Review Article

CNS Tuberculosis

K Muralidharan[1], Mugundhan Krishnan[2], Jyotirmoy Pal[3]

Tuberculosis can involve almost any organ of the body. In the Central Nervous System (CNS) it can cause meningitis, tuberculoma, abscess,spondylitis, arachnoiditis, myeloradiculitis or other manifestations. Around 10% of all patients with tuberculosis have CNS involvement. Tuberculosis is rampant in the developing world and has reemerged as a major public health menace with the HIV pandemic. Compared with HIV-negative individuals, HIV-positive individuals with TB are 5 times more likely to have CNS involvement. Laboratory confirmation of CNS TB is difficult and hence empirical treatment has to be initiated as early as possible based on clinical and radiological features. In this article,we review the CNS manifestations of tuberculosis and their diagnosis and treatment.

[*J Indian Med Assoc* 2022; **120(6):** 47-52]

Key words **: Tuberculoma, Meningitis, Abscess, Spondylitis, Pott's spine, myeloradiculitis, Optochiasmal arachnoiditis, Caseation, Ependymitis, Hydrocephalus, Optic neuritis, Adenosine deaminase.**

Tuberculosis (TB) is caused by the acid-fast bacillus Mycobacterium tuberculosis. TB accounts for 10 million new symptomatic infections and 1.4 million death globally, with a prevalence estimated at 25% of the world's population. Although pulmonary TB is the most common site of active disease, extrapulmonary TB is not uncommon, accounting for 10% to 40% of cases globally[1]. Risk factors for developing Central Nervous System (CNS) TB include malnutrition, alcoholism, concomitant malignancy, use of immunosuppressive medications, HIV infection, recent measles, and measles in childhood[1]. Although nervous system involvement is less common than involvement of other extrapulmonary sites, It is one of the most severe forms of TB and is associated with high mortality, especially among people with HIV[1].

Classification of Neurological Tuberculosis :

(1) Tuberculosis meningitis
(2) Tuberculosis arachnoiditis
- Basal
- Opticochiasmatic
- Spinal

(3) Tuberculoma
- Intracranial
- Spinal

Editor's Comment :
- Around 10 percent of patients with TB have CNS involvement.
- CNS TB includes TB meningitis, TB arachnoiditis, Tuberculoma and TB abscess.
- Cranial nerves 6,7 and 2 are frequently involved in TB meningitis.
- Stroke, seizures and hydrocephalus are frequent complications of TB meningitis.
- TB can also cause optic neuropathy, optochiasmatic arachnoiditis, subarachnoid hemorrhage, limbic encephalitis and NMO.
- Spinal TB causes spondylitis, radiculomyelitis, spinal arachnoiditis, intramedullary tuberculoma.
- Duration of treatment in CNS TB is 9-12 months.
- Laboratory confirmation of CNS TB is difficult and hence empirical treatment should be initiated as early as possible based on clinical and radiological features.

(4) Tuberculosis abscess

Tuberculous Meningitis :

The most common form of CNS TB is tuberculous meningitis, which can present as either insidious chronic meningitis or acute fulminant meningitis

Pathogenesis :

It was initially hypothesized that tuberculous meningitis resulted from an extension of infection into the subarachnoid space from a caseating focus in the adjacent cortex (the Rich focus). A later hypothesis agreed with this theory but also suggested that initial hematogenous dissemination could result in a meningeal or cortical focus that produced immediate or delayed tuberculous meningitis.

[1]DM (Neuro), Postgraduate Trainee, Stanley Medical College, Chennai 600001
[2]MD, DM (Neuro), FICP, FRCP (Glasg), FACP (USA), Professor and Head, Stanley Medical College, Chennai 600001 and Corresponding Author
[3]MBBS, MD (Medicine), FICP, FRCP, WHO Fellow, Professor, Department of Medicine, R G Kar Medical College and Hospital, Kolkata 700004

Received on : 05/05/2022
Accepted on : 02/06/2022

Pathology of TB Meningitis :

- Meningitis
  - Inflammatory leptomeningeal exudate
  - Caseous necrosis
  - Proliferative opticochiasmatic arachnoiditis
- Vasculitis
  - Arteritis
  - Phlebitis
- Ependymitis and choroid plexitis
- Encephalitis
  - Cortical
  - Subependymal
  - Vasculitis and infarction
- Hydrocephalus
  - Communicating
  - Obstructive

Clinical Presentation :

Tuberculous meningitis can develop insidiously or in an abrupt manner similar to bacterial or viral meningitis. The most common symptoms of tuberculous meningitis include fever, headache, vomiting and apathy. Given the frequent involvement of the basilar meninges and ambient cistern in tuberculous meningitis, cranial nerve dysfunction is frequent, with cranial nerves VI (abducens), VII (facial), and II (optic) most often affected[1].

Stroke is one of the most common complications of tuberculous meningitis, occurring in approximately 30% to 60% of cases. These strokes are usually found in the basal ganglia because of involvement of small penetrating arteries that are surrounded by exudates in the basal cisterns, but abnormalities of the large anterior circulation arteries are also common due to tuberculous vasculopathy. Hypothesized stroke mechanisms include endothelial reactions to inflammatory exudates, proliferative and necrotizing arteritis, and hypercoagulable states.

Seizures are also common in tuberculous meningitis, occurring in 34% of individuals. The majority were focal onset, and nearly one-quarter presented with status epilepticus. Early seizures were associated with meningeal irritation, whereas late seizures were more common in those with tuberculomas, infarcts, and hyponatremia.

Hydrocephalus is a common complication of tuberculous meningitis.When CSF protein is greater than 500 mg/dL, obstruction of CSF flow can occur and produce subarachnoid block, leading to hydrocephalus.

Complications of TB Meningitis :

- Raised intracranial pressure, cerebral oedema, stupor
- Basal meningitis with cranial nerve palsies
- Focal neurological deficits
- Hydrocephalus
- Tuberculoma
- Tuberculosis abscess
- Opticochiasmatic pachymeningitis resulting in visual loss
- Tuberculosis arteritis and stroke
- Endocrie disturbances
- Hypothalamic disorder leading to loss of control of blood pressure and body temperature
- Diabetes insipidus
- Syndrome of inappropriate antidiuretic hormone secretion Internuclear ophthalmoplegia
- Hemichorea
- Spinal block
- Spinal arachnoiditis

Investigations[3] :

(1) Radiological Studies

Chest radiograph —

The chest radiographs reveal findings consistent with pulmonary TB in 25 to 50 per cent of adult patients and 50 to 90 per cent of children with TBM.

Neuroimaging —

The CT or MRI of the brain may reveal thickening and enhancement of basal meninges, hydrocephalus, infarction, oedema [often periventricular], and mass lesions due to associated tuberculoma or TB abscess. Common sites of exudates are basal cisterna ambiens, suprasellar cistern and Sylvian fissures. Hydrocephalus, Enhancements of basal meninges, cerebral infarction most frequently in the MCA territory, are seen (Fig 1).

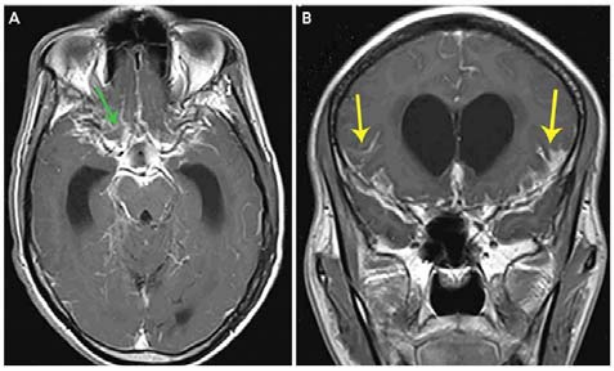

Fig 1 — Axial (A) and coronal (B) postcontrast T1-weighted MRIs reveal a thick basal exudate (A, green arrow) in the basal cisterns and leptomeningealenhancement (B, yellow arrows) in the frontotemporal regions bilaterally as well as acommunicating hydrocephalus.

(2)Tuberculin Skin Test

Tuberculin skin test is positive in 40 to 65 per cent of adults and in 85 to 90 per cent of children with TBM in western studies . However, TST lacks specificity in developing countries because of the possibility of previous sensitization to environmental mycobacteria and BCG vaccination.

(3) CSF

Because of the paucity of TB organisms in the CSF, diagnosis of CNS TB can be difficult.The most common pattern of CSF abnormalities in tuberculous meningitis is a mononuclear (ie, lymphocytic or monocytic) pleocytosis, low glucose, and markedly elevated protein.

Cytology and biochemistry **:** In TBM, the leucocyte count is usually between 100 to 500 cells/ìl, but rarely can exceed 1000 cells/ìl. Predominantly, lymphocytes are increased in the CSF, although in the acute stage a polymorphonuclear response is not unusual. It is transient and replaced by lymphocytic reaction in the course of days to weeks. Occasionally, the cell count may be normal.

The CSF protein is generally between 100 to 200 mg/dl. In the presence of co-existing spinal meningitis and spinal block, the values can exceed 1 g/dl and the fluid may be xanthochromic. If allowed to stand, a pellicle or cobweb may form, indicating the presence of fibrinogen. The pellicle is highly suggestive but not pathognomonic of TBM.

The CSF glucose level is abnormal in majority of cases, being less than 40 per cent of the corresponding blood glucose level. Median glucose levels are reported to be between 18 to 45 mg/dl[3].

Adenosine Deaminase

Elevated ADA in the CSF accompanies most forms of meningitis and is closely correlated with levels of CSF protein. Although elevated ADA levels are not specific for tuberculous meningitis, elevated levels have been associated with poor prognosis of tuberculous meningitis in children. In one meta-analysis, ADA values greater than 8 U/L improved the diagnosis of tuberculous meningitis (sensitivity <59% and specificity >96%).

Acid-fast Bacilli Stain and Culture

CNS TB is difficult to diagnose using traditional Ziehl-Neelsen stain and mycobacterial culture.When only one CSF examination is performed, the sensitivity of smear and culture are 37% and 52%, respectively while if three CSF samples are examined, the yield increases to 87% and 83%.59 Unfortunately, CSF culture typically takes 2 to 4 weeks to become positive, so when CNS TB is suspected, empiric treatment for presumptive CNS TB should be initiated before confirmation[3].

Tuberculosis Polymerase Chain Reaction

Most PCR assays for M. tuberculosis detection amplify the MPB64 gene or IS6110. The sensitivity and specificity of PCR assays for M Tuberculosis are highly dependent upon the diagnostic criteria used, the amount of CSF sampled, and whether antituberculous therapy was administered before the collection of CSF.The PCR assays can be more sensitive than CSF culture, but diagnosis of tuberculous meningitis cannot be excluded on the basis of a negative PCR result

Cartridge-Based Nucleic Acid Amplification Test

This same-day detection of rifampin-resistant bacteria can influence the decision to switch to second-line agents . In tuberculous meningitis cases from India, CSF MTB/RIF Xpert, Xpert MTB/RIF Ultra, and multiplex PCR all demonstrated 100% specificity, but 71%, 28%, and 88% sensitivity, respectively[2].

(4) Biopsy

Biopsy can be a useful ancillary test for patients with solitary enhancing lesions or chronic meningitis with persistently negative cultures. Although the sensitivity of biopsy is unknown, examination of infected tissue with Ziehl-Neelsen staining, culture, and PCR assays should increase the diagnostic yield.

In practice, a combination of clinical and laboratory parameters is used to make clinical decisions in high-TB-burden settings, which often lack extensive CSF diagnostic testing. In these settings, a high degree of suspicion for TB is maintained even in the absence of confirmatory microbiological evidence from the CSF[2].

Tuberculoma:

Tuberculomas are space-occupying lesions consisting of granulomatous reactions to M Tuberculosis infection that are believed to arise from the hematogenous spread of mycobacteria to the brain parenchyma. Microscopic granulomatous foci, called Rich foci, develop over time, organizing into encapsulated granulomatous mass lesions. Tuberculomas are similar to tuberculous abscesses, but abscesses are often larger and have a pus-filled cavitary center[2].

Ten percent of patients with tuberculous meningitis also have tuberculomas; with one-third of such patients having multiple tuberculomas. The clinical presentation of CNS tuberculoma typically includes headache, seizures, focal neurologic deficits, and papilledema. Tuberculomas can develop in the brain; spinal cord; or subarachnoid, subdural, or epidural space and are often accompanied by surrounding edema and ring enhancement[4].

On neuroimaging, tuberculomas are typically space-occupying lesions.As the center of the tuberculoma caseates and becomes liquefied, neuroimaging characteristics on T2-weighted and

FLAIR MRI sequences change from hypointense to isointense to hyperintense[4]. While in adults, tuberculomas are typically supratentorial, in children, lesions are often infratentorial.The CSF of patients with tuberculomas is typically unremarkable, while the tuberculin skin test is positive in up to 85% and chest radiography is abnormal in 30% to 80% (Fig 2).

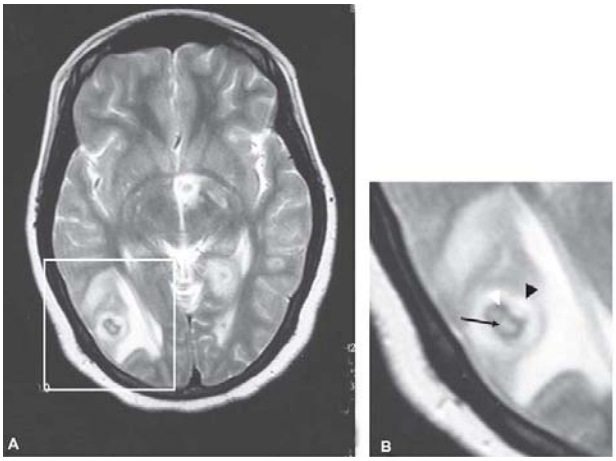

Fig 2 — MRI of the brain [T2-weighted image, axial view] showing characteristic appearance of a tuberculoma [A]. Close-up view of the lesion showing central hyperintense area [solid arrow] suggestive of caseation necrosis; surrounding hypointense rim [white arrow head] of fibrousis capsule; and a significant perilesional white matter oedema [black arrrow head]

Tuberculous Abscess :

Tuberculous abscess occurs in less than 10% of patients with CNS TB and represents a later stage of tuberculoma.An abscess contains many more bacilli than a granuloma.The clinical symptoms produced by a tuberculous abscess typically include fever, headache, and focal neurologic deficits.

Differentiation between tuberculoma and tuberculous abscess can be difficult by neuroimaging, but an abscess wall tends to be thicker, can be multiloculated, and typically has contrast enhancement. On DWI sequences, MRI may demonstrate restricted diffusion in tuberculomas or abscesses with liquefied caseation but this is absent in lesions that have only solid caseation.

Other CNS Tuberculosis Manifestations :

TB has a myriad of uncommon CNS manifestations including optic neuropathy, optochiasmatic arachnoiditis, tuberculous encephalopathy, subarachnoid hemorrhage, limbic encephalitis, and a possible unproven association with neuromyelitis optica[1].

Optic neuritis/optic neuropathy

Most optic neuropathies are secondary to chronic increased intracranial pressure, mass effect from tuberculomas, or drug-associated toxicities. However, primary optic neuropathies have also been reported and can be the presenting sign of Central Nervous System (CNS) tuberculosis (TB). In these cases, optic neuritis occurs because of tubercular perineuritis, endarteritis of the optic nerve, or arachnoiditis of the optic nerve and/or chiasm.

Optochiasmatic arachnoiditis

Occurs in conjunction with tuberculous meningitis when accumulation of exudates in the basal cisterns leads to arachnoiditis of the optic nerves and chiasm, which manifests as slowly progressive vision loss and most commonly occurs in younger individuals. It also occurs as part of a paradoxical reaction after initiation of antituberculous treatment.

Tuberculous encephalopathy

It occurs most commonly in the pediatric population. Its clinical presentation ranges from focal neurologic deficits or confusion to seizures or coma. MRI shows extensive white matter changes, usually with contrast enhancement and sometimes diffuse cerebral edema, but CSF is usually normal or only mildly abnormal.It is thought not to be caused by direct infection of the CNS by TB but to be an immune-mediated reaction. Two mechanisms have been postulated : (1) an acute disseminated encephalomyelitis (ADEM)-like mechanism; and (2) an allergic (type IV hypersensitivity) reaction within the nervous systemto systemic TB protein. Early diagnosis and initiation of antituberculous treatment and steroids is imperative to reduce associated morbidity and mortality[1].

Subarachnoid hemorrhage

Occurs as a result of rupture of tuberculous cerebral aneurysms that develop in the setting of tuberculous meningitis[1].

Treatment :

The WHO recommends treatment of tuberculous meningitis in two stages: (1) the intensive phase: rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months followed by (2) the continuation phase: rifampicin and isoniazid for an additional 7 to 10 months (9 to 12 months of total treatment)[2,5]. Of the available antituberculous medications, isoniazid and pyrazinamide have the best penetration into the subarachnoid space.

Multidrug-resistant and extremely drug-resistant TB infections usually require prolonged treatment with additional antituberculous agents such as levofloxacin, bedaquiline, linezolid, clofazimine, cycloserine, and amikacin. In addition to antituberculous agents, concomitant steroids tapered over 6 to 8 weeks have also been shown to reduce mortality, severe disability, and disease relapse[2,5].

Corticosteroids

The WHO recommends initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6 to 8 weeks for all patients

with tuberculous meningitis.

Corticosteroids reduce intracranial pressure and decrease inflammation in the subarachnoid space, cerebrum, spinal cord, and small blood vessels. The theoretical harm of corticosteroids results from reducing meningeal inflammation, thus potentially decreasing penetration of antituberculous medications; from suppressing the immune system, which could lead to bacterial superinfection.

If corticosteroids are administered, dexamethasone is most often used at a dosage of 12 mg/d to 16 mg/d for 3 weeks, then tapered off over 3 weeks. For patients who experience worsening during or after tapering, corticosteroids can be extended for a longer period[6].

Spinal Tuberculosis :

TB can involve every compartment of the spine including bony structures, intradural and extradural spaces, the spinal cord, and nerve roots. The thoracic and lumbar regions are most commonly involved, but cervical involvement occurs in more than one quarter of affected individuals and is associated with more frequent neurologic sequelae than other locations[2].

Majority of cases of spinal TB occur in the absence of pulmonary disease. The most common manifestations of spinal TB are spondylitis and intradural tuberculous spinal infections including radiculomyelitis, spinal arachnoiditis, intramedullary tuberculomas, and myelitis

Spondylitis

Spondylitis, also known as Pott disease, is the most common form of spinal TB and accounts for 50% of cases of skeletal TB.It presents with insidiously evolving nonspecific back pain followed by kyphosis (clinically as a gibbus formation on the back), sensory symptoms, bowel and bladder symptoms, and, finally, paraparesis. Progression through these stages occurs over the course of months to more than 1 year.

Acute presentations of neurologic deficits are not uncommon because of vertebral fracture or abscess formation with subsequent spinal cord compression. Imaging classically shows edema and bony destruction of the vertebral body with paravertebral granulomatous exudates or abscess. The thoracic cord is the most common location, and spondylitis often involves three or more consecutive vertebral bodies while sparing the intervertebral discs[7] (Fig 3).

Intradural Tuberculous Spinal Infections

Intradural tuberculous spinal infections, including radiculomyelitis, spinal arachnoiditis, intramedullary tuberculomas, and myelitis, are seen most commonly in the setting of tuberculous meningitis because of the spread of inflammatory exudates from the cranial to the spinal compartment. These inflammatory exudates often settle in the lumbosacral subarachnoid space and present with a conusmedullaris or cauda equina syndrome. The subarachnoid space may also become irregularly obstructed because of these exudates, resulting in the formation of CSF loculations. Syrinx is a frequent late complication of tuberculous meningitis and spinal TB.

Tubercular radiculomyelitis is the most common intradural spinal manifestation of TB, occurring in nearly 40% of individuals with tuberculous meningitis. Tuberculous radiculomyelitis typically produces a subacute, gradually progressive, lower limb weakness with bladder dysfunction,paresthesia, radicular pain, and muscle wasting. Neuroimaging of tuberculous radiculomyelitis often reveals obliteration of the spinal subarachnoid space, loss of spinal cord landmarks, clumping of nerve roots, and nodular intradural enhancement.

Intradural extramedullary tuberculomas, intramedullary tuberculomas, and tuberculous abscesses occur in 20%, 9%, and 7% of patients, respectively.(2,8) Complications of these infections include spinal cord vasculitis and infarcts (Fig 4).

Diagnosis

For Pott disease, initial investigations usually include spinal imaging, which, in many high-TB-burden

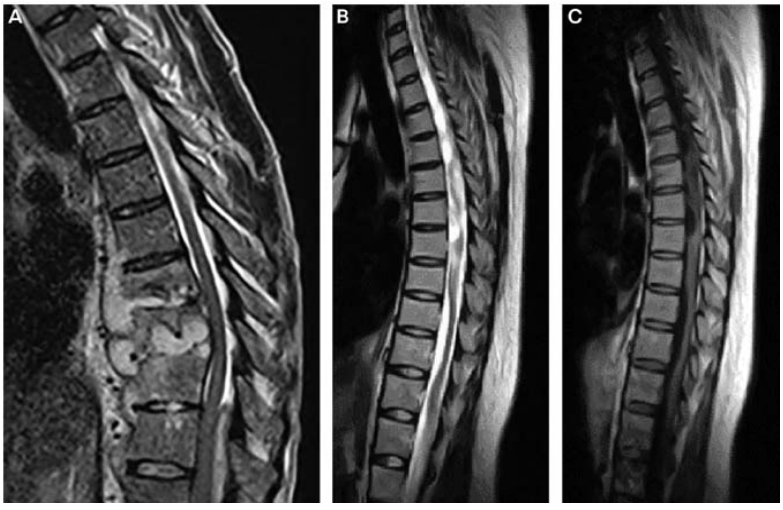

Fig 3 — Sagittal T2-weighted (A) image from thoracic spine MRI demonstrating vertebral body destruction, loss of disc height, erosion, and paravertebral masses consistent with tuberculous spondylitis. Sagittal T2-weighted (B) and T1-weighted (C) images from another

settings, may be limited to plain x-rays. If oblique views are obtained as part of the spine series, plain radiographs can demonstrate sensitivity as high as 70% for the diagnosis of spondylitis, although they may be normal early in the disease[2,9].

Radiolucencies and loss of definition of plate margins are the earliest findings in spondylitis followed by vertebral body destruction (most commonly involving the anterior portion of the vertebral body), endplate erosion, loss of normal disc height, sclerosis, and paravertebral masses. Where MRI is available, the combination of subligamentous spread, vertebral collapse, and large abscess collection with a thin wall was comparable to biopsy-obtained tissue studies in discriminating TB from non-TB etiologies.In cases of spinal arachnoiditis, CSF loculations are often visualized on MRI.

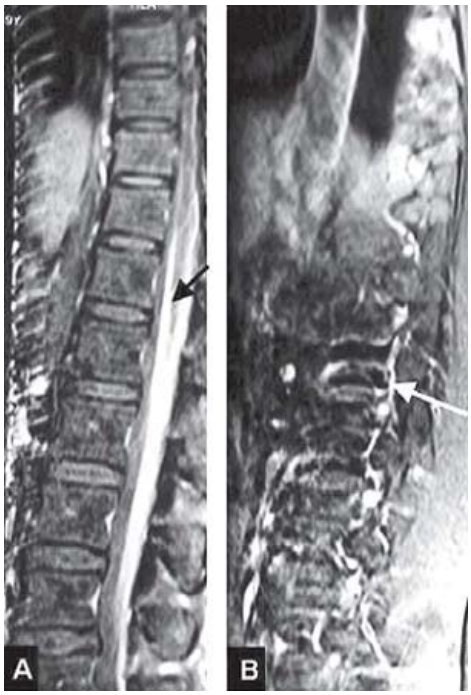

Fig 4 — Contrast enhanced MRI in a patient with spinal pachy arachnoiditis showing post-gadolinium enhancement of meninges [arrow] [A]; and nerve roots [arrow] [B] in a patient with spinal pachy arachnoiditis

With intradural spinal tuberculosis, CSF is often abnormal and shows a profile similar to tuberculous meningitis. In Pott disease, however, CSF is often normal, and bone biopsy, which is the gold standard to exclude alternative infectious and neoplastic etiologies, is often difficult in resource-limited settings.

Treatment of Spinal TB

Similar to tuberculomas, a presumptive diagnosis based on clinical presentation and x-ray findings (or other neuroimaging findings if available) is often required for all forms of TB of the spine and is followed by initiation of empiric TB treatment. TB treatment for 9 to 12 months (ie, intensive phase therapy for 2months followed by 7 to 10 months of continuation phase therapy) with adjuvant corticosteroids is recommended. Among individuals with spondylitis, surgical options, including decompression, stabilization, and correction of kyphoscoliotic deformities, are considered on a case-by-case basis[1,10].

Conclusion :

CNS TB is a common complication of pulmonary TB, which is difficult to diagnose. Diagnosis is most efficiently made through combining CSF examination with traditional methods of diagnosis, eg, Ziehl-Neelsen stain and mycobacterial culture, and with newer technologies. As the diagnosis of TB is frequently delayed by weeks, empiric treatment should be started when CNS TB is suspected. When possible, TB infection should be confirmed through culture of CSF or other tissue and drug susceptibility determined, as antituberculous treatment should be adjusted if multidrug-resistant TB or extensively drug-resistant TB is detected.

Concomitant treatment with steroids should be administered to all patients with tuberculous meningitis and strongly considered for other forms of CNS TB that are accompanied by edema. Although HIV coinfection does not typically alter the radiographic or neurologic presentation of CNS TB, ART can influence the natural history of CNS TB (eg, IRIS), so HIV status should be determined in all patients presenting with TB infection.

References

1 Saylor D — Neurologic Complications of Tuberculosis ; *Continuum (Minneap Minn)* 2021; **27(4, Neuroinfectious Disease):** 992-1017.
2 Zunt JR — Tuberculosis of the Central Nervous System; Continuum (Minneap Minn) 2018; 24(5, Neuroinfectious Disease): 1422-38.
3 World Health Organization — Global tuberculosis report 2020. Geneva, Switzerland: World Health Organization, 2020.
4 Sharma K, Sharma M, Shree R — Xpert MTB/ RIF Ultra for the diagnosis of tuberculous meningitis: a diagnostic accuracy study from India. *Tuberculosis (Edinb)* 2020;**125:**101990. doi:10.1016/j.tube.2020.101990
5 World Health Organization — Treatment of tuberculosis: guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva, Switzerland: World Health Organization, 2017.
6 Prasad K, Singh MB, Ryan H — Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2016;4(4):CD002244. doi:10.1002/14651858.CD002244.pub4
7 Jain AK, Rajasekaran S, Jaggi KR, Myneedu VP — Tuberculosis of the spine. *J Bone Joint Surg Am* 2020; **102(7):** 617-28. doi:10.2106/JBJS.19.00001
8 Salvador GLO, Basso ACN, Barbieri PP — Central nervous system and spinal cord tuberculosis: revisiting an important disease. *Neuroradiology* 2021; **69:** 158-68. doi:10.1016/ j.clinimag.2020.07.020
9 Gupta RK, Gupta S, Kumar S — MRI in intraspinal tuberculosis. *Neuroradiology* 1994; **36(1):** 39-43. doi:10.1007/BF00599194.
10 Sharma P, Garg RK, Verma R — Incidence, predictors and prognostic value of cranial nerve involvement in patients with tuberculous meningitis: a retrospective evaluation. *Eur J Intern Med* 2011; **22(3):** 289-95. doi:10.1016/ j.ejim.2011.01.007.