CASE SERIES

Mild Cognitive Impairment in *Tuberculous meningoencephalitis* : A Case Series

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ABSTRACT

Introduction: Tuberculous meningitis is a form of extrapulmonary tuberculosis (TB) characterized by subacute or chronic inflammation of the meninges due to invasion of the subarachnoid space by *Mycobacterium tuberculosis* bacilli. Tuberculous meningitis affects about 100,000 people annually worldwide. Cognitive impairment can occur in tuberculous meningitis. Cognitive impairment has been reported as a common complication of adult tuberculous meningitis, but few studies have systematically assessed the frequency and nature of the disorder. **Case series:** There were two cases regarding mild cognitive impairment caused by tuberculous meningoencephalitis. The first case occurred in a woman, 40 years old, who complained that she often forgot and often daydreamed. The second case, a woman, 25 years old, who complained that she sometimes forgot and find it difficult to tell the time and numbers. In both cases, a cognitive examination was carried out, and the results of the cognitive examination gave results of cognitive impairment caused by inflammation caused by TB. **Conclusion:** Both patients in this case experienced mild cognitive impairment caused by tuberculous meningitis. Therefore, prompt diagnosis and therapy are necessary to increase quality of life, reduce high mortality and severe sequelae. WHO recommends between 9-12 months of treatment is sufficient to successfully treat tuberculous meningitis.
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Keywords: Mild cognitive impairment, Meningoencephalitis, Tuberculosis, Meningitis, Neurocognitive dysfunction

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INTRODUCTION

A type of extrapulmonary TB known as tuberculous meningitis is characterized by subacute or persistent meningeal inflammation brought on by *Mycobacterium tuberculosis* invasion of the subarachnoid space. Despite having similar treatments, tuberculous meningitis is not the same as central nervous system (CNS) tuberculosis, which includes tuberculoma, spinal tuberculosis, and cerebral abscess. The majority of cases of tuberculous meningitis occur in young children and HIV-positive individuals. (1,2)

Nearly 1.5 million people died from TB, the most common infectious agent that causes death (Mycobacterium tuberculosis), in 2018. Extrapulmonary TB is a type of tuberculosis that primarily affects the lungs but can also spread to other parts of the body. Tuberculous meningitis, which arises from *Mycobacterium tuberculosis* spreading into the meninges and cerebrospinal fluid, accounts for about 5% of all extrapulmonary tuberculosis cases. The percentage of all TB cases that are meningitis tuberculosis is unclear because results varied depending on the local prevalence of TB; in settings with high TB burden, a higher proportion (roughly 10%) was suggested than in settings with low prevalence (approximately 1%). Annually, at least 100,000 cases of tuberculous meningitis are thought to be diagnosed. As the most severe form of TB, tuberculous meningitis has a high rate of morbidity and mortality. An estimated 50% of patients either die from the disease or experience neurological complications as a result of it. (3,4)

Globally, meningitis tuberculosis affects roughly 100,000 people each year. Although only four studies have documented this fact, this case can lead to cognitive impairment. Two of the studies assessed cognition using quick screening tests, and one study only used clinical history to gather data on cognition. (5)

There are few data on neuropsychological profiles and cognitive studies in meningitis tuberculosis. When cytokines penetrate the blood-brain barrier, a severe inflammatory reaction results in cerebral oedema and thick exudate, both of which are crucial

for the emergence of complications. Nevertheless, no prior research has examined the connection between cytokines and cognitive features. (6)

A respiratory infection is the first step in the development of meningits tuberculosis, which then spreads hematogenously to the central nervous system (CNS). One of two processes can lead to hematogenous spread to other organ systems, including the central nervous system (CNS): (i) *Mycobacterium tuberculosis* can cause brief bacteraemia if it invades local lymph nodes during primary tuberculosis infection before granulomas form; or (ii) latent infection can progress to active tuberculosis disease due to a delayed or weakened immune response, which can damage lung tissue and especially affect the elderly, immunocompromised, or very young. Tuberculous lesions, are first developed in the brain by TB germs in the meninges, subpial, or subependymal surfaces. (7-8).

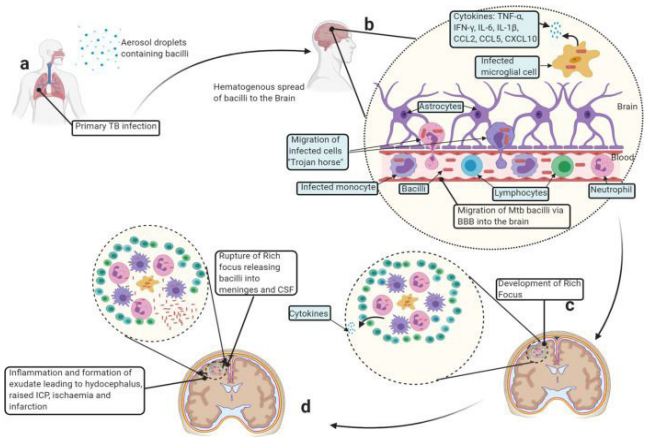

Fig. 1: Pathogenesis of tuberculosis meningitis.(3)

This improves our understanding of whether cognitive impairment in tuberculous meningitis leads to long-term disability. Specifically, we can determine whether cognitive impairment is focal and brought on by distinct structural abnormalities in the brain (such as a stroke or tuberculosis) and/or whether there are clinical characteristics that are consistent with diffuse subcortical involvement or cortical processes. Most importantly, knowing how cognitive and functional impairment in tuberculous meningitis affects treatment adherence will enhance long-term care for patients, including the provision of resources for recovery from the illness (5).

CASE SERIES

Clinical case 1

Woman, 40 years old, with complaints of forgetfulness and frequent daydreaming. However, the patient still remembers the patient's family name, neighbours, and address, and can still carry out daily activities. The patient also complained of intermittent headaches, vomiting, fever seven days before entering the hospital, weight loss for one month, prolonged cough, and night sweats one week before entering the hospital. The patient has a history of being diagnosed with meningoencephalitis TB in November 2021 and the patient is still taking anti tuberculosis drug for seven months.

Physical examination performed from head to extremities was within normal limits. Neurological examination showed N.II visual acuity ODS > 2/60. On special examination, Clock Drawing Test (CDT) score of 4; Ascertain Dementia 8 Indonesia (AD8-INA) score of 2; and Mini-Mental State Examination (MMSE) score of 21. Based on a Magnetic Resonance Imaging (MRI) examination of the head with contrast on February 18, 2022, an increasing process of CNS tuberculosis with Fazekas grade I degeneration was found.

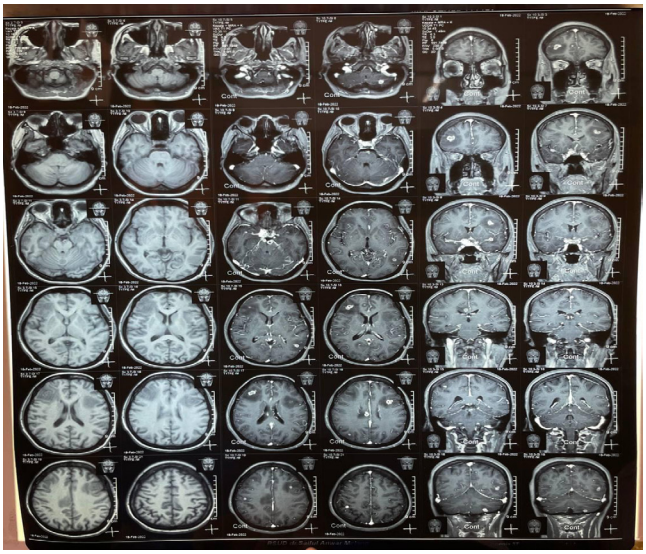

Fig. 2: MRI head results with contrast.

Based on a Magnetic Resonance Angiography (MRA) examination of the head with contrast on February 21

2022, it was found that the CNS tuberculosis had an increasing process, with Fazekas grade I degeneration, and hypoplasia of the right anterior cerebral segment A1 artery.

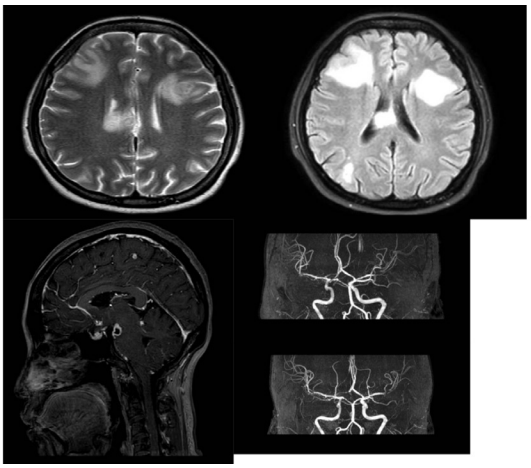

Fig. 3: Head MRA results.

Based on the history, physical examination, and supporting examinations, the patient was diagnosed with Mild Cognitive Impairment due to Meningoencephalitis Tuberculosis, and the patient was given therapy of Anti Tuberculosis Drug 2 FDC 1x4 tablets, Omeprazole 2x20mg, Paracetamol 3x500mg for headaches, Amlodipine 1x5mg, B12 2x50mcg.

Clinical case 2

Woman, 25 years old, with complaints of sometimes forgetting to put things away, difficulty managing finances, difficulty knowing time and numbers. The patient still remembers the names of people and places. There is no disturbance in daily activities. The patient has a history of symptomatic epilepsy, miliary tuberculosis since October 2022, and tuberculous encephalitis since October 24, 2022. The patient's tuberculosis treatment has been running for eight months. The patient has been seizure-free for 8 months.

Physical examination showed normal findings. On neurological examination, there was a slight paresis of the right facial nerve, Upper Motor Neuron (UMN) type, and was in the process of improvement. On special examination, MMSE score of 24 (disturbance in domain orientation, attention/calculation, and language); CDT score of 3 (disturbed); AD8-INA score of 4 (cognitive disorder); Montreal Cognitive Assessment Indonesian Version (MOCA-INA) score of 21 (mild cognitive impairment); Activities of Daily Living (ADL) score of 0; Instrumental Activities of Daily Living (IADL) score of 0; Attention Functional Dementia Scale (FDS) score of 5 (normal), Blessed Dementia Scale (BDS) score of 4 (disturbed); Visuoconstruction Constructional praxis score of 9 (normal) Recall Constitutional Praxis (CP) score of 8 (normal); Executive Function Verbal Fluency Test score of 15 (62 seconds) (normal) Trail Making Test A score of 24 (163 seconds) (normal) Trail Making Test B score of 7 (101 seconds) (interrupted); Memory task Boston Naming Test (BNT) score of 13 (interrupted) Word List Memory : 23 (normal) Word List Recall : 6 (normal) Word List Recognition : 6.0 (interrupted); Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Score = VF 15 + BNT 13 + WLM 23 + CP 9 + WLRecall 6 + WLRecognition 6 = 72 (Mild Cognitive Impairment).

The EEG examination showed a disturbance of brain function in the right mid temporal which could lead to a structural lesion. Impaired brain function can be potentially epileptogenic and mild diffuse encephalopathy.

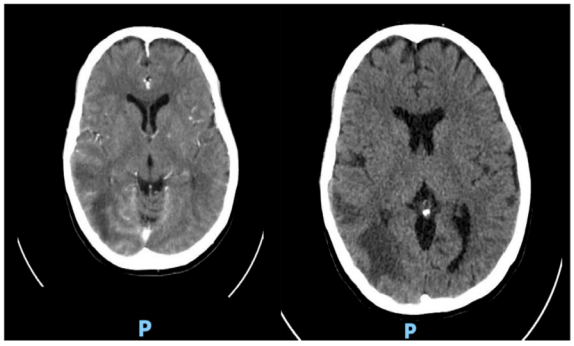

Fig. 4: Head CT scan results with contrast

Based on a head CT scan with contrast, the results showed pathological leptomeningeal amplification in the right occipital region, suspected TB meningoencephalitis; multiple lesions in the right parieto-occipital lobe, suspected tuberculous granuloma; cerebral oedema; bilateral maxillary sinusitis.

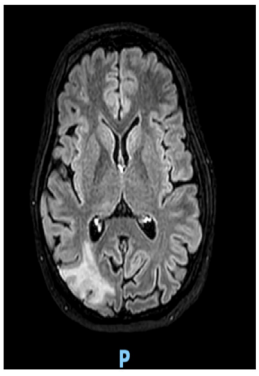

Fig. 5: MRI head results with contrast

Based on an MRI examination of the head with contrast, the results showed pathological leptomeningeal enlargement of the right occipital region accompanied by tuberculoma nodules in the right occipital lobe supporting TB meningoencephalitis ⇒ reduced number of nodules and vasogenic oedema, bilateral ethmoidal sinusitis, right maxillary, and right looping anterior inferior cerebellar artery (AICA) grade II.

Based on the results of anamnesis, physical examination, neurological examination, and supporting examinations, the patient was diagnosed with Mild Cognitive Impairment Related to Encephalitis TB with Epilepsy Symptomatic on Therapy and Encephalitis TB with Tuberculoma + Miliary TB on Advanced Phase for Anti Tuberculosis Drug. The patient was treated with Levetiracetam 2x250 mg, Folic acid 1x1 mg, Vit B6 1x25 mg, Anti Tuberculosis Drugs 2 Fixed Dose Therapy 1x3 tab for eight months.

DISCUSSION

Tuberculous meningitis is extrapulmonary tuberculosis caused by inflammation of the meninges by Mycobacterium tuberculosis. TB germs first enter through inhalation droplets that infect alveolar macrophages. The primary infection is localized to the lungs with spreads to the lymph nodes (9).

Based on the two cases being discussed, each patient was preceded by pulmonary TB. In the first patient he was undergoing TB treatment which had lasted 7 months, and in the second case, the patient had been undergoing TB treatment for 8 months.

Rich foci are subependymal clusters of *Mycobacterium tuberculosis* that form on the meninges in tuberculous meningitis. These foci have the potential to burst into the subarachnoid space, which would set off a severe inflammatory reaction and result in meningitis symptoms. Nerve palsies may result from the exudate this reaction produces encasing the cranial nerves. This may have an impact on blood vessels, leading to vasculitis, or obstruct the flow of CSF, resulting in hydrocephalus. When patients recover from tuberculous meningitis, this immune response may result in chronic after effects and complications related to the disease. (3,9).

Atypical symptoms include dementia that progresses gradually over months, personality changes, memory impairments, social disengagement, progressive meningitis syndrome suggestive of pyogenic meningitis, and loss of libido. In addition, patients may occasionally exhibit encephalitis symptoms, such as seizures, fainting, and coma, without clearly visible meningitis symptoms. (9,10).

Extension of the exudate causes (i) perineuritis, which causes cranial nerve palsies; (ii) obliterative vasculitis of proliferating small vessels, which results in the development of focal and diffuse ischemic brain changes; and (iii) direct parenchymal involvement in severe cases (3).

The acute condition is characterized by personality changes, memory deficits, social disengagement, and impaired executive functioning. It may manifest over years as a slowly progressing dementia, possibly resembling Alzheimer's. Alternatively, instead of meningitis, the patient might exhibit symptoms of encephalitis. Seizures and coma are two of the signs and symptoms of encephalitis (5).

Based on the two cases discussed in this case report, the first patient complained of intermittent headaches, vomiting, fever, coughing, weight loss, and night sweats. On physical examination, left and right vision was >2/60. In the second case, the patient had a facial nerve paresis of the UMN type and was in the process of being repaired. In addition, the patient also had a history of seizures (10).

This complaint matches the clinical picture of meningitis tuberculosis, which includes headache, stiff neck, fever, vomiting, and , nausea, similar to the clinical picture of bacterial meningitis in general. Additionally common are cranial nerve palsies, which primarily affect cranial nerve VI, which controls lateral eye movement, and cranial nerve II, which affects vision. Lastly, the patient may deteriorate into a coma, have seizures, and potentially become paralyzed as the disease advances quickly in the paralytic phase.

Several tests, such as MMSE, Montreal Cognitive Assessment/MoCA, FCSRT/Free and Cued Selective Reminding Test, Boston Naming Test, California Verbal Learning Test, and have been proposed for MCI screening. However, there are no accepted specific tests and recommended cutoff scores for the diagnosis of MCI. Several content tests are recommended because there are complications that cause mild cognitive impairment in tuberculous meningitis (11,12).

Based on the two cases being discussed, both patients complained of disturbances in the cognitive system which includes memory and recognition of clocks and numbers. In both cases, a cognitive examination was carried out, and the results of the cognitive examination gave results of cognitive impairment caused by inflammation caused by TB.

Patients with meningitis tuberculosis may exhibit hydrocephalus, tuberculoma, prior infarction, and basal meningeal enhancement on computed tomography (CT) scans. These characteristics strongly suggest adult tuberculous meningitis. When assessing brainstem disease, magnetic resonance imaging (MRI) is particularly useful for identifying the neuroradiological characteristics of tuberculous meningitis. MRI can be used to differentiate between granulomas. The clinical progression and maturation of the disease process determine how tuberculoma appears on MRI. Compared to tuberculomas, tuberculous abscesses are typically much larger, solitary, thin-walled, and frequently multiloculated, with a diameter of more than 3 cm. The preferred method for assessing vascular disease linked to tuberculous meningitis is magnetic resonance imaging

(MRI). The early infarction and encephalitic border zones, which are recognized as cytotoxic edema, are more visible on diffusion-weighted imaging (13).

In both cases, imaging examinations were performed and provided a picture consistent with the description of TB meningitis. In the first case, CNS tuberculosis results showed an increasing process and Fazekas grade I degeneration, and an MRA examination gave the result of hypoplasia of the right anterior cerebral segment A1 artery. In the second case, CT scan results showed pathological leptomeningeal amplification in the right occipital region, suspected TB meningoencephalitis; multiple lesions in the right parieto-occipital lobe, suspected tuberculous granuloma; cerebral oedema; bilateral maxillary sinusitis and MRI results show pathological leptomeningeal enlargement of the right occipital region accompanied by tuberculoma nodules in the right occipital lobe supporting TB meningoencephalitis, showing reduced number of nodules and vasogenic oedema, bilateral ethmoidal sinusitis, right maxillary, and AICA looping right grade II.

The World Health Organization (WHO) and national guidelines for the treatment of tuberculous meningitis recommend long-term treatment of tuberculous meningitis using a standard four-drug oral regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol) used to treat pulmonary tuberculosis. However, the recommended minimum duration of treatment varies widely from 6 to 24 months (14,15).

In both cases, the first patient was on TB treatment for 7 months and the second patient was on 8 months. In addition, the two patients also received therapy for cognitive complaints, namely vitamin B and piracetam.

CONCLUSION

Tuberculous meningitis is a type of extrapulmonary tuberculosis (TB) which is a serious case, although it is the rarest type. Tuberculous meningitis is associated with high mortality and morbidity. The inflammatory reaction induced by tuberculous meningitis is associated with several complications, including cerebrovascular disease, cranial nerve palsies, hydrocephalus, infarction, and cognitive impairment. As in the two cases discussed, both patients experienced mild cognitive impairment caused by tuberculous meningitis. Therefore, prompt diagnosis and therapy are necessary to reduce the high mortality and severe sequelae associated with this disease. Antituberculous meningitis drugs were standardized in all centers, but the total length of treatment ranged from 6 to 12 months. WHO recommends between 9-12 months of treatment is sufficient to successfully treat tuberculous meningitis.

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