allergy and Asthma in Childhood

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Abstract Childhood asthma is a widespread health problem because of its epidemic prevalence, as asthma affects more than 300 million people worldwide. Results from cross-sectional and cohort studies show that asthma starts in childhood in a large proportion of cases. A proper diagnosis is easier to make in adults and school-age children, as permanent changes in lung development, the strong impact of environmental factors on the airways, the immunologic maturity process, and the use of some diagnostic tools make asthma more difficult to diagnose in preschool children. This period of a child's life is an interesting challenge for pediatricians and specialists. The aim of the present review is to analyze the current knowledge regarding making an early and accurate asthma diagnosis and therefore deciding on the correct treatment to gain control over asthma symptoms and minimize health risks.

Keywords Childhood asthma · Preschool wheezing · Diagnosis · Atopy · Inflammation · Lung function · Phenotypes · Tobacco exposure

Introduction

Asthma is a major global health problem, and the prevalence is increasing in most countries, especially among children [1, 2]. The Global Initiative for Asthma defines asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness (AHR) that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment" [1].

Substantial progress has been made during the past few decades in the development and implementation of national and international evidence-based asthma guidelines. On the one hand, such widespread dissemination has contributed to improved asthma management worldwide and helped identify and treat new asthmatic patients. On the other hand, it might also have led to overdiagnosis of asthma and, more specifically, may have contributed to the increased proportion of inadequately diagnosed asthma cases, particularly among children. Inevitably, misdiagnosed cases lead to overtreatment or inappropriate treatment and thus to increased risk of side effects without any pharmacologic benefit [3].

One third of all children suffer from wheezing during the first 3 years of life, and 1% to 3% of children less than 2 years of age are hospitalized for it [4••, 5]. Young children with recurrent wheezing are part of a heterogeneous group with different genotypes and phenotypes that lead to different outcomes. Genes and environmental factors such as viruses, tobacco smoke exposure, and inhaled allergens can potentially modify the phenotypes of early-childhood wheezing [6].

We have divided this review article into two major parts: 1) preschool children and 2) school-age children and teenagers, taking into consideration the above-mentioned differences.

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Diagnosing Asthma in Preschool Children

Worldwide, about 40% of all young children have at least one episode of asthmatic symptoms such as wheezing, coughing, and dyspnea, and the cumulative prevalence of wheeze is almost 50% at age 6 years [1, 2].

Although many individuals later diagnosed with asthma exhibit their first symptoms during the preschool period, diagnosing asthma in preschool children is difficult, resulting in undertreatment of asthmatic children and overtreatment of transient wheezers [7]. Asthma also manifests in preschool children; therefore, a major effort must be made to avoid delay in establishing a good asthma control plan.

Clinical Assessment

The purpose of history taking and a physical examination is to confirm that the preschool child has a wheezing disorder; to identify the pattern of symptoms, the severity of the condition, and any possible triggers; and to look for symptoms compatible with another diagnosis or associated condition. The younger the child is, the greater the possibility of an alternative diagnosis (eg, gastroesophageal reflux, cystic fibrosis, aspiration syndrome, immune deficiency, congenital heart disease, or bronchopulmonary dysplasia) (Table 1) [1].

History taking is the main diagnostic instrument in the assessment of preschool wheeze in those who are not wheezing during the consultation. Accurately identifying wheeze from the history can be difficult because the word *wheezing* is used by parents and health care workers in different ways [7].

Table 1 Differential diagnosis in wheezy children

Cystic fibrosis
Chronic lung disorder of prematurity
Neuromuscular disorder
Gastroesophageal reflux
Recurrent aspiration
Swallowing problems
Hyperventilation/panic attacks
Tracheal or laryngeal disorder
Chronic rhinosinusitis
Ciliary dyskinesia
Immune deficiency
Bronchiectasis
Tuberculosis
Inhaled foreign body
Congenital heart disease
Compression of airway

Wheeze is defined as a continuous high-pitched sound with musical quality emitting from the chest during expiration [7]. Parents differ widely in their understanding and definition of wheeze; some think it is a sound such as whistling, squeaking or gasping, whereas others define it as a different rate or style of breathing or think it is the same as cough. If it is based on parental report alone, the child could be labeled and treated as a wheezer when he or she is not [7, 8].

Rhinosinusitis with nasal obstruction can lead to a mistaken wheeze diagnosis, especially in infants. Therefore, whenever possible, wheeze should be confirmed by a health professional. Nonetheless, not all health care workers are equally accurate in estimating the severity of wheeze [9, 10]. Some clues can help to determine a correct diagnosis: 1) recurrent attacks of wheezing, especially at night or after physical activity (eg, exercise, crying, laughing) or after exposure to pollutants or airborne allergens; 2) having colds that "go to the chest" or take more than 10 days to clear up; and 3) improvement in symptoms with use of antiasthma medications [1].

Physical Examination

Because asthma symptoms are variable, the physical examination of the respiratory system may be normal. The most typical abnormal physical finding is wheezing on auscultation, a finding that confirms the presence of airflow limitation. However, wheezing may be absent or only detected when the patient exhales forcibly, and can be absent in severe asthma with severe airflow limitation [1].

The level of airway narrowing can only be estimated indirectly by assessing the work of breathing (chest retractions, nasal flaring, and use of accessory respiratory muscles) and by auscultation of the chest to assess the ratio of expiration to inspiration and the degree of wheeze [7]. The aim of further physical examination is to identify unusual or atypical features that would suggest another underlying condition and some signs of comorbidities (eg, allergic shiners, atopic dermatitis, irritated conjunctive and persistent edema of the nasal mucosa, allergic salute, and allergic crease on the bridge of the nose) [11•].

Phenotypes, Risk Factors, and Prediction of Asthma

One of the challenges of asthma diagnosis in preschool children is the absence of a gold standard diagnostic test [12]. This, added to the need to establish a successful treatment for infants who present with symptoms compatible with asthma make it necessary to identify children who are more likely to have persistent wheezing/asthma. Through the existing epidemiologic studies, it is now easier to identify different phenotypes and associated risk factors

in order to approach the diagnosis of asthma in preschool children.

Several long-term cohort studies in children with asthma symptoms who were monitored into adulthood have provided important new information about the origins of the deficits in lung function present in patients with asthma [13]. In the classic Melbourne cohort, children 7 years of age were recruited, and investigators showed that their deficits in lung function tracked from childhood to mid-adult life (42 years) [13, 14]. Similar outcomes were shown in the Dunedin birth cohort study. Unselected newborns were monitored up to age 26 years, and those individuals with persistent asthma and reduced lung function had had lower pulmonary function at 9 years of age [15]. The Tucson Children's Respiratory Study sought to determine whether the deficits in lung function during the early school years were present in newborns or acquired during the course of the disease [16]. In this study, the transient wheezers (wheezers during the first 3 years of life, but not at 6 years) showed reduced lung function prior to the first respiratory illness. Maternal smoking without a family history of asthma was commonly found in this group of children. An antenatal remodeling process has been proposed [7, 17]. The late-onset wheezers (wheezing starting after age 3 years and persisting until age 6 years) were associated with maternal asthma, male sex, and a history of allergic rhinitis. This group tended to be atopic and showed normal lung function at birth and throughout adolescence [16]. Finally, children who wheezed during the first 3 years of life and were still wheezing at age 6 years (persistent wheezers) were also at risk of continued wheezing beyond that age and up to young adult life. In these patients, lung function was lightly, but not significantly, lower at birth. It became significantly lower at age 6 years and tracked up to 16 years. They had an association with allergic sensitization and a family history of asthma [13].

The Perth birth cohort showed that children who had recent wheezing at 11 years of age had significantly reduced maximum expiratory flow rate at 1 month of age compared with those without recent wheezing [18].

In a prospective study, it was shown that some factors, such as eosinophilic inflammation (assessed in both the airways and blood), AHR, and bronchodilator response, were associated with subsequent low lung function and the development of airflow limitation in individuals with asthma and/or persistent wheezing [19].

Taken together, these results suggest that the deficit in lung function in school-age children with asthma could be in part congenital, but in a substantial proportion, it is also acquired during the course of the disease during the first years of life.

As a result of a large longitudinal cohort study (Avon Longitudinal Study of Parents and Children [ALSPAC]), six different phenotypes were described [20]. Four had a very similar pattern to those identified in the Tucson study, and two new phenotypes were proposed. The first was "prolonged early wheeze," characterized by wheezing from 6 to 54 months, with low prevalence at 69 months. This phenotype was not associated with atopy and showed increased AHR and lower lung function at 8 to 9 years. The other was "intermediate onset wheeze," which usually commences between 18 and 42 months. This later phenotype had the strongest association with atopy, decreased lung function, and AHR. The authors suggested that persistent wheezing would be the consequence of the structural airway abnormality in early-onset wheezing and atopic wheezing that develops during early childhood [20].

The European Respiratory Society Task Force has described two phenotypes using an evidence-based approach: episodic (viral wheeze) and multiple-trigger wheeze. The first phenotype is the most common in preschool children, with the child feeling well between episodes. It is associated with clinical evidence of viral respiratory tract infections (rhinovirus, respiratory syncytial virus [RSV], coronavirus, human metapneumovirus, parainfluenza, and adenovirus). The frequency and severity of the episodes are associated with the severity of the first one, atopic markers, prematurity, and exposure to tobacco smoke. The second phenotype, multiple-trigger wheeze, has exacerbations induced by virus infection but also other triggers, such as tobacco smoking and allergen exposure [7]. The clinical application of these phenotypes is not clear, as many of the phenotypes are based on retrospective questionnaires. The classification of phenotypes is likely to change significantly within a 1-year period (54.1% of children changed their phenotype) [21]. From a clinician's perspective, another wheezing classification was proposed: 1) allergic wheeze, 2) nonallergic wheeze due to structural airway narrowing, and 3) nonallergic wheeze due to increased immune response to viral infection [10]. More recently, a phenotype characterized among overweight/obese girls with early menarche was proposed. These girls start wheezing from puberty without any previous lung function reduction. The authors hypothesized that the origin could be an alteration in the regulation of the bronchial tone associated with hormonal changes [22].

The phenotypes used in epidemiologic studies can only be applied retrospectively and are of little use to the clinician. However, it is necessary to identify which children are prone to developing asthma, taking into account factors that can increase the risk of having persistent asthma symptoms later. Asthma can start at any age, particularly if it is associated with allergy sensitization, elevated IgE level, repeated viral infections, and exposure to tobacco smoke.

The role of virus infections in the inception of wheezing in children is widely recognized and may explain the link

between early-life wheezing and subsequent asthma, particularly in children who develop allergy. Long-term follow-up studies have suggested that deficits in interferon-γ responses in the first year of life predispose individuals to recurrent episodes of wheezing from preschool age through adolescence. Persistent wheezers had significantly higher serum IgE levels during the acute phase of the lower respiratory illness (LRI) as compared with the convalescence period, whereas no change in total serum IgE was observed in transient wheezers. An acute eosinophilic response was only present in transient wheezers, not in persistent wheezers. All these studies indicate the immunologic involvement in the pathogenesis of early wheezing and asthma later on [23]. Another investigation among children at high risk of asthma and allergies showed that those who had confirmed rhinovirus LRI during the first 3 years of life were up to ten times more likely to have asthma in their early school years than those who never had an LRI. In addition, children with LRI due to RSV were four times more likely to have asthma at age 6 years than those who did not have an RSV LRI [24]. Asthma at 5 years of age was four times more likely to develop in children who had wheezy illnesses due to rhinovirus or RSV in early life than in those who did not. This association was mainly observed among children who became sensitized to allergens younger than 2 years of age [25]. In a study conducted in Finland, subsequent wheezing and later asthma, including relapsing asthma in young adults, was associated with bronchiolitis with early-life wheezing. This was more common if the first wheezing episode was not caused by RSV [26].

In multivariate analyses, prenatal and postnatal exposures to passive smoking were significant independent risk factors [27]. Environmental tobacco smoke (ETS) can influence innate immunity, diminishing the production of antigen-presenting cells and cytokines, and impairing the response to Toll-like receptor ligands. Therefore, it has been postulated that ETS plays an important role in the development and outcomes of asthma [28]. Genetic variants such as 17q21 are associated with the inception of early-onset asthma, and early-life exposure to ETS has been shown to increase this risk [29].

Predicting Asthma

One tool that has been developed to identify children at high risk of ongoing asthma activity is the Asthma Predictive Index (API). The API is based on the identification of risk factors during the first 3 years of life as predictors of continued wheezing at school entry [30]. A positive API requires recurrent episodes of wheezing during the previous years in addition to one of two major criteria (physician-diagnosed eczema or parental asthma) or two of three minor criteria (physician-diagnosed allergic rhinitis, wheezing without colds, or peripheral eosinophilia [4%]). A positive API by age 3 years was associated with a 76% chance of active asthma from age 6 to 13 years, compared with a less than 5% chance of active asthma in the school years in those children with a negative API at age 3 years [31]. In a different survey, four main risk factors were identified: 1) family history of asthma, 2) recurrent chest infections in infancy, 3) absence of nasal symptoms at the age of 2 years, and 4) atopic sensitization at age 4 years. Parental smoking also was found to be an important environmental risk factor associated with persistent wheezing during childhood [32].

In the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort, it was found that male sex, post-term delivery, parental education and inhaled medication, wheezing frequency, wheeze/dyspnea apart from colds, respiratory infections, and eczema are independent factors to predict subsequent asthma. The investigators suggest a risk score based on these eight clinical parameters to predict asthma at age 7 years among early wheezers [33].

In contrast, Matricardi et al. [34] suggested that considering the great heterogeneity of mechanisms and risk factors for wheezing disorders, multiple algorithms are likely necessary to predict with enough confidence the persistence of wheezing in children with early wheezing. The prediction of asthma-like symptoms using these tools (eg, API) helps to identify those recurrent wheezing children at high risk of developing asthma later on but also to approach a diagnosis in early-onset wheezers.

Other Diagnostic Tools

During the past few years, new diagnostic tools, such as the identification of volatile organic compounds in exhaled breath, were developed to help us distinguish between asthma and transient wheezing [35].

Measuring Inflammation

Although chronic airway inflammation is the most common feature of asthma, measurement of inflammation plays a small role in the diagnosis and monitoring of asthma. Currently, the gold standard to measure airway inflammation is bronchoscopy with biopsy and/or bronchoalveolar lavage. However, this is far too invasive for routine use in children [36]. In spite of the fact that induced sputum promises to be an interesting tool [37], it is technically demanding and time consuming and not yet recommended in clinical practice [38].

Some noninvasive techniques that may be useful for the assessment of airway inflammation have been found in the analysis of exhaled breath. For instance, the nonvolatile compounds in exhaled breath condensate (EBC) and volatile

compounds such as nitric oxide (NO) and carbon monoxide in breath have been used to assess respiratory diseases [4••].

Fractional exhaled NO (FENO) can be considered a noninvasive marker of eosinophilic inflammation because FENO is elevated in children with asthma but is rarely present in nonasthmatic patients [4••]. FENO levels can be modified by height, sex (men have increased levels compared with women), upper respiratory infection (which increases its levels), and smoke (which decreases it). In addition, the presence of other allergic diseases that lead to increased FENO, particularly eczema, allergic rhinitis, and atopy, may confound the diagnosis of asthma based on FENO levels alone [35, 36, 39, 40]. However, when combined with spirometry and AHR, the specificity and sensitivity of FENO for the diagnosis of asthma were shown to be as high as 94% and 93%, respectively [39].

In addition to FENO, other gases can be measured in exhaled breath, including volatile organic compounds. Besides gases in exhaled breath, nonvolatile compounds in EBC can be measured in children [36]. In EBC, inflammatory markers, such as cytokines, chemokines, and adhesion molecules, can be measured. Increased concentrations of various markers in EBC were found in patients with asthma [35, 36].

Early Lung Function Measurements

During the past 10 years, new tools have become available to measure lung function in young children. Techniques to evaluate airway resistance, such as the interrupter technique (MicroRint; CareFusion 232 Ltd., Kent, United Kingdom), impulse oscillation, and forced oscillation, are increasingly applied in young children [36]. In contrast to the forced expiration maneuvers, these measurements are performed during tidal breathing. The measurements are possible in children 1 to 2 years of age and older. However, feasibility increases with age [36].

No studies support the usefulness of pulmonary function tests in children with nonspecific symptoms or in distinguishing between episodic and multiple-trigger wheeze. However, determination of lung function (and bronchodilator response) in preschool children can help in the identification of common wheezing disorders [7]. A useful method to confirm the diagnosis of asthma in children 5 years of age and younger is a trial of treatment with short-acting bronchodilators and inhaled glucocorticosteroids. Marked clinical improvement during the treatment, and deterioration when treatment is stopped supports the diagnosis of asthma [1, 38].

Tests of Sensitization to Allergens: Diagnosing Atopy

Blood eosinophilia can be used as part of an API, but the predictive value of this index is near 76% [7]. Total serum IgE measurements in early life are not predictive of outcome. Today, there are two common ways of demonstrating IgE antibodies used in everyday clinical care: in vivo allergen skin prick testing (SPT) and in vitro measurement of serum allergen-specific IgE (eg, using the widely available ImmunoCAP [Phadia, Uppsala, Sweden]) [41].

The allergen SPT is a safe, practical, and highly patient- and parent-acceptable way to examine allergen sensitivity in infants and children. A small amount of standardized allergen is introduced epicutaneously using a standard single- or double-tined lancette. The Phadiatop Infant test seems to be at least as useful as SPT among children younger than 2 years of age, as well as among children 2 to 4 years of age. These findings support the value of testing children with allergy-like symptoms at an early age with high sensitivity (98%) and specificity (89%) [42].

However, it is likely that in the future, genetic tests may increase the specificity and sensitivity of prediction based on clinical factors alone [43]. In addition, the diagnosis of allergy based on the adoption of microtechnology is yielding new perspectives in this area due to advances in the field of biotechnology that have led to allergic molecule availability, the routine use of protein biochips for IgE detection, and their use in combination with information technology [44••].

Diagnosing Asthma in School-Age Children and Teenagers

International guidelines advise that asthma diagnosis should be based on both the presence of symptoms and objective measurements of variable airflow obstruction [1, 3]. Asthma causes bronchial obstruction characterized by recurrent wheezing, cough, difficulty in breathing, and chest tightness, especially if patients are worse at night or in the early morning. Symptoms occur in response to exercise, exposure to pets, cold or damp air, or emotions. As in preschool children, it is important to consider the personal and family history of atopic disorders, taking into account differential diagnosis (Table 1).

Lung Function Tests

Spirometry is the recommended method to measure airflow limitation and reversibility to establish a diagnosis of asthma [1]. However, in daily practice, there are important barriers to performing lung function tests that can be encountered more frequently in primary care settings but also in secondary care settings [3]. Forced expiratory volume in 1 s (FEV_1) is generally normal in children with asthma, regardless of the severity. Because the FEV_1/

forced vital capacity ratio decreases as asthma severity increases, it is suggested that the FEV_1/forced vital capacity ratio may be a more sensitive measurement of impairment in children [31]. An FEV_1 reversibility of at least 12% (and >200 mL) from the prebronchodilator value suggests asthma [1].

Peak expiratory flow (PEF) measurements are made using a peak flow meter and can be an important aid in diagnosing asthma. PEF measurements should be compared to the patient's personal best measurement. Although spirometry is the preferred method of documenting airflow limitation, a 20% or greater increase in the PEF after the inhalation of a bronchodilator, and/or a diurnal variation of 20% or greater suggest a diagnosis of asthma [1].

Measurement of Airway Responsiveness

In children with an intermediate probability of asthma who can perform spirometry and have no evidence of airway obstruction, consider testing for atopic status, bronchodilator reversibility, and (if possible) AHR measurement using methacholine or exercise [38].

The methacholine or exercise challenge test sensitivity is very high; however, its specificity is lower. AHR can also be present in other conditions (eg, allergic rhinitis, eczema, cigarette smoking, cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease) [1, 3]. Indeed, AHR may not always be present in asthmatic patients [3]. Symptoms and lung function may change rapidly from day to day or even hour to hour (eg, with allergen exposure) and can respond rapidly to initiation of treatment, whereas AHR tends to change relatively slowly with treatment [45]. For most patients with a previous physician diagnosis of asthma, only pre- and postbronchodilator spirometry and a test to measure AHR are required to confirm asthma [46, 47].

Conclusions

In primary care, in which most asthma patients are managed, the diagnosis of asthma is mainly symptom based. In this setting, the assessment of AHR and airway inflammation is not easy; therefore, these domains of asthma are not assessed. Lung function and SPT are not measured as recommended in guidelines. Diagnosing asthma in infants and preschool children remains a challenge despite the new tools available. Clinical approach, predicting tests (eg, API), and a trial of bronchodilators or glucocorticosteroids are still helpful. In the future, research following epidemiologic studies, which tend to present a more accurate phenotypic approach, and the development of newer noninvasive diagnostic tools might be the key to opening a new avenue to early diagnosis and treatment.

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- • Of importance
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