



# Central Nervous System Tuberculosis

## Etiology, Clinical Manifestations and Neuroradiological Features

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### Abstract

**Purpose** As a result of multilateral migration and globalization in times of humanitarian crises, western countries face a possible increase in the incidence of central nervous system tuberculosis (CNS TB). The diagnosis of CNS TB is challenging and often delayed due to the manifold and often non-specific presentation of the disease. The aim of this review is to analyze and summarize imaging features and correlated clinical findings of CNS TB.

**Methods** The different manifestations of CNS TB are explained and illustrated by characteristic neuroradiological as well as neuropathological findings. An overview on diagnostic and therapeutic approaches is provided. For clarity, tables summarizing the lesion patterns, differential diagnoses and diagnostic hints are added.

**Results** The CNS TB can be manifested (1) diffuse as tuberculous meningitis (TBM), (2) localized as tuberculoma or (3) tuberculous abscess or (4) in extradural and intradural spinal infections. Information on clinical presentation, underlying pathology and the distinguishing features is demonstrated. The TBM is further described, which may lead to cranial nerve palsy, hydrocephalus and infarction due to associated arteritis of the basal perforators. The differential diagnoses are vast and include other infections, such as bacterial, viral or fungal meningoencephalitis, malignant causes or systemic inflammation with CNS. Complicating factors of diagnosis and treatment are HIV coinfection, multi-drug resistance and TB-associated immune reconstitution inflammatory syndrome (IRIS).

**Conclusions** Neurologists and (neuro-)radiologists should be familiar with the neuroradiological presentation and the clinical course of CNS TB to ensure timely diagnosis and treatment.

**Keywords** Tuberculous Meningitis · Tuberculoma · Spinal Tuberculosis · Tuberculous abscess · Tuberculous spondylitis

### Introduction

Although the number of tuberculosis (TB) associated deaths decreased by 22% between 2000 and 2015, the disease still accounts for at least 1.8 million deaths in 2015 alone and ranks as 1 of the top 10 causes of death worldwide [1]. It is estimated that one third of the world population is infected with *Mycobacterium tuberculosis*. Conse-

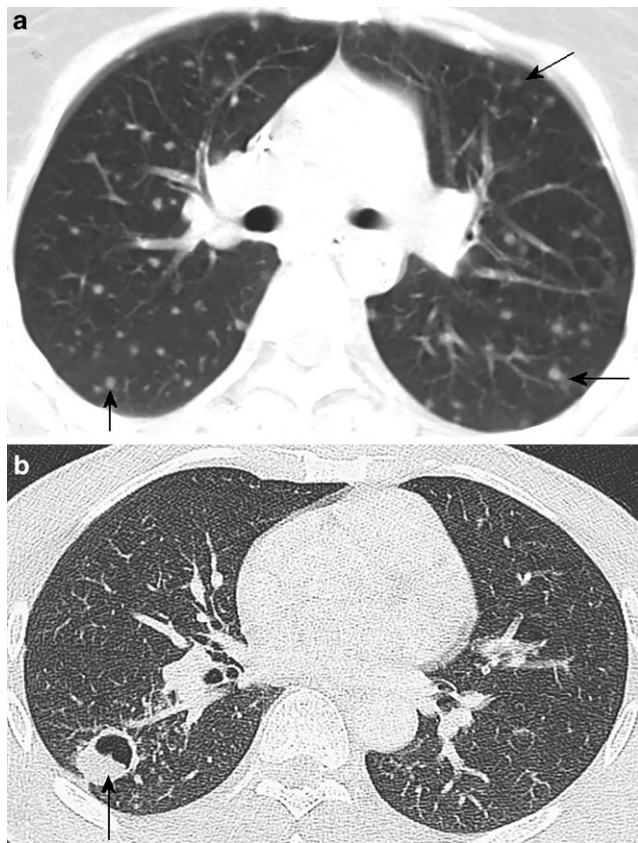
quently, western countries face a possible increase of TB cases in times of multilateral migration and globalization [2]. Complicating circumstances are the co-epidemic of TB and acquired immunodeficiency syndrome (AIDS) and the spread of multidrug-resistant TB (MDR-TB) [2–4]. While the most common manifestation of TB is pulmonary, extra-pulmonary central nervous system tuberculosis (CNS TB) is harder to diagnose and inherently has a worse outcome than pulmonary TB, especially if treatment is delayed ([5, 6]; Fig. 1). The CNS TB is one of the most devastating clinical manifestations of TB and is associated with a high mortality [7–13]. It occurs in 1–5% of all patients with TB and in 10% of those with AIDS-related TB [3, 13–15]. Higher risk of CNS TB is described in children younger than 5 years and patients under immunosuppression, such as HIV-positive patients or under treatment with corticosteroids or tumor necrosis factor alpha (TNF-alpha) blockage [6, 7, 11, 16–23]. The CNS TB can mimic a manifold num-

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**Fig. 1** Pulmonary tuberculosis. Axial post-contrast CT (**a**, **b**) showing multiple small round lesions in miliary tuberculosis (**a**, arrows) and a tuberculous cavern (**b**, arrow)

ber of other diseases and it depicts a formidable diagnostic challenge, often presenting with non-specific symptoms and inconclusive laboratory results [7, 24]. In this matter, modern imaging technology is a cornerstone in the diagnosis of CNS TB and can help to prevent unnecessary morbidity and mortality [3].

This review provides an overview on the clinical and neuroradiological features of CNS TB. After addressing the essentials of the underlying pathology, the most common manifestations of CNS TB are described: tuberculous meningitis, tuberculoma, tuberculous abscess and spinal tuberculosis (Table 1). Furthermore, the numerous differential diagnoses presenting similar to CNS TB including the radiological hallmarks are addressed and summarized (Table 2). The definitive diagnosis of TB is always a result of clinical, radiological, laboratory, histopathological and microbiological findings and a close interdisciplinary cooperation is a vital essence of success.

## Pathology

The principal mode of contagion of *Mycobacterium tuberculosis*, an obligate aerobic acid-fast bacillus (AFB), is by inhalation into the alveolar spaces. From there, secondary spread to extrapulmonary sites through bacteremia and lymphatic drainage is possible, preferably to highly oxygenated sites such as the brain [7, 25, 26]. The CNS TB begins with small caseous tubercles (so-called Rich foci) which can form throughout the brain, spinal cord and meninges [7]. The most common manifestation of CNS TB is tuberculous meningitis (TBM), which manifests when tuberculous bacilli enter the subarachnoid space through a rupturing Rich focus in the cerebral cortex or the meninges ([27]; Fig. 2). After the release of mycobacteria into the subarachnoid space, the brunt of the pathologic process falls on the basilar area and basal meninges [27]. The exudate typically envelops prominent subarachnoid anatomical structures, such as cerebral arteries and cranial nerves and creates a bottleneck situation in cerebrospinal fluid (CSF) flow at the level of the tentorial opening as well as a narrowing of the aqueduct, leading to non-communicating (obstructive) hydrocephalus ([7, 28]; Fig. 3). The most frequent hydrocephalus in TBM is of the communicating type, secondary to blockage of focal CSF resorption by the inflammatory exudate in the basal cisterns [3, 6, 25]. If tubercles in the brain parenchyma enlarge without rupturing, tuberculomas arise [7, 29].

## Manifestations

### Tuberculous Meningitis (TBM)

A TBM often presents with non-specific symptoms and inconclusive laboratory results, making diagnosis difficult [3, 12]. It is the most frequent and severe manifestation of CNS TB with the highest likelihood of an adverse outcome ([15, 30, 31]; Fig. 2). In addition, in high prevalence countries patients are often children younger than 3 years [27, 32, 33]. Most cases in low prevalence countries such as northern Europe are adults who immigrated from areas of high prevalence [31, 33].

### Clinical Presentation

A prodromal period of 2–4 weeks with non-specific symptoms such as fatigue, malaise, myalgia and fever commonly precedes CNS TB [3, 7, 20, 30, 34]. If a meningitic state ensues, TBM presents with headache, fever, vomiting, photophobia and stiffness of the neck (75% of cases [30, 35–37]). In comparison to bacterial meningitis these symptoms evolve slower, usually taking more than a week

**Table 1** Clinical and neuroradiological findings in most common CNS TB manifestations

Entity	Imaging hallmark	Clinical presentation
Tuberculous meningitis	<i>Basal meningeal enhancement</i> (in up to 90%) <i>Hydrocephalus</i> (in ~66%) <i>Infarction</i> (in >50%) <i>Tuberculoma</i> (in ~30%) Tuberculous meningoencephalitis: possible symmetrical restricted diffusion of cortical and adjacent subcortical structures on DWI (Fig. 6) <i>CT non-contrast</i> : hyperdense basal cisterns <i>pc CT</i> unmasks basal enhancement	Unspecific prodromes over weeks precede a meningitic state with neck stiffness, photophobia, vomiting and eventually change in mental state Complications <i>Cranial nerve palsy</i> (VI>III>IV>VII>VIII) Disturbance of consciousness and vigilance <i>Focal deficits</i> (e.g. hemiparesis, aphasia) <i>Hyponatremia</i>
Miliary TB	Small sized dispersed focal lesions MRI lesions: T1w isointense with hypointense center on T2WI/FLAIR and hyperintense circumference Surrounding edema may be present; T1 WI pc: marked rim enhancement	Unspecific prodromes Headache, seizures, impairment of consciousness and vigilance
Tuberculoma	<i>pc CT</i> shows homogenous enhancement if non-caseating and ring enhancement if caseating Rarely “target sign” representing central calcification Perifocal edema (ca. 1/3 of patients) MRI: hypointense on T1 WI, T2 WI depends on stages; pc T1 WI similar to pc CT	Focal deficits depending on lesion site, seizures <i>Complication</i> : TBM if tuberculomas rupture into the subarachnoid space
Tuberculous Abscess	<i>CT</i> : hypodense with perifocal edema and sometimes mass effect <i>pc CT</i> : rim-enhancement MRI: center is T1-hypointense and T2-hyperintense with restricted diffusion of the center and rim-enhancement on pc T1 WI MRS: lipid peaks are suggestive of mycobacteria	Fever, headache, seizures and focal deficits
Tuberculous spondylitis (extradural)	Well-defined paraspinal abnormal signal with a thin and smooth abscess wall Subligamentous spread and relative preservation of the intervertebral space	Back pain, kyphosis vertebral fracture in later stages <i>Complication</i> : radicular, cauda equine or spinal cord symptoms, e.g. sensory disturbances, bladder and bowel dysfunction, flaccid or spastic paresis
Spinal tuberculosis (intradural)	Meningeal and radicular enhancement Myelitis Longitudinal extensive transverse myelitis (LETM) Intramedullary spinal tuberculoma Syringomyelia	(Sub) acute spinal cord or cauda equine symptoms

*CT* computed tomography, *pc CT* post contrast computed tomography, *T2w* T2 weighted image, *FLAIR* fluid-attenuated inversion recovery, *MRI* magnetic resonance imaging, *DWI* diffusion weighted imaging, *MRS* magnetic resonance spectroscopy, *TBM* tuberculous meningitis, *T1 WI* T1 weighted image

to manifest [28]. Complications involve cranial nerve (CN) palsies, which occur in approximately 25–50% of patients, involving mainly the VI CN (N. abducens) and less often CN III (see Figs. 2 and 3). Disturbance of CSF circulation with subsequent hydrocephalus is common, leading to disturbance of consciousness. Seizures occur in about 10–15% of patients [6, 30]. Parenchymal damage results from infarction due to vasculitis or direct inflammatory involvement of meninges and brain parenchyma. Hemiparesis and altered consciousness are the most common deficits after TBM-related infarction; nonetheless, other symptoms such as aphasia or hemianopsia can occur [38–41]. Attention should be paid to the frequent occurrence of hyponatremia due to renal salt-wasting syndrome or SIADH (syndrome of inappropriate antidiuretic hormone secretion; 40–50% of cases)

[30, 42]. If TBM remains untreated, it progresses over time with accretive focal neurologic deficits, raised intracranial pressure and altered mental state with confusion and coma, inevitably leading to a fatal outcome within 4–8 weeks of onset [6, 28].

### Diagnosics

The diagnosis of TBM depends on the combined interpretation of the clinical course, imaging findings, laboratory analysis of blood and CSF and possible presence of TB in other sites (e.g. pulmonary, urogenital, osseous). A CSF analysis typically shows a lymphocytic pleocytosis with an average cell count around 200 cells/ $\mu$ l (10–1000 $\times$ 10<sup>3</sup> cells/ml), moderately to severe elevated pro-

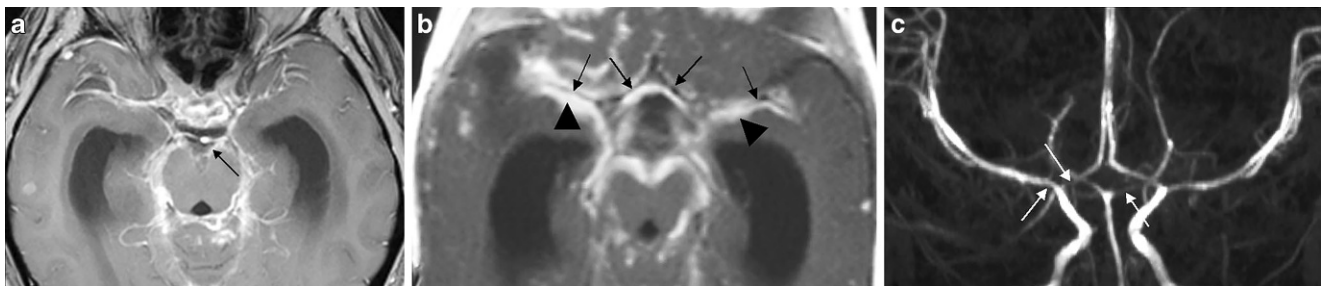
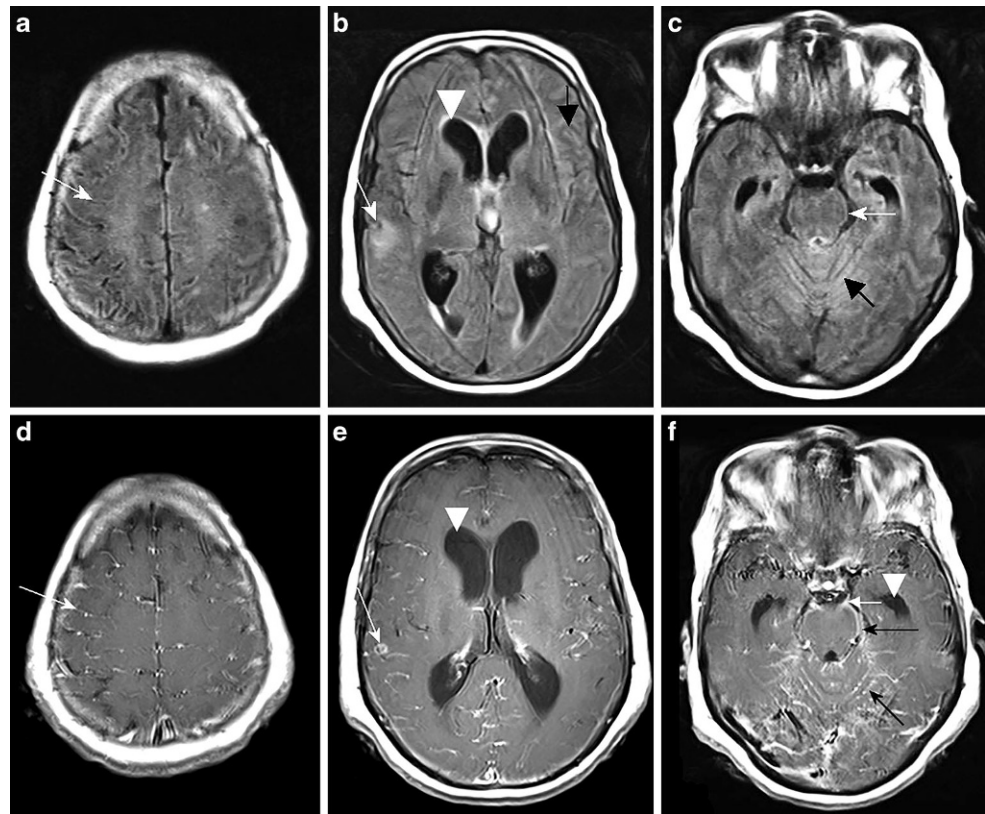
**Table 2** Differential diagnoses of tuberculous meningitis [101, 102]

Disease	Characteristic features	Imaging hallmarks
Bacterial meningitis [103, 104]	Mostly caused by <i>S. pneumonia</i> , <i>N. meningitidis</i> or <i>H. influenza</i> Fever, neck stiffness and headache May mimic subacute meningitis of TBM, especially under antibiotic treatment <b>CSF</b> : high neutrophil counts (>1000/μl), low glucose, high lactate and protein	<b>Leptomeningeal enhancement</b> <b>Mnemonic “HACTIVE”</b> : (hydrocephalus, abscess, cerebritis, cranial nerve lesion, thrombosis, infarct, ventriculitis/vasculopathy and extra-axial collection)
Fungal meningitis (cryptococcosis, coccidioidomycosis)	Subacute or chronic meningitis in immunocompromised patients <b>CSF</b> : mononuclear pleocytosis, increased protein, decreased glucose	<b>Hydrocephalus</b> , leptomeningeal and perivascular enhancement, granuloma or <b>abscess formation</b> and infarction possible <b>Pulmonary involvement</b> common
Leptomeningeal carcinomatosis	Subacute or <b>chronic meningeal syndrome</b> often with cranial nerve or radicular involvement and hydrocephalus <b>Progressive headache</b> and/or <b>back pain</b> <b>CSF</b> : <b>pleocytosis</b> with malignant cells, (immuno-)cytology is essential, protein and lactate often increased, glucose can be very low	Diffuse and <b>partially nodular leptomeningeal enhancement</b> and sometimes <b>metastatic lesions</b> Primary tumor site should be sought
Mycobacteria other than tuberculosis (MOTT) and non-tuberculous mycobacterial meningitis (NTMM) [105–107]	Clinical syndrome identical to CNS TB caused by <i>M. tuberculosis</i> NTMM is frequently associated with immunosuppression, mainly affecting patients with AIDS and low CD4 counts <50 cells/μl <b>CSF</b> : similar to CNS TB; definitive differentiation is only revealed through <b>CSF culture</b>	<b>Similar to CNS TB</b> caused by <i>M. tuberculosis</i>
Neurobrucellosis [108–110]	<b>Fever, headache, agitation</b> , behavioral changes, muscle weakness and <b>neck rigidity</b> are common <b>Impaired hearing</b> more common than in CNS TB Testing for anti-Brucella <b>antibodies in CSF</b> is quite sensitive and specific	Basal meningeal and lumbar nerve root <b>enhancement, granuloma</b> of the suprasellar region, and <b>diffuse white matter changes</b> White matter lesion resembles <b>demyelinating disease</b> , which is unusual in CNS TB
Neurosarcoidosis	Subacute or chronic meningitis Cranial nerve (mainly of the <b>facial nerve</b> ) and <b>pituitary involvement</b> common <b>CSF</b> : pleocytosis and elevated protein content; ACE and IL2-Receptor can be increased	<b>Leptomeningeal</b> and <b>angiocentric</b> (perivascular) <b>enhancement</b> (40%) Intraparenchymal <b>enhancing granulomas; Cranial nerve enhancement</b> Pituitary/hypothalamic mass lesion with <b>enhancement</b> <b>Systemic manifestations</b> should be sought for diagnosis (e.g. lymph node biopsy, chest imaging)
Neurosyphilis	Occurs in <b>secondary syphilis</b> and presents as a subacute <b>meningitic syndrome</b> Antibody and PCR testing of CSF can ascertain the diagnosis	Leptomeningeal enhancement Isolated or multifocal white matter lesions, infarcts, mesial temporal lobe (mimicking limbic encephalitis), atrophy Syphilitic gumma
Systemic lupus erythematosus (SLE)	Often presenting as aseptic meningitis Neurologic complications (stroke, seizures) occur in <5% of SLE-patients Antinuclear and anti-dsDNA antibodies commonly positive	Infarcts and white matter lesions may occur
Viral meningitis/meningoencephalitis [111]	<b>Headache, fever</b> , altered mental status, <b>seizures</b> and <b>focal neurological symptoms</b> (aphasia) in HSV I-encephalitis <b>CSF</b> : <b>pleocytosis</b> and <b>normal glucose</b> suggests viral infection, <b>specific diagnosis</b> requires detection of antibodies or DNA by <b>PCR</b>	Leptomeningeal enhancement White matter lesions HSV I, (II), HHV 6: typically starting mesotemporally, extending laterally and along anatomically related structures, extrahippocampal; involvement seems to be more frequent with HHV 6 Hemorrhagic transformation (HSV I)

PCR polymerase chain reaction, SLE systemic lupus erythematosus, AIDS acquired immunodeficiency syndrome, HSV herpes simplex virus, HHV human herpesvirus, DNA deoxyribonucleic acid, CSF cerebral spinal-fluid, ACE angiotensin-converting enzyme, IL interleukin, CNS TB central nervous system tuberculosis



**Fig. 2** A 73-year-old woman suffering from fulminant course of tuberculous meningitis. Axial fluid attenuated inversion recovery (FLAIR) images (a–c) showing hyperintense leptomeninges and narrowed sulcal spaces (a, arrow; c, black arrow). Axial pc T1 WI (d–f) demonstrating increased contrast enhancement (d, arrow; f, black arrows), caseating tuberculoma temporal right (b, e: arrow), hydrocephalus with enlarged lateral ventricles (b, d: arrowhead) and widened temporal horns (f, arrowhead). Note involvement of the brainstem surface (c, white arrow; f: black arrow) and enhancement of the oculomotor nerve (f, white arrow)



**Fig. 3** Axial pc T1 WI (a, b) demonstrating enhancement of basilar structures and the third cranial nerve (a, arrow); b, c: extensive exudates in the subarachnoid space (b, arrowheads) with negative contrast of the proximal arterial segments (anterior, middle and posterior cerebral artery; b: arrows) and multisegmental vascular narrowing on MR angiography (c, arrows; time-of-flight [TOF] MRA). MRA MR angiography, T1 WI T1 weighted image

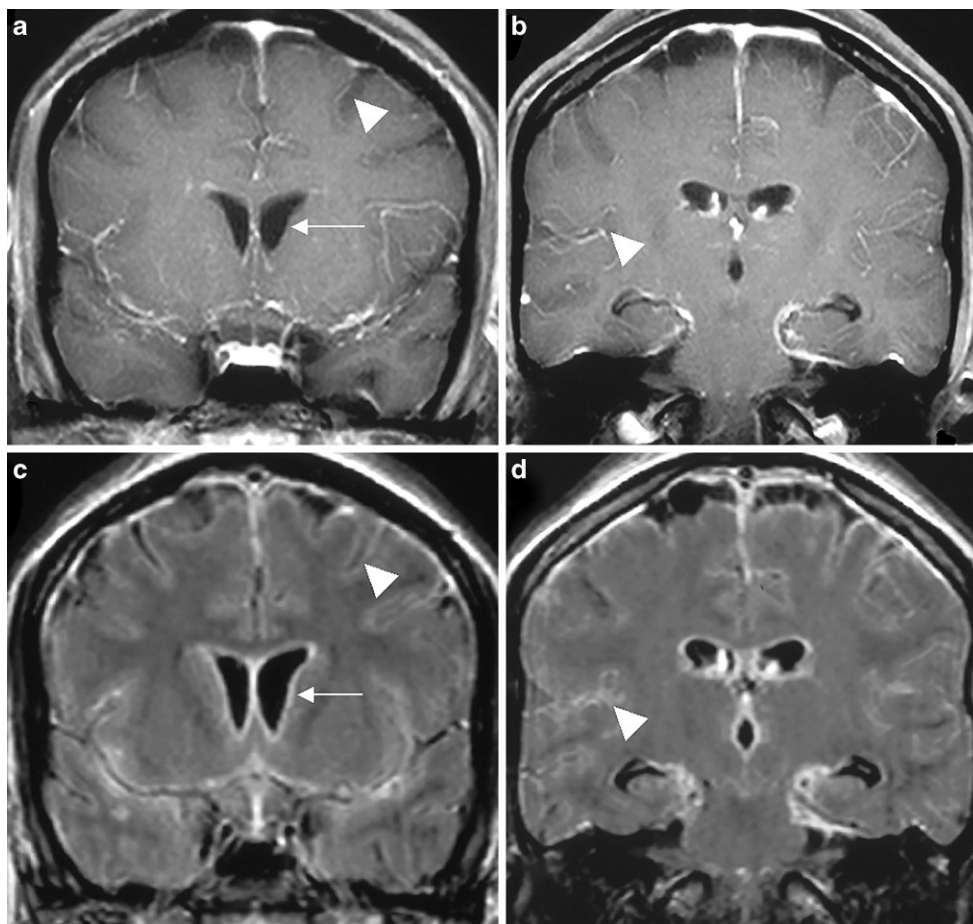
tein content (0.5–3.0 g/l) and glucose levels lower than 45 mg/dl or below 40–50% of serum glucose (hypoglycorrhachia). It is noteworthy that in addition to decreased CSF glucose, the CSF lactate levels may be increased from 5.0–10.0 mmol/l [5, 7, 16, 30, 33, 34, 43]. Determination of intrathecal IgG synthesis may provide supporting evidence for differentiating the diagnosis of TBM from aseptic meningitis (sensitivity 100%, specificity 83.3%) [44].

Unlike bacterial meningitis, TBM is characterized by the following features: duration of symptoms longer than 6 days, total cell count in the CSF  $<1000/\mu\text{l}$ , and peripheral blood white cell count  $<15,000 \times 10^{-3}/\text{ml}$  [30]. It should be noted that mycobacteria other than tuberculosis (MOTT;

non-tuberculous mycobacterial meningitis, NTMM) are an important differential diagnosis in patients with AIDS, because CSF findings are often similar to TBM and clinical syndrome and progress for the most part do not allow differentiation.

Culture of CSF specimens for mycobacteria is essential, even though CSF samples are only positive in 5–58% of patients [45, 46]. Identification of AFB in the CSF through both smear and culture methods, such as Ziehl-Neelsen staining techniques remains the most important and especially most widely available method to diagnose CNS TB, allowing drug sensitivity testing and strain subanalysis [7].

**Fig. 4** Coronal pc T1 WI (a, b) and coronal pc fluid attenuated inversion recovery (FLAIR) images (c, d) in tuberculous meningitis. Note prominent hyperintense signals of pial (arrowhead) and ependymal (arrow) structures on pc FLAIR images (c, d)



The time-costly character of traditional microbiological techniques formed the necessity for faster diagnostic molecular and biochemical analysis techniques to facilitate early diagnosis [7, 28]. Several molecular-based techniques, often drawn from successful techniques used for the diagnosis of tuberculosis in respiratory specimens, have been evaluated for their applicability in the diagnosis of TBM [7]. The techniques include nucleic acid amplification (NAA) methods, antibody and antigen detection or chemical assays such as adenosine deaminase and tuberculostearic acid measurements [7]. A tissue diagnosis (by histopathology and mycobacterial culture) should be attempted whenever possible, either by biopsy of focal lesions or through diagnostic sampling from extraneural sites of disease, e.g. lungs, gastric fluid, lymph nodes, liver and bone marrow [16, 33].

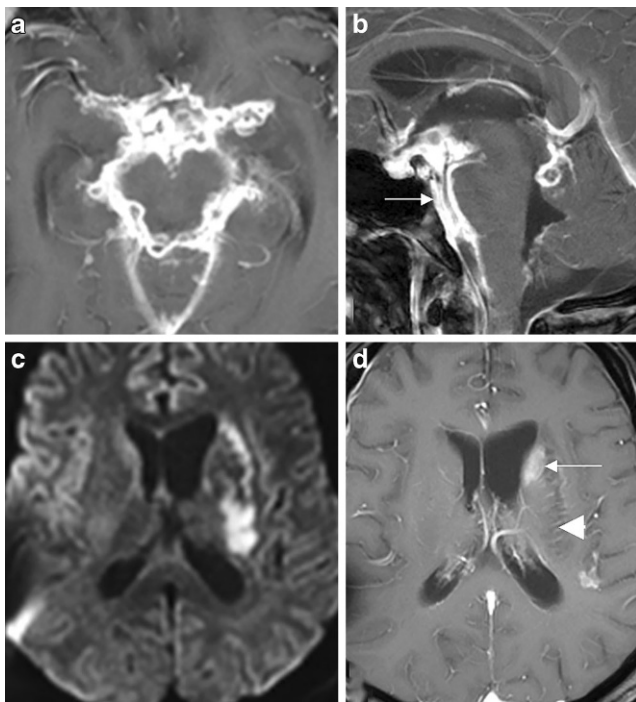
### Neuroradiological Findings

Computed tomography (CT) and magnetic resonance imaging (MRI) may show characteristic findings in TBM. When clinical symptoms and history raise the suspicion of CNS TB, neuroimaging poses a cornerstone in early diagnostics and should include the whole neuro-axis [33].

Furthermore, as most CNS TB infections are a secondary result of hematogenous spread, a close look for co-existing extra-neural manifestations of TB, especially pulmonary through chest radiography, is rewarded in at least 30–50% of cases [34, 47–49].

Contrast-enhanced MRI is considered the modality of choice in assessment and detection of CNS TB and superior to CT in sensitivity and specificity, thus providing more diagnostic information for an earlier and more confident diagnosis [3, 7, 20, 50–55].

The presence of (1) basal meningeal enhancement and basal exudates, (2) hydrocephalus and (3) infarctions is the diagnostic triad of tuberculous meningitis [3]. These three and tuberculoma are the four most common features seen in TBM ([56], Figs. 3 and 4). The manifestations can occur alone or in combination and may not be detected radiographically until advanced stages [6]. In two large community-based series of CT findings, hydrocephalus was seen in approximately 75%, basal meningeal enhancement in 38% and cerebral infarcts in 15–28% of patients ([57, 58]; Fig. 5). A smaller case study based on MRI in children with TBM found meningeal enhancement in 91%, hydrocephalus in 64% and cerebral infarction in 46% of



**Fig. 5** Axial (a) and sagittal (b) pc T1 WI showing basilar menigitis surrounding the proximal arterial segments including basilar artery (b, arrow). c, d Axial diffusion weighted images (DWI; c:  $b = 1000\text{s/mm}^2$ ) revealing acute infarct in the left basal ganglia due to associated arteritis; d: axial pc T1 WI exhibiting subacute infarct in the caput caudati with blood brain barrier disruption (arrow) and prominent contrast enhancement of the lenticulostriate perforators (arrowhead)

cases. Tuberculomas (27%) and cranial nerve involvement (27.2%) were common [59].

Even though the combination of these imaging features is highly specific for TBM (95–100%), most radiographic findings by themselves lack sufficient sensitivity [3, 6, 32, 60]:

The most sensitive feature of TBM is basal enhancement, which was present in 89% of cases in children with TBM [32]. Enhancing exudate in the basal cisterns either as visualized on CT or on MRI using post-contrast (pc) T1 weighted images (WI) is a common feature of leptomenigeal tuberculosis. It most likely reflects microabscesses and intense inflammation of the basal meninges and predicts a poor outcome ([28, 61], Figs. 3 and 4). In HIV-infected patients meningeal enhancement seems to be more common, as a study showed prominent meninges in 23% of HIV-infected patients but only 6% of HIV-negative patients [21]. In later stages of disease, the meningeal enhancement can be seen over the cerebral convexities, the Sylvian fissures and the tentorium [3]. In MRI, Parmar et al. suggest that pc fluid attenuated inversion recovery (FLAIR) sequences provide a higher specificity compared to pc T1 WI in detection of leptomenigeal enhancement, while show-

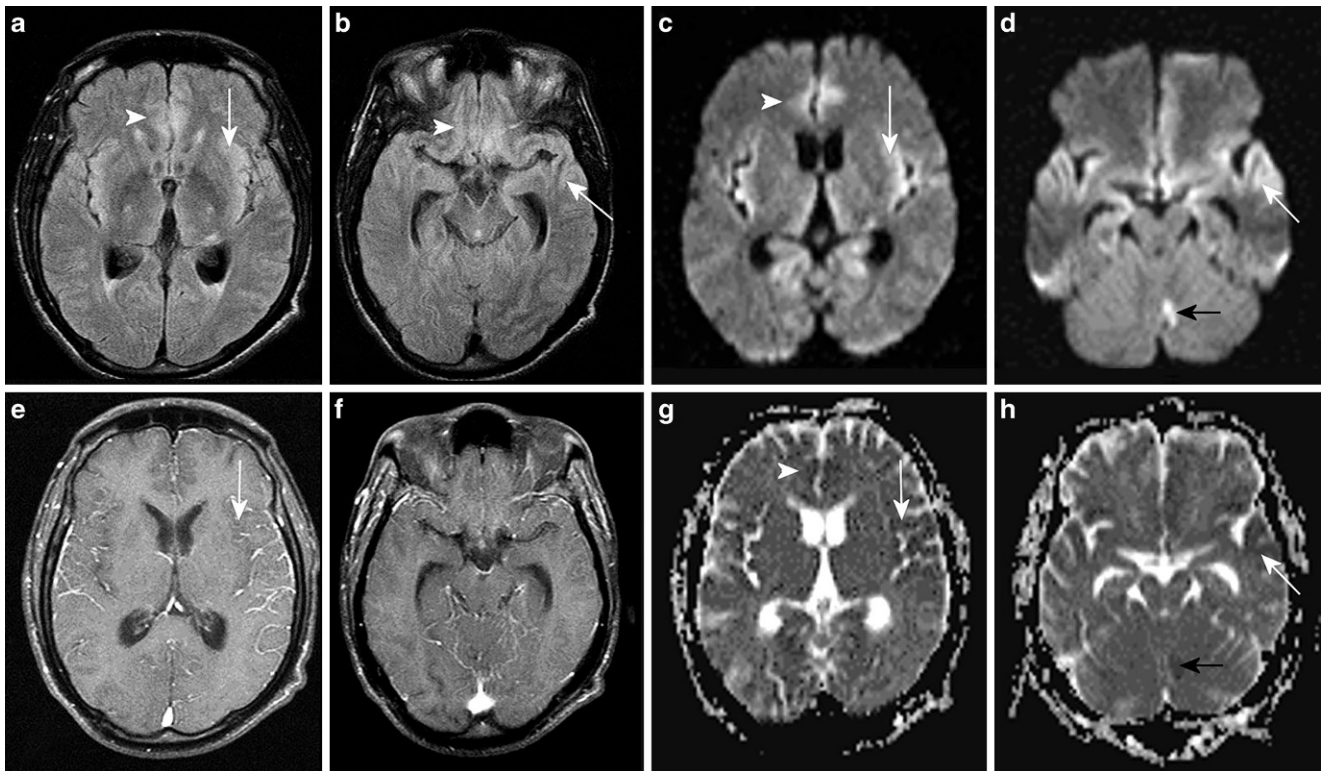
ing a similar sensitivity ([62]; Fig. 4). Additional DWI may exhibit possible symmetrical restricted diffusion of cortical and adjacent subcortical structures and the subsequent diagnosis is tuberculous meningoencephalitis. (Fig. 6). Inflammatory exudate in the subarachnoid space around the brain stem can affect cranial nerves and thin layer MRI sequences may catch correlating focal cranial nerve enhancement, though sensitivity is likely to be limited.

On non-contrast CT, basal cistern hyperdensity is a typical sign for TBM and a visual diagnosis, though not as sensitive as in contrast-aided CT and MRI ([32]; Fig. 7); however, other diseases causing hyperdensity in the basal cisterns, e.g. subarachnoid hemorrhage (SAH) or anoxic brain injury presenting as pseudo-SAH should be excluded [63]. Predilection areas are the interpeduncular fossa, the cisterna ambiens and the chiasma region, obliterated by isodense to hyperdense exudate ([30]; Fig. 8). In areas of limited MRI availability and high TB prevalence basal cistern hyperdensity is highly suggestive of CNS TB [32].

Hydrocephalus occurs in approximately two-thirds of patients with TBM and is associated with basal exudates, tuberculoma, infarcts and cranial nerve palsies [64]. Hydrocephalus of the communicating type is more common in TBM, but non-communicating hydrocephalus caused by exudative obstruction of the aqueduct or the lateral apertures of Luschka (Aperturae laterales ventriculi quarti) also occurs. While in early stages it may still resolve completely, hydrocephalus is the most frequent cause of raised ICP (intracranial pressure) in TBM [6]. In a study conducted in 2013, hydrocephalus was associated with advanced stage of disease, and high morbidity and mortality [64]. Former CT-based studies reported similar findings and also reported a decrease of hydrocephalus with age [57].

Cerebral vasculitis resulting in infarcts is the main cause of irreversible brain damage in TBM and is among the worst consequence of CNS TB [41, 65]. About 20% of patients with TBM develop an ischemic neurological deficit and up to 57% of patients have a correlate of cerebral infarction on imaging. Diffusion weighted imaging (DWI) is the imaging technique of choice for acute stroke [41, 52, 66–69], subacute or chronic infarcts are best visible on T2 or FLAIR sequences (Fig. 5). The exact pathogenesis of stroke in TBM remains unclear and is subject of intensive research. Whereas vasospasm may mediate strokes in early stages of the disease, in later stages a localized proliferative intimal reaction with consecutive reduction of the vessel lumen, so-called tuberculous vasculitis, is discussed (Fig. 8). Due to predominant basal involvement of the subarachnoid space, especially the vascular territories of the basal perforators originating from the proximal segment of the middle cerebral artery (M1 segment), from the circulus arteriosus of Willis and from the (distal) basilar artery are affected. An MR angiography may show irregular vascular narrow-





**Fig. 6** A 57-year-old man suffering from progressive disorientation, disturbance of vigilance, oculomotor nerve palsy left and headache due to tuberculous meningoencephalitis. Axial fluid attenuated inversion recovery (FLAIR) images (**a, b**) showing nearly symmetrical hyperintense signal changes of the insular (**a, arrow**), temporal (**b, arrow**) and paramedian frontobasal cortex and subcortical white matter (**a, b: arrowhead**) with restricted diffusion on DWI (**c, d; b=1000s/mm<sup>2</sup>; arrow, arrowhead**); **g, h**: corresponding apparent diffusion coefficient (ADC) maps; note additional cerebellar lesion left sided (**d, h: black arrow**) and also restricted diffusion in the periventricular region of the third ventricle. Axial pc T1 WI (**e, f**) exhibiting slight enhancement in the Sylvian fissure (**e, arrow**) and temporopolar (**f**)

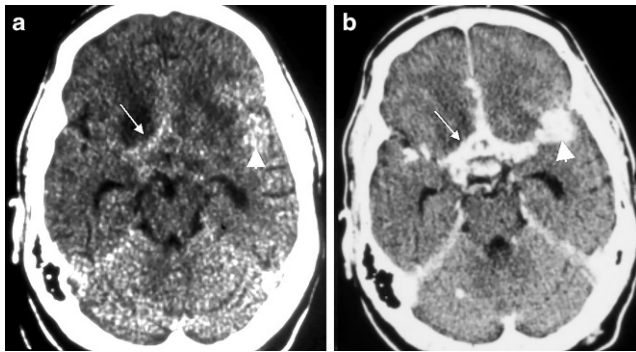
ing especially of the basal arterial segments and also indirect signs of hydrocephalus, e.g. shifting of the pericallosal artery. Most infarctions in TBM are multiple, bilateral and located in the basal ganglia and the anterior thalamus [69]; nonetheless, cortical ischemia is possible and not a rare finding [67].

### Treatment

The presence of TBM is a medical emergency and therapy should be started promptly, even when microbiological or molecular diagnostic confirmation is pending [33]. Unlike pulmonary TB, the optimal therapy of CNS TB is not firmly established, lacking controlled studies and international standards. While isoniazid (INH), pyrazinamide (PZA) and the chinolones levofloxacin and moxifloxacin show a sufficient CNS availability, rifampicin (RMP), streptomycin (SM) and ethambutol (EMB) have less because they have poorer CSF penetration and require higher dosages, leading to more adverse side effects [30, 70, 71]. The typical treatment regimen as suggested by the WHO and British Infection Society is a 2-month course of INH, RMP, PZA and SM or EMB, followed by a 6-month or 10-month

course of INH and RMP, depending on the regional guidelines [33, 70, 72]. Corticosteroids such as dexamethasone and prednisolone seem to reduce the mortality in adults with TBM and improve overall survival, possibly through reducing hydrocephalus and preventing infarction, even though exact mechanisms are not yet understood [17, 73, 74]. A Cochrane review showed that adjunctive corticosteroids in TBM treatment reduced mortality and disabling residual neurologic deficits in children and HIV-negative patients [24, 33, 75]. Experimental studies in animal models from the 1930s and modern immunology suggest that much of the tissue damage done in TBM is attributed to a dysregulated host inflammatory response through erratic production of cytokines and chemokines and not necessarily through the mycobacteria themselves [6, 76, 77]. Especially HIV-infected patients are at increased risk of immune reconstitution inflammatory syndrome (IRIS) once antiretroviral therapy has been started, thus worsening the symptoms of TBM [78, 79]. Related to IRIS, a paradoxical worsening of imaging findings during effective antitubercular or antiretroviral treatment is commonly observed. In one cohort study from India including 34 patients with TBM, more than 64% showed paradoxical deterioration





**Fig. 7** Axial CT demonstrating inhomogeneous hyperdense basal cisterns (**a**, *arrow*) and hyperdense Sylvian fissure (**a**, *arrowhead*) with marked and nearly homogeneous contrast enhancement (**b**: *arrow*, *arrowhead*)

in 3 and 6-month follow-up MRI scan. More than half of the patients remained clinically asymptomatic in this period [80]. Also, development of tuberculomas during TBM treatment is a well-described phenomenon, but it has not been shown to affect clinical outcome or mortality [6, 74].

Facing complications of TBM such as hydrocephalus with increased intracranial pressure, neurosurgical consultation should be sought for external drainage, if available [30, 81]. The rising incidence of multidrug-resistant (MDR-TB) or even extensively resistant (XDR) strains of *M. tuberculosis* poses a continuous challenge for the treating physician and patients should be treated in specialized centers whenever possible [82]. Additionally, all patients with TB

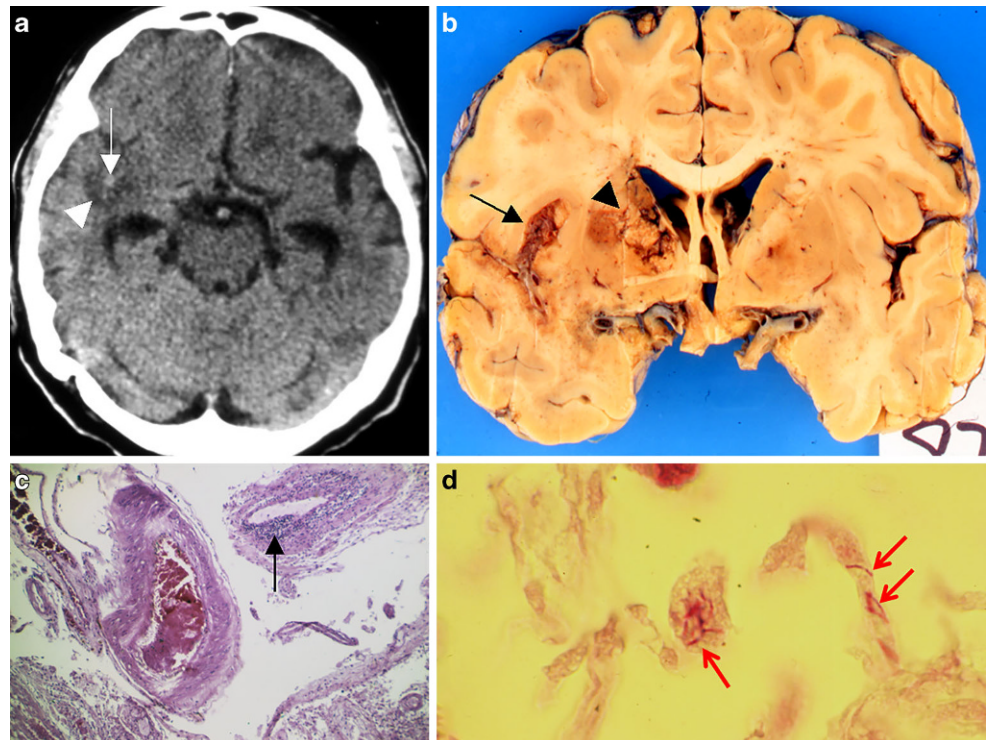
should be tested for HIV, as approximately 15% of patients globally with TB are HIV-coinfected, and about 3% of patients in western countries [70]. The effect of HIV infection on the clinical outcome and survival rates of TBM remains controversial and the optimal timing for starting antiretroviral treatment (ART) in newly diagnosed HIV in a patient with TB remains uncertain. [21, 48]; however, more recent studies as well as the WHO suggest an advantage of early ART independently of CD4<sup>+</sup>-cell count [83, 84].

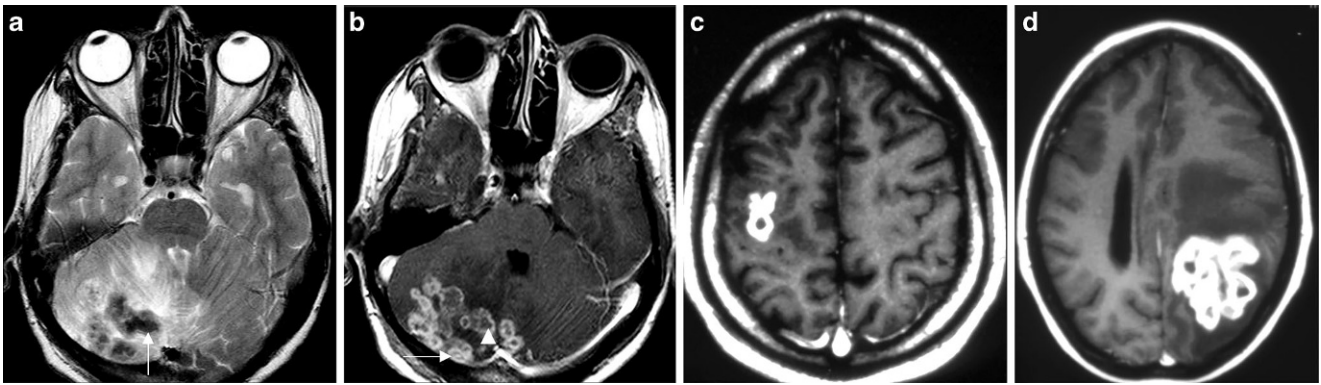
Table 2 presents imaging hallmarks, characteristic clinical findings and distinguishing features of the most relevant differential diagnoses [85].

### Tuberculoma of the CNS

It is believed that hematogenous spread of mycobacteria to the CNS result in microscopic granulomatous foci (Rich foci), which can either cause tuberculous meningitis, when infection disseminates into the subarachnoid space, or tuberculomas, when infection is contained by a granulomatous inflammatory reaction [3, 85]. Tuberculomas feature the pathological hallmark of mycobacterial infection: a granulomatous lesion consisting of epithelioid cells, Langhans giant cells, lymphocytes and often central caseation. Macroscopically, tuberculomas are rounded and encapsulated space-occupying lesions ([86]; Fig. 9). Clinical features of tuberculomas depend on their location and correspond to other space-occupying lesions of the CNS. Neuroradiological features of tuberculomas depend on the

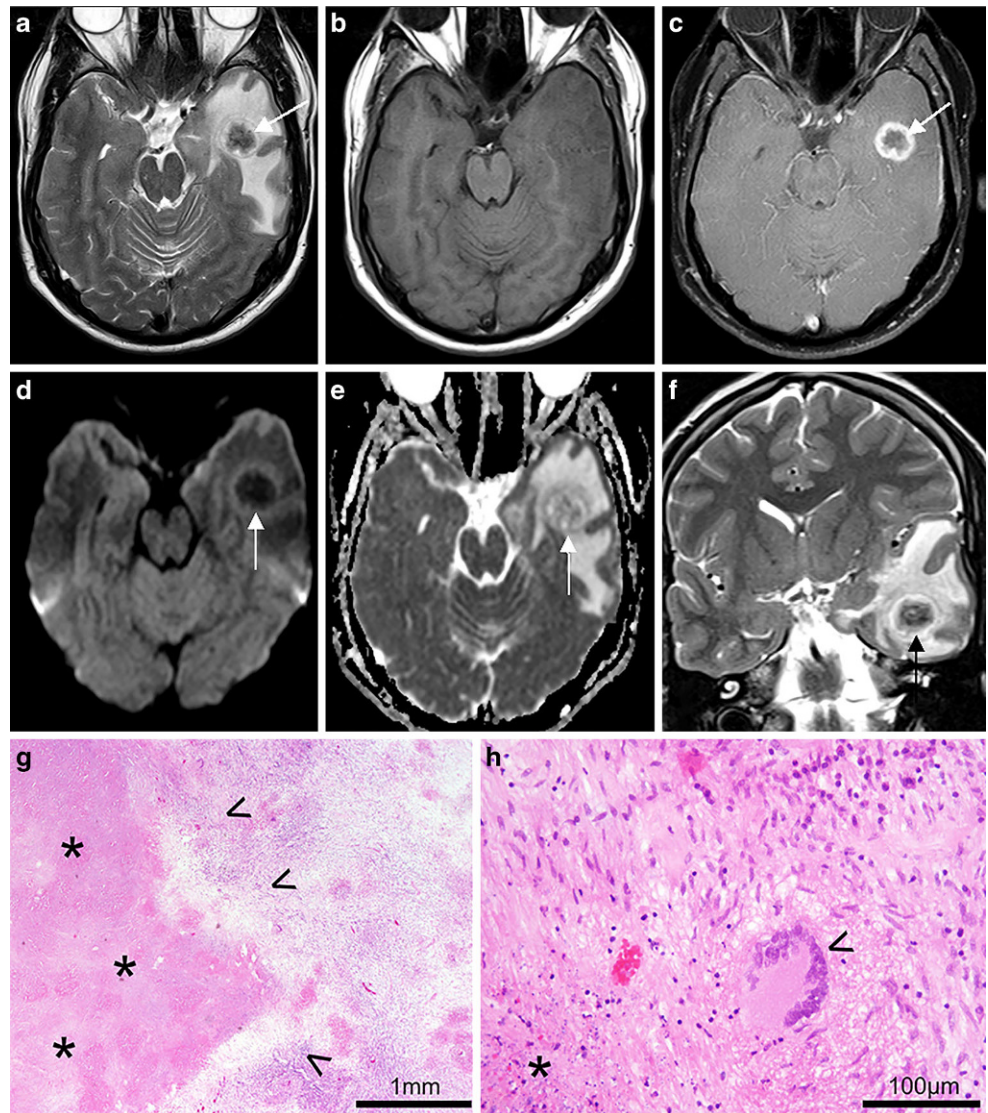
**Fig. 8** Immunocompromised 57-year-old man suffering from longstanding alcohol misuse and diabetes, who was admitted because of rapid progressive impairment of consciousness and left-sided hemiparesis. Axial CT (**a**) revealing small hyperdense lesion (*arrow*) with hypodense rim (*arrowhead*) adjacent to the right Sylvian fissure. **b**, **c**: Autopsy (**b**, coronal section) disclosing tuberculous masses in the right Sylvian fissure (*arrow*), ischemic necrosis in the basal ganglia (*arrowhead*) and arteritis with inflammatory infiltrates within the vessel wall (**c**, *arrow*; hematoxylin eosin staining, 100 $\times$ ). Ziehl-Neelsen staining (1000 $\times$ ) exhibiting mycobacterium tuberculosis (**d**, *red arrows*) in the cerebrospinal fluid





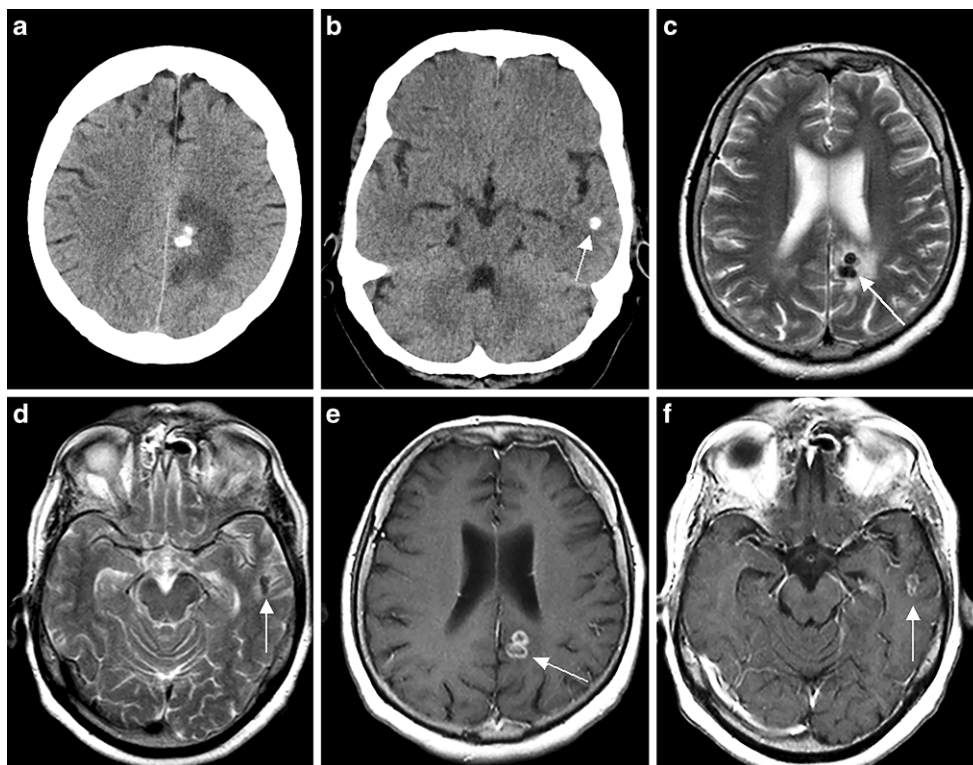
**Fig. 9** Dura adherent and parenchymal cerebellar masses with hypointense signal on T2 WI (a, arrow) and peripheral polycyclic enhancement on pc T1 WI (b, arrowhead), typical for caseating tuberculoma; note target sign (b, arrow). c, d: Axial pc T1 WI showing supratentorial parenchymal rim enhancing tuberculomas in the precentral gyrus right (c) and the left parietal lobe (d)

**Fig. 10** Tuberculous granuloma. 29-year-old immunocompetent man suffering from first generalized seizure. Caseating granuloma with hypointense center on T2 WI (a axial, f sagittal arrow) and distinct perifocal edema in the left temporal lobe; b, c (T1 WI) showing peripheral rim enhancement on pc T1 WI (c, arrow); d, e: DWI ( $b=1000 \text{ s/mm}^2$ ) disclosing in difference to bacterial abscess elevated apparent diffusion coefficient (ADC) within the granuloma. g histological overview (20 $\times$ ) of the granuloma with central necrosis (asterisks) and surrounding inflammatory rim (arrowheads); (hematoxylin and eosin staining) h higher magnification (200 $\times$ ) of perinecrotic area with a large multinucleated giant cell (arrowhead), epithelioid cells and lymphocytic infiltration





**Fig. 11** 67-year-old woman with recurrent motoric Jackson seizures in the right leg and a history of tuberculosis 30 years ago. Axial CT (a, b) demonstrating calcified lesions paramedian left (a: with perifocal edema) and the left temporal lobe (b, arrow); c, d: hypointense signal on axial T2 WI (arrow) due to Ca<sup>++</sup> deposits and rim enhancement on axial pc T1 WI (e, f: arrow)



pathological state of its center, which can be noncaseating, solidly caseating or caseating with central liquefaction (Table 3; Fig. 10). Additionally, about 10% of tuberculomas [87] show central calcification, which has been described as a specific target sign ([3, 88]; Figs. 9 and 11). In a case series of 100 patients by Wasay et al. [87], one third of patients had a solitary tuberculoma and two thirds had multiple tuberculomas with a mean count of 4–5, but up to >100 tuberculomas in exceptional cases. Perifocal edema was reported in one third of patients. Tuberculomas are usually up to 1 cm in diameter, about 10% are between 1–3 cm, and rarely they reach sizes of up to 8 cm [85]. They can occur anywhere in the CNS (Figs. 2, 9, 10 and 11).

Differential diagnosis of CNS tuberculoma should include neoplasms, PCNSL (primary central nervous system lymphoma), pyogenic abscess, fungal infection, cysticercosis and toxoplasmosis [90]. Rarely a paradoxical enlarge-

ment in response to treatment due to immune reconstitution (IRIS) has been observed [3, 85].

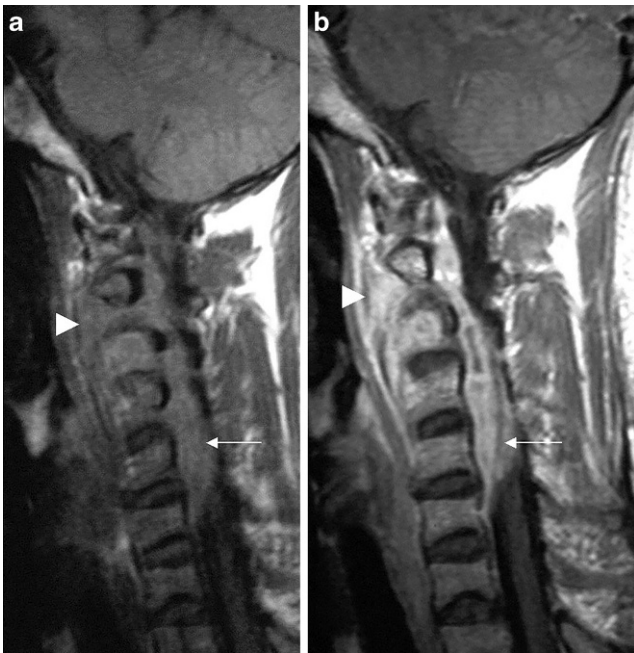
**Tuberculous Brain Abscess**

Tuberculous abscess is a rare manifestation of CNS tuberculosis. Its appearance is more similar to pyogenic brain abscess than to tuberculomas, typically being larger than tuberculoma and characterized by cavity formation with central pus [89]. On CT the abscess is hypodense with perifocal edema and often mass effect with rim enhancement on pc images. On MRI the center is T1-hypointense and T2-hyperintense with restricted diffusion and rim enhancement on pc T1 WI [30]. Structural neuroimaging does not allow differentiation of tubercular and pyogenic abscesses but lipid peaks on MR spectroscopy are suggestive of mycobacteria ([90]; Fig. 10). Definite diagnosis requires microscopy and culture of pus following stereoscopic aspiration. Overall

**Table 3** Neuroradiological features of CNS tuberculomas [3, 85, 87]

Tuberculoma	CT	MRI	Post-contrast CT/MRI
Noncaseating	Commonly isodense, sometimes hypodense or hyperdense	T1: hypointense T2: hyperintense	Homogenous enhancement
Caseating with solid center	Hypo-/hyperdense	T1: hypo-/isodense T2: hypo-/isodense	Ring enhancement and heterogeneous central enhancement
Caseating with liquefaction	Hypodense	T1: hypointense T2: hyperintense	Ring enhancement





**Fig. 12** Spinal tuberculosis in a young woman positive for HIV. Sag. T1 WI (a, b) showing prevertebral (a, b: *arrowhead*) and epidural inflammatory masses with distinct enhancement on pc T1 WI (a, b: *arrow*). Note hypointense delineation of the dura mater (b) and involvement of the intradural space

brain abscess is much more likely to be caused by streptococci (34%), staphylococci (18%) and other agents, mycobacteria being rare (0.7%) according to the systematic review by Brouwer et al. [91].

### Spinal Tuberculosis

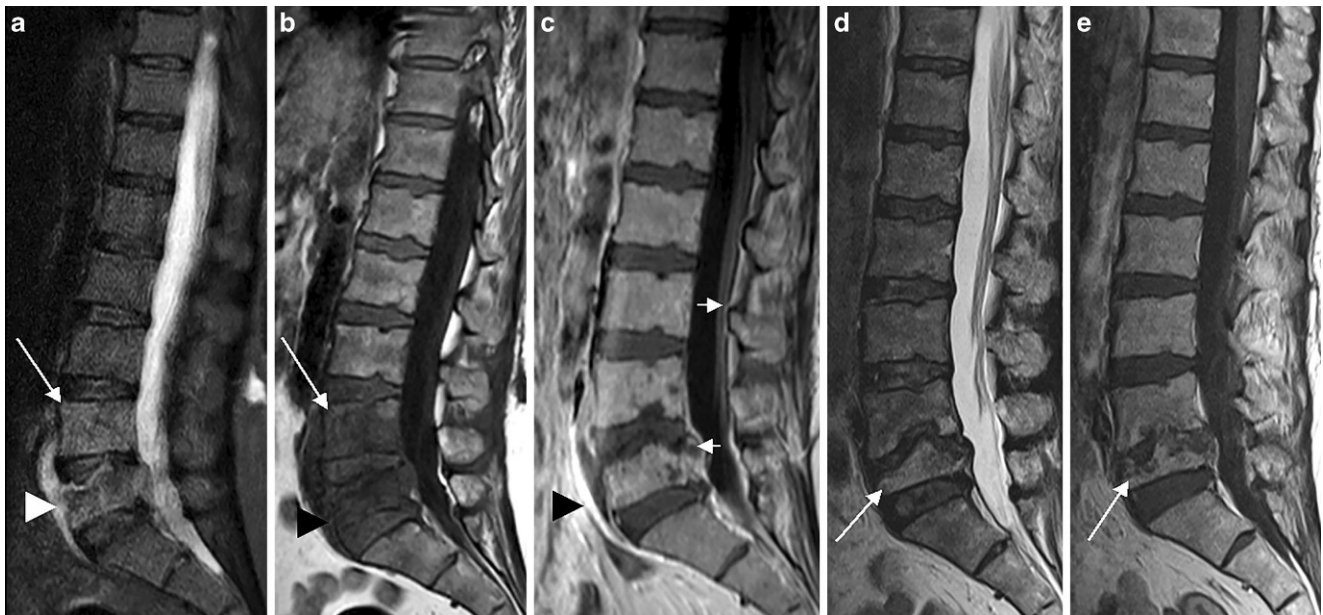
A TB can affect all structures of the spine. Anatomically the manifestations can be classified as extradural and intradural (tuberculous infections; Figs. 12, 13 and 14).

#### Extradural Tuberculous Spinal Infection

Extradural tuberculous spinal infection includes tuberculous spondylitis, paraspinal and epidural abscess (Figs. 12 and 14). Tuberculous spondylitis is among the most frequent manifestations of skeletal tuberculosis ([92]; Fig. 14) and was first described by Percival Pott in 1779. The clinical presentation of Pott's disease is the development of back pain, kyphosis, sensory disturbances, bowel and bladder dysfunction and eventually paraparesis over the course of months. Vertebral infection is thought to result from hematogenous spread of mycobacteria from a primary focus [93]. In contrast to pyogenic bacteria, mycobacteria do not produce proteolytic enzymes that degrade the collagenous annulus of the intervertebral discs. In children, where



**Fig. 13** Sag. pc T1 WI (a–c) demonstrating intradural tuberculous infection with inhomogeneous enhancement of the spinal cord surface (a, b: *arrow*) as well as the radix (e: ax. pc T1 WI; *arrow*) and the cauda equina (c, *arrow*). Additional extravasation of contrast medium within the subarachnoid space (f, ax. pc T1 WI: white arrow; black arrow: anterior and posterior radix); d (sag. T2 WI): longitudinal extensive transverse myelitis with hyperintense signal changes (*arrow*) of the enlarged spinal cord and additional syrinx (*arrowhead*) due to arachnoid adhesion with impairment of CSF flow



**Fig. 14** Tuberculous spondylitis in a 53-year-old woman suffering from disseminated tuberculosis and lumbago for 1 month. Sag. T2 WI (a) showing hyperintense signal of lumbar vertebra 4 and 5 (arrow), hypointense signal on T1 WI (b, arrow) and nearly homogeneous enhancement (c: pc T1 WI); prevertebral (a–c: arrowhead) and epidural (c, short arrow) abscess sparing the intervertebral disc; note enhancement of the cauda equina (c). Follow-up MRI 14 months later (d: sag. T2 WI; e: sag. pc T1 WI) revealing obvious compression of the fifth lumbar vertebra (d, e: arrow)

vasculature of the discs is preserved, discitis can occur but in adults the relative sparing of discs is a typical finding. The classical features of tuberculous spondylitis that results are edema and bony destruction of the vertebral body with subligamentous, paravertebral spread of exudate to adjacent or distant vertebral bodies [92–94]. Paraspinal cold abscess formation, e.g. psoas abscess and calcification is common. Severe complications of tuberculous spondylitis include vertebral collapse resulting in kyphosis, and cord compression due to abscess formation or vertebral fracture. The main differential diagnosis of tuberculous spondylitis is pyogenic spondylitis. According to Jung et al. [95] the overall appearance on MRI findings allows a highly specific and sensitive differentiation of the two. Findings suggestive of tuberculous spondylitis are: (1) a well-defined paraspinal abnormal signal, (2) a thin and smooth abscess wall, (3) the presence of paraspinal or intraosseous abscess, (4) subligamentous spread over three or more vertebral levels, (5) thoracic spine involvement, [95] and (6) relative preservation of the intervertebral space [92, 96]. Laboratory confirmation should be sought. Epidural tuberculous abscess can be present without spondylitis. Then, differential diagnoses include pyogenic epidural abscess and also malignant infiltration, especially lymphoma [92].

### Intradural Tuberculous Spinal Infection

Subarachnoid spread of inflammatory exudates surrounding the spinal cord is a common complication of TBM ([97]; Fig. 13). The pathologic sequelae of the resultant granulomatous leptomeningitis can be compared to intracranial tuberculous meningitis: inflammatory exudate causes radiculitis, affection of nearby vessels leads to vasculitis and spinal infarcts, and disturbance of CSF flow due to adhesion of arachnoid layers may cause syringomyelia ([97]; Fig. 13). Due to the accumulation of exudate around the lumbosacral segments, the clinical picture often resembles a cauda equina syndrome with flaccid paraparesis, bladder disturbance and saddle anesthesia [97]. However, also subacute transverse spinal cord symptoms up to paraplegia may occur. The pc MRI is the method of choice disclosing paraspinal exudates, thickening of nerve roots and meningeal enhancement as well as complications like CSF loculations or syringomyelia [3, 98].

Intramedullary manifestations of TB besides concomitant affection in granulomatous leptomeningitis are intradural or spinal tuberculoma and tuberculous myelitis. Acute transverse myelitis as well as longitudinal extensive transverse myelitis (LETM) have been described [3, 95, 99, 100].

## Conclusion

The diagnosis and treatment of extrapulmonary TB remains a challenge for the treating physician. The field of differential diagnoses is vast and symptoms of CNS TB often present as unspecific in early stages. With an imminent re-emergence of TB in western countries due to increased migration and the spread of multidrug-resistant mycobacteria, the knowledge of radiological signs and possible mimics is likely to prove valuable over the coming years. Although MRI may show characteristic neuroradiological features for CNS TB, additional clinical and laboratory information with special respect to CSF analysis is essential to establish the diagnosis.

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**Conflict of interest** M.A. Schaller, F. Wicke, C. Foerch and S. Weidauer declare that they have no competing interests.

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