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Review

Diagnosing allergic bronchopulmonary aspergillosis in children with cystic fibrosis

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SUMMARY

Allergic bronchopulmonary aspergillosis (ABPA) is an important complication of cystic fibrosis. It is a hypersensitivity reaction to *Aspergillus fumigatus*, leading to a Th2 CD4 response mediated by the release of specific IgE. If ABPA is not treated early, it can cause severe impairment in lung function and long-term lung damage. Hence, early recognition with a prompt diagnosis is important. Due to clinical and radiological features of ABPA overlapping with those of bacterial or viral pulmonary exacerbations in cystic fibrosis, diagnosis can sometimes be difficult. Specific criteria for making the diagnosis of ABPA have been suggested. Newer serological tests, such as specific IgE to recombinant allergens and the detection of thymus- and activation-regulated chemokine, are being developed to improve early detection and monitoring of ABPA with greater sensitivity and specificity.

INTRODUCTION

Aspergillus is a common spore-bearing fungus that is readily found in organic waste, dust, compost and rotted plants. There are many different species, but *Aspergillus fumigatus* is responsible for 80% of clinical infections in humans.[1] These can include an aspergilloma in those with pre-existing lung cavities; chronic necrotizing aspergillosis in those with mild immunocompromise or chronic lung disease; invasive aspergillosis in severe immunocompromise; and finally allergic bronchopulmonary aspergillosis (ABPA) in those with cystic fibrosis (CF) or adults with asthma. ABPA is a lung disease resulting from hypersensitivity to aspergillus species, clinically characterized by impaired mucociliary clearance, mucoid impaction and airway obstruction, and pulmonary infiltrates. This review is concerned with the diagnosis of ABPA in patients with CF.

PREVALENCE

The prevalence of ABPA ranges from 1–8% in patients with asthma, and it occurs primarily in adults.[2] In CF, it occurs mainly in older children and adults, with a prevalence rate of 6–25%.[3] The overall prevalence in Europe is 7.8%,[4] with a lower reported prevalence in the USA (2%).[5] In the North American Epidemiologic Study of Cystic Fibrosis (ESCF)[5] and the European Epidemiologic Registry of Cystic Fibrosis (ERCF),[4] there was increased prevalence of ABPA in those over 6 years of age, adolescents, those with lower lung function, wheeze, and microbial chronic infection with *Pseudomonas aeruginosa, Burkholderia cepacia, Stenotrophomonas maltophilia* and *Candida albicans*. The variation in ABPA prevalence is possibly related to different diagnostic criteria being applied for diagnosis of ABPA, but may also relate to different patterns of antibiotic use, including nebulized antipseudomonal antibiotics. Although *A. fumigatus* is isolated relatively frequently in the sputum of CF patients (9–57%),[5] the mere presence of *A. fumigatus* is not associated with ABPA.[6]

PATHOGENESIS/STAGES

Inhalation of the *A. fumigatus* spores leads to a Th2 CD4 cellular response, with an IgG and IgE antigen-specific humoral immune response. Interaction of these antibodies with *A. fumigatus* antigens in the bronchial tree leads to activation of complement and mast cells, resulting in mediator release and cytokine production [interleukin (IL)-4 and IL-5]. Due to increased mucus in CF airways, inhaled spores are 'trapped'. The continued presence of the allergen leads to persistent airway inflammation and subsequent lung damage.[7]

Patterson et al divided ABPA syndrome into five stages to guide the management of this disease.[8,9] Stage 1 (acute stage) is characterized by acute wheeze and reversible airway obstruction. It is identified by a markedly raised IgE level, peripheral eosinophilia, presence of specific IgE and IgG to *A. fumigatus*, and pulmonary infiltrates. Stage 2 (remission stage) is reflected by

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a drop in IgE level, but not to the normal range, absence of peripheral eosinophilia and resolution of pulmonary infiltrates on chest radiograph; IgG antibodies to *A. fumigatus* may be elevated. Stage 3 (exacerbation stage) occurs in patients with known ABPA and shows characteristics similar to those seen in stage 1. Stage 4 (corticosteroid-dependent stage) is when a patient is steroid-dependent and any attempt to reduce or stop steroid leads to worsening ABPA with evidence of central bronchiectasis on computed tomography (CT) scan. Stage 5 (fibrotic stage) is characterized by end-stage respiratory failure; serum IgE levels and eosinophil count may be high or low at this late stage.

CLINICAL IMPACT

The relationship between sensitization to *A. fumigatus* and progression of pulmonary function is not clear as there are conflicting studies and few that are longitudinal.[4,5] Wojnarowski et al studied CF children with *A. fumigatus* sensitization and found an association with lower lung function, but only in those with elevated total IgE.[10] Kraemer et al showed that children with ABPA demonstrated more severe decline in multiple lung function parameters than those with chronic *Pseudomonas* infection.[11] The best differentiation between ABPA and *A. fumigatus* sensitization was reflected by an increase in lung clearance index in ABPA, indicating airway narrowing, air trapping and small airway disease.[11] Poorer lung function was also reflected in those with *A. fumigatus* sensitization in the study by Kathan et al, but they found that those treated with oral antifungal therapy had better lung function.[12] Therefore, early diagnosis and treatment of ABPA would seem to be important in order to prevent serious and potentially irreversible lung damage. The association between *P. aeruginosa* chronic infection and the development of ABPA may advocate regular screening for ABPA in those with chronic *P. aeruginosa* infection.

DIAGNOSTIC CRITERIA

If ABPA is diagnosed early and treated promptly, respiratory symptoms may be reduced, lung function improved and unnecessary treatments reduced, such as intravenous antibiotics. It is hoped this may also prevent long-term damage such as bronchiectasis and fibrosis. However, due to clinical and radiological features of ABPA overlapping with those of infective exacerbations in CF, the diagnosis of ABPA can be difficult. Maintaining a high level of clinical suspicion and then investigating for ABPA is important. The diagnosis should be suspected if there is a poor response to intravenous antibiotics, markedly increased or new-onset wheeze, or pleuritic chest pain. Diagnosis needs to confirmed by radiological and serological testing.

Different sets of diagnostic criteria have been established for the diagnosis of ABPA in asthmatic and CF patients.[13] In the UK, diagnostic criteria were published by the Cystic Fibrosis Trust in 2002 (Table 1),[14] and the Cystic Fibrosis Foundation of North America in 2003 (Table 2).[15] They also proposed annual screening, advocating that early suspicion and treatment would prevent lung function decline and irreversible lung damage (Table 3).[15] At our institution, we base the diagnosis of ABPA on a combination of criteria from those set out in the UK and US consensus statements (www.rbht.nhs.uk/childrencf). We advocate screening of ABPA through routine annual serological testing; measuring markers at the start of a course of intravenous antibiotics and regular culture for aspergillus in sputum and cough swabs. Retrospective confirmation is obtained by a positive response to oral corticosteroid therapy, with clinical improvement, reduction in serological markers and clearing of infiltrates on a chest radiograph.

Table 1
The UK Cystic Fibrosis Trust 2002 diagnostic criteria for allergic bronchopulmonary aspergillosis in cystic fibrosis.[14]

- Asthma symptoms
- New chest radiograph changes
- Total serum IgE >500 IU/ml *or* four-fold increase in IgE titres:
- Raised specific IgE aspergillus RAST or positive skin prick test to *A. fumigatus*
- Blood eosinophilia >500/mm^3
- Positive aspergillus culture in sputum or fungal hyphae

Table 2
US Cystic Fibrosis Foundation 2003 diagnostic criteria for allergic bronchopulmonary aspergillosis in cystic fibrosis.[15]

- Acute/subacute clinical deterioration
- Serum total IgE > 1000 IU/ml
- Immediate cutaneous reactivity to *A. fumigatus* >3 mm or raised specific IgE to *A. fumigatus*
- Precipitating IgG antibodies to *A. fumigatus*
- New or recent changes on chest radiograph/CT

Table 3
US Cystic Fibrosis Foundation 2003 guidelines for screening criteria for allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis.[15]

- Maintain a high level of suspicion for ABPA in patients >6 years of age
- Measure total serum IgE annually
- If >500 IU/ml, determine immediate cutaneous reactivity to *A. fumigatus* and consider diagnosis
- If 200–500 IU/ml, repeat IgE level and perform further diagnostic tests

DIAGNOSTIC DIFFICULTIES

Despite clearly defined diagnostic criteria for the diagnosis of ABPA, making a definitive diagnosis in CF can be difficult. This is due to clinical, radiological, serological and microbiological features of ABPA overlapping with those seen in CF without ABPA, particularly during infective bacterial exacerbations (Table 4). The differential diagnosis for the clinical picture that may be seen in a child with CF and ABPA is outlined in Table 5, and needs to be considered while waiting for the results of investigations.

Table 4
Features of ABPA that may occur in patients with cystic fibrosis who do not have allergic bronchopulmonary aspergillosis.

Clinical	• Wheeze, dyspnoea and cough may occur in chest exacerbations • Many CF patients have bronchial hyper-reactivity
Radiology	• Fleeting pulmonary infiltrates on chest radiograph may occur in chest exacerbations • Bronchiectasis on CT chest is a common feature of CF regardless of ABPA status
Serology	• Raised total IgE may reflect underlying atopy rather than ABPA • Skin prick test can be positive in 29% of CF without ABPA[40] • Aspergillus precipitins may be present in CF with or without ABPA • Eosinophilia may be due to chronic infection with *P. aeruginosa* rather than ABPA
Microbiology	• Aspergillus commonly found in sputum without ABPA

Table 5
Differential diagnosis of clinical picture of allergic bronchopulmonary aspergillosis.

- Bacterial or viral chest exacerbation
- CF asthma
- Atopy
- Severe small airways disease
- Gastro-oesophageal reflux ± aspiration
- Pneumothorax

CLINICAL FEATURES

Symptoms of ABPA include worsening or new-onset wheeze, dyspnoea, fevers, malaise and expectoration of brown or black mucous plugs. Not infrequently, patients may be asymptomatic.[16] Suspicion should also be raised if a patient fails to respond to a course of intravenous antibiotics given for chest symptoms. Physical examination of ABPA in CF can often be normal or non-specific with the presence of wheeze and crackles.

CHEST RADIOGRAPH

Transient or persistent pulmonary infiltrates may be seen. They are usually distributed in the mid-lung zones and sometimes in the upper lobes.[17,18] These changes can also be seen in a CF patient in the absence of ABPA. However, with a positive clinical context for ABPA in a CF child, new pulmonary infiltrates on a chest radiograph are suggestive. It is suggested that the clearing of pulmonary infiltrates, either partially or completely with oral corticosteroid therapy, may be a useful way of identifying infiltrates due to ABPA (Figure 1). However, radiographic resolution with treatment varies among CF patients with ABPA and resolution may not always coincide with clinical improvement.

CT CHEST SCAN

CT of the chest is considered more sensitive in detecting changes seen in CF and ABPA. High attenuation mucous plugs have been described as a feature of ABPA but not regular CF.[19,20] However, mucoid impaction with normal attenuation and centrilobular nodules seen in CT scans can be found in CF, both with and without ABPA. Mucoid impaction on CT is seen in $>$ 80% of adults with CF, and centrilobular nodules can be found in 50% of asymptomatic CF patients, so these CT findings are less specific for ABPA.[21,22] Pleural thickening seen on CT is found frequently in asthmatics with ABPA, but in CF, pleural thickening is also seen in advanced disease, irrespective of the presence of ABPA.[23]

Central bronchiectasis is one of the hallmarks of ABPA, but central and peripheral bronchiectasis is found commonly in CF with and without ABPA. Nonetheless, a predominant central distribution in the absence of peripheral bronchiectasis is suggestive of ABPA (Figure 2). The appearance of bronchiectasis can be divided into cylindrical, varicose (beaded) and cystic (saccular dilatation). Cylindrical bronchiectasis has been reported more frequently in CF, whereas varicose and cystic bronchiectasis are more typical of ABPA (Figure 3).[23,24] Nevertheless, reports have shown that varicose and cystic bronchiectasis are not uncommon in CF and have been seen in 11% and 34%, respectively, of bronchiectatic CF lobes, irrespective of ABPA.[23]

MICROBIOLOGY

Reports of the prevalence of *A. fumigatus* in the sputum of CF patients range from 10% to 60%. The wide variation in prevalence is related to the degree of exposure to its spores; people living in rural areas and inadequately ventilated houses have higher rates of colonization.[5] As expected, there is a higher rate of aspergillus colonization in CF patients with ABPA. In the ERCF, *A. fumigatus* colonization occurs in 45% of patients with ABPA, compared to 16% without ABPA.[25] Studies have suggested a positive association between *P. aeruginosa* and *S. maltophilia* and increased risk of ABPA. This may possibly be explained by the use of more antibiotics for infective exacerbations, hence promoting the growth of fungal infections. The mere presence of *A. fumigatus* in sputum or bronchoalveolar lavage fluid in CF patients does not signify ABPA if there are no other clinical features. The simple presence of the fungus is not associated with worsening of lung function if no sensitization has taken place. Besides, the presence of *A. fumigatus* is certainly not a prerequisite for the diagnosis of ABPA, if other diagnostic criteria are not met.

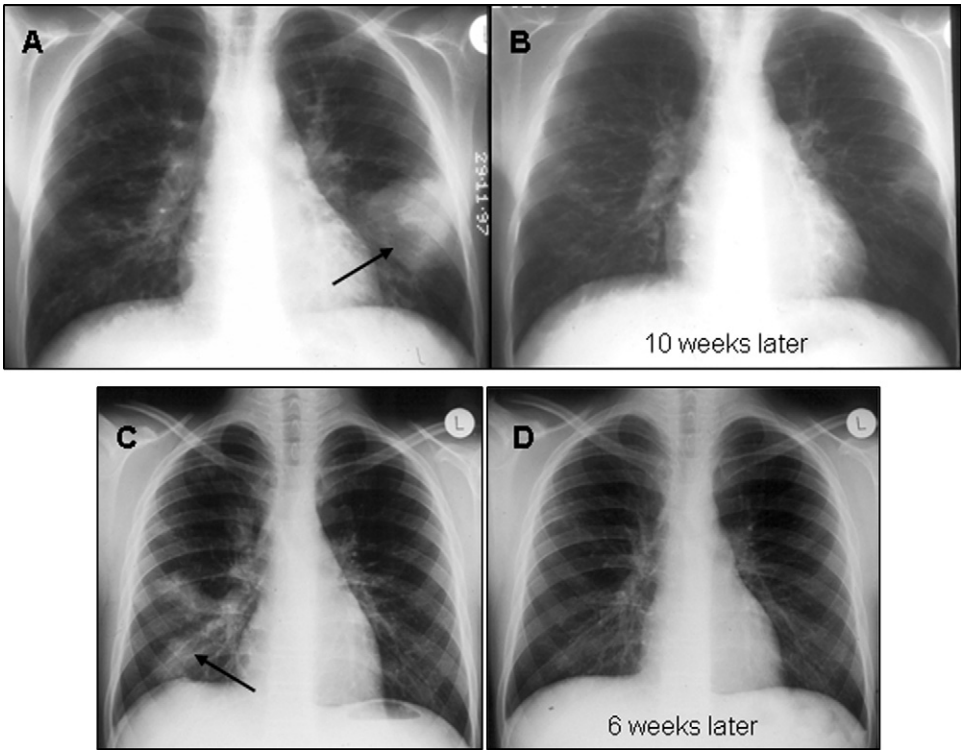

Figure 1. Examples of pulmonary infiltrates (arrowed) in children with cystic fibrosis and allergic bronchopulmonary aspergillosis that cleared with oral corticosteroid and oral antifungal therapy. (a, b) Child with radiographic resolution after 10 weeks. (c, d) A different child with radiographic resolution after 6 weeks.

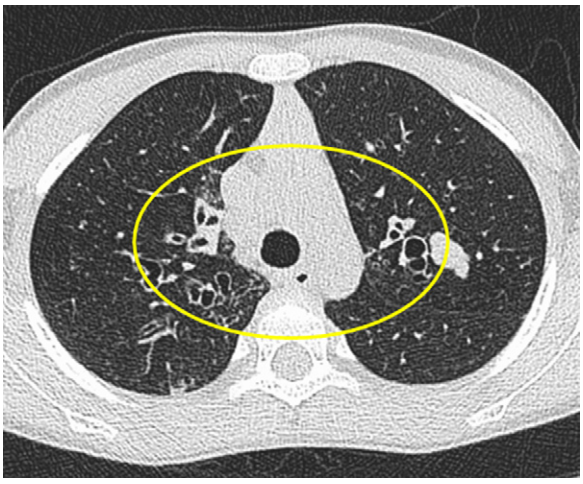

Figure 2. Chest CT scan showing central bronchiectasis in a child with cystic fibrosis and allergic bronchopulmonary aspergillosis.

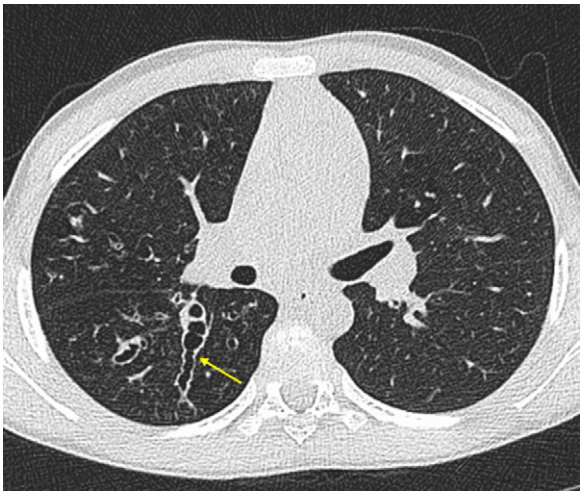

Figure 3. Chest CT scan demonstrating varicose bronchiectasis (arrowed) in a child with cystic fibrosis and allergic bronchopulmonary aspergillosis.

SKIN PRICK TESTING

Skin prick testing for sensitization to aspergillus can be carried out cheaply, easily and quickly in patients suspected of ABPA. Those with severe eczema may have a false-positive or an exaggerated response to the allergen on skin prick testing, while those taking antihistamines within 24–48 h may have a false-negative test. In most circumstances, the skin prick test to aspergillus is sensitive enough that the absence of a positive skin test reduces the likelihood of an ABPA diagnosis. However, the specificity of the skin test is moderately low: a positive reaction does not necessarily indicate ABPA. The prevalence of skin reactivity to aspergillus is 23–28% in patients with asthma,[26] and 29% in patients with CF without ABPA.[27] Therefore, a positive skin test must always be followed up with serological and radiological testing to confirm ABPA; for this reason, the test is often not performed and blood is taken in the first instance.

SEROLOGICAL TESTS

Serological testing plays an integral part in diagnosing ABPA.

Serum total IgE

A high total serum IgE count reflects increased sensitization to any allergen, so it can be high due to atopy itself rather than ABPA. In the North American diagnostic criteria for ABPA, a total IgE count of >1000 IU/ml constitutes a major criterion.[15] In the UK, guidelines suggest a total IgE count of > 500 IU/ml or a four-fold rise in titres from baseline is diagnostic.[14] There is variable response of the IgE count in different individuals. Despite its limitations, it is nonetheless a valuable tool for the diagnosis of ABPA in CF. The IgE fluctuations can serve as a marker for exacerbations and responses to therapy, in conjunction with clinical symptoms.[28]

Specific IgE antibodies to A. fumigatus

The presence of specific IgE antibodies to *A. fumigatus* is a sensitive indicator for ABPA in CF and in asthma compared to total serum IgE alone.[29,30] Increased levels of specific serum IgE (>17.5 IU/ml) against *A. fumigatus*, measured by radioallergosorbent test (RAST), suggest sensitization to the fungus and, together with raised total IgE, increase the likelihood of an ABPA diagnosis. Similarly to total IgE, the level of specific IgE to *A. fumigatus* can act as a marker of an exacerbation or remission. Increasingly, RAST testing for specific IgE to *A. fumigatus* is preferred to skin testing. Although the levels of total and specific IgE can be useful in detecting and monitoring ABPA, problems exist in those patients in whom the levels are persistently raised. When this is the case, there is a real challenge in deciding whether new symptoms are due to an acute ABPA exacerbation.

Blood eosinophil count

Blood eosinophilia has a limited role in the diagnosis of ABPA in CF, although it contributes towards a minor criterion. It is important to note that blood eosinophilia may be present in a CF patient due to chronic *P. aeruginosa* infection rather than ABPA.[15]

Aspergillus precipitins

Demonstration of precipitating IgG antibodies to *A. fumigatus* is widely used for serodiagnosis of ABPA. The prevalence of detectable IgG antibodies to *A. fumigatus* has been reported to increase with age in patients with CF, irrespective of ABPA.[31,32] Detection of aspergillus precipitins may represent previous exposure rather than current disease. However, if high levels of precipitins are detected, the probability of ABPA increases.

NEWER SEROLOGICAL TESTS

There are a number of newer tests that may prove useful. Mostly, these are not yet generally available in CF centres, other than as research tools. This means that costs for their clinical use are not known.

Specific IgE antibodies against recombinant A. fumigatus (rAsp) allergens

Since the identification of aspergillus allergens is now possible, using recombinant allergens, the detection of specific IgE produced against these allergens may aid the diagnosis of ABPA. Recombinant allergens have become more widely used in Europe as they are more sensitive and specific than total serum IgE and aspergillus-specific IgE levels. However, in the US, it is not widely used clinically. The detection of IgE to recombinant *A. fumigatus*

allergens is possible through an ELISA or an ImmunoCAP system, which allows quantitative and fully automated testing.[15]

The recombinant allergens Asp f1, Asp f2, Asp f3, Asp f4 and Asp f6 have been evaluated for their diagnostic performance in differentiating CF with and without ABPA.[33,34] These studies found the detection of IgE antibodies against rAsp f1 and f3 in sensitized CF individuals without ABPA to have 100% specificity and 88% sensitivity. In contrast, specific IgE antibodies against rAsp f4 and f6 were exclusively detected only in those with ABPA. Eighty per cent of subjects with ABPA showed an IgE response to Asp f4, 55% to Asp f6 and 90% to at least one of these allergens.[35] Further studies involving these recombinant antigens (rAsp f1 and f3) showed poor discrimination between sensitized patients and those with ABPA, whereas positive response to any of the recombinant allergens Asp f2, f4 and f6 showed 100% sensitivity and specificity in the diagnosis of ABPA. To increase the diagnostic sensitivity, a panel of recombinant allergens will be required. Hence, recombinant *A. fumigatus* allergens may point to the diagnosis of ABPA before clinical symptoms arise, as well as differentiating between sensitization and actual disease. However, multicentre studies involving large numbers of patients with ABPA or aspergillus sensitization alone are required to fully assess the diagnostic value of these new tests.

Specific IgG antibodies to A. fumigatus

Measurement of IgG and IgG subclasses to *A. fumigatus* (Af) may also be helpful in making the diagnosis, especially as a screening test. Confirmation of the diagnosis would still require other serological testing. There appears to be a specific pattern of increase in Af-IgG_1, Af-IgG_2 and Af-IgG_4, but not Af-IgG_3 antibody levels in patients with ABPA. Measurement of Af-IgG_4 antibody was the most specific in establishing the diagnosis of ABPA.[36] Further longitudinal studies of IgG subclass antibodies are needed to determine whether fluctuations reflect disease activity.

Thymus- and activation-regulated chemokine (TARC)

ABPA is a T-helper cell (Th2) type 2-mediated hypersensitivity to *A. fumigatus*. TARC is a chemokine produced as a result of the antifungal immune response. Studies have revealed that serum levels of TARC are elevated in CF patients with ABPA.[37] A recent longitudinal study involving 48 patients confirmed elevated levels of TARC in CF patients with ABPA compared to those without ABPA.[38] TARC, compared to other serum markers (serum total IgE, specific *A. fumigatus* IgE and IgG and specific IgE against recombinant *A. fumigatus* allergens f1,3,4 and 6), is a more sensitive and specific marker of ABPA. TARC levels appear to differentiate between CF with and without ABPA; CF colonized with or sensitized to *A. fumigatus* and atopic CF patients. It is said that TARC levels are elevated even before the development of clinical features of ABPA and before total IgE elevation.[38] TARC stays elevated for a prolonged period of time and there are suggestions that the rise and fall of TARC levels could be used to monitor exacerbations and remissions of ABPA.[37,38] Overall results from recent studies are promising. Nonetheless, more studies involving larger groups of patients are still required to investigate this new marker, which appears to have a great clinical potential for early detection of ABPA.

Cellular allergen stimulation test (CAST)

The cellular allergen stimulation test is used in the diagnosis of allergic and pseudoallergic reactions. This test measures cysteinyl-leukotrienes which are produced by allergen-stimulated basophils in vitro. The potential role of using CAST in the diagnosis of ABPA has been looked at in a small study of 27 CF patients where 8 had confirmed ABPA according to the Nelson criteria and serological testing.[39] CAST results were positive in all ABPA patients and in five controls without ABPA but positive for specific IgE against *A. fumigatus*. The CAST assay on its own confers a high sensitivity of 100% but a lower specificity of 74%. The combination of a positive CAST test, total serum IgE $>$ 500 IU/ml and positive IgE antibodies against rAsp f4 and f6 was found only in those with ABPA, giving rise to 100% specificity. Again, further studies involving larger number of patients are required for further evaluation, before CAST becomes a routine investigation for ABPA.

CONCLUSION

ABPA is a recognized complication of CF which occurs with variable prevalence. Due to some overlap between features seen clinically and radiologically in ABPA and pulmonary exacerbations of CF, the diagnosis remains a challenge despite guidelines. Confirmation is necessary through serological testing and newer tests involving the detection of specific immunity against recombinant aspergillus antigens and TARC level may eventually improve the diagnostic accuracy for ABPA. CF centres should regularly screen CF patients for ABPA. It is suggested testing is carried out at annual review and during exacerbations requiring intravenous antibiotics. By maintaining a high level of suspicion, ABPA can usually be diagnosed and treated promptly.

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