

# Chronic cough in children: the etiology and medical history of 420 cases in Shanghai

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## Abstract

**Objective:** Chronic cough is one of the most common and frequently-occurring diseases in children. We investigated the etiologies and clinical features of children with chronic cough (CC), in order to improve the diagnostic and treatment of the disease by pediatricians. **Methods:** Participating 420 children, aged 1-14 years old, from 5 hospitals in different regions of Shanghai, between September 2017 and July 2019. Children with chronic cough were enrolled to identify the specific cause and clinical information based on a questionnaire survey. All the data were collected and statistically analyzed by Chi-square test to identify the constituent ratio of each cause. **Results:** The etiology component ratio showed that 146 cases (34.8%) had PIC; 96 cases (22.9%) had UACS; 90 cases (21.4%) had CVA; 75 cases (17.9%) had AC; 11 cases (2.6%) had TS; 2 cases (0.5%) had GERD. For the children with CC, the mainly age of onset is 3-6 years (54.05%). The mainly cough character is wet cough (65.7%). 67.1% of children with chronic cough were prescribed antibiotics, of which 41.7% were azithromycin. Various cough drops, antihistamines, aerosolized inhalation, montelukast, etc. were often used in the treatment of children's chronic cough. **Conclusion:** The leading 3 causes of chronic cough in children were PIC, UACS and CVA. The mainly age of onset is 3-6 years; mainly cough character is wet cough. Antibiotics are the mainly treatment, often combined with cough medicine and atomization.

## 1. Introduction

Chronic cough is one of common and frequently-occurring diseases in children. It refers to those who cough for more than 4 weeks [1], cough is the main or only clinical manifestation, and chest film shows no obvious abnormality. According to the nature of cough, it can be divided into dry cough and wet cough.

A long-term cough without definite diagnosis and repeated use of antibiotics will cause significant impairment to the quality of life, including children's sleep, school attendance and play and parents' experience distress and anxiety [2-4].

Therefore, we studied the constituent ratio of various causes of chronic cough in children, analyzed and sorted out their medication history, in order to improve the diagnosis and treatment of non-specific chronic cough by pediatricians.

## 2. Materials and Methods

### 2.1 Study population

The survey was carried out in five hospitals in different regions of Shanghai, including Longhua Hospital of Shanghai University of TCM, Pudong New District Hospital of TCM, Fengxian District Hospital of TCM, Jiading District Hospital of TCM, Shanghai Seventh People's Hospital.

Prior to the start of the project, training sessions on research plan and questionnaires will be held. After that, 420 children with chronic cough who met the diagnostic criteria were collected and analyzed statistically.

## 2.2 Selection criteria

The inclusion criteria was:1) a cough of >4 weeks duration; 2) cough is the main clinical manifestation; 3) aged 1-14 years old; 4) there was no abnormalities in the chest X-ray film[1].

The exclusion criteria was:1) children had abnormal chest X-ray; 2) had serious systemic diseases; and 3) unwilling/unable to cooperate with researchers to complete the questionnaire.

## 2.3 Survey development

Each of the patients underwent the following procedures for the investigation of the cause of cough: 1) recording of medical history including symptoms and history of ear, nose, throat, respiratory tract, and digestive tract problems; 2) detailed physical examination with the targeted evaluation of throat congestion, follicular hyperplasia, and retropharyngeal postnasal drip; and 3) chest X-ray examination, bronchodilator test, methacholine-challenge test, CT imaging of the sinuses, or endoscopy in patients with suspicious symptoms or signs.

## 2.4 Methods

The diagnosis of the etiology of all children with non-specific chronic cough was referenced to the diagnosis and differential diagnosis of chronic cough in children guidelines[1,5].Each of the patients underwent the following procedures for the investigation of the cause of cough: 1) detailed recording of medical history(duration and nature of the cough, associated symptoms, the history of medication, family history of allergic disease or related disease and information about the living environment of the patient); 2) detailed physical examination with particular attention to the heart and lower and upper airways; and 3) Allergen test, Pulmonary function assessment, chest X-ray examination/further chest computed tomography (CT) examination, nasal endoscopy, bronchoscopy and bronchoalveolar lavage fluid cytology and pathogen isolation and culture or ethacholine-challenge test in patients with suspicious symptoms or signs.

## 2.5 Analyses

SPSS 24.0 was used to calculate the incidence rates of the clinical characteristics. The percentage of distribution of causes/medical history of each group was expressed by the percentage of ascertained causes/medical history of each group to the total number of causes/ medical history of each group. The chisquare (X<sup>2</sup>) test was used to evaluate the variable. Statistical significance was defined as a two-tailed P-value less than 0.05.

## 3. Results

The General conditions: The 420 study subjects included 235 male (55.9%) and 185 female (44.1%) patients, with an average age of  $5.67 \pm 2.59$  years.

### 3.1. The etiological composition and cough character

**Table 1** showed etiological composition and cough character of chronic cough. The number of children between 1 years and 3 years was 48 (11.4%), the number of children between 3 years and 6 years was 227 (54.0%), and the number of children between 6 years and 14 years old was 145 (34.5%).

Etiological composition of chronic cough: PIC is the most common (34.8%) cause of chronic cough in children of 1-14 years old, followed by UACS (22.9%), CVA (21.4%), AC (17.9%), TS (2.6%) and GERD (0.5%). Among these, in the young children (1-3 years old), the sequence of the common cause of chronic cough was PIC (35.4%), UACS (25.0%), CVA (16.7%), AC (18.7%), GERC (2.1%) and TS (2.1%). In the preschool

children (3-6 years old), the sequence of the common cause of nonspecific chronic cough was PIC (37.9%), UACS (21.1 %), AC (19.8%), CVA (18.9%), TS (2.2%) and GERD (0.0%). In the school-age children (6-14 years old), the sequence of the common cause of nonspecific chronic cough was PIC (29.7%), CVA (26.9 %), UACS (34.8%), AC (14.5%), TS (3.4%) and GERD (0.7%). There was no significant difference in etiological components among different ages ( $P > 0.05$ ).

In respect of cough character, 144 children (34.3%) were dry cough, and 276 children (65.7%) were wet cough. The common causes of wet cough were PIC (39.9%), UACS (26.1%), CVA (17.8%), AC (14.9%), TS (1.1%) and GERD (0.4%). The common causes of dry cough were CVA (28.5%), PIC (25.0%), AC (23.6%), UACS (16.7%), TS (5.6%) and GERD (0.7%). There was a significant difference in the cause of dry cough and wet cough ( $P < 0.001$ ).

### 3.2. The attack time and associated symptoms

**Table 2** showed attack time and associated symptoms of chronic cough. The clinical manifestations of the patients in the PIC group included nasal congestion and runny nose. The patients in the CVA group presented with cough at night, in the morning, after exercise as the most characteristic feature. The clinical signs of the patients in the UACS group included cough in the morning, at night, nasal congestion, runny nose and sneezing. The patients in the AC group typically exhibited cough in the morning, in the evening and itchy throat. The characteristics of TS cough group were cough in daytime and disappear after sleep, accompanied by throat itching and throat clearing. The patients in the GERD group showed typical acid regurgitation.

### 3.3. The medication history

**Table 3** showed the medication history of children with chronic cough. 281 children (67.1%) had a history of using Antimicrobial, 158 children (37.6%) had a history of using cough medication, 191 children (45.5%) had a history of using antihistamine, 136 children (32.4%) had a history of using Montelukast, 120 children (28.6%) had a history of using atomization inhalation preparation and 60 children (14.3%) had a history of using nasal spray.

Among Antimicrobials, 175 children (41.7%) had a history of using azithromycin, 13 children (3.1%) had a history of using clarithromycin. 5 children (1.2%) had a history of using penicillin. 154 children (36.7%) had a history of using  $\beta$ -lactam antibiotics.

Among cough medications, 133 children (31.7%) had a history of using Procaterol and 32 children (7.6%) had a history of using apophlegmatisant.

Among atomization inhalation preparation, 120 children (28.5%) had a history of using terbutaline combined with budesonide, 2 children had a history of using Seretide.

185 children (44.1%) had a history of using Chinese patent drug. 264 children (62.9%) had a history of using Chinese herbal medicine.

### 3.4. The past medical history, allergic history, family medical history and living environment

**Table 4** showed the past medical history, allergic history, family medical history and living environment of children with nonspecific chronic cough. 273 children (65.0%) had past medical history, including 133 cases of eczema history (31.7%), 139 cases of rhinitis history (33.1%), 38 cases of adenoid vegetation history (9.0%), 33 cases of pneumonia history (7.8%), 13 cases of anaemia history (3.1%), 5 cases of gastritis history (1.2%) and 3 cases of obesity history (0.7%).

63 children (15.0%) had allergic history, including 21 dust mites-allergic children (5.0%), 20 egg-allergic children (4.8%), 18 milk-allergic children (4.3%), 7 seafood-allergic children (1.7%), 7 nut-allergic children (1.7%), 3 pollen-allergic children (0.7%), 3 beef/mutton-allergic children (0.7%), 3 animal hairs-allergic children (0.7%) and 6 allergy to other substances (1.4%, 2 mango-allergic children, 1 chocolate-allergic child, 1 chicken-allergic child, 1 mycete-allergic child, 1 Penicillin-allergic child).

84 cases (20.0%) had family medical history, including 68 cases of family rhinitis history (16.2%), 16 cases of family asthma history (3.8%).

133 children's family (31.7%) had smokers among the surrounding. 134 families (31.9%) grew plants. 22 families (5.2%) kept pets. 105 children's (25.0%) home was along the street.

## 4. Discussion

### 4.1. The etiology of chronic cough

In 2006, the top 3 causes of chronic cough were asthma, asthma-like diseases, UACS and GERC in children of the United States [1]. In 2012, the "Prospective multicenter clinical study on the etiology component ratio of chronic cough in Chinese children" revealed that [6] the sequence of top 3 causes of chronic cough were CVA, UACS and PIC in Chinese children. What's more, PIC was the most common cause in children under 6 years old. Kantar Ahmad [7] et al suggested chronic cough in preschool children is caused by protracted bacterial bronchitis (PBB), tracheobronchomalacia, foreign body aspiration, PIC or some combination of the above in most cases in Europe. They and ACCP [8] recommend that when evaluating and managing children's chronic cough, their age and the clinical settings should be taken into consideration. The present study found that PIC (34.8%) was the most common cause of chronic cough in children in Shanghai, and UACS (22.9%) and CVA (21.4%) ranked second and third in the composition ratio of etiology, respectively. In this study average age of children was  $5.67 \pm 2.59$  years (under 6 years old), which matched the result of the research in China in 2012. In analysis of the causes, the differences in the proportion of causes of disease may be related to the ethnic group, society environment, living habits and age structure.

### 4.2. The medication history of children with chronic cough

We collected the medication history of children in the course. The present study shows most children (67.1%) had a history of using antimicrobials. Studies showed using appropriate antibiotics improves cough resolution, especially for the chronic wet cough [9-12].

175 children (41.7%) had taken Azitromycin in the course. Mycoplasma pneumoniae is extensively regarded as major cause for CVA in clinics [13]. Hodgson David [14] et al found that Antimicrobial may have a place in the treatment of chronic cough associated with asthma. Martin Matthew J [15] et al found that those chronic cough patients, who were similar to the paediatric condition protracted bacterial bronchitis, had a good symptoms' response to low-dose azithromycin. What's more, Azithromycin has a well-described anti-inflammatory properties which can be attributed to the interactions with cPLA2, causing inadequate translocation of the enzyme or disturbing physical interactions with its substrates [16]; or attributed to the inhibition of the STAT1 and NF- $\kappa$ B signaling pathways through the drug's effect on p65 nuclear translocation and IKK $\beta$  [17]. Τηρς, Μανψ πεδιατρικιαν ζηροσε αζιτηρομψιν το τρεατ ζηρονικς ζουγη.

206 ζηιλδρεν (49.0%) ηαδ α ηιςτορψ οφ υςινγ ζουγη μεδικατιονς. 136 ζηιλδρεν (32.4%) ηαδ α ηιςτορψ οφ υςινγ Μοντελυκαστ. Μιωα Ναναχο [18] ετ αλ φουνδ τηατ λευκοτριενε ρεζεπτορ ανταγονιςτ (ΑΤΡΑ) ωας υςεφυλ ιν ιμπροινγ ζουγη ιν πατιεντς ωιτη  $\sim$ A. Ταμαοκι Θυν [19] ετ αλ φουνδ τηατ ΑΤΡΑ ωας μορε εφφερςτιε τηαν τηε σαλμετερολ ιν τηε τρεατμεντ οφ  $\sim$ A. Ωηερεας ιτ ωας νοτ εφφερςτιε ιν νον-προδυςτιε ζουγη ιν Α $^{\sim}$  [20].

185 ζηιλδρεν (44.1%) ηαδ τακεν ηινεσε πατεντ δρυγ. Τηις σηρωεδ τηατ ηινεσε πεδιατρικιαν προφερ το υσε ηινεσε πατεντ δρυγ το ρελιεε ζουγη σψιμπτομς. 62.9% ζηιλδρεν ηαδ τακεν ηινεσε ηερβαλ μεδικινε. Τηερε ωας α γρεατ αριετψ οφ ηινεσε πατεντ δρυγ, ανδ ηινεσε ηερβαλ μεδικινε ωερε μοστλψ ζομπουνδ. Αλτηουγη τηεψ ηαδ ζερταιν ζυρατιε εφφερςτ ιν ζλινις, τηε μεςηανιςμ ωας νοτ ζλεαρ.

### 4.3. Τηε λιινγ ενιρονημεντ οφ ζηιλδρεν ωιτη ζηρονικς ζουγη

Ωε φουνδ 133 ζηιλδρεν'ς φαμιλψ (31.7%) ηαδ σμοκερς αμονγ τηε συρρουνδινγ. Çolak Yunus [21] et al found that smoking is one of the chronic cough risk factors. The prevalence of chronic cough in the current smokers was 8%. Johannessen Ane [22] et al believed that exposure to environmental tobacco smoke (ETS) is associated with impaired lung function in childhood. ETS might be one of the chronic cough risk factor.

105 children's (25.0%) home were along the street. Fang Zhangfu[23] et al found that the traffic-related air pollution (TRAP) exposures induced cough hypersensitivity and non-allergic eosinophilic inflammation of airways in guinea-pigs. De Sajal [24] et al found that shopkeepers working in heavily trafficked roadside shops suffer from respiratory morbidity and the risk increases with higher total exposure period. We believe TRAP might be one of the chronic cough risk factor; this is worthy of further investigation.

### **Conflict of interest**

The authors have no financial relationships related to this work to disclose. The authors declare that there are no conflicts of interest.

### **Author contributions**

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