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Original Research Article

Active case finding and evaluation of IL-6 production among household contacts of pulmonary tuberculosis patients in a high disease setting

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ABSTRACT

Background: Tuberculosis (TB) is a top infectious disease killer worldwide and remains a huge public health concern. However, most TB case findings are limited to self-referral (passive case finding), when individuals develop symptoms of TB. Only 15% of disease burden in Nigeria are reported. In view of this, it is important to assess the latent and active disease burden amongst HHC of TB patients suffering from pulmonary TB. In addition, it has been suggested that IL-6 levels could be used as a prognostic marker in exposed individuals. IL-6 levels were assessed in this cohort.
Methods: A total of 205 subjects participated in this study, comprising 62 pulmonary TB index cases and 143 of their household contacts. Also, 54 apparently healthy subjects were recruited to serve as controls. Active case finding was performed amongst the HHC, using sputum and blood samples; they were tested for active TB. Blood samples were also collected for measuring IL-6 levels.
Results: Findings reveal 6.3% previously undiagnosed active TB among the HHC of the TB patients and a significantly higher number of latently infected TB cases compared to the control population (p=0.0078). There were significant differences when comparing HIV co-infected index group to their HIV negative counterparts (P=0.032). Significantly different IL-6 levels were found among the study groups and sub-groups (p<0.0001), with significantly higher levels in TB mono-infection compared to in TB/HIV co-infection (p=0.031).
Conclusions: These results demonstrate the importance of active TB case finding for TB control and the possible role of IL-6 as a diagnostic marker in TB control.

Keywords: Active case finding, Active tuberculosis, House-hold contacts, Latent tuberculosis, Tuberculosis

INTRODUCTION

Tuberculosis (TB) remains one of the World's deadliest communicable diseases, and is a huge public health challenge especially in developing countries.[1] The emergence and spread of human immunodeficiency virus (HIV) among TB patients compound the problem of TB.[2] HIV infection increases TB susceptibility such that TB is

the leading cause of death in HIV infected people.[3] There are high incidences of HIV-associated deaths and high incidence rates of TB despite therapeutic intervention.[4] Increased use of new diagnostics ensures that significantly more TB patients are correctly diagnosed, but major treatment gaps remain.[1]Active case finding (via contact investigation) is extremely important for TB control. However, most case findings in the Nigerian setting is limited to self-referral (passive case finding) when individuals develop symptoms of tuberculosis and present to hospital themselves due to symptoms of the disease. Only 15% of the total burden of tuberculosis in Nigeria is being notified as at 2015.[1] This would likely increase the risk of disease spread.

Latent TB infection (a condition in which a person is infected with *M. tuberculosis* but does not currently have tuberculosis disease), is an important consideration since some household contacts (HHC) of the TB disease patients could be latently infected. It has been reported that close contact with someone who has active tuberculosis disease is one of the common risk factors for progression from latent TB infection (LTBI) to active disease.[5] In view of this, it is important to assess the latent and active disease burden amongst household contacts (HHC) of TB patients suffering from pulmonary TB in this part of the world which has a high TB burden.

Macrophage activation by cytokines is the main mechanism underlying acquired resistance to pathogens.[6] IL-6 is a multi-functional cytokine and has been implicated in the immunopathogenesis of tuberculosis.[6-8] M. tuberculosis regulates IL-6 production to inhibit type 1 interferon signalling and consequently, disease progress.[9] IL-6 has also been described as an activation biomarker and is a predictor of opportunistic diseases in patients with HIV.[10]

It has been suggested that IL-6 could be used either alone or with other cytokines as a potential biomarker of mycobacterium infection.[2] In addition, the authors suggested that IL-6 levels can be used as a prognostic marker in individuals exposed to tuberculosis. In view of the overlapping epidemiology of tuberculosis and HIV, it is necessary to assess the role of IL-6 as a marker in exposed individuals. Thus, IL-6 levels were assessed in this cohort, that is, in tuberculosis disease, TB disease/HIV co-infection as well as in latent TB infection. Thus, the major aims of this study are to assess for cases of previously undiagnosed TB disease among household contacts of TB patients enrolled in the directly observed treatment short course (DOTS) in a tertiary healthcare facility in south-east Nigeria and also to evaluate the role of IL-6 as a marker in tuberculosis and in TB/HIV co-infection.

METHODS

The ethical approval for the research design was obtained from the Nnamdi Azikiwe University Teaching Hospital ethics committee; reference number NAUTH/CS/66/3/21. Written informed consent was obtained from all participants enrolled in the study.

Study site

The study location was in the semi-urban town of Nnewi and other satellite towns served by the Nnamdi Azikiwe University Teaching Hospital, a tertiary health care facility. A total of 205 subjects were recruited for this study comprising 93 males and 112 females. Sixty-two (62) confirmed pulmonary TB index cases (first cases to be identified that led to other cases from contacts) and 143 of their house hold contacts (Age range 12-58 years) participated in the study. Also, 54 apparently healthy subjects (27 males and 27 females) within the age bracket were recruited from the study community as study controls.

Inclusion criteria

The inclusion criteria were that the TB index patients were enrolled after clinical assessment revealed clinical features of TB disease and laboratory testing for tuberculosis using Ziehl-Neelsen and auramine-phenol fluorochrome technique for Acid-fast bacilli (AFB), and the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) tested positive. TB and HIV co-infected patients were included. Only newly diagnosed patients who had not commenced drug therapy were included. Close household contacts of the TB index cases and apparently healthy control subjects were included. Subjects aged 12 years and above were recruited.

Exclusion criteria

Exclusion criteria for all groups were other co-morbidities, pregnancy, smoking, alcoholism, lactation and use of supplements or herbal remedies, age below 12 years (in order to exclude the effect of BCG vaccination). TB and HIV positive subjects who had commenced on anti-TB or anti-HIV therapy were excluded. Using a questionnaire, demographics such as age, history were obtained from the index cases, HHC and apparently healthy controls. Active TB case finding was performed amongst the HHC by testing using various methods for TB diagnosis as further described in the methods sections.

Recruitment/enrollment of participants

The study period was September 2018 to June 2019.In this cross-sectional study, structured questionnaires were administered to potential participants. The information requested using the questionnaires include demographic and other information as related to the inclusion and exclusion criteria. Information such their household population, relationship and proximity to each other was also requested. Sixty-three TB index cases (who are confirmed pulmonary TB patients) with suitable

household contacts were identified. They were contacted via telephone and/or visited in their homes after we received approval by the HHC or the index patients and encouraged to visit the clinic. Others reported to the clinic after communication via telephone, or when convinced by the index patients to do so. The protocol for evaluation of the patients was according to the World Health Organization (WHO) guidelines, which include physician evaluation; chest radiograph and sputum smear microscopy.[11]

Laboratory analyses

Five (5) milliliters of blood samples were collected from all participants -TB patients, household contacts and apparently healthy control subjects who accepted our invitation and presented at the TB clinic. Volunteers who were coughing were asked to express sputum samples for PCR testing using GeneXpert MTB RIF assay and for AFB tests. All the participants who had symptoms were referred to the TB clinic for chest X-rays. After samples for laboratory testing had been collected, tuberculin skin test (TST) was performed on all HHC and control subjects to test for latent TB infection.

Though the TST has its limitations, after due considerations, we considered it best for this population. They were administered with 0.1ml/5TU purified protein derivative (Mantoux test). The diameter of the ensuing papule was measured after 48-72 hours. Children in Nigeria are routinely immunized at birth with the Bacille Calmette-Guerin (BCG) vaccine.

Adults especially health workers, students and researchers in contact with infected patients could also receive the vaccine if they are not already immunized. Due to this, children less than 12 years and adults who had received the BCG vaccine in adulthood were excluded from this study to rule out false positive reactions. There were no further restrictions on age in recruiting participants. HIV testing was performed on all participants' samples using Determine (Inverness Medical, Shinjuku-ku, Japan) and STAT-Pak (Chembio, Medford, NY, USA) and where results were discordant, Uni-Gold (Trinity Biotech, Bray, Ireland) was used as the tie-breaker according to the national serial algorithm.

The IL-6 levels in serum samples were measured using commercial ELISA test kits (Abcam, Cambridge, UK). The human IL-6 ELISA from Abcam (ab46027) was used for the invitro quantitative determination of IL-6 in sera according to manufacturer's instruction. Samples were assayed in duplicate. The lower limit for assay sensitivity was <5pg/ml, as stated by manufacturer.

Statistical analysis

Data were analyzed and comparisons performed using Kruskal-Wallis test with Dunn's multiple comparison correction, Mann-Whitney and ANOVA using SPSS version 21 and Graph Pad Prism version 8.0.1. Level of significance was set at $p<0.05$.

RESULTS

A total of 205 subjects and 54 apparently healthy controls were recruited for this study and the demographics are as shown in Table 1.

Table 1: Demographics of the tuberculosis index patients, their household contacts (HHC) and healthy controls.

Group	Age range (years)	Sex N (%)
TB Index cases N=62	12-58	Male: 32 (51.6)
		Female:30 (48.4)
House-hold contacts N=143	12-55	Male:61 (42.7)
		Female: 82 (57.3)
Control group N=54	16-58	Male: 27 (50)
		Female: 27 (50)

Among the 143 HHC of TB positive index cases, 9 (6.3%) were found to have active tuberculosis, 71 (49.6%) were latently infected as shown by a positive TST, while 63 (44.1%) had no TB infection. On the hand, among the control group (54 subjects), none had active TB, 18 (33.3%) had latent TB infection while 36 (66.7%) were not infected. These findings were found to be significantly different (p=0.0078) (Figure 1).

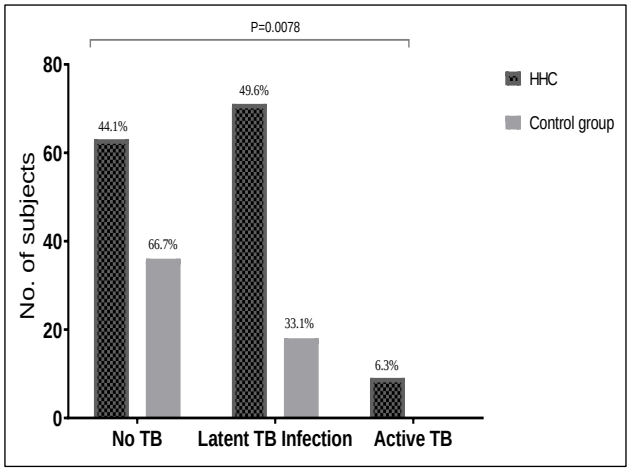

Figure 1: Household contacts (HHC) and the control group who are not infected, latently infected or have active tuberculosis. TB infection status and total number of patients are shown in x and y axes respectively. Statistical significance was determined using Chi^2 (p=0.0078).

It is interesting to note that at the time of active TB diagnosis in some of the HHC, 2 subjects reported no symptoms, while another (1) subject only accepted to enroll in the study because of observed irregular haemoptysis.

Of the 62 index cases, 14 (22.6%) were HIV positive while 15 of 143 (10.5%) HHC were HIV positive. One of the 54 apparently healthy controls (1.9%) was HIV positive (see Table 2). Two (3.2%) of the TB index cases had multi-drug resistant tuberculosis. There were significantly higher numbers of HIV positive individuals among HHC of HIV positive TB index group compared to their HIV negative counterparts (p=0.032).

Table 2: HIV and tuberculosis infection status among the study population.

Infection status	Index TB case group	Household contact	Apparently healthy
Frequency (%)	**N=62**	**(HHC) group N=143**	**Control group N=54**
HIV Pos	14 (22.6)	15 (10.5)	0 (0)
HIV Neg	48 (77.4)	128 (89.5)	54 (100)
Active TB	62 (100)	9 (6.3)	0 (0)
LTBI	n/a	71 (49.6)	18 (33.3)
No LTBI	n/a	63 (44.1)	36 (66.7)

*Key: n=number, LTBI=Latent TB infection, No LTBI=No latent TB infection, Pos=positive, Neg=negative

Among the HHC latently infected with TB, 7 out of 71 (9.8%) were infected with HIV. On the other hand, among the control group who were latently infected, none of the 18 was positive for HIV (Table 2).

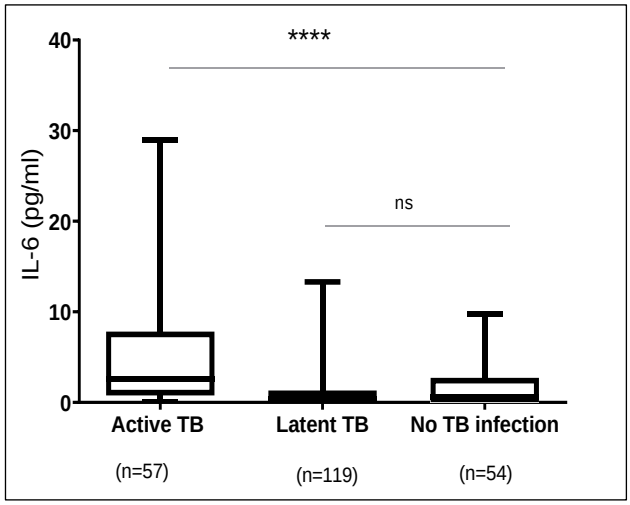

Figure shows median and 5-95 percentiles. Statistical significance was determined using Kruskal-Wallis test. ****P<0.0001. ns: non-significant.

Figure 2: IL-6 levels in HIV negative TB positive index cases (n=57), Household contacts (n=119) and control group (n=54).

Participants were assessed for serum levels of IL-6. After initial findings revealed the HIV, active TB and latent TB status of the participants in the active TB index group, HHC and apparently healthy control groups, the participants were assessed according to their disease status for the assessment of IL-6 levels.

First, IL-6 was assessed in the HIV negative population in the groups. When comparing the 3 groups, significantly different levels were found (p<0.0001). Also when comparing Active TB index case group and control group, P<0.001. However, when comparing HHC and control group, there was no significant difference, p=0.1395 (Figure 2).

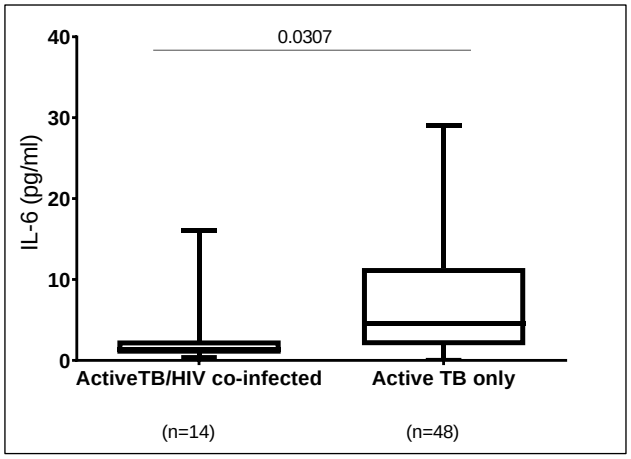

Figure shows median and 5-95 percentiles. Statistical significance was determined using Mann-Whitney test. *p=0.0307.

Figure 3: IL-6 serum levels in index cases with TB/HIV co-infection (n=14) and TB mono-infection (n=48).

Next, we assessed IL-6 levels among HIV negative index TB cases (n=48) and their HIV/TB positive counterparts (n=14). Findings revealed a significantly higher level in TB mono-infection compared to TB/HIV co-infection, P=0.0307 (Figure 3).

DISCUSSION

The early detection of active TB is important for TB control. With the WHO calling for an end to the global TB epidemic by 2035, efforts to curb TB must be improved and active case finding should be implemented otherwise, TB eradication could remain a mirage.[12] Hidden burden of tuberculosis have been reported by various studies in high TB burden countries.[13-15] Findings from our study demonstrated cases of previously undiagnosed active TB because active TB case finding is not currently in place.

It is important to point out that not all close contacts consented to be tested, which means figures could be higher. Similar to our findings, studies in relatively high TB burden countries also found previously undiagnosed active TB cases in disturbing proportions.[15-17] The international union against tuberculosis and lung disease, as well as the WHO recommends contact investigation as a strategy for identifying new TB cases and preventing TB disease transmission among household contacts.[18] A reliance on passive case finding has resulted in millions of missed TB cases every year, leading to transmission of

infection within families and communities.[19] Investigation of HHC exposed to TB is widely recommended by international guidelines to identify secondary cases of TB and limit disease spread.[20]

It has been suggested for long that identification and treatment of latent tuberculosis infection (LTBI) are essential for the elimination of tuberculosis.[21] According to Jasmer et al, LTBI screening is effective in two groups of persons; those at risk of contracting M. tuberculosis and those at risk of progressing from LTBI to active tuberculosis.[22] In a high TB burden setting, which also has a relatively high HIV disease burden, co-infection with HIV is definitely a great risk factor for progressing from latent TB to active TB disease. People, who are latently infected with TB and co-infected with HIV, are estimated to have between 12 and 20 times greater risk of progressing to active TB than those without HIV infection.[23]

Findings from this study showed that among the 71 HHC who were latently infected, 7 of the 71 were HIV positive (9.8%), while none of the control group was positive. The reason is not far-fetched. Most of the HIV positive HHC are partners of HIV positive TB patients. These clearly would have an increased risk of progressing to active TB.

Latent TB infection among household contacts of patients suffering from tuberculosis is a very important factor due to their level of exposure. As previously mentioned, close contact is considered a risk factor for progression from latent infection to active disease.[1] Among our study population, 49.6% were latently infected with TB. There is also clearly a higher risk of latent TB among HHC than in control subjects. This is similar to findings from other high burden TB countries where prevalence of LTBI range from 27% to 93% based on TST.[24,25] In a study in South Korea (which has intermediate TB burden), they found a prevalence of 38% in close contacts of active TB patients.[25]

Our results demonstrate the importance of active TB case finding for TB control in regions with a high TB disease burden and buttress the role of HIV as a driver of TB disease. This is hardly surprisingly as this has been established. Higher numbers of HIV positive individuals were found in the TB disease group compared to the control group. Findings from this study suggest that TB control strategies will benefit immensely from active case finding and treatment of HHC. It is clear that active TB case finding is resource intensive especially in high TB burden countries.

Due to resource challenges faced by many high TB burden countries, streamlining active case finding to only selected groups, who are at higher risk could be quite beneficial and prevent resource dissipation. It is important to note that two (2) of the TB index cases in this study had multi-drug resistant TB. These should be a priority group for contact tracing. According to Elmi et al, close contacts of multi-drug resistant TB (MDR-TB) cases, such as household members, are most likely to become infected because of intense and/or prolonged exposure to index cases.[26] Contact tracing and possibly early diagnosis for such at-risk groups would be very beneficial in controlling the spread of MDR-TB.

Previous studies have found significant differences in serum IL-6 levels between active TB subjects, in contacts and controls similar to our findings.[27,28] This is important considering reports that virulent Mycobacteria strategically upregulate IL-6 production to combat innate immunity.[29] However, while Lopes et al, found significantly higher IL-6 in contacts when comparing to non-contacts, Joshi et al, found significantly higher levels of IL-6 in healthy controls compared to household contacts.[27,28] We on the other hand found no significant difference between the contact group who did not have active tuberculosis and the control group.

This is could likely be due to relatively high latent TB infection in the general study population. This would then suggest that though IL-6 has been suggested as a marker to differentiate between active and latent TB disease, subjects in high TB burden areas with high latent TB infection could have different responses. In a previous study, we found a distinct effect of HIV infection on TB-specific cytokine responses during active TB.[30] IL-6 is associated with HIV disease progression.[31] In addition, it has been reported that M. tuberculosis regulates host IL-6 production to inhibit type 1 interferon signaling and consequently disease progression.[9] Thus, HIV and its effect on production of this cytokine should be taken into account to ensure maximum benefit, if using IL-6 as a biomarker in all affected populations.

Though active case finding could be considered resource-intensive, the cost benefit analysis is important for effective TB control. It is important to note that in this malaria endemic region, symptoms of TB could be confused with the symptoms of malaria; as some individuals actually reported no symptoms of TB despite having active TB. Training and engaging community health workers to move into the field (communities) could be highly efficient and cost effective. Findings from a study in Nigeria suggests that training and engaging incentivized community workers to assist in referrals under the supervision of a responsive TB program would be highly beneficial and a key driver of community case finding.[13]

CONCLUSION

In conclusion, our results demonstrate previously undiagnosed active tuberculosis among household contacts of tuberculosis patients attending a TB DOTS clinic in South-east Nigeria. The fact that a number of the previously undiagnosed active TB cases did not demonstrate the classic clinical signs of tuberculosis, and yet were infectious buttresses the need for active TB case

finding in high TB burden locations. Utilizing IL-6 as a possible diagnostic marker since it is able to differentiate latent and active pulmonary TB appears promising. Future work could assess its possible early diagnostic application in extra pulmonary TB.

We recommend that HIV positive TB infected patients should be priority for active TB case finding, because members of their household could also be infected with the virus which would directly render them more susceptible to TB. In addition, individuals with multi-drug resistant TB should also be a priority for active TB disease case finding even in resource poor settings. This would help curb community spread and inch us closer to the goal of ending the TB epidemic.

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