CHEST

Original Research

SIGNS AND SYMPTOMS OF CHEST DISEASE

# Children With Chronic Nonspecific Isolated Cough

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***Background:*** **This study observed children with chronic nonspecific isolated cough (NIC) to investigate clinical differences between children whose symptoms resolved spontaneously and those who eventually developed asthma and then explored the differences among the children who eventually developed asthma in terms of their time of response to a trial of inhaled corticosteroid (ICS).**
***Methods:*** **Children with chronic NIC were managed either with a wait-and-review approach or with a 2-week trial with 400 μg/d inhaled budesonide according to the preference of their parents. Responses were monitored with a validated cough score. Treatment was prolonged to 8 weeks in the case of partial responders. All children were followed up at 3-month intervals.**
***Results:*** **A total of 109 children (median [interquartile range] age, 5 [3.5-9] years; cough duration, [8-16] weeks]) were followed for a mean (± SD) time of 21(± 5) months. Cough did not recur in 71% (spontaneous resolution) but relapsed in 28% of the children who later responded to ICS treatment again (asthma). Aeroallergen sensitization (relative risk, 2.86; 95% CI, 1.17-6.99) and previous history of chronic cough (relative risk, 2.68; 95% CI, 1.10-6.49) increased the risk of asthma. Cough duration, the cough score, the family history of asthma, and serum eosinophilia were not found discriminative for the final diagnosis. There were no differences among children who eventually developed asthma and responded to either the 2-week or 8-week trial in terms of the study parameters.**
***Conclusions:*** **Chronic NIC does not recur in the majority of children. Initial response to the ICS trial may be misleading but the trial may be preferred for children who have atopic sensitization, a previous history of chronic cough, or both.** ***CHEST 2014; 145(6):1279–1285***

**Abbreviations:** CVA = cough variant asthma; ICS = inhaled corticosteroid; NIC = nonspecific isolated cough

Cough is one of the most common reasons for presentation to a doctor.[1-4] Nonspecific isolated cough (NIC) is a common category of chronic cough, especially in children.[5,6] Evidence suggests that only a minority of children with chronic NIC have asthma.[5-10] A trial of inhaled corticosteroid (ICS) treatment is generally recommended for children with chronic NIC who have persistent symptoms. However, chronic cough guidelines in children emphasize that the response to ICS treatment may be a period effect rather than an indication for a diagnosis of asthma. Therefore, an early relapse of cough that again responds to ICS treatment may represent a diagnosis of asthma.[5,6] Nevertheless, it is difficult to decide on the final diagnosis without a follow-up.

Many previous research studies have focused on the evaluation and outcome of chronic cough.[1,2,4] There are studies in the past that have examined cough in terms of "recurrent cough," "persistent cough," "night cough," or "persistent nocturnal cough" in children.[10-14] However, there are limited data available about chronic NIC. The primary aim of this study was to observe children with chronic NIC and to investigate clinical differences between children whose symptoms resolved

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spontaneously and those who eventually developed asthma. As a secondary aim, we examined the differences among children who eventually developed asthma in terms of their time of response to ICS treatment.

## Materials and Methods

Children aged < 18 years with chronic cough lasting ≥ 4 weeks who were referred to the Department of Pediatric Allergy and Asthma at our hospital were screened for inclusion in the study. All children were evaluated by at least two allergists for specific cough pointers and characteristic cough patterns using a form we designed according to the recommendations in the guidelines.[5,6] A chest radiograph and a pulmonary function test with bronchodilator responsiveness (for children old enough to conduct the maneuvers) were performed in all participants. Children with a specific cough pointer, characteristic cough pattern, and wet cough or with an abnormality in the chest radiograph or pulmonary function test were excluded from the study. Children with a previous diagnosis of a chronic respiratory disorder, those who had been on ICS or leukotriene receptor antagonist or bronchodilator treatment, or those using angiotensin-converting enzyme inhibitors were also excluded from the study. All other children with dry chronic cough and a normal physical examination were included in the study.

### *Laboratory Investigations and Child Management*

Chest radiographs were taken in posteroanterior and lateral positions and reported by the radiology department. Pulmonary function tests were performed with a daily calibrated spirometer (Vmax 20C; SensorMedics, CareFusion Corp) in accordance with the American Thoracic Society Guidelines.[15,16] We used the Knudson reference set for spirometry prediction. Age, sex, height, weight, and ethnicity were entered before each measurement. All children were white.

Atopy was determined with a panel of skin prick tests that included house dust mites, pollens, alternaria, animal dander, latex, and histamine (10 mg/mL histamine phosphate) as positive controls and 0.9% sterile saline as negative controls. The skin prick test was considered positive if the mean wheal diameter was ≥ 3 mm than the negative control. The serum eosinophil count was determined with an automatic complete blood count analyzer.

The Gazi University Hospital ethics committee approved the study, and written informed consent was obtained from all children and/or their parents (project approval No. 293).

Definitions were as follows:

- Chronic cough: cough lasting ≥ 4 weeks.[6]
- Specific cough pointers: Any auscultatory abnormality, classic cough characteristics, cardiac abnormalities, chest pain, chest wall deformity, daily moist or productive cough for > 3 months, digital clubbing, dyspnea, exertional dyspnea, failure to thrive, feeding difficulties, hemoptysis, immune deficiency, neurodevelopmental abnormality, recurrent pneumonia, wheeze, allergic rhinitis/postnasal drip, atopic eczema, passive smoking, symptoms of gastroesophageal reflux.[5,6]
- Characteristic cough patterns: Barking or brassy cough, cough productive of casts, honking cough, paroxysmal (with/without whoop), staccato cough.[5,6]
- Nonspecific isolated dry cough: Persistent dry cough lasting ≥ 4 weeks with no other respiratory symptoms.[5,6]
- Cough score: A validated verbal category cough scale scoring daytime plus nighttime cough scores.[17]
- Daytime score: 0 = no cough; 1 = cough for one or two short periods only; 2 = cough for more than two short periods; 3 = frequent coughing but does not interfere with school or other activities; 4 = frequent coughing which interferes with school or other activities; and 5 = cannot perform most usual activities due to severe coughing.
- Nighttime score: 0 = no cough at night; 1 = cough on waking or on going to sleep only; 2 = awoken once or awoken early due to coughing; 3 = frequent waking due to coughing; 4 = frequent coughs most of the night; and 5 = distressing cough.
- Complete cough resolution (complete response): Improvement of ≥ 75% or total resolution according to the recorded cough score for ≥ 3 consecutive days.[18-20]
- Partial cough resolution (partial response): Improvement of 25% to 75% according to the basal cough score.
- Nonresolution of cough (no response): Improvement of ≤ 25% according to the basal cough score.
- Chest radiograph abnormality: Any abnormality (other than peribronchial thickening) as interpreted by a radiologist.
- Spirometry abnormality: As determined by the American Thoracic Society and European Respiratory Society Criteria with predicted values used.[15,16] $FEV_1 < 80$, $FEV_1/FVC < 80$, $FEF_{25-75} < 70\%$ predicted and ≥ 12% or 200 mL increase in $FEV_1$ 20 min after 400 μg of salbutamol inhalation were considered a spirometry abnormality.
- Serum eosinophilia: ≥4% eosinophils in the complete blood count.
- Classic asthma: Recurrent episodes of wheeze, dyspnea, or both that respond to inhaled $\beta_2$-agonist, or bronchodilator responsiveness documented on spirometry (≥ 12% change in $FEV_1$% predicted after 400 μg of salbutamol).
- Cough variant asthma (CVA): Nonspecific chronic dry cough that resolves completely with ICS treatment 400 μg/d budesonide or equivalent within a 2-week to 8-week period and relapses after stopping treatment, and then again responds to the same treatment.
- Relapse: A new chronic cough period or a cough with a wheezing after complete response to either ICS treatment of 2 or 8 weeks or after a wait-and-review period.

All children were managed according to Figure 1. To ensure effective delivery of the inhaled treatment, parents of each child were trained by the same inhalation technician in a standard manner. All patients were followed up and their cough diary entries were reviewed by the same physician (O. Y.). Parents recorded daytime and nighttime cough scores according to the verbal descriptions detailed in the definitions given previously. This is a validated verbal category score that has been previously used in chronic cough studies in children.[17,20,21] Parents filled in the cough diary daily during coughing periods lasting ≥ 4 weeks. Response to treatment was evaluated according to the mean cough score. The treatment of children who were partially responsive to the 2-week treatment with ICS was prolonged to 8 weeks with the same dose of the drug. A plan to consult with other departments (pediatric pulmonology, cardiology, immunology, gastroenterology, and ear, nose, and throat) was made in the case of children who were nonresponsive to the 2-week treatment or partially responsive to the 8-week ICS treatment to ensure a differential diagnosis. All children were examined at 3-month intervals for any recurrence of cough. Children were admitted to the outpatient clinic for reevaluation any time they had symptoms.

### *Statistical Analysis*

Statistical analysis was performed using the Statistical Package for Social Sciences 16.0 software (IBM). Descriptive analysis was