Investigation of transient hypogammaglobulinemia of infancy in the etiology of chronic cough in children under five years old

Sevgi Pekcan1, MEHMET ALPTEKİN1, Gökçen Unal1, Ashı İmran Yılmaz1, Hanife Tuğçe Çağlar1, Fatih Ercan1, Sevgi Keleş3, and İsmail Reisli1

1Necmettin Erbakan University Meram Medical Faculty

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Abstract

Chronic cough is one of the most common complaints of childhood to consult a doctor. There are many causes such as respiratory tract infections, gastroesophageal reflux, persistent bacterial bronchitis, asthma, cystic fibrosis, congenital malformations, and foreign body aspiration in children under the age of five. However, neither transient hypogammaglobulinemia of infancy (THI) among the causes of chronic cough, nor chronic cough among the application complaints of THI are not questioned. In this study, we aimed to draw attention to the role of THI in the etiology of chronic cough under the age of five. Our study included 55 pediatric patients under the age of five who applied to the pediatric pulmonary diseases outpatient clinic in between January 2015 and December 2020 with the complaint of chronic cough, who were excluded from other causes of chronic cough in etiology, and who met the criteria for THI according to the European Society for Immunodeficiencies (ESID). Demographic, clinical and laboratory characteristics and follow-ups of these patients were reviewed retrospectively. In our study, the mean age of 55 patients at admission was 21.73 ± 11.50 months (median age: 18 months), and the mean age of IgG recovery was 38.65 ± 16.81 months. The mean recovery time was 16.93 ± 12.85 months. Of the patients, 22.4% had a history of consanguinity, 23.4% had prematurity, and 18.2% had a frequent sickness in siblings. The most common complaint accompanying chronic cough in patients was frequent respiratory tract infection, 16.3%. Along with IgG, 26.4% of the patients had low IgA and 31.5% had low IgM in laboratory testing. In antibody responses, isohemagglutinin, anti-tetanus, anti-pneumococcal, anti-HBs vaccine responses were found to be positive in 90.6%, 63.9%, 66.7% and 97.7% of the cases, respectively. 72.7% of the patients received inhaler treatment, 45.5% received antibiotic prophylaxis, and 2.2% received intravenous immunoglobulin (IVIg) treatment. After the IgG value of the patients returned to normal, it was observed that 86.3% of the patients’ cough complaint have disappeared. Transient hypogammaglobulinemia of infancy mostly presents with recurrent lower and upper respiratory tract infections. The most common complaint accompanying chronic cough in patients was frequent respiratory tract infection, 16.3%. Along with IgG, 26.4% of the patients had low IgA and 31.5% had low IgM in laboratory testing. In antibody responses, isohemagglutinin, anti-tetanus, anti-pneumococcal, anti-HBs vaccine responses were found to be positive in 90.6%, 63.9%, 66.7% and 97.7% of the cases, respectively. 72.7% of the patients received inhaler treatment, 45.5% received antibiotic prophylaxis, and 2.2% received intravenous immunoglobulin (IVIg) treatment. After the IgG value of the patients returned to normal, it was observed that 86.3% of the patients’ cough complaint have disappeared. Transient hypogammaglobulinemia of infancy mostly presents with recurrent lower and upper respiratory tract infections. The most common complaint accompanying chronic cough is cough. It is not questioned whether the cough is chronic or not. In this study, we aimed to investigate the follow-up and prognosis of patients under the age of five who had a chronic cough complaint, when other causes of cough were ruled out and THI was detected. In the study, when the IgG levels of the patients return to normal, the cough complaints disappear to a large extent, showing that THI may also be among the causes of chronic cough.

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Mehmet Fatih Alptekin1, Gökçen Ünal2, Ashı İmran Yılmaz2, Hanife Tuğçe Çağlar2, Fatih Ercan2, Sevgi Keleş3, İsmail Reisli3, Sevgi Pekcan2 *

1. Necmettin Erbakan University Meram Medical Faculty, Department of Pediatrics
2. Necmettin Erbakan University Meram Medical Faculty, Division of Pediatric Chest Diseases
3. Necmettin Erbakan University Meram Medical Faculty, Division of Pediatric Immunology and Allergy

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Chronic cough is one of the most common complaints of childhood to consult a doctor. There are many causes such as respiratory tract infections, gastroesophageal reflux, persistent bacterial bronchitis, asthma, cystic fibrosis, congenital malformations, and foreign body aspiration in children under the age of five. However, neither transient hypogammaglobulinemia of infancy (THI) among the causes of chronic cough, nor chronic cough among the application complaints of THI are not questioned. In this study, we aimed to draw attention to the role of THI in the etiology of chronic cough under the age of five.

Our study included 55 pediatric patients under the age of five who applied to the pediatric pulmonary diseases outpatient clinic in between January 2015 and December 2020 with the complaint of chronic cough, who were excluded from other causes of chronic cough in etiology, and who met the criteria for THI according to the European Society for Immunodeficiencies (ESID). Demographic, clinical and laboratory characteristics and follow-ups of these patients were reviewed retrospectively.

In our study, the mean age of 55 patients at admission was 21.73 ± 11.50 months (median age: 18 months), and the mean age of IgG recovery was 38.65 ± 16.81 months. The mean recovery time was 16.93 ± 12.85 months. Of the patients, 22.4% had a history of consanguinity, 23.4% had prematurity, and 18.2% had a frequent sickness in siblings. The most common complaint accompanying chronic cough in patients was frequent respiratory tract infection, 16.3%. Along with IgG, 26.4% of the patients had low IgA and 31.5% had low IgM in laboratory testing. In antibody responses, isohemagglutinin, anti-tetanus, anti-pneumococcal, anti-HBs vaccine responses were found to be positive in 90.6%, 63.9%, 66.7% and 97.7% of the cases, respectively. 72.7% of the patients received inhaler treatment, 45.5% received antibiotic prophylaxis, and 2.2% received intravenous immunoglobulin (IVIg) treatment. After the IgG value of the patients returned to normal, it was observed that 86.3% of the patients’ cough complaint have disappeared.

Transient hypogammaglobulinemia of infancy mostly presents with recurrent lower and upper respiratory tract infections. The most common complaint is cough. It is not questioned whether the cough is chronic or not. In this study, we aimed to investigate the follow-up and prognosis of patients under the age of five who had a chronic cough complaint, when other causes of cough were ruled out and THI was detected. In the study, when the IgG levels of the patients return to normal, the cough complaints disappear to a large extent, showing that THI may also be among the causes of chronic cough.

Keywords: chronic cough, infant, transient hypogammaglobulinemia

Introduction

Cough is an important reflex that protects the airways from secretions and foreign substances. It is the most common reason in pediatric patients to seek for treatment all over the world. Prolonged coughing reduces the quality of life of children and their families. Children’s sleep patterns are disrupted and it becomes a source of stress for parents. However, cough leads to frequent doctor visits and many unnecessary examinations. In addition, excessive drug treatment causes a serious increase in health expenditures.

The American College of Chest Physicians and the European Respiratory Society define a cough that lasts longer than four weeks as a chronic cough. Many factors are involved in the etiology of chronic cough. Differential diagnosis is made according to the patient’s symptoms accompanying cough, history and physical examination findings. It can also be the first symptom of a simple upper respiratory tract infection or a serious diseases such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD), immunodeficiency. Studies have shown that recurrent viral infections, gastroesophageal reflux disease (GERD), persistent bacterial bronchitis (PBB), asthma, transient whetting in infants, congenital malformations, CF, PCD, and sinusitis are among the most common causes of chronic cough in children under the age of five. However, neither transient hypogammaglobulinemia of infancy (THI) among the causes of chronic cough, nor chronic cough among the complaints of THI are not questioned.

Transient hypogammaglobulinemia of the infancy is a primary immunodeficiency characterized by a transient low serum IgG level. The diagnosis is made when IgG value is below the normal value for age in the first three years of life, defined causes of hypogammaglobulinemia are excluded, and spontaneous resolution before 4
years of age (ESID 2019). In some patients, low IgG may be accompanied by low IgA and IgM. Normal flow cytometric analyzes are a finding that supports THI. Although the age of recovery of hypogammaglobulinemia is reported as 4 years, studies have also shown that the age of recovery extends up to 6-10 years 9-11.

Patients usually present with recurrent upper respiratory tract infections, bronchiolitis, pneumonia, otitis, atopy; and less frequently, diarrhea and urinary tract infections10,12,13. The most common complaint is cough. In the etiology of THI, it is usually the nature of cough.

Generally, the nature and duration of cough are not questioned in the etiology of THI. In our study, we aimed to retrospectively evaluate the follow-up and prognosis of patients under the age of five who presented with the complaint of chronic cough, and whose other causes of cough were excluded.

Materials and Methods

Patient Selection

Our study included 55 pediatric patients aged 8 months to 5 years who applied to the pediatric pulmonary diseases outpatient clinic with the complaint of chronic cough between January 2015 and December 2020. Demographic, clinical and laboratory characteristics and follow-ups of these patients were reviewed retrospectively. Inclusion criteria; 1) Patients whose other causes of chronic cough (GERD, PBB, etc.) have been excluded, 2) Patients whose IgG value is below normal for age at admission and who meet the definition of THI according to ESID criteria. Exclusion criteria; Those with underlying immunodeficiency, congenital anomalies, asthma, tuberculosis, CF, PCD, bronchiectasis and swallowing dysfunction were excluded from the study.

None of the 11 patients with prematurity met the criteria for Broncho Pulmonary Dysplasia, and the Ig values of the patients were evaluated according to their corrected age 14. In our study, 603 of 1690 patients who applied with the complaint of cough resulted in low IgG values. 460 of 603 patients were excluded from the study due to lack of follow-up examination or comorbidities. 55 of 173 patients were included in the study, as 17 of the remaining 143 patients had lymphocyte subpopulations abnormalities and 71 did not have control IgG (Figure 1).

Demographic characteristics of the patients, complete blood count, all immunoglobulins, vaccine responses, and treatments were reviewed retrospectively. It was evaluated whether the chronic cough improved with the normalization of the immunoglobulin level. Ethic committee approval was obtained for our study (23.09.2020/2020/2854).

Statistical Analysis

All data were analyzed using SPSS 25.0 package program. Marginal Homogeneity was used to compare the cases with more than two dependent categories. Independent Group T-Test was used in the analysis of independent paired groups of quantitative data. In the comparison of quantitative data, in the case of more than two groups, the One-Way ANOVA Test was used for intergroup comparisons of normally distributed parameters, and the Kruskal Wallis Test for intergroup comparisons of showing not normal distributed parameters. Post-hoc LSD Test was used in the case of difference found between groups in the One-Way ANOVA Test. In the study, p value <0.05 were accepted as statistically significant.

Results

Demographic characteristics of 55 patients included in the study are shown in Table 1.

The complaints accompanying chronic cough in the patients were frequent respiratory tract infection with 16.3%, frequent bronchitis with 14.5%, wheezing with 12.7%, and pneumonia with 3.6%.

Mean IgG values of the patients according to age; 388.57 ± 56.67 for 9-12 months, 526.55 ± 63.41 for 13-24 months, 515.00 ± 53.81 for 25-36 months, 545.56 ± 58.68 for 37-48 months. The difference of IgG values from the lower limit of normal values was determined according to the age group and prematurity status of the patients, but no significant result could be obtained regarding the difference (p>0.05).
When the laboratory values of the patients were examined; along with low IgG in all patients, 26.4% had low IgA and 31.5% had low IgM. 12.7% had anemia, 1.8% had neutropenia, 1.8% had eosinophilia, and 9.3% had elevated IgE. When we look at specific antibodies, isohemagglutinin, anti-tetanus, anti-pneumococcal, anti-HBs vaccine responses were found to be positive in 90.6%, 63.9%, 66.7% and 97.7% of the cases, respectively. Lymphocyte subpopulations were normal in all patients (Table 2).

As treatment, 72.7% of the patients received inhaled corticosteroids, 45.5% received antibiotic prophylaxis, and 2.2% received IVIG. The mean duration of inhaler treatment was 7.38 ± 10.1 months and the mean duration of antibiotic prophylaxis was 5.55 ± 9.43 months. Duration of inhaler treatment and antibiotic prophylaxis was at least 2 months and at most 36 months (Table 3).

The IgG levels according to the age ranges of the patients are given in Table 4 and the effect of age at presentation on the IgG recovery time is given in Table 5.

During the follow-up period, 75% of the patients had bronchiolitis at least once, and 77.2% of them were hospitalized for lower respiratory tract infection (LRTI) at least once. The mean number of hospitalizations (LRTI) was 2.43 ± 2.62, and the mean number of bronchiolitis was 2.70 ± 2.87. There was no difference in the number of hospitalizations due to LRTI, the number of previous bronchiolitis, the duration of inhaler treatment and the duration of taking antibiotic prophylaxis according to the age groups of patients (9-12 months, 13-24 months, 25-36 months, 37-48 months) (p> 0.05). None of the patients was hospitalized when IgG reached normal values for age. Thirty-eight (86.3%) of the patients no longer had a cough complaint during IgG recovery. When the IgG reached the normal value for age, the cough complaint of six patients continued for a maximum of one year (1-12 months) after the IgG reached the normal value for the age, but then improved.

Discussion

Among the most common causes of chronic cough etiology in children under the age of five, there are recurrent viral infections, GERD, transient whetting in infants, PBB, asthma, congenital malformations, CF, PCD, and sinusitis. THI is not among these reasons.

While investigating the causes of cough in children aged 5 years who are frequently sick, have recurrent respiratory tract infections and chronic cough, it is also useful to evaluate the immune system. Because more than 8 upper respiratory tract infections (URTIs), and 2 or more previous pneumonia are the two of the previous criteria of the Jeffrey Modell Foundation. We also looked at the complete blood count and Ig’s as the first step tests for immunodeficiency in children under 5 years old who presented with the complaint of chronic cough. We retrospectively evaluated the follow-up and prognosis of children under the age of five who had low IgG, other immunodeficiencies were excluded, and the IgG level returned to the normal range for age. Because, when we look at the literature, we could not find any data on THI in the etiology of chronic cough in this age group. Since it is known that immunological maturation is not the same in every child, we thought that it may play a role in the etiology in children under the age of five.

In patients under the age of five who have a chronic cough complaint, other causes of cough have been ruled out, and we have detected THI; we found that 86.3% of the patients no longer had a cough complaint after their IgG value returned to normal. The complaints accompanying chronic cough were frequent respiratory tract infection with 16.3%, frequent bronchitis with 14.5%, wheezing with 12.7%, and pneumonia with 3.6%. As treatment, 72.7% of the patients required inhaled corticosteroid, 45.5% required antibiotic prophylaxis, and 2.2% IVIG.

In the study of Yorulmaz et al., the age at diagnosis of THI varied between 8 months and 48 months, with a mean of 24.6±11.3 months; Karaman et al. found the mean age at diagnosis to be 11.7±7.0 months, with a median of 10 months. In their study involving 30 patients, Doğu et al. reported the age of diagnosis as 6-46 months (15 below 24 months, 12 24-36 months, 3 36-45 months), and the mean age was 22.5 months. In our study, the mean age of THI detection in children presenting with chronic cough was 21.73 ± 11.50 months; min – max: 9 -47 months, which was consistent with the literature. 65% of the applicants were in
the first two years of age, and 16% were in the range of 36-47 months. We thought that the prolongation of the admission age was due to the fact that the patients went to different centers with the complaint of chronic cough until they came to us.

In a large-scale study on patients with primary immunodeficiency (PID) in Turkey, the prevalence of PID was found to be 30.5/100,000. The reason why this rate is higher than in Europe is the high rate of consanguineous marriages in our country. In our patients, 22.4% had parental consanguinity. Yorulmaz et al. found the rate of consanguineous marriage as 30% in their study.

While clinically asymptomatic in THI, it can also be seen as a very serious invasive infection. However, most of the studies have reported that the most common reason for admission is respiratory tract infections. Yorulmaz et al. reported 54% recurrent URTI, 50% LRTI, 41% sinusitis, 28% recurrent otitis in a study involving 287 cases. Keleş et al. most frequently 53% LRTI, 39% URTI; Doğu et al. reported 93% recurrent URTI, 26% pneumonia, 26% otitis. Karaca et al. reported that 70.3% of 101 patients with THI presented with recurrent URTI findings, 6.9% had recurrent wheezing attacks and 8.9% presented with LRTI. In our study, in addition to chronic cough, we found 16.3% had frequent respiratory tract infections, 14.5% had frequent bronchitis, 12.7% had wheezing and 3.6% had pneumonia. These studies are important in terms of emphasizing the role of THI in the etiology of chronic cough. In these studies, cough durations were not defined in the complaint. For this reason, chronic cough is not mentioned in the literature among the complaints of THI. However, it should be kept in mind that cough is the most typical complaint of URTI and LRTI and this cough can last up to 8 weeks.

Low IgG can be accompanied by low IgM and IgA in THI. It was found that 26.4% of our patients had low IgA and 31.5% had low IgG along with low IgG in our patients. In the study of Keleş et al., they found low IgA in 28.1% of the patients and low IgM in 23.4%. In the study of Doğu et al., it was found that all of the patients had low IgG along with low IgA in 43% and IgM in 20%; and they reported that lymphocyte subpopulations were measured in 20 patients and all of them were normal. In our study, low IgA and IgG levels were found to be compatible with the literature.

In our study, seven patients (12.7%) had anemia, one patient (1.8%) had neutropenia, one patient (1.8%) had eosinophilia, and five patients (9.3%) had elevated IgE. Only one of our patients had milk positivity in the skin prick test and the IgE value was the highest. Yorulmaz et al. included 287 patients with anemia in 108 patients (37.63%), neutropenia in 11 patients (3.83%), and lymphopenia in four patients (1.39%). In our study, anemia and neutropenia were lower than in the literature. We did not detect lymphopenia in any of our patients.

Improvement in THI usually takes place up to 3 years of age. In the ESID 2019 guideline, it has been accepted as a criterion to be before the age of 4 as an improvement. However, there are studies indicating that this period may be much longer. In one study, it was found that only 25% of the cases recovered before the age of 3, and the mean recovery age was 68.87 ± 36.5 months (min: 20 months, max: 192 months). In their study, Küttükçüler et al. reported that Ig levels improved at an average of 5 years (62.5±21.8 months), while Dalal et al. reported that the improvement in IgG extended up to 10 years. In our study, the mean age of recovery was 38.65 ± 16.81 months; min-max: 14-78 months; mean recovery time was 16.93 ± 12.85 months; min-max: 3-47 months.

Supportive and infection-oriented symptomatic treatment is given as treatment in THI. Antibiotic prophylaxis is preferred in case of recurrent infections. Rarely, IVIG treatment can be considered in severe infections that do not respond to antibiotics. In our study, 72.7% of the patients were treated with inhaled corticosteroids and 45.5% with prophylactic antibiotics (trimethoprim (5 mg/kg) – sulfamethoxazole) as a single dose three days a week received. Only one patient (2.2%) received 5 doses of IVIG every 3 weeks due to recurrent pneumonia. Yorulmaz et al. administered trimethoprim-sulfamethoxazole prophylaxis to 129 of 287 cases (44.9%), and IVIG treatment to 2 patients (0.69%). Kidon et al. reported that four (23.5%) of 17 patients received antibiotic prophylaxis and two (11.7%) received IVIG. Doğu et al. reported two (6.6%) of 30 patients, Kılıç et al. reported that two out of 40 patients (5%) needed short-term IVIG treatment.
In our study, during the IgG recovery period, 77.2% of the patients had a history of hospitalization due to LRTI and a history of bronchiolitis in 75%. The maximum number of hospitalizations was 10. This was the patient who used the longest inhaler and antibiotic prophylaxis. None of the patients were hospitalized after IgG recovery. When IgG improved, 86.3% of the patients did not have a cough complaint. After the IgG levels of the patients whose cough continued, the cough complaint completely disappeared within one year at the latest. This made us think that THI may play a role in the etiology of chronic cough in infancy and should be investigated in the etiology. The improvement of the patients’ IgG and the disappearance of chronic cough supports our thesis.

The limitations of our study; 1) due to the retrospective nature of our study, all causes of chronic cough in children under the age of five could not be identified separately, 2) where was a lack of data due to the fact that the information was obtained from the patient registry files, 3) we excluded the patients who were thought to have THI but could not see improved IgG because they did not come to the follow-up, which reduced total number of THI patients, 4) not showing for appointments in patients after cough complaints have improved, 5) the disruption of outpatient services due to the COVID-19 pandemic and the prolongation of the follow-up periods due to the patients’ reluctance to come for control.

In conclusion; THI should be considered in recurrent URTI and LRTI under the age of five. Cough is the most common complaint in these patients. There is no information in the literature about THI in the etiology of chronic cough. Our study predicts that THI may be involved in the etiology in chronic cough. This study is of a preliminary nature, and the continuation of the prospective study is planned. Prospective studies with a much higher number of patients are needed in this regard.

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Table 4. Descriptive information on IgG levels according to age ranges of patients
Table 5. Comparison of follow-up time according to age group of patients

Figure
Figure 1. Flow chart

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