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Primary Immunodeficiency Disorders in children with Non-Cystic Fibrosis Bronchiectasis

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Key words

Non-cystic fibrosis bronchiectasis; bronchiectasis; respiratory infections; common variable immunodeficiency; combined immunodeficiency; RASGRP1.

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Summary

Introduction. *Primary immunodeficiency diseases (PID) are common in patients with non-cystic fibrosis bronchiectasis (NCFB). Our objective was to determine ratio/types of PID in NCFB.*

Methods. *Seventy NCFB patients followed up in a two-year period were enrolled.*

Results. *Median age was 14 years (min-max: 6-30). Male/female ratio was 39/31; parental consanguinity, 38.6%. Most patients with NCFB (84.28%) had their first pulmonary infection within the first year of their lives. Patients had their first pulmonary infection at a median age of 6 months (min-max: 0.5-84), were diagnosed with bronchiectasis at about 9 years (114 months, min-max: 2-276). PID, primary ciliary dyskinesia (PCD), bronchiolitis obliterans, rheumatic/autoimmune diseases, severe congenital heart disease and tuberculosis were evaluated as the most common causes of NCFB. About 40% of patients (n=16) had bronchial hyperreactivity (BH) and asthma. Twenty-nine patients (41.4%) had a PID, and nearly all (n=28) had primary antibody deficiency, including patients with combined T and B cell deficiency. PID and non-PID groups did not differ according to gender, parental consanguinity, age at first pneumonia, age of onset of chronic pulmonary symptoms, bronchiectasis, presence of gastroesophageal reflux disease (GERD), BH and asthma ($p > 0.05$). Admission to immunology clinic was about 3 years later in PID compared with non-PID group($p < 0.001$). Five patients got molecular diagnosis, X-linked agammaglobulinemia (n=2), LRBA deficiency (n=1), RASGRP1 deficiency (n=1), MHC Class II deficiency (n=1). They were given monthly IVIG and HSCT was performed for three patients.*

Conclusions. *PID accounted for about 40% of NCFB. Early diagnosis/appropriate treatment have impact on clinical course of a PID patient. Thus, follow-up in also immunology clinics should be a routine for patients who experience pneumonia in the first year of their lives and those with NCFB.*

Introduction

Bronchiectasis is a chronic pulmonary disease of the conducting airways. It produces persistent productive cough, recurrent respiratory infectious exacerbations, and irreversible bronchial dilatation in children and adults. Two different types of bronchiectasis are defined according to the pattern of the lesion, diffuse and focal (1). Focal bronchiectasis is usually associated with bronchial obstruction, such as aspiration of foreign body, that leads to infection (2). Diffuse bronchiectasis is more often found in association with underlying disorders such as cystic fibrosis (CF), primary immunodeficiencies (PID), primary ciliary dyskinesia (PCD), and recurrent aspiration syndromes (3). Bronchiectasis is often a consequence and a complication of recurrent, uncontrolled respiratory infections and inflammation. In many studies, acute, severe or recurrent pneumonia is the

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most common cause (4,5). Subsequent acute or chronic damage in the conducting airways results in a significant physical and social morbidity (6). The diagnosis depends on radiological imaging of the typical changes in addition to clinical findings. Chest X-ray is sometimes insufficient to make the clinicians reach the diagnosis. Thus, a high-resolution computed tomography (HRCT) scan is the gold standard diagnostic procedure.
Nowadays, with early immunization and the widespread use of antibiotics in childhood, acute post-infectious damage is likely to be less relevant (7). However, especially in the countries which the consanguineous marriages are relatively frequent, chronic damage due to hereditary diseases of respiratory system, such as cystic fibrosis, PID and PCD is common cause of bronchiectasis (8).
PIDs are among the frequent causes of non-cystic fibrosis bronchiectasis (NCFB) (9). Bronchiectasis is seen as a common long-term complication especially in patients with primary antibody deficiency (PAD) (10,11). With a detailed history, physical examination and laboratory analysis, it is not difficult to detect the underlying immunological etiology. Our objective was to identify the ratio of underlying PID in patients with NCFB, and also evaluate the characteristic clinical, microbiological or radiological features in patients with and without PID.

Methods

In a two year period, 87 patients who were diagnosed with NCFB in pediatric chest disease department and referred to pediatric immunology department were retrospectively evaluated. Seventy patients come to the control visits in each department routinely. However, 17 out of 87 were lost follow-up.
Patients' clinical parameters such as age, gender, parental consanguinity, age at diagnosis, age at onset of infections were recorded from the files. The diagnosis of bronchiectasis was confirmed with a HRCT scan in each of the patients. Cystic fibrosis was excluded in the patient cohort via sweat chloride test and in some of them by mutation analysis in chest disease department (12). After exclusion of CF, patients underwent investigations for the common etiologies of bronchiectasis which included nasal nitric oxide (NO) test (n=64), gastroesophageal reflux scintigraphy (n=64), pulmonary function tests with spirometry (n=58) and flexible bronchoscopic evaluation (n=65).
Diagnosis of PCD was based on presentation of the characteristic clinical phenotype, nasal NO results, the presence of ciliary ultrastructural defects (visualized by electron microscopy), and the presence of abnormal ciliary function (as determined by video microscopy).
Bronchiolitis obliterans (BO) was defined as the presence of mosaic pattern in chest X-ray in addition to the history of respiratory symptoms which developed after a severe pulmonary infection, and the findings of obstructive airway disease which does not respond to bronchodilator therapy in respiratory function test.
Evaluation for possible immunodeficiencies included complete and differential blood counts, serum immunoglobulin levels (n=70), and lymphocyte subgroups (n=37), serum complement hemolytic activity (CH50) (n=39), nitroblue tetrazolium test (NBT) (n=50) and pneumococcal antibody response (n=26). European Society of Immunodeficiency and Pan-American Group for Immunodeficiency (ESID and PAGID) criteria was used for the diagnosis of PID (13). Selective IgA and selective IgM deficiency are diagnosed according to the ESID criteria (14). Secondary hypogammaglobulinemia is excluded by history, absence of renal, gastrointestinal and cutaneous protein loss, and other drug or disease related causes (15). Urinary analysis for proteinuria was done, total protein and albumin values were measured in all the patients with hypogammaglobulinemia. After exclusion of the secondary causes, some of the patients may be classified as idiopathic primary hypogammaglobulinemia (IPH), or undefined/unclassified hypogammaglobulinemia (16,17).
Sputum (n=64) and bronchoalveolar lavage (BAL) (n=65) results of the patients were also recorded to determine the microbiological etiology. The final diagnosis of the patients with NCFB were recorded after the follow-up period. All patients with NCFB were grouped according to having PID or not according to their final diagnosis (PID and non-PID).
The study is approved by the Institutional Review Board.

Statistical analysis

SPSS 18.0 was used for the statistical analysis. One-way ANOVA analysis was used for analysis of more than two groups. Pearson's correlation coefficient was used to evaluate correlation of two variables.

Results

Characteristics of Patients with Non-Cystic Fibrosis Bronchiectasis

The mean age was 14.23 ± 4.72 years (median: 14 (6-30)). Out of 70 patients, 39 (55.7%) were male, 31 (44.3%) were female. Parental consanguinity ratio was 38.6%. The patients had their first pneumonia at a median age of 6 months (0.5-84). Most patients (84.28%) had their first pulmonary infection within the first year of their lives. The median age of onset of chronic pulmonary symptoms (chronic cough, growling *etc*.) was about two years (24 months (0.5-276)). The median age at diagnosis of bronchiectasis was about 9 years (114 months (2-276)).
Out of 70 NCFB patients, 46 (60%) experiences other infections, such as tonsillopharyngitis, sinusitis, otitis media. Bronchial hyperreactivity was shown in 26 (37.14%) out of 58 patients by pulmonary function test. Gastroesophageal re-

flux disease (GERD) was shown in 12 (18.46%) out of 65 patients by scintigraphy. Lipid laden macrophages were detected in BAL in 18 (30.5%) out of 65 patients who were evaluated by bronchoscopy. The congenital heart disease found in one of the NCFB patients was ventricular septal defect and high venosum ASD. The patient had also pulmonary hypertension. The NCFB patients are grouped as PID (n=29, 41.4%), and non-PID (n=41, 58.6%).

Totally 18.6% (n=13) of NCFB patients, 31.7% of non-PID had the diagnosis of PCD, and among them two patients (15.4%) had Kartagener's Syndrome. One (complement deficiency) out of all PID group were associating with hypogammaglobulinemia (common variable immunodeficiency, combined immunodeficiency, agammaglobulinemia, *etc*. (**table I**)). Bronchial hyperreactivity and asthma (n=16, 39%), PCD (n=13, 31.7%), GERD (n=9, 21.9%), and BO (n=3, 7.3%) associate with non-PID (**table I**). Other associated diseases are rheumatic/autoimmune diseases (n=2, 4.9%), tuberculosis (n=2, 4.9%), and severe congenital heart disease (n=1, 2.4%) (**table I**).

The two groups did not differ according to gender, the age at first pneumonia episode, age of onset of chronic pulmonary symptoms, parental consanguinity, presence of BH and asthma, GERD, and frequency of infections (**table II**). Also, the age of diagnosis of bronchiectasis did not differ between groups

Table I *- Classification of PID and non-PID causes of NCFB.*

PID Group (n= 29 (41.4%))		**Non-PID Group (n= 41 (58.6%))**	
CVID	9 (30.9%)	Unidentified	13 (31.7%)
Combined immunodeficiency	6 (20.6%)	Asthma and bronchial hyperreactivity	16 (39%)
Selective IgA deficiency	4 (13.8%)	Primary ciliary dyskinesis	13 (31.7%)
IPH	3 (10.3%)	Gastroesophageal reflux	9 (21.9%)
Selective IgM deficiency	3 (10.3%)	Brochiolitis obliterans	3 (7.3%)
XLA	2 (6.9%)	Rheumatic/Autoimmune disease	2 (4.9%)
Hyperimmunoglobulin M syndrome	1 (3.4%)	Tuberculosis	2 (4.9%)
Complement deficiency	1 (3.4%)	Congenital heart disease	1 (2.4%)

CVID, common variable immunodeficiency; XLA, X linked agammaglobulinemia; Ig, immunoglobulin; idiopathic primary hypogammaglobulinemia, IPH.

Table II *- Characteristics of patients with PID and non-PID.*

	Non-Cystic Fibrosis Bronchiectasis		
Characteristics	**PID (n=29)**	**Non-PID (n=41)**	**p**
Gender (M/F)	19/10	20/21	0.16
Parental consanguinity	44.8%	34.1%	0.17
Age at first pneumonia*	9.1±13.9 / 6 (0-72)	9.4±13.7 / 6 (0-84)	0.83
Age at onset of chronic pulmonary symptoms *	43.6±53.7 / 24 (0-276)	31.8±35.9 / 18 (0-120)	0.23
Age at diagnosis of bronchiectasis*	139±64.3 / 132 (12-276)	124.4±62.9 / 108 (2-224)	0.22
Age at referral to Immunology department (year)	16.8±5.1 / 16 (10-30)	12.4±3.4 / 13 (6-20)	**<0.001**
Gastroesophageal reflux	4 (14.8%)	9 (24.3%)	0.69
Bronchial hyperreactivity and asthma	10 (38.5%)	16 (50%)	0.93
Frequent infections	16 (55.2%)	24 (58.5%)	0.61
Isolation of microorganism in sputum	13 (44.8%)	21 (51.2%)	0.59
Isolation of microorganism in BAL	9 (34.6%)	22 (66.7%)	**<0.014**
Lobectomy	2 (6.8%)	3 (7.3%)	0.53

* months.

Median (min.-max.) and mean (±standard deviation) ages are given in the table.

(108 months (2-224) in non-PID, and 132 (12-276) in PID) (p=0.223). The admission to immunology clinic in PID was 13 years (6-20), however it is 16 years (10-30) in non-PID ($p < 0.001$) (**table II**). Totally five patients underwent left-sided lobectomy, two was in PID, other two was in the group of unidentified causes of non-PID, one was PCD. The two PID patients who underwent lobectomy were diagnosed with Combined Immunodeficiency (CID) and common variable immunodeficiency (CVID). The patient with CVID developed amyloidosis and died of a severe pneumonia and respiratory failure (18). Genetic tests were not performed routinely to the NCFB patients. However in the follow-up, five patients got molecular diagnosis; X-linked agammaglobulinemia (BTK defect) (n=2), LRBA deficiency (n=1), RASGRP1 deficiency (n=1) (19), MHC Class II deficiency (n=1). They were given monthly IVIG, and HSCT was performed in three patients (with RASGRP1 deficiency, MHC Class II deficiency, and LRBA deficiency). All tranplanted patients are alive and well.

Microbiology

The sputum microbiology was positive in 55% (33) out of 60 patients (*Hemophilus influenza* (*H. influenza*) in 25 (75,75%), *Streptococcus pneumonia* (*S. pneumonia*) in 14 (42.4%), *Candida albicans* (*C. albicans*) in two (6%), group A *beta hemolytic streptococcus* (GAS*)* in two (6%), *Pseudomonas aeruginosa* (*P. aeruginosa*) in two (6%) patients), multiple agents (*H. influenza*, *S. pneumonia, Moraxella catarrhalis* (*M. catarrhalis*)*, Hemophilus parahemolyticus* (*H. parahemolyticus*)*,* GAS*, C. albicans, P. aeruginosa*) in 11 (33.3%) patients.
BAL microbiology was positive in 56.9% (n=37) (*H. influenza* in 59.46% (n=22), *S. pneumonia* in 21.62% (n=8), *H. hemolyticus*, *Hemophilus agnus* (*H. agnus*)*, H. hemolyticus, Hemophilus aphrophilus* (*H. aphrophilus*)*, Hemophilus segnis* (*H. segnis*)*, H. parainfluenza, M. catarrhalis, P. aeruginosa, Stenotrophomonas maltophilia* (*S. maltophilia*) were each isolated in 1 (2.7%) patients), multiple agents (*H. influenza*, *S. pneumonia*, *S. maltophilia*) in 4 (13.5%) of the patients.

The non-PID and PID group did not differ according to the ratio of sputum culture positivity (p=0.59). Increased ratio of positive BAL culture was recorded in younger patients than older ones (p=0.019). Nine patients (34.6%) in PID, 22 patients (66.7%) in non-PID had positive BAL culture, the difference was statistically significant (p=0.014). The results of microbiological analyses in groups are given in **table III**.

Radiology

According to HRCT results, most affected areas were recorded to be right middle and left lower lobe. Diffuse involvement was seen in 41.43% (n=29) of the patients, diffuse right lung involvement in 15.71% (n=11), diffuse left lung involvement in 7.14% (n=5), isolated left lower lobe involvement in 17.14% (n=12) of the patients, isolated right lower lobe involvement in 2.8% (n=2), left or right upper lobe involvement in 5.7% (n=4) patients. The involvement in PID and non-PID groups is given in **table III**. There was no statistical difference ($p > 0.05$).

Discussion

Bronchiectasis is still one of the most common causes of childhood morbidity and mortality (20-22). Main causes are infections, immunodeficiencies, congenital and genetic disorders, aspirations (23). Pulmonary infections account for 17-20.6% of bronchiectasis cases (24,25).
Underlying etiology is not identified in 14.2-37% of children (24,25), and in 35-50% of adults with bronchiectasis (26,27). Undiagnosed PID may be partly responsible for the development of unidentified bronchiectasis. The overall prevalence of brochiectasis in CVID is found as 34% (28) and 62.3% (29) in different series. The diagnosis of PID is generally made at the irreversible state when the disease progressed into the end-stage respiratory disease/failure (30). Physicians usually believe that the PID presents in childhood, and neglect PID especially in adulthood. The median age on admission to immunology clinic was about 3 years later ($p < 0.001$) in PID group. One of the

Table III *- Comparison of the microbiological agents and radiological involvement in PID and Non-PID Groups.*

		PID	Non-PID
Microbiological agents	**Sputum**	*H. influenza, S. pneumonia, P. aeruginosa, K. pneumonia, C. albicans*	*H. influenza, S. pneumonia, P. aeruginosa, M. catarralis, C.albicans*
	BAL	*H. influenza, S. pneumonia*	*H. influenza, S. pneumonia, P. aeruginosa, M. catarralis, H. parainfluenza, H. parahemolyticus*
Radiological involvement (HRCT)		Diffuse, left lower, bilateral lower lobes, right middle and right lower lobe, left total	Diffuse, left lower, right lower, bilateral lower lobes, right upper, and right middle lobes

several reasons of this delay may be due to the later admission of PID patients to the primary physician due to the insidious symptoms and other systemic problems. PID could vary greatly in clinical course, and the presentation of patients are not only with infectious diseases, but with allergy, autoimmunity, inflammation, lymphoproliferation/malignancies. With the increase in awareness and the definition of new PID disorders, PID are becoming one of the most common causes of NCFB. Complete blood count and determination of serum immunoglobulin levels were suggested as the baseline immunological tests in guidelines (31). Immunodeficiencies account for 10-34% of the childhood bronchiectasis (32,33), and among them, antibody deficiencies were common disorders leading to NCFB (34,35). In our study, PID accounts for about 40% of NCFB, and about 90% was primary antibody deficiency (**table I**). CVID (27.6%) was the most common PID. This high ratio of PID may be due to the routine follow-up of patients in an immunology clinic. Detailed evaluation with not only the suggested baseline tests, but other tests during the follow-up period, such as lymphocyte subset analysis, CH50 and NBT tests were performed to some of the patients. In the study of Reisi *et al.*, PIDs associated with bronchiectasis were CVID, XLA, HIGM and Hyperimmunoglobulin E syndrome (29). The ratio of bronchiectasis was found to be 62.3% in CVID, and 43% in XLA patients.

In our study, about 40% of NCFB patients had BH and asthma, and about 1/5 had GERD. Although GERD, asthma and BH, were common in non-PID group, each of them was evaluated as associations, rather than a cause. Bronchiectasis could result in BH, as it leads to airway obstruction, increased bronchial secretions and consequently to increased incidence of pulmonary infections. On the other hand, BH could exacerbate the symptoms of bronchiectasis (36). BH and asthma may associate with PID (29,37). In our series this ratio is about 40%, nearly the same as the ratio in all NCFB patients. Asthma and BH may also associate with PCD, BO and GERD. The presence of BH and asthma and the presence of recurrent infections did not differ in PID and non-PID groups in the present study. These data show that bronchiectasis should be evaluated as a multifactorial disease. Infections, BH/Asthma, PID and PCD may be present in the same patient, and it is not easy to determine accurately the most important reason of bronchiectasis. So, the treatment should be individualized.

Non-typeable *H. influenza* and *S. pneumonia* are the main bacterial pathogens in children with bronchiectasis and predominates in all age groups (38,39). BAL culture results in NCFB shows that most common pathogens are *H. influenza* (47%), *S. pneumonia* and *M. catarrhalis* (40). Data about microbiological agents in NCFB patients with PID is scarce. In a retrospective study, PID ratio was 8.6%, and in half, *H. influenzae, S. aureus, S. pneumoniae and C. parapsilosis* were isolated (41). In our study, most frequently isolated microorganisms were *H. influenza* and *S. pneumonia* both in sputum and BAL. The ratio of microorganism isolation in BAL culture was significantly increased in young and non-PID patients ($p < 0.05$), possibly due to frequent use of antibacterial agents in chronic cases.

Although bronchiectasis tend to appear in upper lobes in CF, it generally locate to the basal segments of lower lobes in children with NCFB (42). Patients with hypogammaglobulinemia was demonstrated to have lower/middle lobe and lingular segment bronchiectasis (43). In our study, most affected areas were right middle and left lower lobe in all NCFB patients. Lower, especially left lower lobe and diffuse involvement were seen mostly in PID group.

In our study, underlying etiology is not identified in about 1/3 of NCFB patients. PID, PCD, BO, rheumatic and autoimmune diseases and tuberculosis were evaluated as causes. Asthma and BH were evaluated as associations.

An important finding was that most patients (84.28%) had their first pulmonary infection within the first year of their lives. As far as we know, this study is the first study which compares the PID and non-PID NCFB. Patients with PID would highly benefit from an early diagnosis and appropriate treatment (44,45). Earlier immunoglobulin replacement therapy and antibacterial prophylaxis will decrease the infectious episodes, preventing the progress of bronchiectasis in patients with primary antibody deficiency. Thus, follow-up in also immunology clinics should be a routine for NCFB patients, and also for patients who experience pneumonia in the first year of their lives.

Conflict of interests

The authors declare that they have no conflict of interests.

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