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SPECIAL ANNUAL ISSUE

Tuberculosis of the central nervous system in children

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Abstract

Background Central nervous system tuberculosis (CNS TB) in children is still a socioeconomic problem in developing countries. It has varied manifestations, symptoms are nonspecific, diagnosis can be challenging, and treatment may be difficult. It is often missed or overlooked. Among the various pathological entities, tuberculous meningitis is the most common and devastating manifestation. The resultant vasculitis, infarction, and hydrocephalus can be life-threatening. It can have grave cognitive, intellectual, and endocrine sequelae if not treated in time resulting in handicap, especially in resource constraint countries. Early diagnosis and treatment of tuberculous meningitis is the single most important factor determining outcome. Tuberculous hydrocephalus needs to be recognized early, and cerebrospinal fluid diversion procedure needs to be performed in adequate time to prevent morbidity or mortality in some cases. Tuberculous pachymeningitis and arachnoiditis are rare in children. Tuberculous abscess can mimic pyogenic abscess and requires high index of suspicion. Calvarial tuberculosis is seen in children and responds well to antituberculous chemotherapy. Drug-resistant tuberculosis is a formidable problem, and alternate chemotherapy should be promptly instituted.
Aim The pathogenesis, clinical features, diagnosis, and management of central nervous system tuberculosis in children are summarized.
Conclusion Heightened clinical suspicion, early diagnosis, appropriate antituberculous treatment, and surgery in relevant situation are essential for a gratifying outcome and preventing complications.

Keywords Central nervous system · Pediatric · Tuberculosis

Introduction

Tuberculosis (TB) is a chronic granulomatous disease caused by acid-fast bacilli of the *Mycobacterium tuberculosis* complex. The incidence of TB is on the decline in developing as well as industrialized countries, but the emergence of multidrug-resistant form of tuberculosis (MDR TB) is of concern since it has worsened morbidity and mortality. Children who are persistently exposed to individuals with tuberculosis are usually at high risk of contracting the dreaded illness. Low immunity, malnutrition, and overcrowding are the principal contributing factors in the developing world. It accounts for about 10% of all cases of TB, especially TB meningitis (TBM) [1]. The occurrence of vasculitis, arachnoiditis, direct parenchymal injury, and raised intracranial pressure is responsible for the poor outcome [1, 2]. Delay in proper diagnosis is another significant cause for mortality in underdeveloped parts of the world as well as unfamiliarity with the disease may result in similar problems in the well-developed areas.

Involvement of the spine, also known as Pott's disease, accounts for 1 to 2% of the world spinal deformity [3–5]. It can also result in complications, such as spinal arachnoiditis, intramedullary tuberculoma, and spinal cord compression from epidural abscess.

There are no specific international guidelines for the diagnosis and treatment for CNS tuberculosis, and the treatment is largely institution specific. There are no studies which demonstrate the superiority of one treatment protocol over another.

Pathogenesis

Mycobacterium tuberculosis commonly causes CNS TB, although in immunocompromised patients, other species may

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be involved. Following initial pulmonary infection, the tuberculous bacteria may enter the systemic circulation and subsequently reach the CNS, which is rich in oxygen establishing in the meninges, subpial, or subependymal regions of the brain or the spinal cord. It is known as the Rich focus, which may rupture into the subarachnoid space or ventricular system leading to meningitis. Alternatively, the meninges can be involved due to rupture of a tuberculoma into a vessel in the subarachnoid space or rupture of miliary tubercles in disseminated TB. The brain can rarely be involved following contiguous spread of infection from the skull or paranasal sinuses. It forms dense, gelatinous, inflammatory exudates along the basal surface of the brain. In advanced cases, it may involve the leptomeninges over the cerebral convexities and extend into the ventricular system causing ependymitis and choroid plexitis [1, 2].

Clinical presentation

The most common signs of brain tuberculosis include fever, headache, vomiting, and an altered sensorium. Neck rigidity and cranial nerve palsies are commonly seen [1, 6]. Variable degrees of encephalitis, hydrocephalus, and infarction are responsible for altered sensorium in patients with TBM (Tables 1 and 2). In contrast to TBM, patients with brain tuberculomas without TBM most often do not have fever. Focal deficits may occur in the forms of mild to total weakness of the limbs or varying degrees of cranial nerve paresis. Among the cranial nerves, the abducens and oculomotor nerves are frequently involved. Patients with tuberculomas usually present with headache, seizures, focal neurologic deficit, and features of raised intracranial tension. Infratentorial tuberculomas may present with brainstem syndromes, cerebellar symptoms, and multiple cranial nerve palsies [7]. Fever is not a prominent symptom. Hydrocephalus has been described as a marker of visual impairment. Tuberculous abscesses have an acute clinical presentation and a more rapidly deteriorating course than tuberculomas, with symptoms of fever, headache, and focal neurologic signs. Calvarial TB commonly presents as a scalp swelling with or without a discharging sinus and pain. Rarely, the patient may present with seizures or motor deficit.

Central nervous system tuberculosis has varied clinical manifestations and therefore requires different investigations and management strategies.

Table 1 Vellore grading for TB meningitis induced hydrocephalus

Grade		Clinical features
I.	1.	Headache, vomiting, fever, and/or neck stiffness
	2.	No neurological deficit
	3.	Normal sensorium
II	1.	Normal sensorium
	2.	Neurological deficit present
III	1.	In altered sensorium but easily arousable
	2.	Dense neurological deficit may or may not be present
IV	1.	Deeply comatose
	2.	Decerebrate or decorticate posturing

Table 2 Modified Vellore grading system for TB meningitis-induced hydrocephalus

Grade variables
I GCS 15
Headache, vomiting, fever ± neck stiffness No neurological deficit
II GCS 15
Neurological deficit present
III GCS 9–14
Neurological deficit may or may not be present
IV GCS 3–8
Neurological deficit may or may not be present

TB tuberculosis, *GCS* Glasgow Coma Scale

Tuberculous meningitis

TBM in developing countries is more common among infants and children. The basal exudates cause abnormal meningeal enhancement and obstruction to cerebrospinal fluid (CSF) flow, causing hydrocephalus. It can also result in obliterative vasculitis due to occlusion of blood vessels at the base of the brain [8, 9]. The complications of meningitis include hyponatremia, hydrocephalus, vasculitis, cranial nerve involvement, and associated multiple tuberculomas [8]. On clinical suspicion of TBM, cerebrospinal fluid (CSF) examination is the initial modality of investigation [8]. Diagnosis of TBM is categorized as definite or probable. Definitive diagnosis of TBM depends upon the detection of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture [6, 10, 11]. The predominance of cerebrospinal fluid lymphocytosis (> 50% of the cells) is highly suggestive of TBM. It is seen in 80–83% of patients with TBM. Low levels of cerebrospinal fluid glucose and elevated levels of protein are also seen. TBM is a paucibacillary disease, and yield of culture studies is low. AFB may be seen in 20–90% of cases when centrifuged CSF is tested. The polymerase chain reaction (GeneXpert test) allows for a rapid and specific diagnosis of TBM [11]. The yield of positive mycobacterial cultures from CSF in TBM varies from 19 to 70% [6, 10–12].

Molecularly based techniques include commercially available nucleic acid amplification (NAA) methods and other polymerase chain reaction (PCR)-based methods,

antibody detection, antigen detection, or chemical assays such as adenosine deaminase (ADA) and tuberculostearic acid measurements [13]. Commercial nucleic acid amplification (NAA) assays for the diagnosis of TBM are 56% sensitive and 98% specific, and the diagnostic yield of NAA increases when large volumes of CSF are processed. The sensitivity of CSF microscopy and culture falls rapidly after the start of treatment, whereas mycobacterial DNA may remain detectable within the CSF until 1 month after the start of treatment. The measured sensitivities and specificities of ADA in the CSF range from 44 to 100% and 71 to 100%, respectively. Standardized cutoffs of ADA values for the diagnosis of TBM have not been established, and the values used in various studies ranged from > 5.0 to > 15 IU/l. It is helpful in predicting poor neurological outcomes among pediatric TBM cases [14, 15]. A raised ADA activity in the CSF of patients with CNS TB lacks specificity. CSF ADA activity is not recommended as a routine diagnostic test for CNS tuberculosis. Tuberculostearic acid has good sensitivity, but requirement of expensive equipment has limited its clinical use [15].

The diagnostic utility of skin testing has been reported to be positive for CNS tuberculosis in 10 to 50% of patients with TBM.

Contrast-enhanced computed tomography (CT) is the investigation of choice since it is easily available and can be quickly performed. It can depict the presence of hydrocephalus, infarcts, and basal exudates (classical "spider web" appearance seen in the suprasellar cisterns) [16]. The presence of periventricular lucency in isolation can suggest ischemia but along with a rounded third ventricle is suggestive of interstitial edema and raised intracranial pressure syndrome. In some series, a normal CT scan has been reported in up to 5% of cases.

Hydrocephalus is a frequent accompaniment of TBM with the incidence varying between 50 and 80%. CT cannot predict the level of CSF block in TBM because both types of hydrocephalus can present with panventricular dilatation [16]. The presence of basal enhancement, hydrocephalus, tuberculoma, and infarction was more common in TBM than in children with pyogenic meningitis (Figs. 1, 2, and 3). They reported that basal enhancement, tuberculomas, or both were 100% specific and 89% sensitive for the diagnosis of TBM. Andronikou and colleagues suggested nine criteria for the diagnosis of TBM on computed tomography (CT). Przybojewski and colleagues evaluated these nine criteria and showed high specificity for all the criteria and 100% specificity for four individual criteria [16]. It has been shown that sensitivity was improved when more than one criterion was present. The presence of hyperdensity on precontrast scans in the basal cisterns might be the specific sign of TBM in children. The reported incidence of infarcts on CT varies from 20.5 to 38%.

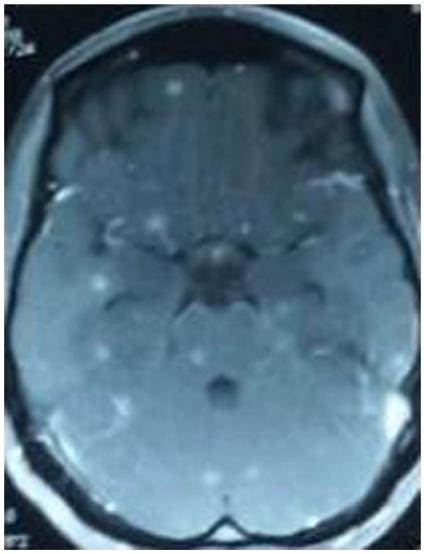

Fig. 1 Axial postcontrast MR image showing basal meningeal exudates without hydrocephalus

Magnetic resonance (MR) imaging has been shown to be superior to CT in evaluating patients with suspected meningitis and its associated complications [17–19] (Table 3). Noncontrast MR imaging shows little or no evidence of meningitis in early stages of the disease. Contrast-enhanced MR imaging shows abnormal meningeal enhancement in the basal cisterns and sylvian fissures (Fig. 1). The cerebral convexities show enhancement in severe and late-stage TBM. Tentorial and cerebellar meningeal involvement is less common. There could be minimal or absent meningeal enhancement in immunocompromised patients, although some reports show no significant difference. The flow around fourth ventricle may not be easily appreciated. MR ventriculography has been used to evaluate CSF flow dynamics and in patients with hydrocephalus. MR imaging depicts hemorrhagic transformation of infarcts better. Multiple infarcts in the anterior circulation territory favored tuberculous etiology.

MR angiogram reveals small segmental narrowing, uniform narrowing of large segments, irregular beaded appearance of vessels, or complete occlusion with contrast enhanced MR being more sensitive to detect smaller vessels. The infarcts mostly involve thalamus, basal ganglia, and internal capsule regions. Diffusion-weighted MR imaging helps in early detection and delineating extent of infarction (Fig. 3). Magnetization transfer (MT) MR imaging is considered superior to conventional MR imaging for showing abnormal meninges [20]. It also helps in differentiating TBM from other causes of meningitis. The abnormal meninges appearing hyperintense on precontrast T1-weighted (T1W) MT images strongly suggest TBM. Radiograph/CT pneumoencephalography or contrast-enhanced cisternography may help in differentiating communicating and noncommunicating hydrocephalus [16–20].

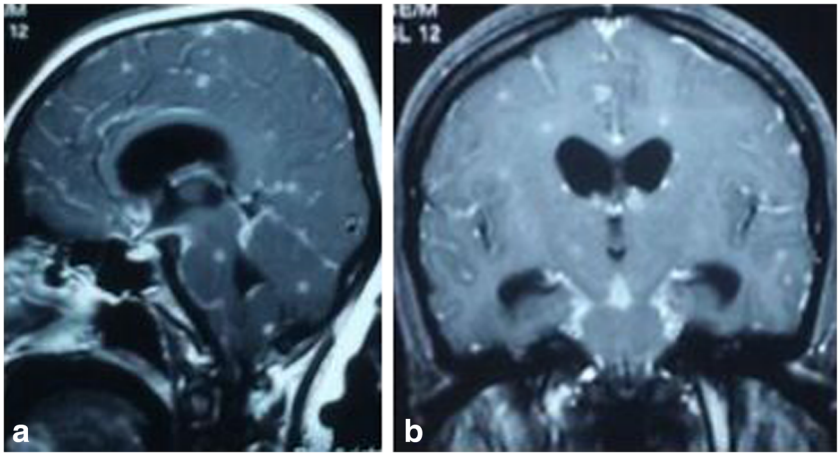

Fig. 2 Postcontrast MR image showing basal meningeal exudates along with hydrocephalus. **a** Sagittal image. **b** Coronal image

Treatment

The primary line of treatment for TBM is medical therapy with antituberculous multidrug chemotherapy [1, 6, 9–12, 15, 21]. The primary drugs include rifampicin (10 mg/kg), isoniazid (5 mg/kg), ethambutol (20 mg/kg), streptomycin (20 mg/kg), or pyrazinamide (25 mg/kg) (three or four drugs) for 3 months followed by isoniazid and rifampicin daily for the next 15 months. The therapy is prolonged and is continued for 18 months [1, 6, 9–12, 21]. In certain situations like relapse, therapy can be continued for one more year. All patients with TBM may receive adjunctive corticosteroids regardless of disease severity at presentation [6, 9–12, 15]. Children can be given prednisolone 4 mg/kg/24 h (or equivalent dose dexamethasone 0.6 mg/kg/24 h) for 4 weeks, followed by a tapering course over 4 weeks. It has been shown to significantly improve survival rate. They are withheld if the patient has also manifested with lung tuberculosis. Patients with multidrug-resistant (MDR) tuberculosis are administered second and third line of antituberculous drugs including kanamycin or ethionamide. The liver and renal functions are closely monitored during the course of therapy. Visual charting is performed to detect abnormality with color vision.

Hyponatremia

Hyponatremia is common in TBM and is independently associated with worse outcome. In conjunction with raised intracranial pressure, it may contribute to poor outcome through worsening cerebral edema, and its surveillance and prevention are of paramount importance. It manifests either as syndrome of inappropriate ADH secretion (SIADH) or cerebral salt wasting syndrome (CSW) [8]. CSW is most often the cause of the hyponatremia than SIADH [22]. It usually results from hypothalamic injury or inflammation. The mainstay of treatment for SIADH has been based on fluid restriction unless patients are severely symptomatic, in which case hypertonic saline is used. Diuretics and urea have been used. Demeclocycline has been used in chronic SIADH. The treatment of CSW revolves around fluid and sodium replacement because these patients develop hyponatremia in the setting of volume depletion [23, 24]. Most patients will respond within 3 days to therapy with fluid and sodium replacement. Central venous pressure monitoring can help guide the diagnosis and management of hyponatremia with natriuresis [23]. Fludrocortisone or hypertonic saline has yielded

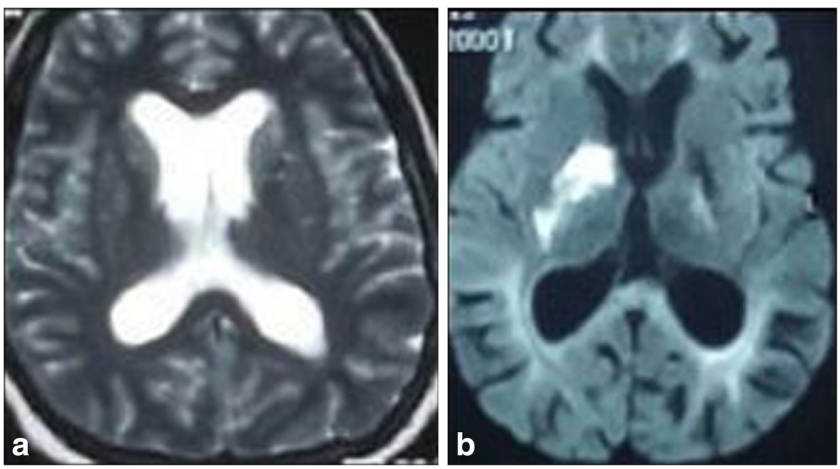

Fig. 3 **a** Axial T2-weighted MR image showing linear hyper intensities in the right basal ganglia suggestive of tuberculous meningitis with infarct. **b**. Axial flair MR image showing restricted diffusion in the right basal ganglionic region suggestive of infarction

Table 3 Imaging features

MR imaging	Tuberculous meningitis	Tuberculoma	Cysticercosis	Fungal granuloma	Hydatid cyst
T1 WI	Hyperintense	Hypointense	Hypointense with hyperintense dot within cyst	Variable, low to intermediate to isointense	Hypointense
T2 WI	Nonspecific	Hypointense	Hyperintense	Hypointense	Hypointense
Contrast	Basal enhancement	Homogenous/ring enhancement with central hypointensity	Present	Peripherally enhancing	Nil
Magnetic transfer	Hyperintense	–	–	–	–
Diffusion WI	Restriction (infarction)	–	–	–	–

good results. Correction of chronic hyponatremia should be performed very slowly (< 0.5 mM/h) to prevent central pontine myelinolysis [1, 8].

Hydrocephalus

Hydrocephalus is a sequela or complication of TBM [1, 2, 8, 9]. The inflammatory basal exudates cause obstruction to the CSF flow resulting in a communicating type of hydrocephalus in about 80% of the cases (Fig. 2). Noncommunicating or obstructive hydrocephalus can occur either because of obstruction of fourth ventricular outlet foramina by the exudates or when there is obstruction of the aqueduct either due to a strangulation of the brain stem by exudates or by a subependymal tuberculoma. Trapped or loculated ventricle is also seen due to entrapment of a part of a ventricle by ependymitis. Sometimes, there is a combination of noncommunicating (obstructive) and communicating (defective absorption) hydrocephalus, which may be difficult to treat. Defective CSF absorption can be a cause of failure of endoscopic third ventriculostomy (ETV). About 50% of patients with TBM have evidence of active or healed pulmonary tuberculosis on chest radiographs; 10% have miliary disease, which is strongly associated with CNS involvement [9, 10].

Patients with symptomatic hydrocephalus or radiologically worsening hydrocephalus benefit from CSF diversion procedures. The modified Vellore grading system is reproducible across different levels of clinical expertise and more reliable system. Both grading systems correlate well with outcome and prognostication.

Medical management with tapering doses of steroids and decongestants including acetazolamide (100 mg/kg) and furosemide (1 mg/kg) can be tried for a few days or a week in patients in grades I and II [25]. Grade II and grade III patients should be monitored closely during this period to detect any worsening or lack of improvement, and a shunt should be promptly offered in case of failure of medical management. In good grade patients, prolonging medical therapy could be harmful and may lead to irreversible brain damage. Grade IV patients should undergo external ventricular drainage, and shunt should be inserted if they show neurological improvement [25, 26]. Ventricular tap is sometimes indicated as an emergency measure to assess and reduce the CSF pressure and stabilize the neurological condition. It can also yield ventricular CSF for exam. Serial ventricular tap every 6 to 8 h can be done till definitive CSF diversion procedure is contemplated.

The initial choice of surgical procedure is ventriculoperitoneal (VP) shunt. Bhagwati et al. have observed that reduction in ICP and size of the ventricles are helpful to improve periventricular perfusion and enhance drug delivery to the tissues in a more effective manner [27, 28]. The complications of shunt surgery include shunt infection and shunt blockage requiring one or multiple revisions. Poor general condition of patient, high CSF protein, and cellular content was responsible for frequent shunt blockages. Agarwal et al. reported shunt-related complications in 11 (30%) children, and three of 37 children had to undergo multiple shunt revisions [29]. Palur et al. reported that 26 of 114 (22.8%) patients had to undergo one or more shunt revisions, one patient requiring more than three revisions [25]. Sil and Chatterjee reported a shunt infection rate of 15.6% and revision rate of 43.8% in their series of 37 children who underwent shunt surgery for TBM with hydrocephalus [30]. Multiple revisions were done in 18.7% of patients.

Endoscopic third ventriculostomy is an option for patients who have completed at least 4 weeks of antituberculous therapy [31]. It is technically demanding and should be performed by a surgeon who is skilled in endoscopic procedures [31–36]. It is difficult to recognize anatomical landmarks since the floor of the third ventricle is frequently thick, and the subarachnoid space is also likely to be obliterated by exudates in early stages of the disease [34, 35]. The basilar artery and its branches are at enhanced risk of injury. The tubercles and granulation tissue on the thick floor of third ventricle bleed when touched and obscure the endoscopic field. Patients with longer duration of symptoms and ATT were more likely to benefit from the ETV [34].

With the advent of effective antituberculous chemotherapy and steroids, the indication for surgery is infrequent [1, 6, 15]. Intrathecal hyaluronidase has been tried in children with communicating hydrocephalus but does not offer any particular advantage over shunt insertion in terms of regression of specific neurological deficit or overall functional improvement [37].

The factors contributing to poor outcome include cerebrovascular involvement with resultant cerebral ischemia, abscess formation, hydrocephalus and raised intracranial pressure, direct parenchymal injury, hyponatremia, seizures, and delayed diagnosis. The grade at presentation is the best and most consistent predictor of outcome following shunt surgery in patients with TBM. The presence of infarcts in the basal ganglia and internal capsule is also likely to indicate a poor outcome following shunting [1, 3, 6, 38–42].

The outcome of TBM with hydrocephalus is dependent on the response of the disease to antituberculous therapy [13, 15, 25, 38]. In case of multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB), the outcome is likely to be poor. There are, however, no studies, which have reported on the outcome following surgery for drug-resistant TBM. Home-based treatment of childhood CNS TB is feasible in selected patients under close supervision in areas where there is high incidence of tuberculosis coupled with HIV infection resulting in severe bed shortages in secondary and tertiary hospitals [43].

Vasculitis

The inflammatory basal exudates are associated with vasculitis of the vessels in the subarachnoid spaces predominantly involving the small arterial branches of the arteries in the circle of Willis [14, 15]. The adventitia and media are affected initially and later the lumen of the vessel. It causes reactive subendothelial cellular proliferation leading to complete occlusion and thrombus formation. Middle cerebral and lenticulostriate arteries are the most common vessels involved.

Cranial nerve involvement

Cranial nerve involvement in TBM is variable and is seen in 17 to 70% of patients. It primarily occurs due to ischemia of the nerve or entrapment of the nerve in basal exudates causing neuritis or perineuritis, or there may be a tuberculoma on the nerve within the subarachnoid course. The proximal portion of the nerve at root entry zone is usually affected. The brainstem nucleus of the nerve in proximity can be affected. Permanent loss of function can ensue in late stages due to fibrosis [1–6].

Tuberculous encephalitis and encephalopathy

Tuberculous encephalitis results from parenchymal inflammation adjacent to the meninges. It shows edema, perivascular infiltration, and a microglial reaction, known as border zone reaction. Tuberculous encephalopathy is a delayed type IV hypersensitivity reaction caused by tuberculous protein. It is a fulminant immunologic mechanism resulting in extensive damage to the white matter with perivascular demyelination. Infants and young children with pulmonary TB are commonly affected. There is a high incidence of mortality in these patients despite antituberculous medication [5, 6].

Tuberculous pachymeningitis

Tuberculous pachymeningitis is rare in children. It is defined as a chronic inflammation causing focal or diffuse thickening of the dura mater resulting in fibrous constriction of the basal meninges [38–40]. It can cause obstructive hydrocephalus, venous hypertension, brain edema, and entrapment of lower cranial nerves. The clinical symptoms resemble migraine, including intense headaches, cranial nerve palsies, cerebellar symptoms, blindness, and optic neuropathy. MR imaging shows nodular or linear dural thickening with intense meningeal enhancement. Differential diagnosis would include connective tissue disorders or malignancies. Empirical antituberculous treatment can be considered in case of a positive history of tuberculosis elsewhere in the body. However, in doubtful cases, a diagnostic biopsy would be helpful [38, 39]. Treatment options include antituberculous treatment and steroids with or without immunomodulating agents. The clinical outcome is variable, and occasionally, there may be steroid dependence [38, 39]. Surgical debulking is rarely needed [38–40].

Tuberculous arachnoiditis

It is a known sequelae of tuberculous meningitis. It results due to organization of the exudates present in the interpeduncular, suprasellar, and sylvian cisterns. It is prominently seen in the optochiasmatic region, skull base, and spine [41, 42, 44, 45] (Fig. 4). The treatment is challenging, and the response is generally unsatisfactory. Corticosteroids, especially methyl prednisolone, have been tried. Thalidomide and hyaluronidase have been used with variable success.

Tuberculoma

Tuberculomas are commonly seen in patients residing in endemic countries [7–12]. They can occur at any age. They can be solitary or multiple and can occur anywhere in the brain

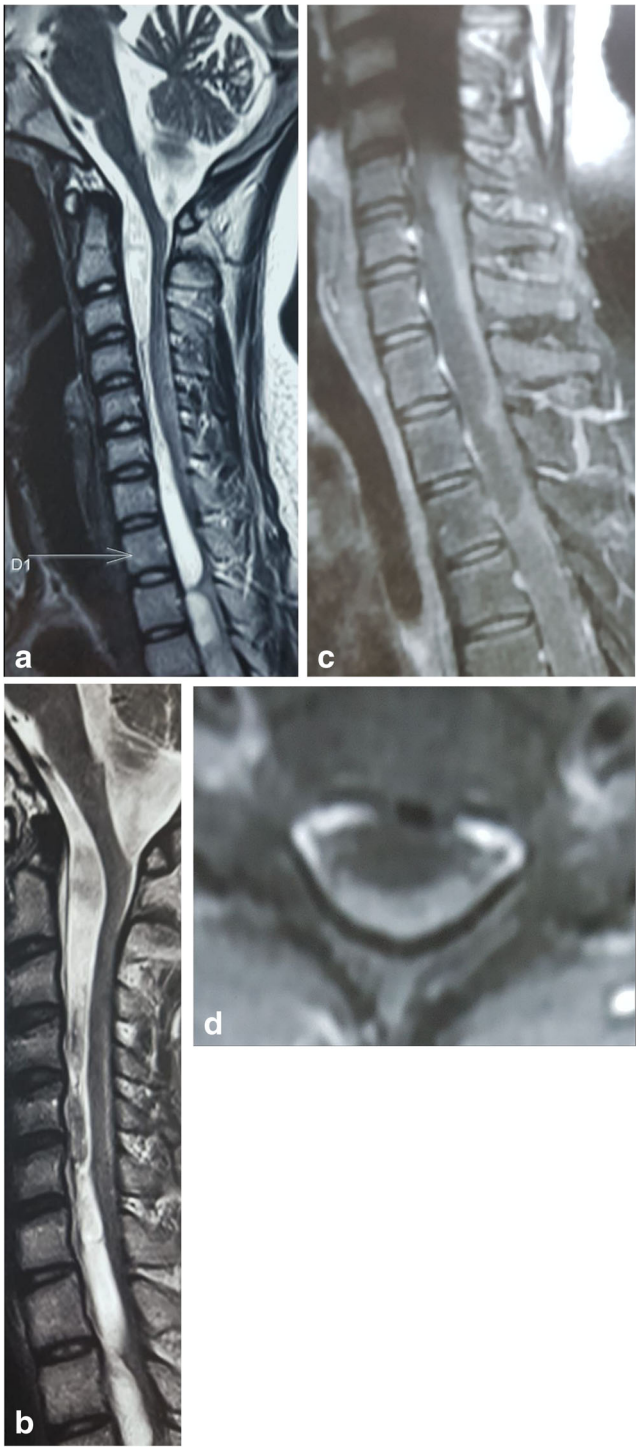

Fig. 4 MR image of cervicodorsal tuberculous arachnoiditis. **a** Sagittal T2-weighted MR image showing widening and cavitation in anterior subarachnoid space C2-D1 associated with spinal cord swelling. **b** Sagittal T2-weighted MR image showing atrophy of the spinal cord in addition to widened and multiloculated anterior subarachnoid space C2-D1 region. **c** Sagittal T1-weighted contrast MR image showing faint enhancement of the widened anterior subarachnoid space C2-D1 as well as the spinal cord. **d** Axial T1-weighted contrast MR image showing the widened anterior subarachnoid space C2-D1 with displaced spinal cord posteriorly

parenchyma [11, 12, 21]. In children, they predominate in the infratentorial compartment [7, 44–46]. Tuberculomas arise when tubercles in the parenchyma of brain enlarge without rupturing into the subarachnoid space. They are usually less than 2 to 5 mm in size. The occurrence of spinal intramedullary tuberculoma is rare [47–49].

Imaging findings of tuberculoma depends on whether it is noncaseating or caseating with solid or liquid center. A solid noncaseating tuberculoma is isodense or slightly hypodense to the surrounding brain parenchyma on CT and hypointense on both T1W and T2W images on MR imaging. It shows homogeneous enhancement on contrast administration (Fig. 5). The cellular components of the noncaseating tuberculomas appear brighter on MT T1W imaging differentiating it from metastases, lymphomas, and other infective granulomas [16–20]. The target sign, a central calcification or nidus surrounded by ring enhancement on postcontrast images, is considered pathognomonic of tuberculoma. Tuberculomas can mimic neurocysticercosis, fungal granulomas, and tumors like lymphomas, gliomas, and metastases. En plaque tuberculomas can mimic meningiomas. In a prospective study, the positive predictive value of CT-based diagnosis of brain tuberculoma was found to be only 33% [50]. Newer imaging techniques, like diffusion imaging, MR spectroscopy (MRS), and MT imaging, may help in differentiating these conditions [17–20]. Tuberculomas shows a large cellular component appearing bright on MT imaging and with a choline peak on spectroscopy. Fluorodeoxyglucose (FDG) positron emission tomography can be helpful in differentiating an atypical tuberculoma from other neoplastic and nonneoplastic CNS lesions. It can also be used in the follow-up of tuberculomas.

The mainstay of therapy for a brain tuberculoma is antituberculous chemotherapy. Hence, empiric therapy for brain tuberculoma should be considered in selected cases who will comply with periodic clinical and imaging follow-up. The main indication for surgery in children with suspected brain tuberculomas is a doubtful diagnosis of tuberculoma. In patients with a reasonably certain diagnosis, surgical excision of tuberculomas or tuberculous abscess is otherwise generally performed when there is clinical deterioration following optimal medical therapy [11, 45–54]. A total excision of the tuberculoma should only be attempted in cases where the tuberculoma is in a noneloquent region of the brain such as the anterior frontal lobe, anterior temporal lobe or cerebellum. In eloquent and deep seated locations, a partial excision or a biopsy may suffice. A stereotactic biopsy may be a good option in children with deep seated suspected tuberculomas such as those in the thalamus, basal ganglia, and brain stem [54]. Biopsy confirmation may be warranted to establish

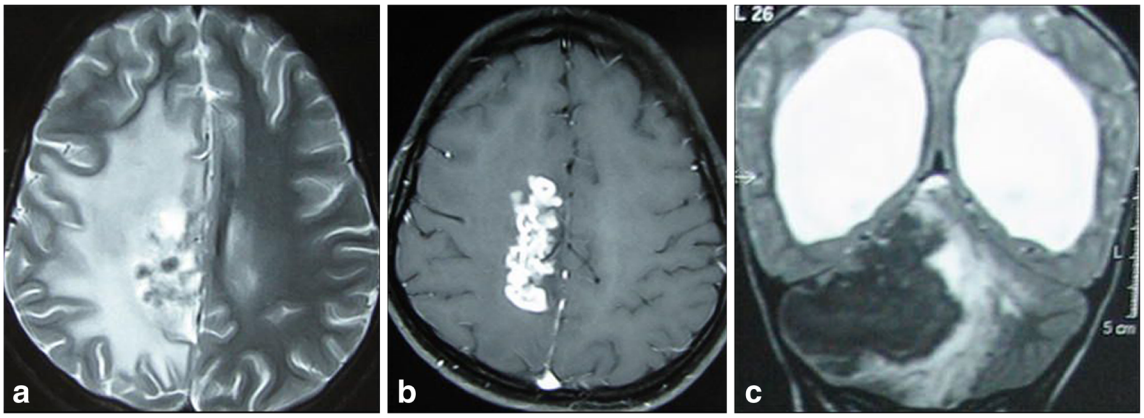

Fig. 5 MR images showing tuberculoma. **a** Axial T2-weighted image showing multiple hypointense lesions in the right frontoparietal region with surrounding perifocal edema. **b** Axial postcontrast MR image showing enhancing conglomerate of lesions in right frontoparietal region suggestive of tuberculoma. **c** Coronal T2-weighted image showing a large hypointense tuberculoma with perifocal edema in the right cerebellum associated with hydrocephalus

diagnosis in cases of co-infection with HIV contributing to differential diagnosis. Antituberculous drugs should be administered even after total excision of a brain tuberculoma for at least 12 months to sterilize the brain of any tuberculous bacteria. In other patients with a residual tuberculoma, the duration of therapy is dictated by the follow-up imaging findings. The presence of a significant enhancing mass with edema is an indication for continued therapy. Some patients may require antituberculous therapy for up to 4 years [53].

Tuberculous brain abscess

Tuberculous brain abscess is rare [55–59]. It can be solitary or multiple. It is an encapsulated collection of pus with abundant viable tubercle bacilli without classic tubercular granuloma formation. The wall is thicker than pyogenic abscess. They can mimic otogenic pyogenic abscesses [55–57]. According to the Whitener criteria for tuberculous abscess, it should reveal macroscopic evidence of abscess formation within the brain parenchyma, and on histologic examination, the abscess wall should be composed of vascular granulation tissue containing acute and chronic inflammatory cells and tubercle bacilli without the typical granulomas associated with tuberculomas [56, 57]. Imaging findings of tuberculous brain abscess are usually nonspecific. They present as large, frequently multiloculated, ring-enhancing lesions with perilesional edema and mass effect (Fig. 6). Diffusion-weighted imaging shows restricted diffusion with low apparent diffusion coefficient (ADC) values because of the presence of inflammatory cells in the pus. MRS helps in differentiating tuberculous abscess from those of pyogenic and fungal causes [17–19]. MRS shows lipid, lactate, and phosphoserine

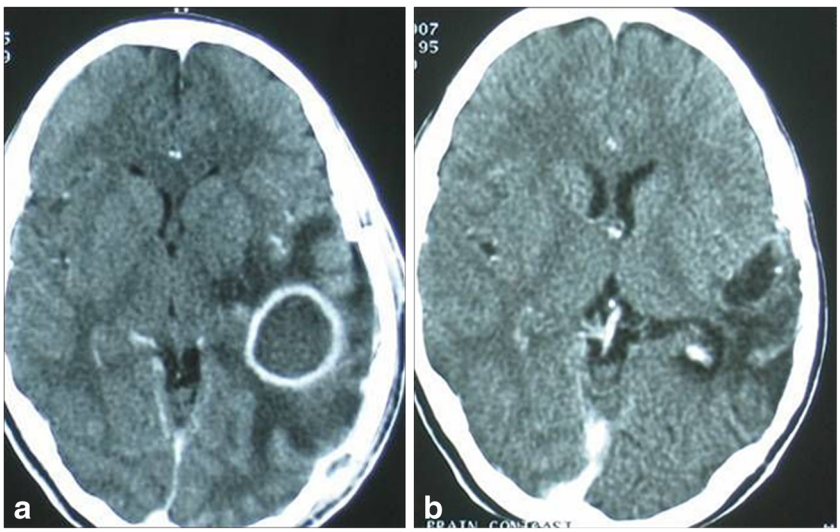

Fig. 6 Tuberculous brain abscess. **a** Axial postcontrast CT image showing a well-defined rounded peripherally enhancing lesion with hypodense center and associated perifocal edema in the left temporoparietal brain. **b** Axial postcontrast CT image showing gliosis in the left temporoparietal brain and resolution of the perifocal edema following surgery and antituberculous therapy for 2 years

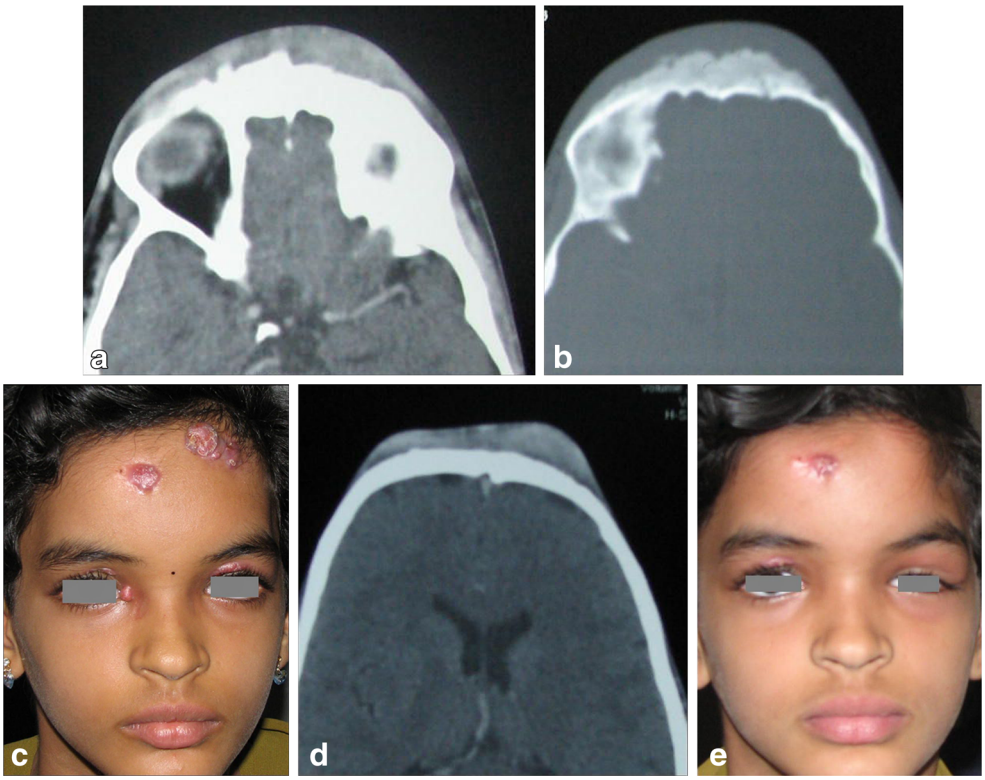

Fig. 7 Calvarial (frontal bone) tuberculosis in a 10-year-old girl. **a** Axial postcontrast CT showing thickening of the frontal bone with erosion of the margins and overlying soft tissue swelling. **b** Bone window of the same image showing erosion of the outer table of the frontal bone with soft tissue swelling. **c** Clinical photograph (frontal view) of the patient showing multiple punched out skin lesions on the forehead, inner canthus, and upper eyelid region. **d** Axial CT image showing healed frontal bone on antituberculous chemotherapy. The overlying soft tissue swelling has also reduced in size. **e** Clinical photograph (frontal view) of the patient showing the healed skin lesions as previously depicted

without evidence of cytosolic amino acids, in contrast to pyogenic abscess. MT imaging can differentiate tuberculous from pyogenic abscesses.

Calvarial tuberculosis

Calvarial tuberculosis is rare, even in areas where tuberculosis is endemic because of paucity of lymphatics in the calvarial bone [58, 59]. Younger population is at higher risk to develop calvarial tuberculosis and it is rare in infancy. The disease might be limited, or there may be widespread destruction of the inner table with abundant extradural granulation tissue in the form of pachymeningitis externa [60, 61]. The most common sites of involvement are frontal and parietal bones as both the bones have large amount of cancellous bone [62–64]. In circumscribed and sclerotic type, there is marked thickening of the bone because of lack of blood supply to the diseased bone.

Plain X-ray of the skull can be helpful. Areas of rarefaction are seen early in the disease, which develop into punched out defects with a central sequestrum later on [65]. Both osteolytic and osteoblastic areas may be seen. Rarely, sclerosis may be seen and indicates secondary infection. CT scan of the brain is helpful in assessing the extent of bone destruction, scalp swelling, and degree of intracranial involvement (Fig. 7) [65–67]. Another infection of the skull, namely melioidosis caused by *Burkholderia pseudomallei*, can cause symptoms and signs having radiological features similar to that of calvarial tuberculosis. Other differential diagnoses include eosinophilic granuloma and unusual tumors such as Ewing's sarcoma.

Combination of surgical excision and antitubercular therapy is the preferred treatment. Surgery is indicated to establish the diagnosis, to obtain pus and tissue for culture and sensitivity studies, and to remove thick extradural granulation tissue and necrotic bone in patients with sinus discharge, intracranial extensions, and large collections of caseating material causing mass effect [60–67].

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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