Neuropsychological Changes in Tuberculosis Patients following Treatment: A preliminary study

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Summary

INTRODUCTION

Tuberculosis (TB) is reported to lead to significant neuropsychological problems such as depression and anxiety in addition to poor quality of life. These problems may impact adherence to treatment and disease outcomes. In the present preliminary study we assessed the effects of TB treatment on the neuropsychological profile of newly diagnosed smear-positive TB patients

MATERIALS AND METHODS

Repeated measures design was adopted. Participants were administered neuropsychological tests and quality of life measures at diagnosis and at month six after treatment.

RESULTS

Significant improvement was observed on the Immediate (Pre-test Mean = 18.5, SD= 9.2, Post-test M= 30.0, SD= 23.2) t(21) = -2.38, p= .027) and Delayed (Pre-test Mean = 4.7, SD= 2.9, Post-test M= 6.6, SD= 2.4), t(21) = -4.98, p< .001) recall of the California Verbal Learning Test (CVLT) Short Form, Further, on the Brief Symptom Inventory (BSI), psychological distress significantly decreased after treatment compared to the initial testing (pre-test M= .709, SD= .601, post-test M= .322, SD= .423), t (20) = 2.41, p= .026 (two-tailed).

CONCLUSION

Neuropsychological functioning among TB patients was impacted positively by anti-tuberculous medications. Neuropsychological assessment should be considered an integral part of treatment and management of TB patients.

Keywords: *Tuberculosis, Smear Positive, Dysglycaemia, Neuropsychological Disorders*

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Introduction

Tuberculosis (TB) prevalence worldwide continues to rise despite efforts to reduce the incidence, morbidity and mortality associated with tuberculosis (TB). TB continues to be a deadly communicable disease. In 2019, 10 million new cases and 1.4 million deaths due to TB were reported by World Health Organisation (WHO) [1], with the greatest burden being experienced in developing countries [1, 2].

Tuberculosis (TB) like many chronic diseases, is associated with a high burden of psychological disorders which may have a negative impact on the psychological health, treatment adherence and outcomes [3].

Common psychological disorders among TB patients include depression, anxiety in addition to poor quality of life [3]. The reasons for these changes include the physiological impact of the disease, the stigma and isolation patients experience coupled with the loss of income. The side effects of medications and the rigour of keeping review appointments could lead to psychological distress in these patients [3]. These problems may affect self-esteem and attitudes towards disease management including compliance to medications and eventually lead to poor disease outcome [3]. Neuropsychological changes have been reported in tuberculosis meningitis [4] and in TB patients with dysglycemia, [5] but little is known about the cognitive and behavioural changes in TB patients before and after treatment.

Our present preliminary study examined and compared the neuropsychological functioning among newly diagnosed smear-positive tuberculosis patients at the time of diagnosis and end of treatment with anti-tuberculous medications.

Materials and Methods

Study Site and Design

The study assessed the effect of treatment on the neuropsychological functioning of tuberculosis patients in Ghana using a pre-treatment and post-treatment design. Participants were tested at baseline before treatment and on completion of treatment at month 6.

The study site was conducted at a Chest Clinic of the Korle-Bu Teaching Hospital, Accra, Ghana. This unit is the main referral centre for all respiratory cases in Ghana.

Participants and Recruitment

Purposive sampling technique was used to recruit participants who met the inclusion criteria and consented to participate in the study. Twenty-two (22) consenting adult participants, all newly diagnosed with smear-positive TB patients (those diagnosed at clinic and those diagnosed in other facilities but referred to Korle-Bu for treatment) were recruited for the study.

Inclusion criteria

To participate in the study, respondents were to be positive by Cepheid GeneXpert nucleic acid amplification tests, be adults at least 18 years or above with no prior history of TB treatment.

Exclusion criteria

Patients with smear negative TB, extrapulmonary TB, current or past history of psychological or neuropsychiatric disorders were exempted from the study.

Measurements

At enrolment, demographic data and anthropometric features such as body mass index (BMI), waist circumference

(WC), hip circumference (HC) and waist-hip-ratio (WHR) as well as medical history were collected.

Waist circumference was measured in duplicates with a non-elastic measuring tape to the nearest 0.1cm at the midpoint between the lower rib margin and the iliac crest at the end of expiration. This was done with clothes removed. The mean of the two was used [6,7]. Similarly, Hip circumference was measured to the nearest 0.1cm at the maximal circumference of the buttocks, horizontally all round the body [7]

Blood pressure was measured in the right arm of seated subjects on two occasions at an interval of one minute using a professional HEM 907 blood pressure monitor after at least a 5-minute rest. The mean of the two measurements was used. Waist-hip ratio (WHR) >0.9 for men and >0.85 for women was indicated as increased WHR [8]

BMI (calculated) was categorized as obese, overweight, normal and underweight with defined values of 30.0 or more, 25-29.9, 18.5 -24.9-and less than 18.5 (Kg/m^2) respectively [9].

The presence of mycobacterium tuberculosis (MTB) was evaluated using the Cepheid GeneXpert system, a rapid, a nucleic acid amplification tests (NAAT) through polymerase chain reaction [10], with 95.2% (95% CI: 87.6-100) sensitivity, and 100% (95% CI: 92.4-100%) specificity [11]. We used patients who demonstrated mycobacterium positivity to increase the probability of the presence of TB infection. Sputum smear microscopy using Ziehl–Neelsen staining for acid fast bacilli (AFB) was however used to ascertain sputum conversion at 2 months (end of intensive phase) and six months (end of treatment) according to WHO recommendations [10].

The tests included below were used for the neurocognitive testing.

Montreal Cognitive Assessment (MoCA) [12]

It screens for cognitive dysfunction including memory, executive function, attention and concentration, fluency, conceptual thinking, visuoconstructional skills, calculations and orientation. The total possible score is 30 points with a cut-off score of 26 as normal. It has a high internal consistency with Cronbach alpha of 0.83 [12].

The Cognitive Failures Questionnaire (CFQ) [13]

This is a self-report 25-item questionnaire, which measures the probability of making mistakes in completion of everyday tasks. Items on CFQ assess aspects of cognitive failures that comprise motor function, perception, and memory. The total possible score is 100 points with scores below 50 deemed normal [13]

California Verbal Learning Test-Second Edition Short Form (CVLT-II) [14]

This is a verbal memory test that assesses the use of semantic connotations as a means of learning words. The CVLT-II Short Form has category lists of words. The List contains names of fruits, clothing and tools. Presentations of items are done in a randomized fashion with instructions to recall the words in any sequence. This is done to assess the participants' use of spontaneous semantic associations [15]. Scoring is done by summing the responses on a trial 1-4 (free recall), short delayed free recall, and long delayed free recall.

The short form of rhe CVLT-II has a Chronbach's alpha of between 0.72 to 0.89 [14].

Brief Symptom Inventory (BSI) [17]

The BSI is a 53-item self-report instrument designed to screen for symptoms of psychological distress in medical, psychiatric, and healthy individuals alike [17]. It assesses nine domains, which include Depression, Obsession-Compulsion, Anxiety, Interpersonal Sensitivity, Hostility, Somatization, Phobic Anxiety, Paranoid Ideation and Psychoticism. The BSI has a high Cronbach's α that ranges from 0.71 to 0.85 [17] The domain scores are calculated by summing up the responses divided by the total number of items.

Quality of Life (QOL) [16]

The Spitzer's Quality of Life (SQOL) assesses five dimensions of quality of life (outlook, health, daily living, activity, and support of family and friends). It was used by physicians to evaluate the relative benefits and risks of various treatments for serious conditions and of supportive programs such as palliative care. It has five items and its range of scores is 0–10. The Sptizer's QOL has been used in individuals with chronic physical conditions and cancer. Assessment of internal consistency demonstrated a high Cronbach's α of 0.78[16]

Statistical Analysis

The Statistical Package for Social Sciences version 23 (SPSS version 23) software was used to analyze the data.

Neurocognitive assessment results of the 22 participants (baseline and month 6) were compared using Paired Sample t-test, and effect sizes recorded. The baseline relationships and associations between socio-demographic and clinical characteristics, and neurocognitive tests were assessed with Pearson's Correlation test (for continuous independent/sociodemographic variables). Statistical significance was determined at 95% confidence level.

Ethical Considerations

The study received approval from the University of Ghana College of Health Sciences Ethics and Protocol Review Committee prior to the commencement of the study with reference number URF/9/ILG-076/2015-2016.

All enrolled patients provided written informed consent and the study complied with the Helsinki Declaration of 1964 (Revised 2013) on human experimentation. Strict confidentiality of data and privacy for study participants were ensured. Data was kept secured and was available only to the principal investigator.

Results

Twenty-two participants were assessed at baseline and month 6. It comprised, 14 (63.6%) males, with a mean age of all participants of 36.55 ± 14.05, Table 1. Ten (45.5%) participants were married and 12 (54.5%) single. Only 1(4.5%) person had no formal education, 9 (40.9%) had Junior high school education, 6 (27.3%) had Senior high school education, 4 (18.2%) had tertiary education and 2 (9.1%) had other forms of education.

All participants had detected MTB by GeneXpert (''very low'', ''low'', ''medium'' or ''high'' detected MTB). At six months, sputum smear microscopies for AFBs were all negative. Refer to Table 1 for further details.

Baseline Relationships

Age was not statistically significantly correlated with neurocognitive function. There was a significant positive relationship between Waist-hip ratio and anxiety, r(20) = .48, p < .05. Again, Waist-hip ratio was significantly negatively correlated with MOCA total score, r(19) = -.52, p < .05; Quality of life, r(19) = -.43, p < .05; and CVLT total free recall, r(19) = -.53, p < .05.

Effect of Treatment on Neurocognitive Test Scores

A Paired Sample t-test was conducted to compare the differences in scores on the pre and post neurocognitive assessment (CFQ, MOCA, CVLT, BSI and QoL). See table 2. There was a statistically significant increase in CVLT Total Free Recall scores from the first assessment (M = 18.54, SD = 9.20) to the post test (M = 30.00 , SD = 23.16), t (21) = -2.38, p = .027 (two-tailed). The mean difference between CVLT Total Free recall scores in pre-test and post-test was -11.45 with a 95% confidence interval ranging from -21.44 to -1.47. The eta-squared statistic (.22) indicated a large effect size.

There was a statistically significant increase in the mean scores of CVLT Delayed recall post-treatment (M = 6.61, SD = 2.35), compared to the pre-treatment (M = 4.70, SD = 2.88), t (21) = -4.98, p = 0.0001 (two-tailed). The mean difference in the Delayed recall of the CVLT between that of pre-treatment and the post-treatment was -1.90, 95% CI (-2.70, -1.11). The eta square statistic (.55) indicating a large effect size. The mean increase in the other cognitive measures (CFQ, and MOCA) was not significant.

A statistically significant difference was observed in Hostility (M= .610, SD = .674), post-test (M= .152, SD = .340) t (20) = 2.76, p = .012 (two-tailed) between the pre and post-treatment tests. The mean difference between the pre and post treatment was .457, 95% CI [.113 to .802]. The eta-squared statistic (.28) indicated a large effect size. Further, a significant decrease was observed in Somatization pre- test (M = 1.34, SD= .703) and post-treatment (M = .520, SD = .892), t (20) = 2.82, p = .010 (two-tailed).

The mean difference between the two assessments is .815, 95% CI [.214 to 1.415]. The eta squared (.28) indicated a large effect size. The Global Severity Index (GSI) of the BSI was observed to have significantly decreased (M= .709, SD= .601) post-test (M= .322, SD= .423), t (20) = 2.41, p= .026 (two-tailed). The mean difference between the pre and post assessments was .387, 95% CI [.052 to .722]. The eta squared (.23) indicated a large effect size.

A significant difference was observed on QOL between the pre and post-treatment respectively (M= 6.24, SD= 3.11) (M= 8.05, SD= 3.47) t (20) = -4.22, P< .001 (two-tailed). The mean difference was -1.81, 95% CI [-2.70 to -.915]. The eta squared (.47) indicated a high effect size. Depression, anxiety and phobic anxiety were not significant.

Discussion

The results of this study reveal that TB patients showed some improvement in their neuropsychological function when they receive treatment with anti-tuberculous medications. First, the patient's physical health improved after treatment.

Further, significant changes were observed on the CVLT Immediate and Delayed recall, which assesses immediate working memory, attention and long term memory. It was observed that recall was better for post-treatment compared to pre-treatment indicating an improvement in memory (immediate and long term) and attention of participants. The improvement in the scores may reflect improvement in the general wellbeing post treatment.

On the BSI, patients' Global Severity Index (GSI) score decreased at month six (post-treatment) compared to the initial testing suggesting significant improvement in perceived psychological distress with treatment. This finding is consistent with work of Tola *et al*. [20] in Ethiopia who reported improvement in psychological distress levels of TB patients 6 months into treatment compared to their initial assessment.

A significant decrease was observed in the measure of Hostility subdomain of the BSI at post-treatment. These findings contrast with the study of Peltzer *et al*. [3] and Theron *et al*. [21] who found depression and anxiety to be more prevalent than hostility in TB patients in South Africa and could reflect methodological differences.

According to Chetty *et al*. (2013) [22], induced high levels of stress might affect the hypothalamic pituitary adrenal (HPA) axis and might lead to increased levels of the stress hormone glucocorticoids, which is closely connected to memory retrieval function and might reduce performance on memory tasks. High levels of the cortisol hormone because of chronic stress, leads to excessive production of myelin sheath and less neurons in the hippocampus through the process of oligodendrogenesis [22]. Lupien *et al*. (2007) [23] investigated the part of the brain associated with cognition and stress hormones and found that receptors are localised in the hippocampus, amygdala and the frontal lobes which are known for memory and learning processes. Based on these finding, it can be inferred that the patients were undergoing severe stress as a result of their ailment and that had a significant negative effect on neurocognitive and behavioural functioning during the pre-test. However, performance improved significantly after treatment when stress levels reduced.

Limitations

Due to the small number of participants involved in this preliminary study, the findings may not be representative of TB patients at this centre. Further, only a few neuropsychological measures were used in this study. Also, co-morbid conditions such as hypertension, diabetes, cancers, cultural and other factors may impact on the neuropsychological functioning of Patients, but which were not explored and may affect our findings.

Conclusion

Notwithstanding the stated limitations, our pilot studies reveal that anti-tuberculosis treatment had a positive effect on neuropsychological functioning of TB patients. Significant changes were observed on memory (immediate and delayed recall), subdomains of the Brief Symptom Inventory **(**BSI) that indicated patients' psychological distress decreased after treatment. These findings may have an impact on patient adherence and care. Thus, a larger multicentre study that also limits the stated possible confounders is needed to validate these findings in the future.

Recommendations

Future studies should consider using extensive neuropsychological measures to address these important issues. The various parts of the brain associated with cognition and stress should be considered. Neuroimaging as part of the assessment could enhance our understanding of the mechanisms involved. We plan to conduct a larger multicentre study to validate the current findings and to give a more holistic picture among TB patients in Ghana.

Abbreviations

BMI: Body mass index
BP: Blood pressure
BSI: Brief Symptom Inventory
CFQ: Cognitive Failure Questionnaire
CI: Confidence Interval
CVLT: California Verbal Learning Test
GSI: Global Severity Index
HC: Hip Circumference
MOCA: Montreal Cognitive Assessment tool
MTB: Multidrug Resistant Tuberculosis
NAAT: Nucleic Acid Amplification Tests
SD: Standard deviation
QLI: Spitzer Quality of Life Index
TB: Tuberculosis
WC: Waist Circumference
WHO: World Health Organisation
ZN: Zeal Nelson

Competing Interests

There is no competing interest involving any of the authors of this manuscript.

Author Contributions

EY conceived the study, participated in its design, data collection, analysis, drafted the manuscript and collation of all drafts. KA, NN, VB, IDD, VG, MBA-A and CCM-K contributed to study design, data collection, analysis and manuscript draft. All authors read and approved the final version of the manuscript.

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Appendix

Table 1: Demographic Characteristics of Newly Diagnosed Smear-Positive Tuberculosis Patients at the Chest Clinic of the Korle-Bu Teaching Hospital in Accra, Ghana, 2017

	Frequency	**Percentage**
Age (mean ± SD)	36.55 ± 14.05	
Sex		
Female	8	36.4
Male	14	63.6
Educational level		
Tertiary	4	18.2
O-Level/A-level/SHS	6	27.3
Middle School/ JHS	9	40.9
None	1	4.5
Other	2	9.1
Marital Status		
Single	12	54.5
Married	10	45.5
Smoking history		
Smoker	1	4.55
Non-smoker	21	95.45
Do you take alcohol?		
Yes	2	9.09
No	20	90.91
Mean ± SD		
Body Mass Index, kg/m^2	18.35 ± 2.76	
Waist circumference, cm	76.52 ± 7.36	
Waist-to-hip ratio	0.86 ± .06	
Systolic BP	128.61 ± 35.61	
Diastolic BP	80.61 ± 15.16	

Table 2: Effect of Treatment on Neuropsychological Test Scores

Tests		N	M	SD	t	df	p
PHQ	Pre	22	6.8	3.7	3.33	21	**.003****
	Post	22	2.5	5.6			
CFQ	Pre	22	11.6	12.0	-0.65	21	.522
	Post	22	14.3	12.6			
CVLT total free recall	Pre	22	18.5	9.2	-2.38	21	**.027***
	Post	22	30.0	23.2			
CVLT S.D	Pre	22	6.8	12.2	0.12	21	.903
	Post	22	6.5	2.1			
CVLT D.R	Pre	22	4.7	2.9	-4.98	21	**<.001*****
	Post	22	6.6	2.4			
MOCA	Pre	22	18.4	5.6	-0.55	21	.591
	Post	22	19.3	7.9			
BSI Depression	Pre	22	0.5	0.5	1.51	21	.146
	Post	22	0.3	0.7			
BSI	Pre	22	0.5	0.6	1.37	21	.187
	Post	22	0.3	0.6			
BSI Phobic anxiety	Pre	22	0.4	0.6	1.95	21	.066
	Post	22	0.2	0.3			
BSI Hostility	Pre	22	0.6	0.7	2.76	21	**.012***
	Post	22	0.2	0.3			
BSI Somatization	Pre	22	1.3	0.7	2.82	21	**.010***
	Post	22	0.5	0.9			
GSI of (BSI)	Pre	22	0.7	0.6	2.41	21	**.026***
	Post	22	0.3	0.4			
QOL	Pre	22	6.2	3.1	-4.22	21	**<.001*****
	Post	22	8.1	3.5			

p < .05 (2-tailed), P-values in parentheses;*p<0.05,**p<0.01,***p<0.001, M = mean; SD = standard deviation; df = degree of freedom; N=sample size; t=t-value; M=sample mean; PHQ = Patient Health Questionnaire; CFQ = Cognitive Failures Questionnaire; BSI= Brief Symptom Inventory; GSI=Global severity index; MOCA= Montreal Cognitive Assessment; CVLT= California Verbal Learning Test (free recall= working memory, S.D.= Short delay/immediate recall, DR= delayed recall); QoL=quality of life.