

Central Nervous System Tuberculosis in Children

PAM Kunju¹, Joe James²

ABSTRACT

The emergence of multidrug-resistant and extensively drug-resistant tuberculosis (TB) and the advent of acquired immunodeficiency syndrome (AIDS) have complicated the diagnosis and treatment of central nervous system tuberculosis in children. Manifestations of central nervous system (CNS) TB varies from meningeal involvement to compressive myelopathy from vertebral TB. Rapid recognition of tuberculous meningitis (TBM) is essential as delays in initiating treatment are associated with poor outcome. Delayed diagnosis and treatment of TBM heralds' poor neurological outcomes. The laboratory diagnosis of TBM is hampered by the low yield from CSF and the slow growth of *M. tuberculosis*. The current schedule of treatment of TBM has undergone a considerable change and is now aimed at the elimination of TB by 2030. In this review, we examine the recent advances in the understanding of TBM, its diagnosis, and the treatment.

Keywords: Antituberculous treatment, Tuberculous meningitis, Tuberculous meningitis diagnosis, Tuberculous meningitis treatment.

Pediatric Infectious Disease (2019): 10.5005/jp-journals-10081-1106

INTRODUCTION

Though our understanding of the pathogenesis and management of CNS tuberculosis (TB) have improved during the last 5 decades, the emergence of multidrug-resistant and extensively drug-resistant TB and the advent of AIDS have complicated the diagnosis and treatment. It is still a diagnostic challenge to pediatricians, mainly due to lack of bacterial diagnosis, its varying manifestations, and its devastating course, despite the availability of good and free antituberculous therapy (ATT).

According to World Health Organization (WHO) global TB report 2018, there was an estimate of 10 million new cases and 1.6 million deaths due to TB.¹ Even though CNS-TB accounts for only 1–10% of all TB cases, it has the highest mortality and morbidity among all TB infections. Risk factors for TBM include age <5 years, household contact, PEM grade III and IV, recent measles and HIV infection.² CNS-TB can have protean presentations. It includes TBM, tuberculoma, tubercular abscess, tuberculous encephalopathy, and hypertrophic pachymeningitis. In the spinal cord, it can cause spinal tuberculoma, tuberculous myelitis, Pott's spine with epidural abscess and spinal arachnoiditis. In this review, we highlight the pathogenesis, clinical manifestations, diagnosis, and treatment of CNS-TB with focus on tuberculous meningitis.

PATHOGENESIS OF TUBERCULOUS MENINGITIS

Mycobacterium tuberculosis is acquired by droplet inhalation into the lung alveoli. The bacilli trigger the innate immune response, which activates macrophages, leading to the formation of granuloma and containment of infection. Early in the course of this process, prior to the containment of infection, bacilli are filtered into the lymph nodes, resulting in a low-level bacteremia.³ It is widely accepted that CNS-TB develops as a result of hematogenous spread of TB bacilli during this phase.⁴ This theory is supported by the fact that intravenous inoculation of TB bacilli in rabbits and guinea pigs lead to the formation of tuberculomas. The inoculum forms a subpial focus of granuloma in the brain, spinal cord, or the meninges, called Rich's focus.⁵ Rupture of this focus into the subarachnoid space leads to an active inflammatory response in the meninges leading to TBM⁶ (Flow chart 1). In children with good cellular immunity, the focus gets organized into tuberculoma. TB bacilli can also remain dormant within Rich's foci and CNS-TB often occurs months after initial dissemination of TB bacilli.⁵

¹Professor and Head, ²Senior Resident

¹Department of Pediatric Neurology, Medical College, Thiruvananthapuram, Kerala, India

²Department of Neurology, Government Medical College, Kozhikode, Kerala, India

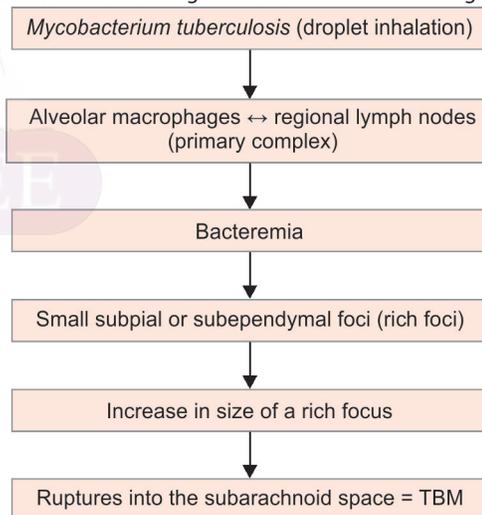
Corresponding Author: PAM Kunju, Professor and Head, Department of Pediatric Neurology, Medical College, Thiruvananthapuram, Kerala, India, e-mail: drpamkunju@gmail.com

How to cite this article: Kunju PAM, James J. Central Nervous System Tuberculosis in Children. *Pediatr Inf Dis* 2019;1(1):23-29.

Source of support: Nil

Conflict of interest: None

Flow chart 1: Pathogenesis of tuberculous meningitis



CLASSIFICATION AND CLINICAL FEATURES

Central nervous system (CNS) tuberculosis can be classified according to the intracranial and spinal involvement (Table 1).

Tuberculous Meningitis

Tuberculous meningitis (TBM) is the most common of CNS TB. About 10% have a history of prior TB and only <50% have active

Table 1: Classification of CNS tuberculosis^{12,18}

Intracranial	Spinal
Tuberculous meningitis (TBM)	Pott's spine and Pott's paraplegia
Tuberculous encephalopathy	Intramedullary tuberculoma
Tuberculous vasculopathy	Spinal arachnoiditis
Serous tuberculous meningitis	
CNS tuberculoma (single or multiple)	
Tuberculous brain abscess	
Hypertrophic pachymeningitis	

pulmonary TB.^{7,8} The onset is usually insidious with irregular fever, malaise, weight loss and anorexia last few weeks. It is followed by headache, photophobia, and meningism. Infants may have bulging fontanelles. If untreated, the illness progresses to a vasculitic phase, with focal neurological deficits like cranial nerve palsies, hemiparesis often accompanied by seizures with worsening sensorium and coma. Three stages of TBM have been described, with prognostic significance⁹ (Table 2).

The manifestations of tuberculous meningitis can develop insidiously or in an abrupt manner similar to bacterial or viral meningitis.¹⁰

The symptomatology of TBM can be either slowly progressive or have an abrupt onset similar to bacterial and viral etiologies. Since these causes predominate the cases of acute meningitis, the possibility of TBM is often not considered in an acute setting. They are usually treated empirically with antibiotics and steroids, with an apparent improvement. Such a missed diagnosis will later present with florid complications and are often fatal.

Cranial nerve palsies occur in 20–30% cases and are an important pointer towards tuberculous meningitis, in a case of undifferentiated meningitis.¹¹ Cranial nerves VI, VII, and II are the most affected. Most commonly involved nerves are the II, VI, VII cranial nerves.

Optic nerve involvement in TBM may be due to optochiasmatic arachnoiditis, optic nerve granuloma, third ventricular compression of optic chiasma (due to hydrocephalus) or ethambutol toxicity.¹² Ophthalmoscopy shows papilledema in many cases. Choroid tubercles, seen in TBM associated with miliary tuberculosis, are pathognomonic but seen only in 10% cases.

Tuberculous Vasculopathy

Tuberculous vasculitis is considered as an important etiology of stroke in the young.¹³ Dastur et al. had established the role of "tuberculous vasculopathy" in the pathogenesis of stroke and focal deficits by the autopsy study.¹⁴ Cerebrovascular complications of TBM that occur typically as multiple or bilateral lesions in the territories of the middle cerebral artery perforating vessels are termed as tuberculous vasculopathy. Vasculopathy is a consequence of its immersion in the inflammatory basal exudate

Tuberculous vasculopathy, a cerebrovascular complication of TBM, which occurs due to its immersion in the inflammatory basal exudate is seen commonly as multiple bilateral lesions in the area of distribution of the perforating vessels of the middle cerebral artery which is typically located in the interpeduncular fossa, encircles the optic chiasma and anterior cerebral vessels, extending along the Sylvian fissures to entrap the internal carotid as well as the middle cerebral arteries and their perforating branches (Fig. 1).

Table 2: Staging of tuberculous meningitis

<i>Prodromal phase (2–3 weeks)</i>
Conscious, fatigue, malaise, fever, myalgia, headache no FND
URTI, disproportional lethargy, irritability, peeishness
<i>Meningitic phase</i>
Meningismus, headache, vomiting, confusion, CN deficit, FND
<i>Paralytic phase</i>
Stupor/coma, seizures, hemiplegia
FND, focal neurological deficits; CN, cranial nerve

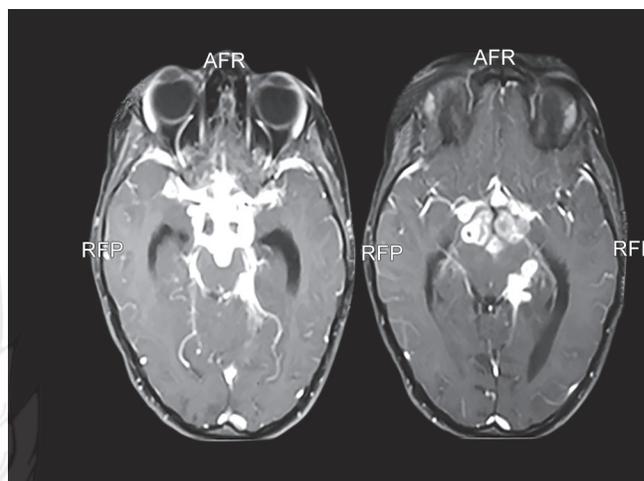


Fig. 1: T1 contrast MRI showing basal inflammatory exudate entrapping internal carotids, basilar artery, optic and oculomotor nerves in the subarachnoid space (central white areas)

Its extension posteriorly, covers the pontomesencephalic, medullary and cerebellar cisterns, the fibrinous tags causing blockage of the Foramina of Luschka and Magendie with resultant hydrocephalus. The consistent distribution of tubercles along the pial vessels and the occasional restriction of tuberculous lesions to an arterial territory prompted the conclusion that infarcts originated from a primary vascular pathology.

The origins of "primary vascular pathology" for the infarct in TBM was supported by the distribution of tubercles consistently along the vessels of the pia mater and selective restriction of tubercles to an area of feeding arterial vessel.

Vessel pathologies include three patterns as (1) infiltrative, (2) proliferative and (3) necrotizing vascular lesions leading to luminal thrombosis.¹⁵ The characteristic angiographic triad of narrowing of supraclinoid part of the internal carotid artery, a widely sweeping pericallosal artery, or outward bowing of the thalamostriate vein, and delayed circulation in the middle cerebral artery with scanty collaterals and early draining veins support vasculitic pathology involving the internal carotid system.¹³

Development of collaterals can give rise to the appearance of the moyamoya pattern in the region of basal ganglia and base of the brain.

Infarcts in TBM are multiple, bilateral and localized to the 'tuberculous zone' involving the caudate nucleus, anterior thalamus, anterior limb and genu of the internal capsule, in contrast to the posterior location of the ischemic thromboembolic infarcts.

Unusual neurological presentations of TBM may result in diagnostic difficulty.¹¹⁻¹³ Abnormal neurological manifestations of TBM pose diagnostic dilemmas.

Movement disorders may occur after infarction of the basal ganglia and present with tremor, chorea, ballismus or myoclonus.¹⁴ Infarctions of the basal ganglia present with movement disorders such as tremors, chorea, ballismus or myoclonus

Hydrocephalus is a common complication of TBM., This occurs due to basal exudates rich in protein, which forms a fibrinous septum and clog the cerebrospinal fluid (CSF) pathways. This can lead to a falsely low CSF opening pressure. A progressive dip in sensorium in a patient with TBM should alert the possibility of this complication, and warrants an emergency imaging.

Serous TB Meningitis

Lincoln used the term tuberculous serous meningitis to describe a condition in which there were signs of early localized meningitis occurring in patients suffering from pulmonary tuberculosis.¹⁶ Serous TB meningitis is characterized by signs and symptoms of mild meningitis with spontaneous recovery. The pathogenesis is uncertain but is considered to be an immune reaction. The signs present in such cases indicated varying degrees of meningeal irritation with minimal changes in the cerebrospinal fluid.

Tuberculous Abscess

Tuberculous abscess is an advanced stage of tuberculoma, a focal collection of pus, with abundant bacilli. Clinical symptoms are similar to tuberculomas except for a higher incidence of fever. A tuberculous abscess can be difficult to differentiate from pyogenic or fungal abscesses, but the finding of lipid lactate peak on magnetic resonance spectroscopy is highly characteristic of TB abscess.¹⁷

Tuberculous Encephalopathy

Like serous meningitis, tuberculous encephalopathy (TBE) is an established disease entity described exclusively in infants and children, characterized by diffuse cerebral damage due to an immune reaction.¹⁸ Symptoms include altered sensorium and seizures, without focal neurological deficits or meningeal signs. CSF is usually normal or may show a slight elevation in protein or cells. Pathologically it is characterized by diffuse cerebral edema, white matter demyelination and loss of neurons from grey matter.¹⁹

Tuberculoma

Tuberculomas are conglomerates of tubercles within the brain parenchyma. About 10% of TBM have coexisting tuberculomas, one-third of which is multiple.²⁰ Common presentations is as a mass lesion, with or without fever. Tuberculomas are 2nd to neurocysticercosis as single enhancing brain lesions (SEs), in patients presenting with focal seizures. One differential is tumefactive ADEM. Tuberculomas are typical, supratentorial in adults, while in children, it is infratentorial. Infratentorial tuberculomas are commonly seen in children as compared to adults where they are located supratentorially. It can also develop in the spinal cord, subdural or epidural space.

Paradoxical enlargement of tuberculomas. Paradoxical reactions (PR) after starting of ATT is seen in 2–23%.²¹ This does not represent the failure of ATT; the most likely explanation for these phenomena is an interaction between the host's immune response and the direct effects of mycobacterial products. PR is to be suspected when there is transient worsening or appearance of new signs or symptoms or radiographic manifestations of TB 2–4 weeks after starting of ATT.

Tuberculous Rhombencephalitis

Tuberculous rhombencephalitis is hindbrain (brainstem and cerebellum) tuberculoma which may be confused with Listeria infection or tumor.

Hypertrophic Pachymeningitis

Hypertrophic pachymeningitis is characterized by fibrosis and diffuse/localized thickening of dura.²² Common sites of involvement are cavernous sinuses, the floor of middle cranial fossa and tentorium. This condition is to be differentiated from common tuberculous leptomeningitis. Pachymeningitis presents with headache, cranial nerve palsies, and other focal neurological deficits.²³⁻²⁵ Many such cases are idiopathic or due to other granulomatous infections. MRI features qv.

Tuberculosis of Spine (Pott's Spine)

Tuberculosis of the spine (Pott's spine) affects the thoracic > lumbar or cervical spine.²⁶ In children, the intervertebral disc is affected first because it is vascularized compared to unlike the anterior aspect of the vertebral body in adults, then destruction and subsequent involvement of the body of the adjacent vertebrae occurs. Narrowing intervertebral space leads to collapse, anterior wedging of the vertebrae, and formation of a Gibbus deformity.²⁷ Epidural and paraspinal abscess also may be formed. All this can compress the spinal cord leading to paraplegia. Pott's spine presents with pain which can be spinal or radicular. We have seen children presenting with severe arching of the back due to severe paraspinal spasm. Constitutional symptoms are present in less than 40% cases and hence early diagnosis is often missed until the patient develops a neurological deficit.²⁸ This includes spinal cord compression with paraplegia, impaired sensation, nerve root pain, and/or cauda equina syndrome.

Spinal Cord Tuberculomas

Nonosseous spinal cord (intramedullary) tuberculomas can occur without evidence of Pott's spine and occur most commonly in the thoracic region, which are indistinguishable from other spinal cord tumors.²⁹

Tuberculous Spinal Arachnoiditis

Tuberculous spinal arachnoiditis and radiculomyelopathy are rare causes of paraplegia in endemic countries.³⁰ The inflammatory exudate surrounds and tethers the spinal nerve roots and compresses the spinal cord. Frequently there is coexisting periarthritis also. Neuronal damage is caused by both compressive and ischemic components. It presents as a sub-acute/progressive sensorimotor paraparesis with bladder involvement, radicular pain, and LMN signs. Contrast MRI reveals intense enhancement of meninges and nerve roots.³¹

HIV/TB coinfection. Children with HIV have an overall risk (5 times more) of involvement of the CNS as against children without HIV and children who received adequate ART and ATT had paradoxical reactions (tuberculomas) and immune reconstitution inflammatory syndrome (IRIS). Children with HIV have an overall risk (5 times more) of involvement of the CNS as against children without HIV and children who received adequate ART and ATT had paradoxical reactions (tuberculomas) and IRIS.

HIV positive children have 5 times high chance to develop CNS involvement than who are HIV negative. Interestingly paradoxical development of intracranial tuberculomas is seen in patients receiving adequate antiretroviral and ATT IRIS.

- Abnormal movements
 - Less than 50% of neutrophils in CSF.
- He also concluded that the sensitivity and specificity was 98% and 44% when one feature was present as compared to 55% and 98% when more than 3 clues were present.

For clinical research, the Lancet consensus scoring system can be used which is applicable irrespective of the patient's age.⁴⁶ It has 20 parameters, which are divided into four categories (clinical, CSF, imaging and TB elsewhere) with a maximum score of 20. A definite diagnosis of TBM is made if there is evidence of AFB in CSF, culture or on histopathology of the brain or spinal cord. A probable diagnosis is considered if the score is >10 points if patients have no imaging, or >12 points if imaging was used. A possible diagnosis is made with scores between 6 and 9 without imaging or 6–11 with imaging.

Radiographic Features

Tuberculous Meningitis

Ideally for TBM diagnosis, contrast scans to be taken as a non-contrast CT/MRI may be normal. However, complications like hydrocephalus can be seen. On both MRI and CT contrast scan basal enhancing exudates, leptomeningeal enhancement along Sylvian fissures, with mild enlargement of ventricles is a helpful clue for diagnosis. Infarcts, ependymitis and associated tuberculoma also may be present.

Magnetization Transfer (MT) Spin Echo

Significantly lower MT ratio is seen in tuberculous meningitis as compared to fungal and pyogenic meningitis

Tuberculomas

On CT/MRI, tuberculomas appear as a round or irregular nodule with moderate to marked edema. Post-contrast disc or ring enhancement is typical. "Target sign" a central focus of calcification with a ring of peripheral enhancement is also described but is not specific to tuberculoma. MR spectroscopy with an elevated lipid-lactate peak and decrease in NAA/Cr ratio is also helpful.

Tuberculous Pachymeningitis

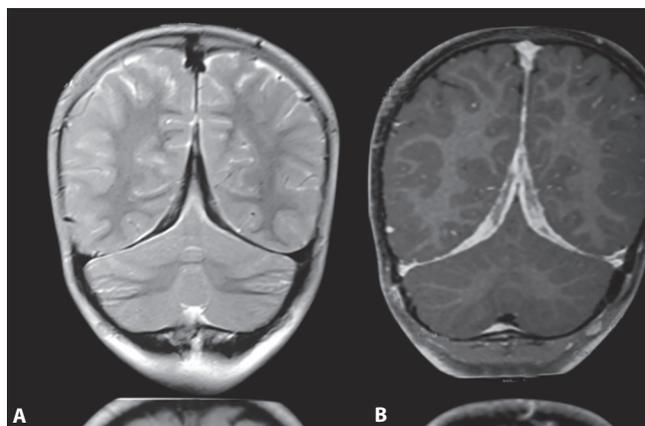
Both T1 and T2 weighted MRI shows hypointense thickened dura and contrast will reveal an intense homogenous enhancement. These enhanced meninges

"Eiffel by night" is a sign due to the involvement of falx and tentorium with hypertrophied dura giving the appearance of the illuminated Eiffel tower by night on contrast-enhanced coronal sections of T1 weighted image⁴⁷ (Fig. 2).

TREATMENT OF TUBERCULOUS MENINGITIS

National Strategic Plan for TB elimination 2017–2025 envisages innovative steps to eliminate TB in India by 2030. The plan is to reduce the estimated TB Incidence rate from 217 (112–355) per 100,000 in 2015 to 44 (36–158) per 100,000 by 2025. Steps included are:

- Mandatory notification of all TB cases
- Integration of the program with the general health services (NHM)
- Expansion of diagnostics services
- Programmatic management of drug-resistant TB (PMDT) service expansion
- Single window service for TB-HIV cases
- National drug resistance surveillance and
- Revision of partnership guidelines.



Figs 2A and B: Pachymeningitis. (A) MRI T2 hypointense and (B) Contrast hyperintense falx and tentorium—Eiffel by night sign

Drug Treatment^{41,42}

Since the treatment for TB falls in general line and described in other articles only specific points pertaining to TBM will be discussed here.

According to the WHO guidelines for national tuberculosis programs on the management of tuberculosis in children the standard first-line regimen for drug-sensitive TBM is a two-month "intensive phase" with isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin followed by a 10-month continuation phase with isoniazid and rifampicin (2HRZE or S/10HR). But the current RNTCP guidance is to use ethambutol in the continuation phase because of the risk of isoniazid mono-resistance. In view of mono resistance for INH, the current RNTCP-guidelines endorse the use of ethambutol in the continuation phase (Table 3).

But it recommends 9 months (2 + 7). Given the potentially devastating outcomes of relapse on the one hand and the disadvantages of long therapy, on the other hand, a pragmatic clinical decision by the treating pediatrician is what is warranted. The decision to balance the fine tilt of disease relapse versus potential side effects of prolonged antitubercular therapy is best left in the hands of the experienced clinician.

Multidrug-resistant Tuberculosis

As it is difficult to isolate AFB in childhood TBM multi drug-resistant TBM (resistant to both isoniazid and rifampin) should be suspected in a child who has a poor response, even after being compliant to standard ATT regimen or/and have a history of exposure to a case of MDR-TB. The treatment of resistant TB required the use of reserve or second-line drugs for up to two years. Now shorter regimen known as Bangladesh regimen have a higher cure rate than "standard" MDR-TB regimens, the Bangladesh regimen is a short course 9-month regimen, for the treatment of "uncomplicated MDR TB," i.e., TB only resistant to first-line drugs rifampicin and isoniazid. The regimen includes seven drugs: isoniazid, kanamycin, prothionamide, gatifloxacin, clofazimine, ethambutol, and pyrazinamide. First three drugs are used only for the first four months. However, in December 2018 WHO recommended not to use injectable in TB treatment.⁴⁸ In 2016, controlled use of Bedaquiline and, the delamanid interim policy, was extended to children aged 6–17 years following a review of data from a 6-month safety, efficacy, and pharmacokinetic trial of pediatric patients.

Table 3: Treatment of TBM as per RNTCP 2016

Firstline treatment for adults and children with TB meningitis	<i>Intensive phase:</i> 2 months 2019 RHZE <i>Continuation phase:</i> at least 10 months RHE Daily therapy
	Presumptive TBM patients should be referred to a secondary/tertiary care center immediately If the patient is critically ill, treatment with ATT may be started prior to transfer. Where possible, CSF sampling prior to initiation of treatment is preferred; but this should not unduly delay initiation of ATT Residual neurological deficits may be permanent and should not be used to assess for active TB infection
Drug-resistant cases	Drug-resistant TBM should be suspected in patients with poor response to standard ATT and a history of exposure to MDR-TB.
Steroids HIV-negative patients	Steroids are recommended for TB meningitis in HIV negative people. Duration of steroid treatment should be for at least 4 weeks, with tapering as appropriate (strong recommendation, high-quality evidence)

Adjunctive Anti-inflammatory Therapies

Steroid

Although the use of steroid in TBM is accepted as a recommendation (Table 3), two aspects are being still debated. Usefulness in the long-term outcome and the mechanism of how steroids benefit TBM. One large trial in 545 Vietnamese adults showed only a reduction in mortality but not in neurological disability in those treated with dexamethasone, compared to placebo.⁴⁹ In published data by Thwaites et al. in adults in Asia showed a reduction in mortality in the Dexamethasone treated group as compared to the placebo; however, there were no significant changes in neurological outcomes.

The role of steroid in reducing the inflammatory response is also studied. In a well-conducted study of the inflammatory response in TBM it is found that steroid did not improve survival from TBM by attenuating immunological mediators of inflammation in the CSF, nor by suppressing peripheral T cell responses to mycobacterial antigens, challenging previously held views of the pathogenesis of TBM.

Contrary to previous hypotheses which concluded that steroids worked by suppressing the cell-mediated immune response to MTB antigens and also by reducing mediators of inflammation in the CSF, published data was not able to show such associations. A few studies have shown that LTA4H genotype may be central to the inflammatory response in TBM and patients with the TT genotype were significantly more likely to survive TBM than those with the CC genotype. Thus, LTA4H genotype may predict adjunctive corticosteroid responsiveness.

Other Inflammatory Modulators

Studies have shown that use of aspirin is found to be associated with a significant reduction in mortality but nonsignificant reduction in stroke at 3 months.⁵⁰ Role of thalidomide is also studied in a number of non-HIV and HIV TBM setting.

CONCLUSION

To have an improved survival rapid and accurate diagnosis and prompt initiation of therapy is mandatory. Early diagnosis and treatment are necessary for improved outcomes.

The current diagnostic techniques are not sufficient enough for confirmation of TBM and much reliance is on imaging. On both MRI and CT contrast scans basal enhancing exudates, leptomeningeal enhancement along Sylvian fissures, with mild enlargement of ventricles is a helpful clue for diagnosis. Certain recent developments like improved smear microscopy and the use of novel biomarkers are promising for improving the diagnostic yield.

Still, the duration of ATT is clinician determined, and the advice by WHO and RNTCP is a bit varied regarding the continuation phase and use of 3 drug or 2 drugs.

According to the WHO guidelines treatment of TBM, is a two-month "intensive phase" with isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin followed by a 10-month continuation phase with isoniazid and rifampicin. A recent development is an advice of not to use injectables. Adjunctive corticosteroids appear to improve survival in HIV-negative patients with TBM, but the mechanism by which they exert their beneficial effects are poorly understood. Corticosteroids are an essential add on treatment for children with TBM and they improve neurological outcomes and morbidity; however, their exact mechanism of action in this aspect has not been clearly elucidated.

Targeted immunomodulatory therapies based on patient genotype is another interesting development that is happening. Further advances in the treatment, especially of drug-resistant TB, is also on the anvil.

REFERENCES

1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
2. YK Amdekar Consensus Statement on Childhood Tuberculosis; Working Group on Tuberculosis, Indian Academy of Pediatrics (IAP) Indian Pediatr 2010;47: 41-55
3. Rom W. Garay S. Tuberculosis. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.
4. Donald PR, Schaaf HS, Schoeman JF. Tuberculous meningitis and military tuberculosis: the Rich focus revisited. J Infect. 2005;50(3):193-195.
5. Rich AR, McCordock HA. The pathogenesis of tuberculous meningitis. Bull Johns Hopkins Hosp. 1933;52:5-37.
6. James J. Central nervous system tuberculosis – The gray area in tuberculosis treatment. J Neurosci Rural Pract. 2019;10(1):6. doi:10.4103/jnrp.jnrp_229_18.
7. Sütlaş PN, Unal A, Forta H, Senol S, Kirbaş D. Tuberculous meningitis in adults: review of 61 cases. Infection. 2003;31(6):387-391. doi:10.1007/s15010-003-3179-1.
8. Cherian A, Thomas SV. Central nervous system tuberculosis. Afr Health Sci. 2011;11(1):116-127.
9. Kennedy DH, Fallon RJ. Tuberculous meningitis. JAMA. 1979;241(3):264-268.
10. Zunt J R, Tuberculosis of the Central Nervous System. CONTINUUM (MINNEAP MINN) 2018;24(5, NEUROINFECTIOUS DISEASE):1422-1438
11. Sharma P, Garg RK, Verma R, et al. Incidence, predictors and prognostic value of cranial nerve involvement in patients with

- tuberculous meningitis: a retrospective evaluation. *Eur J Intern Med.* 2011;22(3):289-295.
12. Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J.* 1999;75(881):133 LP-140. .
 13. Mahadevan A. The enigma of tuberculous vasculopathy - Is it time to review our dogmas?. *Neurol India [serial online]* 2016 [cited 2019 Jan 15];64:864-867. Available from: <http://www.neurologyindia.com/text.asp?2016/64/5/864/190284>
 14. Dastur DK, Lalitha V, Udani PM, et al. The brain and meninges in tuberculous meningitis. *Gross pathology in 100 cases and pathogenesis.* *Neurology* 1970; 18:86-100
 15. Lammie GA, Hewlett RH, Schoeman JF, et al. Tuberculous cerebrovascular disease: A review. *J Infect* 2009;59:156-166.
 16. Lincoln, E. Tuberculous meningitis in children; with special reference to serous meningitis; tuberculous meningitis. *Amer Rev Tuberc* 1947; 56:75.
 17. Luthra G, Parihar A, Nath K, et al. Comparative Evaluation of Fungal, Tubercular, and Pyogenic Brain Abscesses with Conventional and Diffusion MR Imaging and Proton MR Spectroscopy. *Am J Neuroradiol* 2007;28(7):1332-1338.
 18. Kim HJ1, Shim KW, Lee MK, et al. Tuberculous encephalopathy without meningitis: pathology and brain MRI findings. *Eur Neurol.* 2011;65(3):156-159.
 19. Dastur DK, Manghani DK, Udani PM. Pathology and pathogenetic mechanisms in neurotuberculosis. *Radiol Clin North Am* 1995;33(4):733-752.
 20. Bagga A, Kalra V, Ghai OP. Intracranial tuberculoma," *Clinical Pediatrics* 1988;27(10):487-490, .
 21. Cheng VC, Yam WC, Woo PC, et al. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur J Clin Microbiol Infect Dis.* 2003;22:597-602.
 22. Karthik SN, Bhanu K, Velayutham S, et al. Hypertrophic pachymeningitis. *Ann Indian Acad Neurol* 2011;14(3):203-204.
 23. Prabhakar S, Bhatia R, Lal V, et al. Hypertrophic pachymeningitis: varied manifestations of a single disease entity. *Neurol India.* 2002;50(1):45-52.
 24. Yamashita K, Suzuki Y, Yoshizumi H, et al. Tuberculous hypertrophic pachymeningitis involving the posterior fossa and high cervical region--case report. *Neurol Med Chir (Tokyo)* 1994;34(2):100-103.
 25. Tariq R, Ahmed R. Tuberculous hypertrophic pachymeningitis presenting as visual blurring and headaches. *J Pak Med Assoc.* 2012;62(9):966-968.
 26. Dunn RN, Ben Husien M. Spinal tuberculosis. *Bone Joint J* 2018 Apr 1. 100-B (4):425-431.
 27. Turgut M. Spinal tuberculosis (Pott's disease): its clinical presentation, surgical management, and outcome. A survey study on 694 patients. *Neurosurg Rev* 2001;24(1):8-13.
 28. Fuentes Ferrer M, Gutiérrez Torres L, Ayala Ramírez O, et al. Tuberculosis of the spine. A systematic review of case series. *Int Orthop.* 2012;36(2):221-231.
 29. Thakur R , Goyal R, Sarma S. Laboratory Diagnosis of Tuberculous Meningitis – Is There a Scope for Further Improvement? *J Lab Physicians* 2010;2(1):21-24.
 30. Hernández-Albújar S, Arribas JR, Royo A, et al. Tuberculous radiculomyelitis complicating tuberculous meningitis: case report and review. *Clin Infect Dis* 2000;30(6):915-921.
 31. Link-Gelles R, Moultrie H, Sawry S, et al. Tuberculosis Immune Reconstitution Inflammatory Syndrome in children initiating Antiretroviral Therapy for HIV infection: A systematic literature review; *Pediatr Infect Dis J.* 2014;33(5):499-503
 32. Chen P, Shi M, Feng GD, et al. A highly efficient Ziehl-Neelsen stain: identifying de novo intracellular *Mycobacterium tuberculosis* and improving detection of extracellular *M. tuberculosis* in cerebrospinal fluid. *J Clin Microbiol* 2012;50:1166-1170.
 33. Caviedes L, Lee TS, Gilman RH, et al. Rapid, efficient detection and drug susceptibility testing of *Mycobacterium tuberculosis* in sputum by microscopic observation of broth cultures. The Tuberculosis Working Group in Peru. *J Clin Microbiol* 2000;38:pg. 1203-1208.
 34. Sertel Şelale D, Uzun M. The value of microscopic-observation drug susceptibility assay in the diagnosis of tuberculosis and detection of multidrug resistance. *Apmis* 2018;126(1):38-44.
 35. Ekermans P, Dusé A, George J. The dubious value of cerebrospinal fluid adenosine deaminase measurement for the diagnosis of tuberculous meningitis. *BMC Infect Dis* 2017;17:104.
 36. Xu H-B, Jiang R-H, Li L, Sha W, et al. Diagnostic value of adenosine deaminase in cerebrospinal fluid for tuberculous meningitis: a meta-analysis. *Int J Tuberc Lung Dis* 2010;14(11):1382-1387.
 37. Kent SJ, Crowe SM, Yung A, et al. Tuberculous Meningitis: A 30-Year Review. *Clin Infect Dis.* 1993;17(6):987-994.
 38. Pai M, Flores LL, Pai N, et al. Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2003;3(10):633-643.
 39. Thwaites GE, Caws M, Chau TTH, et al. Comparison of conventional bacteriology with nucleic acid amplification (amplified mycobacterium direct test) for diagnosis of tuberculous meningitis before and after inception of antituberculosis chemotherapy. *J Clin Microbiol* 2004;42(3):996-1002.
 40. WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTF/RIF Ultra compared to Xpert MTB/RIF. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.04). Licence: CC BY-NC-SA 3.0 IGO.
 41. Index TB Guidelines. Guidelines on extra-pulmonary tuberculosis for India. World Health Organization; 2016.
 42. Sharma SK, Ryan H, Khaparde S, et al. Index-TB guidelines: guidelines on extrapulmonary tuberculosis for India. *Indian J Med Res* 2017;145(4):448-463.
 43. Kumar GS, Venugopal AK, Mahadevan A, Renuse S, Harsha HC, et al. Quantitative proteomics for identifying biomarkers for tuberculous meningitis. *Clin Proteomics* 2012;9(1):12.
 44. Paris L, Magni R, Zaidi F, et al. Urine lipoarabinomannan glycan in HIV-negative patients with pulmonary tuberculosis correlates with disease severity. *Sci Transl Med* 2017;9(420).
 45. Kumar R, Singh SN, Kohli N. A diagnostic rule for tuberculous meningitis. *Arch Dis Child* 1999;81:221-224.
 46. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis* 2010;10(11):803-812.
 47. Thomas B, Thamburaj K, Kesavadas C. 'Eiffel-by-Night': A New MR Sign Demonstrating Reactivation in Idiopathic Hypertrophic Pachymeningitis. *Neuroradiol J* 2007;20(2):194-195.
 48. "WHO treatment guidelines for drug resistant tuberculosis (2018 update)", WHO, Geneva, 2018 https://www.who.int/tb/features_archive/updated-treatment-guidelines-multidrug-rifampicin-resistant-TB/en/.
 49. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004;351:1741-1751.
 50. Schoeman JF, Janse van Rensburg A, Laubscher JA, et al. The role of aspirin in childhood tuberculous meningitis. *J Child Neurol* 2011;26:956-962.