Indian Journal of Emergency Pediatrics
Volume 2 Number 3, July - Sept 2010

Role of Radiology in emergencies I - Neuroinfections: Tuberculous Meningitis

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ABSTRACT

Tuberculous CNS infections and especially tuberculous meningitis [TBM], still account for major morbidity and mortality in developing countries. While effective treatment is available now, the need for rapid and accurate diagnosis, along with the tendency toward non-invasiveness in this age has turned the attention to the radiologist, who must equip himself with the latest that the field has to offer. Indeed, the role of radiology, especially CT and MR imaging, is rapidly evolving, and includes not just diagnosis but also extent and complication assessment, outcome measures and even treatment. This article reviews the role of imaging in the diagnosis of TBM, along with a discussion of other manifestations of CNS tuberculosis, and the imaging differential that must be kept in mind.

Key words: Tuberculosis; tuberculous meningitis; tuberculoma; meningeal enhancement; magnetic resonance imaging, vasculitis; hydrocephalus; ring enhancing lesion.

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*,[1] accounts for eight million worldwide deaths annually. 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, more so in children in background of protein energy malnutrition.

Tuberculous meningitis (TBM) is the most life-threatening and most common presentation of central nervous system (CNS) tuberculosis in infants and children, with the highest incidence in the first three years of life. Its presentation is often nonspecific, characteristic signs and symptoms of meningitis may be absent, and early recognition of this potentially treatable disease remains a challenge to clinicians. Early diagnosis followed by effective treatment can prevent neurologic damage or a fatal outcome [2, 3].

Clinical manifestations of TBM in children include personality change, irritability, anorexia, and fever. Drowsiness, vomiting, neck stiffness, cranial neuropathies and depressed reflexes follow in 1 to 2 weeks, with stupor, coma, stroke and decerebrate rigidity in late stages.[4] If untreated, TBM rapidly progresses to death within just 3 weeks.

Routine diagnostic techniques involve culture and immunological tests of the tissue and biofluids, which are time-consuming and may delay definitive management. The increasing role of noninvasive imaging modalities such as computed tomography (CT)

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(**Received on 16.09.2010, received on 28.10.2010**)

and Magnetic Resonance Imaging (MRI) in the diagnosis and detection of various complications of CNS tuberculosis is therefore of paramount interest to both the clinician and the radiologist. The current article reviews the role of various imaging techniques in the diagnosis and management of CNS TB with a discussion of the differential diagnosis.

PATHOGENESIS

Most tuberculous infections of the CNS are caused by *Mycobacterium tuberculosis* and less frequently by *M.bovis*.M.tuberculosis enters the pulmonary alveoli as droplets to produce a localized infection of the lungs and draining lymph nodes termed the 'primary complex'. A transient but significant bacteremia ensues during the first week after infection, with resultant hematogenous dissemination of bacilli to various organs of the body including the brain and meninges. Small subpial or subependymal foci of tuberculous caseous lesions termed 'Rich Foci' develop in the CNS and can enlarge and become active after a quiescient period,even several years after initial infection.[5]

The location of the expanding Rich Foci determines the type of CNS involvement. Tubercles rupturing into the subarachnoid space cause meningitis[2,3]. Those deeper in the brain and spinal cord parenchyma cause tuberculoma, abscesses or tuberculous cerebritis.

In TBM, thick gelatinous exudates form around sylvian fissures, basal cisterns, brain stem and cerebellum blocking the subarachnoid spaces resulting in hydrocephalus.

The meningeal inflammatory exudates infiltrate the blood vessels leading to necrotizing panarteritis with secondary thrombosis and occlusion. The basal ganglia and thalamus in the region of lenticulostriate and thalamoperforating arteries are most commonly involved by this vasculitis.[6] The perineurium of cranial nerves is infiltrated causing neuropathies, particularly of cranial nerves II, VI and VII.

Intracranial tuberculomas originate as a conglomerate of microgranulomata in an area of tuberculous cerebritis that coalesce to form a noncaseating tuberculoma with subsequent central caseous necrosis that is initially solid, but may eventually liquefy later.[7]

The symptoms, signs, and sequelae of tuberculous meningitis (TBM) are the result of an immunologically directed inflammatory reaction to the infection.

IMAGING OF TBM

Chest radiography may reveal hilar lymphadenopathy, pneumonia, infiltrates or pleural effusion. Skull radiography may reveal evidence of increased intracranial tension in children, in the form of sutural diastasis. Intracranial calcifications may be rarely evident in the sellar regions on follow-up. CT and MRI of the brain reveal hydrocephalus, basilar meningeal thickening and enhancement, abnormal enhancement of choroid plexus and ependymal lining. Co-existing tuberculomas and underlying infarcts may also be evident.

MRI scores over CT scans in the early detection of meningeal pathologies (8). During the early stages of the disease, non contrast MRI shows little or no meningeal abnormality. With disease progression, non contrast CT or MRI studies show partial or complete obliteration of basal cisterns and sylvian fissures by the purulent tuberculous exudates which show density or signal intensity similar to that of adjacent brain (Fig. 2A,4A, B). On contrast CT or MRI studies, intense and homogenous leptomeningeal enhancement is seen in the basal cisterns (Fig. 1A,B,2C). Commonly involved sites are the interpeduncular fossa, pontine cistern, perimesencephalic and suprasellar cisterns, cerebral convexities and the Sylvian fissures.[8,9,10] The leptomeningeal enhancement in MRI is due to contrast within dilated and engorged vessels in meningeal granulation tissue and also due to the contrast leak from disruption of blood meningeal barrier. Meningeal enhancement is not specific

for TBM, and is also seen in other infections like cryptococcal meningitis, neurosyphilis, Lyme disease, neurosarcoidosis and carcinomatous dissemination. Calcifications can be seen in the basal cisterns few years after the onset of disease and is better shown with CT scans.

COMPLICATIONS OF TUBERCULOUS MENINGITIS

Hydrocephalus

Ventriculomegaly is seen in 50 to 77% of affected patients and may be the only abnormal finding in patients with meningitis. Hydrocephalus encountered in TBM can be broadly divided into two types: **(1) communicating type**, which is common, secondary to obstruction of cisterns by inflammatory exudates or due to arachnoid adhesions impairing extraventricular CSF flow and absorption and **(2) obstructive type**, which is less common, due to cellular debris or parenchymal lesions obstructing the fourth ventricular foramina, cerebral aqueduct or entrapment of a part of the ventricle by granulomatous ependymitis.[11] Periventricular hypodensity on CT scans (Fig. 2B,D) and hyperintensity on proton density and T2-FLAIR images is due to the subependymal seepage of the CSF 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. Ependymitis, when present is seen as linear enhancement along the ventricular margins on post contrast MRI.

VASCULITIS

Ischemic cerebral infarction resulting from the vascular occlusion is a common sequelae of tuberculous arteritis. The middle cerebral and lenticulostriate arteries are most commonly affected. CT and MR angiography help in the detection of vascular occlusion, stenosis and irregularity of medium or small sized blood vessels. The incidence of infarcts detected by CT scan varies from 20.5 to 38%. MRI detects more infarcts, including hemorrhagic infarcts, than does CT[12]. The majority of the infarcts are in the basal ganglia, thalami and internal capsule due to the involvement of the lenticulostriate arteries. [13] (Fig. 4C,D) Cortical infarctions can result from involvement of cortical vessels but are less common. The infarcts appear as low density regions on CT (Fig. 1A-D) and as high signal intensity areas on T2, FLAIR and diffusion weighted MRI images (Fig. 7A,B). Diffusion-weighted imaging helps in the early detection of this complication,[13] with low ADC values pointing toward acute stage of infarction.

TUBERCULOMAS

Tubercular meningitis may be associated with meningeal and parenchymal tuberculomas in 20 to 30 % of cases. When tuberculoma and TBM are seen together, the diagnosis of tuberculosis is easily made. Children predominantly have infratentorial tuberculomas whereas adults usually have lesions in the supratentorial compartment. Tuberculomas may be single or multiple ranging from 1 to 12 lesions or more, the sizes varying from 1mm to 8cm.[14]

On non contrast CT, Tuberculomas are seen as rounded lesions often as dense as or slightly denser than brain with moderate to marked vasogenic edema in adjoining white matter. On contrast enhanced CT, tuberculomas commonly show ring enhancement (Fig. 1C, 2C,D) or less likely nodular or irregular nonhomogenous enhancement. When multiple they are often clustered or conglomerate to form thick walled and irregular peripherally enhancing lesions with hypodense centre and florid perilesional edema. Ring enhancing lesions with central nidus of calcification termed as the target sign is characteristic of tuberculoma.[15] (Fig. 3A,B)

The MRI features of tuberculomas depend on its stage of maturation, i.e., whether noncaseating, caseating with a solid center,

or caseating with a liquid center.[16,17] Tuberculomas show marked perilesional edema seen as high signal intensity on T2W and FLAIR images confined to the white matter.

A noncaseating tuberculoma appears hyperintense on T2W and slightly hypointense on T1W images and show homogenous enhancement after injection of gadolinium contrast on T1W images [18]. A solid caseating tuberculoma appears iso- to hypointense on both T1W and T2W images with an iso to hyperintense rim on T2W images and shows rim enhancement on postcontrast T1W images (Fig 5A-D,6A). 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.

On MR spectroscopy, tuberculomas shows characteristic lipid peaks with additional choline peaks indicating increased cellularity in lesions with heterogeneous appearance[19]. Miliary brain tuberculosis is usually associated with TBM. Contrast enhanced T1W images show numerous, round, small, homogeneous, enhancing tubercles of <2 mm in size. The CT and MRI features of tuberculomas are summarized in Tables 1 and 2.

Intracranial focal lesions like healing stage of neurocysticercosis, fungal granulomas, chronic pyogenic brain abscess, metastases and lymphomas may have features similar to those of tuberculomas and should be considered in the differential diagnoses.[20] Sometimes large tuberculomas showing heterogeneous signal intensity and contrast enhancement can mimic neoplasms like gliomas. The imaging differential diagnosis of intracranial tuberculomas is summarized in Table 3.

TUBERCULOUS BRAIN ABSCESS

It is a relatively rare condition and appears as large, solitary, and frequently multiloculated, ring-enhancing lesions with surrounding edema and mass effect on MRI.[21] They are indistinguishable from pyogenic brain abscesses on CT and MRI and surgery is the treatment of choice.

TUBERCULOUS SPINAL MENINGITIS

Spinal meningitis and spinal arachnoiditis are inflammatory spinal diseases caused by *M.tuberculosis*. MRI features include CSF loculation, obliteration of the spinal subarachnoid space and matting of the nerve roots. Postcontrast images show thick, nodular intradural meningeal enhancement often filling the subarachnoid space Spinal cord infarction and syringomyelia are the possible complications of arachnoiditis. TB myelitis with intramedullary, intradural and extradural abscesses and spinal cord tuberculomas may also occur.[22,23]

ASSESSMENT OF TREATMENT RESPONSE

Follow up imaging of CNS tuberculosis patients on ATT show less intense meningeal enhancement and decrease in size of the lesions within 3 to 4 months of start of ATT with almost complete disappearance of lesions at the end of 12 months. Paradoxical increase in size of the lesions or development of new lesions on imaging during antituberculous chemotherapy has also been recognized as a rare immunological response to ATT.[24]

CONCLUSION

Noninvasive imaging modalities such as CT and MRI supplemented by advanced MRI techniques like MR Spectroscopy and Diffusion weighted imaging offer greater inherent sensitivity and specificity in the diagnosis and follow-up of complications of CNS tuberculosis, thus helping in better management of these patients.

Table 1: Imaging features of intracranial tuberculomas on CT

Non-contrast CT	Contrast-enhanced CT
• Rounded iso-hyperdense lesions. • Perilesional white matter edema.	• Ring/nodular/irregular enhancement. • Conglomerate/tandem lesions. • 'Target sign': REL with central calcific nidus.

REL: Ring Enhancing Lesion

Table 2: Imaging features of intracranial tuberculomas on MRI

Type	T1-W	T2-W	Contrast enhanced	MRS
Noncaseating	Hypointense	Hyperintense	Homogenous	Cholinepeak
Caseating with solid centre	Iso-hypointense	Iso-hypointense with hyperintense rim	Rim enhancement	Lipid peak +/- Choline peak
Caseating with liquid centre	Iso-hyperintense	Hyperintense with hypointense rim	Rim enhancement	Lipid peak

MRS: Magnetic Resonance Spectroscopy

Table 3: Differential diagnosis of intracranial tuberculomas on CT & MRI

Pathology	Salient imaging features
Tuberculoma	Ring enhancing lesions with perilesional edema. Target sign. Conglomerate lesions. Size usually > 1 cm [except miliary tubercles] T2 hypointensity due to solid caseation. Choline and/or lipid peak on MRS. Restricted diffusion on DWI.
Neurocysticercosis	Ring enhancing lesions usually at grey-white junction. Most lesions < 1 cm. Eccentric mural-based scolex seen. Various stages of lesions [vesicular, colloid-vesicular granular-nodular, nodular-calcified]
Fungal granulomas	Immunocompromised state. Predominantly in thalamus/ basal ganglia. T2 hypointense center due to heavy metal accumulation.
Pyogenic abscess	Ring enhancing lesion. Medial wall thinner. Restricted diffusion on DWI. Lipid-lactate peaks on MRS.
Metastasis	Ring/nodular enhancing lesion. Disproportionate white matter edema. Adjacent meningeal spread.

Fig.1: TBM complicated by vasculitis and cerebral infarction. Contrast enhanced CT scan A–D show meningeal enhancement in suprasellar cistern, around left middle cerebral artery and in left frontoparietal sulci. A large hypodensity suggestive of infarct is seen involving left anterior and middle cerebral artery territory. C-Coexisting tuberculoma showing rim enhancement and perilesional edema is seen in right frontal lobe.

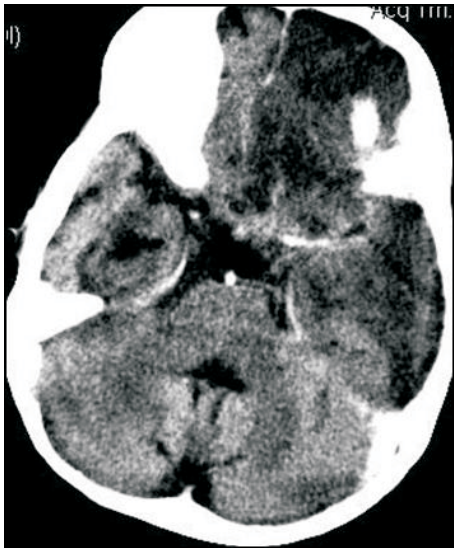

Fig.1A

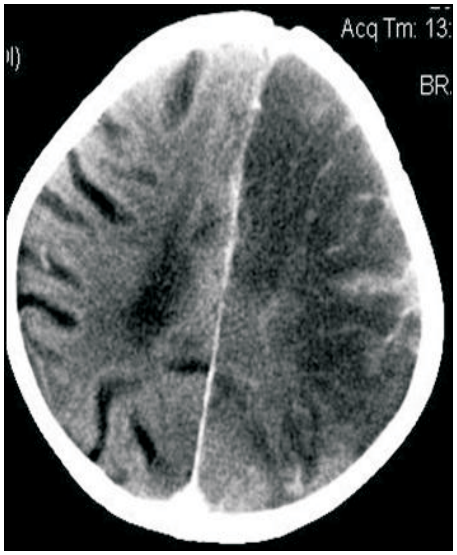

Fig.1B

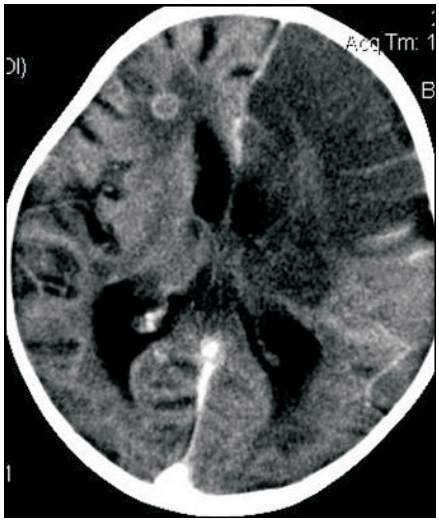

Fig.1C

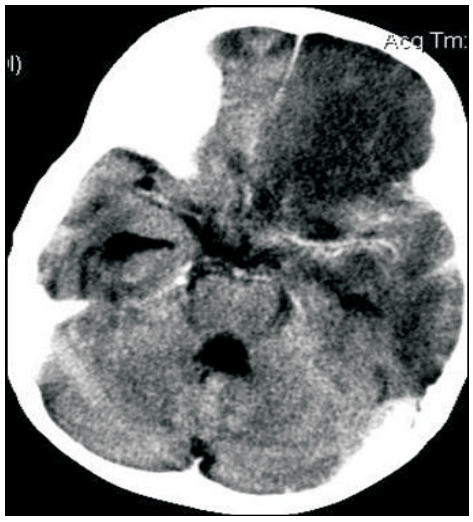

Fig.1D

Fig. 2: TBM and tuberculomas. A&B. Plain CT brain show obliteration of suprasellar and perimesencephalic cisterns by isodense inflammatory exudates. Dilated lateral ventricles with periventricular edema is also seen. C.&D - Contast CT show meningeal enhancement in suprasellar and perimesencephalic cisterns, multiple ring enhancing lesions are seen in right perisylvian region, periaqueductal mid brain and bilateral parasagital frontal lobes. Hydrocephalus with periventricular edema is also seen.

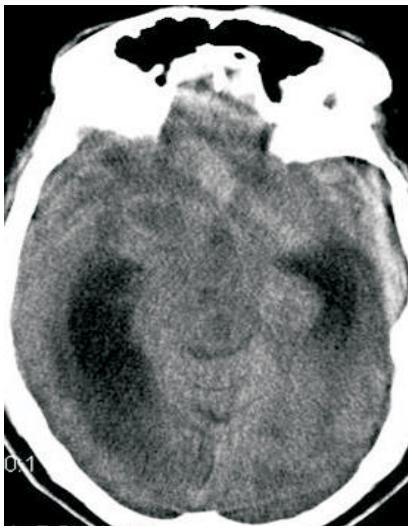

Fig.2A

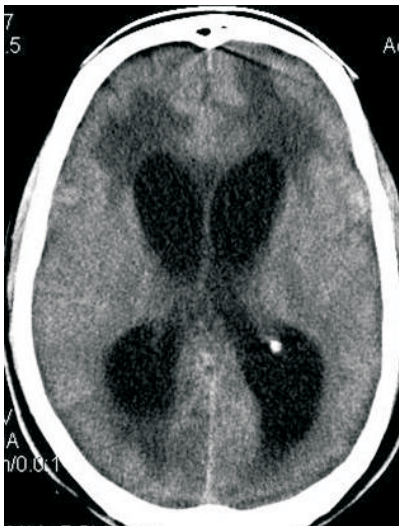

Fig.2B

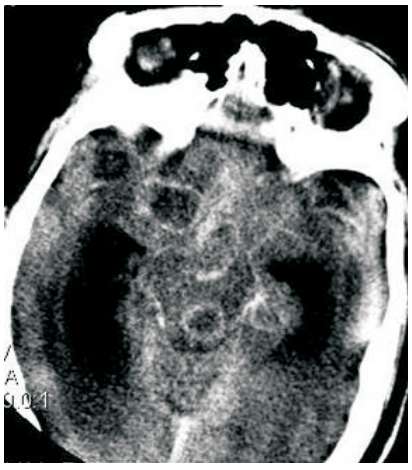

Fig.2C

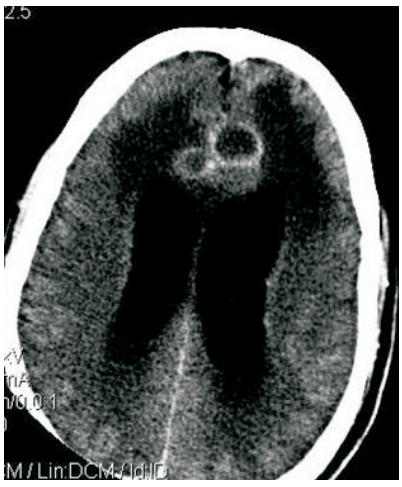

Fig.2D

Fig. 3: Tuberculoma (A) Plain CT brain show a round isodense lesion with central calcification and perilesional edema in left frontal lobe (B)Contrast CT shows ring enhancement with central calcification –"Target sign"

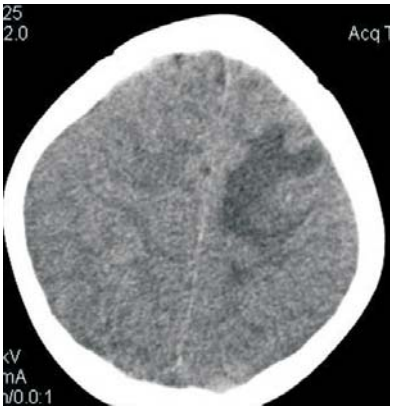

Fig.3A

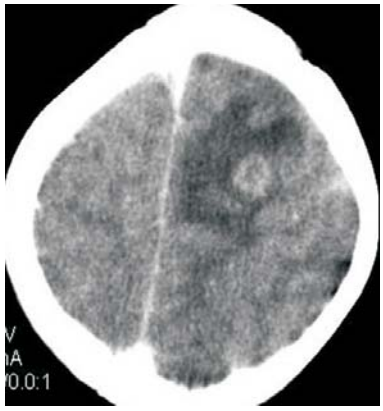

Fig.3B

Fig. 4: CNS Tuberculosis with vasculitis - MRI A –T2W, B- FLAIR MRI axial images show iso to hypointense areas filling the suprasellar and interpeduncular cisterns with hyperintense areas in bilateral temporal whitematter and midbrain suggestive of edema. C-T1W, D-T2W axial images show T1 hypointense and T2 hyperintense region in left lentiform nucleus consistent with vasculitic infarct

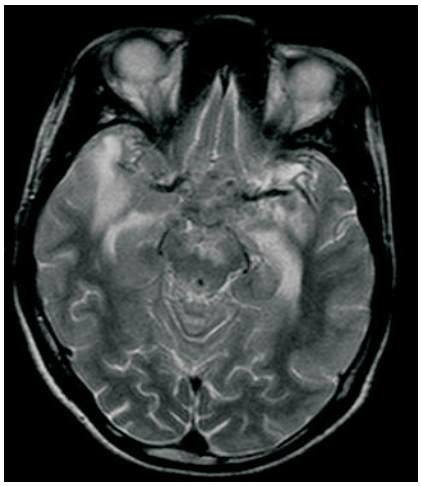

Fig.4A

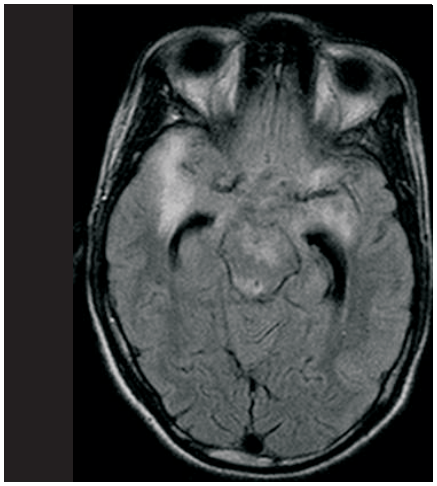

Fig.4B

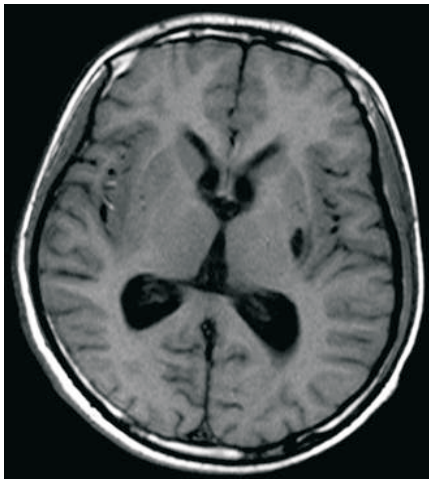

Fig.4C

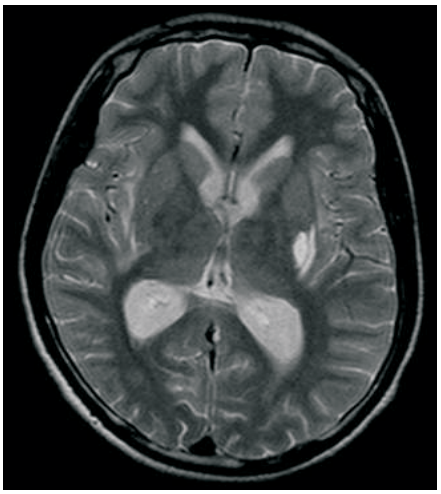

Fig.4D

Fig. 5: Cisternal and parenchymal tuberculomas. Gadolinium enhanced T1W MRI of the same patient as in Fig4. A&B–axial, C-coronal, D-sagital images show mutiple conglomerate ring enhancing lesions with hypointense centre consistent with tuberculomas in sellar, suprasellar, interpeduncular, prepontine, bilateral sylvian, right ambient cisterns and bilateral perisylvian temporal lobes

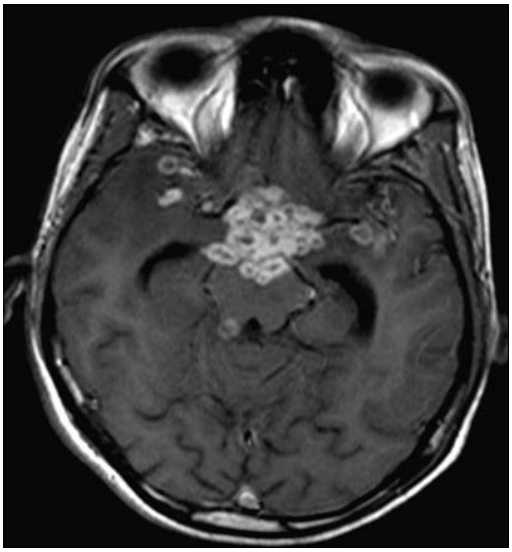

Fig.5A

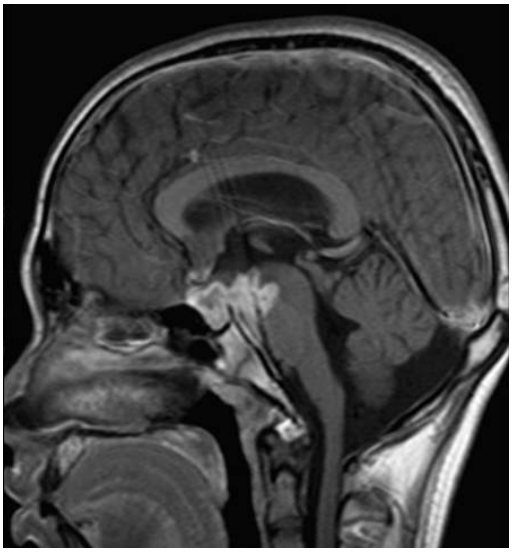

Fig.5B

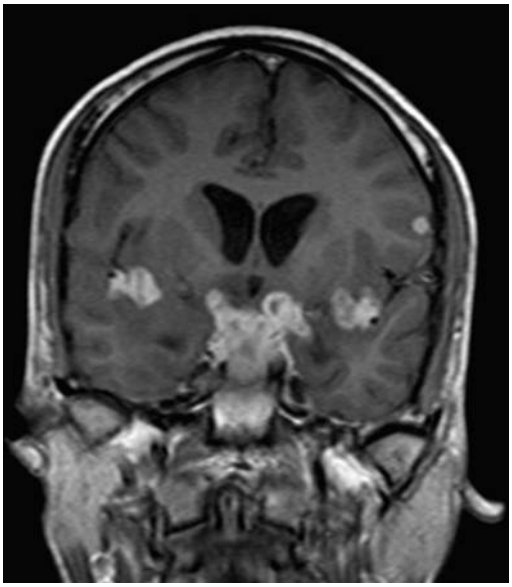

Fig.5C

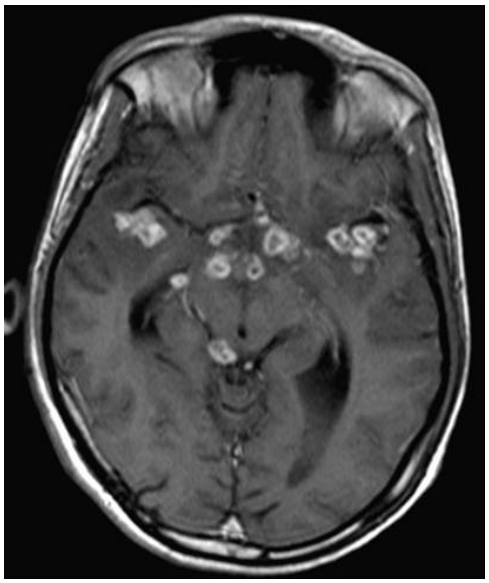

Fig.5D

Fig. 6: Tuberculoma left parietal lobe MRI A- Gadolinium enhanced T1W axial image show hypointense tuberculoma showing rim enhancement. B- FLAIR axial image show hyperintense tuberculoma with thin hypointense rim and perilesional edema. C- Diffusion weighted image show hypointensity with no restricted diffusion suggestive of tuberculoma with solid caseation.

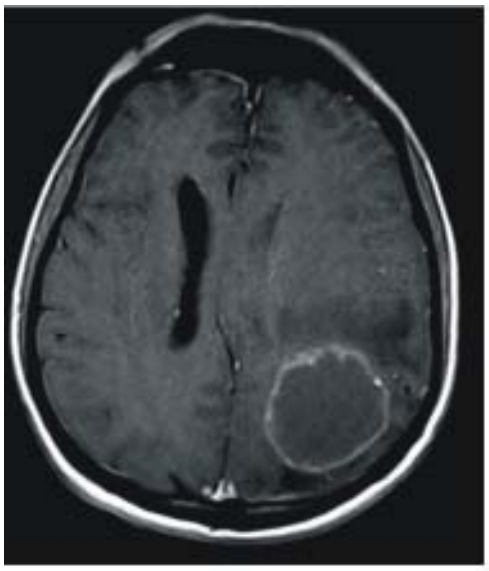

Fig.6A

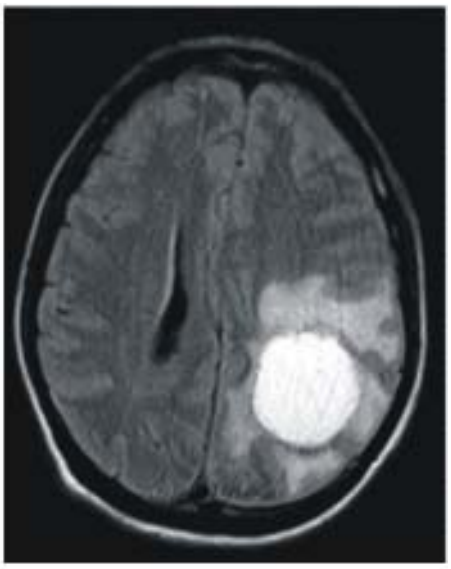

Fig.6B

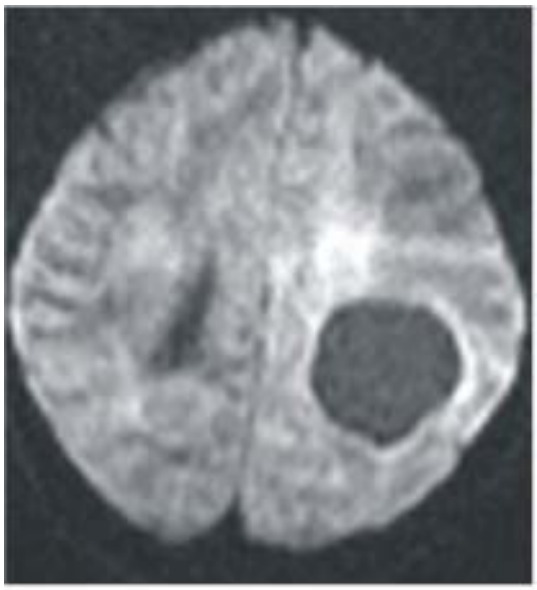

Fig.6C

Fig. 7: TBM complicated by vasculitis- MRI. A-FLAIR & B-Diffusion weighted images – show hyperintense areas consistent with infarcts in bilateral cerebral cortex.

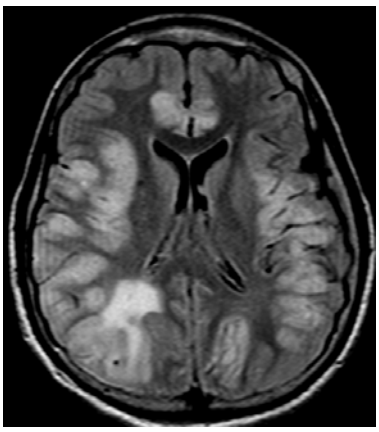

Fig.7A

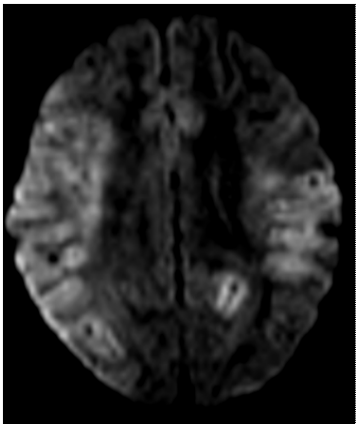

Fig.7B

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