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REVIEW ARTICLE

NEUROCOGNITIVE OUTCOME FOLLOWING TUBERCULOUS MENINGITIS TREATMENT: A SYSTEMATIC REVIEW

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ABSTRACT

Background and objective:

Tuberculous meningitis (TBM) is an infectious disease of the central nervous system that remains to be a global health challenge. Patients who survive after experiencing TBM have a risk of developing functional, cognitive and psychological disorders that can affect daily activities. The objective of this study is to present a comprehensive review of data on cognitive outcome after TBM infection.

Method:

We conducted a systematic literature search to identify studies addressing cognitive outcomes in adult TBM patients. Following a systematic literature search (PubMed, Scopus, EBSCO), studies were reviewed by independent reviewers to assess eligibility for inclusion. Three independent reviewers extracted data from included studies.

Result:

Among the articles identified, 6 studies met inclusion criteria, reporting cognitive outcomes for 330 patients with TBM. All studies followed the patients for 12 months or more. Three studies used Mini-Mental State Examinations (MMSE) to assess cognitive function, while other studies used a variety of tools: HIV-associated neurocognitive disorder (HAND), Montreal Cognitive Assessment (MoCA), neuropsychological (NEUROPSI), and Wechsler Adult Intelligence Scale (WAIS). All studies reported an improvement in cognitive function after completion of TB therapy. Two studies compared TBM with HIV, and showed TBM patients with HIV had worse cognitive outcomes than those without HIV.

Conclusion:

Cognitive function assessment tools in TBM patients are diverse and after approximately 12 months of follow-up following TB therapy, there was improvement in cognitive function. Standardized reporting of cognitive outcomes will be essential to improve data quality and data-sharing potential.

Keywords: Cognition, Prognosis, Tuberculous meningitis, Tuberculosis

INTRODUCTION

Tuberculosis (TB) remains a major global health problem.[1] The World Health Organization's "End Tuberculosis Strategy" calls for a 90% reduction in tuberculosis-related deaths and an 80% reduction in tuberculosis incidence by 2030, 15 years after declaration.[2,3] Tuberculous meningitis (TBM), a severe manifestation of Mycobacterium tuberculosis (MTB) infection, arises when MTB disseminates from primary pulmonary sites to the meninges, forming foci that rupture and induce inflammation in the subarachnoid space.[4] This pathological cascade, characterized by vasculitis, cranial nerve compression, and hydrocephalus, leads to ischemic damage frequently in critical brain regions such as the basal ganglia and thalamus, potentially resulting in long-term neurological and cognitive complications.[4] The inflammatory and ischemic sequelae disrupt neural

circuits, impairing domains such as memory, executive function, and cognitive speed, as observed in survivors of bacterial meningitis.[5] However, there is limited data available on cognitive studies in cases of TBM.[6,7] This study aims to provide insights into the cognitive outcomes following TBM infections from available literature.

METHOD

Literature Search and Data Sources

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] This was registered in PROSPERO (ID: 439481). In November 2022, a thorough computerized search of the literature was done by three independent reviewers to identify studies discussing the neurological outcome in meningitis tuberculosis patients. PICO-related keywords were among the search criteria. PubMed, SCOPUS, and EBSCO host databases were also searched. The titles and abstracts of all studies from the three databases that matched the keywords were separately screened according to the eligibility criteria, and duplicates were removed (Table 1). Furthermore, each study was evaluated for eligibility by three reviewers who worked independently and were blinded to each other. Disagreements amongst reviewers were settled by discussions with supervisor. Figure 1 explains the literature search flow.

Table 1. Keyword for database searches

Database	Keyword
PubMed	(("tuberculous meningitis") OR ("TB meningitis")) AND (((((neurocognitive) OR (cognitive)) OR ("neurological outcome")) OR ("neurological sequelae")) OR ("cognitive impairment"))
Scopus	(TITLE-ABS-KEY ("Tuberculous Meningitis") OR TITLE-ABS-KEY ("TB meningitis")) AND (TITLE-ABS-KEY ("neurocognitive") OR TITLE-ABS-KEY ("neurological outcome") OR TITLE-ABS-KEY ("cognitive") OR TITLE-ABS-KEY ("neurological sequelae") OR TITLE-ABS-KEY ("cognitive impairment"))
EBSCO host	("tuberculous meningitis" OR "TB meningitis") AND (neurocognitive OR cognitive OR neurological outcome OR neurological sequelae OR cognitive impairment)

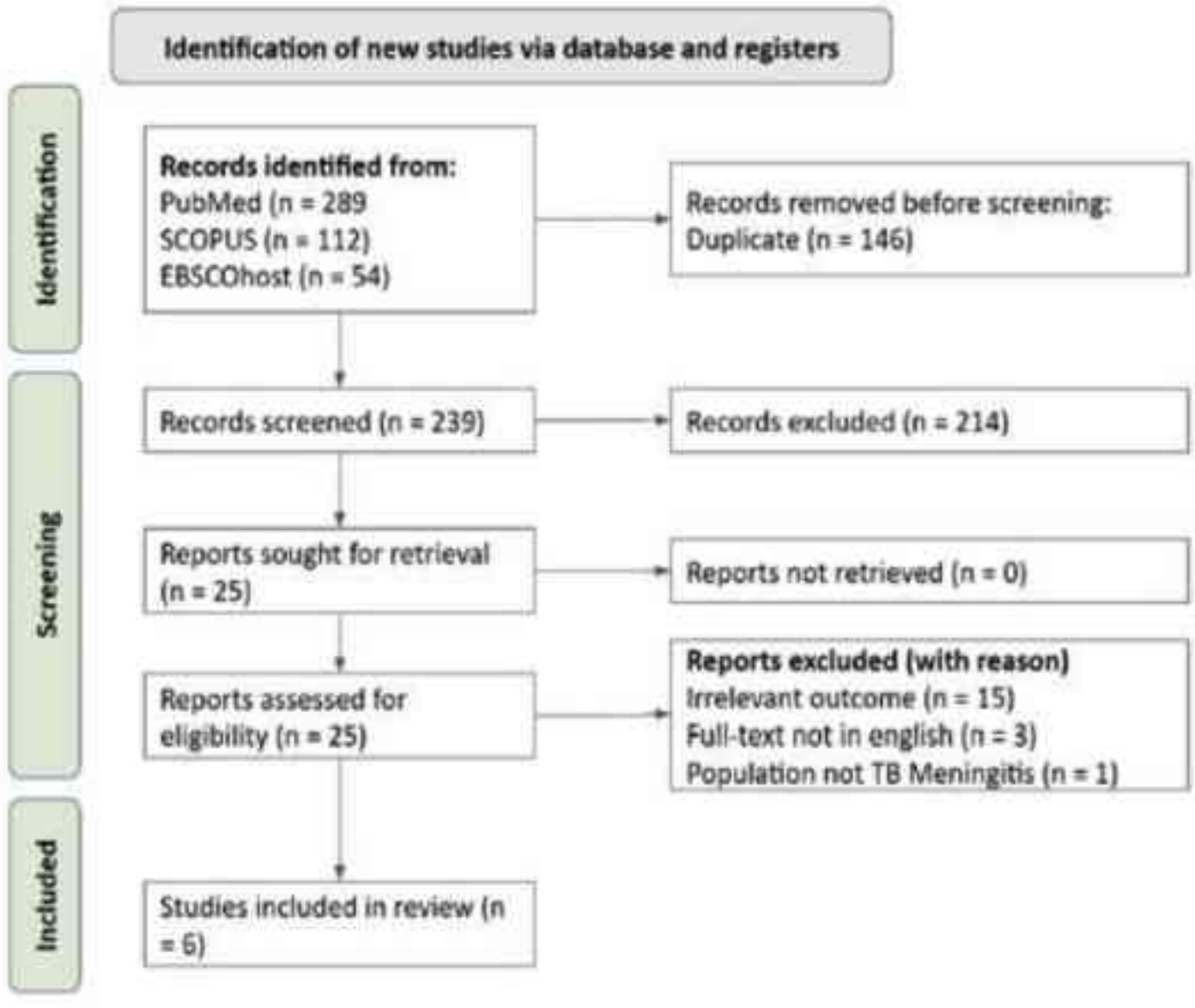

Figure 1. Literature Search Flow

Study Selection Criteria

Studies were included if (1) study design of cohort or cross-sectional studies, (2) confirmed meningitis tuberculosis patients, HIV and non-HIV patients included, and (3) reported cognitive outcome. Studies were excluded if (1) they were case series, case reports, and review article (2) unconfirmed/suspect meningitis tuberculosis, and (3) study with neurobehavioral outcomes.

Quality Assessment and Data Extraction

The risk of bias tool used in the included studies was Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool.[9] The appraisal was carried out by three investigators. All of the reviewers took the following data from each study, including (1) the author and the year of publication, (2) the study's design, (3) the sample size, (4) the characteristics of the patients who were included, and (5) the results reported. Cognitive impairment[10] refers to challenges with memory, attention, executive function, language, perceptual organization, learning processes, or reflecting global cognitive functioning deficits, and it could be measured using any tool.

RESULTS

Characteristic and Quality Assessment of Included Studies

Among the articles identified, six studies (five prospective cohorts and one cross sectionals) met inclusion criteria, reporting cognitive outcomes for 330 patients with TBM (Figure 1).[11–16] Out of 330 subjects, 105 were female. Study by Katrak et al. didn't state the number subject based on their gender. The age varied from six to 80 years. Mean duration of illness was reported from 21 days until 2.8 months.

All studies followed the patients starting from admission, three months, or more. Details of characteristic of selected studies are presented in Table 2. Four studies only included subject with HIV (-),[11,12,14,16] and two studies compared subject with HIV (+) and HIV (-).[13,15] We classified the diagnosis criteria into five forms, (a) clinical presentation of meningitis, (b) CSF analysis, (c) CSF culture for MTB, (d) CSF GeneXpert, and (e) neuroimaging.

Table 2. Characteristic of Studies Included

Author	Design study	No of Subject (n)	Mean Age	Gender		Tuberculous Meningitis (TBM)					Comorbidity	Radiological Findings	Laboratory Findings
				Male (n)	Female (n)	Diagnostic Criteria	TBM Grade	TBM Diagnosis	Duration of TBM Disease/	Regimen and Duration of TBM Treatment			
Chen HL, et al 2015 [32]	PC	17	50.76	13	4	a, c, d, e	NA	Definite (100%)	NA	Not specified	NA	**MRI:** Hydrocephalus (n = 5) Persistent basilar enhancement (n= 2) Old infarcts (n = 5) Old haemorrhage (n = 1) Peri-ventricular signal change (n = 1).	**CSF Analysis** Number of subjects with high CSF white cell counts (≥300/mm3, n = 3) Number of subjects with high CSF lactate concentrations (≥35 mg/dl, n = 8) Number of subjects with high CSF protein concentrations (≥150 g/L, n = 8).
Popoca-Rodriguez , et al 2021 [25]	CS	104	36.6	72	32	a, b, d, e	NA	Probable (70%), Definite (30%)	NA	Anti-TB treatment (2RHZE+16RH) + dexamethasone 0.3 mg/kg for first 3 weeks. Total 18 months.	NA	**MRI:** leptomeningeal enhancement (n=31) abscesses or collections (n = 38) ischemia/infarcts (n = 6); hydrocephalus (n = 5).	**CSF Analysis** HIV Positive Median glucose = 44 mg/dL Median protein = 81 mg/dL Median cell count = 37 cell/mm3 HIV Negative Median glucose = 45 mg/dL Median protein = 115 mg/dL Median cell count = 96 cell/mm3

Author	Design study	No of Subject (n)	Mean Age	Gender		Tuberculous Meningitis (TBM)					Comorbidity	Radiological Findings	Laboratory Findings
				Male (n)	Female (n)	Diagnostic Criteria	TBM Grade	TBM Diagnosis	Duration of TBM Disease/	Regimen and Duration of TBM Treatment			
Ganaraja, et al 2021 [24]	PC	60	32.2	31	29	c, d	Grade I (100%)	Probable (71.6%), Definite (28.3%)	29.9 days	Anti-TB treatment (2RHZE+9RH) + prednisolone 1 mg/kg for first 2 months. Total 12 months.	Diabetes in 5% of subjects.	**MRI:** No brain abnormality	**CSF Analysis** Mean cell count = 262.3 ± 290.7 cell/mm3 Mean lymphocyte count = 209.3 ± 62.8 cells/mm3 Mean neutrophil count = 36.7 ± 57.6 cells/mm3 Mean Protein = 192.5 ± 125.3 mg/dL Mean Glucose = 48.4 ± 34.9 mg/dL Mean TNF-α = 11.57 ± 30.35 pg/mL Mean IFN-γ = 197.02 ± 186.64 pg/mL Mean IL-6 =127.03 ± 88.71 pg/mL.
Katrak, et al 2000 [33]	PC	53	HIV Positive = 33.41 ± 8.99 HIV Negative = 33.96 ± 12.23	unspecified	a, b	Grade I (26.4%) Grade II (43.4%) Grade III (22.6%) Grade IV (7.5%)	NA	HIV Positive = 27.85 days HIV Negative = 21.89 days	Anti-TB treatment (RHZE) without duration detail	NA	NA	**CT Scan:** HIV Positive Basal exudates (n=6) Obstructive hydrocephalus (n=1) Infarcts (n=7) Granuloma (n=6) HIV Positive Basal exudates (n=18) Obstructive hydrocephalus (n=14)	**CSF Analysis** HIV Positive Mean glucose = 46 mg/dL Mean protein = 124 mg/dL Mean cell count = 146 cell/mm3 HIV Negative Median glucose = 50 mg/dL Median protein = 175 mg/dL Median cell count = 206 cell/mm3

Author	Design study	No of Subject (n)	Mean Age	Gender		Tuberculous Meningitis (TBM)					Comorbidity	Radiological Findings	Laboratory Findings
				Male (n)	Female (n)	Diagnostic Criteria	TBM Grade	TBM Diagnosis	Duration of TBM Disease/	Regimen and Duration of TBM Treatment			
												Infarcts (n=9) Granuloma (n=5)	
Ranjan, etl 2003 [12]	PC	31	35.2	18	13	a, b, e	Grade I (16.1%) Grade II (19.3%) Grade III (64.5%)	NA	2.8 Months	Anti-TB treatment (RHZE for adults/RHZS for children) without duration detail	NA	**CT Scan:** Communicating hydrocephalus (12), obstructive hydrocephalus (3), exudates (15), infarcts (10) tuberculomas (13)	NA
Kalita, et al 2007 [13]	PC	65	33.2	38	27	a, c, d, e	Grade I (21.5%), Grade II (23.0%), Grade III (55.4%)	Probable (23.0%), Definite (76.9%)	NA	Anti-TB treatment (8RHZE+4RHE+6HE) + prednisolone 1 mg/kg 2 months. Total 18 months.	NA	**CT Scan:** Communicating hydrocephalus (25), obstructive hydrocephalus (5), exudates (22), tuberculoma (20), infarction (16)	NA

Abbreviations: *PC: Prospective Cohort; CS: cross-sectional CNS: central nervous system; TB: tuberculosis; CSF: cerebrospinal fluid; R: rifampicin; H: isoniazid; Z: pyrazinamide, E: ethambutol, S: streptomycin*

Diagnosis criteria: *a. Clinical presentation of meningitis; b. CSF analysis; c. CSF culture for Mtb; d. CSF GenXpert; e. Neuroimaging*

Risk of bias analysis was performed using ROBINS-E.[9] QoA summary figures were created using Robvis visualization tool.[17] Three studies were categorized as low overall bias and other three studies had some concerns bias.

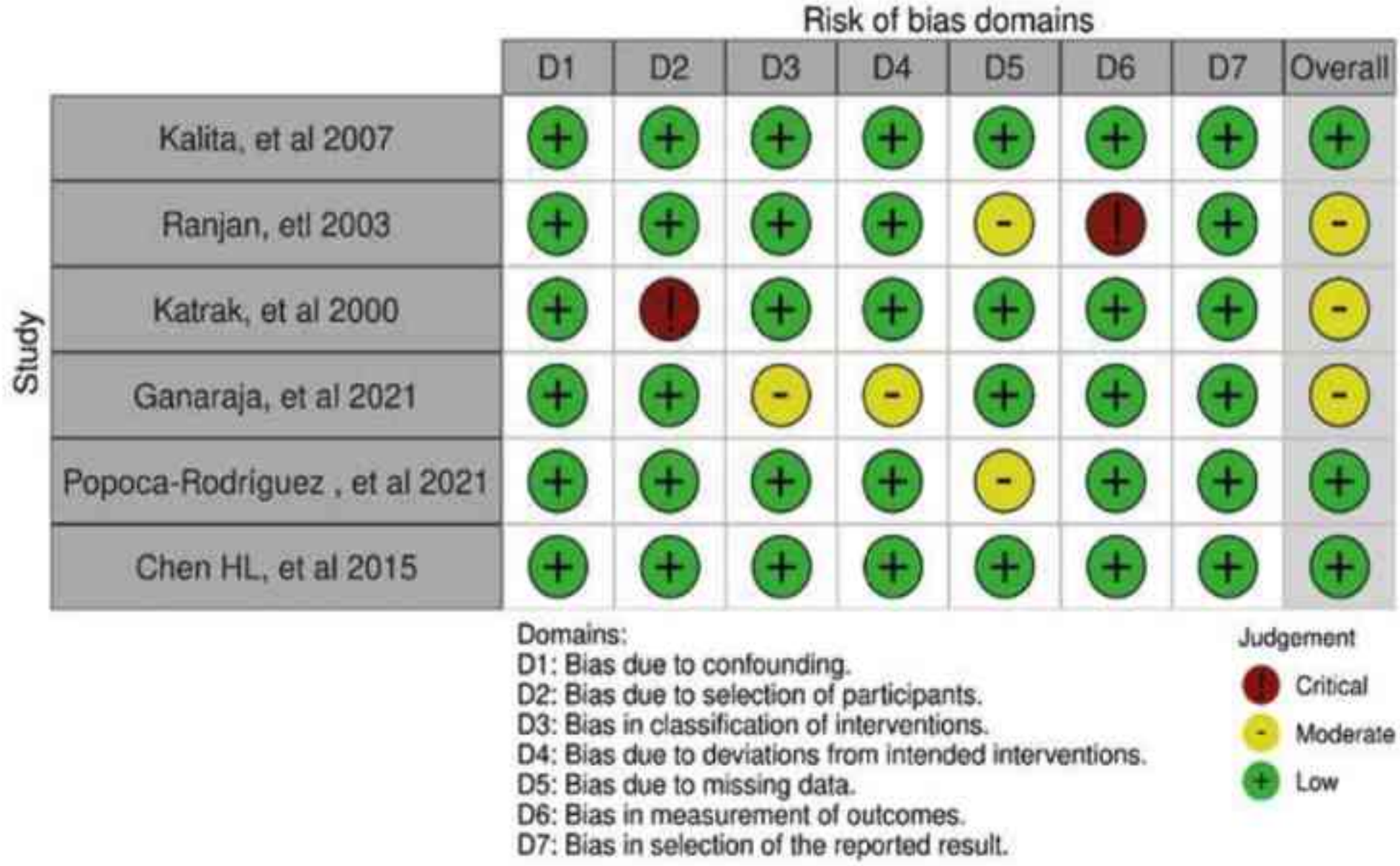

Figure 2. Risk of Bias Analysis

TBM Treatment Difference

Study by Ranjan et al. and Katrak et al. showed all their subjects received a standard antituberculosis treatment (rifampicin, isoniazid, pyrazinamide, and ethambutol; RHZE).[12,13] Same as study by Ganaraja et al. and Kalita et al., but they also added a prednisolone 1 mg/kg for 2 months along with RHZE.[11,14] Meanwhile, study by Popoca-Rodriguez et al., stated that their patients received standard RHZE treatment with pyridoxine and dexamethasone 0.3 mg/day.[15] However, Chen et al. didn't specify the TBM treatment for their subject.[16]

Cognitive Assessment Tools

Three studies used Mini-Mental State Examinations (MMSE) to assess cognitive function, while other used various tools: HIV-associated neurocognitive disorder (HAND), Montreal Cognitive Assessment (MoCA), neuropsychological (NEUROPSI), and Wechsler Adult Intelligence Scale (WAIS) (Table 3). MMSE was used in study by Ranjan et al., Katrak et al., and Kalita et al.[11-13] It consisted of 30-point scale which was validated in the local community. Katrak et al., considered MMSE scores of 19 or less as abnormal.[13] Meanwhile, in the study by Ranjan et al. and Kalita et al., they specified the cognitive impairment into some category, such as below 29 for 9 years of schooling, below 26 for 5–8 years of schooling, and below 22 for 0–4 years of schooling.[11,12] MoCA + NEUROPSI test was used in study by Popoca-Rodriguez et al.[15]

Table 3. *Cognitive Assessment of Included Studies*

Author	Cognitive assessment and results				
	Tools for Cognitive Assessment	**Percentage of cognitive impaired (Baseline)**	**Cognitive Outcome (Baseline)**	**Cognitive Outcome (Follow-up)**	**Follow-up Periods (mo)**
Chen HL, et al 2015	WAIS	NA	NA	**Mean WAIS-III Score at Chronic Stage (after treatment)** Verbal comprehension (VCI) 90.24 ± 14.71 Perceptual organization (POI) 87.53 ± 18.45 Working memory (WMI) 85.25 ± 18.48 TBM patients had worse outcomes compared to healthy controls.	41 mo
Popoca-Rodriguez , et al 2021	MoCA test; NEUROPSI tests	**Mean MoCA score** HIV positive = 23.4 ± 5.7 HIV negative = 24.1± 5.3	There is a significant difference of attention alteration between populations with HIV compared to those without HIV.	**Mean MoCA score at month-12** HIV positive = 26.6 ± 0.5 HIV negative = 24 ± 7.1	12 mo
Ganaraja, et al 2021	(i) Colour Trails Test 1 &2 - Sustained attention, (ii) Animals Naming Test - Category Fluency, (iii)Digit Span Test from WMS-IIIIND (Weschler memory scale; IIIrd edition) -Verbal Working Memory, (iv)Spatial Span Test from WMS-IIIIND - Visual Working Memory, (v) Rey's Auditory Verbal Learning Test - Verbal Learning & Memory, (vi)Complex Figure Test - Visual Learning & Memory; and (vii) Clock drawing test - Executive function	31.7% mild impairment 28.3% mild-to-moderate impairment 28.3% moderate-to-severe impairment 5% severe impairment	**Percentage of subject with aforementioned impairment:** - Auditory verbal learning test (88.3%) - Complex figure test (50%) - Spatial span test (50%) - Clock drawing test (48.3%) - Digit span test (35%) - Color trail test 1 and 2 (30% and 33.3% respectively) - Animal naming test (28.3%)	**Month 12** 58.1% mild impairment 23.3% mild-to-moderate impairment 7% moderate-to-severe impairment 2.3% sever impairment Domain: Attention, working memory, category fluency, and verbal learning.	0 and 12 months
Katrak, et al 2000	MMSE	**Cognitive impairment:** HIV Positive (n=7, 31,8%) HIV Negative (n=0, 0%)	NA	NA	0 months
Ranjan, etl 2003	MMSE	NA	NA	**Month 3** Impairment (11/22 = 50%) **Month 6** Impairment (13/24 = 54.1%)	3 and 6 months
Kalita, et al 2007	MMSE	NA	NA	**Month 12** Severe impairment (7/36 = 10,7%), Mild (29/36 = 44,6%)	12 months

Abbreviations: *MoCA: Montreal Cognitive Assessment; NEUROPSI: neuropsychological tests; WAIS: Wechsler Adult Intelligence Scale; MMSE: Mini Mental State Examinations; WMS-IIIIND: Weschler memory scale, IIIrd edition.*

**Notes: Colour Trails, Animals Naming, Digit Span (WMS-IIIIND), Spatial Span (WMS-IIIIND), Rey's Auditory Verbal Learning, Complex Figure, Clock drawin*

Study by Chen et al. used the WAIS neuropsychological (NP) test.[16] In this study, they used the combined perceptual organisation (POI), verbal comprehension (VCI), working memory (WMI), and processing speed index (PSI) scores from the Chinese version of the WAIS-III, which is based on the full-scale intelligence quotient measure (FSIQ). All the participants performed the subtests, which collectively make up the POI, VCI, and WMI scores separately. These subtests include the block design, image completion, matrix reasoning, vocabulary, similarities, information, digit span, arithmetic, and letter-number sequence subtests.[16]

Study by Ganaraja et al. used eight neuropsychological tests at the second week of diagnosis.[14] The same assessment was repeated after 1 year of follow-up. The test consisted of (1) color trails tests 1 and 2—sustained attention; (2) animals naming test—category fluency; (3) digit span test from Weschler memory scale; IIIrd edition (WMS-IIIIND)—verbal working memory; (4) spatial span test from WMS-IIIIND—visual working memory; (5) Rey's auditory verbal learning test—verbal learning and memory; (6) complex figure test—visual learning and memory; (7) Clock drawing test—executive function.[14]

Characteristic of Cognitive Impairment

All studies reported cognitive impairment in TB meningitis. Study by Ranjan et al, showed the result of MMSE assessment. At three months after diagnosis, the result showed mean score of 23 and 11/22 subjects had cognitive impairment. after 6 months, the mean of MMSE score increased to 24 and 13/24 subjects had cognitive impairment.[12] In the study by Katrak et al., impaired cognition was observed in only 7/22 HIV positive patients (31.8%). Five patients improved after starting anti-tuberculous medication.[13] Study by Kalita et al., showed cognitive impairment appeared more in TBM patients with neurological symptom such as focal motor deficit or cranial nerve palsy. The MMSE score ranged from 6 to 28 (mean 22). The MMSE score was less than 19 in seven individuals, 19-24 in six, and mild cognitive impairment in the other patients.[11]

Study by Chen et al., showed that compared to the controls (healthy subjects), the TBM patients notably underperformed in the WAIS's digit symbol, similarities, block design, matrix reasoning, and letter-number sequencing subtests ($p<0.05$). The verbal comprehension (VCI), perceptual organisation (POI), and working memory (WMI) scores were worse in the TBM patients.[16]

Study by Ganaraja et al. found that TBM patients who were HIV-negative exhibited significant impairments in several neuropsychological tests, particularly auditory verbal learning (90%), complex figure test (50%), and spatial span test (50%).[14] Cognitive impairments were categorized as "mild" in 31.7%, "mild-to-moderate" in 28.3%, "moderate-to-severe" in 28.3%, and "severe" in 5% of patients. After one year, 43 participants underwent follow-up neuropsychological evaluations, revealing that 58.1% showed impairment in one or two tests, while 32.5% were impaired in three or more tests. Only 9.3% had normal evaluations, and 72.1% demonstrated overall improvement, while 18.6% remained unchanged and 9.3% worsened. Tests such as the animal naming test ($p = 0.008$), clock drawing test ($p = 0.014$), color trail test 1 ($p = 0.001$), spatial span test ($p = 0.021$), and digit span test ($p = 0.034$) showed significant improvement in suspected TBM cases. Visual learning and memory also improved significantly ($p = 0.008$), whereas verbal learning remained largely unchanged. These findings highlight the cognitive challenges and recovery patterns in TBM patients over time.[14]

Meanwhile, study Popoca-Rodriguez et al., discovered significant short-, mid-, and long-term memory loss, as well as loss of thinking ability, judgement, and executive skills and verbal fluency alteration, and even mood alterations, with mild depression predominating according to evaluation with the MoCA and NEUROPSI tests. MoCA testing was performed during hospital admission, during outpatient follow-up, 12 months after discharge. Patients with HIV/AIDS coinfection had a mean score of 23.4 ± 5.7 at hospital admission; on follow-up evaluation before 12 months, it was 24.3 ± 4.4, and after 12 months, it was 26.6 ± 0.5; patients without HIV coinfection had a score of 24.1 ± 5.3 at admission, 23.7 ± 5.6 on follow-up before 12 months, and 24 ± 7.1 after 1-year follow-up.[15] Table 4 focuses on HIV-positive patients.

Table 4. *Characteristic of Studies with HIV-positive Patients*

Author	*HIV Infection Status*		*HIV Positive Population*		
	HIV Positive (n)	*HIV Negative (n)*	*Duration of HIV infection*	*HAART Therapy*	*CD4 Count*
Popoca-Rodríguez , et al 2021	*39*	*65*	*NA*	*NA*	***Median CD4+ T-lymphocyte*** *At HIV diagnosis = 111/mm3 (IQR = 198),* *At TB diagnosis = 126/mm3 (IQR = 208).*
Katrak, et al 2000	*22*	*31*	*NA*	*No treatment*	*NA*

DISCUSSION

Study has identified a link between CNS infections occurring in mid-life and the onset of cognitive impairments later in life, even after the infection has resolved.[6,18] CNS infections have also been associated with impaired intellectual development and an increased risk of mental disorders in the future.[19] Persistent cognitive deficits across various domains, including memory, orientation, comprehension, learning, and language, have been documented as a result of CNS infections.[18-20]

Cognitive functions that are usually affected are attention, executive function, short term memory and learning memory. Learning memory is the most impaired in TBM, in contrast to bacterial meningitis which is very short-term memory and working memory.[14,21] This suggests that in TBM after the acute phase, the frontal lobe inflammation improves quicker than temporal function.[14] This is explained by impaired cognitive tests with normal MRI results.[22,23] The cause of cognitive abnormalities can be mediated by various mechanisms, such as inflammation,[24] ischemia due to arteritis[22] or chronically increased intracranial pressure.[25] In people with normal MRI, it can be caused by microvascular ischemia.[22]

Cognitive impairment are more common in the HIV positive group with TB.[13,26] The majority of adults with HIV positive TB have a mean age in the 4th decade, the majority are female, and a low baseline CD4.[27,28] HIV positive patients who have cognitive changes need to be suspected of having TBM.[28,29] With low CD4 and immune response, tuberculomas do not form, this causes the clinical presentation to be subtle in the form of cognitive changes.[13,28,30]

A clinical trial sub-study conducted in Uganda revealed that among TBM patients with HIV, the primary cognitive domains affected include motor abilities, executive function, information processing speed, verbal learning, and memory.[31] Cognitive deficits can be caused by TBM or HAND.[32] It is challenging to differentiate between the two, but the presence of active TBM, absence of cerebral atrophy, and improvement with anti-TB drugs (RHZE), point to the etiology towards TB.[13,28]

Management of TBM patients also influences neurological and cognitive outcomes. Withdrawal from rifampicin and isoniazid will have an impact on poor cognitive outcomes, which are usually caused by hepatotoxicity.[12,33] History of the BCG vaccine gives different results in children with TBM. Some studies conclude there is a decrease in neurological effects[34,35] and study in Turkey showed results that there was no protection.[36] Corticosteroids can suppress inflammation to reduce the impact on TBM,[37] but its use does not have a significant impact on reducing deterioration of the brain tissue damage.[12]

There are several limitations to this review study. The first is the use of diverse cognitive assessment tools, which hinders focused depiction of the specific cognitive domains affected. Additionally, the inclusion of paediatric populations in this review limits the generalizability of the findings to the entire population of TB meningitis patients. To obtain a more comprehensive understanding of cognitive impairment in TB meningitis patients post-treatment, it is recommended to use standardized and uniform cognitive assessment tools that can identify specific domains affected.[6] rather than merely indicating the presence or absence of cognitive impairment.

CONCLUSION

Cognitive function assessment tools in TBM patients are diverse, with most studies using the MMSE. The cognitive domains that were reported to be the most affected were working memory and language, and when compared to TBM patients with HIV-positive there was impaired attentional domain. Improvement in cognitive function on average is noticed 12 months post therapy.

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