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Extrapulmonary tuberculosis among tuberculosis suspects at a tertiary hospital in Benin City, Nigeria: a retrospective study

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Abstract

There is paucity of data on extrapulmonary tuberculosis (EPTB) subsets in Nigeria despite contributing to the burden of tuberculosis. This study investigated extrapulmonary tuberculosis (EPTB) among tuberculosis (TB) suspects presenting at a tertiary health facility in Benin City, Nigeria. Patients' clinical and laboratory records domiciled at the DOTS clinic, University of Benin Teaching Hospital, Benin City, Nigeria, were extracted. Appropriate statistical tools were deployed to analyze data retrieved between January 2018 and December 2020. A total of 683 suspected TB cases were reported, among these, 360 (52.7%) had pulmonary TB while 28 (4.1%) had EPTB. Of this number, 21 (5.6%) males were EPTB positive, while 7 (2.3%) females were positive: an association was observed between the male gender and EPTB (OR = 2.567; 95%CI= 1.076, 6.122; p = 0.0451). A significant increase in yearly prevalence of EPTB was also observed across the years 2018, 2019 and 2020 (p = 0.0442). No statistical significance was observed between age and EPTB as well as HIV status and EPTB (p> 0.05). Lymphadenitis was the most frequent clinical presentation of EPTB. The prevalence of EPTB was 4.1%. Our findings call for concerted efforts of all stakeholders in order to reduce the prevalence of EPTB to the barest minimum.

Keywords: tuberculosis, extrapulmonary tuberculosis, patients, lymphadenitis

Introduction

Tuberculosis (TB) is a major public health problem, a chronic infectious disease that has caused high morbidity and mortality over several centuries (WHO, 2020). Tuberculosis is one of the 10 leading causes of death worldwide and in 2018, it was estimated that 1.5 million people died from the disease (WHO, 2020). The causative agent of the disease is *Mycobacterium tuberculosis* (MTB) and being air-borne, this infectious agent exerts its pathologic effects primarily in the lungs where it can cause pulmonary tuberculosis (Metaferia *et al*., 2018; WHO, 2020). However, MTB can occasionally be recovered bacteriologically, detected or clinically diagnosed in other organs or clinical sites such as the abdomen, meninges, genitourinary tract, joints, bones, lymph nodes and skin. In these instances, it is classified as extrapulmonary tuberculosis (EPTB) (Ohene *et al*., 2019). Although the clinical presentation of EPTB is mostly atypical, thus requiring microbiological evidence (Cantres-Fonseca *et al*., 2018), about 10 to 25% of tuberculosis cases present as EPTB disease and it is usually from haematogenous seeding or lymphatic spread of the organism from the lungs to other organs (Seong-Eun, 2021).

Established risk factors for EPTB include immunosuppression, HIV, black race and younger age (Goni *et al*., 2015; Ohene *et al*., 2019). Some studies have highlighted the male gender as being a risk factor, few others have associated the female gender (Gomes *et al*., 2014). Nigeria ranks 6th among the 30 high burden countries where TB is endemic and among the 12 countries where multidrug-resistant tuberculosis (MDR-TB) and HIV serve to fuel this disease entity (WHO, 2020). Despite global and national efforts, the gains have not yet taken deep root as Nigeria still has the highest

number of TB cases in Africa and accounts for 4.6% of the Global TB burden (WHO, 2020).

Previous studies in Ghana and Ethiopia showed 21.8% and 31.7% prevalence of EPTB respectively (Metaferia *et al*., 2018; Ohene *et al*., 2019). Some Nigerian studies showed differing prevalence rates (Goni *et al*., 2015; Olowe *et al*., 2017). Few studies in South Southern Nigeria have evaluated EPTB among TB suspects. Considering the scarcity of published data on the prevalence of EPTB in our region, this study was conceived to determine the prevalence of EPTB in a tertiary hospital in Benin City.

Materials and Methods

Study Site:
The study was retrospective review of clinical and laboratory records and was conducted at University of Benin Teaching Hospital (UBTH), Benin City, Nigeria. The hospital is an 850-bed facility serving the specialist health needs of the Edo population (over 4 million) as well as five to eight neighboring states. The TB treatment centre (DOTS clinic) is located within the facility and serves as the hub for all suspected TB cases within the facility as well as referred cases from primary and secondary health facilities.

Study Population:
This comprised patients who had been referred for TB screening from primary and secondary health centres, patients who had been referred from the Chest clinic for TB screening as well as patients whose symptoms prompted them to visit the DOTS clinic for TB screening, between 2nd January 2018 and 31st December 2020.

Data sources/Statistical analysis:
Clinical and laboratory records of patients who were enrolled in the DOTS program were obtained and relevant data extracted. The data obtained was analyzed with Chi square (X^2) test using the statistical software INSTAT® (Graph Pad Software Inc, La Jolla, CA, USA). Statistical significance was set at $p < 0.05$.

Inclusion criteria
EPTB - a patient with active tuberculosis of any part of body other than lung parenchyma.

Exclusion criteria
Patients with PTB and patients with incomplete data.

TB Screening:
Sputum specimens were collected from these patients in sterile wide-mouth containers and sent to the Tuberculosis Laboratory, Medical Microbiology Laboratory, UBTH. Sputum samples were thereafter processed for detection of TB/rifampicin resistance using GeneXpert MTB/RIF automated system (GeneXpert® Dx System, version 4.8) Testing was performed according to the manufacturer's instructions. Sample reagent (comprising sodium hydroxide and isopropanol) was added to untreated sputum at a ratio of 2:1. This was manually agitated and kept for 10 minutes at room temperature, then shaken again and kept for 5 minutes; 2 ml of the inactivated material was thereafter transferred to the test cartridge, inserted into the test platform and run. The system automatically interpreted all results from measured fluorescent signal into the following categories: invalid, if PCR inhibitors were detected with amplification failure, negative or positive. Positive results were scaled into 4 categories (very low, low, medium, high) depending on bacterial load and defined susceptible or resistant to rifampicin depending on detection of mutations in *rpoB* gene (Cephid, 2016).

HIV screening
Venous blood was obtained from all participants. Five milliliters of blood samples were collected into properly labeled plain containers, samples were sent to the laboratory and HIV serological tests were carried out on the centrifuged blood samples. For the detection of HIV-1 and HIV-2 antibodies in the blood, Determine® HIV-1/2 Test cards (Inverness Medical, Japan), Unigold™ Kit (Trinity Biotec, Ireland) and HIV - 1/2 Stat- Pak® Assay (Chembio Diagnostic Systems, USA) according to the national algorithm (Mbachu *et al*., 2015). These methods are immunochromatographic and detect the presence of antibodies to HIV-1 and HIV-2 in human blood and are read in-vitro having more than 99.9% sensitivity and 99.75% specificity.

Ethical consideration:
Ethical approval was obtained from the ethics and research committee, UBTH with reference/protocol number: ADM/E 22/A/VOL.VII/14831101.

Results

In the period under review, a total of 683 suspected TB cases were reported at DOTS clinic, UBTH. Among these, 360 (52.7%) were confirmed as pulmonary TB while 28 (4.1%) had EPTB. No MTB strain from patients having EPTB was rifampicin resistant (0%).

A total of 374 (54.8%) males and 309 (45.1%) females constituted the study population. Of this number, 21 (5.6%) males were EPTB positive, while 7 (2.3%) females were positive. An association was observed between the male gender and EPTB, the findings showed statistical significance (OR = 2.567; 95%CI= 1.076, 6.122; p = 0.0451). Extrapulmonary tuberculosis was detected in individuals above 11 years with no age group showing significant likelihood of being TB positive (p > 0.05). In the same vein, there was no association between HIV and EPTB (OR = 0.387; 95%CI= 0.115, 1.300; p = 0.1669) (Table 1).

The yearly prevalence of EPTB is shown on table 2, across years' 2018, 2019 and 2020, a prevalence of 1.7%, 4.5% and 6.6% was observed, showing a steady rise. These findings were statistically significant (p = 0.0442).

The anatomic site with the highest prevalence of TB was lymph node (43%), while the pericardium and spine (thorax) showed the least prevalence (7%). Abdominal fluid and cerebrospinal fluid (from the meninges) showed 21% and 29% respectively (figure I).

Table 1: Prevalence of Extrapulmonary tuberculosis among TB suspects in relation to age and Gender

Parameter	Number of patients screened	Number of EPTB positive	p-value	OR	95%CI
Gender					
Male	374	21 (5.6)	0.0451	2.567	1.076, 6.122
Female	309	7 (2.3)			
Age (Years)					
≤10	0	0	0.8936		
11-20	24	1 (4.2)			
21-30	180	5 (2.7)			
31-40	142	6 (4.2)			
41-50	125	7 (5.6)			
51-60	89	3 (3.4)			
≥ 61	124	5 (4.0)			
HIV Status					
HIV positive	158	3 (1.9)	0.1669	0.387	0.115, 1.300
HIV negative	525	25 (4.8)			

EPTB-Extrapulmonary tuberculosis, HIV-Human immunodeficiency virus, number in brackets= value in percentages

Table 2: Extrapulmonary tuberculosis in relation to year under review

Year	Number of TB suspects	Number EPTB Positive (%)	p-value
2018	232	4 (1.7)	0.0442
2019	269	12 (4.5)	
2020	183	12 (6.6)	

EPT- Extrapulmonary tuberculosis, TB- Tuberculosis

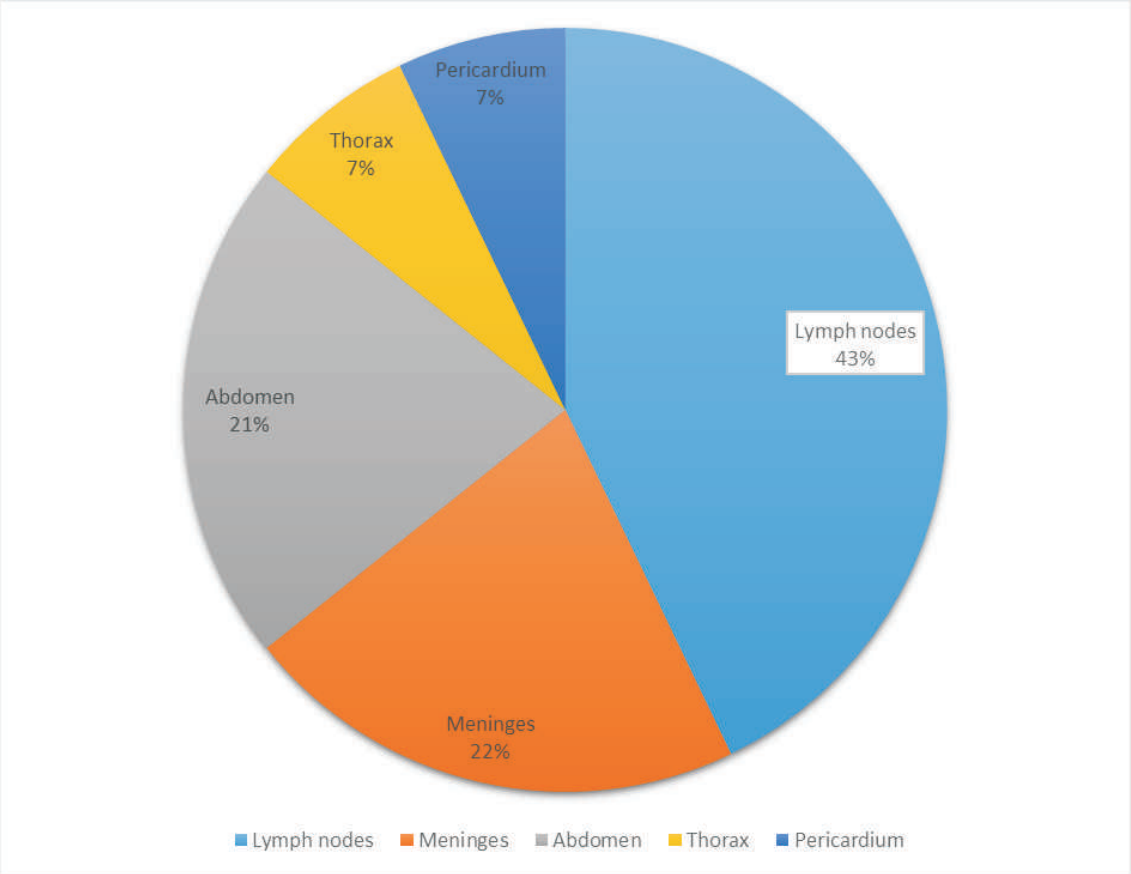

Figure I: Prevalence of extrapulmonary tuberculosis in relation to organ involved.

Discussion

In this study, the prevalence of EPTB was 4.1%. A previous study in Benin City, Nigeria reported the prevalence of EPTB among HIV patients as 7.3% (Affusim *et al*., 2012). However, to the best of our knowledge, no previous study in Benin City has reported the prevalence of EPTB among TB suspects. This finding is also considerably lower than three previous studies in North-Eastern and South-Western Nigeria where prevalence rates of 14.4%, 11.3% and 16.3% were observed (Goni *et al*., 2015; Olowe *et al*., 2017; Ojewuyi *et al*., 2022). It is equally lower than findings in Ethiopia (8.8%), Sudan (22.7%), Benin Republic (9%) and Bangladesh (10.5%) (Abdallah *et al*., 2015; Metaferia *et al*., 2018; Ojewuyi *et al*., 2022; Uddin *et al*., 2021). The differences in prevalence in these studies may be due to the difference in epidemiologic risk factors, study design, study population, socio-

demographic factors and socio-economic determinants of TB such as poverty, low income, low educational status, and unskilled occupation (Goni *et al*., 2015; Ohene *et al*., 2019; Ojewuyi *et al*., 2022). These have been shown to vary from one region to the other. Also, no MTB strain detected using the GeneXpert MTB/RIF assay was rifampicin resistant. Researchers agree that rifampicin resistance can be used as a "surrogate marker" for detecting multi-drug resistant tuberculosis (MDR-TB) as over 90% of rifampicin resistant-TB are also resistant to isoniazid (WHO, 2020). Our finding that no MTB strain was rifampicin resistant is therefore soothing as against the national and global narrative in PTB cases where a rising tide of MDR-TB has been observed (WHO, 2020; Seong-Eun, 2021).

Gender was a risk factor for EPTB in this study as males were significantly more likely to be positive when compared with their female counterpart. This finding agrees with previous studies in Sub-Saharan Africa (Zenebe *et al*., 2013; Abdallah *et al*., 2015; Goni *et al*., 2015; Olowe *et al*., 2017), although some other studies observed that being female was associated with EPTB (Ohene *et al*., 2019; Ojewuyi *et al*., 2022). The reason(s) for this finding is unclear, however, a general trend of males being at increased risk of TB compared to females has been established in a systematic review on social determinants of TB in sub-Saharan Africa (Saidu *et al*., 2014). In studies explored, no concrete reason was advanced for the association (Affusim *et al*., 2012; Saidu *et al*., 2014; Goni *et al*., 2015; Olowe *et al*., 2017), further studies may give insight. Also, in this study, there was no association between HIV and EPTB. This finding is not in line with several studies where HIV was an established risk factor for TB and EPTB (Zenebe *et al*., 2013; Cantres-Fonseca *et al*., 2018; Metaferia *et al*., 2018; WHO, 2020). In a study in Zimbabwe, miliary TB and TB meningitis were associated with HIV/TB co-infection when compared with other EPTB infections such as pleural TB, TB lymphadenitis, abdominal TB and spinal TB which accounted for majority of EPTB cases but did not show any association (Martino *et al*., 2020). This may suggest that different forms of EPTB have different relationships with HIV/TB co-infection. As with the Zimbabwean study, majority of EPTB infections in this study had lymphadenitis and abdominal TB. It is also noteworthy that most socio-economic determinants for TB such as poverty, malnutrition and overcrowding are rife in the study area and may also fuel the disease regardless of HIV status. Patients with low income had previously been shown to be at greater risk of having EPTB (Zenebe *et al*., 2013).

Our finding that majority of EPTB cases were due to TB lymphadenitis is not in line with some studies where pleural TB, miliary/disseminated TB and spinal TB predominated (Gomes *et al*., 2014; Goni *et al*., 2015; Ohene et al., 2019; Martino *et al*., 2020; Ojewuyi *et al*., 2022). However, TB lymphadenitis was the most prevalent form of EPTB in studies in Ethiopia and India (Shrivastava *et al*., 2015; Metaferia *et al*., 2018). Although knowledge of the epidemiology of EPTB in diverse settings is necessary in order tackle TB, in the studies highlighted, the reasons for these discrepancies in the prevalent clinical site of EPTB were unclear.

Interestingly, there was a significant increase in yearly prevalence of EPTB. The global strategy to end TB includes early diagnosis and adequate treatment of all forms of TB (WHO. 2020). However, more emphasis is placed on diagnosis, treatment and control of PTB. The significant yearly increase in prevalence of EPTB in our region is therefore a wake-up call on the need pay closer attention to EPTB, its established risk factors and socio-economic determinants, even though the overall prevalence (4.1%) was considerably lower than previous studies (Goni *et al*., 2015; Olowe *et al*., 2017; Ohene *et al*., 2019).

This study being retrospective, has its inherent limitations such as not having a structured questionnaire to examine the role of some sociodemographic factors in EPTB, some patients had incomplete data and there was also the difficulty in distinguishing patients who had concurrent PTB and EPTB infection based on available data.

Conclusion

The prevalence of EPTB was 4.1% and being male was a risk factor for EPTB. Lymphadenitis was the most frequent clinical presentation of EPTB and a

significant increase in yearly prevalence was observed. Our findings call for concerted efforts of all stakeholders in order to reduce the prevalence of EPTB to the barest minimum.

Conflict of Interest

None to declare.

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