

ORIGINAL ARTICLE

Iran J Allergy Asthma Immunol

June 2008; 7(2): 69-77

Evaluation of Humoral Immune Function in Patients with Bronchiectasis

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Received: 24 November 2007; Received in revised form: 1 January 2008; Accepted: 14 January 2008

ABSTRACT

Bronchiectasis is a chronic debilitating condition characterized by abnormal dilated thick-walled bronchi. To investigate humoral immune function in bronchiectatic patients, this study was performed.

Forty patients with established diagnosis of bronchiectasis, who were referred from two tertiary care pulmonology centers in Tehran, were investigated in this study. Immunoglobulin isotypes concentrations and IgG-subclasses were measured by nephelometry and enzyme-linked immunosorbent assay (ELISA) methods, respectively. All patients received unconjugated pneumococcal vaccine, and blood samples were taken before and 21 days after vaccination. Specific antibodies against whole pneumococcal antigens were measured using the ELISA method.

Fifteen (37.5%) out of 40 patients were diagnosed to have defects in antibody mediated immunity including 5 (12.5%) patients with immunoglobulin class deficiency (2 with common variable immunodeficiency and 3 with IgA deficiency), 3 (7.5%) with IgG subclass deficiency and 7 (17.5%) patients had Specific antibody deficiency (SAD) against polysaccharide antigen despite normal levels of serum immunoglobulins and IgG subclasses.

Our study along with several other studies confirmed that all patients with bronchiectasis should undergo thorough immunological evaluation in order to identify the presence of the underlying immunologic defect. This evaluation should include serum immunoglobulins, IgG subclasses concentrations and also determination of serum antibodies against pneumococcal antigens. Early diagnosis and appropriate treatment will prevent the subsequent complications and improve quality of life of affected individuals.

Keywords: Bronchiectasis; Common variable immunodeficiency; Humoral immunity; IgA deficiency; Primary immunodeficiency

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INTRODUCTION

Bronchiectasis is a chronic debilitating condition characterized by abnormal dilated thick-walled bronchi that are inflamed and colonized by bacteria.¹ Although the prevalence of bronchiectasis is not well-characterized, some documented studies^{2,3} suggest that bronchiectasis still remains a common disease. Predisposing factors for development of bronchiectasis include childhood respiratory infections,^{4,5} congenital anatomical lung abnormalities, cystic fibrosis,⁶ α -antitrypsin deficiency,⁷ inflammatory bowel disease,⁸ primary ciliary dyskinesia,⁹ and primary immunodeficiency.¹⁰⁻¹⁵

Primary antibody deficiency (PAD) is the most common type of the primary immunodeficiency (PID) accounting for approximately half of all PID.¹⁶⁻²⁰ The spectrum of PAD is broad, ranging from the patients with severe reduction of all serum immunoglobulins (Ig) with totally absent of B cells to patients who have a selective antibody deficiency with normal serum Ig.¹⁶ The main clinical manifestation of patients with PAD is recurrent and chronic infections that most commonly are caused by pyogenic bacteria, including *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Pseudomonas* being the most common species.^{12, 13, 15} Delay in diagnosis and / or inadequate management of patients with PAD, may lead to permanent organ damage (e.g. bronchiectasis or bronchiolitis obliterans) or death from overwhelming infections. Unfortunately, many patients with primary antibody deficiency still are found with bronchiectasis due to the delay in the diagnosis of the underlying immunodeficiency.²¹ Because of lack of knowledge among primary healthcare providers, some patients with PAD remain undiagnosed and their delayed diagnosis results in irreversible complications and mortality.²²

Several documented studies²³⁻³¹ showed that significant proportion of patients with bronchiectasis may have variety of immunodeficiency disorders mostly subclass deficiencies and inability to produce specific antibodies against the polysaccharide antigens. Early diagnosis and adequate therapy in patients with underlying immunodeficiencies are the keys to survival and a better quality of life for patients with primary antibody deficiencies.

The purpose of this study was to investigate the detailed humoral immune status in patients with

bronchiectasis. The long-term objective is to improve patients' management by determining the degree of immunological screening which is appropriate in the routine assessment of patients with bronchiectasis on presentation, and to identify those patients who may benefit from specific treatment for antibody deficiency.

PATIENTS AND METHODS

Subjects

Fifty-three children and adult patients with established bronchiectasis referred to our department by pulmonologists were selected as subject of our study. These patients initially were diagnosed and followed in two tertiary care pulmonology centers in Tehran, Iran. The immunological evaluation was carried out in the department of Allergy and Clinical Immunology of University of Tehran Medical Sciences was from December 2005 to December 2006.

High resolution computed tomography (HRCT) was utilized as a precise and non-invasive procedure for bronchiectasis diagnosis.³²

This study was reviewed and approved by the Ethics Committee of Tehran University, Medical Sciences and written informed consents were also obtained from the adult patients and children's parent(s).

Methods

Three-page-questionnaire was designed to collect demographic information and past medical histories of recurrent infections for each patient by reviewing the patient's records. Patients' blood samples were collected to measure immunoglobulin isotypes (IgA, IgM and IgG) concentrations using nephelometry (Behring Nephelometer, Behringwerke, Marburg, Germany)³³ and IgG-subclasses by enzyme-linked immunosorbent assay (ELISA).³⁴ IgA deficiency was defined, if serum IgA was less than 7 mg/dl with normal IgG and IgM in patients older than 4 years old.³⁵ A deficiency in serum immunoglobulin levels and IgG-subclasses were accepted if the serum level was below the age-adjusted 5th percentile in comparison to healthy controls.^{36,37}

All patients received single dose of 0.5 mL unconjugated pneumococcus polyvalent vaccine (PNEUMO 23[®] Aventis, Pasteur, France) intramuscularly and blood samples were taken before vaccination and 21 days after vaccination. Specific

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antibodies against whole pneumococcal antigens were measured using ELISA.³⁸

The control group, made up of forty-five healthy donors, was studied to establish a criterion for normal response to 23-valent pneumococcal vaccine. None of the controls had a history of primary or secondary immunodeficiencies and recurrent infections. Specific antibodies against whole pneumococcal antigens were measured using ELISA and kits obtained from The Binding Site Ltd, U.K. Specific IgG directed towards pneumococcal capsular antigen was determined with the same method and kits in patients and the control group.

The assay was designed for measuring IgG antibody responses to pneumococcal vaccine incorporating 23 polysaccharides isolated from *Streptococcus Pneumoniae*. These polysaccharides represent approximately 80% of the commonly encountered virulent serotypes. The response in 30% of subjects to vaccination with *S. pneumoniae* is attributable to C-polysaccharide (CPS) antibodies and not to specific anti-PCP IgG. These CPS antibodies confer limited protection against pneumococcal infection; consequently CPS absorption has been incorporated in these assays. There are no universal criteria for adequate antibody response to pneumococcal specific antibody levels. Each laboratory has to consider the response in normal healthy controls to generate criteria to define hyporesponsiveness to vaccine. All subjects showing an increase in specific antibody titers equal to or greater than lower limit of the two-tailed 90% probability interval of postimmunization specific IgG of the healthy adults were defined as responders.³⁰

Statistical Analysis

The data were analyzed using standard statistical software SPSS 11.5. Comparisons between groups were performed using student T test and Mann-Whitney U test when the distribution was not normal for the selected variable

RESULTS

Characteristics of Patients

A series of 53 patients, in whom the diagnosis of bronchiectasis was established on the basis of HRCT were assessed during this study. Nine patients were excluded owing to unwillingness to complete investigation. Four patients were also excluded during the course of the study, because of the diagnosis of primary ciliary dyskinesia which was confirmed by

electron microscopy. Forty patients including 26 males and 14 females; age range, 7 to 70 years with bronchiectasis of unknown etiology were finally included in this study. Fifteen (37.5%) out of 40 patients were diagnosed to have defects in antibody mediated immunity including 5 (12.5%) patients with immunoglobulin class deficiency, 3 (7.5%) with IgG subclass deficiency and 7 (17.5%) patients had SAD against polysaccharide antigen despite normal levels of serum immunoglobulin and IgG subclasses (Table 1).

Immunoglobulin Class Deficiency

Two male patients (5%) aged 17 (P1) and 24 (P2) years were diagnosed to have CVID. Both patients had reduced serum levels of IgG, IgA and IgM, and were unable to produce specific antibody against polysaccharide antigen. P1 and P2 also had history of recurrent respiratory infections since age of 4 and 10 years respectively. Delay in diagnosis for these two patients was 13 (P1) and 14 (P2) years.

IgA deficiency was detected in three (7.5%) patients. The first one (P5), an 16-year-old male patient, had IgG4 subclass deficiency and also hyporesponsiveness to polysaccharide antigen. The second one (P3), a 12-year-old girl, had IgG2 subclass and specific antibody production deficiency in addition to IgA deficiency. The third one (P4) had isolated IgA deficiency with normal IgG subclasses and adequate response to vaccine antigen.

IgG Subclass Deficiency

Isolated IgG subclass deficiency (IgG4) was detected in 3 patients including two males aged forty-three (P7) and twelve (P8) years, and one female (P6) aged sixty year. The latter one (P6), was hyporesponsive to polysaccharide antigen while two others were normal responders. In subgroup analysis, all IgG subclasses were found to be low in patients with SAD compared with responder patients (Table 2); although, a significant decrease was observed only in IgG4. The overall incidence of IgG subclass deficiency was 12.5% (5 out of 40) when P3 (combined IgG2 and IgA deficiency) and P5 (combined IgG4 and IgA deficiency) were included.

Specific Antibody Deficiency

In 40 patients and 45 controls who received unconjugated pneumococcus polyvalent vaccine, antibody against polysaccharide antigen was measured before vaccination and 21 days after vaccination.

Table 1. Characteristics of patients with defects in antibody mediated immunity (n=15).

No.	Age	Sex	Type of Deficiency	Low Immunoglobulin Level (mg/dl)*	Age Adjusted Immunoglobulin Level range (mg/dl)	Response to Pneumo 23	Antibody level Before and After Pneumo23
1	17	M	CVID	IgG	190 (853-1463)	Hypo	3
				IgA	0 (139-261)		
				IgM	20 (853-1463)		
2	24	M	CVID	IgG	170 (853-1463)	Hypo	51
				IgA	7 (139 - 261)		
				IgM	40 (72 - 126)		
3	12	F	IgA+G2	IgA	0 (71 - 191)	Hypo	15
				IgG2	90 (110-550)		
4	38	M	IgA	IgA	0 (139 - 261)	NA	NA
5	16	M	IgA+G4	IgA	0 (139 - 261)	Hypo	45
				IgG4	1 (11 - 330)		
6	60	F	IgG4	IgG4	6 (11 - 330)	Hypo	80
7	43	M	IgG4	IgG4	7 (11 - 330)	Normal	170
8	12	M	IgG4	IgG4	4 (7-330)	Normal	170
9	53	M	SAD	Ig	NL	Hypo	60
10	39	M	SAD	Ig	NL	Hypo	60
11	12	M	SAD	Ig	NL	Hypo	80
12	22	M	SAD	Ig	NL	Hypo	70
13	7	M	SAD	Ig	NL	Hypo	70
14	9	M	SAD	Ig	NL	Hypo	100
15	8	M	SAD	Ig	NL	Hypo	20

* Normal immunoglobulins and subclasses levels are not shown in this table.

NA: not assessed; NL: Normal; SAD: specific antibody deficiency; CVID: common variable immunodeficiency; hypo: hypo responsive

The median titers of antibody before and after vaccination titers in the control group were 70 and 450 U/ml, respectively. The lower limit of the two-tailed 90% probability interval of postimmunization specific IgG was 129 U/ml which is utilized as the minimum significant increase for adequate response in the patients' group. Twelve out of 40 vaccinated patients (30%) were found to be hypo responsive to vaccine. Among these 12 patients, 5 (12.5%) cases had defect in immunoglobulin isotypes or IgG subclasses including; 2 with CVID, 2 with IgA deficiency and 1 selective IgG4 deficiency. Excluding these 5 cases, 7 (17.5%) with normal serum immunoglobulin and IgG subclass levels were defined as specific antibody deficiency (SAD).

The median titer of pre immunization and post immunization anti pneumococcal IgG in patients with bronchiectasis were 70 and 400, respectively. In subgroup analysis, we compared characteristics of patients with normal antibody production (n=25) with patients with specific antibody production (n=7). In

patients with SAD, the pre immunization, post immunization and absolute increase were significantly lower than patients with normal antibody production. (Table 2).

DISCUSSION

Bronchiectasis is a pathologic description of the disease process which has a number of possible causes inducing inflammatory response and irreversible damage to the bronchial wall, leading to permanent dilation of the bronchi. Identifying the cause of bronchiectasis may contribute to management and prognosis of the condition, e.g. starting immunoglobulin replacement therapy in patients with primary antibody deficiencies, which may prevent the progression of irreversible lung damage.

In our study, we uncovered 15 (30%) primary antibody deficiencies among studied patients suffering from bronchiectasis. This is in consistent with pervious studies.²³⁻³¹ These studies revealed that about 4 to 50

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percent of patients with bronchiectasis to have a kind of abnormal antibody disorder. The difference in percent of antibody deficiency is probably due to type of studied population, different selection criteria and the utilized methods and also depends on awareness and degree of physicians' awareness and quality of health system.

In this study, 2 patients with CVID (P1, P2) were diagnosed. The incidence is in agreement with to what has been previously reported by Shoemark *et al.* who found 4 CVID out of 165 studied patients.²⁶

In addition to hypogammaglobulinemia, both patients with CVID, had impaired production of specific antibody against polysaccharide antigens which is essential for diagnosis of CVID.¹⁵ After diagnosis, they were started on intravenous immunoglobulin (IVIg) in a dose of 600 mg/kg every 4 weeks and responded dramatically well with a substantial decline in frequency and severity of infections. CVID is a primary antibody deficiency in which patients are susceptible to recurrent pyogenic infections and are particularly prone to developing chronic lung disease. Bronchiectasis has been reported in 37.5% to 73% of CVID patients,^{14,39,40} mainly in those patients with low numbers of IgM⁺ memory B cells associated with inability to produce specific antibody against pneumococcal polysaccharide antigens.^{41,42} Measurement of these parameters may help physician in adopting more aggressive treatment in patients very susceptible to infection and lung disease. The characteristics of these two CVID patients in our series show that delay in diagnosis of patients with underlying immunodeficiency resulted in permanent organ damage such as bronchiectasis. Unfortunately, many patients with primary antibody deficiency are going to be presented with bronchiectasis, because of a delay in the diagnosis. Early recognition and treatment of primary immunodeficiency in patients with history of recurrent infection, even in those patients with bronchiectasis, are the key to prolonged survival and better quality of life of affected individuals.

Among our study population, 3 (7.5%) patients with IgA deficiency were found in which, 1 patient (P5) was associated with IgG4 deficiency and another (P3) was associated with IgG2 deficiency. This finding is similar to the result of previous studies in which the rate of IgA deficiency among patients with bronchiectasis was between 5.3% to 14%.^{29,30} Selective IgA deficiency is a

common immunologic abnormality, affecting approximately 1 in 300 to 700 individuals and most affected individuals are asymptomatic.⁴³

Based on an ongoing study in our department, the prevalence of IgA deficiency among Iranian healthy blood donors is estimated to be about 1 in 800 (unpublished data). Considering these two figures; the prevalence of IgA deficiency in Iran and rate of IgA deficiency in this study population postulates that rate of IgA deficiency is 60 fold higher in patients with bronchiectasis than healthy population in Iran. This finding emphasizes on immunological evaluation in patients with a history of recurrent infection and resultant bronchiectasis.

About two third of patients with of IgA deficiency are asymptomatic requiring no treatment. Those patients with IgA deficiency who have decreased serum antibodies to pneumococcal polysaccharides or decreased serum IgG subclasses (IgG2 and/or IgG4) or association with some polymorphisms of Mannose binding lectin (MBL2) are more susceptible to recurrent infections and would benefit from a more aggressive treatment including IVIg and prophylactic antibiotics.⁴⁴⁻⁴⁷ One out of 3 patients with IgA deficiency (P5) in our series who were associated with IgG4 deficiency and specific antibody deficiency and more severe episodes of infections, were subjected to IVIg and responded well.

The role of IgG subclass measurements in the immunological assessment is controversial since up to 20% of healthy population may have a reduced IgG subclass and need no therapy and should not be marked as immunodeficient. The current literature confirmed that some patients with IgG subclass deficiency associated with other immunologic defects such as IgA deficiency and unresponsiveness to polysaccharide antigen, present with serious recurrent and chronic infections and its sequelae e.g. bronchiectasis as we noted in this series. Our study along with others, confirm that patients with recurrent infections and normal levels of immunoglobulins, should be investigated for IgG subclasses and specific antibody production. In recent reports by Hill *et al.*²³ De Gracia *et al.*²⁸ and Stead *et al.*²⁹ in which IgG subclass deficiency was principally considered, the frequencies of detection were 6%, 48% and 23% respectively. In our study, the incidence of IgG subclass deficiency was 7.5% with the significant contribution of subnormal IgG4 levels which is similar to that found by Hill and colleagues.²³

Table 2. Characteristics of Patients with Bronchiectasis According to Antibody Deficiency. Data are presented as mean (range). Specific antibody titers are presented as Geometric mean (range).

	Normal specific antibody production (n= 25)	Specific antibody deficiency (n=7)	P-value
Age	24 (9-70)	12 (7-53)	NS
<i>Immunoglobulin level (mg/dl)</i>			
IgG	1259.50 (1050 - 1500)	1200 (1050-1470)	NS
IgG 1	758 (484-1060)	716.50 (466-955)	NS
IgG 2	458.50 (99-988)	382(185-397)	NS
IgG 3	136 (36-269)	99 (73-140)	NS
IgG 4	72 (12-222)	47(4-98)	p<0.05
IgA	201 (78-600)	158 (130-380)	NS
IgM	104.50 (57-214)	95 (59-133)	NS
<i>IgG to S pneumoniae, U/mL</i>			
Preimmunization	76 (4-450)	60 (18-60)	p<0.05
Postimmunization	450 (150-450)	120 (80-180)	p<0.001
Increase	300 (0-446)	90 (0-162)	p<0.001

NS: Not significant

However, the findings differ from those of De Gracia and coworkers,²⁸ both in the overall incidence of immunoglobulin deficiency (7.5% compared to 48%), and the subclass involved (principally IgG4 in our study and IgG2 in that of De Gracia *et al.*²⁸). The most common subclass deficiency among patients presenting with recurrent infections is IgG4 deficiency.⁴⁸

In subgroup analysis, Vendrell *et al.*³⁰ found low levels of all IgG subclasses in patients with deficiency of specific antibody production compared with normal responders; This is consistent with our findings. In our study, the only significant decreased subclass in patients with SAD is IgG4 which is in contrast with IgG2 subclass that Vendrell *et al.* has shown.³⁰

In patients with IgG subclass deficiency associated with severe therapy-refractory infections and/or concurrent IgA deficiency and unresponsiveness to polysaccharide antigen may occasionally require IVIG therapy at the usual therapeutic doses.⁴⁹

SAD is an immunodeficiency which is defined as poor response to polysaccharide antigen challenge in individuals with normal total immunoglobulin levels and IgG subclasses.^{50,51} The etiology and immunopathogenesis of SAD as a primary immunodeficiency is still unclear.^{50,52}

Several documented studies have showed that defect in specific antibody production is associated with recurrent respiratory infections and development of bronchiectasis.

Sorenson has identified SAD as the most common immunodeficiency identified among children presenting with increased susceptibility to infection.⁵³

SAD has been found in 3-50 % of patients evaluated for bronchiectasis in other studies.^{29, 30, 54-58} Present study showed SAD in 7 out of 40 (17.5%) of patients with bronchiectasis, in whom most of the known causes had been ruled out. Vendrell *et al.* found 11% of patients with bronchiectasis as SAD.³⁰

They also showed lower preimmunization antibody levels to *S. pneumoniae* in patients with SAD. This is in agreement with our results in which the pre immunization antibody titers is significantly decreased. In contrast, Stead *et al.* found only 1 patient with specific antibody deficiency in a series of fifty-six patients.²⁹

The variations in rates depend on criteria of the study population, different referral population, distinctive age groups, normal reference values, measurement techniques and the serological definition of SAD used in such studies.

A course of prophylactic antibiotics should be tried, at least for 6 months to reduce the number and severity of infections. If there is persistent infection, a trial of IgG replacement therapy should be provided in full therapeutic doses.⁵⁹ This treatment strategy should be considered in the patients with SAD whom had evidence of recurrent infections and severe poor response to polysaccharide antigens.⁶⁰

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Although the whole antigen method, utilized in this study, is less accurate and may mask deficient or immunization responses to one or more individual serotypes, it has some advantages including lower costs and rapidity and easiness to assay.⁶¹ While all patients with a diagnosis of bronchiectasis of unknown etiology, during the study period, in two tertiary-care pulmonology centers were referred for immunologic testing, our findings could be argued by small number of patients. Nine patients were excluded owing to not wishing to complete investigation. However, the small number of patients who declined is unlikely to have influenced conclusions.

In conclusion, our study along with several other studies confirms that all patients with bronchiectasis should undergo thorough immunological evaluation in order to identify the presence of the underlying immunologic defect. This evaluation should include serum immunoglobulin, IgG subclasses concentration and also determination of serum antibodies against pneumococcal antigens. The diagnosis could lead to the appropriate treatment, prevention of the subsequent complications and eventually a better quality of life.

ACKNOWLEDGEMENTS

This study was supported by a grant from University of Tehran Medical Sciences. Additionally, the authors wish to thank all the patients, their families for their kind collaboration in this research project.

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