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Various Manifestation of Central Nervous System Tuberculosis: A Review

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Abstract
Tuberculosis (TB) is the most common disease of the world. The incidence of tuberculosis of central nervous system is on increasing trend day by day. The most common site of tuberculosis is lung. Extrapulmonary TB can occur primarily or by hematogenous spread. Extrapulmonary TB accounts for 20% of all TB cases. Central nervous system TB is common. The diagnosis of central nervous system tuberculosis can be made by combining clinical history, laboratory findings and radiological findings which includes Computed tomography (CT) and Magnetic Resonance Imaging (MRI). Central nervous system tuberculosis may occur in different forms like tuberculous pachymeningitis/ tuberculous en plaque, tuberculous leptomeningitis, tuberculoma, tuberculous abscess, cerebritis, encephalopathy, miliary tuberculosis leading to tuberculous vasculitis and infarction, neuropathy, visual complications and hydrocephalus. The aim of writing this review is to overview all the manifestations of central nervous system tuberculosis. Different MRI modalities have been used to study the features of intracranial tuberculosis. The diagnosis and treatment of central nervous system tuberculosis on time is mandatory in order to prevent other neurological sequelae caused by the disease and thus prevent morbidity and mortality.
Keywords: tuberculosis, central nervous system, magnetic resonance imaging.

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Introduction

According to WHO (World Health Organization), around one third of the world's population is found to be infected with tuberculosis leading to 1.5 million deaths especially in HIV patients [1]. There are around 9 million new cases of TB per year. CNS tuberculosis accounts for 5–10% of extra-pulmonary tuberculosis. Tuberculosis in CNS can occur primarily or secondarily due to hematogeneous spread. Intracranial tuberculoma account for 5 to 30% of all space occupying lesions of brain. The incidence of CNS TB is high in developing countries. It is often endemic affecting mainly the children and immune-compromised population. It is the second cause of death due to infection, the first being HIV. TB ranks as the leading cause of deaths among HIV-positive people and also in women of reproductive age. The distribution of tuberculosis varies dramatically among countries affecting larger populations in Asia and Africa compared to US and Europe [2].

The aim of this review is to understand the different manifestations of CNS tuberculosis. Among other forms of extrapulmonary tuberculosis, central nervous system involvement is the most severe. If not diagnosed and treated on time, it can lead to serious neurological complications leading to morbidity and mortality. So, a thorough review of brain tuberculosis is needed for clinicians and radiologists to understand this severe disease. As MRI is important radiological tool in diagnosis of central nervous system tuberculosis, we tried to focus on radiological manifestation of this disease.

Meningitis (95%), tuberculomas (2%) and abscesses (1%) are most common manifestations of CNS tuberculosis [3]. The disease is in rising trend due to multidrug resistant strains of tuberculosis and epidemic of HIV/AIDS. In HIV patients multiloculated abscess, cisternal enhancement, basal ganglia infarction and communicating hydrocephalus can suggest tuberculous meningitis [4]. Different MRI modalities like conventional MRI, diffusion weighted imaging, perfusion weighted imaging, diffusion tensor imaging, magnetization transfer MRI, proton magnetic resonance spectroscopy etc. have been used to study different characteristics of tuberculous meningitis, tuberculoma, tuberculous abscess etc. Mycobacterium tuberculosis is an aerobic acid-fast bacillus (AFB) bacteria that primarily hosts the human body. The bacteria most frequently affects the regions of the body that are highly oxygenated, including lungs, brain etc. It can affect CNS primarily or by hematogeneous spread from other sites, usually lung [5].

1. Meningitis

1.1 Tuberculous pachymeningitis/ Tuberculous en plaque

It is an unusual manifestation of CNS tuberculosis. It is often localized (so called tuberculoma en plaque) or sometimes diffuses. It is homogeneous and uniformly enhancing [6]. It can be seen over cerebral convexities, basal or tentorial regions and over falx [7]. In 1927, Pardee and Knox first described tuberculous en plaque as plaque like meningitic process without exudation, usually in the frontal and the parietal region [8, 9].

1.2 Tuberculous leptomeningitis

It is seen in 95% cases of CNS TB. It can spread hematogenously from lung or the Rich focus in subpiamater or subependyma can rupture into the subarachnoid spaces or into the ventricular system leading to CNS TB. It is most common in basal cisterns, sulci over the cerebral convexities, sylvian fissures and cerebellar sulci. Choroid plexitis or ependymitis of the ventricular system is rare [10]. It is better demonstrated by contrast-enhanced MRI which shows cisternal and meningeal enhancement. Parmar et al. demonstrated that leptomeningeal enhancement can be better seen at post contrast fluid attenuation inversion recovery (FLAIR) images with higher specificity than contrast-enhanced T1-weighted images [11]. The gelatinous exudate consists of tuberculous bacilli, neutrophils, erythrocytes, mononuclear cell, epithelioid cells and Langerhans giant cells. In a study, Magnetization Transfer (MT) MRI was used to detect and characterize the meningeal enhancement of infectious meningitis of different etiology. The meninges were visible on pre-contrast T_1 weighted MT images only in patients with tuberculous meningitis [12]. Tuberculous meningitis (TBM) can also cause border-zone necrosis (BZN) of the brain parenchyma in areas adjacent to meningeal inflammation and the cytotoxic edema associated with necrosis can be detected by Diffusion weighted imaging (DWI) [13]. Other radiologic manifestations of tuberculous meningitis include hydrocephalus, vasculitis, infarction, and cranial neuropathies [14].

The hydrocephalus in tuberculous meningitis can be communicating (common) or non-communicating type. The basal cisterns are blocked by the inflammatory exudate which can lead to communicating hydrocephalus. The non-communicating type of hydrocephalus may be due to obstruction by tuberculoma or tuberculous abscess. A study showed that linear measures of hydrocephalus are more reliable than volumetric ratios in tuberculous meningitis [15]. The ependymal and subependymal region is destroyed, blood vessels are distorted and capillaries are collapsed, axons and myelin in the periventricular white matter are damaged, and in some cases neurons are injured due to hydrocephalus. It can also affect choroid plexus, extracellular spaces, cortex and basal ganglia [16].

Tuberculous vasculitis and ischemic infarction are common complication in tuberculous meningitis. Tuberculous meningitis leading to infectious cerebral vasculopathy is a rare cause of acute hemiparesis [17]. Stroke is seen in 15–57% of patients with tuberculous meningitis. Acute stroke can be detected by Diffusion Weighted Imaging (DWI) and chronic stroke can be detected by T2- weighted imaging and FLAIR (Fluid Attenuation Inversion Recovery). It can be anterior (caudate, genu, anterior limb of internal capsule, anteromedial thalamus) and posterior (lentiform nuclei, posterior limb of internal capsule, posterolateral thalamus). The arteries involved in this area are medial striate, thalamotuberal and thalamostriate arteries. Cytokines especially tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF) and matrix metaloproteineases (MMPs) play major role in damaging the blood brain barrier, attracting leucocytes and release of vasoactive autocoids [18].

Vascular endothelial growth factor (VEGF) and Matrix Metalloproteinase (MMP-9) are important growth factors for angioneogenesis. VEGF, as name suggests, increases the number of capillaries and MMPs help degrade the proteins that keep the vessel walls solid. VEGF was found in the inflammatory cells and endothelial lining of granuloma. The MMP-9 breaks down the extracellular matrix constituting the blood brain barrier and the blood–CSF barrier leading to brain edema and tissue damage. It degrades type IV and V collagens present in the basement membrane associated with CNS endothelial cells and facilitates leukocyte migration across the blood–brain barrier. Dynamic Contrast-Enhanced MRI parameters like cerebral blood volume (CBV), cerebral blood flow (CBF), k-trans (Influx Volume Transfer Constant) and leakage (V_e) have been used to study angiogenesis in gliomas and tuberculomas. The Cerebral Blood Volume provides information about the angiogenic activity of pathological tissue, while the k-trans and V_e demonstrate integrity of the blood brain barrier and changes in EES (Extravascular Extracellular Space). The mean relative Cerebral Blood Volume (rCBV) ratio for tubercular lesion was 0.9 to 0.49 [19]. There is a

strong correlation between k-trans and MMP-9 and a weak correlation between k-trans and VEGF. There is a direct correlation of VEGF with MVD (Microvascular Density) and Dynamic Contrast-Enhanced derived rCBV which suggests that rCBV can be used as a measure of angiogenesis in tuberculomas [20]. In a study by Gupta et al using DTI (Diffusion Tensor Imaging), MMP-9 showed strong negative correlation with FA (fractional anisotropy), CL (linear anisotropy) and CP (planar anisotropy) and significant direct correlation with CS (spherical anisotropy). Diffusion Tensor Imaging - MRI can study the microstructural organization of tissue in vivo [21-23]. The strong correlation between cerebrospinal fluid MMP-9 and neutrophil count suggests that polymorphonuclear leukocytes may play a central role in the early pathogenesis of tuberculous meningitis [24].

Cytokines are small proteins that are important in cell signaling. Central nervous system cells like astroglia, endothelial cells and monocytes release cytokines by interaction with bacterial cell wall components like peptidoglycan and lipopolysaccharides. TNF-α (Tumor Necrosis Factor-α) and IFN-γ (Interferon-γ) are the main cytokines involved in the pathogenesis of tuberculous meningitis. They are also associated with tissue necrosis [25]. CSF INF-γ levels increase that is > 6.4 IU/mL in TBM patients. Polymerase Chain Reaction and INF-γ can be used for the diagnosis of tuberculous meningitis [26]. The levels of cytokines decline following anti-tubercular therapy [27]. In a study, significant positive correlation of PCs (proinflammatory cytokines) with fractional anisotropy (FA) values and post-contrast signal intensity (PCSI) collected from cerebral cortical regions was observed in tuberculous meningitis patients [28].

Tuberculous neuropathy is seen in 17.4-70% of tuberculous meningitis patients. It usually involves 3rd, 4th and 7th cranial nerves. It may be due to vasculitis due to exudates which can cause ischemia of the nerve or the nerve itself may be damaged in the basal exudates [29]. Vision impairment can occur in one-fourth of patients with tuberculous meningitis. It can lead to blindness. It can be caused by chronically raised intracranial pressure due to hydrocephalus and/or tuberculomas or it can be caused directly by optic chiasm or optic nerves involvement by the basal arachnoiditis or optochiasmatic arachnoiditis due to inflammation and/or compression or optochiasmatic tuberculoma [30]. It may also lead to death or severe disability in these patients [31].

Leptomeningeal carcinomatosis, also referred as neoplastic meningitis (NM) and primary diffuse leptomeningeal gliomatosis, other infective meningitis, inflammatory diseases such as rheumatoid arthritis, sarcoidosis can show similar presentation on MRI as tuberculous meningitis and multiple dural tuberculomas [32]. Similarly, tuberculomas can be confused with intracranial tumors or other space-occupying lesions.

2. Parenchymal tuberculosis

2.1 Intracranial tuberculoma

Tuberculomas are solid firm granulomatous masses measuring 2 to 6 cm in diameter. Intracranial tuberculoma can be single, multiple or miliary. According to C. Arseni, the size of tuberculomas were small (less than 15g) , medium size (15 to 20 g), large (over 20g) and exceptional size (60 to 100g) and the clinical symptoms were not proportional to the size of the tuberculoma [33]. Tuberculomas are common in cerebellum, basal ganglia and cerebral hemispheres, especially in the frontoparietal region. It can also be seen in corpus callosum, quadrigeminal plate, cerebellopontine angle, retroorbital region, anterior optical pathway, suprasellar region and the ventricles [34]. It can occur in meninges, parenchyma or ependymal [35]. Tuberculomas can be represented as any of the following forms on MRI:

Noncaseating granuloma: It is isointense or hypointense on T1 and hyperintense on T2-weighted images. It is homogeneously enhanced on contrast enhanced MRI.

Caseating granuloma with a solid center: It is hypointense on T1 and T2-weighted images. It is due to granulation tissue and compressed glial tissue in the central core which owing to greater cellular density. Rim is enhanced on contrast MRI.

Caseating granuloma with a liquid center: There is central hypointense on T1 and hyperintense on T2-weighted images and a peripheral hypointense rim on T2W images. The capsule is hypointense due to a layer of collagenous fibers with high protein concentration and low water content and a layer of outer inflammatory cells. Rim is enhanced when contrast is used.

In vivo, PMRS (Proton Magnetic Resonance Spectroscopy) shows high choline and lipid and Lipid-lactate resonances and a low creatine resonance in tuberculoma [36]. T1-weighted MT (Magnetization Transfer) MR imaging combined

with MRS (Magnetic Resonance Spectroscopy) can better demonstrate higher cellularity and tissue characterization of CNS tuberculomas [37, 38]. MT MR is also better than FLAIR imaging in characterizing the lesion[39]. The histopathology of tuberculoma with MRI has been compared by various studies [40-42].

2.2 Tuberculous abscess

It is an encapsulated collection of pus containing viable tubercular bacilli without evidence of the classic tubercular granuloma [43]**.** It has smooth, lobulated, or crenated walls with no intracavitary projections. It is more common in HIV patients. The FDG (Fluoro deoxyglucose) accumulates at the periphery of tuberculous abscess [44]. The MT MR can be used to correlate viscosity, viable cell density and total protein concentration in brain abscess and non-abscess lesions. FLAIR signal intensity can be used to correlate only the total protein concentration in abscess and non-abscess lesions [45]. Tuberculous abscesses can be differentiated from pyogenic abscesses by using MT MR imaging and *in vivo* MRS [46]. DWI is highly sensitive and specific to differentiate abscess from non-abscess cystic lesions, tuberculomas and cysticercus granuloma of brain [47].

2.3 Miliary or disseminated neurotuberculosis

Pulmonary miliary tuberculosis can lead to miliary or disseminated neurotuberculosis by hematogeneous spread. It is a rare case of tuberculous meningitis. The tuberculomas are diffusely distributed in the brain parenchyma. It can also be seen in choroid plexus proving the spread can be from choroid plexus. The size of miliary tubercles can be 1 to 2 mm diameter.

2.4 Tuberculous cerebritis

Tuberculous cerebritis can occur as focal or diffuse form. Focal tuberculous cerebritis occurs in gyri of cerebral cortex. The gyrus is enhanced on contrast CT due to inflammation of meninges and represents arteritis induced infarction which is seen as palisade-type gyral blush in angiographic studies [48]. It can be distinguished radiologically from focal tuberculoma, tuberculous abscess, or meningeal manifestations of TB.

2.5 Tuberculous encephalopathy (TBE)

CNS tuberculosis leading to tuberculous encephalopathy is rare [49]. It is more common in young patients. It is characterized by diffuse brain edema and usually extensive demyelination. Microscopically, there is microvascular necrosis with perivascular macrophage reaction, demyelination, focal glial nodules in the white matter and occasional haemorrhagic areas. Tuberculous encephalopathy is the result of 'allergic' or delayed type IV hypersensitivity due to cell-mediated immunity to tuberculoprotein, liberated from Mycobacterium tuberculosis [50]

2.6 Ventricular system tuberculosis

Tuberculous ventriculitis is rare [51, 52]. It occurs in the form of tuberculous ependymitis, intraventricular tuberculoma, intraventricular tuberculous abscess, choroid plexitis and choroid plexus tuberculoma. Septum pellucidum tuberculoma is also rare. Ventricles may be involved due to hematogenous spread which starts as choroid plexitis characterized by a covering of gelatinous exudate, ependymitis and asymmetric hydrocephalus secondary to intraventricular adhesions or septae formation. There is transependymal leakage of contrast into ventricles in tuberculous ependymitis due to dysfunctional Blood-CSF Barrier [53]. Meningitis is the most common underlying condition responsible for the ventriculitis. In severe cases the septations are formed in the ventricles which result in different compartments and multiloculated hydrocephalus making the prognosis worst. The CT and MRI of the brain usually show hyper-dense layering material, particularly in the occipital horns of the lateral ventricles. Hydrocephalus and periventricular low density are frequently seen. The periventricular low density represents reactive edema rather than transependymal edema related to hydrocephalus. Thin regular enhancement of the ependymal lining of the ventricles may be seen after contrast administration. There often is intense restricted diffusion of this intraventricular debris as seen in the center of a brain abscess. MRI is more sensitive to periventricular abnormal signal (high T2) and thin contrast enhancement. The periventricular region may demonstrate restricted diffusion on DWI. The main differential diagnosis is that of ependymal lining enhancement, which includes ependymal spreading of glioblastoma multiforme or primary CNS lymphoma, extracranial neoplasm metastases and germinoma [54].

3. Miscellaneous forms of CNS tuberculosis

Spinal tuberculosis can occur in cervical, thoracic, lumbar or sacral spine. TB can affect any part of spinal cord including nerve roots. It can be tuberculous spondylodiscitis (Pott's disease or tuberculous spondylitis) or tuberculous spondylitis [55]. Bladder dysfunction is uncommon, secondary to spinal arachnoiditis and myeloradiculopathy [56]. Intracranial subdural or epidural abscess formation and calvarial tuberculosis are rare manifestations of CNS TB.

Diagnosis and treatment

The diagnosis of tuberculous meningitis can be made by clinical history, laboratory findings and radiological findings. The clinical history of meningitis is fever, headache and neck stiffness along with focal neurological deficits, behavioral changes, and alterations in consciousness. The laboratory analysis includes cytology, microbiology and molecular and biochemical analysis. The CSF cytology shows lymphocytic predominant pleiocytosis, elevated protein and low glucose. Microbiology study includes identification of Acid Fast Bacillus in the CSF through both smear and culture methods. Molecular and biochemical analysis includes nucleic acid amplification (NAA) methods and other PCR-based methods [57].

The treatment of TBM includes antibiotic therapy, adjunctive steroid therapy and surgical therapy. The antibiotic therapy includes first line treatment as isoniazid, rifampin, pyrazinamide and streptomycin or ethambutol [57]. A study showed that Levofloxacin is superior to rifampicin in reducing 6 month mortality but not disability. It is helpful in patients with hepatotoxicity and without seizure [58]. A study using DCE derived k-trans and edema volume for ATT response showed that the therapeutic response is visible only in the cellular volume with no significant change in necrotic volume and a gradual repair of the BBB [59]. In children, Bacille Calmette-Guerin (BCG) vaccination appears to translate into less tuberculoma formation on MRI [60]. Aspirin can reduce strokes and also significantly reduced 3-month mortality in patients with TBM [61]. The steroids can be used as an adjunctive therapy along with standard first-line therapy. The increased ICP caused by the severe tuberculous meningitis can be treated using osmotic therapy like mannitol and HS (Hyperosmotic Saline), steroids and surgery along with controlling fever and hyponatremia [62]. For communicating hydrocephalus, acetazolamide and furosemide can be used. A contrast CT study showed that there was no significant effect of corticosteroids on ICP or the incidence of basal ganglia infarction [63]. Dexamethasone reduces hydrocephalus and prevents infarction by decreasing CSF MMP-9 concentrations [64]. The surgical therapy is also used for treating TBM. For non-communicating type of hydrocephalus, external drainage and/or VPS (Ventriculoperitoneal Shunt) or ETV (Endoscopic Third Ventriculostomy) is used. Tuberculoma are not often surgically excised except when diagnosis is uncertain. For tubercular abscesses simple puncture and drainage and aspiration or total excision can be done if more severe.

Conclusion

CNS tuberculosis has various manifestations on MRI. Its correct diagnosis and early treatment is mandatory. It may affect meninges, parenchyma, ventricles, blood vessels and nerves. We should be familiar with all the radiological and clinical manifestations of CNS tuberculosis so that there can be correct diagnosis on time and thus reducing morbidity and mortality caused by this life threatening disease.

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Conflict of Interest

The authors declare no potential conflicts of interest in this manuscript.

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