Magnetic resonance imaging in central nervous system tuberculosis

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Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*,[1] accounts for eight million annual, worldwide deaths. Involvement of the central nervous system (CNS) is one of the most serious forms of this infection and is responsible for a high mortality and morbidity. The pandemic of acquired immunodeficiency syndrome (AIDS) has resulted in an increased incidence of CNS TB worldwide.[2] Granulomatous inflammatory reaction in CNS caused by *M. tuberculosis* may involve the meninges, brain, spinal cord, and the bones covering the brain and spinal cord, and may manifest clinically depending on the specific location of the disease process.

Cranial TB

Meningitis

Tuberculous meningitis (TBM) is the most common cause of chronic meningitis, especially in developing countries. Infection may occur either by hematogenous seeding of the meninges or release of the organism into the meningeal space.

Diagnosis of TBM is made by cerebrospinal fluid (CSF) examination, which characteristically shows a lymphocytic pleocytosis, increased CSF protein, and decreased CSF sugar concentration.[3] CSF culture for acid-fast bacilli (AFB) and CSF polymerase chain reaction (PCR) are confirmatory tests for the diagnosis of TBM. The sensitivity of CSF culture for the detection of AFB has been reported to be approximately 50%.[4] CSF PCR examination is a newer technique, capable of amplifying minute amounts of DNA into millions of identical copies. It is more sensitive than the combination of microscopic examination and culture for *M. tuberculosis*.[5] Noninvasive imaging is essential as it helps in demonstrating the complications of TBM besides playing an important role in its diagnosis.

Common findings on imaging are abnormal meningeal enhancement in the basal cisterns, hydrocephalus, and vascular complications. Magnetic resonance imaging (MRI) scores over computed tomography (CT) scan in the early detection of meningeal pathologies.[6] During the early stages of the disease, noncontrast MRI studies usually show little or no evidence of any meningeal abnormality. With disease progression, swelling of the affected subarachnoid spaces occurs with associated mild shortening of T1 and T2 relaxation times in comparison with normal CSF. Postcontrast T1W images show abnormal meningeal
enhancement, especially in the basal cisterns. Commonly involved sites are the interpeduncular fossa, pontine cistern, and the perimesencephalic and suprasellar cisterns [Figure 1]. Involvement of the sulci over the convexities and of the Sylvian fissures can also be seen.\cite{7-9} Cerebellar meningeal and tentorial involvement is uncommon.

Magnetization transfer (MT) imaging is considered to be superior to conventional spin echo (SE) sequences for imaging abnormal meninges, which appear hyperintense on precontrast T1W MT images and show further enhancement on postcontrast T1W MT images.\cite{10} In addition, MT ratio (MTR) quantification helps in predicting the etiology of the meningitis.\cite{6,10,11} Visibility of the infected meninges on precontrast T1W MT images with low MTR is specific for TBM, helping in differentiating it from other nontuberculous chronic meningeal infections [Figure 1].\cite{11} There is no published study of in vivo MRI spectroscopy (MRS) in TBM; however, ex vivo spectroscopy of CSF has been attempted in this context.\cite{12} High-resolution ex vivo MRS of the CSF shows signals from Lac, acetate, and sugars along with cyclopropyl rings (-0.5 to +0.5 ppm) and phenolic glycolipids (7.1 and 7.4 ppm). These have not been observed in pyogenic meningitis. The combination of ex vivo MRS with MT MRI may be of value in the diagnosis of TBM. Complications that are secondary to TBM may either develop as the disease progresses or while the patient is on chemotherapy. The sequelae associated with TBM are discussed in detail below.

**Hydrocephalus:** Hydrocephalus encountered in TBM can be broadly divided into two types: (1) communicating type, which is common, secondary to an obstruction of the basal cisterns by inflammatory exudates and (2) obstructive type, which is less common and either secondary to a focal parenchymal lesion causing mass effect or due to the entrapment of a part of the ventricle by granulomatous ependymitis.\cite{13} Periventricular hyperintensity on proton density and T2W images is due to the seepage of the CSF fluid across the white matter and usually suggests hydrocephalus under pressure, which is an indication for CSF diversion surgery to decompress the ventricular system. Chronic hydrocephalus may result in atrophy of the brain parenchyma. Endoscopic third ventriculostomy is a procedure gaining acceptance as a means of decompression.

**Vasculitis:** It is a complication that is commonly seen at autopsy in cranial TBM.\cite{13} The adventitial layer of small and medium-sized vessels develops changes similar to those of the adjacent tuberculous exudates. The intima of the vessels may eventually be affected or eroded by fibrinoid–hyaline degeneration. In later stages, the lumen of the vessel may get completely occluded by reactive subendothelial cellular proliferation.\cite{14} Ischemic cerebral infarction resulting from the vascular occlusion is a common sequela of tuberculous arteritis. The middle cerebral and lenticulostriate arteries are most commonly affected.\cite{15,16} The conventional angiographic features of cranial TBM consist of a hydrocephalic pattern, narrowing of the arteries at the base of the brain, and narrowed or occluded small or medium-sized arteries.\cite{17} MRI angiography (MRA) may help in the detection of vascular occlusion. High-field MRA with contrast is more sensitive than conventional MRA in the detection of occlusion of smaller vessels that are more commonly involved by the pathology. It has been reported that the incidence of infarcts detected by CT scan varies from 20.5 to 38%. However, MRI detects more infarcts, including hemorrhagic infarcts, than does CT scan.\cite{18} The majority of the infarcts are in the basal ganglia and internal capsule due to the involvement of the lenticulostriate arteries.\cite{16,19} Diffusion-weighted imaging helps in the early detection of this complication [Figure 1].\cite{19}

**Focal or Diffuse Pachymeningitis**

An unusual presentation of CNS TB is isolated involvement of the dura, known as pachymeningitis, which is distinct from the inflammation of the dura adjacent to an intraparenchymal tuberculosis.\cite{20,21} It consists of either isolated dural involvement or pial or parenchymal involvement that is secondary to a dura-based lesion. As in the case of TBM, tuberculous pachymeningitis may also result from hematogenous spread of the bacilli. Pachymeningitis may exist as focal or diffuse involvement of the dura.\cite{20,21} Focal pachymeningitis appears isointense on T1W, iso- to hypointense on T2W, and enhanced on postcontrast images. In contrast to focal lesions, diffuse

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**Figure 1 (a-h):** Tuberculous meningitis with vasculitis. T2W image (a) shows no apparent signal abnormality in the basal brain parenchyma. The corresponding magnetization transfer T1W image (b) shows hyperintensity in the perimesencephalic and suprasellar cisterns. On DWI (c) restriction is noted in the left temporal region. The postcontrast T1W image (d) shows abnormal enhancement along the perimesencephalic and suprasellar cisterns. In the same patient, axial sections at a higher level show hyperintensity on a T2W image (e) in the left middle cerebral artery (MCA) territory with hyperintensity on DWI (f) and low ADC values in the ADC map (g) suggesting a large left middle cerebral artery (MCA) territory infarct. The postcontrast T1W image (h) shows abnormal enhancement in the left caudate nucleus region.
Intracranial tuberculoma

Brain tuberculosis, a space-occupying mass of granulomatous tissue, forms a large percentage of intracranial mass lesions in the developing countries and is responsible for high morbidity and mortality. Earlier recognition and treatment of this condition on imaging may play a critical role in patient management.

Tuberculomas may be single or multiple, and can be seen anywhere in the brain parenchyma. The number of identified lesions per patient may range from one to 12 (or more), with the size varying from 1 mm to 8 cm. Its presence in the ventricular system is very rare. Although no precise patterns of localization have been observed according to race, age, or sex, children develop infratentorial tuberculomas more commonly than do adults. Symptoms are often limited to seizures and mass effect, resulting in an increased intracranial pressure. Neurological deficit reflects the topographic location of the lesion. These lesions originate as a conglomerate of microgranulomata in an area of tuberculous cerebritis that join to form a noncaseating tuberculoma. In most cases, subsequent central caseous necrosis develops that is initially solid, but in some instances, may eventually liquefy.

Intracranial tuberculomas usually show hypo- or isointensity or central hyperintensity with a hypointense rim on T2W images and isointensity and/or hypointensity on T1W images. Certain tuberculomas show a varied range of signal intensities on MRI. Depending on its stage of maturation, a tuberculoma's appearance varies on MRI, i.e., whether noncaseating, caseating with a solid center, or caseating with a liquid center. A noncaseating tuberculoma usually appears hyperintense on T2W and slightly hypointense on T1W images. These granulomas show homogenous enhancement after injection of paramagnetic contrast on T1W images. A solid caseating tuberculoma appears relatively iso- to hypointense on both T1W and T2W images with an iso- to hyperintense rim on T2W images. In the presence of edema, the rim appears inseparable on T2W images. It shows rim enhancement on postcontrast T1W images. The degree of hypointensity of the solid caseating tuberculoma on T2W images depends on the complex relationship between the solid caseation, associated fibrosis/gliosis, macrophage infiltration, and perilesional cellular infiltrate. When the solid center of the caseating lesion liquefies, the center appears hyperintense with a hypointense rim on T2W images. The postcontrast T1W images show rim enhancement. MRI features of tuberculomas are known to overlap with those of other intracranial focal lesions, like the healing stage of neurocysticercosis, fungal granulomas, chronic pyogenic brain abscess, and lymphomas. Some gliomas and metastases may also have features similar to those of tuberculomas and should be considered in their differential diagnoses. Sometimes, large tuberculomas mimic neoplastic lesions on MRI as they appear predominantly hyperintense on T2W images, with mixed intensity on T1W images, and may show heterogeneous enhancement on postcontrast studies. Quantitative MT imaging and in vivo proton MRS may help in the differential diagnosis of tuberculomas.

Noncaseating tuberculomas show similar imaging features as in the case of metastases, lymphoma, and other infective granulomas. On MT T1W imaging, cellular components of the lesions appear brighter and relatively specific for the disease. In addition, lesion conspicuity is greater on T1W MT imaging compared with conventional SE imaging and thus may help in improved assessment of the disease load. In solid caseating tuberculomas, hypointense solid caseation on T2W images often overlaps with the imaging features of lymphoma, glioblastoma, as well as fungal and cysticercus granulomas. On T1W MT images, the solid center appears hypointense, with a hyperintense rim. Calculated MTRs from the rim and the core are reported as 23.8 ± 1.76 and 24.2 ± 3.1, respectively. The significantly lower MTR of the T2W hypointense tuberculoma compared with the cysticercus granuloma helps in its differential diagnosis. The lower MT ratio in different stages of tuberculoma is because of the high lipid content present in tuberculous bacteria. The fluid-attenuated inversion recovery (FLAIR) sequence has been reported to be useful in picking up

Figure 2 (a-e): Atypical presentation of a right frontal tuberculoma in a 24-year-old female patient surgically excised due to nonresponse to therapy. The tuberculoma shows mixed signal intensity on the T2W image (a), slight hyperintensity on the T1W image (b), and hyperintensity on the magnetization transfer T1W image (c), with enhancement on the contrast-enhanced T1W image (d). Single-voxel magnetic resonance imaging spectroscopy (e) from the center of the lesion shows choline at 3.22 ppm and lipid at 1.3 ppm.
more lesions, including brain infections. T1W MT imaging along with FLAIR imaging has been used to evaluate the conspicuity and the number of lesions in individuals with brain tuberculomas. FLAIR imaging has not been found to be useful in the examination of brain tuberculomas as compared with T1W MT imaging, as it neither contributes to the characterization of lesion nor assesses the true disease load.\textsuperscript{19} Diffusion weighted imaging (DWI) shows restriction in tuberculomas with liquid necrosis [Figure 3], whereas there is no such restriction of diffusion in lesions with solid caseation. Restriction of diffusion in T2 hypointense lymphoma may differentiate it from tuberculoma.

Miliary brain tuberculosis is usually associated with TBM. Miliary tubercles are <2 mm in size and are either not visible on conventional SE MRI images or are seen as tiny foci of hyperintensity on T2W acquisitions. After gadolinium administration, T1W images show numerous, round, small, homogeneous, enhancing lesions. SE-invisible lesions that may or may not enhance after intravenous injection of gadolinium are clearly visible on MT-SE T1W imaging. MT-SE imaging helps in defining the true disease load [Figure 4].\textsuperscript{19}

\textit{In vivo} MRS is a powerful technique that can provide biochemical information of the pathophysiological process of the tissue under investigation. When combined with imaging, \textit{in vivo} spectra are found to be specific for intracranial tuberculomas and demonstrate the biochemical fingerprints of tubercle bacilli in a granuloma. Gupta et al. have performed \textit{in vivo}, \textit{ex vivo}, and \textit{in vitro} MRS to fingerprint the metabolites of \textit{M. tuberculosis} in tuberculomas.\textsuperscript{25,26} \textit{In vivo} MRS with a stimulated echo acquisition mode (STEAM) sequence shows lipid resonances at 0.9, 1.3, 2.0, 2.8, and 3.7 ppm, corresponding to a terminal methyl group \(\delta(CH_3)\), methylene group \(\delta(CH_2)\), \(\delta(CH_2)\), \(\delta(CH_2)\) of a \(CH_2\) fatty acyl chain, \(\delta(CH_2)\) of a fatty acyl chain, and phosphoserine, respectively. SE sequences show a mark reduction in the peak intensities at 0.9 and 1.3 ppm peaks whereas the rest of the lipid signals are poorly visible. \textit{Ex vivo} MRS of the excised tuberculomas confirms the resonances seen \textit{in vivo}. Lipid peaks at 1.58, 2.24, 3.22, 4.1, 4.29, and 5.3 ppm are also seen on \textit{ex vivo} MRS in addition to the signals seen \textit{in vivo}, corresponding to OC \(\delta(CH_2)\), \(\delta(CH_2)\), and \(\delta(CH_2)\) of the fatty acyl chain, \(\deltaN(CH_3)_3\) of Cho, and the glycerol backbone of phospholipids and olefinic groups of lipids, respectively. Signals of cyclopropane rings (0.5 and 0.1 ppm) and phenolic glycolipids (7.1–7.4 ppm) have been reported from the lipid extracts of a pure strain of \textit{M. tuberculosis}. Phenolic lipids represent the biochemical fingerprint of \textit{M. tuberculosis} in a granuloma; however, phenolic glycolipids remain present in the virulent as well as nonvirulent strains of \textit{M. tuberculosis}. On \textit{ex vivo} and \textit{in vitro} (lipid extract) spectroscopy, peaks of cyclopropane rings and phenolic glycolipid caseating tuberculomas are seen, which can be attributed to \textit{M. tuberculosis}.

\textit{In vivo} spectroscopy shows only lipid in T2 hypointense tuberculomas, whereas lesions with a heterogeneous appearance show Cho at 3.22 ppm along with lipid. These lesions show a large amount of cellularity and minimal solid caseation, the cellular regions appearing brighter on MT imaging and showing Cho resonance on spectroscopy [Figure 2].

Dynamic contrast enhanced (DCE) MRI has been used for the purpose of \textit{in vivo} quantification of angiogenesis in neoplastic lesions. In general, cerebral blood volume (CBV) provides information about the angiogenic activity of pathological tissue whereas permeability (k\textsubscript{trans}) and leakage (v\textsubscript{e}) give information related to the blood brain barrier integrity and changes in the extravascular–extracellular space.\textsuperscript{38,39} Recently, Gupta et al. have performed DCE-MRI.
in 13 patients with brain tuberculomas and correlated the relative (r) CBV values with their cellular and necrotic components and also with the expression of immunohistochemical markers [microvascular density (MVD) and vascular endothelial growth factor (VEGF)].  

Correlation between the physiological indices (k trans and rCBV) and matrix metalloproteinase 9 (MMP-9) expression in excised tuberculomas, authors have reported a significant positive correlation between the physiological indices (k trans and rCBV) and matrix metalloproteinase 9 (MMP-9) expression (a marker of BBB disruption) in excised tuberculomas. However, a weak correlation has been reported between physiological indices and VEGF expression in excised tuberculomas, suggesting a limited role of VEGF in leakage of the BBB. Correlation between k trans and MMP-9 tuberculomas, suggesting a limited role of VEGF in physiological indices and VEGF expression in excised tuberculomas. MVD also correlates significantly with VEGF. Correlation among rCBV, MVD, and VEGF confirms that rCBV is a measure of angiogenesis in the cellular fraction of brain tuberculomas. In a recent DCE-MRI study in brain tuberculomas, authors have reported a significant positive correlation among rCBV, MVD, and VEGF with areas of caseation and tubercles with eventual development of fibrous tissue in chronic or treated cases.  

Tuberculomas.  

In vivo MRS has also been used for the differentiation of tuberculous abscesses from other lesions such as pyogenic abscesses and fungal lesions. In vivo proton spectra in tuberculous abscesses show only Lac and lipid signals (at 0.9 and 1.3 ppm) without any evidence of cytosolic amino acids. More lipid peaks may also be apparent on ex vivo spectroscopy.  

Spinal TB  

Intraspinal TB  

Spinal meningitis and spinal arachnoiditis are inflammatory spinal diseases caused by M. tuberculosis.[55] The pathophysiology of spinal meningitis is similar to that of TBM: a submeningeal tubercle forms during primary infection and ruptures into the subarachnoid space, eliciting mediators of delayed hypersensitivity.[55] As with intracranial lesions, there is granulomatous inflammation with areas of caseation and tubercles with eventual development of fibrous tissue in chronic or treated cases. MRI features include CSF loculation and obliteration of the spinal subarachnoid space with a loss of outline of the spinal cord in the cervicothoracic spine and matting of the nerve  

Figure 5 (a-g): Tuberculomas.  

Tuberculomas in the left parasagittal region of a 20-year-old woman. A well-defined hyperintense lesion with a hypointense wall is seen in a T2W image (a). A T1W image shows a hypointense lesion with a hypointense wall. A magnetization transfer (MT) T1W image (c) shows more conspicuity of the T2 hypointense wall as compared with the T1W image. A postcontrast MT T1W image (d) shows rim enhancement. A diffusion-weighted image (e) shows homogeneous hyperintensity in the cavity with low ADC on the ADC map (f). Magnetic resonance imaging spectroscopy (G) from the center of the lesion with a voxel size of 1.2 ml shows a predominant lipid peak (Lip, 1.3 ppm)
roots in the lumbar region. Sometimes, patients who appear normal on unenhanced MRI images may show nodular, thick, linear, intradural enhancement, often completely filling the subarachnoid space on postcontrast images.\[56,57\]

In chronic stages of the disease, the postcontrast images may not show any enhancement even when unenhanced images show signs of arachnoiditis.\[56,57\] Spinal cord involvement in the form of infarction and syringomyelia may occur as a complication of arachnoiditis [Figure 6]. Parenchymal TB myelitis and tuberculosis formation may also occur;\[56,57\] Syringomyelia is seen as cord cavitation that typically demonstrates CSF intensity on T1W and T2W images but does not enhance on postcontrast images.\[56,57\]

TB myelitis: The MRI imaging features of TB myelitis are similar to those of cerebritis. After 1 week of initiation of treatment, the region of myelitis becomes less diffusely hyperintense on T2W images, with more clearly defined marginal enhancement on postcontrast T1W images.\[57,58\] The surrounding edema continues to be more extensive than the margins of enhancement. These findings suggest the beginning of intramedullary abscess formation. The central cavitory portions of the intra-axial necrotic areas are seen as hypointense and hyperintense foci on T1W and T2W images, respectively.\[58\] Although the abnormalities visible on T2W images subside in several weeks, foci of contrast enhancement on postcontrast images may persist for several months.\[58\]

Dural and subdural pathology: Tuberculous pus formation occurs between the dura and the leptomeninges and may appear loculated. It appears hyperintense on T2W and iso- to hypointense on T1W images. The dural granulomas appear hypo- to isointense on T2W and isointense on T1W images. Rim enhancement can be seen on postcontrast images.\[57\]

Epidural TB lesions generally appear to be isointense to the spinal cord on T1W images and have mixed intensity on T2W images. In postcontrast images, uniform enhancement can be seen if the TB inflammatory process is phlegmonous in nature whereas peripheral enhancement is seen if true epidural abscess formation or caseation has developed.\[57,58\] Epidural tuberculous abscess may occur as primary lesions or may be seen in association with arachnoiditis, myelitis, spondylitis, and intramedullary and dural tuberculomas.\[57,58\]

**Tuberculous spondylitis**

Tuberculous spondylitis is an important cause of spinal disease in developing countries. Early diagnosis and prompt treatment are essential to avoid permanent damage or deformity in the spine.

Tuberculous spondylitis involves one or more extradural components of the spine. The vertebral bodies are the most commonly involved; the posterior osseous elements, epidural space, paraspinal soft tissue, and intervertebral discs are also involved either secondarily or sometimes as the primary area to be first involved [Figure 7].\[59\]

**Figure 6 (a-c): Intramedullary tuberculosis with arachnoiditis.** Heterogeneous hyperintensity is seen at the conus on this T2W image (a), appearing hypo-isointense on a T1W image (b) and showing intense enhancement (arrow) on a postcontrast T1W image (c). Note the nerve roots as well as dural enhancement consistent with arachnoiditis (arrows).
of tuberculous spondylitis. Although rim enhancement classically suggests abscess formation, it may also be seen in solid caseating tuberculomas. During chemotherapy, a progressive increase in signal intensity on T1W images in previously affected vertebrae suggests fatty marrow replacement and healing [Figure 8].

CT scan demonstration of bone fragments in the intraspinal or extraspinal soft tissue has been described as being characteristic of tuberculous spondylitis. This feature is attributable to the lack of proteolytic enzymes required to lyse bone in the tuberculous inflammatory exudate. CT scan is considered superior to MRI for the demonstration of these small bone fragments. T2*W images have been shown to better demonstrate calcification compared with SE images by accentuating the diamagnetic susceptibility properties of calcium salts. The low signal is more prominent on T2*W than on SE images and closely matches the calcification seen on CT. Demonstration of bone fragments on T2*W images is also considered to be characteristic of tuberculous spondylitis even in the absence of abscess formation.

Therapeutic response assessment
MRI is the modality of choice for following the benefits of treatment in patients with CNS tuberculosis. Most patients are treated with ATT after the diagnosis is suggested by imaging and other laboratory investigations. However, the duration of medical treatment is largely empirical and is based on data from a small number of publications. Serial imaging in patients on ATT may show a decrease in the lesion size within 3 and 4 months and complete disappearance at the end of 12 months. Paradoxical progression of intracranial tuberculomas or development of new lesions during treatment has been recognized as a rare response to ATT. Using DCE-MRI, it has been shown that changes in $k^\text{trans}$ and $v_c$ are associated with therapeutic response even in the presence of a paradoxical increase in the lesion volume [Figure 9].

Less-intense meningeal enhancement on postgadolinium MRI studies following ATT in patients with TBM is considered as a response to treatment. A recent serial DTI study in TBM has reported increased FA values in cerebral cortical regions in TBM patients (0.15 ± 0.03) as compared with controls (0.10 ± 0.02) at the time of the baseline study [Figure 10]. On follow-up after 3 months of ATT, these regions in the TBM patients have shown significantly decreased FA values (0.13 ± 0.02) compared with the initial study in the entire cerebral cortical region as well as basal meninges. They have reported a significant positive correlation between FA and proinflammatory molecules (PMs), and suggested that DTI metrics may be used as a noninvasive surrogate marker of PMs in TBM in assessing therapeutic response.
We conclude that conventional imaging supplemented by advanced MRI techniques helps in improved tissue characterization of CNS tuberculosis and may help in better management of these patients.

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