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# The Role of Aspergillus Antibody Detection in Allergic Bronchopulmonary Aspergillosis

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## ABSTRACT

*Allergic bronchopulmonary aspergillosis (ABPA) is an allergic lung disorder characterized by an exaggerated immune response to fungal allergens, particularly from Aspergillus fumigatus. ABPA leads to excessive mucus production and impaired mucociliary clearance. When A. fumigatus conidia are inhaled, they germinate, release exoproteases and other substances that further impede mucociliary clearance, and activate the immune response. The immune response is known by an exaggerated Th2 response to Aspergillus antigens, leading to production of IgE antibodies, eosinophilic infiltration of the lungs, and the formation of immune complexes. These immune complexes can deposit in the lung tissue, leading to airway inflammation, bronchiectasis, and fibrosis. This disease mainly occurs in individuals diagnosed with bronchial asthma and cystic fibrosis. Increased levels of A. fumigatus total IgE and specific IgE, IgG, and IgA antibodies, play a role in diagnosing patients with ABPA.*

**KEYWORDS** *ABPA, Aspergillus, immune response, antibody, immunoglobulin*



## INTRODUCTION

Saprophytic fungi which is found in the environment have the potential to induce allergic conditions in humans. One of the known fungal allergens is Aspergillus, especially A. fumigatus which is often as a trigger (Agarwal et al., 2013, 2016, 2020). One of the allergic effects caused by Aspergillus is ABPA. ABPA primarily affects individuals with asthma and cystic fibrosis (Denning et al., 2013). Its prevalencevaries depending on the population studied. It is estimated that approximately 1 to 2.5% of asthma patients experience ABPA. The majority of individuals with ABPA have a history ofasthma that is inadequately managed, frequently leading to the production of thick sputum. This can contribute to the progression of bronchiectasis. In cases of cystic fibrosis, the prevalence of ABPA is between 1 and 15%. Moreover, more than 60% of individuals with cystic fibrosis have a history of atopy (Kurup et al., 2006).

The diagnosis of ABPA presents numerous challenges due to the frequent overlap between clinical and radiological signs and the underlying disease. Hence, it is crucial to employ serological detection methods. In instances of chronic aspergillosis and allergic aspergillosis, the assessment of specific Aspergillus antibodies is crucial in the diagnostic procedure. Increased levels of Aspergillus-specific IgG are typically observed in chronic conditions, whereas total IgE and Aspergillus-specific IgE are primarily detected in allergicconditions. However, it is important to note that there is some overlap among these clinical syndromes, and many patients exhibit both

clinical and serological characteristics simultaneously. [4,5] Therefore, the aim of this paper is to explore the significance of Aspergillus antibody detection in ABPA.

## RESEARCH METHOD

The research method on *Aspergillus* antibody detection in *Allergic Bronchopulmonary Aspergillosis* (ABPA) is designed to understand the immune response involved in this disease. First, the study focuses on collecting clinical and radiological data from patients with a history of asthma or cystic fibrosis. Common symptoms such as shortness of breath, cough, and brown sputum serve as key indicators. Chest X-ray examinations are used to detect signs of bronchiectasis and lung infiltration, helping to differentiate ABPA from other respiratory conditions.

Next, serological methods are used to measure levels of *Aspergillus*-specific antibodies, such as IgE, IgG, and IgA, which play roles in the allergic response. *Aspergillus*-specific IgE is a primary marker in detecting significant allergic reactions, while IgG and IgA are useful for monitoring long-term exposure or chronic conditions. The *Aspergillus* skin test is also applied to assess sensitivity to the antigen, which, together with blood and radiology tests, provides a more comprehensive diagnosis.

This research further explores the immunological mechanisms involving Th2 helper T cells and B cells in producing *Aspergillus*-specific antibodies. By understanding the genetic influences and cytokines like IL-4 and IL-5, which trigger inflammation, this study aims to identify more accurate diagnostic and therapeutic approaches in managing ABPA.

## RESULT AND DISCUSSION

### Antigen of *Aspergillus*

*Aspergillus* antigens are components of the fungus that can induce an immune response in susceptible individuals. The immune system identifies these antigens. This particular species of *Aspergillus* produces various antigens, including proteins such as Asp f1, Asp f2, Asp f3, Asp f4 and Asp f6, that can elicit an immune response. These antigens are recognized by the immune system, leading to an allergic reaction and the characteristic symptoms of ABPA (Kurup, 2005; Manti et al., 2020).

### *A. fumigatus* and Host Interactions

The interaction between the host and *A. fumigatus* involves a series of complex immune responses. Individuals can be exposed to *A. fumigatus* through inhalation of mold spores. *Aspergillus* spores are very small, measuring 3-5 µm so they can reach the distal airways. The inhaled spores have the ability to survive and start growing, leading to the release of exoproteases and other substances that disrupt the clearance of mucus and triggerimmune reactions. Studies have revealed that specific types of *A. fumigatus* strains secrete proteolytic enzymes that possess the ability to break down elastin and collagen (Tracy et al., 2016).

Recent research has indicated that human bronchial and alveolar epithelial cells generate pro-inflammatory cytokines like IL-6, IL-8, and MCP-1 when exposed to cultures containing the *A. fumigatus* protease (Barry et al., 2020). Based on these findings, it can be inferred that the proteolytic enzymes released by *Aspergillus* during its growth on play a role in inducing chemoattractive cytokines in epithelial cells. This, in turn, leads to the initiation of an inflammatory response. The activation of epithelial cells directly can induce a severe

inflammatory response, which may result in further damage to the epithelial tissue (Barry et al., 2020; Dietschmann et al., 2020).

In vulnerable individuals, the conidia undergo expansion and initiation of growth, leading to the development of hyphae and triggering a robust inflammatory reaction. When exposed to *A. fumigatus* conidia and hyphae, the immune system of the host initiates a response by recognizing PAMPs. The cell wall of *A. fumigatus* contains various PAMP components, such as β-glucan, chitin, galactomannan, and galactosaminogalactan. Innate immune cells rely on PRRs, present on APCs, to recognize PAMPs. This recognition processis essential for the immune response (Croft et al., 2016).

**Innate Immune Response in ABPA**

The early recognition of *A. fumigatus* heavily rely on the innate immune system. Macrophages and dendritic cells recognize the presence of *A. fumigatus* by utilizing PRRs located on their surfaces. PRRs are specialized receptors that can identify specific PAMPs (Shah & Panjabi, 2014). In the case of ABPA, PRRs play a crucial role in detecting PAMPs present on *A. fumigatus*. Two main types of PRRs are C-type lectin receptors (CLRs), with dectin-1 beingthe prominent CLR, and Toll-like receptors (TLRs), mainly TLR2 and TLR4 (Greenberger et al., 2014).

Dectin-1, a type of C-type lectin receptor (CLR), specifically detects and binds to β-glucan, a prominent constituent of the cell wall in *A. fumigatus*. When dectin-1 binds to β- glucan, it initiates a series of signaling events that result in the activation of immune responses.. This activation includes the production of pro-inflammatory cytokines, such IL-6, IL-1β, and TNF-α, which initiate and promote inflammation. TLRs, particularly TLR2 andTLR4, recognize other cell wall components of *A. fumigatus*, such as chitin, galactomannan, and galactosaminogalactan. Activation of TLRs also results in the generation of pro- inflammatory cytokines (Muthu et al., 2020).

The stimulation of innate immune cells and the release of pro-inflammatory cytokines contribute to the activation of other immune cells, such as neutrophils and eosinophils. Thesecells play crucial roles in the clearance of *A. fumigatus* and the subsequent elimination of thefungal infection.

**Adaptive Immune Response in ABPA**

In ABPA, the adaptive immune response plays a significant role in the pathogenesis of the condition. The adaptive immune response is a specific and targeted immune response thatdevelops after the initial innate immune response. The adaptive immune response primarilyinvolves two key components: T lymphocytes (T cells) and B lymphocytes (B cells) (Asano et al., 2021; Sehgal et al., 2016).

1. T lymphocyte response:. T cells recognize specific antigens derived from *A. fumigatus*. These antigens are presented to T cells by antigen-presenting cells (APCs),such as dendritic cells.
    a) Th2 cell activation: Th2 cells become activated upon recognition of *Aspergillus* antigens, leading to their proliferation and release of cytokines such as IL-4, IL-5, and IL-13. These cytokines promote the recruitment and activation of other immune cells, especially eosinophils, which are involved in the allergic response.
    b) Regulatory T cells: Tregs helps control and suppress excessive immune responses. However, in ABPA, there is evidence of impaired Treg function, which contributes

to the exaggerated immune response and inflammation seenin the condition.

2. B lymphocyte response: B cells are responsible for the production of antibodies, which are proteins that specifically target and neutralize foreign substances. In ABPA, B cells recognize antigens from *A. fumigatus* and differentiate into plasma cells, which produce specific antibodies called immunoglobulin E (IgE). The production of IgE antibodies is a characteristic feature of ABPA and contributes tothe allergic response.

The interaction between Th2 cells and B cells is critical in ABPA. Th2 cytokines, likeIL-4, facilitate the differentiation of B cells towards IgE production. Upon binding to specificreceptors on basophils and mast cells, IgE antibodies trigger the release of inflammatory mediators, including histamine. This results in the symptoms associated with ABPA, including airway inflammation, mucus production, and bronchoconstriction (Patel et al., 2019).

Overall, immune response in ABPA involves the activation of T lymphocytes, particularly Th2 cells, and the production of IgE antibodies by B cells. This immune responseleads to an exaggerated allergic reaction characterized by inflammation, eosinophilic infiltration, and the release of inflammatory mediators. Understanding the adaptive immuneresponse in ABPA is crucial for developing targeted therapies to modulate and regulate immune responses in affected individuals.

**ABPA and Genetic Factor**

Genetic predisposition plays a significant role in determining an individual's susceptibility to allergic bronchopulmonary aspergillosis (ABPA). Specific genetic variations have been identified that are linked to a higher susceptibility to developing ABPA.[24] One of the well-studied genetic factors is the HLA (human leukocyte antigen). HLAgenes are responsible for encoding proteins that have function in the immune system, as theyare involved in presenting antigens to T cells. Several studies have shown an association between specific HLA alleles and ABPA susceptibility. In particular, the HLA-DRB1*15:01 and HLA-DQB1*06:02 alleles have been consistently linked to an increased risk of ABPA invarious populations. These alleles are involved in antigen presentation and immune regulation, suggesting that genetic variations in these HLA genes may affect the immune response to *Aspergillus* antigens (Overton et al., 2016).

In addition to HLA genes, other genetic variations have been associated with an increased susceptibility to ABPA. Polymorphisms in genes involved in the immune response,such as IL-4, IL-13, and IL-10, have been linked to a higher risk of developing ABPA. Thesegenes encode cytokines that regulate immune cell function, including Th2 cell differentiationand IgE production. Variations in these genes contribute to the development of ABPA.

Furthermore, genetic variations in genes associated with airway epithelial function and mucociliary clearance have also been implicated in ABPA susceptibility. For example, polymorphisms in genes encoding surfactant proteins (SP-A, SP-D) and mucin genes (MUC5AC) have been linked to an increased risk of ABPA. These genes play crucial roles in maintaining airway integrity and clearing pathogens, and variations in their structure or expression may affect the host defense against *Aspergillus*.

**Diagnosis**

Diagnosis is established by considering clinical symptoms, radiographic results, and immunological findings. In the anamnesis, it can be found as follows:

- Patients may have a history of recurrent wheezing, although wheezing may not

always be present. Some patients may exhibit asymptomatic lung consolidation.
- Despite appropriate asthma medication, patients may have a history of uncontrolled asthma
- Patients with cystic fibrosis may have a relevant medical history.
- Clinical manifestation such as dyspnea, cough, chest pain, presence of blood or brown mucus in sputum.
- Non-specific complaints may include fever, loss of appetite, fatigue, loss of weight and general body aches
- It may occur concurrently with fungal allergic sinusitis, which is characterized by chronic sinusitis symptoms and purulent sinus secretions.

During the physical examination, the following findings may be observed:
- In cases of ABPA and asthma Wheezing and/or crackles may be heard on auscultation.
- In cases of ABPA and cystic fibrosis, crepitation may be observed on auscultation due to bronchiectasis.
- Tachypnea

Other evaluation can be found as follows:
- *Aspergillus* skin test: It is diagnostic test to determine sensitization to *A. fumigatus*. It measures the skin's direct hypersensitivity reaction to *A. fumigatus*, indicating the presence of *A. fumigatus*-specific IgE antibodies.
- Blood test:
    - Increased levels of specific IgE antibodies specific to *A. fumigatus*.
    - Increased levels of total serum IgE (typically exceeding 1000 IU/mL).
    - Detection of precipitins in serum or increased levels of *A. fumigatus*-specific IgG antibodies.
    - Eosinophilia
- Radiology: Chest X-ray has a sensitivity of 50% in diagnosing ABPA. It may reveal infiltrates and bronchiectatic, predominantly in the upper lobe.
- Lung function test: This test is used to assess the severity of lung function impairment and monitor any improvements during follow-up.
- Bronchoscopy: The presence of a mucous plug filled with hyphae is considered a characteristic sign of ABPA. Analysis of bronchoalveolar lavage (BAL) fluid from ABPA patients often shows eosinophilia and elevated levels of *Aspergillus*-specific IgE and IgA antibodies.
- Sputum culture for *A. fumigatus*. This is not a common diagnostic test, but if organisms are found, it assists in drug susceptibility testing.

Table 1 Rosenberg-Patterson criteria.

| | |
|---|---|
| Major criteria | 1. The presence of asthma symptoms.<br>2. A positive skin test indicating an immediate hypersensitivity reaction to Af<br>3. Increased levels of total IgE antibodies (> 1000 IU/mL)<br>4. Positive antibody precipitation against Af<br>5. Eosinophilia<br>6. Increased spesific IgE /IgG to Af<br>7. Presence of pulmonary infiltrates<br>8. Central/proximal bronchiectasis |

| | |
|---|---|
| Minor criteria | 1. Sputum plugs are golden brown<br>2. Positive result of *Aspergillus* species in the sputum culture<br>3. A positive skin test result indicative of a delayed hypersensitivity reaction of the Arthus type to Af |

Table 2. ISHAM working group criteria

| | |
|---|---|
| Predisposition conditions | 1. Cystic fibrosis<br>2. Bronchial asthma |
| Mandatory criteria (both must be present) | 1. Increased levels of total IgE (> 1000 IU/mL)<br>2. A positive *Aspergillus* skin test indicating immediate skin hypersensitivity to *Aspergillus* antigen, or a increased level of IgE specific to *A. fumigatus*. |
| Other criteria (A minimum 2 of 3 criteria) | 1. Consistent pulmonary opacities on radiographs<br>2. Positive precipitins or IgG antibodies to Af in serum<br>3. The total eosinophil count is more than 500 cells/µl (Ifthe patient fulfills all other criteria, an IgE value below1000 IU/mL may still be considered acceptable.). |

**The Role of *Aspergillus* Antibody Detection**

In ABPA, antibodies specific to *Aspergillus*, have a crucial role in the disease. ABPAis an allergic reaction to the presence of *Aspergillus* in the respiratory system, primarily affecting the lungs. The immune system recognizes *Aspergillus* as a foreign invader and responds by producing various types of antibodies, which are proteins that help identify and neutralize harmful substances.

1. *Aspergillus*-specific IgE

   Elevated levels of *Aspergillus*-specific IgE are commonly found in individuals with ABPA. IgE is associated with allergic reactions and plays a central role in immediate hypersensitivity responses. When a person with ABPA is exposed to *Aspergillus*, the immune system releases IgE antibodies that bind to specific components of the fungus, known as allergens. This interaction triggers the release of inflammatory mediators, such as histamine, which leads to clinical manifestation like coughing, dyspnea. and wheezing (Agarwal et al., 2014).

2. Total IgE:

   In ABPA, there is an excessive inflammatory response triggered by exposure to fungal allergens. This leads to an increased presence of Th2 and Th17 CD4+ cells and a reduction in the number of T-regulator cells (Tregs). Consequently, patients with ABPA exhibit increased levels of *Aspergillus*-specific IgE and total IgE in theirblood serum.[22,23]

   The assessment of total serum IgE level is a valuable tool for diagnosing and monitoring ABPA in patients. Although it has a high sensitivity (96%) in screening ABPA in asthmatic patients using a cut-off of 500 IU/ml, its specificity is low (24%), making it less suitable for ABPA screening. However, it is effective in monitoring the progress of patients as serum total IgE levels typically decrease after treatment (Maturu & Agarwal, 2015).

3. *Aspergillus*-specific IgG

In ABPA, *Aspergillus*-specific IgG antibodies are produced, particularly in chronic cases. IgG is a class of immunoglobulins that plays a critical role in providing long-term immunity and defending against infections. The detection of increased levels of IgG antibodies specific to *Aspergillus* indicates exposure to *Aspergillus* antigens over an extended period. These antibodies may not directly cause immediate allergic symptoms but are important markers for identifying chronic ABPA and monitoring the disease progression.

4. IgA

Immunoglobulin A is an antibody class that plays a vital role in mucosal immunity, protecting the respiratory, gastrointestinal, and genitourinary tracts from pathogens. While IgA is not typically associated with ABPA, there is evidence indicating its potential involvement in the pathogenesis of the disease.

Research findings indicate that certain individuals with ABPA may exhibit increased levels of *Aspergillus*-specific IgA antibodies., although the significance of this finding is not fully understood. Some researchers have suggested that *Aspergillus*-specific IgA might have a role in the initial phases of the disease, beforethe production of IgE and IgG antibodies. Others have suggested that it may be involved in modulating the immune response, preventing excessive inflammation and tissue damage.

The precise role of IgA in ABPA remains uncertain, and additional studies are required to determine its significance. At present, the diagnosis of ABPA relies primarily on the measurement of total IgE and *Asp*-specific IgE, with *Asp*-specific IgG also being a useful marker in some cases.

Table 3. Biomarkers of ABPA stage.

| **Stage of ABPA** | **Clinical features** | **Eosino -phil** | **Total IgE** | **Af spesifi cIgE** | **Anti-Af precipit ins or IgG** | **Anti -Af IgA** | **Spesific IgEto recombina ntallergens** |
|---|---|---|---|---|---|---|---|
| I (acute) | cough with sputum, hemoptysis, chest discomfort, Fever | + | +++ | ++ | + excepted $IgG_3$ | ++ | rAsp f2 +++<br>rAsp f3 +++<br>rAsp f4+++<br>rAsp f6 ++ |
| II (remission) | Asymptomatic/sta ble asthma | ~ | + | +/- | +/- | | rAsp f3 ++<br>rAsp f4 ++ |
| III (exacerba-tion) | Symptoms are similar to an acute condition | + | +++ | + | + | ++ | rAsp f1 +++<br>rAsp f2+++<br>rAsp f3+++<br>rAsp f6 ++ |
| IV (steroid-dependent) | Persistent severe asthma | +/- | +/++ | +/- | +/- | | |
| V (fibrosis) | Cyanosis, severe shortness of breath | - | + | +/- | +/- | ++ | |

## CONCLUSION

In conclusion, ABPA is a complex immune-mediated lung disease with an exaggerated Th2 response to *Aspergillus* antigens. The immune response involves a variety of immune cells, cytokines, and chemokines. It is characterized by the production of IgE antibodies, eosinophilic infiltration of the lungs. The measurement of these antibodies, both IgE and IgG, through serological tests is crucial for diagnosing and managing ABPA. Increased levels of *Aspergillus*-specific IgE and IgG, in conjunction with additional clinicaland radiological evidence, aid in confirming the diagnosis of ABPA and distinguishing it from other respiratory conditions. Regular monitoring of antibody levels is also important inassessing treatment response and disease activity.

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