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TB MENINGITIS IN PEDIATRIC POPULATION- A REVIEW OF PATHO-PHYSIOLOGY, CLINICAL MANIFESTATIONS AND DIAGNOSIS

Paediatrics

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ABSTRACT

In developing countries like India, childhood tuberculosis is highly prevalent and TB meningitis is the most common cause of death. Despite early initiation of anti-tubercular therapy, it carries high rates of morbidity and mortality. TB meningitis in pediatric population is often diagnosed late because of its varied presentation. In order to diagnose TB meningitis, one must have a very high index of suspicion to diagnose this condition early in its course. This review provides a systematic approach on how to assess a patient based on clinical features, laboratory and investigations including neuroimaging. This review also aims to provide on how to initiate the treatment in order to bring down the morbidity and mortality in Indian setup.

KEYWORDS

Childhood tuberculosis, TB meningitis, mortality, pediatric.

INTRODUCTION:

Around 10-20% of the children with TB live in developing countries like India [1]. Childhood tuberculosis (TB) constitutes approximately 10%–20% of all TB cases in India, causing almost 8%–20% of TB-related deaths. Children <5 years of age and HIV affected children are usually affected by disseminated for of tuberculosis. Of the total tuberculosis nearly 20-30 % have extra-pulmonary tuberculosis [2]. TB meningitis is caused by AFB positive bacteria i.e Mycobacterium tuberculosis. Although TB meningitis constitute less percentage of overall tuberculosis burden in population, however it has poor prognosis as survivors often suffer from severe neurological disabilities [3]. TB meningitis has varied presentation and presents with non-specific symptoms in the early phase of the illness and thus diagnosed late. Early diagnosis and early anti-tubercular therapy is of paramount importance in order to decrease the morbidity and mortality. TB meningitis is diagnosed based on the clinical features backed with high index of suspicion, laboratory tests, neuroimaging and advanced nucleic acid amplification tests.

EPIDEMIOLOGY:

Despite advancement in tuberculosis testing, detection of extra-pulmonary TB, especially in pediatric population is a real challenge. There is significant lack of data on global burden of tuberculosis in pediatric age group. According to surveillance data collected in Germany, of the total paediatric TB patients, 3.9% children (<5 yrs), 2.2% in 5 to 9 yrs of age and 1.3% in 10 to 14 yrs of age were affected by TB meningitis[4]. Most reports are hospital based and very few are surveillance based. Country wise data is largely unavailable and understudied.

PATHOGENESIS:

Arnold Rich and H. Mc Cordock revealed caseating focus in brain parenchyma on children affected from children in post-mortem studies [5]. Nervous system is rarely affected primarily, initial infection sets in pulmonary parenchyma and then gets disseminated to other parts of body via haematogenous route. Initially, caseating foci i.e Rich Focus, are formed around the bacteria, located in the subpial or subependymal surface of the brain, meninges and bacteria remains in a dormant state for a prolonged duration. The onset of TBM follows the growth and rupture of these lesions into the ventricular system or subarachnoid space [6]. In general, TB meningitis usually occurs 6 to 12 months after the primary infection. The bacteria invades and traverses the BBB and sets up the infection or inflammatory changes in brain parenchyma and meninges. One study showed that there was significant elevation of cathelicidin LL-37, interluekin (IL)-13 and vascular endothelial growth factor (VEGF) and reduction of IL-17 in the CSF of children with TBM when compared to children with viral and bacterial meningitis [7]. This type of host immune response is disease specific and carries diagnostic and therapeutic implication. TB meningitis causes meningo-encephalitic disease, where thick gelatinous exudate containing erythrocytes, neutrophils, macrophages and lymphocytes is formed around the basal cisterns, brain stem and sylvian fissures leading to obstruction of the flow of CSF from the cerebral aqueduct or fourth ventricle leading to obstructive hydrocephalus. Absorption of CSF is also interfered at the level of subarachnoid granulations, leading to raised intracranial pressure (ICP) and communicating hydrocephalus. The basal exudates may lead to peri-arteritis of the cerebral arteries leading to infarction of the caudate nucleus and internal capsule, called as tubercular zone. There may be edema of the brain, perivascular infiltration and inflammation of the blood vessel walls leading to occlusion by thrombi leading to infarcts in the distribution of the medial striate and thalamic perforating arteries [8].

Clinical Featues:

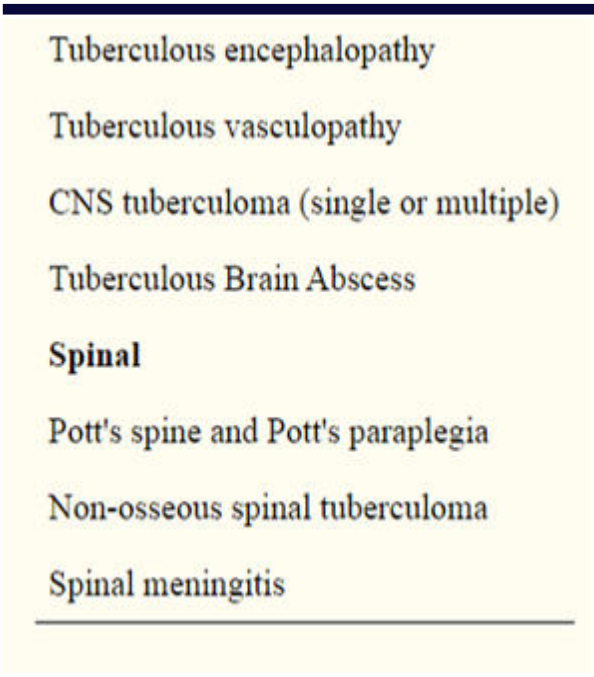
TB meningitis is rarely seen in children < 3 months [9], but reported cases range from six weeks to 18 yrs. The peak incidence occurs between 2 and 4 yrs of age [10], with male preponderance. The clinical onset of TB meningitis may be acute, subacute or gradual [11] and is characterized by non-specific symptoms in the early stages, such as malaise, low-grade fever, symptoms related to pulmonary TB and/or flu-like illness. Most children present for initial evaluation with symptoms such as headache, fever, vomiting and irritability. Children with more advanced disease may have signs of meningeal irritation, raised ICP (bulging fontanelle, sunsetting sign, papilloedema), cranial nerve palsies, neurological deficits, altered sensorium and movement disorders. The various cranial nerve palsies documented in different studies include second, third, sixth and seventh cranial nerve palsies [12-14].

Glasgow coma scale (GCS) is used to measure the consciousness level in these children as well as to determine the prognosis. Eye opening, motor responses and verbal responses contribute to GCS scoring. The British Medical Research Council (BMRC) staging is used to evaluate the disease severity as well as to establish the prognosis of TB meningitis [15]. The 'modified' MRC scale categorizes patients into three clinical stages. The 'refined' MRC scale and 'modified' MRC scale are similar except that Stage 2 is divided into Stage 2a and Stage 2b in the latter based on GCS score and absence or presence of neurological deficit[16].

Table 1

Classification of CNS tuberculosis [17]

Intracranial
Tuberculous meningitis (TBM)



DIAGNOSIS:

A. Clinical criteria [18]:

Symptomatic period >5 days (score: 4)
Constitutional symptoms of TB (>1 of the following): weight loss/poor weight gain,

night sweats,
cough >2weeks (score: 2)

History of recent (past 1 year) close contact with pulmonary TB or positive tuberculin sensitivity test or interferon (IFN) gamma release assays, only in children <10 years (score 2)
Focal neurological deficit (excluding cranial nerve palsies) (score: 1)
Cranial nerve palsy (score: 1)
Altered Sensorium (score: 1)
Maximum score is 6.

Cerebrospinal Fluid Criteria

Clear appearance (score: 1)
Cells 10–500/μL (score: 1)
Lymphocytic predominance >50% (score: 1)
Protein concentration >1g/L (score: 1)
Cerebrospinal fluid (CSF) to plasma glucose ratio <50% or absolute CSF glucose <2.2 mmol/L (score: 1)
Maximum score is 4.

Cerebral Imaging Criteria

Hydrocephalus (score: 1)
Basal meningeal enhancement (score: 2)
Tuberculoma (score: 2)
Infarct (score: 1)
Pre-contrast: basal hyperdensity (score:2)
Maximum score is 6.

Evidence Of Tuberculosis Elsewhere

A. Chest X –Ray
Signs of active TB = 2
Miliary TB = 4 (score: 2/4)
B. CT/MRI/USG evidence for TB outside the CNS (score: 2)
C. AFB identified or *Mycobacterium tuberculosis* cultured from another source (i.e., sputum, lymph node, gastric washing, urine, and blood culture) (score: 4)
D. Positive commercial *M. tuberculosis* nucleic acid amplification technique (NAAT) from extra neural specimen (score: 4).

Maximum score is 4.
The patient is labeled as a case of definitive TBM when the clinical criteria plus one or more of the following criteria are met: AFB seen in the CSF, *M. tuberculosis* cultured from CSF, or a CSF *M. tuberculosis* positive commercial NAAT from a patient who presents with symptoms or signs suggestive of meningitis; acid-fast bacilli seen in the context of histological changes consistent with TB in the brain or spinal cord together with suggestive symptoms or signs and CSF changes; or visible meningitis (on autopsy). A case of probable TBM is labeled when the clinical entry criteria plus a total diagnostic score is of 10 or more points (when cerebral imaging is not available) or 12 or more points (when cerebral imaging is available) plus exclusion of alternative diagnoses. At least 2 points should either come from CSF or from cerebral imaging criteria. Clinical entry criteria plus a total diagnostic score of 6–9 points (when cerebral imaging is not available) or 6–11 points (when cerebral imaging is available) plus exclusion of alternative diagnoses is used to label a case of possible TB meningitis. Hence, a possible TB meningitis cannot be diagnosed or excluded without performing a lumbar puncture or cerebral imaging [19].

CSF Analysis

A classic case of TBM usually presents with a CSF of 10–500 cells/μL that are polymorphs initially and lymphocytes later. A low glucose <40mg/dL (rarely <20mg/dL) or a CSF/plasma glucose ratio <50% or a high-protein content (400–5000mg/dL) is suggestive of the diagnosis of TBM. Cobweb formation may be seen.

Ziehl–Neelsen (ZN) staining has a sensitivity of approximately 50%, whereas a bacterial culture of 60%–70%.[20] The aforementioned CSF findings are not specific for TB meningitis and can be seen in other conditions including non-mycobacterial tuberculosis (MTB) bacterial meningitis, fungal meningitis, carcinomatous meningitis, and subarachnoid hemorrhage. For all patients with suspected TB meningitis, CSF samples should be examined by ZN staining for acid-fast bacilli, Gram staining for bacteria, India ink preparations for fungi, and antigen testing for *Cryptococcus neoformans*. The yield of the CSF examination can be increased by some simple measures such as taking at least 10mL CSF sample, carrying out repeated sample examination, also it needs to be centrifuged at a high centrifugal force for 20min followed by a careful examination for at least 20min.

The best performing biochemical parameter for "ruling in" TBM was adenosine deaminase (ADA), with a specificity of 95% at a cutoff point of >6U/L. A cutoff value of 10 U/L for patients with TB meningitis gave a sensitivity and specificity of 90.62% and 95.65%, respectively; thus proving that CSF ADA activity is a rapid and affordable adjunct in differentiating TB meningitis from non-TB meningitis [20-22].

Two manual liquid medium systems, the Mycobacteria Growth Indicator Tube (MGIT) and MB Redox tube systems and the radiometric BACTEC-460 semiautomated system for identification of *Mycobacterium tuberculosis* from specimens and detects drug resistance.

A recent diagnostic advance is Xpert MTB/ rifampicin (RIF), an automated rapid nucleic acid amplification test for MTB endorsed by WHO in December 2010 to detect MTB and RIF resistance simultaneously in almost less than 2h With a sensitivity of 67%–85% and a specificity of 94%–98%. A positive result confirms the diagnosis of TB meningitis but a negative result doesn't rule out.

The routinely measured CSF parameters are almost similar in HIV positive and negative patients with TBM [23] A few studies report lower CSF leukocyte count and protein level in HIV-positive patients.

Other Tests

These are ancillary tests that help us to reach to the diagnosis of TB meningitis.
1. Mantoux test- It may be nonreactive in 50% cases of CNS TB. Largely helpful in assisting the diagnosis of TB meningitis when positive, but an isolated positive Mantoux cannot be used to label a case of TB meningitis.
2. Chest X-ray: It helps to localize the signs of active TB but it may be normal in 20%–50%.
3. Measurement of IFN-γ released by lymphocytes: It is a specific (70%–90%) test but with a low sensitivity (50%–70%). It is available as enzyme-linked immunospot (ELISpot) and QuantiFERON Gold for the diagnosis of latent TB.

Neuroimaging In TB Meningitis

MRI or contrast MRI has a higher sensitivity than a CT scan. A CT scan may itself be normal initially in almost 30% of the cases. Hence, a normal neuroimaging initially does not rule out the possibility of TB meningitis.

Usual neuroimaging findings are basal exudates, infarcts, hydrocephalus, tuberculomas, opto-chiasmal aracnoiditis [24-25].FIGURE1,2.

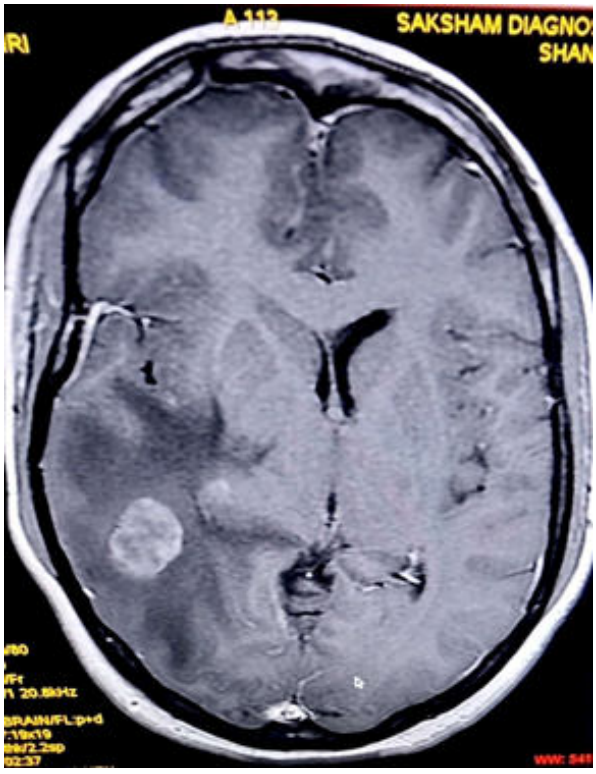


Figure 1. Contrast Enhanced Tuberculoma With Marked Vasogenic Edema In Right Parietal Region.

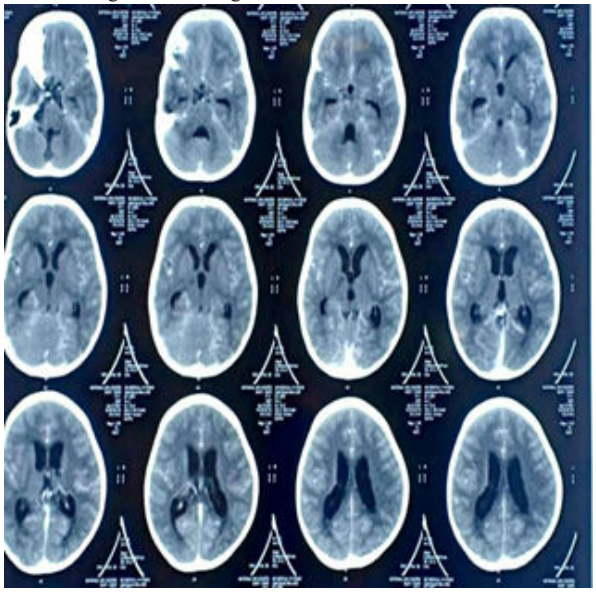


Figure 2. CECT Head Showing Basal Exudates With Communicating Hydrocephalus.

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