Original Article

The Effect of Pulmonary Tuberculosis on Neurocognitive Function in HIV infected Adult Patients in Lusaka, Zambia

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ABSTRACT

***Objective*:** To explore the effects of Pulmonary Tuberculosis on neurocognitive functions in HIV+ adults in Lusaka, Zambia.

Materials and methods: In a retrospective and prospective case-control study, Global Deficit Score (GDS) was used as an overall measure for cognitive impairments between groups and also within the PTB+/HIV+ group, and Domain Deficit Scores (DDS) were used to summarize cognitive impairments within each of the seven domains. To examine group differences in neurocognitive status, we used Wilcoxon ranked sum tests to compare the performance between groups on neuropsychological test battery.

***Results*:** Out of 324, only 244 were studied. Results indicated significant neurocognitive impairment in PTB+/HIV+ group than PTB-/HIV+ in the GDS, $p<.001$, significant lower CD4 cell count with a mean of 323 cells/µl compared to 510 cells//µl for the control group. The PTB+/HIV+ group, CD4 cell count was in the range 201-499 cells//µl compared to their cohort CD4 cell count above 500 cells//µl indicating immune compromise in the PTB+/HIV+. 95% of PTB+ were stages 3 and 4 indicating AIDS defining stage, whereas 95% of PTB negative were stage 1 suggesting immunocompetent. Linear regression model ($p<.01$), PTB status was predictive of GDS even while accounting for demographic and medical variables that have previously been associated with neurocognitive impairments. Specifically, a linear regression model identified PTB status ($F=6.26$, $p < .02$) as a significant predictor of Global Deficit Score (GDS). Age ($F=3.21$, $p <.08$) approached significance, while years of schooling ($F=0.54$), current WHO stage ($F=1.41$) and gender ($F= .13$) were not significant independent predictors of GDS (all ps > .10).

***Conclusion*:** This study highlights the fact that PTB has neurocognitve impairment in HIV+ adult individuals. Findings of the present study show the presence of neuropsychological impairments in all the seven domains except motor in the PTB+/HIV+ adults in Lusaka district, Zambia.

INTRODUCTION

Immunodeficiency virus (HIV) infection and Pulmonary Tuberculosis (PTB) are so closely connected that their relationship is often described as a co-epidemic. They are far more destructive and lethal together than either disease alone; each speeding the other's progress with PTB killing up to half of all AIDS patients.[1] HIV that causes AIDS weakens the immune system; and so does mycobacterium tuberculosis the causative agent of PTB.[2] As a result, 5-10% of people with TB (but who are not

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infected with HIV) become ill or infectious at some time during their life.[3] HIV positive individuals who are infected with *Mycobacterium tuberculosis* bacilli are more likely to develop PTB than HIV negative individuals infected with *M. tuberculosis*. PTB is a leading cause of death among people who are HIV positive.[4] Both infections are associated with neurocognitive deficits. HIV infection enters the CNS early during the course of infection and frequently results in neurological disease marked by a set of cognitive, motor, and behavioural symptoms.[5,6,7] TB can have neurocognitive impairment due to the following: granulomatous meningeal inflammation with exudate and adhesion formation, an obliterative vasculitis, and an encephalitis or myelitis.[8,9,10] A study by Gupta *et al* in India showed that the HIV+ had more cognitive impairment compared to the HIV negative.[11] Robertson *et al* designed a prospective study to follow a US cohort to look for sex differences in neuropsychological functions over time in HIV-infected subjects.[12] They found no evidence of differential declines regarding neuropsychological functioning between women and men. Similar inconsistent findings have been reported concerning sex differences in clinical symptoms not involving the central nervous system.[13,14,15]

Most literature addressing Neurocognition in HIV is from Europe and the United States where the predominant virus strain is clade B.[16] In Zambia, the virus strain is predominantly clade C.[17] Epidemiological trends show that HIV infection due to clade C is increasing in Asia and Africa.[18] It has caused the world's worst HIV epidemics and is responsible for more than half of all infections.[19] Almost 60 % HIV positive individuals (more than 22 million people) are infected with HIV clade C.[20] The International Neurobehavioural test battery, which is sensitive to HIV associated neurocognitive disorders (HAND), was used to measure performance on neuropsychological tests with Zambian Norms (used as a diagnostic test). [21] The current study used the Global Deficit Score (GDS) to detect neurocognitive impairment. The Global Deficit Score (GDS) approach is an alternative method employed to determine cognitive impairment among individuals living with HIV.[22]

The purpose of the study was to the effect on neurocognitive functions of the co-infection of pulmonary tuberculosis (PTB) and HIV+ in adults in Lusaka district, Zambia.

METHODOLOGY

The study was both retrospective and prospective case-control. The population included all HIV+ and PTB+ on AVRs and Anti PTB therapy in Lusaka district, Zambia. The sample sites were 6 Lusaka district based urban clinics namely: Kalingalinga, Matero Main, Matero Referral Centre, Kabwata, Chipata and Chilenje clinics respectively. The clinics were chosen due to their high numbers of HIV+ and TB patients on HAART and anti-TB therapy respectively.

Sample size and sampling

The study included 324 research participants; the number was based on the large sample criteria, with 39 PTB+. This was done on Tuesdays and Fridays when there were TB clinics in the study sites. The TB Sister-In charge identified potential PTB subjects who where HIV+ during reviews or adherence counselling and screened them for possible enrolment in the study group. The 39 subjects in the study group were statistically compared with their 205 cohort in the control arm in terms of age, gender, level of education and WHO- HIV staging on neurocognitive function. The two research arms were statistically compared in terms of their neurocognitive profiles and bio-makers (CD4 lymphocyte count and viral- load).

Research participants who volunteered to participate were asked to sign a written informed consent and completed a demographic questionnaire. After completing self-report and Zambia Achievement Test (ZAT) measures, the neurocognitive battery was administered. This took between two to two and half hours to complete. After the administration of the neurocognitive test battery, blood was drawn from the upper arm in order to analyze HIV bio-markers.

Those with active PTB (on anti-PTB treatment) and HIV+ (on HAART), were enrolled in the cases arm, while individuals who were negative for all types of TB but were HIV+ (on HAART) were enrolled in the control arm. Data collection involved the following laboratory investigations, CD4 lymphocyte count, full blood Count (FBC) Hb and viral load, medical files,

sociodemographic questionnaire and the administration of the neurobehavioural test battery.80 patients were excluded because 47 had missing neuropsychological data of Wisconsin card sorting Test and Halstead Category test (two major tests of Executive Function) and 33 because they had extra-pulmonary tuberculosis.

Instruments

Data collection and instruments included four sections: A sociodemographic survey, medical history, laboratory tests and functional status survey, subjective neurological symptoms questionnaire, and a neuropsychological test battery. Chest X-ray and sputum were already done at the time of diagnosing PTB by the attending Medical Doctor or trained Clinician in PTB/HIV as routine investigations.

The following constituted screening instruments for both inclusion and exclusion criterion; Functional status survey (general mental state), subjective neurological symptoms questionnaire (Screened any neurological conditions), A sociodemographic survey (screened for levels of education), medical history (screened for any previous TB treatments and other medical conditions with neurological effects). The instruments were administered before enrollment.

Diagnostic instruments included: Laboratory test (CD4 cell count and viral load). Neuropsychological test battery was administered to diagnose neurocognitive impairments. The instruments were administered after enrolment of the research subject.

Ethical consideration

The study was approved by The University of Zambia Biomedical Ethics Committee after approval from the Ministry of Health.

Statistical analysis

The Global Deficit Score (GDS) was used as an overall measure for cognitive impairment between groups and also within the PTB+/HIV+ group, and Domain Deficit Scores (DDS) were used to summarize cognitive impairments within each of the seven domains. The CD4 cell count and current WHO HIV disease staging were also compared using Chi-square. The CD4 cell count represented the levels of immune suppression and was categorised as; <200cells/mm?, 201-499 cells/mm? and > 500 cells/mm?. Next, we used multiple regressions to identify any variables that may independently predict neurocognitive status. SPSS 16.0 and JMP 9.0 were used to complete these analyses. All raw scores for the seven domains were converted T scores to generate Domain Deficit Scores (DDS) and Global Deficit Scores (GDS) with a cut-point of $\geq$0.50, were used in the final analyses. P value of 0.05 was considered significant.

The Global Deficit Score (GDS) approach was used because it is an alternative method employed to determine neurocognitive impairment among individuals living with HIV.[23] The GDS was originally created to be a "user friendly," automated approach that also emphasizes deficits in performance. Specifically, it considers both the number and severity of deficits in performance throughout the test battery while assigning less weight to performances considered to be in the normal range.[24 25 26] In the GDS approach, individual test scores (i.e., T-scores) from a comprehensive Neuropsychological test battery are each converted to a deficit score ranging from zero *(no impairment)* to five *(severe impairment)*. The deficit scores are then simply averaged across all tests in the battery to create the GDS. Therefore, the GDS overcomes the same disadvantages as clinical ratings do compared to averaging absolute level of performance on a test battery (the latter giving equal weight to good and poor scores) and has been shown to be able to detect mild, HIV-associated cognitive impairment involving variable patterns of domains.[27] Additionally, the GDS has been found to be associated with biomarkers of HIV disease progression, including CD4 count and HIV RNA viral load in cerebrospinal fluid, as well as aspects of everyday functioning, such as antiretroviral medication adherence.[28,29]

RESULTS

Participant's demographic characteristics

In total, 324 patients were enrolled and only 244 were studied. Men; 95 (38.93%), Women; 149 (61.06%). The men: women ratio was 95:149. The age range was 21-65 years with a median of 41 years. Out of 244, 205 had no any history or form of Tuberculosis. Of the 205, men 70 (34.15%) and women 134(65.37%) one patient missing. Out of the total number of patients studied, 39 had PTB+,

men 25(64.10%) and women 14 (35.89%).21 (53.85%) had smear positive sputum PTB and 18(46.15%) smear negative sputum PTB. Within the study group, 22 (56.41%) PTB was diagnosed first and 17 (43.59%) PTB was diagnosed second (after HIV infection). Levels of education range were 5- 20 years of schooling with a mean of 10 years. 33 were excluded because they had other forms of tuberculosis or the type was not defined. 47 were also excluded because they had missing raw scores for Wisconsin Card Sorting and Halstead Category Tests. See table 1 and 2 for summary of participant's demographic characteristics.

Table 1. Levels of education and age

Levels of Education	Frequency	Percentage
5 – 7 years	39	16.0
8 – 9 years	71	29.2
10 – 12 years	115	47.3
13 years and above	18	7.4
AGE		
20 – 35 years	74	30.5
36 – 45 years	100	41.2
46 – 55 years	53	21.8
56 – 65 years	16	6.9

Table 2. PTB status

PTB status	Female	male	SS+	SS-	PTB first	PTB second	Total number
PTB+	14	25	21	18	22	17	39
PTB-	149	70	0	0	0	0	205
Total studied							244

Note: *PTB+ = patients with active PTB, PTB- =patients without any form of TB, SS+ = Sputum smear positive, SS= Sputum smear negative, PTB first = PTB was diagnosed before HIV infection, PTB second = PTB was diagnosed second to HIV infection.*

Global Deficit Impairment

The PTB+/HIV+ group had mean of 0.749 (SD, 0.596), while PTB-/HIV+ group had mean of 0.442 (SD, 0.420). Results showed that the PTB+/HIV+ group had statistically more neurocognitive deficits compared to the PTB-/HIV+ group and results were statistically significant (z= 2.95558, p<. 001). This high statistical difference in the levels of neurocognitive deficits was further confirmed by Chi-square $\chi 2$ =11.2499, *df=1*, p=0.0008. The statistical difference in the Global Deficit Score (which predicted neurocognitive impairment) mean that the PTB+/HIV+ group has more neurocognitive deficits compared to the PTB-/HIV+ group.

Overall neuropsychological performance between PTB+/HIV+ and PTB-/HIV+ groups

In order to investigate the differences in performance between the two groups in the seven domains, Wilcoxon ranked sum tests using the Global Deficit Scores (GDS) and Domain Deficit Scores (DDS) were used.

Executive function domain

Neurocognitive performance being measured by Domain Deficit Score (DDS). The PTB+/HIV+ group had mean of 0.602 (SD, 0.525), while non TB/HIV+ group had mean 0.397 (SD 0.511). Results indicated that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in executive function domain and results were statistically significant z= 2.61675, p<.001. Further analysis using chi-square confirmed the results as being statistically significant $\chi 2$ =6.8541, *df=1, p*=0. 0088.

Fluency domain

The PTB+/HIV+ group had mean of 0.795 (SD, 0.800), while PTB-/HIV+ group had mean of 0.462 (SD 0.658). Results indicated that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in Fluency domain and results were statistically significant z= 2.96800, p<. 001.Chi-square test also confirmed that neurocognitive performance was statistically significant between groups ÷2=8.8168, *df=1, p*=0.0030.

Recall domain

Using Wilcoxon/Kruskal-Wallis Tests and confirmed the results using a 2 sample test. The results showed that PTB+/HIV+ group had mean of 0.718 (SD, 0.750), while PTB-/HIV+ group had mean of 0.463 (SD, 0.712). Results indicated that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in Recall domain and were statistically significant z= 2.64342, p<. 001.It was

further confirmed by chi-square to be statistically significant $\chi 2=6.9949$, $df=1$, $p=0.0082$.

Motor domain

The PTB+/HIV+ group had mean of 0.115 (SD, 0.421), while PTB-/HIV+ group had mean of 0.240 (SD, 0.676). The Wilcoxon/Kruskal-Wallis 2-sample tests indicated no statistical difference in performance in motor domain between the groups and results were statistically non-significant $z= -0.72394$, $p>0.4691$

Learning / Memory domain

Using Wilcoxon/Kruskal-Wallis Tests, the PTB+/HIV+ group had mean of 1.000 (SD, 1.124), while PTB-/HIV+ group had mean of 0.517 (SD, 0.727). Results showed that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in Learning/memory domain and results were statistically significant $z= 2.59144$, $p<.001$. This was further confirmed by Chi-square test $\chi 2=6.7225$, $df=1$, $p=0.0095$.

Working memory domain

PTB+/HIV+ group had mean of 1.231 (SD, 1.044), while PTB-/HIV+ group had mean of 0.608 (SD, 0.838). Results indicated that the PTB+/HIV+ group's performance was worse than the PTB-/HIV+ group in working memory domain and results were statistically significant $z= 3.80867$, $p<.001$. Chi-square also confirmed the statistical difference in neurocognitive performance $\chi 2=14.5160$, $df=1$, $p=0.0001$.

Speed of information processing domain

PTB+/HIV+ group had mean of 0.795 (SD, 0.783), while PTB-/HIV+ group had mean of 0.440 (SD, 0.596). Results indicated that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in speed of information processing domain and results were statistically significant $z= 2.95558$, $p<.001$. The statistical difference in neurocognitive performance was further confirmed by Chi-square test $\chi 2=8.7430$, $df=1$ $p=0.0031$.

Multiple Regression analysis

Regressions were run using GDS and DDS as the dependent variable, with PTB status in the model. The independent variables included were; age, level of education, current CD4 cell count, and current WHO disease staging

Multiple Regressions Predicting Global and Domain Neurocognitive Performance

We found that levels of education and age independent variables had statistically significant effects only in two domains (levels of education on executive functions domain and age on Fluency domain). In a significant linear regression model ($p<.01$), PTB status was predictive of global deficit score even while accounting for demographic and medical variables that have previously been associated with neurocognitive impairments. Specifically, a linear regression model identified PTB status ($F=6.26$, $p < .02$) as a significant predictor of GDS. Age ($F =3.21$, $p <.08$) approached significance, while years of schooling ($F=0.54$), current WHO stage ($F=1.41$) and gender ($F= .13$) were not significant independent predictors of GDS (all $ps > .10$.

Global Deficit Impairment across gender

The results indicated that the difference in overall performance was not statistically significant between males and females within the PTB+/HIV+ group ($p>.311$). This lack of statistical significance was also observed in neuropsychological test performance in all cognitive domains ($ps > .10$).

Medical characteristics (clinical, biomarkers and WHO HIV staging)

The PTB+/HIV+ group had lower mean CD4 cell count compared to PTB-/HIV+ group, $p<.01$. 95% of PTB+ were stages 3 and 4, whereas 95% of non PTB were stage 1. The viral load mean in the study group was also higher than the control group, $p<.01$. WHO staging f (959.221), $P<.01$ and Viral load detection f (30.983), $p< .01$. All the PTB+ had a lower mean CD4 cell count with WHO HIV disease staging of 3.

The PTB+/HIV+ group had a CD4 cell count mean of 69.026 while the non TB/HIV+ had 121. 665. The 2-sample test confirmed that the PTB/HIV+ group had a lower CD4 cell count compared to the non TB/HIV+ and this was statistically significant $z=-4.60846$, $p<.001$. The CD4 cell count mean, was lower in PTB+/HIV+ compared to the PTB-/HIV+ group. 95% of PTB+ were stages 3 and 4, whereas 95% of PTB negative were stage 1. Results were statistically significant for both CD4 cell count and WHO HIV disease staging $z= -4.60846$, $p<.001$.

The PTB+/HIV+ group's neurocognitive performance was statistically worse compared to the control group in all the 7 the domains except motor domain. Overall neurocognitive performance between the groups showed the PTB+/HIV+ Global Deficit Score performance to be lower than the PTB-/HIV+ in executive function, fluency, recall, learning memory, working memory and speed information processing domains. We also found significant neurocognitive impairment in PTB+/HIV+ group compared to PTB-/HIV+ in the GDS with the study group recording lower CD4 cell count which was compatible with their levels of immunity and detectable viral load. Results also showed both levels of impairment (GDS) and test performance were not statistically significant across gender. We also found the PTB+/HIV+ group to have more neurocognitive impairment compared to the control group. In a significant linear regression model, PTB status was predictive of Global Deficit Score even while accounting for demographic and medical variables. Consistent with previous studies using different subject samples and different neuropsychological test batteries, the GDS cut- point of ≥ 0.50 yielded optimal balance between sensitivity and specificity in classifying neuropsychological impairment, thus supporting the generalizability of the method

DISCUSSION

These results may suggest that adult Zambians with the dual infection of PTB/HIV are most likely going to have problems in decision making, planning, evaluation and monitoring due to impairments in the executive function. Since the Fluency domain is affected, this may lead to patients having problems with generating new information in their day to day life. The implication of the results may indicate that patients with the co- infection may have problems in recalling and retrieving stored information from the brain, making them prone to forgetting. Results may suggest that PTB+/HIV+ individuals may have problems with learning memory (difficulties with learning and storing of new information). This will make patients have difficulties in learning and keeping new information due to impairment in the learning memory domain. Another important fact is that the duo infection of PTB and HIV will slow down the rate at which individuals process information in the brain due to the impairment in the speed of information processing domain. The implications of the study results are that, adult Zambians with the duo infection of PTB+/HIV+, may require human resource placement and care at work depending on the kind of work involved, some may require rehabilitation and clinicians will have to be vigilant as to when to start treatment for both PTB and HIV infections so as to protect the CNS from further damage. This should be done in order to promote continued quality of life/productivity over the lifespan. These results are similar to international studies that have showed cognitive impairments in patients with PTB/HIV.

Our results are supported by the study done in Vietnam which found that patients who had Tuberculosis Meningitis/HIV+ had lower CD4 count, haematocrit and immunosuppression.[30] The pilot study conducted **in Zambia, showed** that greater cognitive deficits were seen in female relative to the male seropositive participants.[31] To the contrast, in our study, results indicated no significant gender differences in their cognitive profiles and test performance. A similar study conducted in 2007 in south India investigating neuropsychological deficits in HIV+ type 1 clade c adults, reported that cognitive performance on the neuropsychological test battery did not differ according to immune suppression levels, except for visual working memory.[32] In the present study, we also found that CD4 count, viral load detection and WHO HIV disease staging which determined immune suppression levels did not have any significant effect on test performance and global deficit score. This Indian study compared HIV+ individuals to healthy seronegative individuals. To the contrast, our study had compared PTB+/HIV+ to PTB-/HIV+. The pre-dominant HIV type in Zambia is clade c and this might explain why all the neuropsychological test performance was affected in all the domains except motor. Available data indicates that HIV disturbs the dopaminergic neuronal function hence motor dysfunction. In our study, the non-significance in motor domain may be due to the fact that clade C does not affect the dopamine system.

It is therefore very important in resource limited environment like Zambia, with high PTB and HIV co-

infection rates, for clinicians to have a high clinical suspicion of PTB so that it can be detected early and treated. Every HIV+ individuals should be screened for PTB and every PTB+ patient should be counselled and tested for HIV.

This study has highlighted the fact that PTB is associated with neurocognitive impairments in HIV+ adult individuals. Previous studies have reported a lower prevalence of HIV dementia and other immune suppression in PTB+/HIV+ groups. However, the absence of severe cognitive deficits in the present sample may be due to individuals being on both anti- PTB treatment and anti-retroviral therapy. Another reason for this finding may be that the study had a stringent exclusion criteria resulting in sample bias. Individuals with any symptoms associated with any form of TB, including TB meningitis, which could have had severe neuropsychological deficits were excluded.

CONCLUSION

Adult patients in Zambia who have the co-infection of PTB/HIV perform worse than the HIV+ adult patients without PTB on Neurocognitive test battery in almost all the seven domains except the motor domain. The current study has shown that if a patient has the duo infection, they are likely to have more Neuropsychological impairments (based on the Global Deficit Score) than adult individuals who are HIV+ but without PTB. There are no gender differences in neurocognitive performance and impairments between males and females with co-infection of PTB and HIV among the adult Zambian population.

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