



Diagnostic challenges of childhood asthma

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Purpose of review

Diagnosis of asthma in childhood is challenging. Both underdiagnosis and overdiagnosis of asthma are important issues. The present review gives information about challenging factors for an accurate diagnosis of childhood asthma.

Recent findings

Although underdiagnosis of asthma in childhood has always been the most important diagnostic problem, overdiagnosis of asthma has also been increasingly recognized. This is probably due to diagnosis of asthma based on symptoms and signs alone. Demonstration of variable airflow obstruction by lung function tests is the most common asthma diagnostic tests used in practice and is therefore strongly recommended in children who can cooperate. Recently, an asthma guideline combining the clinical and economic evidences with sensitivity and specificity of diagnostic procedures was developed to improve accuracy of diagnosis and to avoid overdiagnosis. This guideline provided an algorithmic clinical and cost-effective approach and included fractional exhaled nitric oxide measurement as one of the diagnostic tests in addition to lung function.

Summary

Diagnosis of asthma in children should be made by combining relevant history with at least two confirmatory diagnostic tests whenever possible. Diagnosis based on short-period treatment trials should be limited to young children who are unable to cooperate with these tests.

Keywords

asthma, childhood, diagnosis, exhaled nitric oxide, lung function tests

INTRODUCTION

Although asthma is the most common chronic respiratory disorder in children, its diagnosis is a challenging work for many reasons [1^{*},2,3,4^{*}]. Both underdiagnosis and overdiagnosis of childhood asthma are common. Although underdiagnosis of asthma in children is well known and was previously documented both in epidemiological [5] and clinical studies [6], data on the extent of over diagnosis are new [7]. Asthma guidelines are the main references that physicians can depend on for both diagnosis and management [8–10,11^{**}]. A recent asthma guideline developed by the National Institute for Health and Care Excellence (NICE) provided data not only based on clinical but also on economic evidence of diagnostic procedures as well as their sensitivity and specificity [11^{**}]. Signs, symptoms, symptoms after specific triggers such as exercise or drugs, history of atopic disorders and laboratory tests for diagnosis of asthma were evaluated in this context and were proposed in an algorithmic approach. Furthermore, NICE guideline aimed to prevent overdiagnosis and to increase the accuracy of diagnosis in a cost-effective way. The present

review will describe different challenges in the diagnosis of childhood asthma referring to the evidence provided by the guidelines to overcome these issues.

Challenges of diagnosing asthma in children may be related to many factors involving the evaluation of medical history, physical examination, confirmatory laboratory tests, and treatment trials.

MEDICAL HISTORY

Classic asthma symptoms such as cough, wheezing, and breathlessness are common to many respiratory conditions in childhood. The most common reason of these symptoms is viral respiratory infections, which may account for more than 10 episodes a

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KEY POINTS

- Both underdiagnosis and overdiagnosis are important challenges in children.
- Recurrent variable respiratory symptoms without confirmatory diagnostic tests may lead to overdiagnosis of asthma.
- There is no single diagnostic test that has high sensitivity and specificity to confirm asthma diagnosis in children.
- Careful assessment of a treatment trial with a low-dose inhaled corticosteroid for a short period (6–12 weeks) and follow-up after treatment is stopped is the only way to diagnose asthma in young children until they can perform diagnostic lung function tests.
- The most important diagnostic challenge of asthma in children is the absence of standardization in diagnosis even between evidence-based asthma guidelines.

year especially in preschool children. Although most symptoms gradually decrease within 2 weeks, it is not uncommon that they last longer especially in nurseries during autumn and winter months because of increased frequency of viral infections, and in some situations when comorbid conditions such as adenoid vegetation and exposure to passive smoking at home are prevalent [12]. Therefore, the first diagnostic challenge is awareness of the frequency and duration of respiratory symptoms caused by common respiratory infections that may mimic asthma [1[¶]].

The second diagnostic challenge when taking history is to ask about respiratory symptoms that point to an alternative diagnosis other than asthma (Table 1) [1[¶],8–10]. Several infectious, inflammatory, immunologic, metabolic, neurologic, cardiac diseases which directly or indirectly affect the respiratory system, perinatal problems, or congenital anomalies may present with similar respiratory symptoms.

The third diagnostic challenge in history is the presence of a single bothersome respiratory symptom. Asthma generally presents with more than a single respiratory symptom with varying combinations of dry cough, wheezing, and breathlessness. Isolated recurrent cough both in the community [13,14] and referral centers [15,16] is rarely because of asthma in children. Similarly, isolated dyspnea without cough or wheezing especially in adolescents may be related with physical deconditioning in almost half of the cases [17].

The fourth diagnostic challenge in history is whether the child truly wheezes or not. Wheezing is mostly reported as noisy breathing and some languages have no word corresponding to wheezing.

Table 1. Symptoms and items in history suggestive of alternative diagnosis other than asthma [1[¶],8–10]

Onset in the newborn period
Perinatal lung problem
Chronic productive cough
Family history of chronic supportive chest disease
Persistent symptoms without any asymptomatic periods
Recurrent or severe infections involving different systems
Sudden onset of symptoms without a viral prodrome
Prominent upper respiratory symptoms such as rhinorrhea, sinusitis and snoring
Excessive vomiting
Feeding/swallowing difficulties
Persistent diarrhea

Parental report of wheezing is not always a reliable one [18]. Video questionnaires may help recognition of parents about what they mean by noisy breathing [19] and it is best if wheezing was heard by the examining physician. In the absence of all these, it is better to ask the family to record the noise on a mobile phone or invite the patient and the family to the clinic when the child is symptomatic.

A clinician has to be familiar with respiratory symptoms that increase the probability of an asthma diagnosis. Asthma symptoms worsen during night and early in the morning. They are triggered or worsened mostly with upper respiratory infections, passive and active smoking, exposure to sensitized aeroallergens and pets, exercise, and cold air [8–10]. Although every asthma guideline points to these features that increase the probability of asthma diagnosis, only NICE guideline investigated their accuracy compared to a gold standard of doctor-diagnosed asthma and a positive confirmatory diagnostic test in children at least 5 years old and to a doctor diagnosis of asthma in young children less than 5 years old [11^{¶¶}].

NICE guideline recommends checking specifically for cough, wheeze, and breathlessness and any variations in these symptoms over the course of 24 h or seasonally [11^{¶¶}]. In this guideline, sensitivities and specificities of majority of individual symptoms to diagnose asthma in patients presenting with respiratory symptoms and signs under investigation of asthma were reported moderate to low in adults and young people more than 16 years old. They found no diagnostic study performed in children 5–16 years old and only one study in children under 5 years old to analyse the sensitivity and specificity of symptoms compared to standard reference of doctor diagnosis plus a diagnostic objective test. One study used a combined symptom score with a

moderate sensitivity but low specificity for asthma diagnosis [20]. The guideline concluded that use of symptoms alone without an objective test to diagnose asthma is not recommended to avoid inappropriate overtreatment, waste of resources and lack of a correct diagnosis [11[¶]].

NICE guideline found no study investigating the diagnostic accuracy of symptoms triggered upon exercise for asthma in children, therefore, did not recommend to use an isolated clinical history of symptoms after exercise to diagnose asthma [11[¶]].

Personal or family history of atopic disorders is important in assessing asthma diagnosis. Although the presence of these atopic disorders was accepted major or minor criteria in asthma predictive index, the sensitivity of diagnosing asthma using a personal or family history of atopic disorders alone was also shown to be low for children 5–16 years old in NICE guideline [11[¶]]. The guideline development group stated that these features may help in identification of atopic asthma but may miss non-atopic asthma; therefore, history of atopic disorders alone should not be used to diagnose asthma.

PHYSICAL EXAMINATION

Physical examination of children may not be significant except during exacerbations of asthma and therefore a normal physical examination does not rule out asthma. However, absence of true polyphonic wheeze in every symptomatic period in a child with suspected asthma may point to other diagnosis. Physical examination is important to detect signs of alternative diagnosis (Table 2) [1[¶],8–10].

LABORATORY TESTS

Among many laboratory tests readily available in most of referral centers, few are recommended to use for the diagnosis of asthma.

Physiologic tests

Spirometry is the first recommended confirmatory test to use in diagnosing asthma in children [8–10]. Although spirometric measurement is a routine practice in many centers for asthma diagnosis, it may not be feasible in many primary care centers. In addition, very few preschool children can perform a valid and reproducible spirometry and therefore its use at this young age group for diagnosis of asthma is not recommended by any guidelines [8–10,11[¶]]. Although there are other lung function tests which can be performed during normal breathing in preschool children, they are only available in research

Table 2. Physical findings suggesting alternative diagnosis other than asthma [1[¶],8–10]

Syndromic appearance
Upper airway disease: adenoid face, tonsillar hypertrophy rhinitis
Systemic signs: growth failure, weight loss, clubbing
Absence of polyphonic wheeze in any symptomatic period
Localized or persistent sounds or monophonic wheeze on auscultation
Palpable secretions on chest palpations during coughing
Stridor
Unusually severe chest deformity
Cardiac murmur
Cleft lip/palate
Hypotonia, mental/motor retardation
Prominent dizziness, light-headedness, peripheral tingling

centers and do not have yet the capacity to differentiate between the health and disease state [21].

Spirometry as a diagnostic test may prevent overdiagnosis or mis-diagnosis of asthma. In a retrospective study of four academic primary care centers in the Netherlands, more than 650 children aged 6–18 years old who were diagnosed either as asthma or were being treated as asthma by their general practitioners were analysed whether they have real asthma confirmed by spirometry [7]. The study demonstrated that asthma was confirmed by spirometry in only 16.1% of them; in 23.2% although asthma was likely, no confirmatory spirometry was done and in more than half of the children asthma was unlikely by clinical assessment. Not only numeric indices but also the shape of flow volume loop may suggest alternative diagnosis [22] but no study investigated the diagnostic accuracy of flow volume loops for asthma in children [11[¶]].

There are differences between the guidelines with respect to the recommendations to use spirometry and peak expiratory flow (PEF) measurements, definition of expiratory airflow obstruction and PEF variability in lung functions for diagnosis of asthma in children [8–10,11[¶]] (Table 3). In the Global Initiative of Asthma (GINA), normal forced expiratory volume in one second to forced vital capacity (FEV₁/FVC) ratio in children is given as more than 90% which means that values lower than 90% may be taken as intrathoracic obstruction. On the other hand, the cut-off value for intrathoracic obstruction is given as a FEV₁/FVC value of less than 70% in NICE guideline in order to decrease false positive results. The guideline development group of NICE found no study in children comparing FEV₁/FVC ratio less than 70% to doctor diagnosis of asthma but only one study comparing FEV₁ less

Table 3. Differences between asthma guidelines with respect to recommendations of spirometry and PEF measurement as diagnostic tests for asthma in children [8–10,11^{***}]**Recommendation: spirometry**

GINA, NAEPP EPR-3, NICE: all children >5 years old under investigation for asthma

BTS/SIGN: children >5 years old with an intermediate probability of asthma

Definition of expiratory obstructive spirometryGINA: reduced FEV₁/FVC ratio when FEV₁ is low (normal FEV₁/FVC ratio is given as >90% in children)NAEPP EPR-3: reduction in the values for both the FEV₁ and the FEV₁/FVC relative to reference or predicted values

BTS/SGN: not given

NICE: FEV₁/FVC ratio less than 70%**Recommendation: bronchodilator reversibility**

GINA, NAEPP EPR-3: at the initial assessment with pre bronchodilator test

BTS/SIGN: for children with intermediate probability of asthma with obstructive spirometry and as an additional test with atopic status and bronchial hyperresponsiveness in those with normal spirometry

NICE: only for children who have obstructive spirometry

Definition of bronchodilator reversibilityGINA: increase in FEV₁ of >12% predictedNAEPP EPR-3: either an increase in FEV₁ of ≥12% from baseline or by an increase ≥10% of predicted FEV₁ after inhalation of a short-acting bronchodilator

BTS/SIGN: not given

NICE: an improvement in FEV₁ of ≥12%**Recommendation: PEF variability**

GINA: PEF variability is recommended one of the tests to document excessive variability in lung functions

NAEPP EPR-3: not recommended when spirometry is available

BTS/SIGN: not mentioned

NICE: if there is diagnostic uncertainty after initial assessment (normal spirometry and FeNO <35 ppb or obstructive spirometry, no bronchodilator reversibility and FeNO ≥35 ppb)

Definition of PEF variability

GINA: average daily diurnal PEF variability ≥13%

NICE: a value of >20% variability

than 80% to doctor-diagnosis asthma for their diagnostic accuracy in asthma [23]. In this study FEV₁ alone had a moderate sensitivity and specificity for asthma diagnosis and the quality of evidence was low. Therefore, the use of FEV₁ or FEV₁/FVC alone are not recommended to diagnose asthma in children although they give information whether obstruction is present or not or whether there is a restrictive pathology explaining the symptoms of the patient.

The other controversy between asthma guidelines is the place and definition of PEF variability (Table 3). In the National Asthma Education and Prevention Programme Expert Panel Report 3 (NAEPP EPR-3), PEF variability monitoring is not recommended when spirometry is present due its wide variability [10]. Here again, NICE guideline used a higher cut off for PEF variability in order to avoid overdiagnosis but a negative PEF variability result on its own would not be used to rule out asthma within NICE asthma diagnostic algorithm, either.

There are also differences between guidelines in both recommendations and definitions of bronchodilator reversibility test in diagnosis of childhood asthma (Table 3). NICE guideline stated that the recommendation for bronchodilator reversibility test for children 5 to 16 years old was extrapolated from adult data with no evidence of its diagnostic accuracy in children.

Assessment of airway responsiveness by bronchial challenges is another challenging asthma diagnostic test with different recommendations by different guidelines (Table 4). The NICE guideline found no evidence for diagnostic accuracy of bronchial challenge with methacholine at the preferred cut-off threshold of 8 mg/ml in children aged 5–16 years, so evidence was included at a cut-off of 16 mg/ml. The sensitivity and specificity of the test in children aged 5–16 years was moderate and the clinical evidence for the diagnostic accuracy of these tests was poor [11^{***}]. In addition, the cost of using these tests is very high, therefore they are not recommended in

Table 4. Differences between asthma guidelines with respect to recommendations of other diagnostic tests for asthma in children [8–10,11^{***}]**Recommendation: bronchial challenge tests**

GINA: exercise challenge as one of the tests to demonstrate excessive variability in lung functions depending on availability; other challenges are usually only performed in adults

NAEPP EPR-3: methacholine, histamine, cold air, or exercise challenge may be useful when asthma is suspected and spirometry is normal or near normal

BTS/SIGN: methacholine, exercise or mannitol in children with an intermediate probability of asthma and have no evidence of airways obstruction with spirometry

NICE: not recommended in children ≤ 16 years old due to lack of data to demonstrate diagnostic accuracy

Definition of positive bronchial challenge test

GINA: exercise challenge fall in FEV_1 of $>12\%$ predicted, or $PEF >15\%$

NAEPP EPR-3: not given

BTS/SGN: not given

Recommendation: fractional exhaled nitric oxide

GINA, NAEPP EPR-3, BTS/SIGN: not recommended

NICE: in children aged 5–16 years if there is diagnostic uncertainty after initial assessment and they have either normal spirometry or obstructive spirometry with negative bronchodilator reversibility; in young people >16 years old if a diagnosis of asthma is being considered

Definition of positive fractional exhaled nitric oxide

NICE: in children aged 5–16 years, a $FeNO$ value of ≥ 35 ppb; in young people >16 years old, a $FeNO$ of ≥ 40 ppb

Recommendation: skin prick tests, serum total and specific IgE, serum eosinophilia

GINA, NAEPP EPR-3, BTS/SIGN, NICE: not recommended; just increase the probability of atopic asthma in children under investigation but nonatopic asthma is as frequent as atopic asthma

Recommendation: chest X-ray

GINA, NAEPP EPR-3, BTS/SIGN, NICE: not recommended; may be requested when clinical clues suggest other diagnosis

Recommendation: treatment trial

GINA, NAEPP EPR-3, NICE: ≤ 5 years old with symptoms suggestive of asthma

BTS/SIGN: children with intermediate probability of asthma

BTS/SIGN, British Thoracic Society/Scottish Intercollegiate Guidelines; $FeNO$, fractional exhaled nitric oxide; FEV_1 , forced expiratory volume in one second; GINA, Global Initiative of Asthma; NAEPP EPR-3, National Asthma Education and Prevention Programme Expert Panel Report 3; NICE, National Institute for Health and Care Excellence.

the diagnostic pathway. NICE guideline reported that the studies in children where exercise challenge was tested to make a diagnosis of asthma are very small. Larger population based studies exist in children, but these were excluded as they represented the use of exercise as a screening tool for the general population and thus the results could not be extrapolated to give a sensitivity or specificity in a population suspected of asthma.

Fractional exhaled nitric oxide

Airway inflammation markers such as fractional exhaled nitric oxide ($FeNO$) and sputum eosinophilia measurements were not routinely recommended in diagnostic procedures of the asthma guidelines in children more than 5 years (Table 4) [8–10]. In contrast, $FeNO$ measurement has found a place in the diagnostic steps of asthma in NICE guideline [11^{***}]. In this guideline, $FeNO$ was reported to have a moderate sensitivity and a

high specificity for diagnosis of asthma in children between 5 and 16 years old and in young people more than 16 years old. However, a positive $FeNO$ test is not enough to diagnose asthma in children 5–16 years old who have normal or obstructive spirometry and still requires a positive PEF variability of more than 20% during 2–4 weeks of monitorization.

Treatment trial

Treatment trial is probably the only diagnostic tool for children under 5 years old who have variable asthma-like symptoms, personal or family history of atopic disorders and other asthma risk factors, and no features suggesting alternative diagnosis. The important point in diagnosing asthma with treatment trials is that treatment should be with a low dose of inhaled corticosteroids (200 micrograms beclomethasone or equivalent twice daily with a suitable spacer) and for a limited period (minimum

of 6 weeks to a maximum of 12 weeks) [1[¶],8]. Assessment of the response at the end of treatment is mandatory. If no response is demonstrated, treatment should be stopped and the child should be referred for further investigation because a diagnosis of asthma is unlikely. If a good response is demonstrated, treatment should again be stopped and the child should be followed up for recurrence of the symptoms. If the symptoms do not recur in a short interval, spontaneous recovery (period effect) is possible. If symptoms recur after treatment withdrawal, the treatment should be started at a lower dose (100 micrograms beclomethasone or equivalent twice daily with a suitable spacer) and be adjusted according to the response [1[¶]]. When the same child is old enough, objective diagnostic tests such as spirometry should be done to confirm the diagnosis.

Controlled treatment reduction can also be used as confirmation of asthma diagnosis in children who have already been taking an inhaled corticosteroid medication but asthma is unlikely. In these children, adjustment of the treatment according to the symptoms, signs, and spirometry was recommended. For asymptomatic children with normal spirometry, a reduction of treatment by 25–50% or stopping add-on treatment and monitoring of symptoms, chest auscultation and spirometry by 2–4 week intervals are recommended as a diagnostic procedure in GINA guideline [8].

Atopy tests

Atopy tests are not recommended in diagnosis of childhood asthma except by the British Thoracic Society/Scottish Intercollegiate Guideline (BTS/SIGN) which recommends testing for atopic status together with bronchodilator reversibility and, if possible, bronchial hyperresponsiveness in children with intermediate probability of asthma without evidence of airway obstruction [9].

Chest X-ray

Chest X-ray is not a diagnostic tool used in asthma; however, it may give clues for alternative diagnosis [8–10,11^{¶¶}].

CONCLUSION

There are many challenges in every step of diagnosis in childhood asthma. There is no single test or feature that can be used on its own for accurate asthma diagnosis in any age group of children. Diagnosis in young children with asthma-like symptoms relies solely on a short treatment trial and review of response at the end of treatment and

thereafter. In older children combination of detailed history with at least two positive diagnostic tests are necessary to confirm asthma diagnosis.

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Conflicts of interest

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- of special interest
- of outstanding interest

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