CASE REPORT

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Tuberculous meningitis and decision to initiate antituberculosis drug even without bacteriological confirmation: Case reports

Jumasri Tandi Rapang[1*], I Wayan Aryanta Putra[1], William Mallisa Rantemarampa[1], Dini Heryani[2], Grace E.P.M. Sianturi[2], Arie Ibrahim[2]

[1]General Practitioner, Faculty of Medicine, Universitas Mulawarman, Samarinda, Indonesia;
[2]Neurosurgeon, Department of Neurosurgery, Faculty of Medicine, Universitas Mulawarman, Samarinda, Indonesia.

*Corresponding author:
Jumasri Tandi Rapang;
General Practitioner, Faculty of Medicine, Universitas Mulawarman, Samarinda, Indonesia;
jumasritandirapang@gmail.com

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ABSTRACT

Introduction: Diagnosis and management of tuberculous meningitis remain challenging as it is difficult to find the causative agent due to the low sensitivity and delays of the current microbiological techniques. Decisions about when to start antituberculosis therapy remain controversial and often late. The disease commonly presents with nonspecific symptoms at early stages. Consequently, it is recognized only after inflammation at the base of the brain has caused obstructive hydrocephalus, cranial nerve involvement, or vasculitis leading to infarction. When these occur, it is linked to an unfavorable outcome and even death. This study aimed to report case reports of definite and probable tuberculous meningitis and to discuss the need to start an antituberculosis drug.

Case presentation: Description of three case reports and explanation of the literature review. The patient of 11-month-old, 7-month-old, and 5-year-old male infant, presented with a progressive altered level of consciousness, focal to generalized tonic-clonic convulsion, prolonged fever, and history of chronic productive cough. The electrolyte tests all showed hyponatremia. Cerebrospinal fluid (CSF) analysis from the ventricle and lumbar puncture appeared clear, with pleocytosis with mononuclear predominance, raised protein, and reduced glucose. The tuberculosis test using several methods was negative, except for one patient with military tuberculosis and very low MTB detected in cerebrospinal fluid gene X-pert MTB/RIF testing. Head computed tomography (CT) scans with and without contrast showed hydrocephalus, basal meningeal enhancement, and hypodensity in the thalamic region. Patients were evaluated using Lancet criteria which resulted consecutively of two probable tuberculosis and one definite tuberculosis. The first patient was not treated with antituberculosis, the second and third were treated with antituberculosis, but only the third patient survived with a favorable outcome.

Conclusions: The decision to start antituberculosis drug should be promptly initiated in any patient with clinical and CSF findings strongly suggestive of tuberculous meningitis without waiting for bacteriological confirmation, especially in the presence of hyponatremia, hydrocephalus, and abnormal head CT scan consistent with tuberculous meningitis.

Keywords: antituberculosis drug, hydrocephalus, thalamic infarct, tuberculous meningitis.
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INTRODUCTION

Tuberculosis meningitis (TBM) is a life-threatening form of central nervous system (CNS) infection caused by *Mycobacterium tuberculosis* (MTB), or rarely, *Mycobacterium bovis*.[1-3] It is a medical emergency associated with high rates of mortality and disability.[4] According to World Health Organization (WHO), up to 15% of childhood tuberculosis (TB) may present as TBM, and the risk of death among pediatrics aged 0 – 14 years with TBM was estimated at 19.3%. The risk of neurological sequelae among TBM survivors was estimated at 36.7%.[1] More than 96% of all TB deaths occurred in children not receiving TB treatment.[5] TBM is associated with higher rates of mortality and severe morbidity.[6]

The diagnosis of TBM remains difficult as its presentation is non-specific.[7] To establish a diagnosis of TB, it is vital to identify the causative agent of the disease.[8] Bacteriological confirmation of diagnosis is ideal but is often difficult because of its paucibacillary nature as well as the decreased sensitivity and specificity of diagnostic tests.[6] Treatment is most effective when started in the early stages of the disease, but diagnosis confirmation is very difficult and delays in therapy are associated with death.[5] In a patient with compatible clinical features, the combination of meningeal enhancement and any degree of hydrocephalus is strongly suggestive of TBM. Vasculitis leading to infarcts in the basal ganglia occurs commonly and is a major determinant of morbidity and mortality.[5] This case reports focuses on the diagnosis difficulty and decision to initiate antituberculosis drug even without bacteriological TB confirmation.

CASE PRESENTATION

Case 1

An 11-month-old male infant presented with a subacute progressive decreased level of consciousness, new onset of generalized tonic-clonic convulsion, prolonged fever, increased physiologic reflexes, positive pathological reflex, and a history of chronic productive cough. The laboratory test was anemic and hyponatremia. Cerebrospinal fluid (CSF) analysis taken from lumbar puncture (LP) appeared xanthochromic, pleocytosis with mononuclear predominance, raised protein, and reduced glucose. The TB test using several methods was negative. The bacterial culture was negative. Non-contrast head computed tomography (CT) scan showed communicating hydrocephalus with hypodensity in the bilateral thalamic region (Figure 1). The patient was pronounced dead after 28 days of hospitalization.

Case 2

A 7-month-old male infant presented to the emergency department (ED) with a decreased level of consciousness, a history of generalized convulsion with status epilepticus, prolonged fever, and chronic productive cough. The laboratory test was hyponatremia. Head CT scan with contrast showed communicating hydrocephalus, pre-contrast basal hyperdensity, and bilateral hypodensity in basal ganglia and internal capsule (Figure 2). Patient was treated surgically for hydrocephalus with ventriculoperitoneal shunt (VPS) procedure. Analysis of CSF taken from the ventricle revealed pleocytosis with mononuclear predominance, raised protein, and reduced glucose. The bacterial culture was negative. LP was also performed, which resulted in a negative for Gene X-pert MTB-RIF Assay. The patient was then treated with the antituberculosis drug on the 5th day of hospitalization. The patient was pronounced dead on day 13th of hospitalization due to sepsis and respiratory failure.

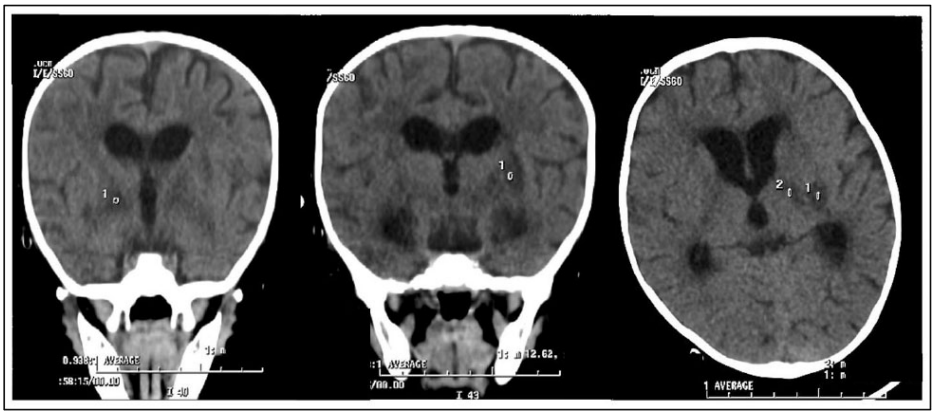

Figure 1. Non-contrasted head computed tomography scan in coronal (left, middle) and axial (right) plane showed hydrocephalus and bilateral infarction seen as hypodensity in the thalamic region.

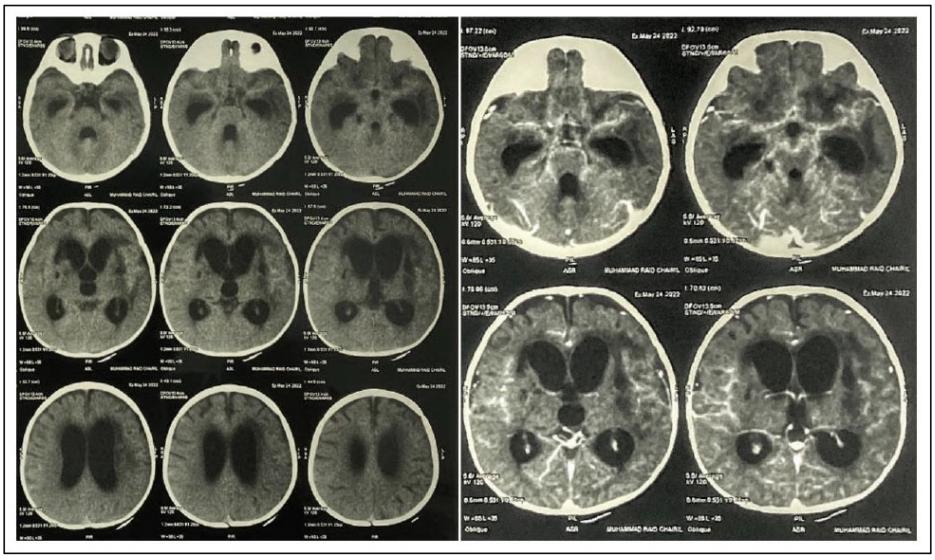

Figure 2. Head computed tomography scan in the axial section showed communicating hydrocephalus, pre-contrast basal hyperdensity, and bilateral infarction in basal ganglia and internal capsule (left). The head computed tomography scan with contrast in the axial section showed basal meningeal enhancement (right).

Case 3

A 5-year-old male infant with miliary TB on antituberculosis treatment was referred to the ED with a history of generalized tonic-clonic convulsion. The patient was fully conscious on admission. A new onset acute focal seizure occurred two weeks prior, accompanied by two weeks of prolonged fever, diarrhea, and chronic productive cough. The laboratory test on admission was hyponatremia with a natrium of 124 mmol/dL. CSF analysis a few days later appeared clear, pleocytosis with mononuclear predominance, increased protein, and decreased glucose. Gene Xpert MTB-RIF Assay test for CSF analysis was negative. Head CT scan with contrast showed non-communicating hydrocephalus with meningeal enhancement in suprasellar and sylvian cistern, right basal ganglia, and thalamic infarction (Figure 3). The patient underwent a VPS procedure, including repeated Gene Xpert test for CSF taken from the ventricle, with MTB detected as very low. The patient was discharged after the 16th day of hospitalization, fully consciousness, and no neurological deficit was found.

DISCUSSION

Central nervous system TB appears in three clinical forms which are TBM, intracranial tuberculoma, and spinal tuberculous arachnoiditis.[9] TBM, a non-suppurative inflammation of the meninges,[2,9] is the most common presentation of CNS TB and the most severe life-threatening form

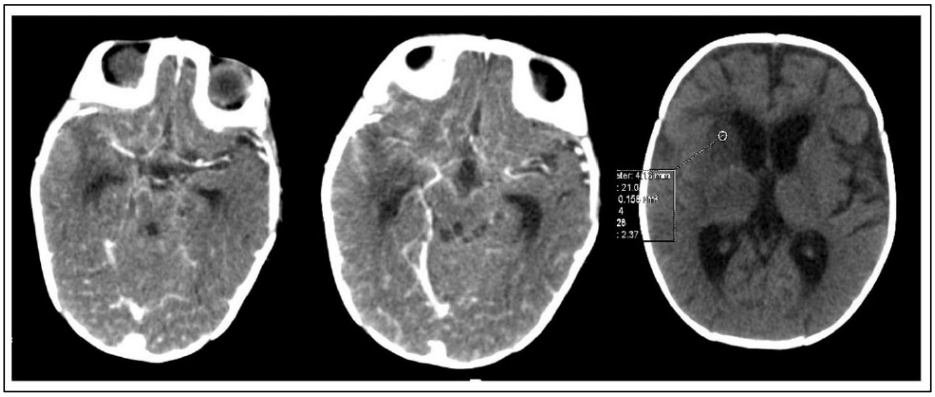

Figure 3. Head computed tomography scan with contrast in the axial plane showed basal meningeal enhancement (left, middle), and head computed tomography scan without contrast in the axial plane showed unilateral hypodensity in the right thalamus and basal ganglia (right) and hydrocephalus.

of TB in infants.[2,9,10] TBM often occurs in younger children and is more likely to present with miliary TB or to have Human Immunodeficiency Virus (HIV) co-infection.

Diagnosis of meningitis in general requires a high index of suspicion, as the typical symptoms of headache and fever are not pathognomonic.[2] Like the meningitis of other etiology, the initial symptoms of TBM are also non-specific.[11,12] Patients typically present with fever, headache, neck stiffness, malaise, irritability, confusion, and vomiting, especially in the early stages,[2,12,13] Lethargy, cough, weight loss, poor weight gain in children, and night sweats are systemic signs of TB infection, however, they are also non-specific. Many patients present with advanced severity of disease and neurological symptoms such as convulsions, altered mental state, cranial nerve palsies, or limb paresis.[12] TBM tends to occur as subacute or chronic meningitis compared to bacterial meningitis, usually within several weeks to months, with an average duration between 5 – 30 days.[2,11,12,14]

All three patients in this case report were initially present with prolonged fever for at least two weeks to two months before a decreased level of consciousness occurred, along with focal seizure that progressed to generalized tonic-clonic convulsion. Due to its non-specific symptoms at early stages, the disease is often recognized only after inflammation at the base of the brain has caused cranial nerve involvement, obstructive hydrocephalus, or vasculitis leading to infarction.[11]

Given the wide range of clinical presentations and disease severity, it is critical to rate TBM severity systematically and consistently.[12] Based upon clinical features, the severity of TBM at the time of admission was assessed using the British Medical Research Council (BMRC) TBM grading. Grade I is defined as a Glasgow Coma Scale (GCS) of 15 without focal neurological deficits. Grade II is defined as a GCS of 15 with a neurological deficit or a GCS of 11 – 14. Grade III is defined as a GCS of ≤ 10. The patients in this case report presented with BMRC TBM grade III on admission. Widely accepted, grade II and III were defined as advanced stages and associated with poor prognosis.[15]

Diagnostic criteria vary in different studies.[12] TBM can be differentiated from subacute bacterial meningitis by the Thwaites and the Lancet criteria, but only Lancet criteria can help differentiate TBM from meningitis caused by fungal, viral, subacute bacterial, and unknown causes.[2,13,14] Based on the Lancet Consensus Scoring System for TBM, all patients with suspected TBM should be categorized into definite, probable, possible, and not TBM depending on the strength of clinical suspicion, laboratory, or radiological findings. Definite TBM, a bacteriologically confirmed diagnosis, includes the clinical entry criteria and a positive acid-fast bacilli (AFB) smears or MTB culture or positive *Mycobacterium* nucleic acid amplification test (NAAT) of CSF, or histological examination. Probable TBM was made from the clinical criteria plus a total diagnostic score of 12 (if cerebral imaging was available), and 10 points (if cerebral imaging was not available). At least two points should either come from CSF or cerebral imaging criteria. Possible TBM included clinical criteria, plus a total diagnostic score of 6 to 9 points (when cerebral imaging is not available) or 6 to 11 points (when cerebral imaging is available). Possible tuberculosis cannot be diagnosed or excluded without doing a CSF analysis or cerebral imaging.[12] In case 1, the patient had a score of 13 points and was therefore compatible with probable TBM criteria. In case 2, the score was 18 points compatible with probable TB and in case 3 was compatible with definite TB.

The definitive diagnostic test for meningitis is ultimately a prompt lumbar puncture (LP) with analysis of CSF.[2] The CSF analysis typically shows a clear yellowish color, lymphocytic pleocytosis, low glucose, and high protein concentrations. The CSF findings in tuberculous meningitis are almost pathognomonic when they occur in combination, as seen in all three cases.[23] Even the best test may not detect MTB when there is a low bacillary load such as in TBM, in patients with HIV infection, and in young children.[8] Identification of MTB from CSF, either by detection of AFB or culture, is difficult, but the chances of positive diagnosis can be increased by doing more LP.[12] Although there has been a warning of herniation precipitated by LP, it carries no risk of herniation in the absence of hemiparesis or papilledema whether CSF pressure is raised or not. If brain imaging reveals no evidence of abscess, subdural empyema, or brain infarct, LP can be performed safely in clinically suspected tuberculous meningitis patients[10]. The LP was not performed in case 1 even though there was no papilledema on funduscopic examination, but infarction was seen in the thalamic region. A study found that the initial LP sample shows the sensitivity of microscopy to be 37% and the sensitivity of culture to be 52%. When up to four LPs were done, the sensitivity of microscopy increased to 87% and the sensitivity of culture increased to 83%. A greater volume of CSF obtained and meticulous microscopy (for at least 30 min) further increases the chance of

positive diagnosis.[2,12]

As part of the assessment of TBM, when possible, CT or magnetic resonance imaging (MRI) should be done. The complication of TBM in CNS appears as abnormalities in imaging which include hydrocephalus, basal meningeal enhancement, infarcts, tuberculoma, and pre-contrast basal hyperdensity/exudates (on CT imaging).[2,12] Abnormalities are most frequently detected in patients with severe disease. On CT, hydrocephalus and basal meningeal enhancement are the most common radiological features of TBM.[12] All these three patients presented with hydrocephalus, but we cannot evaluate the basal meningeal enhancement in case 1 as we ordered a non-contrasted head CT scan.

Hydrocephalus, the most common complication of TBM, might be a presenting symptom or occur unexpectedly after starting anti-tuberculosis treatment.[16] TBM infection causes a thick gelatinous exudate that is predominantly found in the basal regions of the brain. On MRI, this can be seen as contrast enhancement within the basal cisterns, subpial cortex, and subependymal areas.[2] Exudate encases and strangulates cranial nerve trunks such as the optic nerve, optic chiasma, and vessels of the circle of Willis. This basal exudate blocked the CSF flow in the brain, leading to ventriculomegaly.[16] In TBM with hydrocephalus (TBMH), progressive hydrocephalus is clinically manifested with a potentially life-threatening high intracranial pressure (ICP). Patients with deteriorating vision loss and deteriorating consciousness, often need a surgical CSF diversion procedure (VPS or endoscopic third ventriculostomy) to be performed. The decision of which type of CSF diversion strategies should be performed is commonly based on the Vellore grading system[17] VPS has been accepted as the standard of care in patients presenting with good neurological grades (I and II). There is still no consensus on the treatment protocol for patients of TBMH presenting with poor neurological grades (III and IV). In general, a trial of external ventricular drain (EVD) is an accepted method of treatment to decide whether a patient will benefit from shunt surgery,[17] so patients can receive a shunt only if their condition improves with trial EVD.[18] However, a prospective study in the pediatric population with TBMH with Vellore grade III and IV that had undergone direct VP shunt surgery without EVD trial demonstrated a good 3-month follow-up.[18]

In pathological studies of TBM patients, vasculitis and intimal proliferation have been considered to contribute to cerebral vessel damage and cause brain infarcts.[19] Infarct in TBM occurs in 15 – 57% of patients, especially in advanced stage and severe illness,[20] mostly in basal ganglia region, and predicts poor outcome at three months.[21] Involvement of medial striate, thalamotuberal, and thalamostriate arteries which are embedded in exudates and likely to be stretched by a coexistent hydrocephalus results in most of the infarct in TBM which presents multiple, bilateral and located in the basal ganglia especially the 'tubercular zone' which comprises of the caudate, anterior thalamus, anterior limb and genu of the internal capsule.[20] Cortical stroke can also occur due to the involvement of proximal portion of the middle, anterior and posterior cerebral arteries as well as the supraclinoid portion of the internal carotid and basilar arteries.[20]

The coexistence of tuberculous meningitis and hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting syndrome (CSWS) is well known.[10] Hyponatremia has long been recognized as a potentially serious metabolic consequence of TBM occurring in 35 – 65% of children with the disease.[22] All three patients presented with hyponatremia that repeatedly occurred to a critical level even with repeated corrections.

Treatment is most effective when started in the early stages of disease, and should be initiated promptly based on strong clinical suspicion without waiting for laboratory confirmation.[5] In patients with high suspicion of meningitis, the decision to empirically start antituberculosis therapy is a must because delay in therapy is associated with death.[14] The WHO guidelines on TBM recommend an induction treatment period of two months of rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA), and ethambutol (ETB) followed by up to 10 months of RMP and INH to complete a 1-year course of therapy. The adjunctive treatment with corticosteroids has been shown to reduce inflammation in all but late stage of TBM.[2,5] The surgical management aims to relieve high ICP in hydrocephalus patients.[2] Despite antituberculosis treatment in case 2, the patient was still unable to recover. We highlighted the importance of very early treatment with antituberculosis of suspected tuberculous meningitis for a better outcome.

CONCLUSION

The decision to start antituberculosis drug should be promptly made in any children with a clinical and CSF finding strongly suggestive of TB meningitis without waiting for bacteriological TB confirmation, especially in the presence of hyponatremia, hydrocephalus, and abnormal head CT scan consistent with tuberculous meningitis.

CONFLICT OF INTEREST

No conflict of interest to declare.

AUTHOR CONTRIBUTION

Authors took part in the case report, contributed to data collection, participated in writing the manuscript and all agree to accept equal responsibility for the accuracy of the content of this case report.

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