



Study of *Candida albicans* & *Aspergillus fumigatus* Sensitization among Egyptian patients with allergic Bronchial Asthma

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Abstract

Asthma is a major cause of disability, health resource utilization and poor quality of life for those who are affected. The global prevalence rates of doctor diagnosed asthma, clinical/treated asthma and wheezing in adults were 4.3%, 4.5%, and 8.6% respectively among 70 countries.

Sensitization to fungi is an important factor in patients with allergic respiratory tract diseases, playing a major role in the development, persistence, and severity of lower airway disease, particularly asthma.

The aim of this study was to determine the sensitization to *Candida albicans* and *Aspergillus fumigatus* fungi among Egyptian patients with allergic Asthma.

This design of this study was cross-sectional, with enrolling of consecutive 100 adult asthmatic patients attended the allergy outpatient clinic; Ain Shams University hospital in the years 2015-2016.

We found that 28 and 12 patients had positive Skin Prick Test to *Candida albicans* and *Aspergillus fumigatus* respectively, from those 22 and 10 were positive at Broncho-provocation test with positive predictive value of skin prick test 78.6% for *Candida albicans* and 83.3% for *Aspergillus fumigatus*.

Keywords: Asthma, to *Candida albicans*, *Aspergillus fumigatus*.

Introduction

The word asthma is a derivation from the ancient Greek, *aazein*, meaning “gasping” or “panting” (Marketos et al., 1982). Asthma is one of the commonest chronic diseases that carries the risk of mortality with known economic burden and social hazards for both patients and their families and care givers. It affects the respiratory system with direct effect on daily activities and productivities. Fortunately, asthma can be treated with achievement of good control and prevention of the fatalities (Levy et al., 2015).

Sensitization to mold allergens known to be related to allergic rhinitis and asthma, with association of mold exposure and the persistence and severity of asthma symptoms and exacerbations (Denning et al., 2006).

Aspergillus; spore forming fungi found worldwide and related to many allergic airway disease including *Aspergillus* sensitized asthma, allergic bronchopulmonary aspergillosis and allergic *Aspergillus* sinusitis (Shah et al., 2002).

While the role of mold sensitization is studied thoroughly in asthma, the fungus *Candida albicans* didn't have the appropriate attention in the studies, earlier studies found a relation between sensitization to *Candida albicans* and the chronicity of asthma, allergic rhinitis and atopic eczema (Asero et al., 2004, Khosravi et al., 2009).

Our study aimed to determine the prevalence of *Aspergillus fumigatus* and *Candida albicans* among asthmatic patients.

Subjects and Methods

This design of this study was cross-sectional, with enrolling of consecutive 100 adult asthmatic patients attended the allergy outpatient clinic; Ain Shams University hospital in the years 2015-2016.

Diagnosis of asthma was done by using the Global Initiative for Asthma (GINA) 2015 guidelines (Reddel et al., 2015), we enrolled patients with partly controlled and controlled asthma assessed according to GINA 2015 guideline at the time of enrollment.

Exclusion criteria:

Patients with septic conditions, current infections, autoimmune diseases, organ or system failure, smokers, pregnant or lactating females and patients on Specific Allergen Immunotherapy.

Methods:

Each patient was subjected to:

1. Thorough history and medical examination with special emphasis on factors causing increase of the asthma symptoms, presence of nocturnal symptoms, seasonal variation and family history.
2. Chest X ray.
3. Complete Blood count.
4. Renal & liver function tests.
5. Serum Total IgE assessed by enzyme-linked immunosorbent assay (ELISA).
6. Pulmonary Function Test (PFT) by spirometer (Microspiro HI -601).
7. Skin Prick Test (SPT) for *Candida albicans*, *Aspergillus fumigatus* and other common allergens.

The patients who proved to be sensitized to *Candida albicans* and/or *Aspergillus fumigatus* by

SPT are further subjected to Broncho Provocation Test (BPT) using *Candida albicans* and/or aspergillus extract according to each patient sensitization as following; if the patient was sensitized to only one of those two antigens he subjected to BPT for this antigen, but if he was sensitized to both antigens then he subjected to BPT for each one of them in two separate sessions 2-3 weeks apart.

Skin Prick Test:

Patient preparation for SPT:

1. All antihistamines were prohibited for an appropriate period of time before testing between 48-72 hours.
2. The test was not conducted in the presence of acute infections.
3. The skin of the testing was clear (Arbes et al., 2005).

Procedure:

After sterilization of the forearm with propyl alcohol swab, a drop of each allergen extract was put on marks 1 centimeter apart. Additionally, a drop of histamine phosphate and a drop of saline 0.9% were used as positive control and negative control respectively. Then, introducing the allergen drops into the skin by a prick with a needle that raises the epidermis without bleeding (Tripathi et al., 2001).

The following 18 allergen extracts were the ones used in the skin testing:

1. *Candida albicans*
2. *Aspergillus fumigatus*
3. House dust mite mix (dermatophagoides farinae, dermatophagoides pteronyssinus (1:1))
4. Tobacco
5. *Alternaria alternata*
6. Hay dust
7. Horse hair
8. Mixed Grass pollens
9. Goat hair
10. Cat hair
11. Cotton dust
12. Pigeon feather
13. Dog hair
14. Cockroach
15. Straw
16. Feather
17. Wool
18. Latex

The extracts of the SPT were prepared in allergy extract unit, Ain Shams University. The extract of 10 histamine equivalent used in prick testing (HEP) (Jeong et al., 2011).

The SPT response was assessed after 20 minutes (Reddel et al., 2015). SPT panel was considered valid if show a difference in wheal diameters between the positive and negative controls at least 1 mm (Gammeri et al., 2005). A measure of wheal diameter ≥ 3 mm than the negative control was considered to be positive (Hill et al., 2003).

Bronchial provocation test

Patient preparation:

Use of short-acting β_2 -agonists was prohibited 8 hours before the challenge, whereas long-acting β_2 -agonists, leukotriene antagonists, and sustained-release theophylline was stopped 48 hours before the test (Subbarao et al., 2005).

Use of inhaled cromolyn and steroids were withheld 1 week before the BPT. Antihistamines were withheld for at least 72 hours.

If medications couldn't be withheld without worsening of symptoms and maintaining the FEV1 at 70% or more of the normal predicted value, the test was postponed because symptomatic, unstable asthma may lead to false positive results (Agache et al., 2015).

Determining the initial allergen dose:

Conventional allergen extracts were used. The starting concentration of test material nebulized was that which gave a skin prick test reaction of 3 mm diameter or less. Only single inhalation test was performed each day (Bernstein et al., 2008).

We started by diluting the 0.05 ml of the extract in 2 ml of normal saline in the 1st session, then we increased the amount according to each patients response to (0.1 ml, 0.2 ml and 0.5 ml) of extract in 2 ml of normal saline.

Procedures:

Resuscitation equipment were readily available in case of life-threatening anaphylaxis or asthmatic reactions (Spector et al., 2008).

The diluent used in the allergen extract was used as the control aerosol at the beginning of the specific bronchial challenge test (Ryan et al., 1981).

Since the early airway response occurs within 10 to 12 minutes after challenge, the subject was dosed with increasing concentrations of allergen every 15 to 20 minutes. Pulmonary function test was performed 10 to 15 minutes after aerosol challenge (Fish et al., 2003).

Inhaled short-acting β_2 -agonist was given to restore FEV1 to within 10% of baseline. Since late-phase asthmatic responses may occur, arrangements were made for direct observation of such reactions, which usually appear 6 to 12 hours later (Pepys et al., 1975).

Criteria for a positive inhalation test:

A sustained fall in FEV1 of 20% or more from the baseline at any time was considered a positive response, and the testing is stopped if this occurs (Pepys et al., 1975, Vandenplas et al., 2006).

Serum Total IgE Level:

Serum total IgE was measured by ELISA technique (Genzyme Diagnostics, Medix Biotech, San Carlos, Calif).

Statistical Methodology:

Data were analyzed using IBM[®] SPSS[®] Statistics version 22 (IBM[®] Corp., Armonk, NY, USA) and MedCalc[®] version 14 (MedCalc[®] Software bvba, Ostend, Belgium).

The Shapiro-Wilk test was used to examine the normality of numerical data distribution. Normally distributed numerical variables were presented as mean \pm SD and inter-group differences were compared using the unpaired t test.

Skewed numerical variables were presented as median (interquartile range) and between-group differences were compared non-parametrically using the Mann-Whitney test.

Categorical variables were presented as ratio or number (%) and differences were compared using Fisher's exact test.

P-value <0.05 was considered statistically significant.

Results

The demographic, clinical and laboratory characteristics of the whole study population at the time of enrollment are shown in (Table 1).

Table 1. Characteristics of the study population:

Variable	Value
Age (years)	34.9 ± 10.2
Gender (Males/Females)	17/83
Duration of asthma (years)	5 (3 – 13)
Associated allergic conditions	67%
• Allergic rhinitis and sinusitis	55%
• Urticaria or atopic dermatitis	12%
Positive family history	50%
FEV1 (%)	79.0 ± 19.7
FVC (%)	80.9 ± 19.9
FEV1/FVC	97.7 ± 15.8
Total IgE (kIU/l)	176.5 (92.5 – 286)

Data are presented as mean ± SD, ratio, number (%), or median (interquartile range).

The results of SPT are shown in (Table 2). The patients were classified according to SPT to two groups. 68 cases (68%) non -allergic to *C.albicans* or

A.fumigatus and 32 cases (32%) allergic to *C.albicans* and/or *A.fumigatus*.

Table 2. Results of the SPT, BPT, and ultimate classification of the whole study cohort

Variable	Value
Positive SPT	
<i>C. albicans</i>	28 (28%)
<i>A. fumigatus</i>	12 (12%)
House dust mite	36 (36%)
<i>Alternaria</i>	9 (9%)
Hay dust	13 (13%)
Horse hair	13 (13%)
Grass pollens	24 (24%)
Goat hair	1 (1%)
Cat hair	18 (18%)
Cotton dust	16 (16%)
Tobacco	18 (18%)
Pigeon	15 (15%)
Dog hair	20 (20%)
Cockroaches	5 (5%)
Straw	8 (8%)
Latex	3 (3%)
Feather	16 (16%)
Wool	15 (15%)

Data are presented as ratio, number (%), or median (interquartile range).

Results of BPT to *Candida albicans* and *Aspergillus fumigatus* in patients with positive SPT are presented in (Table 3). The patients were classified according to

BPT to two groups; group A: 68 cases (68%) non -allergic to *C.albicans* or *A.fumigatus* and group B :32 cases (32%) allergic to *C.albicans* and/or *A.fumigatus*.

Table 3: Results of BPT to *Candida albicans* and *Aspergillus fumigatus*;

Result of BPT	
Positive <i>Candida</i> BPT/Positive <i>Candida</i> SPT	22/28 (78.6%)
Positive <i>Aspergillus</i> BPT/ Positive <i>Aspergillus</i> SPT	10/12(83.3%)
Ultimate patient classification according to SPT reactivity	
GROUP A: non -allergic to <i>C.albicans</i> or <i>A.fumigatus</i>	68 (68%)
GROUP B: allergic to <i>C.albicans</i> and/or <i>A.fumigatus</i>	32 (32%)

Data are presented as number (%).

In (Table 4) the characteristics of patients in each group were displayed, there was no statistical significant difference among the two groups as regard

age, gender, duration of asthma, associated allergic conditions, and positive family history of allergic conditions.

Table 4. Characteristics of patients in each group.

Variable	Non-allergic to <i>Candida</i> and/or <i>Aspergillus</i> (n=68)	Allergic to <i>Candida</i> and/or <i>Aspergillus</i> (n=32)	T	df	P-value
Age (years)	34.3 ± 10.4	36.3 ± 9.7	0.930	98	0.355¶
Gender (M/F)	13/55	4/28			0.571
Positive history of allergic skin conditions	10 (14.7%)	1 (3.1%)			0.100
Positive history of allergic rhinitis	36 (52.9%)	19 (59.4%)			0.667
Family history of allergic conditions	32 (47.1%)	18 (56.2%)			0.521
Duration of asthma (years)	8.1 ± 7.9	10.1 ± 7.5	1.210		0.229¶

Data are presented as mean ± SD, ratio, or number (%).t, t statistic; df, degree of freedom; ¶Unpaired t test.

The total IgE level in both groups shown in (Figure 1). The interquartile range was higher in group B (allergic to *Candida* and/or *Aspergillus*) than group A (non-allergic to *Candida* and/or *Aspergillus*). The

median total IgE in group A was 175 KIU/l with a range from 86.9 KIU/l to 286 KIU/l while in group B was 183 KIU/l with a range from 131 KIU/l to 462.5 KIU/l.

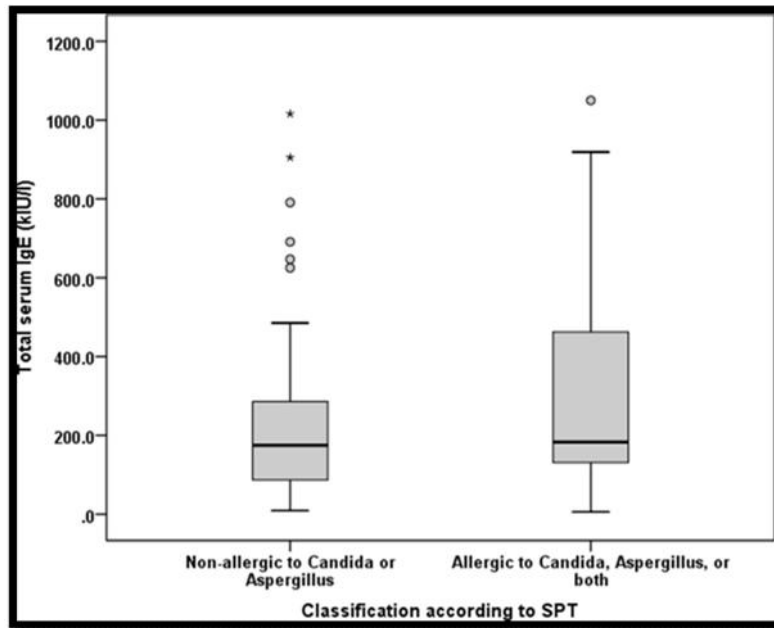


Figure 1. Box plot showing total serum IgE level in patients who were classified as non-allergic to *Candida* or *Aspergillus* and those allergic to *Candida*, *Aspergillus*, or both agents by SPT. Box represents the range between the 1st and 3rd quartiles (interquartile range). Line inside the box represents the median (2nd quartile). Error bars represent the minimum and maximum values excluding outliers (rounded markers) and extreme observations (asterisks).

The median number of sensitizers in group A which was 2 with interquartile range from 1 to 3 sensitizers while in group B it was 3 with interquartile range from

2 to 5 sensitizers (**Figure 2**). Group B had more number of sensitizers than group A (p-value = 0.001)

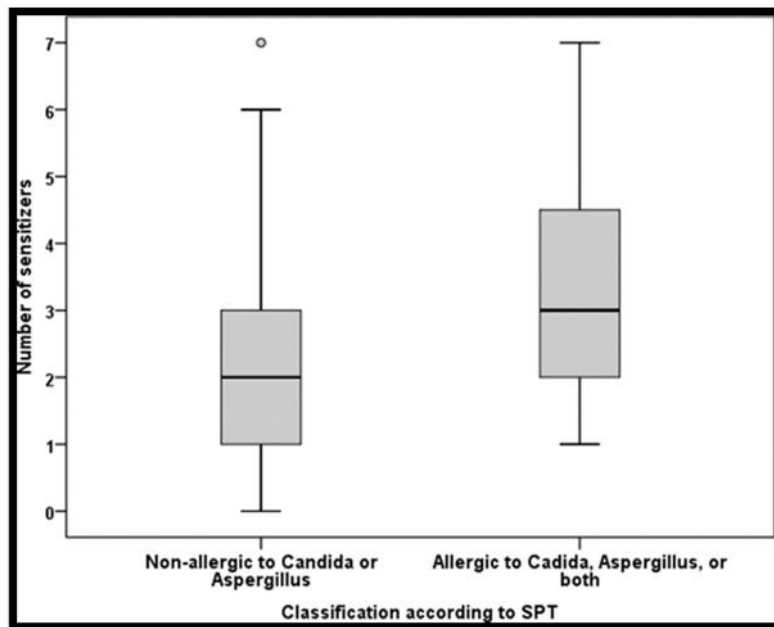


Figure 2. Box plot showing the number of sensitizers in patients who were classified as non-allergic to *Candida* or *Aspergillus* and those allergic to *Candida*, *Aspergillus*, or both agents by SPT. Line inside the box represents the median (2nd quartile). Error bars represent the minimum and maximum values excluding outliers (rounded markers).

Tables 5 and 6 denote that the positive predictive values for SPT were 78.6% and 83.3% for candida and Aspergillus respectively.

Table 5. Positive predictive value of Candida BPT

<i>Candida</i> BPT				
	Positive <i>Candida</i> BPT	Negative <i>Candida</i> BPT	Total	Positive predictive value (PPV) of <i>Candida</i> SPT
Positive <i>Candida</i> SPT	22	6	28	$(22/28) * 100 = 78.6\%$

Data are number of patients.

Table 6. Positive predictive value of Aspergillus BPT

<i>Aspergillus</i> BPT				
	Positive <i>Aspergillus</i> BPT	Negative <i>Aspergillus</i> BPT	Total	Positive predictive value (PPV) of <i>Aspergillus</i> SPT
Positive <i>Aspergillus</i> SPT	10	2	12	$(10/12) * 100 = 83.3\%$

Data are number of patients.

Discussion

Bronchial asthma is inflammatory condition affecting the airways with many triggers that worsen this condition (Agarwal et al., 2011), among that triggers the environmental allergens are well known from which fungal allergens are considered important due to persistent exposure, and there is increasing link for the presence of fungal sensitization in patients with severe asthma (Mari et al., 2003).

Fungi disseminate their spores in the environment through air, water, insects, man and animals (Cramer et al., 2005). The incidence of mold allergy ranges from 6 to 24% in the general population, up to 44% among atopic patients and 80% among asthmatics (Pourfathollah et al., 2014).

Our study aimed at studying *Candida albicans* and *Aspergillus fumigatus* sensitization among Egyptian patients with allergic Asthma.

In a meta-analysis study, the prevalence of *Aspergillus* sensitization by cutaneous testing ranged from 15% to 48%, with the pooled prevalence being 28% (95%CI 24-34) in patients with bronchial asthma. The prevalence of AH did not differ when stratifying the results based on reports from industrialized or

developing countries. From 21 studies nine used locally prepared extract and the others used commercial extract. The prevalence of AH was higher if an intradermal test was used compared to a prick test; this difference was statistically significant (p -value = 0.002) (Agarwal et al., 2009), but in our study only SPT was done, and we used *Aspergillus fumigatus* only not *Aspergillus* mix as other studies.

This variation is probably due to; variable methods of the standardization of mould allergen extracts or skin testing procedures; also fungal sensitization is commoner in younger and decrease with age (Heinzerling et al., 2013).

The prevalence of *Candida albicans* in our study was 28%, in earlier studies this ratio is much less. Tsai and Chen founded a prevalence of 10% and elevated to be 27.3% with the age between 51 and 60 years in older ages (Tsai et al., 1999).

Another study on 86 bronchial asthma patients were examined using mycological, immunological and allergological methods including the prick-test, basophil degranulation test (direct Shelley's test) and leukocyte migration inhibition test with *Candida* antigen. Hypersensitivity to *Candida* was identified in 83.3% of patients mainly that of the delayed type (37%). In children with confirmed *candidiasis*,

hypersensitivity to *Candida* fungi was also demonstrable in 83.3% of cases, but in the majority of patients (47%), it was of the immediate type. In the control group, allergic *candidiasis* was diagnosed in 20% of cases (Pronina et al., 1989).

Fukutomi *et al* studied the incidences of sensitization to fungal allergens among adult patients with asthma. Sensitization to *Malassezia*, *Alternaria*, and *Cladosporium* tended to decrease with age (Fukutomi et al., 2015). However, the frequency of *Aspergillus fumigatus* did not decrease with age, assuming that sensitization to this species is associated with severe persistent asthma with extended disease period (Fairs et al., 2010).

Our patients with fungal sensitization to *Candida* and/or *Aspergillus* did not have higher incidence of associated allergic conditions (urticarial and/or allergic rhinitis) than non-sensitized patients. Although many studies correlate between fungi and associated allergic rhinitis and sinusitis especially *Aspergillus fumigatus*. In Kautz *et al* study; Patients with asthma and rhinitis were significantly more often positive than controls (non-allergic patients) with *Mucor*, *Cladosporium* and mixed-mould (Kautz et al., 1983).

In our study positive family history of allergic conditions were more common in fungal sensitized patients to *Candida* and/or *Aspergillus* (56.2% Vs 47.1%). History of asthma in parents, siblings or grandparents was reported by Sheikh *et al* study in 575 (69.8%) patients including father (17.8%) and mother (26.5%) (Sheikh et al., 2016).

The total serum IgE levels were higher in the *Candida* and *Aspergillus* sensitized patients than non-sensitized patients in our study. This agrees with Ma *et al* study where total IgE levels were higher than patients with negative skin test and those who had positive skin test results for aeroallergens rather than molds (Ma et al., 2015). Also in Galante *et al* study, patients showed elevated total IgE levels when persons were exposed fungal spores. The serum IgE level was more elevated in patients with fungal spore exposure (Galante et al., 2004). The total serum IgE levels in the polysensitized group were significantly increased than that of the monosensitized group (Kim et al., 2006), this may explain the higher levels of IgE in the sensitized group to *Candida* and/or *Aspergillus* where most of the patients in this group were polysensitized.

The progressively increasing number of sensitizations in the same allergic patient seem to characterize the

natural history of allergy and represent a common feature of allergic patients. In our study, number of sensitizers in the group non-sensitized to *Candida* and/or *Aspergillus* ranged from 1 to 3 sensitizers i.e monosensitized or paucisensitized as described by de Jong *et al* who proposed to use the term “paucisensitization” to describe 2 to 4 sensitizations and “polysensitization” to describe 5 or more sensitizations (Baatenburg et al., 2011), while in the group sensitized to *Candida* and/or *Aspergillus* patients were polysensitized with range from 2 to 5 sensitizers. This may be attributed to number of factors including the older age of the patients sensitized to *Candida* and/or *Aspergillus*. Older age of the patients is usually associated polysensitization as stated by Fasce *et al* study where the number of sensitizations increased with age (Fasce et al., 2007).

The reactivity of asthmatic patients to multiple mould allergens could be due to genuine sensitization to a variety of molds or it could be due to cross-reactivity between mould allergens. In our study 32 patients were sensitized to *Candida* and/or *Aspergillus*, 20 of them were sensitized to *Candida albicans* alone, 8 were sensitized to both *Candida* and *Aspergillus* and 4 patients were sensitized to *Aspergillus* only. Hemmann *et al* suggest that *Aspergillus* and *Candida* allergens may share IgE-binding epitopes (Hemmann et al., 1997). However, it is believed that multiple mould sensitization skin test reactions are commonly due to sensitivity to multiple antigens rather than cross reactivity (Sporik et al., 1992).

In Prasad *et al* study, 10.4% of the patients showed negative reaction to all reagents in SPT, while the majority (89.6%) showed positive reaction (Prasad et al., 2009). This is similar to our study where 8% of the patients had negative skin test, while remaining 92% showed positive reactions.

In a study of asthmatic subjects, 71 of 149 were *Candida albicans* SPT. Fifty-five (77%) of the positive patients had reaction to specific allergen PBT, and 43 (86%) of 50 of the inhalation-positive subjects had positive A radioallergosorbent test to *Candida albicans* antigens. This agree with our results where the positive predictive value was 77.8% in case of *Candida albicans* and was 83% in case of *Aspergillus fumigatus* (Akiyama et al., 1981).

The reactivity of SPT to allergen differ from BPT results and the differences varies between groups of Antigens eg. Molds, animal danders, house dust mite and others.

So the SPT may be considered a good a good screening test easily performed with good predictive values (Aas K., 1970, Fernandez et al., 2011).

Conclusions:

Fungal sensitization constitutes a high percentage of patients with Bronchial Asthma. Adding fungal antigens to routine SPT is essential for early diagnosis and management of fungal sensitization. BPT is gold standard in assessing bronchial hypersensitivity to different antigens including fungi. We recommend its use in case of doubtful diagnosis. Further studies are needed to assess the efficacy of subcutaneous immunotherapy and antifungal treatment in cases of asthma with fungal sensitization.

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