Ann Med Res 2021;28(4):685-8

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.03.278

Original Article

Non-cystic fibrosis bronchiectasis: Etiologic approach and effects of long-term azithromycin in children

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Abstract

Aim: Non-cystic fibrosis bronchiectasis (NCFB) is a chronic pulmonary problem that includes a group of heterogeneous diseases. Macrolide antibiotics are increasingly prescribed for patients with NCFB, but there are very few studies on their use in children. This study aimed to search the clinical features of children with NCFB and the effect of long-term use of azithromycin on the frequency of aggravation, microbiological reproduction, and pulmonary function tests.

Materials and Methods: A total of 79 cases diagnosed with NCFB were recorded. Clinical, laboratory, and radiological evaluations were also recorded. Exacerbation frequency, sputum cultures, and pulmonary function tests of 27 children who received azithromycin before and during prophylaxis were also analyzed.

Results: The median age of children was 7.6 years old (1 to 16 years), when the children were diagnosed with NCFB. Bronchiectasis etiology was detected in 62 patients. Primary ciliary dyskinesia (PCD) was the most common cause of bronchiectasis, which 24 (30%) children were diagnosed with PCD. Azithromycin treatment was given to 27 bronchiectasis patients for six months. A statistically significant decrease was detected in pulmonary aggravation frequency and sputum microbiology during azithromycin treatment ($p < 0.01$). No significant difference was detected in the pulmonary function tests with azithromycin treatment ($p > 0.05$)

Conclusion: The use of azithromycin in children with NCFB improves aggravation frequency but has no significant effect on the pulmonary function test.

Keywords: Azithromycin; non-cystic fibrosis bronchiectasis; primary ciliary dyskinesia; pulmonary exacerbation

INTRODUCTION

Bronchiectasis is an abnormal and permanent enlargement of the bronchi. While in some cases it is asymptomatic, it is often accompanied by chronic sputum, persistent cough, airway obstruction, and recurrent episodes of infection (1). Cystic Fibrosis (CF) is the most common hereditary reason of bronchiectasis; however, there are so many reasons of bronchiectasis, including immune deficiency, primary ciliary dyskinesia (PCD), postinfectious etiologies, protracted bacterial bronchitis, and aspiration syndromes (1-3). Postinfectious bronchiectasis incidence has reduced with the development in vaccination programs, proper antibiotherapy, and nutritional status. Impaired mucociliary clearance and permanent damage to the airways due to recurrent lung infections are the main factors involved in its pathophysiology. Haemophilus influenzae, pseudomonas aeruginosa, and streptococcus pneumonia are the most common isolated pathogens (4). The goals of the management of non-cystic fibrosis bronchiectasis (NCFB) are to decrease aggravation severity and frequency, improve respiratory function, and enhance quality of life. Recently, long-term use of macrolides has been reported to improve respiratory function and decrease the number of pulmonary aggravations (4,5). Macrolides have positive effects on the immunomodulatory and anti-inflammatory system in addition to its antibacterial effect (5). However, there have been few studies on the effect of macrolides on NCFB in children.

This study aimed to identify the underlying causes of bronchiectasis in children with a history of bronchiectasis diagnosis. We also aimed to find the effect of long-term use of azithromycin on aggravation frequency, microbiological reproduction, and pulmonary function tests.

MATERIALS and METHODS

Children with NCFB who visited Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Pediatric Pulmonology in Istanbul, Turkey between 2015 and 2020 were included in the study. The study was approved by the Medical Ethics Committee of Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey (document submission number: 2020/ 83045809-604.01.02)

Received: 29.03.2020 **Accepted:** 03.07.2020 **Available online:** 21.04.2021
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The study included 79 children diagnosed with bronchiectasis with clinical and radiological findings. A history of a cough with chronic productive sputum lasting at least three months was considered as chronic bronchiectasis. Patients with CF were excluded from the study group. The following demographic and clinical variables were evaluated; age, gender, age at symptom onset, age of diagnosis, coughing, wheezing, sputum, shortness of breath and weakness, findings such as dyspnea, ral and roncus. In all patients, total blood count, immunoglobulin levels (IgA, IgE, IgG, IgM), lymphocyte subgroups, chest X-rays, chest computerized tomography (CT), sputum cultures, and flexible bronchoscopy findings were evaluated. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in older than six years age of children who have ability to perform a pulmonary function test, bronchoalveolar lavage analysis, skin prick applications, nitroblue tetrazolium (NBT) tests, echocardiogram,tuberculin tests, alpha-1 antitrypsin levels, and gastroesophageal reflux were also investigated. A spirometry test was made according to the American Thoracic Society standards. Patients with a Primary Ciliary Dyskinesia Rule score ≥6 were considered to have PCD [6]. Exome analysis was performed in all these patients for the diagnosis of PCD, and the variants were evaluated using databases such as Online Mendelian Inheritance in Man (OMIM), ORPHANET, ExAC, 1000Genomes, and ESP; analysis programs such as Mutation Tester, PolyPhen2, PROVEAN, SIFT, GERP, and CADD.phred; and segregation patterns. We could not perform nasal nitric oxide measurements, electron microscopy, or rapid videomicroscopic examinations.

Twenty-seven bronchiectasis patients who were given 10 mg/kg of azithromycin prophylaxis a day three days a week for six months were evaluated retrospectively. The patients receiving azithromycin consisted of those who had more than two pulmonary aggravations in the past six months. The patients were called for follow up evaluations to the hospital every month and their physical examinations were performed and their symptoms were questioned. Sputum culture was taken from all 27 bronchiectasis patients just before starting azithromycin treatment and only patients with symptoms during treatment. Some patients had more than one growth in sputum cultures. Acute exacerbation was defined as a persistent (>24 h) increase in respiratory symptoms (fever, cough, sputum, dyspnea), new opacification on chest Xrays or worsening in physical examination findings of the chest or decrease more than 10% in FEV1 levels. In patients receiving six months of azithromycin, the following factors were checked:

- Number of infective aggravations and sputum cultures six months prior to and during treatment

- FEV1 levels before and after azithromycin treatment

Statistical Analysis

Data were analyzed using SPSS ver. 25.0 software and a p-value <0.05 was considered to reflect significance. The independent-samples t-test or the Mann-Whitney U-test was used to compare continuous variables, depending on their distributions. We present means ± standard deviations (SDs).

RESULTS

Our study had 79 children with NCFB with a median age of 13.7 years (4 to 18 years), of whom 45.5% (n = 36) were male and 54.5% (n = 43) were female. The median age of children was 7.6 years old (1 to 16 years), when the children were diagnosed with NCFB. Thirty-two (41%) children exhibited consanguineous marriages, and two children had a history of bronchiectasis in their siblings.

Productive cough was the most common complaint (n = 76, 96%), while crackles was the most common finding during physical examination (n = 62, 78.5%) (Table 1). Bronchiectasis etiology was detected in 62 patients. PCD was the most common cause of bronchiectasis, which 24 (30%) children were diagnosed with PCD. This was followed by a history of pneumonia (n = 15, 19%), immune deficiency (n = 9, 11.3%), tuberculosis (n = 7, 8.8%), aspiration/foreign body (n = 3, 3.7%), congenital malformation (n = 2, 2.5%), and scoliosis (n = 2, 2.5%). No etiologic cause of bronchiectasis could be specified in 17 (21.5 %) patients (Table 2).

Table 1. Symptoms and physical examination of children with NCFB

	N	%
Symptoms		
Productive cough	76	96
Sputum	63	**79.7**
Respiratory distress	32	40
Malaise	5	**6.3**
Hemoptysis	2	**2.5**
Physical examination		
Crackle	62	**78.5**
Rhonchus	23	29
Dyspnea	11	**13.9**
Clubbing	4	5

N: Number of children, NCFB: Non-Cystic fibrosis bronchiectasis

Table 2. Etiological factors of bronchiectasis in children with NCFB

	N	%
Etiological Factors		
Primary ciliary dyskinesia	24	30
Idiopathic bronchiectasis	17	**21.5**
History of pneumonia	15	19
Immunodeficiency	9	**11.3**
Tuberculosis	7	**8.8**
Aspiration /foreign body	3	**3.7**
Congenital malformation	2	**2.5**
Scoliosis	2	**2.5**

N: Number of children, NCFB: Non-Cystic fibrosis bronchiectasis

According to the results of chest CT, bilateral involvement in both lungs was observed in 53 patients (67%). Bronchiectatic lesions were most commonly seen in the left lower lobe in 49 patients (62%) and the right lower lobe in 37 patients (46.8%).

Azithromycin treatment was given to 27 bronchiectasis patients. 52.1% were female, and the median age was 13.7 years (8 to 18) in children. The etiology of these patients was detected to be PCD in 44% (n = 12), idiopathic in 41% (n = 11), an anamnesis of previous pneumonia in 11% (n = 3), and aspiration/foreign body in 4% (n = 1). The efficacy of azithromycin on aggravation frequency, sputum microbiology and FEV1 was evaluated. The monthly exacerbation frequency was 0.6 before azithromycin and 0.23 during azithromycin treatment. Similarly, the number of bacterial sputum growths was 31 before azithromycin and 12 during azithromycin treatment. There was also a significant decrease in aggravation frequency ($p < 0.01$) and the number of sputum cultures ($p = 0.01$). In the pre- and post-azithromycin treatment period, the most common isolated pathogen in the sputum culture was H. influenza, while P. aeruginosa was the second (Table 3). Spirometry was made to 27 patients. Mean FEV1 was 77 ± 19 % for the pre- azithromycin period and 78 ± 21 % for the post-azithromycin period. No significant improvement in FEV1 percentage was detected with azithromycin prophylaxis ($p > 0.05$). There was not any side effects related to azithromycin during treatment.

Table 3. Effects of long-term azithromycin treatment in children with NCFB

	n	Pre-azithromycin tr.	Post- azithromycin tr.	p values
Exacerbation frequency (pm)	27	**0.6**	**0.23**	**< 0.001**
FEV1% (mean + SD)	27	77 + 19	78 + 21	**> 0.05**
Bacterial sputum growths	27	31	12	**< 0.001**

N: Number of children, pm: per month, tr: treatment, SD: standard deviation, NCFB: non-cystic fibrosis bronchiectasis

DISCUSSION

This study was aimed to find the etiology of bronchiectasis and the effects of long-term use of azithromycin on aggravation frequency, respiratory function tests, and number of sputum cultures. We confirmed that long-term use of azithromycin reduces the frequency of aggravation and the amount of microbiological reproduction but has no effect on FEV1 levels.

Bronchiectasis is an important pulmonary problem and may result from genetic disorders, recurrent infections, airway irritants, malnutrition and inadequate vaccination (7). Due to the early diagnosis of the disease, improvements in vaccination, nutrition, and antibiotic treatment, the incidence of the disease has been decreasing in recent years (8).

In our study, the median age was 7.6 years (1 to 16 years), when the children were diagnosed and 41% patients exhibited intermarriages. In the study by Karadag et al. 111 cases were reported with a mean age of 7.4 ± 3.7 years old and a prevalence of intermarriages of 42.6 % (7). Although the intermarriage rate in the general Turkish population is 21.2%, the higher intermarriage rate of their study may explain that hereditary factors are contained in the development of bronchiectasis in these populations.

A productive cough is the most common complaint in patients with bronchiectasis. In one study, chronic cough was detected in 35% of patients, and wheezing was detected in 10% of patients (9). In another study, Satırer and et al. found that a chronic cough was responsible for 94% of clinical applications (10). In present study, we found that the most common symptoms of bronchiectasis were 96% chronic cough, 79.7% sputum, and 40% respiratory distress.

Although the pathophysiology of bronchiectasis is well described, there are various etiologic factors of NCFB. Brower et al. studied 989 patients for etiological purposes between 1997 and 2002 years (11). The meta-analysis suggested that primary immunodeficiencies, infections, aspiration and PCD account for most patients. They also reported that 60% of children with bronchiectasis have an underlying etiology. In another study from our region, Karadag et al. identified bronchiectasis etiology in 62.2% of patients between 1987 and 2001 (7). The most common causes of bronchiectasis were infectious (29.7%), immunodeficiency (15.3%), and PCD (6.3%). Recently, PCD and primary immune deficiency have been increasingly more responsible for bronchiectasis. Bahceci et al. evaluated 110 patients with bronchiectasis between 2005 and 2015, with the most common causes in the etiology PCD (26.4%), bacterial bronchitis (22.8%), immune deficiency (11.8%), bronchiolitis obliterans (8.2%), and pulmonary problem due to gastro-esophageal reflux (3.7%) (12). In another study conducted by Satırer et al. the etiology of bronchiectasis was identified in 145 (78%) patients. Fifty-one percent of these patients were detected as having PCD (10). The prevalence was followed by immune deficiency (15%), tuberculosis (6%), a history of pneumonia (3.2%), and other anomalies (2.1%) in their study. In the present study, we found an underlying cause of bronchiectasis in 78% of patients, which was similar to Satirer et al. Specifically, PCD was demonstrated in 30% patients, a history of pneumonia in 19%, immunodeficiency in 11.3%, tuberculosis in 8.8% and other causes in 8.7%.

The damage and irreversible dilatation of the bronchial walls due to inflammation and repeated infection is the pathophysiology of bronchiectasis (1,4). Recently, long-term antibiotic therapy has been used to eliminate pathogens in the pulmonary system, which may, in turn, interrupt infection and inflammation. Studies have demonstrated that long-term antibiotics have exhibited better clinical responses as well as a reduction in lung inflammation in NCFB patients (4,13). Macrolides are frequently used in bronchiectasis patients in long-term treatment due to their anti-inflammatory, anti-infective, and immunomodulatory effects (4,5). Some studies have also shown decreased pulmonary aggravations, decreased sputum volumes, and improvements in pulmonary function with long-term macrolide treatment (13,14). In the study by Wong, the treatment with azithromycin reduced the amount of aggravations requiring antibiotic treatment during the six-month treatment period but had no statistically significant increase on FEV1 (14). In another study, it was found that azithromycin treatment was associated with lower aggravation frequency and higher FEV1 levels (15). Yalcin et al. described children with NCFB and found that treatment with macrolides reduced IL8 levels in bronchoalveolar lavages but had no effect on FEV1 (16). In addition, Anwar et al. reported azithromycin treatment improved exacerbation frequency, spirometry, and sputum microbiology in patients with bronchiectasis (5). In the present study, azithromycin treatment for six months in children with NCFB reduced exacerbation frequency and the number of bacterial sputum growths but produced no improvement in FEV1 levels.

LIMITATIONS

The limitation of this study include the 6-month follow-up period is limited and improvement in FEV1 may be detected during longer time.

CONCLUSION

In conclusion, the long-term azithromycin treatment in the children with NCFB reduces aggravation frequency and sputum microbiology. This treatment option should be considered in cases of challenging bronchiectasis.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study was approved by the Medical Ethics Committee of Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey (document submission number: 2020/83045809-604.01.02).

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