Improving early diagnosis of tuberculous meningitis in children

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2 Update on the diagnosis and management of tuberculous meningitis in children

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ABSTRACT

Tuberculous meningitis (TBM), the most devastating manifestation of tuberculosis, is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis. It continues to be an important cause of neurological handicap in resource-poor countries.

Due to the suboptimal performance of diagnostic tests of TBM, diagnosis relies on thorough history, clinical examination and relevant investigations. The development of affordable, accurate diagnostic tests for TBM in resource-poor settings remains a priority.

Short intensified treatment is safe and effective in both HIV-infected and HIV-uninfected children. Treatment of tuberculous hydrocephalus depends on the level of the cerebrospinal fluid (CSF) obstruction. Corticosteroids reduce risk of neurodisability and death in HIV-uninfected children. Thalidomide should be considered in children compromised by TB abscesses and tuberculous-related optochiasmic arachnoiditis. In resource-poor countries, home-based TBM treatment after initial in-hospital stabilization is feasible in carefully selected patients. Early diagnosis and treatment of TBM is the single most important factor determining outcome.

INTRODUCTION

Tuberculous meningitis (TBM) is the most devastating manifestation of tuberculosis and it continues to be an important cause of neurological handicap in resource-poor countries. A recent study in the Western Cape Province of South Africa found TBM to be the commonest cause of pediatric meningitis.[1] South Africa is one of the 22 high tuberculosis (TB) burden countries that account for 80% of the world TB cases. The estimated incidence of TB in SA is 1000 or more per 100 000 people. One of the Millennium Development Goals (MDG) targets are to halt and start to reverse the rising incidence of TB and to halve the 1990 prevalence and death rates by 2015.[2] Unfortunately, most African regions, including SA, are not on track to achieve this objective due to reasons such as resource constraints, conflict and instability and generalized HIV epidemics.

Bacille Calmette-Guerin (BCG) is currently the only available vaccine against TB, and is widely administered within the World Health Organization (WHO) Expanded Programme for Immunization. It provides protection against disseminated TB and TBM (73%; 95% confidence limits 67-79%) but has highly variable and often low efficacy against pulmonary TB in adults.[3] The impact of BCG vaccination on transmission of *Mycobacterium tuberculosis* (*M.tb*) is therefore limited. The variable efficacy of BCG vaccination together with the not inconsequential threat of multi-drug resistant TB highlights the neccessity of new vaccine development, but this is hindered by the lack of immune correlates, suboptimal animal models, and limited funding.[4]

CLINICAL MANIFESTATIONS

TBM may present at any age but is less common at the extremes of life. The peak incidence is in children between 2 to 4 years of age.[5] Early clinical diagnosis is notoriously difficult and often delayed, with disastrous consequences. Although delayed diagnosis of TBM is common, the very young infant, patients with another co-existing illness and those from non TB-endemic regions carry the highest risk for missed diagnosis. The classical presentation of TBM is as a subacute meningitic illness. The resulting dilemma is that the classical sign of meningitis, neck stiffness, is usually absent during the early disease stage in children and adults.[6] Early diagnosis and treatment of TBM has been long recognized as the single most important factor determining outcome.[5]

Although much effort has gone into improving diagnostic investigations, these may not be requested if the possibility of meningitis has not crossed the physician's

mind. This is applicable to health practitioners in resource-poor, as well as resource-equipped countries, where the increase in migrant populations could potentially lead to an increased incidence of TBM. It is therefore important to recognize TBM during the early stage, mainly characterized by non-specific symptoms of general ill health rather than specific, classical signs of meningitis. In young children these include poor weight gain, low-grade fever and listlessness. Most early symptoms relate to underlying pulmonary tuberculosis present in the vast majority of infants who develop TBM as a complication of primary infection. The only factor differentiating these symptoms of TBM from common illnesses such as influenza is their persistence[7]; however, this is often not recognized because care-givers may not return to the same health professional (especially if treatment failed) and often do not inform subsequent doctors of previous diagnoses and treatments of the current illness.[7] Thus early stage, fully curable TBM may progress to the final stages of coma, opisthotonus and death following this course of events.

In older children common non-specific symptoms of early TB meningitis are fever, headache and vomiting, closely representing a flu-like illness. Recent close contact with an infectious pulmonary TB patient is an important diagnostic clue. Once the classical neurological signs of advanced TBM (including meningeal irritation, coma, seizures, signs of raised intracranial pressure, cranial nerve palsies, hemiparesis, movement disorders) appear, the diagnosis is usually apparent but at a considerable cost to the patient. It should be noted, however, that the initial presentation of TBM may be acute and accompanied by any of the above-mentioned "late" signs and without a distinct prodromal period. Neither organism genotype, resistance patterns (MDR TB), co-infection with HIV or BCG immunization status consistently modify the disease presentation as described above.[6]

COMPLICATIONS OF TBM

Tuberculous hydrocephalus and raised intracranial pressure

Hydrocephalus occurs in up to 80% of TBM patients.[5] In 70% of cases the hydrocephalus is of a communicating nature. This occurs when the exudate that fills the basal cisterns causes a bottle-neck obstruction of the cerebrospinal fluid (CSF) pathways at the level of the tentorium. In 20% of cases, CSF obstruction occurs when the basal exudates obstructs the outflow foramina of the 4th ventricle leading to a non-communicating hydrocephalus. Other rare causes of non-communicating hydrocephalus are obstruction of the foramina of Munro or the aqueduct by strategically located tuberculomas.

Tuberculous hydrocephalus is often complicated by raised intracranial pressure (ICP).[5] Studies have shown that clinical diagnosis of the presence and degree of raised ICP is unreliable, especially in children with closed anterior fontanels.[8] The value of computed tomography (CT) is limited by the poor correlation that exists between the degree of hydrocephalus (ventricular size) and severity of ICP.[9] Signs of raised ICP may also mimic signs of brainstem dysfunction.[10] It is therefore often difficult to distinguish between raised ICP and brainstem ischemia in the deeply comatose child with stage III TBM.

Tuberculous cerebrovascular disease

Stroke is a common and most devastating complication of TBM. Vessel pathology appears to be a consequence of its immersion in the local inflammatory exudate.[11] The terminal segments of internal carotid artery (ICA) and proximal portions of middle (M1 portion of MCA) and anterior (ACA) cerebral arteries are most frequently involved. Anti-tuberculous chemotherapy is relatively ineffective in preventing the vascular complications, suggesting an immune mechanisms. This has led to clinical intervention studies aimed at halting the progressive nature of the vasculitis.[12]

TB-IRIS

Central nervous system TB Immune reconstitution inflammatory syndrome (IRIS) often manifests as a life-threatening condition and should be considered when new neurological symptoms or signs develop shortly after initiation of antiretroviral therapy (ART) in children.[13] Two clinical scenarios may occur; "unmasking" IRIS when subclinical, previously unrecognized TB infection flares up after starting ART while "paradoxical IRIS" is diagnosed when new or worsening symptoms of TB develop despite adherence to appropriate antituberculous treatment in a patient who initiated combination antiretroviral ART.[13] Neurological manifestations described, include neck stiffness, intracranial and spinal tuberculous mass lesions, radiculomyelitis, hydrocephalus, visual compromise and seizures.[13] Paradoxical TBM-IRIS tends to occur within 3 weeks of initiation of ART in children.[13]

The frequency and mortality of neurological TB-IRIS in children is not well documented; only 1 case series has been published.[14] In adults, TBM-IRIS complicates the course of treatment of HIV-associated TBM in 47% of cases, despite the use of adjunctive corticosteroid therapy.[15] Mortality is high (up to 30%) in those affected.[14]

As yet, no means exist to predict the syndrome. The optimal time to initiate ART in children or adults with HIV-associated TBM is unknown. A recent randomized double-blind placebo-controlled trial of immediate versus deferred ART in adult Vietnamese

patients with TBM showed that HIV-associated TBM in the study population had such a poor prognosis that the timing of ART made no appreciable difference regarding survival probability.[16] Early initiation of ART was not associated with an increased risk of IRIS. Corticosteroids are the mainstay of treatment for TBM-IRIS, with interruption of ART reserved for life-threatening complications. Other immune-modulatory agents that have been used to treat IRIS in a limited number of patients include thalidomide, chloroquine, mycophenolate mofetil and cyclosporine.[13]

TB mass lesions

Tuberculomas of the central nervous system may occur in isolation or in association with TBM. Intracranial tuberculomas are often silent and unsuspected, especially if no clinical evidence of TB is present. A focal seizure in an otherwise normal child is the most common mode of presentation in TB endemic populations. Tuberculomas may also manifest with focal neurological signs or raised intracranial pressure due to obstruction of cerebrospinal pathways. Diagnosis is dependant on neuroimaging as the cerebrospinal findings and culture is negative in most patients. Most tuberculomas will resolve uneventfully in response to antituberculous treatment. Corticosteroids (prednisone 2mg/kg/day) should be reserved for cases with paradoxically enlarging tuberculomas.

TB mass lesions (large tuberculomas or abscesses) are known to develop or enlarge despite appropriate anti-TB treatment. This phenomenon, the result of IRIS, is often more severe in the setting of HIV co-infection and may be life threatening.[13] Clinical manifestations depend on the size and location of the lesion(s) and include focal neurological signs, ataxia, spastic paraplegia and raised intracranial pressure due to obstruction of cerebrospinal fluid pathways. In our experience TB abscesses are responsive to thalidomide, a potent tumor necrosis factor alpha (TNF-α) inhibitor.[17]

DIAGNOSIS

Due to the suboptimal performance of diagnostic tests of TBM, the diagnosis in children relies on a thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations. About 60% of children with TBM will have radiological evidence of pulmonary TB.[5]

There have been efforts to create clinical prediction rules to differentiate TBM from other forms of meningitis, especially in resource-poor settings. When comparing TBM and bacterial meningitis in adults, using a composite clinical reference standard,

sensitivities of 86-97% and specificities of 71-97% were obtained.[18,19] When using a microbiologically proven *M.tb* reference standard, sensitivities (86-96%) and specificities (71-79%) were similar.[18,20] However, a prediction rule performed less well in an area of high HIV seroprevalence (sensitivity 78% and specificity 43%).[21]

As CSF in both TBM and viral meningitis is clear and lymphocyte predominant, distinguishing between them is more difficult. A recent prediction rule, comprised of a diagnostic scoring system, performed well with sensitivity 92% and specificity 94%.[22] Despite numerous reports in the literature describing clinical prediction rules, standardized diagnostic criteria are lacking.[23]

The tuberculin skin test (TST) performed with a sensitivity of 61% in a large retrospective cohort of children with TBM.[5] However sensitivity decreases (34%) when HIV co-infection is present due to the high rate of false negative results.[24] In the young infant population (< 6 months) with BCG vaccination, specificity is decreased due to high false-positivity. Furthermore, a positive TST implies probable *M.tb* infection, but cannot delineate active TB disease.[25]

Although a 2011 meta-analysis of the use of interferon gamma release assays (IGRAs) in adults with pulmonary TB showed that there is no value for the diagnosis of active TB,[26] CSF IGRA showed sensitivity of 59-84% and specificity 73-89%.[27-30] However, the large CSF volumes needed in order to obtain enough cells to perform IGRA,[31] is a limiting factor in children where much smaller CSF volumes are obtained.

A 2003 systematic review evaluated the test accuracy of nucleic acid amplification tests (NAATs) in the diagnosis of TBM.[32] The studies with commercial NAATs revealed a pooled sensitivity and specificity of 56% and 98%, respectively. The review concluded that commercial NAATs provided valuable information when positive, but due to poor sensitivity a negative test did not exclude TBM.[32] The World Health Organization has recently endorsed the Xpert MTB/RIF assay (Xpert; Cepheid, Sunnyvale, CA, USA) for both smear microscopy-positive and -negative sputum specimens.[33] When using Xpert for CSF specimens, promising sensitivities of 67-85% and specificities 94-98% were obtained.[34,35]

Neuroimaging plays an important role in the diagnosis of TBM especially during the early stage of the disease and in cases of diagnostic uncertainty. Computed tomography (CT) is most often used in resource-poor countries and a combination of hyperdense exudates on pre-contrast CT, basal meningeal enhancement, infarctions and hydrocephalus is highly suggestive (Figure 1).[36] Bilateral basal ganglia infarcts are

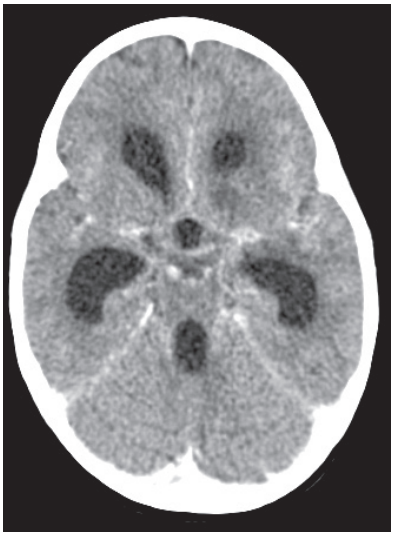

Figure 1. Contrasted computed tomography showing a combination of hydrocephalus, basal meningeal enhancement and infarction.

particularly characteristic of TBM and this finding on CT suggest a high likelihood of brainstem involvement. Approximately a third of children with stage 1 TBM disease will have a normal CT scan.[6]

Magnetic resonance imaging (MRI) is superior to CT for diagnosing TBM, by detecting basal enhancement and granulomas in more patients, and prognosis, by detecting many more infarcts in strategic locations such as the brainstem (Figure 2).[37] Gado-

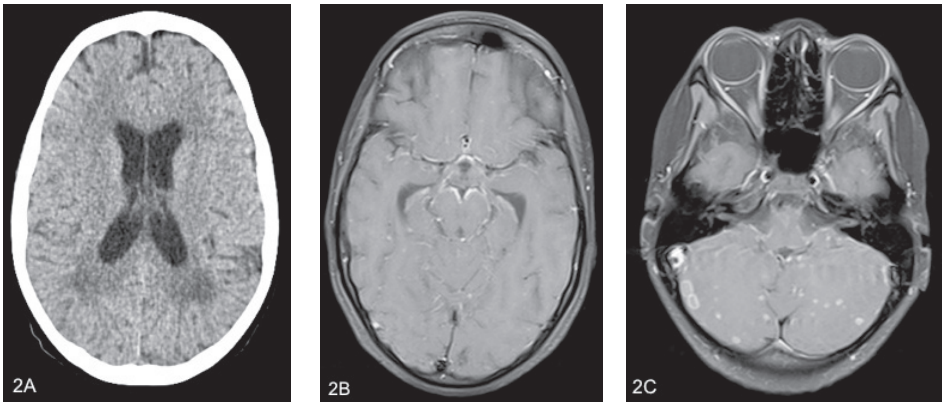

Figure 2A. Computed tomography of a 13-year old child presenting with disseminated TB and loss of consciousness. The initial CT only revealed bilateral periventricular hypodensities and hydrocephalus. Figure 2B-C. T1-weighted post-gadolinium MRI 2 days later revealed basal meningeal enhancement and multiple ring-enhancing lesions (miliary nodules) in the cerebellar hemispheres.

linium enhanced MRI allows detection of miliary leptomeningial tubercles which have been reported to be present in 88% of children with TBM.[38] MRI is also valuable for identification of optochiasmic arachnoiditis, which requires urgent intervention to reduce the risk of blindness.[39] Magnetic resonance angiography (MRA) is useful for assessment of vascular involvement. Vessels most commonly affected include the terminal portions of the internal carotid arteries, as well as the proximal parts of the middle and anterior cerebral arteries.

TREATMENT

Fluid management

Hyponatremia occurs in up to 85% of children with TBM and is thought to be secondary to either syndrome of inappropriate anti-diuretic hormone (SIADH) or cerebral salt wasting. Fluid restriction has traditionally been recommended to counter the presumed threat of SIADH and reduce the risk of cerebral edema. There is however no evidence that indicates that fluid restriction is beneficial in children with meningitis. It may precipitate hypovolemia, which should be avoided at all costs as maintenance of adequate cerebral perfusion is of critical importance in TBM patients. TBM is known to induce a hypercoagulable state, which would then increase the risk of venous thrombosis and infarction in the setting of inadequate cerebral perfusion.[40] A safer option is to partially correct symptomatic hyponatremia (associated with seizures) by slow infusion of 5% hypertonic saline.

Antimicrobial therapy

There is limited evidence regarding the most appropriate treatment regimen for TBM or optimal duration of treatment.[41] The WHO recommends 12-months treatment (2RHZE/10RH) for children with suspected or confirmed TBM. Short, intensified anti-TBM therapy is advocated by several groups as similar completion and relapse rates have been reported when 6-months therapy was compared to 1-year.[42] High dose intravenous rifampicin may also be associated with a survival benefit in adult patients with severe disease.

Local experience is that short, intensified therapy (6RHZEth for HIV-uninfected and 9RHZEth for HIV-infected children) is safe and effective in children with drug susceptible TBM.[42] This regimen was prospectively evaluated in 184 consecutive TBM children and resulted in a good outcome in 80% of cases and mortality of 3.8%.[42] The incidence of antituberculous drug-induced hepatotoxicity in the study was low (5%) and in all cases the original regimen was restarted without recurrence.[42] The

rational for using ethionamide as the 4th drug is that it has good CSF penetration and less adverse effects compared to streptomycin and ethambutol. Another advantage is that isoniazid mono-resistant TBM may be overcome when ethionamide and pyrazinamide are used continuously for a 6-month period.[43]

In resource-poor countries, lengthy in-hospital treatment of TBM is often not a realistic option. Local experience is that home-based TBM treatment after initial in-hospital stabilization is feasible in carefully selected patients under close supervision.[44]

Multidrug-resistant TBM should be considered in cases where there is deterioration despite compliance with adequate antituberculous treatment. In such cases it is vitally important to obtain cultures from source contacts. Newer NAAT allows resistance to rifampicin and/or isoniazid to be detected. Second-line agents for MDR TBM include levofloxacin, amikacin, terizadone and para-aminosalicylic acid (PAS).

Treatment of tuberculous hydrocephalus

Treatment of tuberculous hydrocephalus depends on the level of CSF obstruction. Air-encephalography is the most reliable way of determining the level of CSF obstruction (Figure 3).[45] CT is not a useful tool as panventricular dilatation occurs in both communicating and non-communicating types of hydrocephalus.[45] Communicating hydrocephalus can be successfully treated with medical therapy consisting of acetazolamide 50 mg/kg/day and furosemide 1 mg/kg/day in 3 divided daily doses) for a

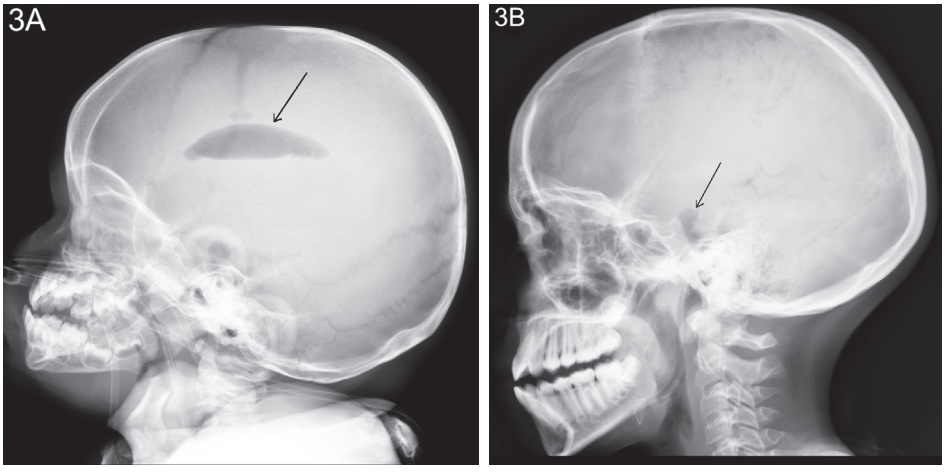

Figure 3A. The lateral skull X-ray shows air in the basal cistern and lateral ventricles. This indicates communicating hydrocephalus (arrow) due to basal cistern obstruction to the flow of cerebrospinal fluid. **3B.** The lateral skull X-ray shows only air at the level of the basal cistern (arrow). This indicates non-communicating hydrocephalus due to obstruction of the 4th ventricle outlet foramen.

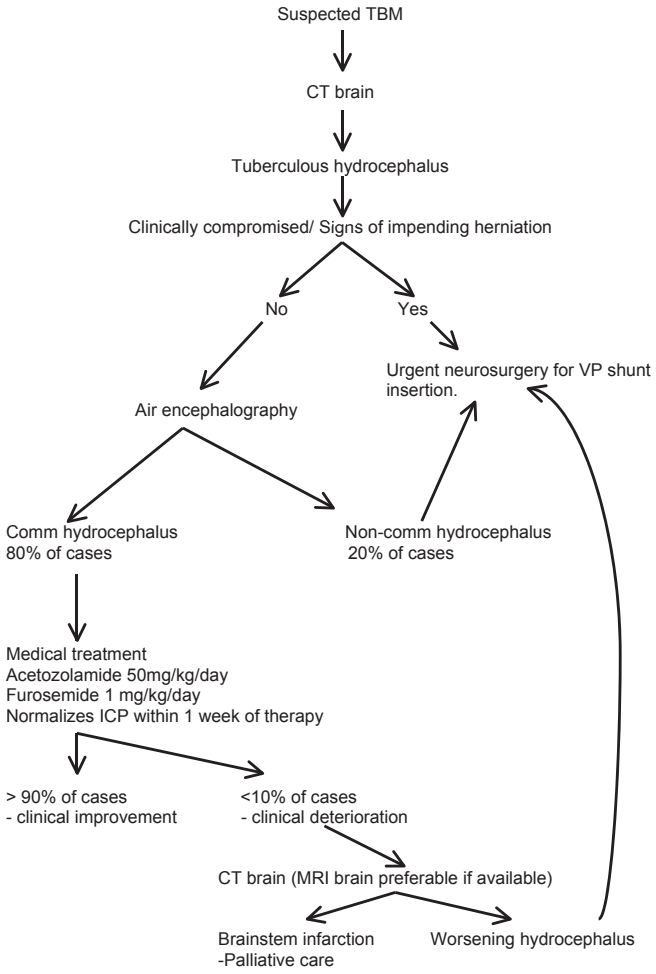

Figure 4. Tygerberg Children's Hospital treatment algorithm for tuberculous hydrocephalus.

period of 4 weeks.[9] This drug combination reduces CSF production by blocking carbonic anhydrase activity and reduces ICP by decreasing the rate of CSF production. It is our experience that normalization of intracranial pressure occurs within days in more than 90% of children. Figure 4 illustrates our suggested treatment algorithm for children with tuberculous hydrocephalus.

Adjunctive anti-inflammatory therapy

Corticosteroids

A 2008 Cochrane systematic review of 7 clinical trials involving 1140 participants found that corticosteroids reduce the risk of death (RR 0.78, 95% CI 0.67-0.91) or

disabling neurological deficit (RR 0.82, 95% CI 0.70-0.97) in HIV uninfected TBM patients.[46] The benefit of corticosteroids in HIV infected patients has not been demonstrated. There are also no controlled trials comparing corticosteroid regimens. Local preference is to prescribe prednisone 2 mg/kg/day (maximum 60 mg/day) for the first month of treatment and then to gradually wean over the next 2-weeks.

Aspirin

The value of aspirin's antithrombotic, anti-ischemic and anti-inflammatory properties in TBM was explored in two studies. An adult TBM study reported a significant reduction in mortality at 3 months (p=0.02).[47] In contrast, a childhood TBM study found no significant benefit in morbidity (hemiparesis and developmental outcome) or mortality at 6 months.[40]

Thalidomide

TB abscesses are notoriously resistant to therapy and require total surgical excision for cure.[48] Surgical excision is often not achievable due to the proximity of the abscesses to vital brain structures and the lack of neurosurgical care in resource poor countries. TB abscesses often teem with tubercle bacilli, which induce a strong cytokine response. The most important cytokine implicated is tumour necrosis factor alpha (TNF-α). Insufficient TNF-α production delays granuloma formation, which is required for control of bacillary growth whilst excessive production leads to extensive liquefaction necrosis as is evident in TB abscesses. Thalidomide 3-5 mg/kg/day, given orally, is our drug of choice in children who develop life-threatening TB mass lesions (IRIS) despite corticosteroids.[12] The use of Thalidomide should also be considered in children with visual compromise due to tuberculous optochiasmic arachnoiditis.[39]

Outcome in childhood TBM

Prognosis in TBM largely depends on the stage the disease has reached at the time of treatment intervention. Children with stage I TBM disease are likely to have a normal outcome, whereas children with stage III disease have a high risk of mortality.[42] Multidrug-resistant TBM in children has a poor clinical outcome and is often associated with death.[43] Inpatient mortality rates are generally similar between HIV-infected and uninfected children with TBM.[42] However, mortality after hospital discharge is substantially worse in HIV-infected TBM children due to HIV-related illnesses. Long-term behavioural complications of TBM survivors include general behavioural disinhibitions and internalized emotional disorders.[49]

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