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Update on the Diagnosis and Management of Tuberculous Meningitis in Children

Ronald van Toorn, FCP and Regan Solomons, MMED

Tuberculous meningitis (TBM), the most devastating manifestation of tuberculosis, is often missed or overlooked because of nonspecific symptoms and difficulties in diagnosis. It continues to be an important cause of neurologic handicap in resource-poor countries. Owing 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 human immunodeficiency virus (HIV)-infected and HIV-uninfected children. Treatment of tuberculous hydrocephalus depends on the level of the cerebrospinal fluid obstruction. Corticosteroids reduce risk of neurodisability and death in HIV-uninfected children. Thalidomide should be considered in children compromised by tuberculosis 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.
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Introduction

Tuberculous meningitis (TBM) is the most devastating manifestation of tuberculosis (TB) and it continues to be an important cause of neurologic handicap in resource-poor countries.

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

The bacille Calmette-Guerin (BCG) vaccine is currently the only available vaccine against TB and is widely administered within the Expanded Programme for Immunization by the World Health Organization (WHO). 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 effect 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 multidrug-resistant (MDR) TB highlights the necessity 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 and 4 years of age.[5] Early clinical diagnosis is notoriously difficult and often delayed, with disastrous consequences. Although delayed diagnosis of TBM is common, very young infants, patients with another coexisting illness, and those from non–TB-endemic regions carry the highest risk for missed diagnosis. The classic presentation of TBM is as a subacute meningitic illness. The resulting dilemma is that the classic 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

Department of Paediatrics and Child Health, Stellenbosch University, Western Cape, South Africa.
Both authors contributed equally.
Address reprint requests to Ronald van Toorn, FCP, Department of Paediatrics and Child Health, Stellenbosch University, PO Box 19063, Tygerberg 7505, Western Cape, South Africa. E-mail: vtoorn@sun.ac.za

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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 nonspecific symptoms of general ill health rather than specific, classic signs of meningitis. In young children, these include poor weight gain, low-grade fever, and listlessness. Most early symptoms relate to underlying pulmonary TB present in most 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 caregivers may not return to the same health professional (especially if the 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 nonspecific symptoms of early TBM 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 classic neurologic signs of advanced TBM (including meningeal irritation, coma, seizures, signs of raised intracranial pressure [ICP], cranial nerve palsies, hemiparesis, and movement disorders) appear, the diagnosis is usually apparent but at a considerable cost to the patient. However, it should be noted that the initial presentation of TBM may be severe and accompanied by any of the aforementioned "late" signs and without a distinct prodromal period. Organism genotype, resistance patterns (MDR TB), coinfection with HIV, or BCG immunization status do not consistently modify the disease presentation as described earlier.[6]

Complications of TBM

Tuberculous Hydrocephalus and Raised Intracranial Pressure

Hydrocephalus occurs in up to 80% of patients with TBM.[5] In 70% of cases, the hydrocephalus is of a communicating nature. This occurs when the exudate that fills the basal cisterns causes a bottleneck obstruction of the cerebrospinal fluid (CSF) pathways at the level of the tentorium. In 20% of cases, CSF obstruction occurs when the basal exudates obstruct the outflow foramina of the fourth ventricle leading to a noncommunicating hydrocephalus. Other rare causes of noncommunicating hydrocephalus are obstruction of the foramen of Monro or the aqueduct by strategically located tuberculomas.

Tuberculous hydrocephalus is often complicated by raised 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 a deeply comatose child with stage III TBM.

Tuberculous Cerebrovascular Disease

Stroke is a common, 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 and proximal portions of the middle and anterior cerebral arteries are most frequently involved. Antituberculous chemotherapy is relatively ineffective in preventing the vascular complications, suggesting an immune mechanism. This has led to clinical intervention studies aimed at halting the progressive nature of the vasculitis.[12]

Tuberculosis–Immune Reconstitution Inflammatory Syndrome

TB-immune reconstitution inflammatory syndrome (IRIS) of the central nervous system often manifests as a life-threatening condition and should be considered when new neurologic 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, and "paradoxical" IRIS, diagnosed when new or worsening symptoms of TB develop despite adherence to appropriate antituberculous treatment in a patient in whom combination ART was initiated.[13] The neurologic 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 neurologic 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 vs 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 immunomodulatory 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