Prevalence of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis in the state of Bahia, Brazil*

Prevalência de aspergilose broncopulmonar alérgica em pacientes com fibrose cística na Bahia, Brasil

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Abstract

Objective: To determine the prevalence of allergic bronchopulmonary aspergillosis (ABPA) in patients with cystic fibrosis treated at a referral center in the state of Bahia, Brazil. Methods: A cross-sectional study, with prospective data collection, carried out at the Cystic Fibrosis Referral Center of Bahia of the Octávio Mangabeira Specialized Hospital. We evaluated 74 patients diagnosed with cystic fibrosis, older than six years of age, treated between December 9, 2003 and March 7, 2005. We analyzed the following variables: gender, age, forced vital capacity, forced expiratory volume in one second, pharmacodynamic response, chest X-ray findings, facial sinus X-ray findings, wheezing, cultures for Aspergillus spp., total immunoglobulin E (IgE), specific IgE for Aspergillus fumigatus and immediate skin test reactivity to A. fumigatus antigen. Results: Of the 74 patients, 2 were diagnosed with ABPA. We found total IgE levels > 1,000 IU/mL in 17 (23%), positive immediate skin reactivity to A. fumigatus antigen in 19 (25.7%) and wheezing in 60 (81.1%). Conclusions: The prevalence of ABPA was 2.7%. The high levels of total IgE, high incidence of wheezing and high rate of immediate skin test reactivity to A. fumigatus antigen suggest that these patients should be carefully monitored due to their propensity to develop ABPA.

Keywords: Cystic fibrosis; Aspergillosis, allergic bronchopulmonary; Immunoglobulin E/diagnostic use; Hypersensitivity, immediate/diagnosis; Gliotoxin.

Resumo

Objetivo: Determinar a prevalência de aspergilose broncopulmonar alérgica (ABPA) em pacientes com fibrose cística acompanhados em um centro de referência da Bahia. Métodos: Estudo transversal, com coleta prospectiva de dados, realizado no Centro de Referência de Fibrose Cística da Bahia do Hospital Especializado Octávio Mangabeira. Foram incluídos no estudo 74 pacientes que tinham diagnóstico de fibrose cística, com idade acima de 6 anos e tratados entre 9 de dezembro de 2003 e 7 de março de 2005. Foram analisadas as seguintes variáveis: gênero, idade, capacidade vital forçada, volume expiratório forçado no primeiro segundo, resposta a prova farmacodinâmica, achados em radiografia torácica e de seios de face, presença de sibilância, culturas para Aspergillus spp., imunoglobulina E (IgE) total, IgE específica para Aspergillus fumigatus e teste cutâneo de leitura imediata para aspergilina. Resultados: Dos 74 pacientes, 2 foram diagnosticados com ABPA. Níveis de IgE total > 1.000 IU/mL foram observados em 17 pacientes (23%), teste cutâneo imediato para A. fumigatus positivo em 19 (25,7%) e sibilância em 60 (81,1%). Conclusões: A taxa de prevalência de ABPA foi de 2,7%. As altas taxas de IgE total, de teste cutâneo imediato para A. fumigatus positivos e de sibilância sugerem que estes pacientes devam ser acompanhados cuidadosamente por haver a possibilidade do desenvolvimento de ABPA.

Descritores: Fibrose cística; Aspergillosis, allergic bronchopulmonary; Immunoglobulin E/uso diagnóstico; Hipersensibilidade imediata/diagnóstico; Gliotoxin.

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Financial support: None.

Introduction

Cystic fibrosis (CF), which is the most common autosomal recessive genetic disease among whites, has a highly varied phenotypic presentation. The clinical presentation of CF depends on genetic mutation, genetic load of the individual and environmental factors. Pulmonary disease is characterized by bronchopulmonary suppuration caused by typical CF pathogens, such as Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa and Burkholderia cepacia. The last two are difficult to eradicate. (3)

Morbidity and mortality in CF are correlated with pulmonary complications resulting from the disease. (2, 4) The presence of fungi, such as Aspergillus spp., can be an aggravating factor. In humans, this fungus can cause diseases with different clinical manifestations, among which are invasive pulmonary aspergillosis, aspergilloma and different forms of hypersensitivity. (4, 5) The form most commonly found in CF is ABPA, (3) which is thought to be a major risk factor for the development of ABPA. Among atopic and non-atopic patients, total IgE ≥ 1,000 IU/mL occurs in 22% and 2% of the cases, respectively. (5)

The diagnostic criteria for ABPA are divided into major—immediate skin reactivity to A. fumigatus antigen, positive A. fumigatus serology, increased total serum IgE levels, episodes of bronchial obstruction, eosinophilia in peripheral blood, history of pulmonary infiltrates and increased specific IgE/IgG for A. fumigatus—and minor—presence of A. fumigatus detected by direct sputum smear microscopy or culture, history of expectoration of bronchial casts and delayed skin test reactivity (Arthus reaction) to Aspergillus spp. (19)

The present study was carried out in order to determine the prevalence of ABPA in patients treated at a CF center in the state of Bahia.

Methods

This was a cross-sectional study, with prospective data collection, involving a sample of 74 patients (≥ 6 years of age) diagnosed with cystic fibrosis, aged 6 years or older, treated between December 9, 2003 and March 7, 2005 at the Cystic Fibrosis Referral Center of Bahia – Octávio Mangabeira Specialized Hospital. The project was approved by the Ethics in Research Committee of the Foundation for the Development of Science/School of Medicine and Public Health of Bahia, and was initiated after written informed consent had been obtained from the patients older than 18 years of age and from the legal guardians of those younger than 18.

Clinical forms were filled out for all patients, and the sweat test was performed twice. Each patient...
The onset of CF symptoms occurred before the age of 2 years in 42 patients (56.8%) and after the age of 16 years in 14 (18.9%). The symptoms that motivated the diagnostic suspicion of CF were predominantly respiratory.

The nutritional status assessment, based on body mass index, showed a nutritional profile with mean values of $18.8 \pm 4.5$ kg/m$^2$.

The microbiological profile revealed $P. aeruginosa$ colonization in 15 patients (20.3%), $S. aureus$ colonization in 17 (22.9%), $Klebsiella pneumoniae$ colonization in 5 (6.7%), $H. influenzae$ colonization in 1 (1.3%), colonization with saprophytic flora in 12 (16.2%), $S. aureus$ colonization together with $P. aeruginosa$ colonization in 4 (5.4%) and $S. aureus$ colonization together with $K. pneumoniae$ colonization in 4 (5.4%). The presence of methicillin-resistant $S. aureus$ was found in 10 patients (40%), and the presence of multidrug-resistant $P. aeruginosa$ was found in 6 (31.5%).

The use of antibiotics was necessary in 87.7% of the patients in the previous 12 months and in 59.5% in the previous 3 months. Of those, 12.7% had been hospitalized at least twice in the previous year. In this population, 58 patients (78.4%) were using DNase and 28 (37.9%) were using pancreatic enzymes.

The analysis of the facial sinus X-rays revealed normal results in 13 patients (17%), sinusitis in 60 (80%) and sinusitis with polyps in 3 (4%). In 68 patients (92%), alterations were seen on chest X-rays, and the following patterns were found: hyperinflation in 27 (36.5%); bronchial wall thickening in 65 (87.8%); bronchiectasis in 48 (64.9%); consolidation in 20 (27%); and atel-
ectasis in 19 (25.7%). These alterations were found in isolation or in combination.

Clinical complaints indicative of bronchial hyperreactivity, such as wheezing during follow-up, present in 60 patients (81.1%), were investigated. Pulmonary function was assessed by spirometry. A total of 47 patients (63.5%) presented obstructive lung disease, ranging from mild to severe, with a mean FEV$_1$ of 67.8 ± 26.8%. In addition, an immediate bronchodilator response was observed in 24 patients (32.4%).

Of the 74 patients, 17 (23%) presented IgE > 1,000 IU/mL, 19 (25.7%) presented immediate skin reactivity to A. fumigatus antigen, and 21 (28.4%) presented eosinophilia.

Table 2 shows the comparison of a series of variables in patients with IgE > 1,000 IU/mL and in those with IgE < 1,000 IU/mL, demonstrating that only age (being younger) was significant.

Cultures for Aspergillus spp. were positive in 3 patients (4.1%), none of whom had ABPA.

Table 3 shows the analysis of the 4 cases in which the criteria for a diagnosis of ABPA were met.

In 2 of those 4 cases, two major criteria and two minor criteria were met, whereas, compared with two major criteria and one minor criterion in the other 2 cases. Therefore, the prevalence of ABPA was 2.7% (2 cases)—if we are stricter in the evaluation—or 5.7% (4 cases) if we require only two major criteria and one minor criterion for the diagnosis.

**Discussion**

Concomitance between ABPA and CF is a well-recognized complication, although prevalence data vary significantly in the various studies. It is likely underdiagnosed, as is the underlying disease itself. In practice, this combination is suspected in patients with CF when there is acute or subacute clinical deterioration, not attributed to another etiology, or when the attempt to reverse the pulmonary infiltrate with the antimicrobial treatment for the bacterium isolated in culture fails. It can occur in patients with various degrees of severity of the CF presentation, including those with the mild form of the disease. However, there are reports that ABPA is associated with greater impairment of nutritional status and pulmonary function. In our study, since it involved a small sample and the prevalence of ABPA was low, we could not draw conclusions regarding the severity of the disease, although the 2 patients definitively diagnosed with ABPA both presented impaired nutritional status, with a body mass index of 16 kg/m$^2$. One of those patients presented mild obstructive ventilatory insufficiency, with a positive pharmacodynamic response, and the

Table 2 - Demographic and clinical characteristics, as well as laboratory test and spirometry results, by total serum immunoglobulin E levels.

<table>
<thead>
<tr>
<th>Characteristic/result</th>
<th>Serum IgE levels</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years), mean ± SD (range)</td>
<td>≥ 1,000 IU/mL</td>
<td>&lt; 1,000 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Wheezing, n/total (%)</td>
<td>10.6 ± 16 (11-69)</td>
<td>25.3 ± 21 (61-78)</td>
<td>21.9 ± 21 (31-78)</td>
</tr>
<tr>
<td>Number of hospitalizations per year, mean ± SD (range)</td>
<td>12/17 (70.6)</td>
<td>48/57 (84.2)</td>
<td>60/74 (81.1)</td>
</tr>
<tr>
<td>Use of antibiotics, n/total (%)</td>
<td>1.0 ± 1.270 (0-5.0)</td>
<td>0.67 ± 1.210 (0-5.0)</td>
<td>0.7 ± 1.20 (0-5.0)</td>
</tr>
<tr>
<td>FEV$_1$, mean ± SD (range)</td>
<td>69.7 ± 21.235 (0-115.0)</td>
<td>67.3 ± 28.420 (0-120.0)</td>
<td>67.8 ± 26.820 (0-120.0)</td>
</tr>
<tr>
<td>Response to bronchodilator, mean ± SD (range)</td>
<td>8.7 ± 8.80 (0-28.0)</td>
<td>4.8 ± 4.60 (0-25.0)</td>
<td>5.6 ± 6.00 (0-28.0)</td>
</tr>
<tr>
<td>Immediate skin test reactivity to Aspergillus fumigatus</td>
<td>4/17 (23.5)</td>
<td>15/57 (26.3)</td>
<td>19/74 (25.7)</td>
</tr>
<tr>
<td>Mycobacterial culture (tuberculosis), n/total (%)</td>
<td>1/17 (5.9)</td>
<td>1/57 (1.8)</td>
<td>2/74 (2.7)</td>
</tr>
<tr>
<td>Mycobacterial culture (atypical), n/total (%)</td>
<td>1/17 (5.9)</td>
<td>1/57 (1.8)</td>
<td>2/74 (2.7)</td>
</tr>
<tr>
<td>Fungal culture (Aspergillus sp.), n/total (%)</td>
<td>0/15 (0.0)</td>
<td>3/54 (5.6)</td>
<td>3/69 (4.3)</td>
</tr>
<tr>
<td>Culture for pyogenic organisms, n/total (%)</td>
<td>3/15 (20.0)</td>
<td>16/54 (29.6)</td>
<td>19/69 (27.5)</td>
</tr>
</tbody>
</table>

IgE: immunoglobulin E; and FEV$_1$: forced expiratory volume in one second. *Statistically significant.
In a study carried out in 1984, it was concluded that skin test reactivity to *Aspergillus* sp. antigens, total IgE and IgG antibodies to *A. fumigatus* were the best screening tests for ABPA in CF. In that study, antibodies (precipitins) were found in more than 50% of the patients with CF but without ABPA.\(^{(25)}\)

In our pilot study, all serological test results were negative.

In a longitudinal study involving 118 patients with CF, it was reported that 42% of the patients without ABPA presented skin test reactivity to *A. fumigatus* antigen, 42% presented antibodies (precipitins), 54% presented IgE positivity to *A. fumigatus*, and 23% had IgE levels > 500 IU/mL. According to those studies, the best screening tests continue to be immediate skin test reactivity to *A. fumigatus* antigen, determination of total serum IgE levels and determination of the presence of antibodies (precipitins) to *A. fumigatus*.

Our findings can be superimposed, with values of total IgE ≥ 1,000 IU/mL in 23% of the cases and immediate skin test reactivity to *A. fumigatus* antigen in 25% (Table 2).

In one study,\(^{(22)}\) there was discordance between the results (determination of serum precipitin levels) obtained in the laboratory at their facility—all samples yielded negative results—and those obtained in another laboratory—8 of the 11 samples tested yielded positive results. The authors attributed this discrepancy to the use of more potent *A. fumigatus* antigens or to the greater skill of the professionals who performed the tests in the second laboratory.

Another problem related to determination of precipitin levels is level fluctuation, resulting from characteristics inherent to ABPA, which presents remission and exacerbation. Since all serological test results were negative in our pilot study, we decided to include only patients with normal spirometry results at the time of the test, although wheezing was observed.

In the literature, there are a large number of variations in terms of criterion grouping for the diagnosis. The criteria proposed by the Epidemiologic Study of Cystic Fibrosis, a study on the prevalence of ABPA carried out in the United States and Canada, indicate that two of the following three criteria are necessary: immediate skin reactivity to *A. fumigatus* antigen; antibodies (precipitins) to *A. fumigatus*; and total IgE > 1,000 IU/mL. In addition, there should be at least two of the following criteria: bronchoconstriction; peripheral eosinophilia > 1,000 eosinophils/µL; history of pulmonary infiltrates; specific IgE or IgG for *A. fumigatus*; presence of *A. fumigatus* detected by direct sputum smear microscopy or culture; and response to corticosteroids.\(^{(23)}\)

In the European Epidemiologic Registry of Cystic Fibrosis (ERCF), four diagnostic criteria were required: immediate skin reactivity to *A. fumigatus* antigen; total IgE levels > 1,000 IU/mL; antibodies (precipitins) to *A. fumigatus*; and clinical suspicion based on the presence of at least one of the following—bronchospasm, reversible asthma, pulmonary infiltrates, peripheral eosinophilia (> 1,000 eosinophils/µL), *A. fumigatus* detected by direct sputum smear microscopy or culture and response to corticosteroids.\(^{(24)}\)

The diagnosis of ABPA in CF is difficult and can be delayed because many of the diagnostic criteria overlap with common manifestations of CF. Atopy and a variety of immune responses triggered by *A. fumigatus* antigens, at a very early age in patients with CF, also complicate the interpretation of various serological parameters for the diagnosis of ABPA.\(^{(25)}\)

In our study, we found a high rate of atopy, with total IgE ≥ 1,000 IU/mL in 23% of the patients, eosinophilia in 28.4% and wheezing in 81.1%.

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Wheezing</th>
<th>Eosinophilia</th>
<th>Aspergillin</th>
<th>Total IgE</th>
<th>Specific IgE for <em>Aspergillus fumigatus</em></th>
<th>FVC</th>
<th>FEV(_1) %</th>
<th>Response to bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-ABPA</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>2,000</td>
<td>yes</td>
<td>74</td>
<td>75</td>
<td>yes</td>
</tr>
<tr>
<td>t-ABPA</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>1,371</td>
<td>no</td>
<td>100</td>
<td>100</td>
<td>no</td>
</tr>
<tr>
<td>a-ABPA</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>2,000</td>
<td>no</td>
<td>34</td>
<td>38</td>
<td>yes</td>
</tr>
<tr>
<td>a-ABPA</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>1,157</td>
<td>no</td>
<td>89</td>
<td>84</td>
<td>no</td>
</tr>
</tbody>
</table>

t-ABPA: typical allergic bronchopulmonary aspergillosis (two major criteria and two minor criteria); a-ABPA: atypical ABPA (two major criteria and one minor criterion); IgE: immunoglobulin E; FVC: forced vital capacity; and FEV\(_1\): forced expiratory volume in one second.

Table 3 - Analysis of the four cases in which two major criteria and at least one minor criterion for allergic bronchopulmonary aspergillosis were present.
Prevalence of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis in the state of Bahia, Brazil

not to use serum precipitin level determination for the diagnosis of ABPA.

In a study conducted in the United States from 1993 to 1996, 14,210 CF patients over 4 years of age were evaluated, and the mean prevalence of ABPA was found to be 2%, ranging regionally from 0.9% in the southwest to 4% in the west.\textsuperscript{19}

The ERCF, which comprised 12,447 patients with CF and involved 224 CF referral centers in nine countries, revealed the mean prevalence of ABPA to be 7.8%, ranging from 2.1% in Sweden to 13.6% in Belgium.\textsuperscript{20} The prevalence was 10% in patients older than 6 years of age, being irrelevant in those younger than that. There were no gender-related differences. High levels of microbial colonization (\textit{P. aeruginosa}, \textit{B. cepacia} and \textit{Stenotrophomonas maltophilia}) were associated with ABPA, as was pneumothorax, hemoptysis, increased rate of FEV\textsubscript{1} decline and worsening of nutritional status.

A study carried out in 58 centers in the United Kingdom revealed that 45 of those centers had no standardized protocol for the diagnosis and treatment of ABPA. Among the criteria applied, specific IgE for \textit{A. fumigatus} was required at 54% of the centers, dyspnea and cough were required at 46%, and total IgE levels > 1,000 IU/mL were required at 45%.\textsuperscript{11}

In a study involving 3,089 patients with CF, carried out in Italy, the prevalence of ABPA was 6.2%, mostly affecting adolescents and young adults. In addition, there was greater sensitivity for the following diagnostic tests: determination of total IgE levels (84.5%); specific IgE for \textit{A. fumigatus} (81.6%); and skin prick test (68.3%). It was also concluded that, in the absence of symptoms and of a gold standard for the diagnosis, neither positive serology nor positive skin test results constitute sufficient evidence of ABPA.\textsuperscript{27}

The ABPA prevalence observed in our study was similar to that found in Sweden (2.1%) and to the mean prevalence in North America (2%). In our study, ABPA was not found to be correlated with age bracket, gender or microbial colonization profile. However, it should be considered that all of the studies described above were multicenter surveys, with larger sample sizes, whereas ours was carried out in a single center, the only referral center for the state of Bahia.

Regarding the test results considered indicative of ABPA, it was possible to observe, in our population, that some can be altered in patients with CF who do not have ABPA. We found immediate skin reactivity to \textit{A. fumigatus} antigen in 17 of the CF patients (23%), and none of those 17 patients had aspergillosis. This rate is lower than that found in the literature, in which it ranges up to 42%.\textsuperscript{6} In terms of IgE, when we consider a cut-off value \(\geq 1,000\) IU/mL, this value was found in 15 (20.3%) of our patients. If we consider a cut-off value \(\geq 500\) IU/mL, the percentage of patients without aspergillosis presenting positive test results rises to 27.1%. Data in the literature indicate that 23% of patients without ABPA have IgE levels > 500 IU/mL.\textsuperscript{6}

Fungal culture with evidence of \textit{Aspergillus} spp. growth was found in 3 (4.1%) of our patients. Of those, none met the criteria for a diagnosis of aspergillosis. Our findings confirm the general impression in the literature that positive culture plays a supporting role, rather than a diagnostic role, since \textit{A. fumigatus} is frequently isolated in the lower airways of patients with CF, although the clinical consequences of its presence are unclear.\textsuperscript{20} One group of authors related the presence of \textit{A. fumigatus} detected by culture to an increased risk for more advanced lung disease if accompanied by two indicators of atopy (total IgE and eosinophilia), although no association among the variables was established.\textsuperscript{29}

Colonization with \textit{Aspergillus} spp. leads to chronic antigen stimulation throughout the respiratory mucosa, already affected by the underlying disease, and can cause subsequent sensitization in the susceptible (atopic) host.\textsuperscript{22} Patients with ABPA are atopic, as seen in a study in which 13 of the patients with ABPA had a history of allergic rhinitis, asthma or both.\textsuperscript{23} Our data reveal high IgE levels and a high rate of immediate skin reactivity to \textit{A. fumigatus} antigen, which makes our population, especially those presenting fungal colonization, more susceptible to developing ABPA at some point. However, these associations are not well established in the literature, and there is a consensus that such patients should be observed more carefully.

The prevalence of ABPA in the patients treated at the Cystic Fibrosis Referral Center of Bahia is low (2.7%). A large number of patients with CF (23%) present high serum IgE levels (> 1,000 IU/mL) and immediate skin reactivity to \textit{A. fumigatus} antigen (25.7%). This finding, as indicated in the literature,\textsuperscript{5,6} is an important risk marker for the development of...
ABPA, and such patients should be monitored as to the possible occurrence of the disease.

Acknowledgments

We would like to thank Dr. Daniel Adans Wenzinger, Dr. Mariana Andrade Carvalho and Hugo Costa Carneiro (medical student) for their willing participation in the data collection. We are also grateful to Dr. Eliana Mattos for her participation in the data analysis. In addition, we would like to thank the Associação Baiana de Apoio ao Controle da Tuberculose/Núcleo de Pesquisa em Pneumologia (ABACONNT/NUPEP, Tuberculosis Control Support Association of Bahia/Pulmonology Research Group) and the medical staff of the Octávio Mangabeira Specialized Hospital, Bahia State Health Department.

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