Tuberculous meningitis

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Abstract

Tuberculous meningitis (TBM) is caused by *Mycobacterium tuberculosis* and kills or disables around a half of sufferers. It is most common in young children and individuals infected with HIV, but can affect all age groups. TBM presents with non-specific symptoms over days or weeks, followed by worsening headaches, fever and vomiting. Without antituberculosis chemotherapy, cranial nerve palsies (typically VIth and IIIrd) and hemiplegia may develop, and consciousness becomes impaired. Mortality exceeds 50% if the Glasgow Coma Scale score is <10/15 by the time the patient starts treatment. Early diagnosis and treatment improves outcome but is notoriously difficult as current laboratory tests lack sensitivity. Early empirical therapy is often required to improve survival. Rifampicin-based antituberculosis chemotherapy should be used whenever possible and given for 9–12 months. Adjunctive corticosteroids are recommended for all patients with TBM for the first 6–8 weeks of treatment, regardless of age, disease severity or HIV infection. Hydrocephalus, cerebral infarction and expanding tuberculoma are common complications of TBM, occurring at any time before or after treatment starts. Brain imaging, preferably with MRI, is recommended to assess the evolution and management of these complications. Ventriculo-peritoneal shunting should be considered in patients with hydrocephalus and falling consciousness.

Keywords Diagnosis; management; MRCP; treatment; tuberculous meningitis

Key points

- Strongly consider tuberculous meningitis (TBM) in all patients with meningitis and >5 days of symptoms
- If TBM is suspected, take a large volume of cerebrospinal fluid (>8 ml) for Ziehl–Neelsen staining and mycobacterial culture
- Never rule out TBM on the basis of negative microbiological/molecular tests; treat early and empirically if TBM is strongly suspected
- UK guidelines currently recommend four drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) for 2 months, followed by 10 months of rifampicin and isoniazid for the treatment of TBM
- Adjunctive dexamethasone should be given to all patients with TBM, regardless of disease severity
- Hydrocephalus is the most common serious complication of TBM; an external ventricular drain/shunt should be considered if it is associated with falling consciousness
- TBM is prevented through assiduous community control of tuberculosis and *Bacillus* Calmette–Guérin vaccination of neonates

Introduction

Tuberculous meningitis (TBM) represents around 1% of all forms of tuberculosis, but with >8 million cases of tuberculosis worldwide each year, and successful vaccination programmes against other causes of meningitis (e.g. *Neisseria meningitidis*), *Mycobacterium tuberculosis* is now the most common cause of bacterial meningitis in many settings. In the UK, approximately 200 cases of TBM are reported annually.

Epidemiology

TBM is most commonly seen in young children and individuals infected with HIV. In populations with a high prevalence of tuberculosis, the peak age of TBM incidence is 0–4 years. In populations with a lower prevalence of tuberculosis, most cases of TBM are in adult immigrants from areas of high tuberculosis prevalence. Other risk factors for TBM include alcoholism, diabetes mellitus, malignancy, recent corticosteroid use and treatment with tumour necrosis factor-α inhibitors.

Pathology

TBM results from the haematogenous dissemination of *M. tuberculosis* from the lung. Blood-borne bacteria travel to the brain, where they can settle and initiate a localized granulomatous inflammatory response called a 'Rich focus' (after the early 20th century pathologist Arnold Rich). TBM develops when a Rich focus comes into communication with the subarachnoid space, releasing *M. tuberculosis* into the cerebrospinal fluid (CSF).

Classically, the basal meninges are affected, with inflammatory exudates in the basal cisterns obstructing normal CSF flow and causing hydrocephalus. Localized necrotizing granulomatous inflammation can lead to tuberculoma formation (ring-enhancing space-occupying lesions) and vasculitis, with stroke syndromes. The perforating arteries of the middle cerebral artery are most commonly affected, leading to basal ganglia and internal capsule infarcts.

Clinical features

The clinical features of TBM are non-specific and, as summarized in Figure 1, progress to death if not treated. The most important differential diagnoses are partially treated pyogenic bacterial meningitis and cryptococcal meningitis.

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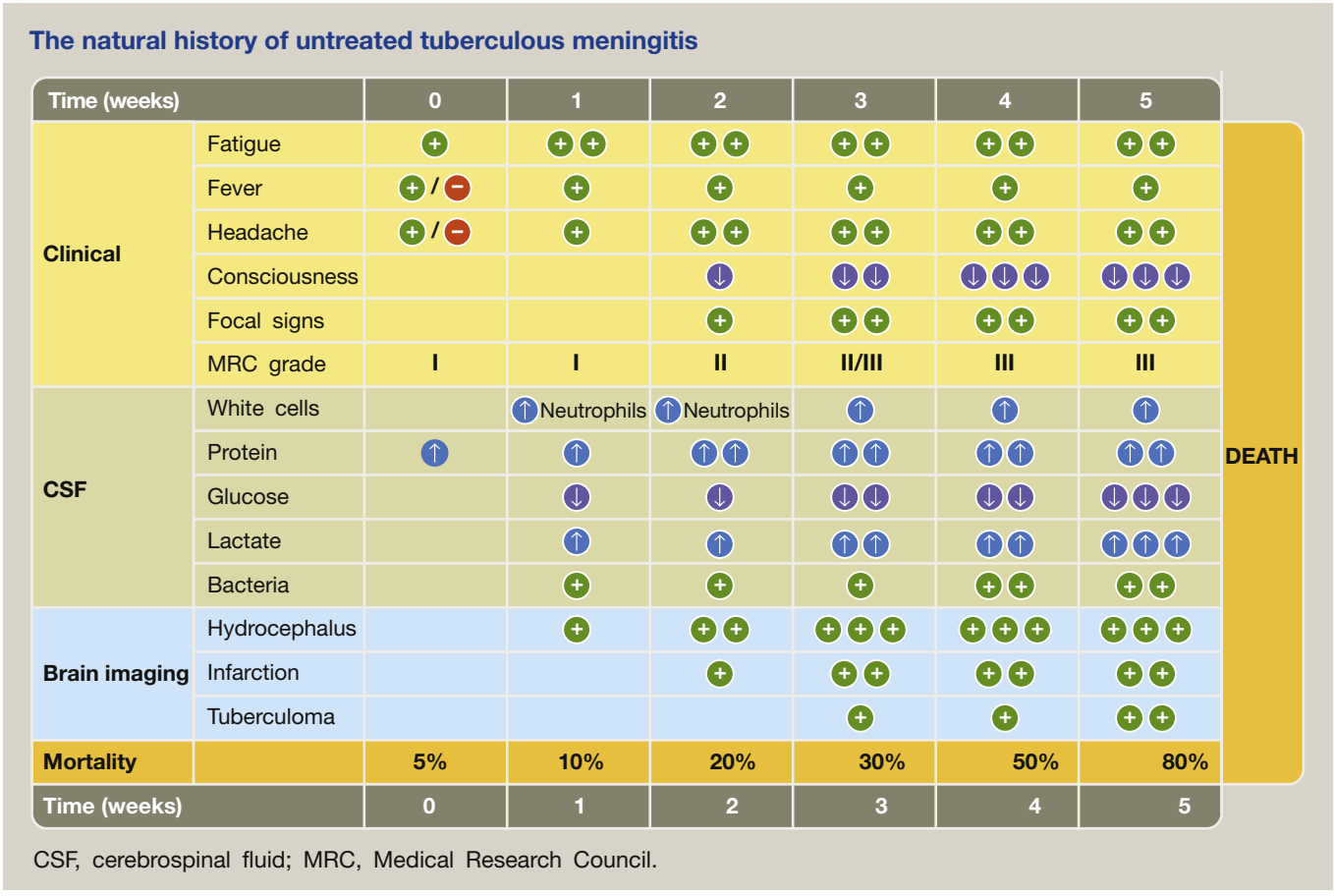

Figure 1

The onset of symptoms is usually insidious: young children may come irritable, feed poorly and lose weight, while adults feel fatigued, lose their appetite and may suffer night sweats. These prodromal symptoms can last from a few days to several weeks before more pronounced meningitic symptoms are reported, with headache, fever and neck stiffness. If the patient is left untreated, confusion and coma follow over the ensuing days, and around 50% develop focal neurological deficit, either cranial nerve palsies (VIth and IIIrd are the most common) or hemiplegia.

CSF analysis is essential in the diagnosis of TBM and typically reveals 50–1000 white cells/mm^3 with a mixture of neutrophils and lymphocytes. CSF protein is elevated, typically 1.5–5.0 g/litre, and the CSF:plasma glucose ratio is <50% in >95% of patients.[1]

Laboratory diagnosis

The performance of the commonly available laboratory diagnostic tests for TBM is summarized in Table 1. Nucleic acid amplification tests (e.g. GeneXpert MTB/RIF) are highly specific but only around 60% sensitive and cannot be used to rule out the diagnosis. The inadequacies of all currently available diagnostic tests mean that empirical treatment, without microbiological confirmation, is often required.[2]

Other investigations

Computed tomography and magnetic resonance imaging (MRI) of the brain can demonstrate the typical pathological features of TBM, and imaging of other organs (e.g. lungs, liver, spleen) may assist in the diagnosis of tuberculosis. The most common brain imaging features of TBM are hydrocephalus and basal contrast-enhancing exudates; both are more common in children (around 80%) than adults (around 40%) and may be absent in elderly or immunosuppressed patients with TBM.

Drug treatment

The principles of successful TBM treatment are:

- antituberculosis treatment must be started early, before the onset of coma, to give the best chance of disability-free survival
- isoniazid and rifampicin are the key components of the treatment regimen and should be used whenever possible
- interruption of therapy during the first 2 months of treatment is an independent risk factor for death
- prolonged therapy (9–12 months) is required to prevent disease relapse.

The currently recommended treatment regimens for children and adults are the same as for all other forms of tuberculosis, except that the continuation phase of treatment should be extended to at least 7 months (9–12 months' total treatment).[3]

The merits of adjunctive corticosteroid treatment of TBM have been debated for 50 years. A recent Cochrane systematic review and meta-analysis of seven randomized controlled trials, involving 1140 participants, concluded that corticosteroids

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