Tubercular Meningitis – A Tale of 50 Years

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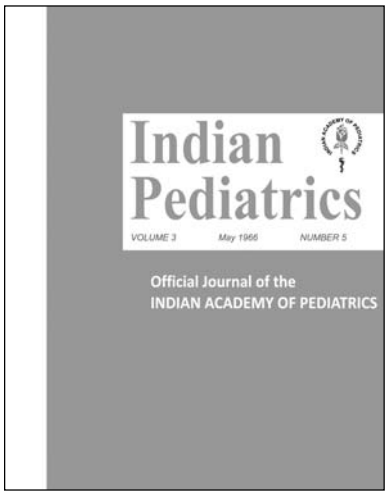
In 1966, the 34-paged May issue of *Indian Pediatrics* had four original articles besides two case reports, current literature, notes and news. Amongst these, we decided to review the original article on tubercular meningitis as despite the advances in diagnosis and management, it still continues to be a major scourge responsible for mortality and morbidity in Indian children.



THE PAST

The article by Manchanda, *et al.* [1], in May 1966 issue of Indian Pediatrics, is a retrospective review of records of tuberculosis (TB) cases in children (age <14 y) admitted at VJ Hospital, Amritsar from 1955 to 1965. Of 21,728 pediatric admissions over 10 years, 742 (3.4%) were due to TB, of which 249 (33.6%) were complicated by tubercular meningitis (TBM). Amongst the cases with TBM, 75.1% were boys, 57.5% were aged below 3 years, 71.9% were from urban areas, and 50% were in clinical stage III at admission. The mortality rate was 51% (127/249); 65.4% of the deaths were in children aged below 5 years, and 80% of those who died were in clinical stage 3 at admission. The chief causes of death were progressive hydrocephalus, bulbar palsy and hyperpyrexia. Of the 122 cases who were discharged, 70 were designated as relieved, while 52 (20.9%) were in such a poor state that authors thought they were unlikely to have survived. Thus, the presumed mortality was 71.9%. The follow-up data was available in 49 of the 70 survivors. Of these, 28 were labelled as cured (11.2%) without sequelae while 21 had sequelae, including hemiplegia (8), generalized rigidity (3), facial palsy (1), deafness (3), optic atrophy (6), choreoathetoid movements (2), hypotonia (1), hydrocephalus (2) and behaviour disturbances (3). The article did not describe the diagnostic criteria for TBM or the treatment given to the included cases.

Historical background and past knowledge: The earliest published clinical vignette on TBM is credited to Robert Whyth in 1768 for his treatise 'Dropsy in the brain' [2]. The patho-physiology of TBM was unravelled by Arnold Rich and McCordock in 1933 [3]. Before the mid-20th century, childhood TB was uniformly fatal. The introduction of isoniazid in early 1950's revolutionized the treatment of TB. For nearly two decades, the standard treatment comprised of combination of isoniazid and streptomycin, following which rifampicin was introduced. Still, the mortality was very high, and significant proportions were left with physical and mental disabilities due to delay in treatment initiation and poor compliance. To strengthen the fight against TB, the Government of India launched "District Tuberculosis Control Programme" in 1962 which focussed on prevention, control and management of the disease in both urban as well as rural areas. At the time of publication of this article [1], there existed wide disparity in the reported incidence (0.5-13%) of TBM in India, and its true situation was difficult to determine because of diagnostic uncertainties and poor case notification. In most cases, the diagnosis was presumptive, based on clinical suspicion and circumstantial evidence as bacteriological confirmation was often not possible.

THE PRESENT

In India, pediatric TB has received attention as a major public health problem, especially during the last two decades. After lymphadenopathy, TBM is second commonest cause of extra-pulmonary TB affecting children < 3 years of age [4]. TB-Immune reconstitution inflammatory syndrome (IRIS) has emerged as a dreaded complication in HIV-TB co-infection due to restoration of immune function after initiation of anti-retroviral therapy.

The diagnosis of TBM in children in most resource-limited settings with high disease prevalence is still based

on comprehensive clinical assessment along with supportive investigations such as a positive tuberculin skin test, a family history of tuberculosis, and/radiological evidence of pulmonary TB. The bacteriological confirmation is not always possible due to poor sensitivity of Z-N staining of acid fast bacilli in CSF and low yield and delay in processing culture results. The diagnostic precision in CSF cultures has however improved by concordant use of L-J medium and Automated Culture Systems. The advent of Cartridge-based Nucleic Acid Amplification Test (CBNAAT) like Xpert MTB/Rif/Gene Xpert has enhanced the diagnostic yield from various body specimens, including CSF. The Xpert for CSF specimens offer higher sensitivity (59-84%) and specificity (73-89%) than conventional tools [5]. It is endorsed by WHO [6] and recommended as preferred initial test in suspected TBM, MDR-TB, co-infection with HIV and severe illness. CSF biomarkers (interleukin-13, vascular endothelial growth factor and cathelicidin LL-37) have a huge potential for improving diagnosis and management but are still in experimental phase [7]. Neuro-imaging has a significant adjunctive role in diagnosis of TBM especially at an early stage of disease, in cases of diagnostic dilemma and to detect complications.

As recommended by the WHO, British Infection Society, as well as the current National guidelines for Pediatric TB [8], treatment regimen of TBM consists of initial 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 10 months of isoniazid and rifampicin. Corticosteroids have an undisputed supportive role in reducing mortality and morbidity from severe neurological disability [9], and have been recommended by the above guidelines. The addition of newer generation fluroquinolones to standard anti-tubercular regimen or intensified regime of fluroquinolones with high dose Rifampicin is shown to improve outcome [10]. The evolution of MDR-TB has posed new challenges for which WHO has recently published guidelines [11]. The Food and Drug Administration (FDA) approved new drug 'Bedaquiline fumarate' for MDR-TB has been introduced in India on World Tuberculosis Day, March 2016. Surgical interventions like ventriculo-peritoneal shunt placement and endoscopic third ventriculostomy are now available in cases of non-communicating hydrocephalus and failure of medical management.

In the present era, prompt optimal treatment along with good supportive care initiated in clinical stage 1 of TBM offers almost universal survival. A recent meta-analysis on treatment outcomes on children with TBM reported risk of mortality as 19·3% (95% CI 14·0, 26·1). Among survivors, risk of neurological disability was 53·9% (95% CI 42·6, 64·9) while the probability of intact survival was 36·7% (95% CI 27·9, 46·4) [12]. However, long term behavioral disinhibitions and internalized emotional disorders may persist despite optimal management.

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