Original Article

Evaluation of humoral immune deficiency in Indian patients with bilateral bronchiectasis with no apparent aetiology

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ABSTRACT

Background: Infections continue to be the leading aetiology of bronchiectasis in developing countries like India. Among non-infectious cases, the majority will have no identifiable cause despite extensive evaluation. Recently, immunodeficiency has been recognized as an important aetiology, but data on its prevalence remain rather sparse. **Objectives:** The objective of this study is to evaluate the prevalence of humoral immunodeficiency in a cohort of adults with bilateral bronchiectasis with no apparent aetiology. **Methods:** This is the single-site study from Christian Medical College (Vellore, India) of adults with HRCT-proven non-infectious bronchiectasis. Humoral immunity was assessed through quantitative analysis of immunoglobulins and IgG subclass levels. **Results:** Among 158 cases, immunoglobulin deficiency was found in 15%. Low IgM was the most predominate finding (7%), followed by common variable immunodeficiency (3%) and low IgA (2.5%). In addition, IgG subclass deficiency was found in 5%. In 53% of cases, no specific aetiology could be identified. **Conclusion:** Humoral immune deficiency is present in a significant proportion of patients with non-infectious bronchiectasis. Routine measurement of serum immunoglobulins should therefore be considered as part of the evaluation.

KEY WORDS: Bronchiectasis, humoral immunity, IgG subtypes, immunodeficiency

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INTRODUCTION

Bronchiectasis is a heterogeneous disease characterized by abnormal dilatation and distortion of bronchi associated with recurrent respiratory tract infections and sputum production.[1] It is a progressive disease associated with high morbidity and reduced quality of life.[2]The management of bronchiectasis focuses mainly on two aspects: sputum clearance and appropriate use of antibiotics. Identifying the aetiology will refine the management.[3]

Bronchiectasis can be considered as an end result of multiple factors. It is a heterogeneous disease with varying clinical, radiological and microbiological features.[4] The most common cause for bronchiectasis is post-infective sequelae.[3,5,6] Other important causes include ciliary dyskinesia, allergic bronchopulmonary aspergillosis (ABPA), immunodeficiency and connective tissue disorders.[7] In many cases, no specific aetiology is found.[5] In developed countries, childhood immunizations, early and frequent use of antibiotics, and improved sanitation and nutrition have led to a reduced incidence of non-cystic fibrosis bronchiectasis.[8] However in developing countries like India, tuberculosis and other infections are the leading aetiology.[9]

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The primary objective of this study was to evaluate the prevalence of humoral immune deficiency in a cohort of adult patients with bilateral non-infectious bronchiectasis.

METHODS

This is a single-site study conducted within the department of pulmonary medicine at Christian Medical College (Vellore, India) from February 2015 to July 2016. Both outpatient and inpatient adults with (HRCT) high-resolution computed tomography-proven non-infectious bronchiectasis were recruited to participate. Patients were triaged according to the protocol illustrated in Figure 1. Ethics committee agreed the project on 8-12-2014.

The primary inclusion criterion was the presence of bilateral bronchiectasis on HRCT of the chest. Exclusion criteria included a positive acid-fast bacillus smear, a positive *Mycobacterium tuberculosis* culture, a positive *M. tuberculosis* polymerase chain reaction, active tuberculosis and radiological features suggestive of post-infectious bronchiectasis. Patients with a previous history of post-infectious bronchiectasis, interstitial lung disease, connective tissue disease, COPD and any other chronic lung disorder other than asthma were also excluded.

After obtaining informed consent, eligible participants were evaluated for humoral immune deficiency by measurement of serum immunoglobulins (IgM, IgG, IgA and IgE). ANA and rheumatoid factor were also obtained to screen for connective tissue disease. Subjects with a serum IgE >1000 IU/ml and a history of symptoms consistent with asthma were screened for ABPA via skin prick test and measurement of *Aspergillus*-specific IgE (IMMULITE 2000 3g Allergy, Siemens). Subjects with no obvious aetiology and normal serum immunoglobulin levels were further assessed for IgG subclass deficiency (Invitrogen Human IgG Subclass Profile, ThermoFisher Scientific). Values were compared with reference values derived from age- and sex-matched normal individuals. A sputum culture was obtained from 97 subjects.

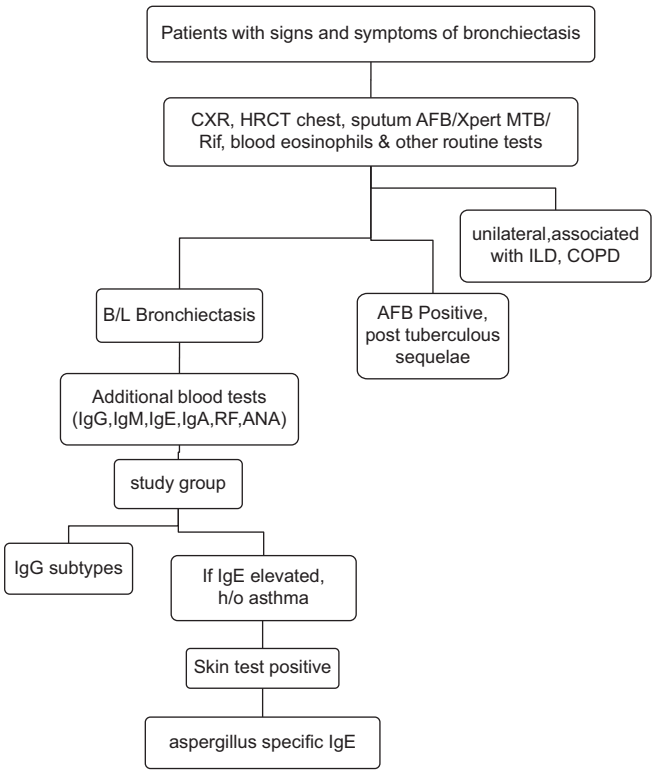

Figure 1: Algorithm for bronchiectasis evaluation

Statistical analysis

The data were recorded in Excel (Microsoft), and statistical analysis was done using SPSS 16.0 (IBM). Association of normal or abnormal immunoglobulin levels was tested using Chi-square test. A Fisher's test was used for categorical variables such as sex, symptoms, lower versus higher age group and so on. Comparison of mean immunoglobulin levels with respect to sex was done using two independent "*t*" test after checking for normality assumption. One-way ANOVA was used for more than two categories like immunoglobulin levels in normal, above or below ranges.

RESULTS

A total of 158 adults with bilateral non-infectious bronchiectasis were recruited from February 2015 to July 2016. Baseline characteristics of the subjects are shown in Table 1.

The mean age of patients was 42.1 ± 13.8 years; 57% of subjects were males; 12% were active smokers. Mean age at onset of symptoms was 25.7 ± 17.8 years, while mean

Table 1: Baseline characteristics

Baseline characteristics	
Mean age	42.1±13.8 years
Males	90 (57%)
Smokers	19 (12%)
Mean age at onset of symptoms	25.7±17.8 years
Mean age at diagnosis	36.4±16.1 years
Diagnostic delay	10.6±11.2 years
Empirical ATT	15.1%
Comorbidities	
Diabetes	16 (10.1%)
Hypertension	17 (10.7%)
Coronary disease	3 (1.8%)
Clinical features	
Cough	157 (99.3%)
Dyspnoea	144 (91.1%)
Haemoptysis	78 (49.3%)
Recurrent respiratory infections	48 (30.3%)
Asthma	37 (23.4%)
Sinusitis	29 (18.3%)
Investigations	
Pseudomonas aeruginosa in sputum culture	32 (33%)
Haemophilus influenzae in sputum culture	15 (16%)
ANA	15 (9.7%)
RF	9 (5.8%)

ATT: Anti-tuberculosis treatment, ANA: Antinuclear antibodies, RF: Rheumatoid factor

Table 2: Immunoglobulin levels

Immunoglobulin level	IgG (800-1700 mg/dl) (%)	IgM (50-190 mg/dl) (%)	IgA (140-420 mg/dl) (%)	IgE (5-100 mg/dl) (%)
Low	5.2	10.5	6.5	5.8
Normal	66.7	77.1	66.7	28.4
High	28.1	12.4	26.8	65.8

Table 3: Immunoglobulin deficiency

Immunoglobulin deficiency	Number of patients
Low IgM	11
Low IgG, IgM, IgA, IgE	5
Low IgA	4
Low IgG	2
Low IgA, IgG	1
Low IgM, IgA, IgE	1

Table 4: IgG subtype deficiency

IgG subtypes	Normal range (mg/dl)	Deficiency
IgG1	240-1118	0
IgG2	111.50-893.10	2
IgG3	30.20-281.40	5
IgG4	3.35-189.60	1

age of diagnosis was 36.4 ± 16.1 years (diagnostic delay of 10.6 ± 11.2 years). A percentage of 15.1 of subjects were empirically treated with anti-tuberculosis therapy.

Cough, dyspnoea and haemoptysis were among the most common clinical features [Table 1]. Two subjects presented with symptoms of malabsorption. They were subsequently diagnosed with common variable immunodeficiency (CVID) and cystic fibrosis, respectively.

Sputum culture was obtained from 97 subjects. The most common isolated organism was *Pseudomonas aeruginosa* (33%) followed by *Haemophilus influenzae* (16%). The presence of either was not found to have any significant association between age of onset and duration of illness. A positive ANA was found in 9.7% of subjects whereas 5.8% of subjects tested positive to the rheumatoid factor. However, none of them had clinical manifestations suggestive of an underlying connective tissue disorder.

One hundred and fifty three of 158 subjects underwent measurement of serum immunoglobulins (IgM, IgG, IgA and IgE). Five subjects did not undergo immunoglobulin evaluation, as they were suspected of having other diseases: Young syndrome,[2] cystic fibrosis,[1] Kartagener syndrome[1] and Mounier–Kuhn syndrome.[1] The majority of subjects had normal immunoglobulin levels except for IgE, which was elevated in 66% of subjects [Table 2]. Among subjects with a serum IgE >1000 U/ml and a history of symptoms suggestive of asthma, five were diagnosed with ABPA based on positive skin prick test and *Aspergillus*-specific IgE assay.

Immunoglobulin deficiency was found in 24 subjects (15%). Low IgM deficiency was the most predominant finding (7%), followed by CVID (3.2%) and low IgA (2.5%) [Table 3].

Out of 129 subjects with normal immunoglobulin levels, 93 subjects underwent IgG subclass assay. Out of these, eight subjects [Table 4] were found to have IgG subtype deficiency (8.6%). The majority (7/8) were female. Most commonly observed finding was low level of IgG3. No patients had combined deficiency.

DISCUSSION

To our knowledge, this study is the first one of its kind to assess humoral immunodeficiency among Indian patients with non-infectious bronchiectasis. Our study found a significantly higher incidence of immunoglobulin deficiency compared with other studies [Table 5]. This could be explained by the fact that our institution is a large referral centre across India for respiratory-related diseases. The most common immunodeficiency was low IgM. Note that IgM and IgA are both physiologically important for protecting mucosal surfaces from microbes, and it has been suggested that IgA and/or IgM deficiency may create a permissive mucosal environment for the development of infective complications.[10]

IgG1 to IgG4, respectively, constitute 60%, 32%, 4% and 4% of total serum IgG.[14] Consequently, deficiencies of IgG2, IgG3 or IgG4 may occur in the presence of normal concentrations of total serum IgG.[15] We therefore conducted IgG subclass analyses among subjects in whom serum immunoglobulin levels were normal. Interestingly, out of eight subjects found to have IgG subclass deficiency, seven were females. Among children with IgG subclass deficiencies, there is 3:1 male: female predominance with IgG2 deficiency being the most common, whereas the situation is reversed after puberty, with IgG3 deficiency becoming more common.[15] Unfortunately, our study is limited by the fact that antibody titres to proteins and polysaccharide antigens, such as diphtheria toxoid, tetanus toxoid, *H. influenzae* type b (Hib) and *Streptococcus pneumoniae* pneumonia, were not obtained.

We recommend screening for immunoglobulin deficiency by obtaining IgG, IgA, IgM and IgE levels, and IgG subclasses when serum immunoglobulin levels are normal. Immune globulin replacement will reduce the rate of bacterial infections, and consequently, may slow the progression of bronchiectasis and improve lung function. Several studies have also demonstrated reduced days of antibiotic usage, hospital admissions and increased patient quality of life.

Our data showed an average delay of 10.6 years from symptom onset to diagnosis of bronchiectasis, which

Table 5: Different studies and aetiologies of bronchiectasis

Study/Aetiology	Pasteur *et al.*[1] 2000	King *et al.*[11] 2006	Shoemark *et al.*[5] 2007	Anwar *et al.*[12] 2012	Aliberti *et al.*[13] 2015	Our study
Number	150	103	165	189	1145	158
Mean age	52.7±15.2	56±14	49±16	66±11	66	42.1±13.8
Male: female	38:62	37:63	35:65	94:95	455:690	90:68
Idiopathic %	53	74	26	43	34	53
Immunoglobulin deficiency %	8	-	7	2	5	15
IgG subclass deficiency %	<1	9	0	1	-	5
ABPA %	7	4	8	8	4.9	3.1
Cystic fibrosis %	3	0	1	1	-	1.9
Ciliary dysfunction %	1.5	1	10	2	1.8	3.1
Young syndrome %	3	1	3	1	-	1.3

is shorter than the study by Anwar *et al.*[12] (17 years). This could be accounted for the fact that Kartagener syndrome, Young syndrome and cystic fibrosis all present early in life. In addition, ABPA also tends to present earlier in life.

Clinical history is critical when trying to determine the aetiology of bronchiectasis. History-taking may also help identify infective causes and their temporal relation to developing bronchiectasis. Though our study revealed 9.7% and 5.8% ANA and RF positivity rates, respectively, none of our patients had a history of arthralgias or other signs or symptoms suggestive of a connective tissue disorder. These patients, nonetheless, will require long-term follow-up to monitor for early symptoms. Similar results were found by Anwar *et al.*,[12] in which 10% of bronchiectasis patients had a positive RF, but none had any definite clinical features of a connective tissue disorder.

CONCLUSION

Our study, similar to other studies, demonstrated the presence of immunoglobulin deficiency in a significant number of patients with non-infectious bronchiectasis. While such evaluations may not always be economically feasible in low-income countries like India, they should nonetheless be encouraged. Indeed, immune deficiency can play an important role in the pathogenesis of bronchiectasis, and it is vital to identify this since immunoglobulin replacement therapy may slow the progression of the disease and offer an improved long-term prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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