Comparison Of Clinical Characteristics Between Two Non-Cystic Fibrosis Bronchiectasis Children Cohorts Followed Up From A Single Tertiary Center At Different Time Intervals

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Abstract

Background The diagnosis of non-cystic fibrosis (CF) bronchiectasis is increasing in both developed and nondeveloped countries in recent years. Although the main features are similar, etiologies seem to change. Our aim was to evaluate the clinical and laboratory characteristics of non-CF bronchiectasis patients and to compare these data with our previous cohort in 2001. Methods 104 children with non-CF bronchiectasis being followed-up between 2002 and 2019 were enrolled. Age of diagnosis, underlying etiology and distribution of microorganisms in sputum culture were recorded. Clinical outcomes were evaluated in terms of lung function tests and annual pulmonary exacerbation rates at presentation and within the last 12 months of the follow-up. Results Mean FEV1 and FVC % of predicted at presentation were improved compared with previous study (76.6±17.1 vs. 63.3±22.1 and 76.6±15.1 vs. 67.3±23.1, respectively; $p<0.001$). There was a significant decrase in pulmonary exacerbation rate from 6.05±2.88 at presentation to 3.23±2.08 during follow-up ($p<0.0001$). In 80.8% of patients, an underlying etiology was identified. There was an increase in primary ciliary dyskinesia (PCD) (32.7% vs. 6.3%;p:0.001), decrease in idiopathic cases (19.2% vs. 37.8%;p: 0.03) with no change in postinfectious and immunodeficiencies. Sputum cultures were positive in 77.9% of patients which was 46.9% in the previous study ($p=0.001$). Conclusion Baseline pulmonary function tests were better and distribution of underlying etiology had changed with a remarkable increase in diagnosis of PCD. Recent advances in diagnosis also makes it easier to evaluate the patients in a better way, still awaiting for international consensus and guidelines on non-CF bronchiectasis in children.

Background

Childhood bronchiectasis is a chronic pulmonary disorder defined as a clinical syndrome (persistent or recurrent [>3] episodes of chronic wet or productive cough, sometimes with coarse crackles and digital clubbing), confirmed by the presence of bronchial dilation in high resolution chest tomography (HRCT) [1]. Although bronchiectasis has been called as an orphan disease in the past, it is now considered as one of the most common causes of chronic respiratory disease in both developed and undeveloped countries [2].

The exact incidence of non-cystic fibrosis (CF) bronchiectasis in children is not known, but studies from England and New Zealand people of European heritage reported the incidence as 0.2/100,000 and 1.5/100,000 per year respectively; whereas incidence was highest in Pacific children as 17.8/100.000 [3,4]. Main etiologies for non-CF bronchiectasis are infections, immune deficiencies, primary ciliary dyskinesia (PCD), and aspirations, but in 34% of patients no underlying cause was identified [5]. Both in developed and non-developed countries, postinfection was the leading etiology of non-CF bronchiectasis in the past years [3]. Highest incidences were reported in socially disadvantaged populations of developed countries as 90% by Chang et al from Australia and 93% by Singleton et al from Alaska [6,7]. Brower et al in a review including 12 studies found recurrent lower respiratory tract infections as the most commonly seen underlying cause (61%), followed by measles (14%), tuberculosis (11%) and pertussis (5%) [5]. With improvement in vaccination programs, prevention of diseases like measles and pertussis, effective tuberculosis control programs, easy access to health care and effective treatment of lower respiratory tract infections incidence of postinfectious bronchiectasis decreased to 7-12% in developed countries [8-10]. Immune deficiencies (10-34%) and PCD (2-24%) as the underlying reason were generally reported more frequently in developed countries with no change in the frequency over the years [8-13]. Idiopathic cases did not seem to change in the frequency in both developed and underdeveloped countries in the last years. Kapur et al in a recent study found no underlying etiology in 55% of patients in a developed country [9]. Also in a study conducted with 80 children from India by Kumar et al, 36% patients were classified as idiopathic [14].

Although there is a decrease in post infectious bronchiectasis in developed countries, overall prevalence of non-CF bronchiectasis appears to be increasing particularly in adults [15-16]. This increase in prevelance may partly be related with improved diagnostic rates secondary to less severe childhood respiratory infections, widely use of HRCT and other diagnostic tests.

We previously reported clinical features of non-CF bronchiectasis followed in our department between 1987-2001 [17]. To our knowledge, changes in general characteristics of patients with non-CF bronchiectasis in time in the same center have not been reported previously. Due to the changes in

treatment of lower tract infections, increase in vaccination and having a better access to diagnostic facilities, underlying etiologies may be affected. And we hypothesized that the etiology and other characteristics of non-CF bronchiectasis were changed over time. Our aim was to evaluate the changing characteristics of non-CF bronchiectasis in a decade with the patients totally different from the previous cohort and compare the results between two study population.

Methods And Materials

This was an observational study including two cohorts in the same center. Cohort 1 consisted from non-CF bronchiectasis patients (<18 years of age) who have been followed in the Marmara University Pediatric Pulmonology Department between 2002-2019. Cohort 2 consisted from patients enrolled in our previous study which was done between 1987-2001. Collected data were compared with our previous cohort. Study was approved by the local ethical comity and informed consent was taken from the patients families.

Diagnosis of bronchiectasis was based on the clinical and radiological features. Patients with a clinical history of recurrent or persistent productive cough, sputum, wheeze, breathlessness unresponsive to treatment and recurrent lower respiratory tract infections were evaluated for bronchiectasis. Bronchiectasis confirmed by the HRCT which was obtained during an asymptomatic period and at least 3 months later after the last infectious exacerbation. Bronchiectasis was diagnosed if there was evidence of bronchial dilation (internal bronchial diameter greater than the accompanying pulmonary artery) and a lack of bronchial tapering on sequential slices [18]. The bronchi were evaluated on a lobar basis (regarding the lingula as a separate lobe). Bronchiectasis was defined as localized if only one lobe, and multilobar if more than one lobe was was affected.

Study Design

Patients were followed up at 3 months intervals. At each visit, patients or parents were asked about the presence of symptoms (cough, sputum, wheezing, dyspnea, hemotysis) and frequency of antibiotic usage since last visit. Demographic, clinical and laboratory data including gender, age at the of onset of symptoms, duration of symptoms before diagnosis, age at diagnosis, presence of consanguinity, presenting symptms; history of previous lower respiratory infections including

pertussis, measles, varicella, tuberculosis before the diagnosis; number of lower respiratory tract infections within the previous 12 months at presentation and within the last 12 months of the follow-up requiring peroral or intavenous antibiotics or hospitalization), history of surgery for bronchiectasis, localization of bronchiectasis and pulmonary fuction test results were retrieved from medical records. Pulmonary exacerbation was defined as change in cough quality from dry to wet and/or sputum production, breathlessness, chest pain, crepitations, wheeze and increase in values of infectious markers [19]. The presence of clubbing of the fingers, chest deformities and nasal polyps were noted on physical examination. For microbiological evaluation, sputum samples were obtained and cultured for bacteria.

For the etiological work-up of bronchiectasis, immunological evaluation including IgG, M, A and E, IgG subclass levels, specific antibody responses to tetanus toxoid, capsular polysaccharides of *Streptococcus pneumonia* and surface antigen of Hepatitis B virus, T lymphocyte subsets and neutrophil function tests were done to all patients. In order to exclude CF, sweat test and genetic analysis (if required) were performed and patients with positive sweat tests (chloride levels >60 mEq/l) or two CF mtations were excluded from the study.

Postinfectious etiology was evaluated by asking history of childhood lower respiratory infections including measles, pertusis, varicella and tuberculosis. We performed tuberculin skin test (TST) to all patients and patients with positive TST were re-evaluated further for tuberculosis.

PCD was diagnosed by the electronic microscopic evaluation of nasal cilia biyopsy and/or positive immunofluorescence staining and/or decreased nasal nitric oxide level measurement and/or the presence of dextrocardia with the typical findings of PCD and PICADAR score>5. In patients with the presence of dextrocardia with the typical findings of PCD and/or PICADAR score >5, nasal nitric oxide measurement or electronic microscopic evaluation of nasal cilia biyopsy was performed. Nasal nitric oxide cutoff value for PCD was defined at 77 nl/minute [20]. In patients with a decreased nasal nitric oxide levels but a negative electronic microscopic result or in whom evaulation could not be done, immunofluorescence staining was performed in Muenster University Hospital. Antibodies against DNAH5, GAS8, DNAH11 and RSPH9; in some selected cases DNALI1 and CCDC39 were asessed.

Asthma was diagnosed if a patient had symptoms suggesting bronchial hyperreactivity and positive bronchodilator response. Patients followed up with diagnosis of asthma in a pediatric pulmonology clinic before the diagnosis of bronchiectasis with a normal HRCT scan during this period were labelled as asthma. Patients without an underlying etiology for bronchiectasis classified as idipathic bronchiectasis.

Spirometry (MIR Srl Spirobank, Rome, Italy) was performed according to the criteria of the American Thoracic Society by all children able to cooperate. Measurements included forced vital capasity (FVC) and forced expiratory volume in 1 second (FEV1); values were expressed as percentage of the predicted normal values [21]. Measurements were repeated 15 min after inhalation of 2 puffs (200 microgram) salbutamol given by metered dose inhaler via a spacer (Volumatic, Allen & Hanburys, Uxbridge, UK). A positive bronchodilator response was defined as an FEV1 improvement of more than 12% of baseline [22].

Statistical Analysis

Statistical analysis was carried out with with SPSS for Windows version 20.0. Continuous variables were described through means, standart deviations and medians, whereas catergorical variables were presented as frequency and percentages. Categorical variables were compared with Chi-square or with Fisher’s exact test when 20% of the expected frequencies were less than five. Continuous variables among two groups were compared with Mann–Whitney U test, since the data did not follow a normal distribution. Continous variables for paired groups were compared through Wilcoxon test. Results were evaluated in 95% confidence interval and significance level was set at *p* value of 0.05.

Results

Demographic characteristisc:

Current study included 104 patients diagnosed as bronchiectasis after 2002 (45% male) with a median age of 8 years (range, 0.1-16.5) at presentation.

Table-1 shows the general characteristics comparing two cohorts. In the present cohort, median age of diagnosis was 7 years. The most common presenting symptom was cough (95.2%) followed by sputum (77.9%), wheezing (42.3%) and dyspnea (51%), respectively. There was a history of

hemoptysis in 6.7% of patients which was found 10% in the previous study (p=0.40). On physical examination, clubbing was present in 21.2% and chest deformity in 11.5% of the patients (p=0.02 and p=0.53, comparing both groups, respectively).

In terms of pulmonary functions of the patients, there was an statistical increase in the mean values of FEV_1 and FVC % of predicted (p=<0.001) in the current study. Similar to the previous study, annual lower respiratory tract infection rate was also decreased from 6.05±2.88 at presentation to 3.23±2.08 during follow-up (p<0.0001). There was no change between the basal and last FEV_1 % in their follow-up (76.6±17.1 vs. 76.96±18.1; p:0.91) which was statistically significant in the previous one (63.3 ± 22.1 vs. 75.2± 25.2; p<0.001).

Etiology

Underlying etiology was identified in 80.8 % (n:84) of the patients in the Cohort 2. (Table-2). Most common cause was PCD (32.7%), followed by infections (26%), immunodeficiencies (17.3%). There was a significant increase in the frequency of PCD (6.3% *vs*. 32.7%, p:0.001), and decrease in idiopathic cases (37.8% *vs.* 19.2%, p: 0.03) compared with the previous study. In the current study, there was no patient with history of foreign body aspiration. One patient with esophageal atresia and tracheoesophageal fistula (n:1) and two patients operated for complicated cardiac disease were classified in other group.

Localization of Bronchiectasis

Localizations of bronchiectasis were also similar with the previous study, and left lower lobe was the most affected lobe. In 38.5% of the patients there was one lobe involvement, mostly the left lower lobe (21.2%) similar to the previous study (p:0.75). Although statistically insignificant, there was a trend to decrease of multilobar involvement (31.9% vs. 21.4%, p=0.26) and trend to increase of bilobar involvement (28.1% vs 41.3% (p=0.09) in the current study compared with the previous study.

Sputum culture

Presence of positive sputum cultures was found to be increased in the current study (46.9% *vs*.

77.9%, p=0.001). Most frequently isolated organisms were *Hemophilus influenza* (71.8%), *Streptococcus pneumonia* (47.1%), *Morexella catarrhalis* (14.4%), *Pseudomonas aeruginosa* (11.5%) and *Staphylococcus aureus* (11.5%). Among these cultures, statistical differences were seen in *Hemophilus influenza*, *Streptococcus pneumonia* and *Morexella catarrhalis* (p:0.001, p: 0.001 and p: 0.03, respectively) between two studies (Table-3).

With regard to the treatment approach, surgery rate was decreased in the current study (23.4% *vs*. 6.7%, p=0.001).

Discussion

This study describes the changes in the patient characteristics and etiology of bronchiectasis in chidren from a single tertiary reference center beween 2002 and 2019. The results demonstrate that there was a major change in pulmonary function tests, distribution of etiology, sputum microbiology over the years. Baseline FEV1 values of the patients were found to be better suggesting milder form of bronchiectasis. Although post-infectious reasons seemed to be unchanged, availability of advanced diagnostic techniques made it possible to diagnose PCD in patients.

Diagnosis of bronchiectasis is often delayed in the whole world. In a study from Italy Santamaria et al reported that the median age at diagnosis was 7 years though the children were symptomatic from the median age of 6 months [10]. In developed countries late referral to specialist or misdiagnoses are the most common reasons for diagnostic delay. In the current study median age at diagnosis was 7 years whıch was same with our previous cohort. Three different studies from Turkey and studies from indigenous populations were also reported similar diagnostic age ranges (6.2-8.5 years) [23-26]. In developing countries lack of resources and difficulty in accessing medical services are the most probable causes of the delay in diagnosis [27]. In a recent review, Wurzel and Chang stated that better and more standardized definition of bronchiectasis in pediatric patients will facilitate earlier diagnosis, timely management and improve clinical outcomes in children with bronchiectasis [28]. Spirometry results of bronchectatic patients differ between the developed and developing countries. Lung functions of children from the developed countries were normal or near normal on diagnosis and stay stable longitudinally [10,29,30]. In a study conducted among 991 PCD patients from International

PCD cohort comparing with reference values, mean FEV1 and mean FVC were found to be lower than the mean reference values in all age groups with best lung function in children aged 6-9 years and the worst in adults [31]. Patients diagnosed at an early age had better lung functions and milder disease [29]. Studies from developing countries demonstrate a negative correlation between lung function and body mass index and quality of life [32]. Interestingly, a follow-up study enrolling Alaskan Native children confirmed patients with bronchiectasis had significantly lower FEV_1/FVC ratios than the chronic suppurative pulmonary patients without bronchiectasis [33]. In our study, baseline FEV_1 values were higher compared with the previous study. Although, there was an increase in FEV_1 during the follow-up in the previous study, there was no change in the current study. Early and intensive treatment of bronchiectasis has been shown to be preventing decline in FEV_1 [29]. Consistent with our study, Kapur et al reported that pulmonary functions remained stable in patients with a mean FEV_1 of 76.8±20.1% of predicted after five years follow up [29]. In the current study, better baseline pulmonary functions can be an explanation of a better treatment regimen for bronchectasis. In addition, presence of clubbing of the fingers was significantly decreased compared to the previous study supporting a milder form of bronchiectasis. Clubbing varies with a ratio of 20.7-52% and more common in developing countries [26,34,35]. In a study conducted with non-CF bronchiectatic patients, 52% had digital clubbing and patients with digital clubbing were found to have more extent bronchiectasis but there were no association with pulmonary functions [35]. In the current study, there was no association with the clubbing of the fingers and lung functions or severity of the bronchiectasis. Although age of diagnosis did not differ, having better pulmonary functions and decreased incidence of clubbing may suggest patients in the current study had a milder form of bronchiectasis compared to 2000s. Possible explanations for these changes may be due to increased annual income, better vaccination and easy access to health care.

Besides similarity of main characteristics of bronchiectasis in developing and affluent countries, underlying etiology, nutritional status, frequency of exacerbations and severity of the disease are different [27]. In children with bronchiectasis, an underlying disease process is identified in 63% of

cases as shown in a systematic review of 12 studies including 989 children [5]. Previous pneumonia (17%), primary immunodeficiency (16%), recurrent aspiration, including inhaled foreign body (10%), and primary ciliary dyskinesia (9%) were among the most underlying etiologies. In developed contries, immunodeficiency is more commonly observed as the underlying disease in 9-34% of patient with bronchiectasis [4,8-13,26,35,36]. On the other side, in non-affluent countries bronchiectasis consequent to previous infection are more common, causing 17% to 28% of cases [23-25,37]. An important difference between affluent and non-affluent countries in terms of etiology is PCD reported to be higher in affluent countries (15-23.8%) [10,12]. In the current study, 32.7% of patients with non-CF bronchiectasis were diagnosed as PCD which was significantly increased compared with the previous study. Bahceci et al reviewed 110 patients between 2005-2015 and compared with their previous data for etiological reasons, reporting that the frequency of asthma and tuberculosis in etiology had decreased but primary ciliary dyskinesia (26.4%) and primary immune deficiency had increased in 10 years [24]. Underlying etiologies of non-CF bronchiectasis can be detected due to increased availability of diagnostic procedures. In our study only in 19.2% of the patients underlying etiology could not be identified similar with the studies from affluent countries [12,13]. PCD is more easily diagnosed by early recognition of signs and symptoms by physicians and availability of nasal nitric oxide, electrone microscopy, high speed videomicroscopy, immunoflorescence and genetic analysis.

Bronchiectasis has been reported to have multilobar involvement in most pediatric studies [10,12,23,25,34]. Kapur et al reported 73% children as having bilateral disease in their cohort of 52 children [29]. In the aspect of a developing country view, multilobar disease predominates with 71% in a study from Saudi Arabia [34]. In our study group, multilobar involvement was lower in contrast with literature. Although, there is a difference in involvement of lobes (less multilobar, more bilobar) between the previus and the current study, it did not reach statistical significance.

The British Thoracic Society bronchiectasis guideline emphasizes microbiological assessment for evaluating airway colonisation and infection [38]. Distribution of microorganisms in pediatric bronchiectasis is similar throughout the world. Studies from affluent countries have shown that *H.*

influenzae, *S. pneumoniae* and *M. catarrhalis* to be the major infecting lower airway organisms, whereas patients were colonized with Pseudomonas aeruginosa in 5-16% of children [39]. In the current study, in 22.1% of the patients sputum cultures were negative, which was significantly decreased compared with the previous study. Identification of *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* in sputum cultures were increased in this study. Increased numbers of positive sputum cultures may be due to the better qualified staff and equipment in microbiology laboratories leading to more accurate results, as the leading agents were similar in the current and the previous study. Early identification of microorganisms and effective treatment of infections may prevent progressive lung disease.

Surgery has been performed in fewer cases as the diagnosis is made promptly and the medical treatment improved. There are few data about long-term results of medical and surgical treatment, Nevertheless, correctly chosen cases may benefit from surgery. Resection of the affected lobe or segment may be another treatment option in patients with localised disease who does not respond or noncompliant to medical treatment [40]. In our study, only seven children (6.7%) underwent lobectomy, compared to 26 of 111 children (23.4%) the previous tudy showing the changing approach in time.

This study has some limitations. It was conducted in a single reference center. As a tertiary reference centre, many patients with suspicion of PCD were referred and this approach may cause a higher proportion of PCD patients. Increased availability of the diagnostic facilities for PCD may also support this finding.

In conclusion, this longitudinal study highlights the changing underlying etiology of pediatric non-CF bronchiectasis in a developing country setting. We have demonstrated a better lung function results, higher incidence of PCD, decreased incidence of idiopathic cases. An early and etiological diagnosis is essential not only to improve the course and prognosis of disease, but also to prevent a progressive decline in lung function. By the availability of non-invasive and effective diagnostic technologies, it is more easier to diagnose underlying etiology; but still early diagnosis is a problem worldwide. Unfortunately, most of the current data reflects individual center experiences. Establishment of both

national and international pediatric bronchiectasis registry is required to estimate the real prevalence, demonstrate the differences in characteristics of the disease between countries, to show the burden of the disease, and to facilitate researches and quality improvement initiatives across healthcare system.

Abbreviations

CF: Cystic fibrosis

PCD: Primary ciliary dyskinesia

HRCT: High resolution chest tomography

TST: tuberculin skin test

FVC: Forced vital capasity

FEV1: Forced expiratory volume in 1 second

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethical Committee of Marmara University Medical Faculty and informed consent was taken from the patients families.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTEREST

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

EEE, YG, RE, FK, BK researched literature and conceived the study. EEE, EA, NBI, PE, CYY, AK were

involved in protocol development, gaining ethical approval, patient recruitment and data analysis was performed by EEE and BK. EEE wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Tables

Due to technical limitations, the tables are available as a download in the supplementary files.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

Tables BE.pdf