

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

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Abstract

Background

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

The clinical data of 420 cases of children, aged 1–14 years old, from 5 hospitals' Outpatient Department in different regions of Shanghai, who suffered from chronic cough between the period of September 2017 and July 2019 were prospectively analyzed. 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 post-infection cough (PIC); 96 cases (22.9%) had upper airway cough syndrome (UACS); 90 cases (21.4%) had cough variant asthma (CVA); 75 cases (17.9%) had allergic (atopic) cough (AC); 11 cases (2.6%) had tourette cough (TS); 2 cases (0.5%) had gastroesophageal reflux cough (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. Background

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 the Outpatient Department of 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) allergen test, chest X-ray examination, routine blood test, pulmonary function assessment and gastrointestinal dynamic ultrasound 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, 5–7].

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, routine blood test, chest X-ray examination, Pulmonary function assessment, gastrointestinal dynamic ultrasound 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 (χ^2) 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 ± 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%).

Table 1
Comparison of etiological composition and cough character of chronic cough in Children

Item	n	PIC	CVA	UACS	AC	TS	GERD	χ^2	p	
Age	1~3	48	17(35.4)	8(16.7)	12(25.0)	9(18.7)	1(2.1)	1(2.1)	11.242	0.339
	~6	227	86(37.9)	43(18.9)	48(21.1)	45(19.8)	5(2.2)	0(0.0)		
	~14	145	43(29.7)	39(26.9)	36(24.8)	21(14.5)	5(3.4)	1(0.7)		
Cough character	Dry	144	36(25.0)	41(28.5)	24(16.7)	34(23.6)	8(5.6)	1(0.7)	25.948	< 0.001
	Wet	276	110(39.9)	49(17.8)	72(26.1)	41(14.9)	3(1.1)	1(0.4)		
Total	-	420	146(34.8)	90(21.4)	96(22.9)	75(17.9)	11(2.6)	2(0.5)	-	-

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.

Table 2
The attack time and associated symptoms of children with nonspecific chronic cough

Item		PIC	CVA	UACS	AC	TS	GERD
n		146	90	96	75	11	2
Attack time	morning	91(62.3)	59(65.5)	62(64.6)	40(53.3)	6(54.5)	1(50.0)
	afternoon	42(28.8)	3(3.3)	9(9.4)	13(17.3)	6(54.5)	0(0)
	evening	55(37.7)	1(1.1)	45(46.9)	38(50.7)	7(63.6)	1(50.0)
	night	76(52.1)	73(81.1)	6(6.3)	11(14.7)	0(0)	1(50.0)
	After exercise	31(21.2)	39(43.3)	13(13.5)	33(44.0)	3(27.2)	1(50.0)
Associated Symptoms	nasal congestion	87(59.6)	16(17.8)	73(76.0)	13(17.3)	0(0.0)	0(0.0)
	runny nose	75(51.4)	0(0.0)	61(63.5)	6(8.0)	0(0.0)	0(0.0)
	sneezing	57(39.0)	12(13.3)	63(65.6)	24(32.0)	2(18.1)	0(0.0)
	itchy throat	57(39.0)	18(20.0)	28(29.2)	67(89.3)	7(63.6)	1(50.0)
	feeling of mucus attachment	29(19.9)	3(3.3)	45(46.8)	27(36.0)	0(0.0)	0(0.0)
	Snoring	20(13.7)	19(21.1)	21(21.9)	12(16)	4(36.3)	0(0.0)
	sour regurgitation	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(100.0)
	sigh	2(1.4)	0(0.0)	0(0.0)	1(1.3)	2(18.1)	0(0.0)
	molar	2(1.4)	0(0.0)	0(0.0)	0(0.0)	3(27.3)	0(0.0)

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.

Table 3

The medication history of children with nonspecific chronic cough (n = 420)

		Total sample n(%)
Have medication history		371(88.3)
Antimicrobials	had used	281(67.1)
	Azithromycin	175(41.7)
	Clarithromycin	13(3.1)
	Penicillin	5(1.2)
	First-generation cephalosporin	4(1.0)
	Second-generation cephalosporin	94(22.4)
	Third-generation cephalosporin	56(13.3)
Cough Medication	have used	158(37.6)
	Procaterol	133(31.7)
	Apophlegmatisant	32(7.6)
	Antihistamine	191(45.5)
	Montelukast	136(32.4)
	Inhalation preparation	120(28.6)
	Nasal spray	60(14.3)
	Chinese patent drug	185(44.1)
	Chinese herbal medicine	264(62.9)

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 β -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%).

Table 4
The past medical history, allergic history, family medical history and living environment of children with chronic cough (n = 420)

		Total sample n (%)
Past medical history	eczema	133(31.7)
	rhinitis	139(33.1)
	adenoid vegetation	38(9.0)
	pneumonia	33(7.8)
	anaemia	13(3.1)
	gastritis	5(1.2)
	obesity	3(0.7)
	Allergic history	dust mites
	egg	20(4.8)
	milk	18(4.3)
	seafood	7(1.7)
	nut	7(1.7)
	pollen	3(0.7)
	beef/mutton	3(0.7)
	animal hairs	3(0.7)
	others	6(1.4)
Family medical history	rhinitis	68(16.2)
	asthma	16(3.8)
	passive smoking	133(31.7)
	cultivate plants	134(31.9)
Living environment	keep pets	22(5.2)
	along the street	105(25.0)

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 2009, the top 3 causes of chronic cough were GERD, asthma, asthma-like diseases and AC in children of the United States [8]. In 2012, the "Prospective multicenter clinical study on the etiology component ratio of chronic cough in Chinese children" revealed that [9] 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 [10] 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 [11] 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 ± 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 [12–15].

175 children (41.7%) had taken Azithromycin in the course. *Mycoplasma pneumoniae* is extensively regarded as major cause for CVA in clinics [16]. Hodgson David [17] et al found that Antimicrobial may have a place in the treatment of chronic cough associated with asthma. Martin Matthew J [18] et al found that those chronic cough patients, who were similar to the pediatric 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 cPLA α , causing inadequate translocation of the enzyme or disturbing physical interactions with its substrates [19]; or attributed to the inhibition of the STAT1 and NF- κ B signaling pathways through the drug's effect on p65 nuclear translocation and IKK β [20]. Thus, Many pediatrician chose azithromycin to treat chronic cough.

206 children (49.0%) had a history of using cough medications. 136 children (32.4%) had a history of using Montelukast. Miwa Nanako [21] et al found that leukotriene receptor antagonist (LTRA) was useful in improving cough in patients with CVA. Tamaoki Jun [22] et al found that LTRA was more effective than the salmeterol in the treatment of CVA. Whereas it was not effective in non-productive cough in AC [23].

185 children (44.1%) had taken Chinese patent drug. This showed that Chinese pediatrician prefer to use Chinese patent drug to relieve cough symptoms. 62.9% children had taken Chinese herbal medicine. There was a great

variety of Chinese patent drug, and Chinese herbal medicine were mostly compound. Although they had certain curative effect in clinic, the mechanism was not clear.

4.3. The living environment of children with chronic cough

We found 133 children's family (31.7%) had smokers among the surrounding. Çolak Yunus[24] 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[25] 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[26] 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 [27] 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.

5. Conclusion

Among children aged 1–14, the leading 3 causes of chronic cough in Shanghai were PIC, UACS and CVA. The mainly age of onset is 3–6 years. The mainly cough character is wet cough.

By collecting the medical history of children in the course, we found antibiotics are the mainly treatment, often combined with cough medicine and atomization. Azithromycin is the most commonly used antibiotic. More than half of the children used to seek traditional Chinese medicine treatment.

Abbreviations

AC, allergic (atopic) cough; CC, chronic cough ; CVA, cough variant asthma; GERC, gastroesophageal reflux cough; PIC, post-infection cough; TS, tourette cough; UACS, upper airway cough syndrome.

Declarations

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Authors' contributions

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Written informed consent was obtained after detailed explanation of the study aim from the patient's parents. Parents could withdraw consent in any moment during the study.

Consent for publication

Not applicable.

Competing interest

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

References

1. Chang AB, GlombWB. Guidelines for evaluating chronic cough in pediatric: ACCP evidence-based clinical practice. *guidelines J Chest.* 2006;129(1):260–83.
2. Cornford CS, Morgan M, Ridsdale L. Why do mothers consult when their children cough? *Fam Pract.* 1993;10:193–6.
3. Traisman Edward S. Clinical Evaluation of Chronic Cough in Children. *J. Pediatr Ann.* 2015;44:303–7.
4. Newcombe Peter A, Sheffield Jeanie K, Petsky Helen L, et al. A child chronic cough-specific quality of life measure: development and validation. *JThorax.* 2016;71:695–700.
5. Kurlan R. *Handbook of Tourette's syndrome and related tic and behavioral disorders [M].* 2nded. New York: Maecel Dekker; 2005. pp. 155–71.
6. Bao YX, Chen AH, FU Z, et al. The Subspecialty Group of Respiratory Diseases, The Society of Pediatrics, Chinese Medical Association, editorial board of chinese journal of pediatrics Guide for diagnosis, prevention and treatment of san bronchial asthma in pediatrics. *Chinese J Pediatr.* 2016;54:167–81.
7. Gedik AH, Cakir E, Torun E, et al. Evaluation of 563 children with chronic cough accompanied by a new clinical algorithm. *Ital J Pediatr.* 2015;41:73.

8. Khoshoo V, Edell D, Mohnot S, et al. Associated factors in children with chronic cough. *Chest*. 2009;136(3):811–5.
9. Yuan D, Tang SP, Chen Q, et al. Clinical Research Coordination Group of the Causes Constituents Ratio of Chronic Cough in Chinese Children Prospective multicenter clinical study on the causes constituents ratio of chronic cough in Chinese children. *Zhonghua Er Ke Za Zhi*. 2012;50:83–92.
10. Kantar Ahmad B, Roberto P, Francesco, et al. Chronic cough in preschool children. *J..Early Hum. Dev.*, 2013, null: S19-24.
11. Chang Anne B, Oppenheimer John J, Weinberger, Miles, et al. Etiologies of Chronic Cough in Pediatric Cohorts: CHEST Guideline and Expert Panel Report. *JChest*. 2017;152:607–17.
12. Wong O, Yin M, Julie M, Yerkovich Stephanie T, et al. Predictors of time to cough resolution in children with chronic wet cough treated with antibiotics after bronchoscopy. *JPediatr Pulmonol*. 2019;54:1997–2002.
13. Chang Anne B, Oppenheimer John J, Weinberger Miles M, et al. Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis: CHEST Guideline and Expert Panel Report. *JChest*. 2017;151:884–90.
14. Chang Anne B, Oppenheimer John J, Weinberger, Miles, et al. Children With Chronic Wet or Productive Cough–Treatment and Investigations. A Systematic Review *JChest*. 2016;149:120–42.
15. Marchant Julie M, Petsky Helen L, Morris Peter S, et al. Antibiotics for prolonged wet cough in children. *JCochrane Database Syst Rev*. 2018;7:CD004822.
16. Li Wen B, Cunfang Z. Junxia et al. Correlation study of cough variant asthma and mycoplasma pneumonia infection in children. *J. Pak J Pharm Sci*. 2017;30:1099–102.
17. Catherine HDavid, AJohn, R, et al. The Effects of Azithromycin in Treatment-Resistant Cough: A Randomized, Double-Blind, Placebo-Controlled Trial *JChest*. 2016;149:1052–60.
18. Martin Matthew J, Lee Helen C, Carly, et al. Idiopathic chronic productive cough and response to open-label macrolide therapy: An observational study. *JRespirology*. 2019;24:558–65.
19. Banjanac Mihailo, Munić K, Vesna, Nujić K, et al. Anti-inflammatory mechanism of action of azithromycin in LPS-stimulated J774A.1 cells. *J..Pharmacol. Res.*, 2012, 66: 357 – 62.
20. Haydar Dalia, Cory Theodore J, Birket Susan E, et al. Azithromycin Polarizes Macrophages to an M2 Phenotype via Inhibition of the STAT1 and NF-κB. Signaling Pathways *J Immunol*. 2019;203:1021–30.
21. Miwa Nanako N, Tatsuya O, Hisashi, et al. An Open-Label, Multi-Institutional, Randomized Study to Evaluate the Additive Effect of a Leukotriene Receptor Antagonist on Cough Score in Patients with Cough-Variant Asthma Being Treated with Inhaled Corticosteroids. *J. Kobe J Med Sci*. 2018;64:E134–9.
22. Tamaoki Jun Y, Naoko T, Etsuko, et al. Comparable effect of a leukotriene receptor antagonist and long-acting beta₂-adrenergic agonist in cough variant asthma. *JAllergy Asthma Proc*. 2010;31:78–84.
23. Kita Toshiyuki F, Masaki O, Haruhiko, et al. Antitussive effects of the leukotriene receptor antagonist montelukast in patients with cough variant asthma and atopic cough. *JAllergol Int*. 2010;59:185–92.
24. Çolak Yunus N, Børge G, Laursen Lars C, et al. Risk Factors for Chronic Cough Among 14,669 Individuals From the General Population. *JChest*. 2017;152:563–73.
25. Johannessen Ane, Bakke Per S, Hardie Jon A, et al. Association of exposure to environmental tobacco smoke in childhood with chronic obstructive pulmonary disease and respiratory symptoms in adults. *JRespirology*. 2012;17:499–505.

26. Fang Zhangfu H, Chuqin ZJ, Jim, et al. Traffic-related air pollution induces non-allergic eosinophilic airway inflammation and cough hypersensitivity in guinea-pigs. *J. Clin Exp Allergy*. 2019;49:366–77.
27. De Sajal KGaganD, Singh D, Dharmendra, et al. Respiratory Morbidity of Roadside Shopkeepers Exposed to Traffic-related Air Pollution in Bhopal, India. *JJ Health Pollut*. 2019;9:190305.