LETTER TO EDITOR

Recurrent Wheezing

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Nothing to declare

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Introduction

Wheezing is the most frequent clinical finding in pediatric pulmonary disorders, approximately 30% of children manifest an episode of wheezing during their lives [1,2].

Recurrent wheezing, demonstrated by repeating attacks of wheezes is a common complaint in pediatric everyday practice. Having a high chance to happen, the progression into asthma in some cases with recurrent wheezing lay down a possibility of early treatment modalities before development of pulmonary remod-

elling phenomenon and deterioration of pulmonary functions [3].

Accordingly, noticable discussions have erupted regarding the classification and treatment of preschoolers complaining of wheezing episodes and in order to wrap them up, the primary aetiology and pathophysiological mechanisms of these episodes have to be accurately explained [1,4,5].

Epidemiology

Recurrent wheeze and dyspnea in preschool children was studied in more cohort studies on a large-scale age. As a landmark study

is Tucson Children's Respiratory Study with the following results: 30% of children had at least one episode of wheeze until the age of 3 years and half of these children had wheezed more than once, 60% of wheezy preschool children discontinue to wheeze before sixth birthday, while they were associating transient wheeze with maternal smoking or viral episode wheeze, 40% of children continued to wheeze even beyond the age of six [1]. The last group had a persistent wheeze associated with eczema, maternal asthma and elevated cord blood IgE [6].

Classification

The condition called recurrent wheezing has 2 phenotypes:

- Viral induced wheezing (EVW): intermittent episodes, no symptoms between the exacerbations [7].

- Multiple triggers wheezing (MTW): various factors are the cause of the exacerbations as viral colds, mist, exercise [8].

This is the ERS classification proposed in 2008 that does not take the severity and frequency of wheeze episodes in consideration. Meanwhile in clinical practice the initiation and choice of maintenance the therapy is determined more by these factors instead of the temporal pattern of symptoms. Over time, some prospective studies proved these phenotypes are not stable because based on patient's history collected from parents about their preschool children's wheeze symptoms the pattern changes from early viral wheezing (EVW) to multiple trigger wheezing (MTW) and vice versa [9]. Talking about physiology and pathology, significant differences have been demonstrated between the two phenotypes. Though, both shows a considerable clinical overlap [10].

Considering the time, the wheezing can be classified as:

- Transient wheeze – the onset symptomatology is before the age of 3 years and disappears earlier than the age of 6 years; it can be a viral episode or multiple triggers wheeze.

- Persistent wheeze – the symptoms continues even beyond the age of 6 years; it can be induced by multiple triggers.

- Late-onset wheeze – symptoms starts after the age of 3 years, having multiple triggers as viral infections or other factors.

For a correct evaluation and diagnosis of a recurrent wheezing patient, the case history point the presence of the atopy or risk factors in the past [11] and the release pattern [12].

As the most important risk factor during early childhood is atopy [11] that was often as-

sociated to persistent wheeze after the age of 6. The persistent wheeze in childhood was related to the quantity of allergens the child is sensitised to and to the stronger the degree of sensation [13].

The main issue of preschoolers complaining of irritating wheezing and dyspnea will have "typical wheeze", after elimination of the dubious predisposing factors listed in the following tables.

• Atopic versus non-atopic wheeze

Atopic wheeze (or allergic asthma)	Non-atopic (or viral) wheeze
three or more episodes of wheeze and dyspnea AND demonstrated sensitisation to inhaled or ingested stimulants.	three or more episodes of wheeze and dyspnea, only occurring during UR-TIs, AND no proof of allergic sensitisation to inhaled or ingested stimulants

• EVW versus MTW

EVW (early viral wheezing)	MTW (multiple trigger wheezing)
wheezing during discrete time-periods, often in association with clinical proof of a viral cold, with absence of wheeze between episodes	wheezing that shows discrete episodes, but also symptoms between episodes

• Mild and infrequent wheeze versus severe or frequent wheeze

Mild and infrequent wheeze	Severe or frequent wheeze
wheeze with little impact on daily life of affected children, and with a low frequency of episodes (less than one episode per month)	wheeze with considerable impact on daily life of affected children (requiring hospital admission or emergency room visit), or with a high frequency of episodes (two or more per month)

Clinical Presentation

Wheezing is continuous expiratory high-pitched sound emitted from the chest [6]. Considering parents differ from physicians in their perception of the term "wheeze", existing

wheeze should be verified by a pediatrician prior to induction of treatment [14].

Additionally, wheezing may be demonstrated by various clinical presentations as functional respiratory syndrome. Pulmonary auscultation: present bronchial rales.

Paraclinical investigations

In children with confirmed typical wheeze, the standard diagnostic test is a test of allergic sensitisation (either skin prick test or estimation of specific IgE to a panel of allergens in blood) [15,16].

For classification purposes are used the following blood test (Blood count test, Inflammation markers, Immunogram, Cationic Eosinophilic Protein, Allergies tests) [15,16] Bacteriology cultures, microbiological investigations [17], imaging investigations (Radiography, EKG, Cardiac echography, CT Angiography, Barium swallow test) [18], sweat test, Ph meter test, bronchoscopy, biopsy [19,20,21].

Differential diagnosis of recurrent wheezing should take into consideration the structural abnormalities, like tracheoesophageal malformation-bronchomalacia, bronchial stenosis, or extrinsic compression: vascular ring, tumors, acute conditions: foreign body aspiration, and other diseases: GERD, cystic fibrosis, alpha 1-antitrypsin deficiency, primary ciliary dyskinesia [8,22].

Evolution of the patients with recurrent wheezing is marked by the risk of developing asthma. In children with recurrent wheeze almost one third of children develops asthma as adults [23]. The probability of progressing towards asthma can be evaluated in younger children with repeated wheeze episodes. Castro-Rodriguez developed a criteria system in order to find the most "at risk" to develop asthma patients, improved by the American Academy of Asthma and Allergy. The association of one major criteria, 2 minors criterias for a child who had more than 4 wheeze attacks during past 6 months is predictive for developing asthma. The major criterias may include: a 1st grade relatives with asthma, history of atopic dermatitis, exacerbation triggered by different allergens. While the minor criterias are eosinophilia, hyper IgE syndrome, specific IgE, positive prick test, peanuts allergies, cow milk protein allergy [24].

Treatment

Non medical therapy of asthma involves environmental control such as: avoid-

ance of stimulants, cessation of smoking and prevention of infecting factors [25]. Parental cooperation is a must to achieve effective goals of treatment [26]. That's why a collaboration of Pediatrician, Patient & Parents is needed to be formed. Whenever sensitivity to inhaled allergens is suspected, avoiding stimulation by these allergens is considered helpful. However, more proofs are needed regarding this [27,28].

Since not all cases of recurrent wheezing progress towards asthma, medical therapy is provided to a certain variety of asthmatic patients with a potential liability to develop chronic inflammations and lung remodelling [3]. Medical therapy is used in cases with predictive index of asthma as follows:

Leukotrienes Inhibitors are preferred in viral induced wheezes.

Inhaled Corticosteroids are preferred in multiple trigger induced wheezes [29].

The acute wheeze treatment of choice is an inhaled bronchodilator (salbutamol) [30] by meterdose inhaler-space with a superior effectiveness comparing to nebuliser treatment [31]. With a lower effect in preschool children exacerbation, the oral corticosteroids have a precise indication, being used in children who require hospitalisation, supplemental oxygen or those with atopic wheeze [32].

After a systematic review of all available studies using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, the Dutch Paediatric Respiratory Society, in collaboration with the Dutch Cochrane Centre, recommended ICS as maintenance treatment in preschool children with troublesome wheeze, irrespective of wheezing phenotype [33].

The assumed superiority of inhaled steroid preparations with ultrafine particles is theoretical, with no evidence from randomised trials to support their use. Although data on side-effects of long-term use are lacking, inhaled steroids in this age group appear to be safe [34]. The treatment of choice as a controller therapy is Montelukast, with a less effective than ICS in recurrent wheeze [29].

The fail to improve symptoms during the inhaled steroid or montelukast maintenance treatment should guide the physicians to exclude the other factors of influence before starting additional medication [33]. Among the treatment failure influencing factors are insufficient adherence to medication, poor inhalation technique [34], an alternative diagnosis such as bronchomalacia, or other pathologies such as allergic rhinitis [35]. If these are properly addressed and treated, and symptoms remain problematic,

addition of other controllers (montelukast, ICS or long-acting β -agonists) can be considered. There is no evidence from randomised trials to prefer any add-on treatment schedule over another. Most cases of troublesome preschool wheeze can be controlled effectively by inhaled steroids or montelukast alone, or by a combination of controller medications [10].

In conclusion, for a correct and reliable treatment of a patient with recurrent wheezing, a previous good history is mandatory, for a correct classification with subsequent treatment and exclusion of other severe treatable diseases [36].

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