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ORIGINAL ARTICLE

Evaluation of children with chronic cough including obstructive sleep apnea: a single-center experience

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Abstract

Chronic cough in children may be due to a diverse range of etiologies. We aimed to evaluate children with chronic cough following a standardized cough algorithm and assess obstructive sleep apnea (OSA) as a possible etiology. In addition, cough resolution rates of two different treatment protocols in children with non-specific cough were compared. A total of 237 children referred for chronic cough were assessed and classified according to etiologies. Children with non-specific cough were assigned either in the early-arm (group-1, $n = 13$) or delayed arm (group-2, $n = 23$). The presence of OSA was evaluated using a pediatric sleep questionnaire, and polysomnography was handled in indicated patients. Asthma ($n = 82$) and protracted bacterial bronchitis (PBB) ($n = 73$) were the most frequent etiologies. Cough resolution was higher in group-1 (100%) compared with group-2 (50%) (absolute risk reduction (rr) = 43.48% [95% CI 21.38–65.58%]). Polysomnography revealed mild ($n = 6$), moderate ($n = 7$), or severe ($n = 5$) OSA in 18 children, with adenoid/adenotonsillary hypertrophy as the leading cause.

Conclusion: We recognized asthma and PBB as the most frequent causes of chronic cough in our cohort. Early treatment of patients with high parental anxiety might be beneficial. We also believe that further studies including larger series might eventuate in incorporation of assessment of OSA to standardized algorithms.

What is known?

- *Chronic cough in children may be due to a diverse range of etiologies, including serious respiratory disorders. Thus, its correct diagnosis and treatment are essential.*
- *Although a well-defined reason of chronic cough in adults, obstructive sleep apnea (OSA) has not been been evaluated so far in children with chronic cough.*

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What is new?

- *We examined OSA for the first time as a possible cause of chronic cough in children and detected OSA with polysomnography in cases who scored high pediatric sleep questionnaire (PSQ) scores.*
- *We believe that studies including larger series might eventuate in incorporation of assessment of OSA to standardized algorithms for children with chronic cough.*

Keywords Asthma · Children · Chronic cough · Obstructive sleep apnea · Protracted bacterial bronchitis

Abbreviations

ACCP	American College of Chest Physicians
AHI	Apnea–hypopnea index
FFB	Flexible fiber-optic bronchoscopy
GERD	Gastroesophageal reflux disease
Ig	Immunoglobulin
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PBB	Persistent bacterial bronchitis
Pc-QOL	Pediatric cough specific quality of life
PSG	Polysomnography
PSQ	Pediatric sleep questionnaire
UACS	Upper airway cough syndrome

Introduction

Chronic cough is defined as cough lasting > 4 weeks in children < 15 years and > 8 weeks for adolescents ≥ 15 years [6]. It represents amongst the most common reasons for respiratory physician visits [11]. Data concerning the frequency of chronic cough in children is restricted and studies report a prevalence of 1–3% [15, 27]. Estimated values are probably much higher as many cases do not seek medical care, and might be as high as 10–25% [22].

The most frequent etiologies of chronic cough in children < 14 years are protracted bacterial bronchitis (PBB) and asthma [1]. By adolescence, adult causes such as gastroesophageal reflux disease (GERD), asthma, and upper airway cough syndrome (UACS) are encountered predominantly [19].

Chronic cough might be a symptom of a serious respiratory disorder which may cause progressive lung damage if not diagnosed [9]. Thus, its correct diagnosis and intervention are of utmost importance.

The first pediatric guideline concerning chronic cough was released by American College of Chest Physicians (ACCP) (CHEST guideline) and was followed by several guidelines [6, 8, 26]. These algorithms facilitate earlier diagnosis, improve clinical outcomes, and increase quality of life.

Childhood obstructive sleep apnea (OSA) is a disorder mostly related to adenotonsillary hypertrophy in children [28]. If left untreated, OSA may cause impairment of cognition, attention and growth, low school performance, and cor pulmonale [2, 14]. It is a well-defined reason of chronic cough in adults [4]. Chronic cough in OSA is thought to be related with increased risk of aspiration during sleep in the presence of airway obstruction and/or stimulation of cough receptors because of vibrations which occur during airway collapse [28]. To date, studies which have incorporated assessment of OSA in children with chronic cough do not exist.

The primary aim of this study was to evaluate children with chronic cough following a standardized cough algorithm and assess OSA for the first time in cases presenting with suggestive signs and symptoms [6]. The secondary aim was comparison of cough resolution rates of two different treatment protocols (early and delayed arms) in children with chronic non-specific cough.

Methods

This prospective cohort study was conducted in a tertiary hospital between January 2016 and January 2017. The study protocol was approved by the local Institutional Ethics Committee (Approval number: 19-800-15; Dec 2015). Written informed consent was obtained from each parent.

Selection criteria

Children, aged 1 month–14 years, who admitted with chronic cough to the primary care clinic of our tertiary hospital were included. Exclusion criteria were outlined as previously diagnosed chronic respiratory illness by a pediatric respiratory/allergy physician (e.g., bronchectasis, cystic fibrosis, asthma), congenital/acquired heart disease, neuromuscular disease, immune deficiency, syndromes, prematurity (< 37 weeks), low birth weight (< 2500 g), and missing informed consent.

Study protocol

All patients were evaluated by the same primary care pediatrician and pediatric pulmonology physician, consecutively, using a standardized cough algorithm (Fig. 1) [6]. As it was not planned as a randomized clinical study, grouping of children with chronic non-specific cough according to clinical approaches was mainly based on parental concerns (anxiety and demand for treatment) and less predominantly cough diary scores.The physicians were not blinded to each other as comparison of clinical approaches was not amongst the aims.

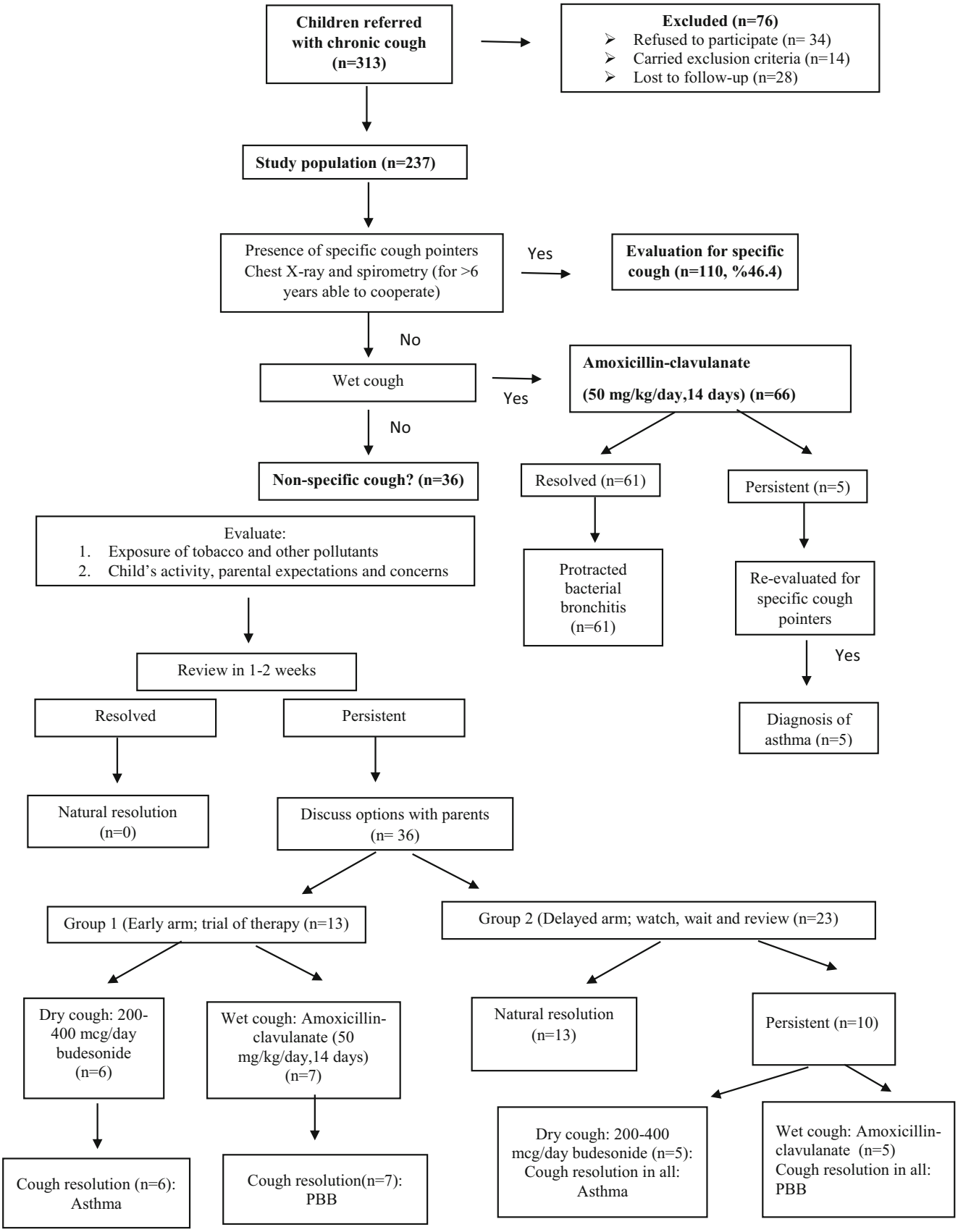

Fig. 1 Pathway of management of chronic cough (ACCP evidence-based clinical practice guideline for evaluating chronic cough in pediatrics)

Initial evaluation

History and physical examination A detailed history was obtained with particular attention on specific cough pointers. The duration and characteristics of the cough, wheezing, allergy history, accompanying symptoms, signs of GERD, sinusitis, family history of asthma, chronic cough or tuberculosis, and passive/active exposure of tobacco were questioned. A comprehensive physical examination was performed.

Cough diary Each family filled a cough diary, a validated scale which scores the intensity of daytime and nighttime chronic cough (0–5) [7].

Pediatric sleep questionnaire Families of children (≥ 2 years) filled the validated Turkish version of pediatric sleep questionnaire (PSQ), a reliable tool for the evaluation of sleep related breathing disorders [31]. Total score of PSQ is defined as the mean values of all items, and cutoff value for OSA is 0.33. Polysomnography (PSG) was handled if OSA was suspected.

Baseline investigations Chest radiograph was undertaken in all patients. Spirometry (Spirolab III, Medical International Research, Roma, Italy) was performed in children > 6 years who were able to cooperate.

Further investigations Based on ACCP 2006 evidence-based clinical practice guidelines for evaluating chronic cough in children, further tests and consultations (pediatric allergy and immunology, gastroenterology, otorhinolaryngology, psychiatry) were carried out if indicated [6]. These individually based tests were sweat chloride test, flexible fiber-optic bronchoscopy (FFB) (with Olympus®Tokyo, Japan), microbiological analysis of bronchoalveolar lavage samples, thorax computerized tomography, cilia biopsy and electron microscopic evaluation, total immunoglobulin (Ig) and subgroups, absolute lymphocyte and neutrophil count, allergic skin tests, specific IgE levels, esophageal pH monitoring, esophagogastroduodenoscopy, purified protein derivative (PPD) test, echocardiography, mycoplasma pneumonia and chlamydia IgM–IgG levels, real-time PCR analysis of nasopharyngeal aspirate for viral and bacterial agents, and autoimmune tests.

Polysomnography A standardized in-laboratory overnight PSG using a computerized system (Compumedics® Voyager Digital Imaging E-series system, Melbourne, Victoria, Australia) was implemented in patients with high PSQ scores. Sleep stages and respiratory events during sleep were scored and interpreted in accordance with American Academy of Sleep Medicine 2016 guideline [3]. Apnea–hypopnea index (AHI) signifies to the average number of apneas and hypopneas per sleep hour. The obstructive sleep apnea syndrome (OSAS) is defined as AHI ≥ 2 or AHI ≥ 1 in the context of sleep disordered breathing symptoms [18]. The severity of obstructive sleep apnea is based on AHI (mild [1–5], moderate [6–9], and severe [≥ 10]). As children tend to have clinical complications related with OSAS with lower AHI than adults, same AHI measures are accepted as more severe in children.

- Comparison of treatment approaches to "non-specific" chronic cough: Children initially diagnosed as non-specific cough were categorized into group-1 (early-arm) and group-2 (delayed arm) in 1–2 weeks. Group-1 was managed in accordance with the cough algorithm while usual care was provided for group-2 [6]. Group-1 received amoxicillin–clavulanate (50 mg/kg/day,14 days) if cough was "wet," while inhaled budesonide (200–400 mcg) was administered in "dry" cough. Patients were re-evaluated in 2 weeks, and cough resolution rates were compared.
- Follow-up: Patients were repeatedly examined every 2 weeks until a final diagnosis was made, and complete cough resolution was achieved. After cough resolution, patients were followed up monthly for the assessment of repeated attacks of cough and alteration of the initial diagnosis. Total follow-up period varied between 4 and 12 months.
- Definitions:

– Cough resolution: An improvement of ≥ 75% or total resolution of cough based on cough diary scores for ≥ 3 consecutive days.
– Natural resolution: Resolution of cough on follow-up without treatment.
– Asthma: Recurrent episodes of wheezing ± dyspnea, which respond to inhaled $ß_2$ agonist or spirometry abnormalities as determined by the American Thoracic Society Criteria [24]. Based on asthma predictive index, a diagnosis of "viral induced wheeze" was made for children < 5 years. We included children diagnosed with viral induced wheeze in the category of "asthma" in the results section for a simpler classification.
– Protracted bacterial bronchitis: The presence of wet/moist chronic cough not related with any underlying disease and without specific cough pointers, which resolves following 2 weeks of treatment with amoxicillin–clavulanate [12].
– Gastroesophageal reflux disease: A pediatric gastroenterology physician made a GERD diagnosis in patients showing suggestive clinical manifestations using esophageal pH monitoring and/or gastroduodenoscopy, who responded to a 4 week treatment (lansoprazole for patients ≥ 1 year, ranitidine for patients < 1 year).
– Psychogenic (habit) cough: A repetitive loud barking cough that persists for prolonged periods which has a

negative impact on quality of life and tends to cease during sleep [13].

- Statistical analysis: Descriptive analyses were performed using the SPSS statistical package (v.21.0). For continuous variables; mean ± SD was used for normal distribution, while median values and ranges were reported for non-normally distribution. Counts and percentages were used for categorical variables. Chi-square test/Fisher's exact test was used for comparison of categorical variables, where applicable. Comparison of cough resolution between the early and delayed arms in children initially diagnosed as non-specific cough was demonstrated with "risk reduction" (rr) including 95% confidence interval levels. p value < 0.05 was considered significant.

Results

A total of 313 children with chronic cough admitted during the study period. Amongst these, 34 refused to participate, 14 carried exclusion criteria, and 28 were lost to follow-up. Finally, 237 children (122 [51.5] female, 115 [48.5%] male) with a median age of 5.00 (0.28–13.95) years were included. The median time elapsed from the onset of cough until admission was 9 (4–52) weeks. Wet/productive cough was more common ($n = 142$, 59.9%). The presence of specific cough pointers was detected in 135 (57%) patients. Tobacco exposure (passive/active) was reported as 41.8% and 0.8%, respectively. A previous history of chronic cough was mentioned in 59 (24.9%) children. Mean daytime and nighttime cough scores were 2.61 ± 0.99 and 2.93 ± 1.48, respectively.

Table 1 Etiologies of patients

	Number	Percent
Asthma	82	34.5
Protracted bacterial bronchitis	73	30.8
Pneumonia	18	7.6
Obstructive sleep apnea	18	7.6
Rhinosinusitis	13	5.5
Gastroesophageal reflux disease	13	5.2
Non-specific chronic cough	12	5
Adenotonsillary hypertrophy	10	4.2
Allergic rhinitis	8	3.4
Psychogenic cough	3	1.3
Tuberculosis	1	0.4
Interstitial lung disease	1	0.4
Primary ciliary dyskinesia	1	0.4

Etiologies

Asthma ($n = 82$) and PBB ($n = 73$) were recognized as the most frequent etiologies (Table 1). The distribution of etiologies in different age groups is shown in Table 2. Comparison of most frequent etiologies revealed that PBB was highest in ≤ 2 years ($p = 0.005$) while asthma was highest > 2 years ($p = 0.005$). More than one etiology was detected in 16 patients (6.7%) (Table 3).

Asthma Of 82 patients diagnosed with asthma, 61 were diagnosed following initial evaluation. Initial diagnosis of non-specific cough in 11, pneumonia in 5, and PBB in 5 children altered to asthma later because of either unresolved or repeated chronic cough.

Protracted bacterial bronchitis A preliminary diagnosis of PBB was made in 66 children. Of these, five were diagnosed with asthma subsequently. The remaining 61 patients with chronic wet cough without any specific cough pointers and whose cough resolved following amoxicillin–clavulanate treatment were diagnosed with PBB. An additional of 12 patients who were initially thought as non-specific chronic cough were diagnosed with PBB in the follow-up. Finally, PBB was diagnosed in 73 children.

Pneumonia Twenty-five children had pneumonia on admission. Five of them were subsequently diagnosed with asthma. Two children whose cough did not respond to treatment were further diagnosed with tuberculosis and interstitial lung disease (related with scleroderma).

Obstructive sleep apnea Polysomnography was planned in 28 children with high PSQ scores and could be performed in 23 of those whose parents agreed. OSA was detected in 18 children (mild [$n = 6$], moderate [$n = 7$] or severe [$n = 5$]), with adenoid/adenotonsillary hypertrophy representing as the most frequent reason (Table 4). Twelve children with adenoid/adenotonsillary hypertrophy were operated (adenoidectomy/adenotonsillectomy ± tympanostomy tube insertion) with further resolution of cough while nasal steroids or asthma treatment controlled chronic cough in three patients with accompanying asthma. Treatment of allergic rhinitis in two patients and weight loss in one obese child resulted in cough resolution.

Rhinosinusitis Thirteen children were diagnosed with rhinosinusitis and cough resolved in all following treatment.

Gastroesophageal reflux Twelve patients were diagnosed with GERD. Cough recovery was observed in all following 4 weeks of treatment.

Table 2 The leading causes of chronic cough in different age groups

0–2 years (n = 34)	> 2–< 6 years (n = 118)	≥ 6–< 14 years (n = 85)
PBB (n = 18, 52.9%)	Asthma (n = 43, 36.4%)	Asthma (n = 33, 38.8%)
Asthma (n = 6, 17.6%)	PBB (n = 31, 26.3%)	PBB (n = 24, 28.2%)
GERD (n = 3, 8.8%)	OSA (n = 12, 10.2%)	GERD (n = 6, 7.1%)
Pneumonia (n = 3, 8.8%)	Pneumonia (n = 10, 8.5%)	Pneumonia (n = 5, 5.9%)

PBB protracted bacterial bronchitis, *GERD* gastroesophageal reflux disease, *OSA* obstructive sleep apnea

Non-specific chronic cough Thirty-six children, initially diagnosed as chronic non-specific cough, were categorized into group-1 ($n = 13$) and group-2 ($n = 23$) within 1–2 weeks (Fig. 1). The proportion of children whose cough resolved was significantly higher in group-1 (absolute risk reduction (rr) = 43.48% [95% confidence interval (CI) 21.38–65.58%]).

Adenoid/adenotonsillary hypertrophy Ten children diagnosed as adenoid/adenotonsillary hypertrophy did not have accompanying OSA. Seven of them had comorbidities (asthma, allergic rhinitis, or pneumonia). Cough resolution was achieved following adenotonsillectomy in two patients and with medical treatment (nasal corticosteroid ± systemic antihistaminic) in six patients. Two patients whose cough persisted despite medical treatment refused to be operated.

Allergic rhinitis Eight patients were diagnosed with allergic rhinitis with response to systemic antihistaminic ± nasal corticosteroids in all.

Psychogenic cough Three children who exhibited typical cough pattern were diagnosed with psychogenic cough.

Interstitial lung disease One patient was diagnosed with interstitial lung disease related to scleroderma.

Primary ciliary dyskinesia One patient was diagnosed with primary ciliary dyskinesia.

Table 3 Patients with more than one etiology of chronic cough

Etiology	Number
Asthma and adenoid hypertrophy	4
Asthma and OSA (secondary to adenotonsillary hypertrophy)	3
Asthma and GERD	2
Pneumonia and adenotonsillary hypertrophy	2
Allergic rhinitis and OSA	2
Allergic rhinitis and adenotonsillary hypertrophy	1
Rhinosinusitis and OSA	1
GERD and OSA	1

OSA obstructive sleep apnea, *GERD* gastroesophageal reflux disease

Coexisting hypogammaglobulinemia Hypogammaglobulinemia (IgG, IgA, and/or IgM) was detected in 16 children presenting with frequent respiratory tract infections.

Follow-up findings Median period of total follow-up was 6 (minimum–maximum 4–12) months. Cough resolution, either at week 6 or later in the period of follow-up, was observed in 220 (95.4%) patients. After cough resolution, 20 patients (8.4%) were lost to follow-up. Of patients who continued on follow-up, repeated chronic cough was encountered in 42(17.7%) (Fig. 2). The final diagnosis differed from preliminary diagnosis in 34 (14.3%) cases because of either recurrence or persistence of cough.

Discussion

Although usually encountered in the course of non-serious conditions, chronic cough in children may be due to a diverse range of etiologies, including serious respiratory disorders [8]. Consequently, its correct diagnosis and treatment is sometimes challenging, yet always essential. The aim of this article was to call attention to chronic cough in children with particular emphasis on OSA. To the best of our knowledge, this is the first clinical study to examine OSA as a possible cause of chronic cough in children.

As compatible with previous reports, we encountered PBB and asthma as the most frequent reasons for chronic cough [1, 9, 13, 16]. We also detected OSA with PSG in suspected cases. Furthermore, we observed higher cough resolution rates in the early-arm in comparison with the delayed arm in children

Table 4 Underlying conditions of patients diagnosed as obstructive sleep apnea

	Number
Adenoid or adenotonsillary hypertrophy	11
Asthma and adenoid hypertrophy	3
Allergic rhinitis	2
GERD and adenotonsillary hypertrophy	1
Obesity	1

GERD gastroesophageal reflux disease

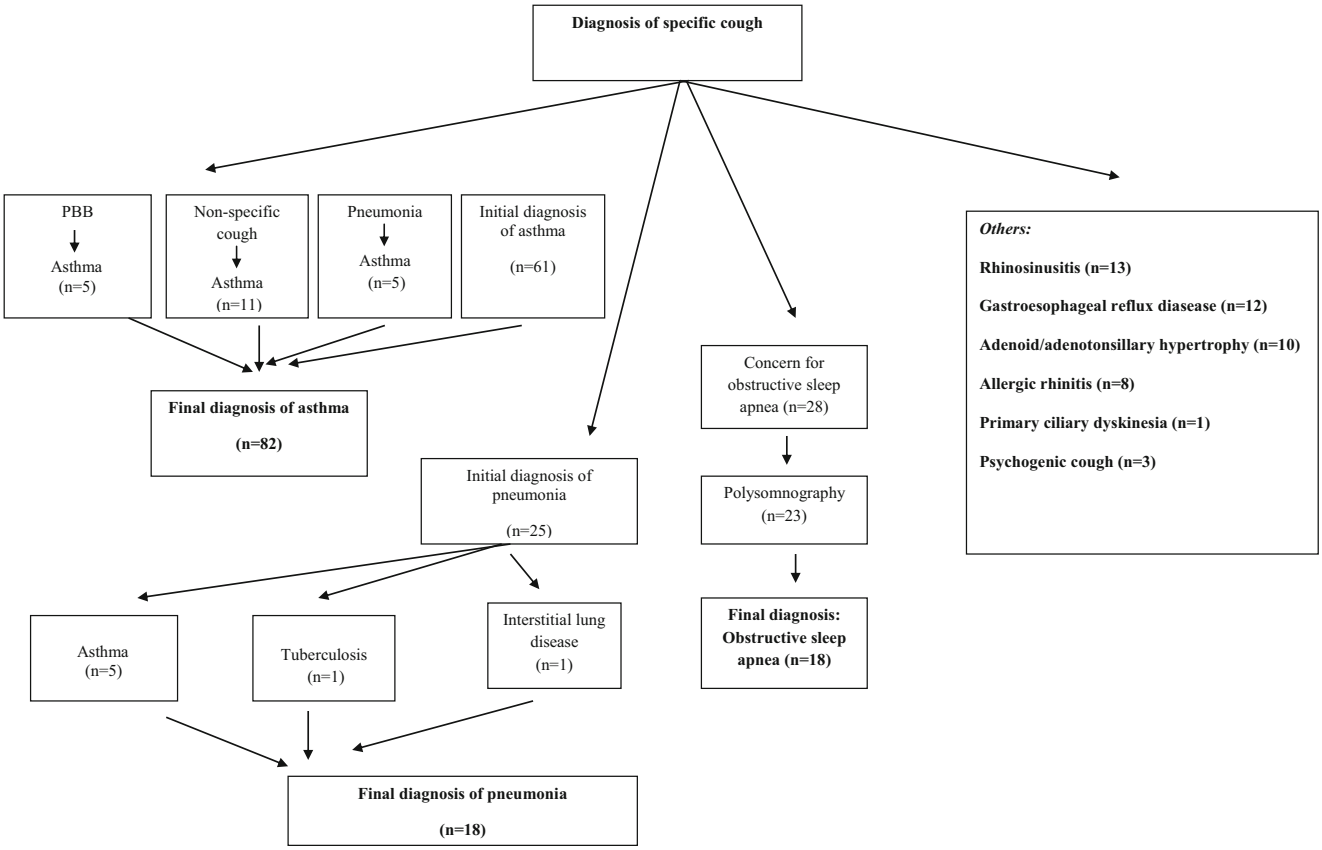

Fig. 2 Classification of patients with chronic specific cough according to etiologies

initially diagnosed with non-specific cough. This outcome was also similar to previous data [10].

The first study about chronic cough in children reported asthma as the most common cause (66.7%) [27]. A current systematic review including 14 studies revealed that the majority reported asthma and PBB as common etiologies [13]. Few studies carrying major limitations delineated GERD as a common etiology [5, 21]. Only two studies, both conducted in Turkey, found UACS as common [1, 29]. It should be noted that variations of common etiologies in this review might have resulted from differences in terms of practice settings, definition of chronic cough, preferred algorithms, inclusion/exclusion criteria, age distribution, and the size of the study groups. As UACS is considered as a controversial cause of chronic cough in children, many clinical studies do not mention UACS amongst etiologies [16, 30]. Similarly, we did not consider it amongst causes and rather defined patients with nasal discharge and clearing of the throat as rhinosinusitis and/or allergic rhinitis.

Few studies which investigated the impact of age on etiologies of childhood chronic cough suggested that common reasons varied in different age groups. Gedik et al. reported asthma as the most common condition for all ages while the second most common etiology was PBB < 6 years and psychogenic > 6 years [16]. A multicenter study of Chang et al. notified predominance of PBB under 2 years [9]. A systematic review recommended to consider the age of the child when determining further investigations [13]. Thus, we attempted to interpret our results by dividing our cohort into different age groups. Similar to Chang et al.'s study, we realized that PBB was more common in the first 2 years of life while asthma was predominant in older children [9].

PBB is a medical condition which can be diagnosed following clinical evaluation and observation of cough resolution with antibiotics. However, a substantial proportion of PBB cases are misdiagnosed as asthma, causing unnecessary examination and treatment [20]. It might be difficult to distinguish between asthma and PBB, especially for children < 2 years. The British Thoracic Society Guideline recommends 4–6 weeks of antibiotics for PBB while a recent CHEST guideline suggests a 2-week course of treatment [12, 26]. We followed CHEST guideline which also advises to repeat the antibiotic course in persisting cough and carry further investigations such as FFB only in persistent cases following 4 weeks of treatment. Common bronchoscopic findings of PBB are known as purulent airway secretions and airway malacia. We assessed only one case of PBB with FFB, which revealed increased airway secretions.

Studies evaluating children with non-specific chronic cough have concluded higher resolution rates in patients who were given early treatment in comparison with watch,

wait and review approach [10, 16]. We grouped patients mostly according to parental concerns and observed similar results. Therefore, we suggest early treatment of patients with high parental anxiety.

A recent report concerning etiologies of chronic cough in children suggests that children ≤ 14 years with chronic cough who represent with OSA signs and symptoms should be managed according to pediatric sleep guidelines [13]. Nevertheless, data concerning this issue are scarce as yet. Lewis and Gurgel et al. published single case reports of OSA secondary to tonsillar hypertrophy [17, 23]. A Cochrane review evaluating the association between OSA and chronic cough in children could not ascertain any clinical trial [28]. Ours is the first study evaluating the association between OSA and chronic cough in children.

Although the exact mechanism of chronic cough in OSA is not fully elucidated, it is thought to be related with increased risk of aspiration and/or stimulation of cough receptors during sleep [28]. At the same time, the majority of our patients with OSA had adenotonsillary hypertrophy, a clinical condition which causes chronic cough as a result of chronic inflammation. Moreover, three patients with OSA had asthma with resolution of chronic cough with asthma treatment. Even though it is hard to claim that OSA is a single cause of chronic cough in children, we believe that it should be considered as a contributing factor.

Study limitations

This study has a few limitations. Firstly, we believe that implementation of a validated cough specific tool such as pediatric cough specific quality of life (PC-QoL) questionnaire, in addition to cough diary scores, would have enabled better assessment [25]. Secondly, the majority of our small subgroup of patients with OSA had accompanying diseases, making it impossible to evaluate OSA as a single etiology of chronic cough. Lastly, a longer period of follow-up would have provided better understanding of the natural course, recurrence rates, and changes in diagnosis.

Conclusion

As compatible with previous research, we recognized asthma and PBB as the most frequent causes of chronic cough in our pediatric cohort. We suggest clinicians to keep in mind the influence of age on etiologies. Early treatment of patients with high parental anxiety might be beneficial. Based on our data forming the first clinical trial which examined OSA in children with chronic cough, we believe that studies including larger series might eventuate in incorporation of assessment of OSA to standardized algorithms.

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Author Contributions NC and NECI designed the study. NECI conducted and interpreted the statistical analysis and had the primary responsibility in the formation of the initial draft. All authors provided substantial contributions to the design of the work, or the acquisition, analysis, or interpretation of the data, revised the initial draft, approved the final manuscript, and agreed to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all individual participants' parents included in the study. Additionally, participants above 8 years approved a pediatric informed consent.

Ethical approval The study protocol was approved by the Ankara University School of Medicine Institutional Ethics Committee (Approval number: 19-800-15; Dec 2015). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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