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Mini Review

Management of cough in children

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SUMMARY

Cough is a common symptom among children, accounting for many consultations, and affecting the quality of life of both children and their families. Clinically, coughing is described by a forceful expulsion of air from the lungs which is expressed by a characteristic sound. Generally, cough is self-limiting (acute cough) since among healthy children it is most often induced by respiratory tract infections triggered by viral, bacterial, and fungal airway pathogens. In children ≤14 years of age, a cough lasting more than 4 weeks is considered chronic and needs specific management protocols taking account of a systematic validated approach to establish the cause and initiate appropriate treatment.

KEYWORDS: children, chronic cough, pediatric cough

INTRODUCTION

Cough represents an important physiological reaction to airway irritation and attempts to defend the respiratory tract by clearing it from irritant agents and extra mucous [1]. Clinically, cough starts with an inspiratory phase since inhalation of air lengthens expiratory muscles. Subsequently, the compressive phase concerns a short closing of the glottis to stand lung volume during a preliminary contraction of expiratory muscles resulting in a clear increase of intrathoracic pressure. Lastly, the expiratory phase begins with the opening of the glottis and the release of high velocity air flow. This results in a dynamic compression of the airways and high-velocity airflow creating the characteristic cough sound and encouraging mucociliary clearance.

DEFINITION

The duration of cough is usually < 2 weeks, but may be longer in a small minority of children. If cough persists for more than 4 weeks in children aged ≤ 14 years, it is defined as chronic [2].

When dealing with a child affected by cough lacking a particular objective and anamnestic picture, we must firstly establish whether if child has a "normal" cough. "Expected cough" indicates coughing pediatric diseases reflective of common upper airway infections lasting less than 2-3 weeks [3].

International guidelines state that a child coughs an average of 10 times daily, but the upper limit of the norm reaches up to 140 times. This alone makes one simple thing clear: normal cough values are very dispersed in the pediatric population [4].

PHYSIOPATHOLOGY

Cough activation is linked to mechanical or chemical stimulants in the airways that act

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through neuronal membrane receptors. The conduction routes of these impulses start from C-fibers and Aδ-fibers that run inside the vagus nerve, coming from neurons of the peripheral nervous system located at the level of the jugular ganglion and the nodose ganglion.

It must be considered that Aδ-fiber subtypes are usually sensitive only to mechanical stimuli; however, it seems that they play a key role in neuropathic mechanisms of amplification of the cough.

In turn, the nerve endings in central nervous system of these fibers make synapses with other neurons located at the level of the nucleus of the solitary tract, from which the ascending subcortical and cortical pathways originate; these are responsible for the central control of the cough, which can also have a voluntary component of the reflex, as demonstrated by functional MRI studies [5,6].

These nerve fibers are loaded with receptors belonging to the TRP family, which are sensitive to thermal, mechanical, osmotic and chemical stimuli. The best-known one is TRVP-1, the receptor for vanilloids, i.e. for capsaicin, a substance that is the main irritant of chili pepper. Next to TRPV1 there is another receptor, which is TRPA-1, normally co-expressed with TRPV-1 but probably more important than the former, because it is sensitive to stimuli not capable of acting on the first receptor, such as acrolein and other organic combustion products. These receptors can be promoted directly by specific agonist stimuli or indirectly by non-specific ones, such as inflammation mediators and in particular PGE2 and neurokines [5].

Definitively, cough can be affected by functional interactions among sensory fiber subtypes in the brainstem. In fact, the mechanical stimulation of the external ear evokes coughing with the known Arnold's reflex, which is ascribed to activation of the auricular branch of the vagus nerve that designs to the paratrigeminal nucleus [2].

RISK FACTORS

What defines pathological cough duration is not how many times one coughs during the day as a response to any stimulus. Indeed, how much one coughs during the day is probably genetically determined.

Genetic risk factors have been identified in a few studies, such as TRPV1 mutations (encoding transient receptor potential cation channel subfamily V member 1) and TAC2R (encoding neurokinin 2 receptor) and RFC1 (encoding replication factor complex subunit 1) expansion associated with sensory neuropathy [2]. Genetic variations in neurokinin-2 have been associated with enhanced cough sensitivity to capsaicin in patients with chronic cough compared to healthy controls. The prevalence of enhanced cough sensitivity to capsaicin is higher in chronic cough patients with the 231Glu allele of neurokinin-2 receptor gene. Moreover, the sensitivity to five consecutive coughs was significantly increased in patients with 231Glu and in those with 231Glu_375Arg SNPs [7]. In addition, angiotensin-converting enzyme (ACE) inhibitor-induced cough has been associated with polymorphisms in the neurokinin-2 receptor gene, PNPT1 and PCGF3 variants, and other genetic polymorphisms [7-9].

Passive smoking has been identified as a risk factor for cough in children by several studies [10-13]. Moreover, day care attendance has been linked with an increased risk for cough in pediatric studies [13,14].

CHRONIC COUGH

What defines a "pathologic" cough in a well appearing child without any significant history and abnormal chest findings is the duration of symptoms. Chronic cough, i.e. daily cough symptoms with a duration of at least 4 weeks in children (aged ≤ 14 years) needs to be carefully evaluated since it may hide serious respiratory diseases such as bronchiectasis, aspiration lung disease, or cystic fibrosis. An important underlying disease was discovered in 18% of children among 346 patients with chronic cough in a multicenter study [15]. Establishing the cause of chronic pediatric cough requires a systematic approach that considers clinical history and the presence of some "specific cough pointers", i.e. clinical and laboratory signs of an underlying disease. Therefore, the approach to children with chronic cough is different according to the presence or absence of one or more "specific pointers". Chronic wet cough itself is now considered a "specific pointer" and represents a red flag suggestive of an endobronchial suppurative infection. It must be considered that in 25% of cases parents confuse dry cough with wet cough and vice versa, since they are not accurate to describe the pattern and nature of the cough [18]. Thus, a holistic approach to the management of chronic non-specific cough in children is mainly based on clinical history and appropriate treatment. A chest radiograph and, when age appropriate, spirometry (pre and post ß2 agonist) should be performed in all children with chronic cough aged ≤ 14 years [16]. Non-specific cough is dry/nonproductive and usually resolves without treatments. In this case, CXR and spirometry are normal. On the other hand, symptoms and signs suggestive of respiratory or systemic diseases address a specific etiology of chronic pediatric cough.

When such an approach is not successful, we propose the flow-chart indicated in Figure 1.

In the case that no specific pointers have been identified, an empirical trial is recommended based on features consistent with a hypothesized diagnosis since the most frequent causes of chronic cough in children are post-infectious or natural resolution, asthma, and protracted bacterial bronchitis (PBB) [17].

PBB represents the most common cause of wet chronic cough in children, representing 30-50% of cases of chronic cough in childhood. It is a subacute suppurative inflammation of the conductance airways caused most commonly by *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella*. PBB has two definitions: clinical and microbiological. Clinically, it is defined as chronic wet cough lasting > 4 weeks in children (especially preschoolers), in the absence of specific pointers and which resolves after 2-4 weeks of antibiotic treatment. Microbiological definition of PBB requires the presence of chronic catarrhal cough lasting more than 4 weeks; lower airway infection defined by identification of bacterial pathogens in sputum

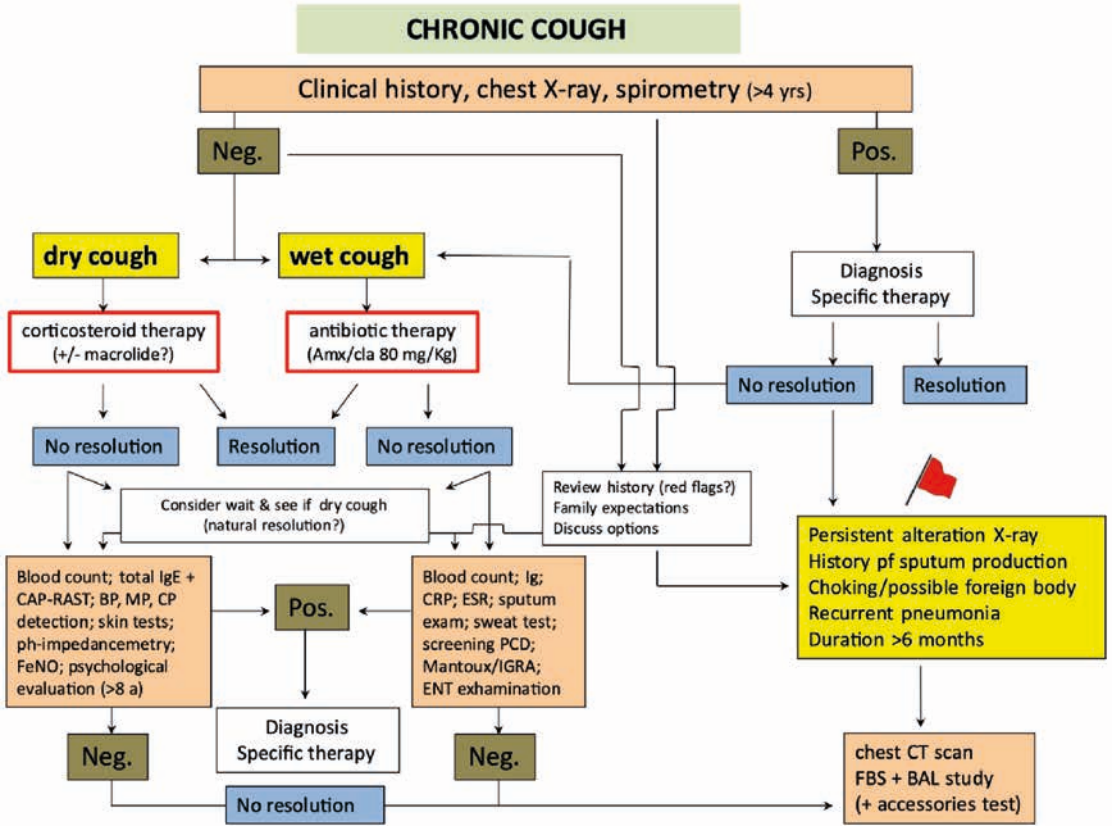

FIGURE 1. Diagnostic and therapeutic flow chart of chronic cough in children according to clinical features of the cough.

or BAL with burden bacterial ≥ 104 CFU/ml; resolution of cough after a 2-week course of appropriate oral antibiotic therapy (usually amoxicillin-clavulanate).

Specifically, wet cough should be treated with oral antibiotics for 2 weeks targeted to common respiratory bacteria (suspecting PBB) and dry cough with a trial of inhaled corticosteroids for 2-4 weeks (suggesting asthma) [18].

A sudden onset of cough in otherwise healthy preschool children should advise foreign body aspiration and demand bronchoscopy. When pertussis is clinically suspected, tests evaluating recent *Bordetella pertussis* infection are suggested. If there are suspected causes for the chronic cough, further analyses are mandatory [19]. For example, flexible bronchoscopy and/or chest CT, assessment for aspiration and/or evaluation of immunologic competency should be undertaken in case of chronic wet/productive cough unconnected to an underlying illness and with specific pointers (e.g., coughing with feeding, digital clubbing). Gastroesophageal reflux disease should be explored when gastrointestinal clinical features of gastroesophageal reflux are present, such as recurrent regurgitation, dystonic neck posturing in infants or heartburn/epigastric pain in older children. Lastly, somatic cough disorder can be diagnosed after an extensive evaluation.

CONCLUSIONS

All children with chronic cough should receive a detailed clinical evaluation to recognize pointers that are indicative of an underlying respiratory and/or systemic disease. A holistic approach to chronic cough in children should use pediatric-specific cough management procedures based on the most frequent etiologies of cough.

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Ethical considerations

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Author's contribution

All authors contributed to the creation of the manuscript and approved its publication.

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