

Etiology analysis of nonspecific chronic cough in children of 5 years and younger

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Abstract

This study aims to analyze the etiology of nonspecific chronic cough in children of 5 years and younger, in order to improve the diagnostic and treatment levels of pediatricians for nonspecific chronic cough in young children.

The clinical data of 85 cases of children of 5 years old and below, who suffered from nonspecific chronic cough between the period of January 2015 and August 2016 were retrospectively analyzed.

The etiology distribution of 85 cases of children with nonspecific chronic cough were as follows: 27 cases had cough variant asthma (31.8%), 32 cases had upper airway cough syndrome (37.6%), 16 cases had cough after infection (18.8%), 3 cases had gastroesophageal reflux cough (3.5%), 2 cases had allergic cough (2.4%), and 5 cases had unknown causes of cough (5.9%).

The main composition ratio of the etiology of chronic cough in children of 5 years old and below is as follows (in sequence): upper airway cough syndrome, cough variant asthma, and post infection cough.

Abbreviations: AC = allergic (atopic) cough, ACCP = American College of Chest Physicians, BHR = bronchial hyperresponsiveness, CT = computed tomography, CVA = cough variant asthma, ENT = ear, nose, and throat, GERC = gastroesophageal reflux cough, PIC = post-infection cough, UACS = upper airway cough syndrome.

Keywords: child, chronic cough, cough variant asthma, post-infection cough, upper airway cough syndrome

1. Introduction

Chronic cough is one of the most common clinical symptoms, and its etiology is various and has a wide range.^[1] Especially for children with nonspecific chronic cough, in which no abnormalities could be found via chest imaging and there is a lack of corresponding clinical symptoms, the diagnosis and treatment are difficult; and its etiology often involves the disciplines of pulmonology, gastroenterology, ENT (ear, nose, and throat), neurology. Many children patients have long been misdiagnosed as “bronchitis”, “chronic pharyngitis”, “whooping cough” and so on. Large dosages of antibacterial drugs have been used for treatment, while no significant effects have been obtained, and a variety of inspections have been repeatedly given to children, because there is no definite diagnosis. All these not only increase the

sufferings of the children, but also increase the economic burden of the family.^[2–5] Young children (below 5 years old) is considered as a special group, and the effects of factors such as age, physiological and immunological characteristics, and the majority of examinations (such as lung function, induced sputum test, exhaled nitric oxide, etc) are difficult to perform for this age group. This makes finding the etiology of nonspecific chronic cough more difficult. Therefore, it is necessary to conduct studies for this special age group, in order to improve the diagnostic and treatment levels of pediatricians for young children with nonspecific chronic cough. The analyses of the etiology of nonspecific chronic cough in children under 5 years of age were performed in this study.

2. Materials and methods

2.1. General data

We collected the medical records of children who visited our Outpatient Department from January 2015 to August 2016. Our inclusion criteria was that the children had to be 5 years and younger, with cough as the main or unique clinical manifestation, the course of the disease was more than 4 weeks and no significant abnormalities were found in the chest X-ray film^[6] and follow-up of at least 3 months. Exclusion criteria included children having other symptoms besides cough, abnormal chest X-ray, serious systemic diseases and unwilling or unable to cooperate with researchers.

2.2. Methods

The diagnosis of the etiology of all children with nonspecific chronic cough was referenced to the diagnosis and differential diagnosis of chronic cough in children guidelines, which include:

- (1) detailed inquiry of the disease history (duration and nature of the cough, presence of snoring, history of foreign bodies

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inhalation, drug use as angiotensin-converting enzyme inhibitors, history of wheezing rhinitis and sinusitis, family history of allergic disease or related disease and information about the living environment of the patient);

- (2) comprehensive clinical examination (evaluation of psychological and nutritional status of children with particular attention to the heart and lower and upper airways);
- (3) auxiliary examination (chest X-ray routinely performed in all children).

These patients who could not be clearly diagnosed by chest X-ray check due to complex conditions would further undergo chest computed tomography (CT) examination; these ill children suspected with rhinitis, sinusitis, nasal polyps and adenoid hypertrophy would undergo nasal endoscopy; these patients suspected with airway development abnormalities, airway foreign body and persistent bacterial bronchitis would undergo bronchoscopy and bronchoalveolar lavage fluid cytology and pathogen isolation and culture; these patients suspected with primary ciliary dyskinesia, cystic fibrosis would undergo nasal mucosal brush biopsy, sweat test and genetic testing; these patients with cough variant asthma would undergo methacholine bronchial challenge and peak expiratory flow rate test.

Specific treatment was performed according to the clues of the etiology obtained in the initial diagnosis. The patient's condition was followed-up after half a month, 1 month and 3 months, in order to timely correct the diagnosis and perform treatment procedures for the next step. According to the advice proposed in the "Multi-Center Study on the Etiology of Chronic Cough in children in China", diagnostic treatment is helpful for the diagnosis of chronic cough in children, in the absence of clear clues, diagnostic treatments were performed in the order of cough variant asthma (CVA), upper airway cough syndrome (UACS) and post-infection cough (PIC).^[7]

2.3. The diagnostic clues of common etiologies of nonspecific chronic cough

Diagnostic clues of CVA^[8]:

- (1) chronic cough, more often dry cough, often aggravates or onsets at night and/or early morning;
- (2) no infection signs in clinic or ineffective anti-infection therapy;
- (3) Diagnostic treatment of bronchodilators for bronchial asthma significantly relieved cough symptoms;
- (4) exclusion of other causes of chronic cough;
- (5) pulmonary ventilation function is normal and bronchial provocation test shows bronchial hyperresponsiveness (BHR);
- (6) the history of atopic disease in patient or one and 2 degrees of relatives, or the positive result of allergy work up.

Diagnostic clues of UACS: ^[8,9]

- (1) chronic cough, more often wet cough aggravating when the posture is changed or in the early morning, often accompanied by nasal congestion, running nose, dry throat, and foreign body sensation, repeatedly clearing of the throat and other symptoms;
- (2) tenderness of the paranasal sinus and discharged at sinus openings, significant follicular hyperplasia at the throat wall showing a cobblestone-like appearance with detection of the mucoid material;
- (3) Antihistamines, leukotriene receptor antagonist, and intranasal corticosteroids are effective for chronic cough induced

by allergic rhinitis, while chronic cough caused by suppurative sinusitis requires 2 to 4 weeks of antimicrobial drug treatment;

- (4) nasopharyngeal lesions detected with a nasopharyngolaryngoscope and nasal sinuses studied with plain X-ray or CT examination.

The diagnostic clues of PIC^[8]:

- (1) history of recent definite respiratory infection;
- (2) a chronic irritating dry cough accompanied by a small amount of white phlegm;
- (3) no significant abnormalities in the chest X-ray examination;
- (4) normal pulmonary ventilation function;
- (5) self-limited cough (if the time of cough is more than 8 weeks, other diagnosis should be considered);
- (6) exclusion of other causes of chronic cough.

The diagnostic clues of gastroesophageal reflux cough (GERC)^[8,10]:

- (1) obvious cough related to food intake, such as postprandial cough;
- (2) presence of gastroesophageal reflux symptoms such as acid reflux, belching, and retrosternal burning sensation;
- (3) effectiveness of anti-reflux therapy (the cough disappeared or is relieved);
- (4) exclusion of other causes of chronic cough;
- (5) positive pH impedance.

The relationship between the reflux and cough can be identified by the 24 hour-esophageal pH monitoring, which is the gold standard for the diagnosis of GERC. When the condition of esophageal PH monitoring is absent, GERC can be clinically diagnosed if items (1) to (4) are satisfied.

The diagnostic clues of allergic (atopic) cough (AC)^[4,8]:

- (1) chronic cough, more often irritated cough (often accompanied by itchy throat);
- (2) normal pulmonary ventilation function and negative bronchial provocation test;
- (3) increased of sensitivity of the cough receptor;
- (4) history of allergic disease, positive allergen skin test and increase of the serum total IgE and/or specific IgE;
- (5) exclusion of other causes of chronic cough.

2.4. Statistical methods

Rank sum test was used.

3. Results

The general conditions: Totally 85 patients with chronic cough were enrolled. Among these 85 cases of children in the study, 50 cases were (58.8%) male and 35 cases (41.2%) were female; The age of these patients ranged between 5 months and 5 years old, with an average age of 3.8 ± 1.1 years old. The number of patients between 5 months and 3 years was 27 (31.8%), and the number of patients between 3 years and 5 years old was 58 (68.2%). At the visit time 25 patients (29.4%) had a course of disease of ≤ 8 weeks, 22 patients (25.9%) had a course of disease of 8 to 12 weeks, 38 patients (44.7%) had a course of disease of >12 weeks, the mean course of disease was 10.3 ± 3.4 weeks. In respect of symptoms, 47 patients (55.3%) had a dry cough, and 38 patients (44.7%) had a wet cough. A total of 80 cases (94.1%) were diagnosed with definite etiology, and 5 cases (5.9%) were

Table 1**Comparison of etiological composition of nonspecific chronic cough in 5-years- old or under Children [n; (%)].**

Group	n	CVA	UACS	PIC	GERC	AC	Unknown etiological	u _c	P
5 months~	27	7(25.9)	9(33.3)	6(22.2)	1(3.7)	1(3.7)	3(11.1)	1.37	>.05
3~5 years old	58	20(34.5)	23(39.7)	10(17.2)	2(3.4)	1(1.7)	2(3.4)		
Total	85	27(31.8)	32(37.6)	16(18.8)	3(3.5)	2(2.4)	5(5.9)		

unknown. Among the 80 cases with definite etiology, In 68 children the cause of the disease was identified according to the diagnostic clues recommended in the 2006 ACCP guidelines; in 12 patients there were no definite diagnostic clue, thus diagnostic treatments were performed in the order of CVA, UACS and PIC according to the “multi Multi-Center Study on the Etiology of Chronic Cough in children in China”.^[7]

Etiological composition of nonspecific chronic cough: UACS is the most common (37.6%) cause of nonspecific chronic cough in children of 5 years old and below, followed by CVA (31.8%), PIC (18.8%), GERC (3.5%) and AC (2.4%). Among these, in the infant group (5 months and older), the sequence of the common cause of nonspecific chronic cough was UACS (33.3%), CVA (25.9%), PIC (22.2%), GERC (3.7%) and AC (3.7%). In the preschool children group (3–5 years old), the sequence of the common cause of nonspecific chronic cough was UACS (39.7%), CVA (34.5%), PIC (17.2%), GERC (3.4%) and AC (1.7%). There was no statistical significance in the difference in proportion of CVA, UACS, PIC, GERC, AC, and unidentified etiologies ($P > .05$) in the group of preschool children (Table 1).

Diagnosis: A total of 32 children were diagnosed with UACS. All of the patients were diagnosed with upper airway abnormalities by the consultation of the otorhinolaryngology (rhinitis and sinusitis and (or) adenoid hypertrophy and (or) pharyngeal cobblestone change), The nasal cavity was rinsed, and nasal corticosteroids were given then cough was quickly relieved, hence the diagnosis was drawn. Children who had been treated effectively with nasal glucocorticoids were evaluated every 2 weeks and were followed up for 3 months without recurrence of any symptoms. A total of 27 children were diagnosed with CVA. Among these patients 12 patients were positive for bronchial provocation test, 10 patients were monitored by PEF and the daily variability (continuous monitoring for 1–2 weeks) $>13\%$, Diagnosis of 5 patients was drawn because the cough symptoms significantly relieved after diagnostic treatment with bronchodilators. A total of 16 children were diagnosed with PIC, all of which were diagnosed by the self-limited course of disease. There were a total of 3 GERC children. Since our unit has no conditions to carry out early childhood PH impedance monitoring, the cause of disease of all of the 3 cases were confirmed by diagnostic treatment. Two children were diagnosed with AC. Since our unit has no conditions to carry out the capsaicin cough challenge test, the cause of disease of these 2 cases were also confirmed by diagnostic treatment.

4. Discussion

In 2006, the top 3 causes of chronic cough in children in the United States were asthma, asthma-like diseases, UACS and GERC,^[6] in this sequence. In 2012, the “Multi-central study on the composition ratio of etiology of chronic cough in Chinese children” revealed that^[7] the top 3 causes of chronic cough in Chinese children were CVA, UACS and PIC, in sequence. In 2014, Usta Guc B^[11] et al found that asthma, asthma-like diseases

and UACS remained as the most common cause of chronic cough in children, while GERC is no longer a common cause of chronic cough in children. The present study found that UACS (37.6%) is the most common cause of nonspecific chronic cough in children of 5 years old and below, and CVA (31.8%) and PIC (18.8%) ranked second and third in the composition ratio of etiology, respectively. In analysis of the causes, the differences in the proportion of causes of disease may be related to the age structure and geographical factors. In addition, it was found in the present study that searching for the causes of nonspecific chronic cough in the children was difficult; in which 5 cases (5.9%) had unknown etiology among the 85 cases; among the 80 cases with definite etiology, 12 cases (15%) without diagnostic clues were etiologically identified according to the diagnostic treatment of CVA, UACS and PIC, in this sequence. The reasons may be related to difficulties in the majority of inspections, in which some of these could not be performed in children or carried out in the hospital (including our hospital). However, the present study continues to show the importance of diagnostic treatment in searching for the etiology of chronic cough in children.

In the past, we used to call UACS as postnasal drainage syndrome (PNDS), this means that cough is caused by the backward flow of nasal secretions to the pharynx through the choana. Furthermore, it was found in the study later that PNDS can trigger cough either by the stimulation of nasal secretions drainage to the throat, or by the stimulation of neurotransmitters and neuropeptides to cough receptors in the absence of a backward drainage of secretion. Therefore, it was renamed as UACS by ACCP in 2006.^[6] The most common cause of UACS is rhinosinusitis.^[12] CT is the gold standard for the diagnosis of sinusitis. However, sinus CT or X-ray examination is not recommended as a routine examination, especially in children below 5 years old (the relative risk ratio of X-ray radiation in childhood cancer was higher than that of adults, and since the development of the children’s nasal cavity and paranasal sinus are not yet perfect, the excessive diagnosis of “sinusitis” by CT may be caused due to the performance of “local mucosal thickening”). Therefore, this disease is often examined by nasopharyngolaryngoscopy. This study revealed that rhinosinusitis is the main cause of UACS. The possible reasons of this may be as follows: the subjects of the study were young children, the immune functions of young children were relatively low, and most of the children are in the nurseries agency, which increases the probability of cross-infection and makes them are susceptible to be suffered from rhinosinusitis. Therefore, UACS is triggered.

Some studies have shown that^[6,7,11] CVA is the most common cause of chronic cough in children. The present study revealed that CVA ranked second in the composition ratio of the etiology of nonspecific chronic cough in children. Normal pulmonary ventilation function and airway hyperresponsiveness are important features of CVA. Since the pulmonary ventilation function is often normal, the bronchial dilation test is of little value in the diagnosis of CVA, while the therapeutic response of bronchodilators is an important condition for CVA diagnosis. Chronic

cough in children with a highly suspected CVA but negative airway reactivity can be diagnosed by bronchodilator therapy, hence the Japanese cough guidelines and the Chinese guidelines for chronic cough in children both regard the effectiveness of bronchodilator treatment as one of the criteria for the diagnosis of CVA.^[18,13] In this study, a total of 27 children were diagnosed with CVA. Among these children 20 patients were diagnosed as they were positive for bronchial provocation test, the other seven children had no diagnostic clue and were negative for bronchial provocation test, but were diagnosed based on significant remission of cough after one week of oral treatment of β_2 receptor agonist (procaterol).

PIC refers to persistent cough after respiratory tract infection, while the pathogen of cough had been cleared. Hence, it is not necessary to continue to use anti-infection drugs. The possible mechanism that may be involved in the integrity of the airway epithelium is disrupted by infection; and/or the squamous metaplasia of ciliated columnar epithelial cells; and/or persistent airway inflammation accompanied by the transient high airway responsiveness.^[14] PIC is normally self-limited and does not require special treatment, oral leukotriene receptor antagonist or inhaled glucocorticoid therapy can be considered to trial on patients with severe symptoms.^[15] In this study, all PIC patients were diagnosed based on clues of recent definite respiratory infection history, no abnormalities revealed by chest X-ray examination, invalid anti-infection therapy and the self-limitation of duration of cough (no more than 8 weeks).

GERC is a respiratory syndrome associated with gastroesophageal reflux with cough as the main manifestation. Typical patients often have gastroesophageal reflux symptoms, such as sour regurgitation, belching and retrosternal burning sensation. But manifestations of young children are not typical, they may have no reflux symptoms, only present with chronic cough.^[16,17] The report of the “*Multi center study on the composition ratio of etiology of chronic cough in Chinese children*” revealed that GERC only accounted for 0.62% of the composition ratio of etiology of the chronic cough. However, it pointed out at the same time that it accounted for 30.77% in cases that completed 24 hour-pH monitoring of the lower esophagus.^[7] The present study revealed that GERC accounted for 3.5% in the etiology of nonspecific chronic cough. Moreover, the etiology of all these cases was identified through the diagnostic treatment of the oral administration of antacids (cimetidine or omeprazole) and gastro-kinetic agent (domperidone). Such a low incidence may be related to the selection of the study subjects, and our unit has no the conditions to carry out the 24-hour pH impedance monitoring for early childhood.

AC was first proposed by Japanese scholars Fujimura and others^[18] in 1992, and was later found to be one of the main etiologies of chronic cough in Japan.^[4] AC children patients are often atopic physiques, and better efficacy can be obtained by antihistamines therapy (be careful to distinguish with non-asthmatic eosinophilic bronchitis, the relative percentage of the eosinophil in the sputum of the later was more than 3%, and the anti-histamine drugs are ineffective).^[19] Increased sensitivity of cough receptor is the key to diagnose AC. However, our unit has no conditions to carry out the capsaicin cough challenge test for children, in this study, 2 children first underwent methacholine bronchial challenge to exclude CVA, then underwent diagnostic treatment with antihistamines to determine AC.

In this study, 5 patients had no definite diagnosis, all presented with chronic wet cough, and the cause of disease could not be found according to the above examinations and diagnostic

treatments. In recent years, protracted bacterial bronchitis gradually attracted more attention, which is an important cause of chronic wet cough in children.^[20] We had high hopes for that the final diagnosis of these 5 patients was this disease. Unfortunately, there was no abnormality in bronchoalveolar lavage fluid cytology and pathogen isolation and culture. Bronchiectasis is also one of the causes of chronic wet cough, but HRCT of the 5 children showed no abnormality. Furthermore, the sputum induction test also excluded the possibility of non-asthmatic eosinophilic bronchitis. Nose hairbrush biopsy, sweat test and analysis of gene excluded primary ciliary dyskinesia and cystic fibrosis. Tic cough is also one of the rare causes of chronic cough, which poses a diagnostic challenge and should be considered by clinicians. It is commonly seen in children aged 4 to 18 years old, who present with short, single dry coughs (tics). The physical examination is normal apart from the cough.

In summary, the etiology of nonspecific chronic cough in young children is more subtle. Hence, we should provide more effort in its observation, analysis and identification in clinic. Diagnostic treatment is helpful for the diagnosis of chronic cough in children. Due to differences in race, habits, pathogens and other factors, the proportion of causes of nonspecific chronic cough may be different in young children in different regions. In this study, the children were from northern Anhui of China, we suggest that in the absence of clear clues, diagnostic treatments should be performed in the order of CVA, UACS, and PIC.

Author contributions

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