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ORIGINAL RESEARCH

Assessment of Systemic Fungal Infections among Diabetic Patients in Enugu, Nigeria

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Abstract

Opportunistic invasive fungal infections are emerging health challenges worldwide, especially among immunocompromised hosts. This study investigated systemic fungal infections in diabetic patients. The diabetic patients were recruited from the Diabetic Clinics; Enugu State University Teaching Hospital Parklane, Enugu. A structured questionnaire was used to obtain information on the demographic and risk factors from the subjects. Sputum samples were collected from the patients and analyzed mycologically using Sabouraud dextrose agar with actidione and brain heart infusion agar fortified with 5% sheep red blood cells. Those with fungal growth were identified using needle mount, Gram stain and sugar fermentation/assimilation tests. Of 120 diabetic patients analyzed, 63 (52.5%) had fungal isolates. The females had higher isolates than the males, 36 (30%) and 27 (22.5%) respectively. The age range above 61-years-olds had more fungal isolates, 27 (22.5%) followed by those of 51-60 years-old with 21 (17.5%). The subjects with primary education had 24 (20%) of fungal isolates while those that were traders, 22 (18.3%) fungal isolates were obtained. The duration of diabetes was statistically significant as those with less than 5 years of diabetes had higher fungal infections of 40 (33.3%). The diabetic patients with FBS levels > 5.8 mmol/l had higher isolates, 51 (42.5%), (P = 0.001) while the subjects on insulin therapy and with persistent elevated fasting blood sugar level had 40 (33.3%) systemic fungal isolates. The frequency of fungal isolates showed that opportunistic and dimorphic fungi were implicated as infectious complications in diabetics. The dimorphic fungal isolates, *Blastomyces dermatitidis* 10 (8.3%) and *Coccidioides immitis* 6 (5%) are not common in this environment. These systemic fungal infections are of public health challenge due to its high transmission rate.

Keywords

Diabetes, Systemic mycoses, Dimorphic fungi, Insulin therapy, Enugu

Introduction

Opportunistic invasive fungal infections are emerging health challenges worldwide [1]. Severity of these fungal infections ranges from asymptomatic-mild mucocutaneous infections to life threatening systemic infections [2]. The main determinants of burden of fungal infections are linked to socio-economic, geographical characteristics and increasing number of at-risk populations. Individuals susceptible to fungal infections include those with immunosuppressive illnesses such as HIV/AIDS, tuberculosis, chronic pulmonary diseases (COPD), cancer and diabetes [3-5]. It has been reported that patients with systemic fungal infections are at high risk of disseminated fungemia and prolonged stay in hospital [6]. This scenario may be worsened if the patient has a metabolic disorder due to diabetes mellitus. This is because the diabetic patients are prone to high blood sugar concentration which weakens the immune system and causes several health complications [7].

In general, infectious diseases are more frequent and serious in patients with diabetes mellitus which potentially increases morbidity and mortality [8]. Diabetes mellitus is a clinical syndrome associated with deficiency of insulin secretion or action. It is considered as one

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of the largest threats to health in the 21st century. It is estimated that there will be 380 million people with diabetes in 2025, besides the classical complications of the diseases; diabetes has been associated with reduced response of T cell, neutrophil function and disorder of humoral immunity [9]. Diabetes increases susceptibility to various types of infection. The most common fungal infections consists of pulmonary aspergillosis, cryptococcal meningitis complicating HIV/AIDS, invasive candidiasis and mucormycosis [7,10,11].

The diabetic patients, due to their condition, lack adequate immunity to defend the body system against invading pathogenic fungal organisms thus they can be exposed to these agents either by inhalation of the spores of these fungal agents from the environment or by close contacts. The aim of this study was to determine the prevalence of systemic fungal infections in diabetic patients. The study also evaluated the risk factors and association of insulin therapy on outcome of systemic fungal infection.

Materials and Methods

Study population

This is a cross-sectional survey carried out at Diabetic Clinic, Enugu State University Teaching Hospital (ESUT) between November 2015 and March 2016. The participants were recruited during normal routine check-up (out-patients) or those admitted into the hospital wards (in-patients). The participants selected were those with persistent cough and/or complaints of pneumonia.

A total of one hundred and twenty diabetic patients aged 18 years and above were recruited for the study. The diabetic patients with co-infections of human immunodeficiency virus and pregnant women were excluded from study. The information on insulin therapy was obtained from the patient's hospital medical records.

A structured questionnaire was used to collect data about demographic factors, social life styles. All the participants completed and signed an Informed Consent Form.

Ethical considerations

The Ethical Committee of Ethical Review Board of ESUT Teaching Hospital Parklane Enugu revived and approved the study protocol.

Sample collection and mycological methods

Sputum samples were collected from the patients using sterile wide mouth container. The patients were well guided on the collection.

The sputum samples were inoculated onto Sabouraud dextrose agar, and brain heart infusion agar fortified with 5% sheep red blood cell and bird seed agar. They were incubated at 37 °C and observed for fungal growth daily for 14 days. The fungal isolates were processed using standard mycological techniques [12]. The agar plates with growth were grouped according to their morphological pattern: Those that appeared creamy and pasty were Gram-stained for the presence of yeast cells and by needle mount. Those that had hyphae spreading across the agar were identified by needle-mount using lactose-phenol cotton blue. The *Candida* isolates: were characterized by Germ-tube test, oxidation and assimilation test and Chlamydospore production.

Estimation of fasting blood sugar

Blood samples were collected from the participants and serum separated. The serum was used the estimate the fasting blood sugar by Glucose Oxidase Test.

Data Analysis

All data obtained from the questionnaire were matched with the results and entered in spread sheet. Descriptive statistics were used to obtain the mean ± SD of age FBS values and percentages. Chi-square test was used to compare the variables, and any case with $P \leq 0.05$ was taken as being statistically significant. All data were analysed using SPSS version 21.

Results

Demographic characteristics of the diabetic patients

A total of 120 diabetic patients were enrolled for the study which comprises of 47 (39.2%) males and 73 (60.8%) females. The mean age of the subjects was 58.39 ± 11.15 (range of 26 to 80-years-old). Of the 120 diabetic patients, 63 (52.5%) had fungal isolates (Table 1). It was observed that there was no multiple fungal growths in each of the patients thus the colonization of the fungal isolates were specific for each participant. The frequency of the fungal isolates indicates that *Candida* species was 25 (20.8%) while *Aspergillus* species accounted for 22 (18.3%). The dimorphic fungi, *Blastomyces dermatitidis* and *Coccidioides immitis* were isolated at a frequency of 10 (8.3%) and 6 (5.0%) respectively. The *Aspergillus* species isolated included *Aspergillus flavus* 19 (15.8%) and *Aspergillus niger* 1 (0.8%) and *Aspergillus fumigatus* 2 (1.7%) while *Candida albicans* was 14 (11.7%), *Candida kefyr* 5 (4.2%) and *Candida tropicalis* 6 (5.0%) (Table 1).

The gender distribution of the fungal isolates indicat-

Table 1: Summary of fungal isolates from diabetics.

Fungal isolates	*f* (%)
Aspergillus flavus	19 (15.8)
Candida albicans	14 (11.7)
Blastomyces dermatitidis	10 (8.3)
Candida tropicalis	6 (5.0)
Candida kefyr	5 (4.2)
Aspergillus fumigatus	2 (1.7)
Aspergillus niger	1 (0.8)
Coccidioides immitis	6 (5.0)
Total	63 (52.5)

ed that the females 36 (30%) had more fungal infections than the males 27 (22.5%), although the difference was not statistically significant (Table 2). The fungal isolates were obtained from the age group with an increasing frequency, those that were more than 61-years-old had the highest of 27 (22.5%) followed by those of age group 52-60 with 21 (17.5%) fungal isolates though it was not statistically significant. The assessment of educational background indicates that those with a maximum of primary education had the highest of 24 (20%) followed by the secondary school participants with 16 (13.3%). The participants without formal education and those of higher education showed fungal isolate of 9 and 14 respectively (7.5% and 11.7%).

The type of occupation, the participants engaged themselves, indicates that traders and civil servants had the highest isolates of systemic fungal infection 22 (18.3%) and 21 (17.7%). The artisans and housewives had 15 (12.5%) and 4 (3.3%) fungal isolates respectively (Table 2).

Risk factors for fungal infections

The risk factors that were assessed indicated that duration of diabetes was statistically significant for systemic fungal infection in diabetics, with a p = 0.010. The diabetic patients with less than 5 years duration had 40 (33.3%) fungal isolates than those with greater than 5-years, 25 (20.8%). The other parameters assessed, like family history of diabetics, previous antifungal therapy and previous antibiotic therapy were not statistically significant. Of importance are those that were on insulin therapy though not statistically significant, but remain vital. Out of 88 of the subjects that were on insulin therapy, 50 (56.8%) had systemic fungal infections. It was observed that none of the participants had a previous history of antifungal therapy (Table 3).

Influence of fasting blood sugar

The fasting blood sugar was assessed along with fungal isolate and insulin therapy (Table 4). The subjects with higher fasting blood sugar had more isolates than those with normal FBS. The subjects with higher fasting blood sugar accounted for 51 (42.5%), with a mean of 158.6 ± 47.7 Mmol/L had higher fungal isolates as against those with normal FBS mean 94.3 ± 7.3 Mmol/L. The diabetic patients with non-response to insulin therapy indicates that those with higher FBS had more isolates than those with normal FBS 40 (45.5%) and 10 (11.4%) respectively.

Logistic regression analysis

The risk factors for fungal colonization in diabetic patients were subjected to multi-variate analysis. Duration of diabetes, non-response to insulin therapy and fasting blood sugar greater than 5.8 Mmol/L were respectively associated with systemic fungal infection in diabetic patients (Table 5).

Discussion

Diabetic patients are prone to suppressed immunity

Table 2: Demographic characteristics of the diabetic patients.

Variables	n	No. of isolates (%)	P-value
Sex:			0.384
Male	47	27 (22.5)	
Female	73	36 (30)	
Age:			0.850
≤ 40	9	5 (4.2)	
41-50	22	10 (8.3)	
51-60	40	21 (17.5)	
61+	49	27 (22.5)	
Education status:			0.440
None	14	9 (7.5)	
Primary	46	24 (20)	
Secondary	37	16 (13.3)	
Tertiary	23	14 (11.7)	
Occupation:			0.067
Traders	36	22 (18.3)	
Civil servants	48	21 (17.5)	
Artisans	22	15 (12.5)	
Others (e.g. house wives)	14	4 (3.3)	

Table 3: Association of fungal Isolates with diabetic therapy and complications.

Variables	n	No of isolate (%)	P-value
Duration of diabetes (years)			0.010
≤ 5	88	40 (33.3)	
≥ 5	32	25 (20.8)	
Insulin therapy:			0.100
Yes	88	50 (56.8)	
No	28	11 (9.2)	
No response	4	2 (1.7)	
Co-morbid factors:			-
HIV AIDS	5	2 (1.7)	
HBP	65	37 (30.8)	
Liver Disease	3	1 (0.8)	
Family history of diabetes:			0.053
Yes	16	12 (10)	
No	104	51 (42.5)	
Previous antibiotic therapy:			1.000
Yes	9	5 (4.2)	
No	111	58 (48.3)	

Table 4: Assessment of fungal isolates in relation to fasting blood sugar and response to insulin therapy.

	Fungal Isolates	
FBS (mmol/l/mean ± SD)	**General (n = 120) (%)**	**Insulin therapy (n = 88)**
3.1-5.8 (94.3 ± 7.3)	12 (10)	10 (11.4)
> 5.8 (158.6 ± 47.7)	51 (42.5)	40 (45.5)
P-value	0.001	0.006

Table 5: Multivariate analysis of risk factors for fungal infection.

Variable	P-value	OR (95% CI)
Duration of diabetes	0.010	3.07 (1.275-7.375)
Non-response to insulin therapy	0.006	3.6 (1.405-9.226)
FBS (> 5.8 mmol/l)	0.001	6.98 (3.228-15.097)

due to excessive accumulation of sugar resulting from decreased insulin secretion [13]. The outcome of this scenario is that, the diabetic patients are exposed to opportunistic fungal infections. Thus the goal of this study was to assess systemic fungal infections in diabetic patients. This is important because in undiagnosed cases, pulmonary pneumonia may present a serious clinical problem in the affected diabetics.

The prevalence rate of 52.5% was very high and of public health concern. In a similar study in South Africa, Moore, et al. [14] reported that fungal infections in diabetics are twice higher than non-diabetics. The key risk factor for this high prevalence is increase in blood sugar level.

It has been reported that women are more infected with fungal infections. In this study, blood sugar levels of the diabetic patients were higher and most of them cannot be controlled by the use of insulin therapy, hence higher prevalence of fungal infections among this group. This was in line with the report of Santhosh, et al. [15], that fungal infections in diabetes can mean that blood glucose levels are not well controlled or that, the infection can spread to other parts of the body. A prevalent rate of 22.5% of total fungal infection was obtained from those within the age of 61 and above, thus the age difference among the diabetic remains a factor in systemic fungal infections. This may be due to interaction between aging and suppressed immunity due to diabetes [16].

The level of education had no impact on the outcome of fungal infection. It is expected that the higher the level of education the more concern about personal health, personal hygiene and overall health but in this study the systemic fungal infection was distributed among all the educational groups and those with primary education having a higher prevalence rate of 20%. This may be a chance occurrence because both those with tertiary education and secondary education shared in the systemic infection [8].

The duration of diabetes indicates that the patients that were newly diagnosed of diabetes had a greater prevalence of 33.3% than those that were diagnosed of diabetes for more than 5 years. This may be that, the diabetes was not diagnosed on time while opportunistic infection flourished in such patients before knowing their diabetic status [17].

Another important risk factor for systemic fungal infection in diabetes is the family history of diabetes; a total of 42.5% had no record to family diabetic lineage. It can be speculated that diabetes in this group of people may have been due to lifestyle and that they lack poor control measures in checkmating the diabetes, hence the increased prevalence of systemic fungal infection.

The frequency of fungal infection indicates that *Aspergillus flavus* constitutes the majority 17.5% of the fungal isolates. In contrast Santhosh, et al. [15] reported that *Aspergillus fumigatus* is the predominant species followed by *Aspergillus flavus*; but it has been noticed that in certain locales and hospitals, *Aspergillus flavus* is more common in air than *Aspergillus fumigatus* for unclear reasons hedayati, et al. [18]. Invasive Aspergillosis is evident in immunocompetent patients. Those with severe liver disease are at high risk for *Aspergillus* infection, which agreed with Panasiuk, et al. [19] that suggested that invasive Aspergillosis is a potential fatal complication of severe liver disease. This is as a result of immunosuppression following liver transplantation. However, liver disease alone predisposes to bacterial and fungal infection as a result of a depression of both humoral and cell-mediated immunity [20]. From this study, the isolation of *Candida* species was higher than other fungal isolates which is in agreement in a review by Richardson and Lass-Fiori [21] who stated that the rising incidence of *Candida* species can attributed to several risk-factors that are prevalent in critically ill patients such as debility, underlying malignancy, blood and bone marrow transplantation, AIDS, prolonged stay in intensive care unit (ICUs) and hospital stay, neutropenia, use of antibiotics and corticosteroids, and administration of parenteral alimentation.

The development of candidaemia however strongly implies immunodeficiency since it often occurs in immunocompromised patients, myeloproliferative disorders or leukaemia and patients with AIDS [22]. The rising incidence of *Candida* infection and Candidaemia can be attributed to a variety of mostly endogenous and exogenous factors [23].

The occurrence of *Blastomyces dermatitidis* and *Coccidioides immitis* are of public concern because these dimorphic fungi are not common in this environment because of its weather and lack of soil salinity [24] but can be as a result of occupational hazards or occupational exposure to endemic regions with archeology and high dust exposure. This is in agreement with Crum, et al. [25] who stated that it is as a result of exposure to infected tissues or aerosols of infected secretions. The presence of these dimorphic fungi in diabetic patients is a major complication, and can lead to high mortality. In this environment, these fungi can be acquired due to travels to endemic areas [26] and consumption of animal reservoirs like bats especially not-well cooked ones [27]. The implication of these infections is that these agents might result in high rate of pulmonary pneumonia and tuberculosis-like infections [14]. Generally, *Coccidioides* species are highly infectious human pathogens which are able to establish a life-threatening respiratory disease in immunocompetent individuals [24].

In conclusion, diabetics are prone to higher frequency of fungal infections. These infections may be due to failure of insulin use, which may result from non-adherence to drugs and over-use of insulin. Also, some fungal agents like *Blastomyces dermatitidis* and *Coccidioides immitis* which are not common in our environment [28] are of public health challenge due to high transmission rate of these dimorphic fungal infections. Antifungal drugs should be included in the routine drugs of diabetes patients. Early screening of the patients is important in the control and management of the infection.

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