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NEUROIMAGING OF TUBERCULOSIS- MODALITIES, IMAGING PROTOCOLS AND RADIOMICS: A REVIEW

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ABSTRACT
Background and objective:
A large number of review and research articles exists in literature which describe the radiological appearance of various manifestations of nervous system tuberculosis, however there is paucity of text which describes the application of each and every imaging modality in the workup of the entire spectrum of this pathology. The intent of this article is to review the existing literature on the role of different radiological modalities in the stepwise work up of CNS TB. The article focuses on the role of plain radiograph, fluoroscopy, computed tomography, magnetic resonance imaging along with its advanced sequences and nuclear medicine in imaging of the many faces of tuberculosis in CNS. The article also aims to review the existing literature on the role of MR based textural analysis (Radiomics) as a problem-solving tool in various nervous system pathologies.

Methods:
We searched PubMed central databases for articles published in English from January 1 2000 to February 28 2021 along with references from the relevant articles. The search terms included "imaging in central nervous system tuberculosis" "Radiomics in tuberculosis ", "Radomics in central nervous system ". In total 95 articles including case reports, case series, original articles and review articles were included in this review.

Results:
Conventional imaging modalities including radiograph and fluoroscopy are becoming extinct in work up of tuberculosis in the nervous system itself, however a plain radiograph still holds a key position in screening the chest for presence of subclinical respiratory tract infection in patients presenting with brain tuberculosis. In addition, it is a sensitive tool as baseline investigation in workup of spinal tuberculosis (T.B). Fluoroscopy is a useful tool in image guided procedures for collection of samples for histopathology and CSF analysis.

Cross sectional imaging modalities including computed tomography and magnetic resonance imaging have revolutionized imaging of central nervous system pathologies in particular tuberculosis. Computed tomography acts as a screening tool to identify the presence of intracranial tuberculosis and recognize its complications. In addition it is an important tool to determine the extent of spinal T.B. Magnetic Resonance Imaging (MRI) along with its advanced sequences including spectroscopy, Magnetization transfer T1 sequence (MT T1), perfusion imaging, and magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) is an ideal imaging method to work up CNS TB. It can identify numerous manifestations of tuberculosis in the brain, work up its associated complication, and explain the extent of neurological symptoms. Moreover, it has the capability to differentiate TB from other nervous system infections. Furthermore, it can differentiate neoplastic and inflammatory brain disorders from CNS TB. Radiomics, particularly the textural features based on MR imaging is the future of neuroimaging. Its role is getting established in the work up of several intracranial pathologies including brain tumors and neurodegenerative disorders. Certainly, it has significant potential in the imaging work up of CNS tuberculosis, which is underexplored and therefore requires the central attention of upcoming researchers focusing on this topic.

Conclusion:
Cross sectional imaging is the mainstay of imaging workup. Nuclear imaging is becoming an essential adjuvant to determine the burden of the disease. Role of radiomics is evolving in intracranial pathologies and certainly needs the central attention of future researches to establish its role in CNS TB imaging.

Keywords: Imaging, CNS tuberculosis, MRI, Diagnostic algorithm

INTRODUCTION

Tuberculosis (TB) is an endemic infectious disorder with a worldwide disease burden of 10 million new cases each year. Amongst them 87 % cases occur in 30 high burden developing countries.[1,2] Central nervous system (CNS) involvement by mycobacterium tuberculosis results in significant neurological deficit, burdens the health care system and is associated with high morbidity and mortality.[3] Clinical and radiological manifestations of CNS TB infection are extremely varied, where it can affect every structure in and associated with the neural axis. Some of the commonest CNS manifestations of the tuberculosis include but are not limited to intracranial tuberculoma, tuberculous cerebritis, encephalitis, tuberculous meningitis, tuberculous ventriculitis, tuberculous skull base and vertebral body osteomyelitis - Pott's disease, tuberculous arachnoiditis and tuberculous myelitis.[4,5]

A large number of review and research articles exists in literature which describe the radiological appearance of various manifestations of nervous system tuberculosis, however there is paucity of text which describes the application of each and every imaging modality in the workup of the entire spectrum of this pathology.[6-10] The intent of this article is to review the existing literature on the role of different radiological modalities in the stepwise work up of CNS TB. The article focuses on the role of plain radiograph, fluoroscopy, computed tomography, magnetic resonance imaging along with its advanced sequences and Nuclear medicine in imaging of the many faces of tuberculosis in C.N.S. The article also aims to review the existing literature on the role of MR based textural analysis (Radiomics) as a problem solving tool in various nervous system pathologies and therefore requires the central attention of future researches to identify its potential in work up of central nervous system tuberculosis.

METHODS

We searched PubMed central databases for articles published in English from January 1 2000 to February 28 2021 along with references from the relevant articles. The search terms included "imaging in central nervous system tuberculosis" "Radiomics in tuberculosis ", "Radomics in central nervous system ". In total 95 articles including case reports, case series, original articles and review articles were included in this review.

PLAIN RADIOGRAPH AND FLUOROSCOPY

The role of plain radiograph is extinguishing in evaluation of cranial manifestation of CNS TB, however a plain chest x-ray is still a valuable tool in identification of subclinical pulmonary tuberculosis in patients who present primarily with neurological manifestations (Figure 1).[11] In the spine, although with a low sensitivity, a plain radiograph, can be used as primary investigation in work up of tuberculous osteomyelitis of the vertebral body also known as Pott's disease.[12] It is effective at identifying presence of disc space narrowing, anterior vertebral body wedging, vertebral body collapse and can hint at formation of a paravertebral abscess (Figure 2).[13] Rivas et al emphasize the effectiveness of oblique views at identifying findings at anterolateral corners of the vertebral body, which is one of the earliest radiographic manifestations of Pott's disease.[14]

Fluoroscopy is dormant in imaging of cranial and spinal tuberculosis, however procedures like fluoroscopy guided lumbar puncture and CT fluoroscopy guided percutaneous vertebral body biopsy have proven their worth in improving the accuracy of cerebrospinal fluid (CSF)and tissue sampling for confirmation of diagnosis in CNS TB.[15,16]

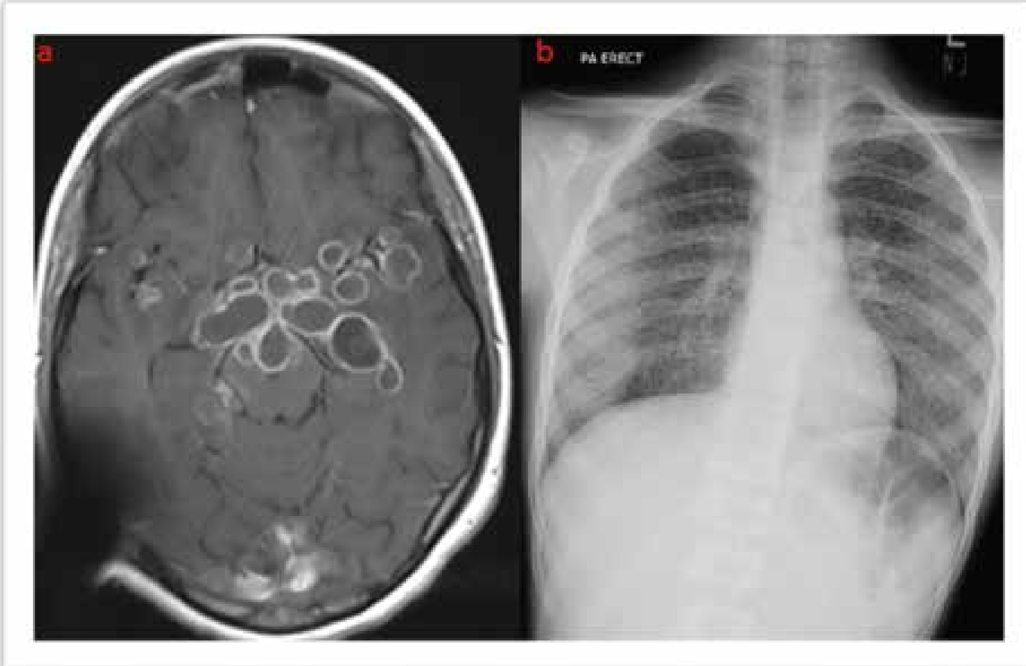

Figure 1: 13-year-old boy presented with history of fever and seizure with no pulmonary symptoms. CSF Sampling was positive for tuberculous bacilli, Subsequently the patient underwent MRI brain with and without contrast. Fig 1a Axial post contrast T1 weighted image shows multiple ring enhancing lesions. Subsequently chest radiograph (fig 1b) shows diffuse widespread miliary nodules in both lung fields representing miliary tuberculosis.

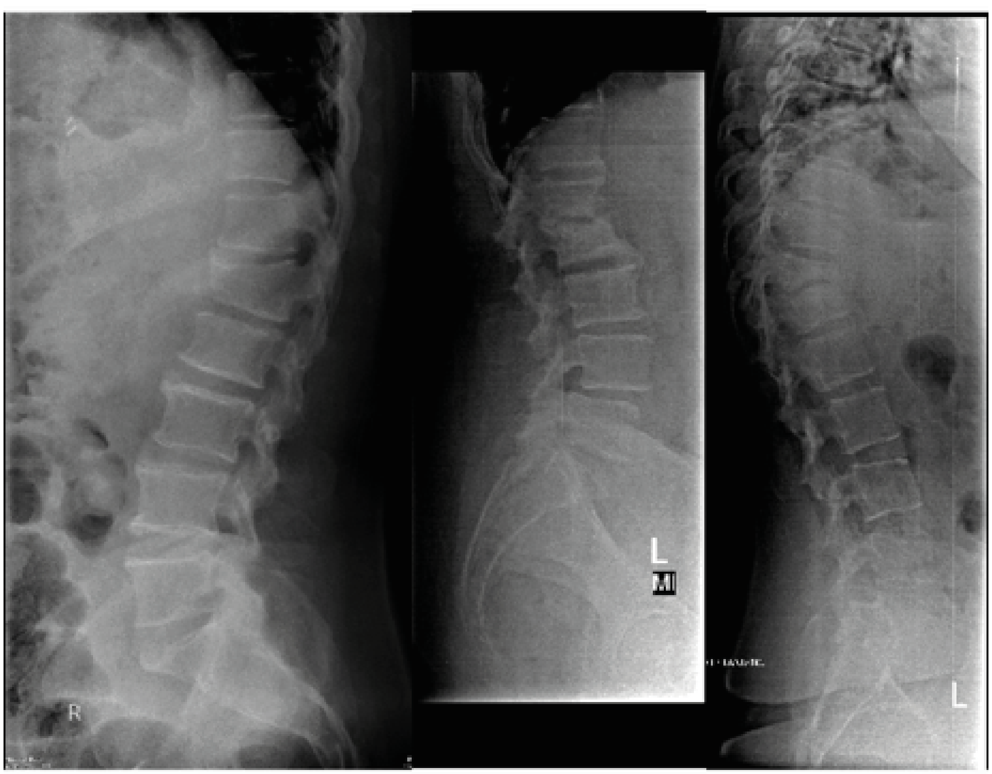

Figure 2: Multiple lateral radiographs of thoracolumbar spine showing varying degree of loss of disc space, vertebral body collapse with anterior wedging in known cases of spinal tuberculosis

COMPUTED TOMOGRAPHY

Computed tomography (CT) scan is the workhorse of the modern radiology department providing certain advantages in comparison to magnetic resonance imaging, including easier availability, cost effectiveness, less claustrophobia and less time consuming.[17]

An unenhanced CT examination can be used to screen complications of TB in the brain. These include infarctions as a sequelae of vasculitis, hydrocephalus and cerebral edema (Figure 3).[8] In spine, the main advantage of cross sectional nature of CT scan is its ability to describe the extent of disease. Typical CT features of Pott's disease include anterior vertebral body destruction along with collapse, disk space narrowing, large para spinal soft tissue abscess with calcification, cloaca formation and in more chronic stage's presence of sequestered disc.[18] In addition CT can also provide guidance for needle localization to drain associated abscess collections for diagnostic and therapeutic purposes.[19]

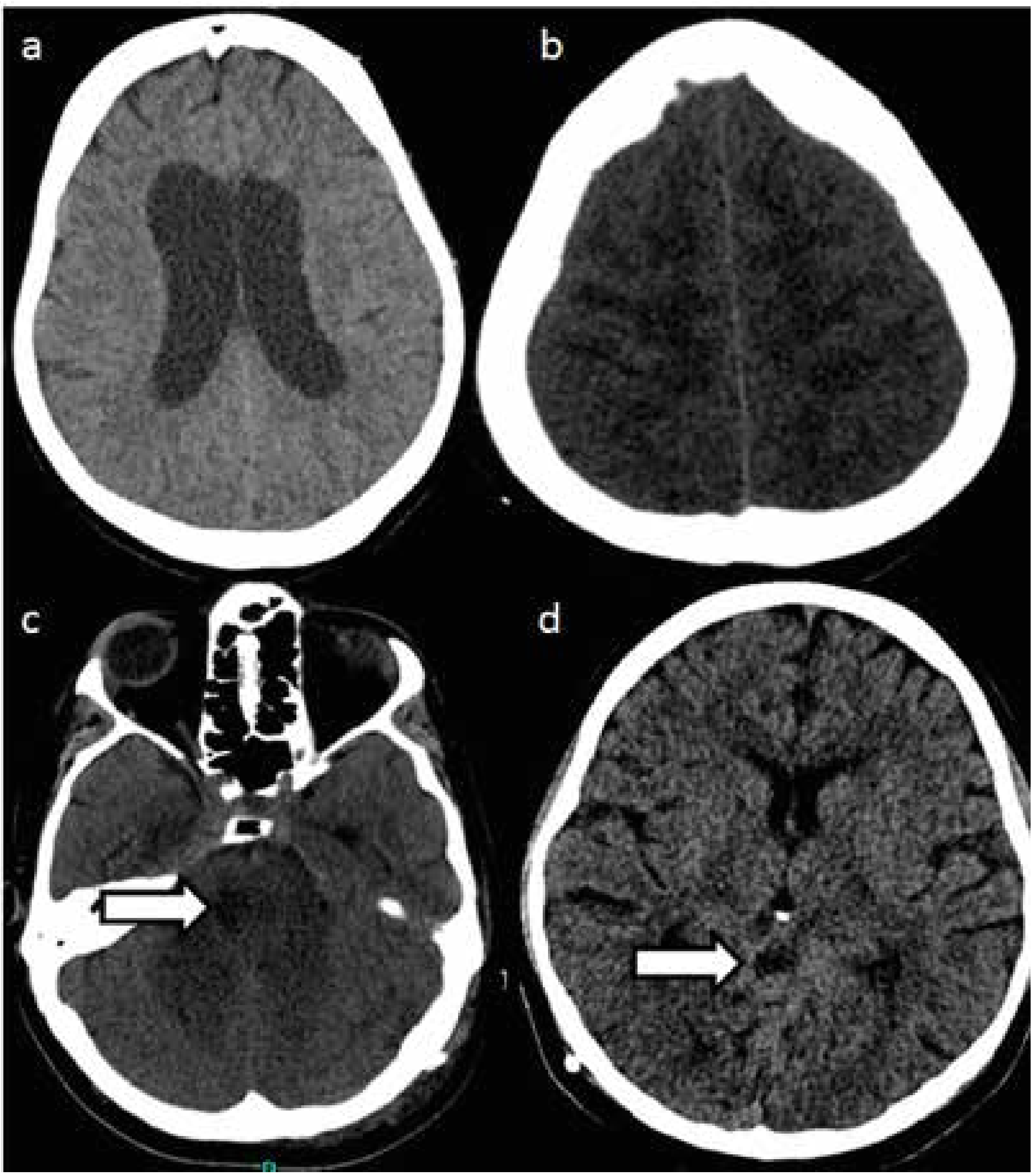

Figure 3: Multiple axial unenhanced CT brain images showing complication of CNS tuberculosis. Fig 3a is showing hydrocephalus, Fig 3b is showing effacement cortical sulci and swollen gyri consistent with diffuse brain edema, fig 3 c (arrow) is showing brain stem infarction, Fig 3d (arrow) is showing infarction of the splenium of corpus callosum

CT scan with contrast is effective at enumerating the lesions associated with CNS TB. It can outline a ring enhancing lesion within the brain parenchyma which could be an intracranial tuberculomas or a tuberculous brain abscess.[20] Moreover, it can also outline the enhancing thick exudate in basal cistern and thick pachymeningeal enhancement associated with tuberculous meningitis.[21] Advanced CT techniques such as perfusion imaging has shown promising results in differentiating treated versus untreated tuberculomas, where untreated tuberculomas show low perfusion markers compared to tuberculomas under treatment for less than two months.[22] CNS TB meningitis has a known association with infectious vasculitis along with arterial narrowing and occlusion. CT angiography is effective at eliciting these occlusions and narrowing, thereby explaining the underlying cause of tuberculosis associated brain infarctions.[23,24]

Inspite of the usefulness described above, CT imaging has certain limitations associated with it, which constraint its role in the imaging of CNS TB. One such feature is its low positive predictive value in detection of intracranial tuberculomas. In addition, the CT features of neurocysticercosis and intracranial tuberculomas are overlapping.[25] Tuberculous brain abscess is indistinguishable from non tuberculous brain abscess on CT brain alone.26 Moreover, the meningeal enhancement in tuberculous meningitis is indistinguishable from the enhancement associated with leptomeningeal carcinomatosis.[27]

Answers to these questions requires advanced imaging techniques such as magnetic resonance imaging (MRI) brain with and without contrast along with advanced MR based sequences The literature is conclusive about the superiority of Magnetic resonance imaging (MRI) over CT scan in explaining the magnitude and severity of disease in CNS TB.[28]

MAGNETIC RESONANCE IMAGING

A standard MRI brain examination protocol to evaluate cranial CNS MTB is a multiplanar, multi sequential scan which includes a spin echo T1, T2, FLAIR Post contrast T1, gradient recalled echo sequence, susceptibility weighted imaging (SWI) and Diffusion weighted imaging.[29,30] The image acquisition parameters of individual sequences vary across different centers. Parameters at our institution are mentioned in TABLE 1. This set of sequences is effective at eliciting various manifestations of intracranial TB which are summarized in TABLE 2. Intracranial tuberculomas are characteristic lesions associated with CNS TB which can give different signals at various stages of its evolution (TABLE 3), however isointense to hypo intense core with peripheral hyperintense rim on T2 and FLAIR weighted images is the most frequently encountered signal.[31-33] All these stages would give thin irregular ring enhancement - a characteristic feature which can help in differentiation of this entity from metastatic deposit. A metastatic deposit would give thick nodular enhancement.[34] Another sequence helpful in differentiating intracranial tuberculomas from metastatic brain disease and glioma is SWI - In a series of 116 patients 58 % tuberculomas revealed peripheral rim of susceptibility – a feature not seen in the other two pathological processes (Figure 4).[35] Gupta et al in a series of more than 100 lesions concluded that diffusion weighted images can reliably differentiate intracranial tuberculomas from neurocysticercosis.[36] One of the commonest manifestations of TB in CNS is tuberculous meningitis (TBM) which is associated with high morbidity and mortality.[37] Standard MRI imaging is valuable in assessing complications of TBM.[38] Characteristic features of TBM are thick nodular, intense, basal leptomeningeal enhancement with a significant minority of cases revealing concurrent ependymal involvement.[39] The pattern of enhancement is less intense in cases of TBM occurring in HIV patients.[40] T2 weighted images are useful in detecting pachymeningitis, which appear hypo intense in focal involvement, however reveal hyper intense signals in case of diffuse involvement.[41] Up to 25 % cases of TBM can have cerebral infarctions.[42] DWI sequence is useful in identifying complications of TBM including cerebral infarction, which has an impact on explaining patients clinical condition and prognostication, as cerebral infarctions along with hydrocephalus are predictors of poor outcome.[43.44] DWI sequence can also help in detection of cytotoxic edema associated with border zone necrosis in the pediatric population as well as identify early brain infarctions in this population (Figure 5).[45] Typical tuberculous brain abscess (TBA) would appear hypointense on T1 weighted images, hyperintense on T2 weighted images, diffusion restricted on DWI sequences showing peripheral ring enhancement, however these features are shared by brain abscesses secondary to other etiologies such as bacterial and pyogenic. In addition, cystic tumors can have similar appearances, while intracranial tuberculomas can also have overlapping features with a brain abscess therefore limiting the effectiveness of a standard MRI brain with contrast's ability to confidently diagnose a TBA .[46,47]

Table 1: Scan parameters and sequences included in standard MRI brain with and without contrast for evaluation of intracranial lesions

Scan parameters	T1	T2	FLAIR	DWI	ADC	SWI	T1 post contrast	FLAIR post contrast
Plane	Axial	Axial / sagittal	Coronal	Axial	Axial	Axial	Axial / sagittal	Coronal
Direction	Row	Row / Row	Row	COL	COL	Row	Row / Row	Row
REP Time (ms)	500	4430 / 6530	9000	3600	3600	49	500 / 500	9000
Echo time (ms)	7.8	97 / 106	109	115	115	40	7.8 / 7.8	109
Echo train (ms)	1	13 / 25	21	96	96	1	1 / 1	21
Echo number	1	1 / 1	1	1	1	1	1 / 1	1
Slice thickness (mm)	5	5 / 5	5	5	5	2	5 / 5	5
Slice spacing (mm)	6.5	6.5 / 6.5	6.5	6.5	6.5	0	6.5 / 6.5	6.5
Acquisition type	2D	2D / 2D	2D	2D	2D	3D	2D / 2D	2D

Table 2: Utility of various MRI sequences in intracranial manifestations of TB

Manifestation of CNS T.B in brain	T1	T2	FLAIR	T1 post contrast	DWI	SWI
Intracranial tuberculoma	Variable	Variable	Variable	Peripheral thin ring enhancement	Can help in differentiation from neurocysticercosis	Peripheral rim of susceptibility helps in differentiating tuberculoma from glioma and metastasis
Tuberculous meningitis		Can help detect pachymeningitis focal and diffuse form.		Thick basal meningeal enhancement, which is less severe in patients with preexisting HIV	Can help detect complications of tuberculous meningitis including early infarctions	
Tuberculous brain abscess	Hypointense	Hyperintense	Hyperintense	Peripheral enhancement	Diffusion restricted	
Tuberculous encephalopathy		Hyperintense	Hyperintense	Enhancement of the parenchyma in abscess of meningeal involvement	Multifocal diffusion restriction.	

Table 3: Various stages of intracranial tuberculomas on MRI

Type of granuloma	Signals on T1 weighted image	Signals on T2 weighted image
Non caseating granuloma	Isointense	Hyperintense
Caseating granuloma with liquified center	Hypointense	Hyperintense
Caseating granuloma with solid center	Hyperintense	Hyperintense

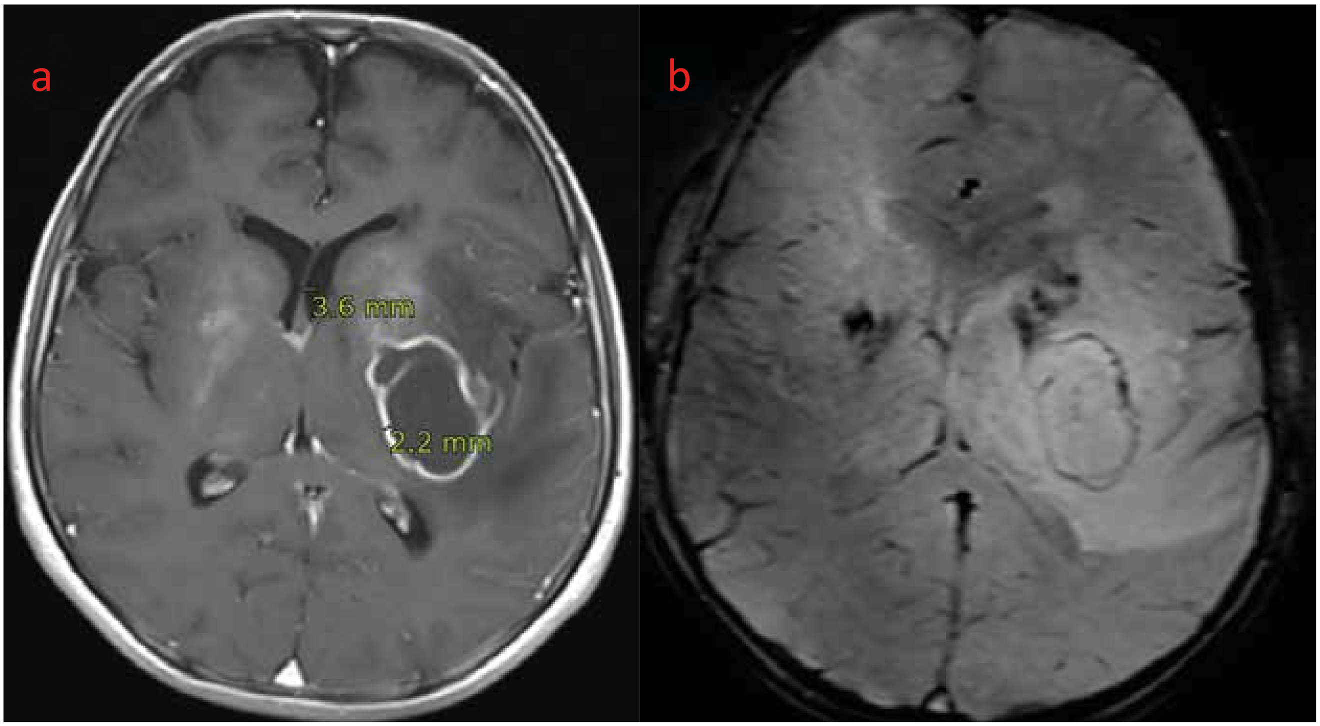

Figure 4: 4a is showing a ring enhancing lesion in involving left basal ganglia and insular cortex in left frontal lobe. The same lesion is showing a peripheral rim of susceptibility on SWI sequence (figure 4b). This was confirmed to be a case of CNS tuberculosis on CSF analysis

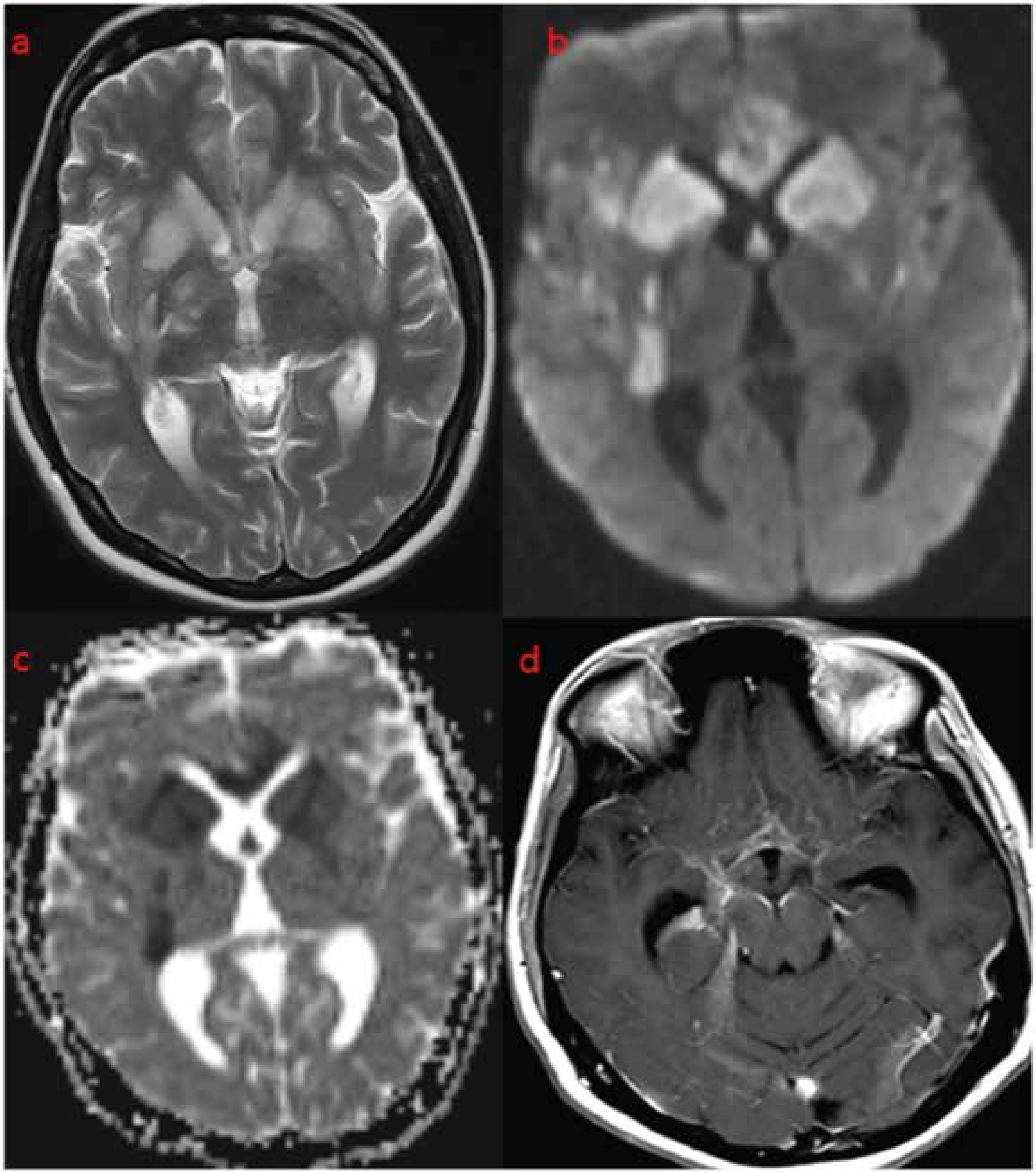

Figure 5: 28 years old female presented with loss of consciousness and fever to ER. Multi planar Multi sequential MRI brain was performed with contrast Figure 5. Multi focal hyper intense signals noted involving bilateral basal ganglia and deep white matter in bilateral frontal lobes (fig 5a). These areas are showing diffusion restriction on DWI / ADC sequences (Fig 5b, c). Subsequently post contrast T1 weighted images shows basal leptomeningeal enhancement (fig 5d)

Tuberculous encephalopathy is a rare distinctive entity with high mortality.[48] It is characterized by presence of parenchymal changes in absence of meningeal involvement, which would appear hyperintense on T2 weighted images, showing multifocal infarcts on DWI sequences and reveal post contrast enhancement on T1 post contrast images .[49,50] One study reported these MRI features, where histopathology revealed demyelination and T.B bacilli in granuloma.[51] MRI is the modality of choice in imaging of spinal manifestations of tuberculosis. A standard MRI for imaging of spinal tuberculosis would be a multiplanar multisequence MRI performed with and without contrast including T1 weighted image, T2 weighted fast spin echo image, T1 fat suppression imaging and T1 post contrast sequences. All these sequences can be obtained in multiple planes depending upon the region of spine being imaged.[52] Arachnoiditis secondary to tuberculosis is part of a spectrum known as tuberculous radiculomyelopathy, which includes radiculitis, arachnoiditis and adhesive arachnoiditis.[53] MR may demonstrate features of nonspecific arachnoiditis which include clumping of intrathecal nerve roots.[54] Other MR features traditionally described include, meningeal enhancement, increased T1 CSF signal resulting in loss of cord CSF interface / shaggy cord outline, loculations in CSF, clumping of cauda equina nerve roots. Cord involvement is a common entity resulting in cord enhancement, with or without cavitation and indistinct dura-arachnoid-cord complex . Correlation of MR features with significantly raised CSF protein level is an important predictor associated with myeloradiculopathy and these patients usually have poor outcome.[55] MRI is an invaluable tool in diagnosis of Pott's disease, with its ability to detect early changes, assessment of the spinal cord and define the extent of soft tissue involvement along with delineating soft tissue abscess.[56.57] MR features associated with tuberculous vertebral osteomyelitis include reduced disc space, wedge collapse, complete destruction of vertebral body, paraspinal abscess, calcification and cord compression.[58.59] Tuberculous myelitis is another known manifestation of MTB in the cord which most commonly involves the thoracic segment of the spinal cord. It can have variable features on a standard MRI examination, most commonly appearing hypointense on T1 weighted images and hyperintense on T2 weighted images, however MRI is most valuable in identifying cord atrophy, cavitation and syrinx which is associated with poor outcome.[60]

ADDITIONAL MR BASED SEQUENCES

In addition to the standard MRI imaging protocol discussed in the previous section, there are certain sequences which can significantly improve detection and characterization of central nervous system manifestations of tuberculosis. Two such important sequences are time of flight magnetic resonance angiography images and post contrast magnetic resonance venography images. These sequences can be performed to enumerate some of the most common complications of CNS TB including venous sinus thrombosis, vasculitis and infarctions.[61] Arterial territories supplying bilateral basal ganglia and thalami are most commonly involved compared with venous systems. MRA images are sensitive at depicting the beaded appearance of vessels when involved (Figure 6).[62] MR based vessel wall imaging is a relatively new imaging technique based on T1 fat suppression acquisition protocol, where high resolution and 3D reconstructed images are acquired pre and post contrast to identify the involvement of vessels specifically in case of vasculitis associated with tuberculous meningitis. It has better sensitivity but lower specificity than MRA for detection of vascular complications in tuberculosis. Nodular or smooth segmental vessel wall enhancement with or without stenosis on this technique is a feature of tuberculous vasculitis.[63]

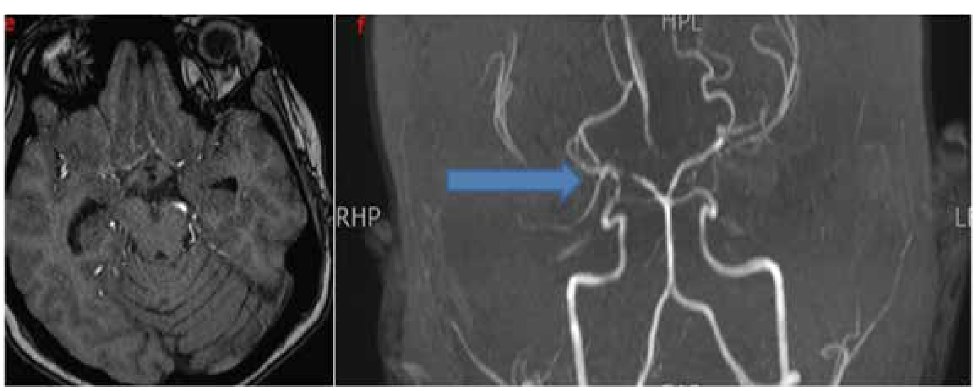

Figure 6: Time of flight MRA and 3-D reconstructed images show multifocal beaded attenuated appearance of branches of bilateral anterior and posterior circulation (blue arrow). Appearances are consistent with vasculitis infarction with basal meningitis. CSF sampling confirmed tuberculous bacilli

MR spectroscopy is imaging based on the metabolic properties of the lesion.[64] This sequence has excellent ability at detection of intracranial tuberculoma and differentiating it from malignant lesions and neurocysticercosis.[65-67] Lipid lactate peak inversion at 1.3 ppm is a sensitive yet non-specific marker for detection of intracranial tuberculomas (Figure 7), however a Morales et all have described the ability of a singlet peak at 3.8 ppm to be specific for intracranial tuberculomas.[68] In addition, intracranial tuberculomas are known to showcase Cho/Cr, Cho/NAA and Cho/Cho ratio values significantly lower than high grade gliomas.[69] MR spectroscopy is also effective at differentiating extra axial tuberculomas from meningioma.[70] Furthermore MR spectroscopy can also differentiate tuberculous and pyogenic brain abscesses, where absence of amino acid peak and presence of lipid lactate peak are characteristics of tuberculous brain abscess.[71] MR perfusion scan can offer value in differentiating intracranial tuberculomas from malignant lesions.[72] The Perfusion values of tuberculomas in general are lower compared to malignant lesions except in cases of hypervascular tuberculomas, where differentiation in perfusion values of both the lesions cannot be reliably differentiated.[73] Magnetization transfer MRI is a unique way of improving image contrast and improving tissue characterization.[74] This special imaging sequence has improved efficacy at imaging CNS tuberculosis compared to standard spin echo imaging.[75,76] Visualization of inflamed meninges as hyperintense on pre-contrast MT T1 weighted images followed by a low magnetization transfer ratio (MTR) is sensitive for tuberculous etiology.[41]

Figure 7: Multi-planar multi-voxel MR spectroscopy image through a lesion in left frontal lobe is showing a prominent lipid lactate peak inversion at 1.3 ppm. The finding is sensitive, however non-specific for intracranial tuberculoma

NUCLEAR MEDICINE INCLUDING FDG-PET CT

Nuclear bioimaging is a powerful tool which can provide a non-invasive method of imaging disease processes including tuberculosis deep within the body in three dimensions.[77] Regardless of the organ involved tuberculous lesions are known to show increased FDG uptake.[78] FDG/PET CT scan although not specific has excellent ability at depicting tuberculous brain abscesses which appear as areas of peripheral hyperactivity and central cold areas known as doughnut sign.[79] Although the features on FDG/PET findings in central nervous system tuberculosis are non-specific, this is a useful tool in mapping the burden of pulmonary and extra pulmonary tuberculosis throughout the body.[80]

RADIOMICS

Radiomics is a translational field which aims to convert medical images into quantifiable data using softwares.[81]

Any type of radiological image including Plain X Ray, CT, MRI and PETCT examination can be used for the purpose of data extraction. The first step in extraction of such data is to define a region of interest (ROI) or Volume of interest (VOI) on a scan image. Subsequently several softwares are available which can be used to segregate the information, known as the agnostic features which is based on the level of grey within the image.[82,83] This information can further be broken down into first order - histogram based, second order - texture based and higher order information.[84] Several sets of radiomic features exist, however adherence to standardized set of radiomic features is important to enable verification and validation of the information extracted.[85] Table 4 provides a list of 38 textural parameters used in life x open-source software. Its role is evolving in various intracranial pathologies including several types of brain tumors and neurodegenerative disorders including Parkinson's disease (PD).[86-91] Diffusion based radiomic models have in particular shows better diagnostic performance compared to conventional radiomic features or Conventional MR imaging in diagnosis of primary central nervous system lymphoma.[92] CT based radiomic models have been developed which have the potential to distinguish pulmonary tuberculosis from lung cancer.[93] Furthermore, preliminary data shows radiomic models based on pretreatment PET-CT images have the potential to differentiate active pulmonary tuberculosis and lung cancer, however utility of radiomics in CNS TB is underexplored.[94] An abstract presented at European conference of radiology (ECR) 2020, suggested the utility of MR based textural featural in differentiating treatment responsive and treatment resistant intracranial tuberculomas.[95] The results of this abstract concluded that MR based radiomic features can reliably differentiate treatment responsive and treatment resistant intracranial tuberculomas, however this requires further scientific workup. Large scale multi software studies involving multiple sequences are needed to develop models which can help in improving the ability and accuracy of diagnosis in central nervous system tuberculosis.

CONCLUSION

Correct use of imaging modalities in the work up of central nervous system tuberculosis can help in early and accurate diagnosis impacting associated morbidity and mortality. Where conventional imaging can help as a screening tool and provide guidance for sampling procedures, cross sectional imaging is the mainstay of imaging workup. Nuclear imaging is becoming an essential adjuvant to determine the burden of the disease. Role of radiomics is evolving in intracranial pathologies and certainly needs the central attention of future researches to establish its role in CNS TB.

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