Diagnosis of asthma

Recommendations regarding the diagnosis or assessment of asthma severity in older children have not changed from previous publications. However, the diagnosis of asthma in the preschool child was a major focus of the current discussions.

Recommendations

1. Physicians must obtain an appropriate patient and family history to assist them in recognizing the heterogeneity of wheezing phenotypes in preschool-aged children (level III).
2. In children who are unresponsive to asthma therapy, physicians must exclude other pathology that might suggest an alternative diagnosis (level IV).
3. The presence of atopy should be determined because it is a predictor of persistent asthma (level III).

Literature review

Literature from January 2000 to 30 June 2003 was reviewed. No systematic reviews of this topic were available. Studies of asthma diagnosis in preschool children were retrieved from a MEDLINE search. Literature arising from these studies was also reviewed.

Table 1: Differential diagnosis of wheezing in preschool children[5]

- Asthma
- Congenital anomalies, e.g., vascular rings
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Gastroesophageal reflux
- Aspiration
- Foreign body aspiration
- Heart failure
- Sinusitis
- Bronchiolitis
- Pertussis
- Tuberculosis
- Immune system disorders

Table 2: Clinical index for the diagnosis of asthma[6]

Stringent index: 3 or more episodes of wheeze during the first 3 years of life with either one of the major risk factors; **parental history of asthma or eczema**, or 2 of 3 minor risk factors; **eosinophilia, wheezing without colds, allergic rhinitis**

Loose index: any wheezing during the first 3 years of life plus 1 major or 2 minor risk factors

Current evidence

Wheezing in preschool children is very common.[1,2] Most wheezing episodes are associated with viral respiratory illness, with respiratory syncitial virus predominating in children <2 years of age and rhinovirus in older preschool children.[3,4] Many other conditions are also associated with wheezing in young children (Table 1).[5]

Preschool wheezing can be divided into 3 categories: transient early onset wheezing, which is often outgrown in the first 3 years; persistent early onset wheezing, which occurs before age 3 and persists in school age; and late-onset asthma, which is less likely to be outgrown. Overall, 50%–60% of preschool children with wheezing outgrow the problem. For practical purposes, asthma in preschool children can be divided into non-atopic, which is likely to be outgrown, and atopic asthma, which is likely to persist. Predicting which wheezing preschool children are likely to have persisting asthma can be achieved using the "clinical index" developed by Castro-Rodriguez and coworkers[6] (Table 2).

Because atopic asthma is more likely to persist, physicians must obtain an appropriate history of personal allergic symptoms in the preschool child and any history of allergy in the immediate family. This will allow recognition of the presence, or the risk, of allergy developing in the preschool child with wheezing. Evidence for atopic dermatitis should be sought during physical examination. Atopy can be distinguished by skin-prick testing, measurement of specific IgE antibodies and, possibly, measurement of peripheral eosinophil counts.

Asthma is defined as a disorder of airway inflammation producing paroxysmal or persistent symptoms associated with variable airflow limitation and airway hyperresponsiveness.[7] However, objective measures are not routinely available in preschool children, contributing to the difficulty of making a diagnosis of asthma.

Wheezing phenotypes

Martinez and coworkers[8] investigated the factors affecting wheezing in children <3 years of age and their relation to wheezing in children 6 years of age. They studied 1246 newborns in the Tucson, Arizona, area and obtained follow-up data at both 3 and 6 years of age for 826 children. At the age of 6 years, 425 children (51.5%) had never wheezed; 164 (19.9%) had had at least 1 lower respiratory illness with wheezing during the first 3 years of life, but no current wheezing; 124 (15.0%) had no wheezing before 3 years but had wheezing by 6 years; and 113 (13.7%) had wheezing both before 3 years of age and at 6 years.

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Children who wheezed before age 3 years but not by age 6 had diminished airway function and were more likely to have mothers who smoked, but were less likely to have mothers with asthma, elevated serum IgE levels or skin-test reactivity.[8]

Children who started wheezing in early life and continued to wheeze at the age of 6 years were more likely than children who never wheezed to have mothers with a history of asthma, to have elevated serum IgE levels and normal lung function in the first year of life, and to have elevated serum IgE levels at age 6 years. At age 6, 60% of these children were skin-test positive for at least 1 local aeroallergen.[8]

The authors concluded that many infants with wheezing had a transient condition associated with diminished airway function at birth and were not at increased risk for asthma or allergies later in life. However, in a substantial minority of infants, wheezing was related to a predisposition to asthma.[8] The Tucson group subsequently reported 3 wheezing phenotypes in childhood: "transient early wheezing" limited to the first 3 years of life and unrelated to increased airway lability; "non-atopic wheezing" at the toddler stage and during the early school years, associated with positive peak flow variability but not with methacholine hyperresponsiveness; and "IgE-associated wheeze/asthma" associated with persistent wheezing at any age and with methacholine hyperresponsiveness, peak flow variability and markers of atopy.[9] In a related study, they proposed a clinical index to assist with the prediction of persistent asthma in young children with recurrent wheezing (Table 2).

Children with a positive loose index were 2.6–5.5 times more likely to have active asthma between the ages of 6 and 13 years than children with a negative loose index, and the relative risk for asthma increased from 4.3 (95% confidence interval [CI] 2.4–7.8) to 9.8 (95% CI 5.6–17.2) times when a stringent index was used. Over 95% of children with a negative stringent index never had active asthma between 6 and 13 years of age. Thus, the specificity of the stringent clinical index was consistently high in terms of diagnosing asthma (96.3% at age 5 years [95% CI 95.1%–96.5%]), but the sensitivity for ruling out asthma was low (only 27.5% [95% CI 24.6%–30.4%]).[6]

Rusconi and colleagues[10] enrolled 16 333 children, 6–7 years old, in a population-based study to examine the risk factors associated with the wheezing groups described above. Having siblings and attending a daycare centre were both risk factors for transient early wheezing (odds ratio [OR] 1.41, 95% CI 1.21–1.64 and OR 1.70, 95% CI 1.48–1.86, respectively). They were also protective factors against late-onset wheezing (siblings OR 0.83, 95% CI 0.70–0.97 and daycare OR 0.72, 95% CI 0.59–0.88). There was a stronger positive association between personal history of eczema or allergic rhinitis and persistent or late-onset wheezing than for transient early wheezing.

Sporik and associates[11] studied a group of 67 babies at risk of developing allergic disorders. At 11 years of age, the group was restudied, symptoms were assessed by questionnaire and bronchial hyperresponsiveness (BHR) to histamine was measured. Prevalence of allergy and hay fever increased with age and that of eczema declined, whereas wheeze showed a bimodal distribution with a peak before the age of 2 years and a gradual increase thereafter. Of the 21 children who wheezed before their second birthday, most never wheezed again and did not have BHR at 11 years. Of the 21 children whose first wheezing occurred after 2 years of age, 17 were still wheezing at 11 years and 12 of the 17 had increased BHR. Ten of 21 children who wheezed before 2 years of age were allergic or became allergic, compared with 20 of the 23 children who wheezed at 11 years.[11] These findings suggest that childhood asthma is a heterogeneous condition with allergy strongly associated with the persistence of wheeze.

In the same patients followed to age 22, annual prevalence of wheeze and atopy increased with age.[12] Twenty-five percent of adults showed both wheeze and BHR (asthma). Remission of wheeze was common in children during the first 5 years of life and likely if wheezing occurred on fewer than 2 occasions, but wheeze at 11 years was likely to persist. Sixty percent of the adults with asthma had developed sensitivity to common allergens by the age of 2 years and were showing BHR by mid-childhood. Sensitization to dietary allergens occurred in infancy and waned after early childhood, but predicted early sensitization to inhaled allergens. At 22 years, 43 (72%) of the 60 patients were atopic. The children who showed sensitivity to ingestants (egg or milk) when younger than 2 years were more likely to develop aeroallergen sensitivity.[12] Positive skin-test reactions to egg or milk tended to be transient, whereas those to airborne allergens tended to be permanent. In this group, adults with asthma began wheezing at any age but tended to become sensitized early and have abnormal airway characteristics by the age of 11 years.

An Australian group[13] studied the role of allergy in the natural history of wheeze and BHR in childhood. They followed 46 children of allergic parents from birth and documented the development of allergic disease. Thirty-three children (70%) wheezed at some time during their first 10 years of life, with 13 starting in infancy. Twenty-two children (47%) were wheezing at 10 years of age. Wheeze in infancy was a poor predictor of wheeze at age 10, whereas wheeze starting after infancy was a good predictor. In contrast, both allergy in infancy and current allergy were strong predictors of current wheeze. These observations confirm the importance of allergy in predicting outcomes in children with asthma and suggest that wheezing in infancy and wheezing in later childhood may have different pathogenetic mechanisms. Allergy in infancy predicted the severity of BHR in later childhood indicating the importance of allergy in preceding both the occurrence and the severity of BHR.[14] Subjects most likely to develop more severe BHR during later childhood were children who manifested allergy in infancy.[14]

In a cohort study of children from birth to age 7 years (German Multicentre Allergy Study), Lau and coworkers[15] showed that children sensitized to any allergen early in life

and sensitized to inhaled allergens by age 7 years were 10 times more likely to be asthmatic than non-sensitized children (OR 10.1, 95% CI 3.81–26.88).

Pulmonary function testing

In children under 3 years of age, lung function testing is unavailable for clinical use.[16–21] The diagnosis of asthma in children under 3 years of age depends on history and, if they are seen during an acute episode of wheezing, physical examination. Children under 5 or 6 years of age have difficulty performing reproducible pulmonary function tests. Despite extensive efforts to standardize such tests in preschool-aged children,[16–21] the best approach is not well-established. Conventional pulmonary function tests in most centres are impractical before 6 years of age.

Methods being investigated include: airway resistance as measured by body plethysmography, oscillation or interrupter techniques,[22–27] transcutaneous fall in oxygen tension[28] or even plain auscultation.[29] These techniques have been used successfully in children over 2 years of age to evaluate airway obstruction and response to airway challenges (histamine, methacholine or cold air). Forced oscillation has been used as an objective measurement against which to establish a clinical score of airway obstruction and response to bronchodilators in children as young as 3 years of age.[23,30] It has also been used and compared favourably to spirometry in young children.[31] Overall, these methods hold some promise, but researchers report poor reproducibility or sensitivity[32,33] and these techniques are not currently recommended for routine use.

Bronchodilator response

Response to bronchodilators can be used to help confirm the diagnosis of asthma[7,34] Response to bronchodilators in children under 2 years of age can be difficult to determine and an extensive review of the literature[35] did not result in any firm conclusion regarding the clinical benefits of inhaled β-agonists in these children. Contradictory evidence emerges from studies of single[36] or multiple doses[37–40] assessing clinical scores, oxygenation and respiratory rates, both in outpatients and inpatients. The contradictory data raise questions as to the usefulness of bronchodilator response as a criterion for diagnosing asthma in young children. We cannot recommend this as a confirmatory test for asthma in young children. In older children, whose technique is reproducible (by age 6–7, FEV_1 is generally reproducible within ±5%), an increase in FEV_1 of 12% is consistent with a diagnosis of asthma as it is in older children and adults.

Bronchial hyperresponsiveness

The association between asthma and BHR (also known as airway hyperresponsiveness [AHR]) is well recognized and is included in the definition of asthma.[4,41] Yet, in children, the relation between BHR and symptoms is not as clear as it is in adults.[42–44]

Hyperresponsiveness of the airways can be seen in young infants even in the absence of any wheezy illnesses.[45–49] A family history of asthma and in utero exposure to tobacco smoke are identifiable risk factors for BHR,[50] thus emphasizing the role of genetic and environmental factors.[51] Infants with a family history of asthma had a PC_{20} of 0.78 g/L (95% CI 0.44–1.15) and those whose parents smoked had a PC_{20} of 0.52 g/L (95% CI 0.43–5.40) compared with those with neither risk factor, who had a PC_{20} of 2.75 g/L (95% CI 1.48–1.00). BHR tends to decrease over time.[52,53] Other factors, especially viral infection, may influence development or persistence of BHR.[54]

Recent studies have looked at the evolution of BHR over time. Palmer and coworkers[55] followed a group of 95 western Australian infants recruited at birth and reassessed at 6 years of age. Although BHR at 1 month and at 6 years were independently related to asthma or asthma-associated factors there was no relation between BHR at 1 month and at 6 years old. As the authors speculated, it is likely that the factors underlying BHR at these ages are different, because of the expected changes in immune response and lung and airway geometry over time. Delacourt and colleagues[56] followed a group of 129 infants under 2 years of age with recurrent wheezing over a 4-year period with repeated methacholine challenges. At the beginning of the study, no correlation was found between the degree of BHR and the intensity of symptoms. Furthermore, the initial level of bronchial responsiveness was not predictive of subsequent persistence of asthma. Although patients with a higher degree of BHR were more likely to have persistent wheezing 4 years later, no early predictive cut-off values could be identified. At 3–4 years of age, a PD_{15} (provocative dose [of methacholine] causing a 15% fall in transcutaneous pO_2) less than 200 μg had a sensitivity of 69% and specificity of 59% for persistent wheezing. Finally, they also found that a low VmaxFRC value was associated with a higher risk of persistent wheezing 4 years later, but the overlap of VmaxFRC values between subgroups of infants with different clinical progressions rendered this variable useless in clinical practice as a predictor of persistent wheezing and asthma for a given infant.

Other investigators tried to relate BHR in young children with atopy. Atopy is a known factor for high risk of persistent airway symptoms and asthma. However, in preschoolers, there seems to be no association between the degree of BHR and indirect assessment of atopy as indicated by measurement of eosinophil cationic protein (ECP) or IgE.[57,58]

Overall, in children under 3 years of age, lung function testing techniques using response to bronchodilator, airway challenges or both have not yet allowed physicians to differentiate between normal children and those at risk of persistent symptoms of long-lasting asthma.

Airway inflammation

Bronchoalveolar lavage of children with atopic asthma

and virus-associated wheeze showed different patterns of inflammation: total cell counts were increased in both groups, but atopic children showed elevated eosinophils and mast cells while neutrophils dominated the pattern in non-atopic children.[59,60] Increase in the neutrophils was also demonstrated in children <3 years with recurrent wheezing who failed to respond to steroids.[61] In children <18 months of age unresponsive to bronchodilators, neutrophil dominance was associated with infections or dysphagia or association aspiration.[62] Finally, in a group of mostly atopic persistent wheezers (mean age 14.9 months) showing clinical benefit from bronchodilators and steroids, suggesting asthma, no difference in cell types was found compared with a control group.[63] Overall, studies in young children demonstrate that we cannot extrapolate data from adult studies to understand the basic mechanisms of asthma in children.

Zimmerman and associates[64] examined preschool children (median age 18 months) and found that non-atopic children who wheezed had lower levels of eosinophils and ECP (a measure of activated eosinophils) in their peripheral blood than atopic children with asthma. Serum ECP has been useful in predicting the onset of asthma in infants.[65,66]

Noninvasive methods of airway inflammation evaluation, such as induced sputum, exhaled gas analysis or exhaled breath condensates, have been described in adults and would be useful in children. Although recommendations for standardization of measurement of fraction of exhaled nitric oxide have been published,[67] there is still controversy over the validity of these measurements in infants.[68] Upper airway levels of nitric oxide overwhelm the much smaller amounts from the lower airways. Overcoming this problem requires end-tidal sampling with a cooperative patient, which is not always possible with younger children. Breath condensate analysis represents an attractive alternative because condensate is flow independent and can be obtained with simple technology. Markers of inflammation, such as cytokines, can be measured in breath condensate, but further work is required to establish standards in children.

In young children, documentation of airway inflammation depends on invasive procedures that in most circumstances cannot be justified ethically. Understanding the cellular and molecular events that trigger and maintain asthma has been based in part on studies of specimens obtained from asthmatic airways. Few such studies have included bronchial biopsies in young children, and those that do have been reported in abstract form only or in non-English literature. Although bronchoscopy, bronchial biopsies and bronchoalveolar lavage are routinely performed in asthma research involving adult volunteers, their use in children is still regarded as invasive and can only be justified for research or management of the patient.[69]

Implications for research

1. Research should be promoted to develop non-invasive, clinically useful, reproducible measures of pulmonary function and airway hyperreactivity in preschool children including symptomatic children.
2. Further research should be done to define the nature of inflammation in the airways of preschool children with viral induced, non-atopic and atopic wheezing.
3. Further research should be done to develop non-invasive, clinically useful methods for assessing inflammation in the airways of preschool children.
4. Long-term studies should be done to follow the course of wheezing in preschool children to confirm that children can outgrow wheezing without lasting changes in their airways.
5. Studies should be done to determine when and if, airway remodeling occurs in preschool children with wheezing.
6. Studies should be done to assess which (if any) form of treatment (pharmacologic or other) is most likely to modify the evolution of asthma in preschool-age children.

Implementation strategies

1. The dissemination of the guidelines on diagnosis of wheezing in preschool children should be achieved through the development of a series of case studies suitable for family physicians, specialists, health care professionals and parents.
2. These can be presented in interactive small group sessions with a facilitator or more broadly by the development of scripted interactive techniques that can be disseminated through the Internet.
3. National organizations (government agencies, pharmaceutical industries, non-profit organizations) can also participate in the dissemination of simple documents, such as cards and pamphlets, emphasizing the major recommendations of these guidelines.

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