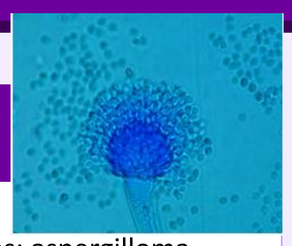
Evaluation of chronic pulmonary aspergillosis (CPA) as a cause of smear negative TB and or anti-TB treatment failure in HIV infected Nigerians.

Oladele Rita1,, Irurhe Nicholas2, Nwosu Tina3, Gbajabiamila Titi4,Ekundayo Ayo,5 Akanmu Sulaimon6, Richardson Malcolm1, Denning David1.

1. University of Manchester
2. 2. Department of Radoilogy, College of Medicine, University of Lagos
3. 3.APIN (Aids Prevention Initiative in Nigeria) central Laboratory, University of Lagos
4. 4. Nigeria Medical Research Institute, Lagos
5. 6 PEPFAR (US President's Emergency Plan for AIDS Relief) clinic, LUTH

Introduction



- Chronic pulmonary aspergillosis (CPA) includes a spectrum of diseases: aspergilloma, chronic cavitary pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis, and Aspergillus nodules[1].
- Prior pulmonary disorders are a major risk factor for CPA[2].
- In all patient groups, tuberculosis, non-tuberculous mycobacterial infection, sarcoidosis and allergic bronchopulmonary aspergillosis remain the leading risk factors for development of CPA, followed by COPD, prior pneumothorax or treated lung cancer[1,3].
- CPA is commonly misdiagnosed as TB.
- In Japan 20% of treated TB patients had antibodies to *Aspergillus*[4]. In India *Aspergillus* antibodies are present in 27% of patients with TB at one centre[5] and 23% of patients with "chronic lung diseases", of whom 96% had prior TB, at another centre[6]. In Brazil, 21% of in-patients with TB at a tertiary chest clinic with *Aspergillus* antibodies had aspergilloma[8]. In Hong Kong the rate of antibodies against *Aspergillus* in patients without aspergilloma, but suffering from haemoptysis following TB treatment is 36%[9].
- The total global prevalence of CPA secondary to TB has been estimated at between 0.8 and 1.37 million cases with 43 cases per 100,000 population in Congo and Nigeria[10].
- There has never been a survey of CPA secondary to TB in Africa to confirm this prediction.
- A number of case series have documented presentations of CPA in Ivory Coast[11], Senegal[12], Ethiopia[13] and Nigeria[14].
- A South African study revealed a 9.9% rate in post-TB treatment patients[15] and another from Senegal involved 35 patients diagnosed as CPA using Aspergillus IgG and histology[16].
- Nigeria has an estimated 3. 2million people living with HIV/AIDS. Tuberculosis (TB) is the recognised leading cause of death in people with HIV and thousands of Nigerians are believed to be living with a multidrug-resistant strain.

Objectives

- Our primary objective is to report the prevalence of *Aspergillus* antibodies along with the prevalence of CXR changes consistent with CPA in patients with TB.
- We compared the rate of CPA in the HIV positive and negative patients with tuberculosis described to establish whether HIV status is associated with a different risk of developing the disease.
- We also compared the rate of CPA in HIV positive patients with high and low CD4 counts to determine if advanced immunosuppression is associated with developing CPA. We then assessed any other potential risk factors.

Methods

Study design and population studied

- Cross-sectional survey in three centers in Nigeria.
- Adults HIV positive and negative consenting patients who were at the end or who were in their last month of TB treatment (smear and/or Xpert positive = documented TB) or currently being treated for 'smear negative TB' were recruited from Directly Observed Therapy Shortcourse (DOTS), chest and ART clinics in Lagos and Ilorin states, Nigeria.
- All were assessed with clinical assessment, chest X-ray and Aspergillus IgG serology.
- Healthy blood donors and HIV positive patients with no respiratory symptons were used as control.
- CPA was defined as a positive Aspergillus IgG titre (>40 IU/mL), compatible chest X-ray and pulmonary or systemic symptoms, despite anti-TB therapy.

Sample processing

- *Aspergillus*-specific IgG was measured by ELISA (Dynamiker Biotechnology (Tianjin), China), which has a sensitivity of 77% and specificity of 97% for the diagnosis of CPA.
- Sputum was collected for fungal culture in those producing sputum.
- Patients' demographic and clinical data was collected using a semi-structured questionnaire.

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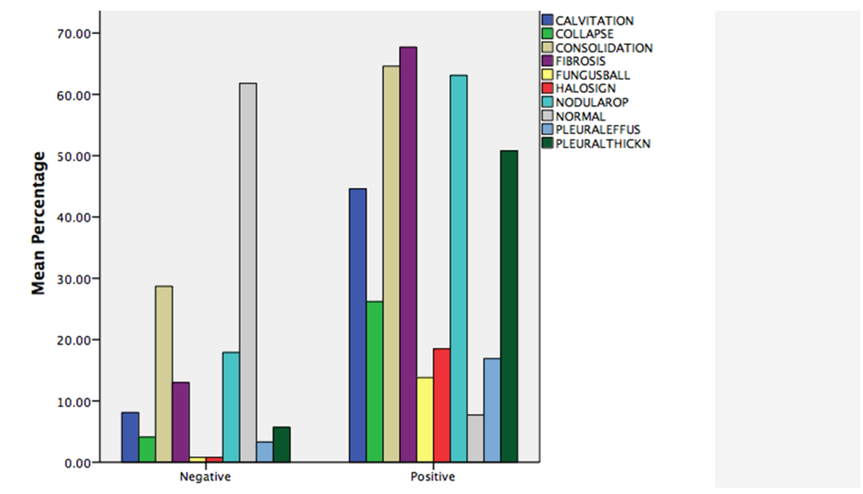
Results

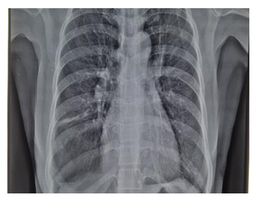
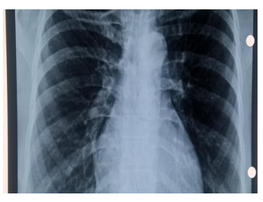
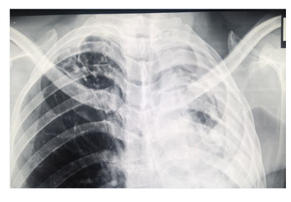
- 209 patients were recruited between December 2013 and September 2014.
  150 (75%) were HIV positive.
- Mean age was 39.46 (95% CI), 59.9% were female and 18.9% were unable to work.
- Mean CD4 (mean±SE) in all HIV patients was 246±39 and 244±45.4 in the HIV infected patients with positive *Aspergillus* IgG.
- One hundred and thirteen (54%) had documented TB and 70.5% had productive cough.
- Forty-one patients had hemoptysis, while one 8/41 had frank blood hemoptysis. Only one patient had a co-existing chronic obstructive airway disease (COPD).
- The prevalence of Aspergillus IgG was 30.0%; 48/149 (32.2%) in HIV positive and 17/60 (28.3%) in HIV negative (p = 0.645)
- The percentages of the common radiographic features observed in this study varied: consolidation 56.7%, nodular opacity 47.1%, fibrosis 43.2%, pleural thickening 25%, cavitation without fungus ball 13.5%, and cavitation with fungus ball 6.7%.
- There were 48 cases of CPA in HIV positive patients, 17 HIV negative CPA patients, 11 documented TB patients with probable CPA and 44 smear negative/genExpert negative probable CPA patient

Table 1: Summary of relationship between frequencies of Aspergillus IgG and clinical features of studied population.

	HIV positive (151)				HIV negative (57)				Total
Smear/GenExpert	Positive 76 (50.3%)		Negative 75(49.7%)		Positive 23(40.4%)		Negative 34(59.6%)		208
p-value	0.21				0.21				
Asp IgG positive	17(23%)		20(27.8%)		8(36.4%)		19(59.4%)		64(30.8%)
p-value	0.51				0.10				
Asp IgG titre mean range	IgG+ve 0.609	IgG=ve 0.141	IgG+ve 0.752	IgG-ve 0.146	IgG+ve 0.745	IgG=ve 0.137	IgG+ve 0.749	IgG-ve 0.125	
p-value	<0.001		<0.001		<0.001		<0.001		
Mean age	38.32		39.26		39.68		42.52		
p-value	0.60				0.49				
Symptons									
Marked haemoptysis	0		1		2		5		8
Fatigue	40(56.3%)		32(45.1%)		11(52.1)		11((55%)		94
p-value	0.18				0.87				
Productive cough	52(72.2%)		47(66.2%)		17(81%)		19(76%)		135
p-value	0.44				0.69				
Chest pain	27(38.0%)		19(26.4%)		8(38.1%)		15(75.0%)		69
	0.14				0.017				

Figure 1: Frequency of Radiological features of CPA



Conclusion

- CPA is a neglected disease and represents a significant public health challenge in Nigeria.
- CPA will fit into the WHO diagnostic criteria for 'smear-negative' tuberculosis in this studied population
- Accurate diagnosis of CPA in this group being misdiagnosed and would avoid unnecessary and potentially toxic TB therapy.

Acknowledgement

This study was supported by Dynamiker, who provided the test kits.

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