

## Classic diseases revisited

# Tuberculosis of the central nervous system

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### Summary

**Tuberculous involvement of the brain and spinal cord are common neurological disorders in developing countries and have recently shown a resurgence in developed ones. Tuberculous meningitis is an important manifestation and is associated with high morbidity and mortality. Diagnosis is based on clinical features, cerebrospinal fluid changes, and imaging characteristics. Bacteriological confirmation is not possible in all cases as serological tests do not have sufficient sensitivity and specificity. The polymerase chain reaction shows promise for the future. Appropriate chemotherapeutic agents should be administered as early as possible, although there is no unanimity concerning chemotherapeutic regimens or optimal duration of treatment. The patient's clinical stage at presentation is the most important prognostic factor. The role of corticosteroids is controversial but they should be administered to all patients presenting in stage III. Surgical procedures are directed at management of the hydrocephalus. Focal lesions, intracranial tuberculomas, and tuberculous abscesses, are usually located in cerebral or cerebellar hemispheres, uncommonly in brainstem and very rarely in spinal cord. They do not usually require surgical intervention and respond well to antituberculous treatment, along with corticosteroids.**

**Keywords:** tuberculosis; central nervous system

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Tuberculosis remains a major global problem and a public health issue of considerable magnitude. In recent times, there has been a resurgence of tuberculosis in both developing and developed countries. Several risk factors have been observed for this serious phenomenon. These include the increasing prevalence of HIV infection, over-crowding in the urban population and in abnormal communities (such as prisons, concentration camps, refugee colonies), poor nutritional status, appearance of drug-resistant strains of tuberculosis, ineffective tuberculosis control programmes, and an increase in migration from countries where tuberculosis is prevalent to the developed world. The incidence of tuberculosis varies from 9 cases per 100 000 population per year in the US to 110-165 cases per 100 000 population in the developing countries of Asia and Africa.<sup>1-3</sup> Tuberculous involvement of the central nervous system (CNS) is an important and serious type of extra-pulmonary involvement. It has been estimated that approximately 10% of all patients with tuberculosis have CNS involvement.<sup>4</sup> The incidence of CNS tuberculosis is directly proportional to the prevalence of tuberculous infection in general. In developing countries CNS tuberculosis is a disease of younger age group, usually childhood.<sup>5</sup>

### Classification

It is extremely difficult to classify the varied manifestations of CNS tuberculosis. The classification given in box 1 includes all well-accepted forms.

### Pathogenesis of CNS tuberculosis

Most tuberculous infections of the CNS are caused by *Mycobacterium tuberculosis*. Less frequently, other mycobacteria may be involved. It is believed that the bacilli reach the CNS by the haematogenous route secondary to disease elsewhere in the body. Rich and McCordock,<sup>6</sup> on the basis of their clinical and experimental observations, suggested that CNS tuberculosis develops in two stages. Initially small tuberculous lesions (Rich's foci) develop in the CNS, either during the stage of bacteraemia of the primary tuberculous infection or shortly afterwards. These initial tuberculous lesions may be in the meninges, the subpial or subependymal surface of the brain or the spinal cord, and may remain dormant for years after initial infection. Later, rupture or growth of one or more of these small tuberculous lesions produces development of various types of CNS tuberculosis.<sup>6-7</sup> The specific stimulus for rupture or growth of Rich's foci is not known, although immunological mechanisms are believed to play an important role. Rupture into the subarachnoid space or into the ventricular system results in meningitis. The type and extent of lesions that result from the discharge of tuberculous bacilli into the cerebrospinal fluid (CSF), depend upon the number and virulence of the bacilli, and the immune response of the host. Infrequently, infection spreads to the CNS from a site of tuberculous otitis or calvarial osteitis. A study of immunological parameters showed a correlation between the development of tuberculous meningitis in children and significantly lower numbers of CD4 T-lymphocyte counts when compared with children who had primary pulmonary complex only.<sup>8</sup> The pathogenesis of localised brain lesions is also thought to involve haematogenous spread from a primary focus in the lung (which is visible on the chest radiograph in only 30% of cases). It has been suggested that with a sizeable inoculation or in the absence of an adequate cell-mediated immunity, the parenchymal cerebral tuberculous foci may develop into tuberculoma or tuberculous brain abscess.<sup>9</sup>

### Tuberculous meningitis

#### PATHOLOGY

In tuberculous meningitis there is a thick, gelatinous exudate around the sylvian fissures, basal cisterns, brainstem, and cerebellum. Hydrocephalus may occur as

### Classification of CNS tuberculosis

#### Intracranial

- tuberculous meningitis (TBM)
- TBM with miliary tuberculosis
- tuberculous encephalopathy
- tuberculous vasculopathy
- space-occupying lesions: tuberculoma (single or multiple); multiple small tuberculoma with miliary tuberculosis; tuberculous abscess

#### Spinal

- Pott's spine and Pott's paraplegia
- tuberculous arachnoiditis (myeloradiculopathy)
- non-osseous spinal tuberculoma
- spinal meningitis

#### Box 1

### Diagnostic features of tuberculous meningitis<sup>13</sup>

#### Clinical

- fever and headache (for more than 14 days)
- vomiting
- altered sensorium or focal neurological deficit

#### CSF

- pleocytosis (more than 20 cells, more than 60% lymphocytes)
- increased proteins (more than 100 mg/dl)
- low sugar (less than 60% of corresponding blood sugar)
- India ink studies and microscopy for malignant cells should be negative

#### Imaging

- exudates in basal cisterns or in sylvian fissure hydrocephalus
- infarcts (basal ganglionic)
- gyral enhancement
- tuberculoma formation

#### Evidence of tuberculosis elsewhere

#### Box 2

### Methods to increase mycobacterial yield of CSF smear examination<sup>44</sup>

- examine the deposit on centrifugation of a 10 ml CSF sample
- examine the deposit for at least 30 min
- examine several CSF samples over a few days

#### Box 3

a consequence of obstruction of the basal cisterns, outflow of the fourth ventricle, or occlusion of the cerebral aqueduct. Hydrocephalus frequently develops in children and is associated with a poor prognosis. The brain tissue immediately underlying the tuberculous exudate shows various degrees of oedema, perivascular infiltration, and a microglial reaction, a process known as 'border zone reaction'. The basal exudates of tuberculosis are usually more severe in the vicinity of the circle of Willis, and produce a vasculitis-like syndrome. Inflammatory changes in the vessel wall may be seen, and the lumen of these vessels may be narrowed or occluded by thrombus formation. The vessels at the base of the brain are most severely affected, including the internal carotid artery, proximal middle cerebral artery, and perforating vessels of the basal ganglion. Cerebral infarctions are most common around the sylvian fissure and in the basal ganglion. In the majority of patients the location of infarction is in the distribution of medial striate and thalamoperforating arteries. Haemorrhagic transformation of infarcted tissue is not unusual.<sup>5 10-12</sup>

#### CLINICAL FEATURES

In most patients with tuberculous meningitis there is a history of vague ill health lasting 2–8 weeks prior to the development of meningeal irritation. These non-specific symptoms include malaise, anorexia, fatigue, fever, myalgias, and headache. The prodromal symptoms in infants include irritability, drowsiness, poor feeding, and abdominal pain. Eventually, the headache worsens and becomes continuous. Neck stiffness is reported by about 25% of patients, but meningismus is detected in a higher number of patients at the time of examination. Bulging fontanelles develop in infants, who become increasingly irritable. Nausea, vomiting and altered sensorium may develop. Continuous low-grade pyrexia is typically present in about 80% of patients. A prior history of tuberculosis is present in approximately 50% of children with tuberculous meningitis and 10% of adult patients.<sup>5 10 13</sup>

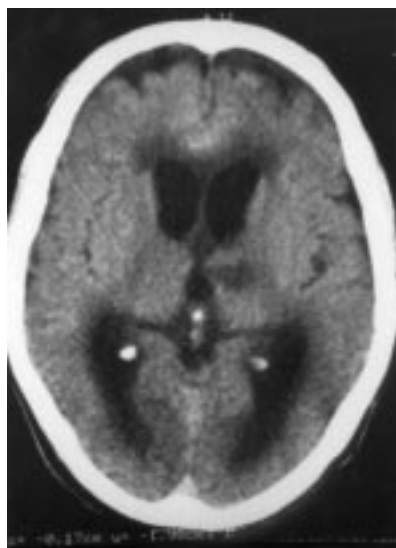
Cranial nerve palsies occur in 20–30% of patients and may be the presenting manifestation of tuberculous meningitis. The sixth cranial nerve is most commonly affected. Vision loss due to optic nerve involvement may occasionally be a dominant and presenting illness. Optochiasmatic arachnoiditis, third ventricular compression of optic chiasma (if hydrocephalus develops), optic nerve granuloma, and ethambutol toxicity are possible factors for vision loss in these patients. Ophthalmoscopic examination may reveal papilloedema. Funduscopy may reveal choroid tubercles, yellow lesions with indistinct borders present either singly or in clusters. These choroid tubercles are more frequent with tuberculous meningitis associated with miliary tuberculosis and are virtually pathognomonic of tuberculous aetiology, although they are present in only 10% of patients in whom the meningitis is not associated with miliary involvement.<sup>7 12</sup>

Hemiplegia may occur at the onset of the disease or at a later stage. Quadriplegia secondary to bilateral infarction or severe cerebral oedema is less common and occurs only at an advanced stage in a few patients. At times, abnormal movements may dominate the clinical picture. Choreiform or hemiballistic movements, athetosis, generalised tremors, myoclonic jerks and ataxia have been observed, more commonly in children than in adults. Seizures, either focal or generalised, may occur during acute illness or months after treatment.<sup>7</sup>

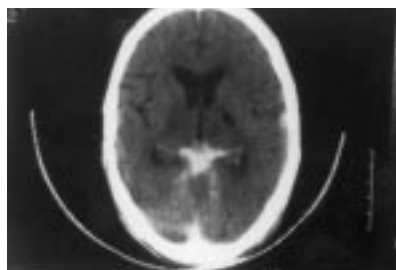
As the disease progresses, increasing evidence of cerebral dysfunction sets in. Apathy and irritability tend to progress to increasing lethargy, confusion, stupor and coma. The terminal illness is characterised by deep coma, decerebrate or decorticate rigidity, and spasm.

#### DIAGNOSIS

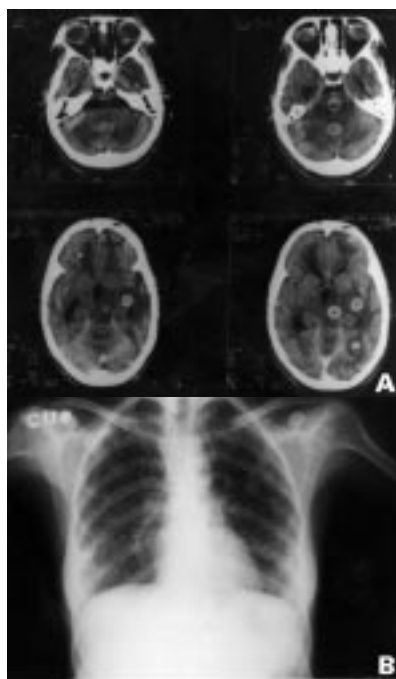
The abnormalities found in CSF of untreated patients with tuberculous meningitis are well described. Usually, there is a predominant lymphocytic reaction (60–400 white cells per ml) with raised protein levels (0.8–4 g/l). In the early stages of infection, a significant number of polymorphonuclear cells may be observed, but over the course of several days to weeks they are typically replaced by lymphocytes. There is a gradual decrease in the sugar concentration of the CSF, which is usually less than 50% of serum glucose concentration, the values may range between 18–45 mg/dl.<sup>5 7 10 12 13</sup> Definitive diagnosis of tuberculous meningitis depends upon the detection of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture. It has been claimed that if large volumes of CSF are carefully examined the organism can be found in over 90% of centrifuged CSF specimens (box 3), the highest detection rates being achieved in ventricular fluid. With repeated examinations of sequential CSF examinations Kennedy and Fallon<sup>14</sup> reported tubercle bacilli in 87% of patients. In other series especially from developing countries bacteriological confirmation of the diagno-



**Figure 1** Contrast-enhanced CT of brain showing hydrocephalus and a right thalamic infarct



**Figure 2** Contrast-enhanced cranial CT of a patient with tuberculous meningitis. Thick basilar exudate and an infarct in right thalamic region is seen



**Figure 3** (A) Contrast-enhanced CT of brain showing multiple tuberculomas in a patient with tuberculous meningitis; (B) chest X-ray showing miliary shadows

sis could be achieved in as few as 10% of the cases.<sup>5</sup> Culture of the CSF for tubercle bacilli are not invariably positive. Rates of positivity for clinically diagnosed cases range from 25% to 70%. It requires several weeks before culture is positive for mycobacterium bacilli.

Because of frequent difficulty in detecting tubercle bacilli in smears or cultures of CSF, a number of tests have been developed to establish an early and definitive diagnosis.<sup>15</sup> In the past, radioactive bromide partition testing and identification of components of the mycobacterial cell wall (eg, tuberculostearic acid) have been reported to have a sensitivity and specificity over 90%. However, the clinical utility of these has not been found to be satisfactory. Antibodies against tubercle bacilli can be detected with enzyme-linked immunosorbent assay (ELISA) with variable success. The latex particle agglutination test, which allows the rapid detection of tubercle bacillus antigen in CSF, has been reported to be a simple and specific test.<sup>16</sup> The intradermal tuberculin skin test is helpful when positive. The test may, however, be falsely negative even in the absence of immunosuppression and in association with a positive reaction to common antigens used to determine anergy (eg, *Candida* and mumps). The tuberculin skin test has been reported to be negative initially in 50–70% of cases and often becomes positive during therapy. The best method for diagnosing mycobacterial infection, however, is the polymerase chain reaction, in which cDNA probes are used to identify mycobacterial RNA or DNA sequences in CSF. This test is highly sensitive and specific in the diagnosis of tuberculous meningitis.<sup>17</sup>

#### IMAGING

Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain may reveal thickening and intense enhancement of meninges, especially in basilar regions. Ventricular enlargement is present in a majority of patients. The degree of hydrocephalus correlates with the duration of the disease. Infarcts are another characteristic imaging feature (figures 1 and 2) of tuberculous meningitis.<sup>13</sup> The reported frequency of infarcts demonstrated by CT varies from 20.5% to 38%, however, in general, the incidence of infarction is significantly higher on MRI than on CT. In addition, a large number of infarcts are seen to be haemorrhagic in nature on MRI, a finding not well documented on CT scan. The majority of infarcts are seen in thalamic, basal ganglion, and internal capsule regions.<sup>7</sup> Thick basilar exudates appear as intensely enhancing areas in the basal cisterns (spider-leg appearance) (figure 2) and in the sylvian fissures.<sup>13</sup> Tuberculomas are infrequently seen on CT or MRI of patients with tuberculous meningitis. Davis *et al*<sup>18</sup> found tuberculomas in 16% of patients with culture-positive or presumptive tuberculous meningitis. Multiple small intracranial tuberculoma are frequent when tuberculous meningitis is part of miliary tuberculosis<sup>19 20</sup> (box 4; figure 3). The carotid or MR angiogram shows changes in vessels of the circle of Willis. These changes include uniform narrowing of large segments, small segmental narrowing, irregular beaded appearance and complete occlusion.<sup>21</sup> These vascular changes are due to either vasculitis or mechanical compression by the basilar exudate.

#### Tuberculous encephalopathy

Tuberculous encephalopathy, a syndrome exclusively present in infants and children, has been described by Udani and Dastur<sup>22</sup> in Indian children with pulmonary tuberculosis. The characteristic features of this entity are the development of a diffuse cerebral disorder in the form of convulsions, stupor and coma without signs of meningeal irritation or focal neurological deficit. CSF is largely normal or may show a slight increase in proteins and cells. Pathologically, there is diffuse oedema of cerebral white matter with loss of neurons in grey matter. A picture resembling haemorrhagic leukoencephalopathy or a post-infectious demyelinating encephalomyelitis may be observed.<sup>11 22</sup>

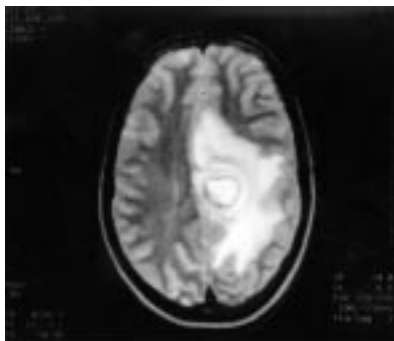
#### Intracranial tuberculoma

Tuberculomas are firm, avascular, spherical granulomatous masses, measuring about 2–8 cm in diameter. They are well limited from surrounding brain tissue which is compressed around the lesion and shows oedema and gliosis. The inside of these masses may contain necrotic areas composed of caseous material, occasionally thick and purulent, in which tubercle bacilli can be demonstrated. Intracranial tuberculomas can occur at any age. In developing countries young adults and children are predominantly affected while in developed countries they are more common in older patients. The symptoms produced by tuberculoma are related to their location. Low-grade fever, headache vomiting, seizures, focal neurological deficit, and papilloedema are characteristic clinical features of

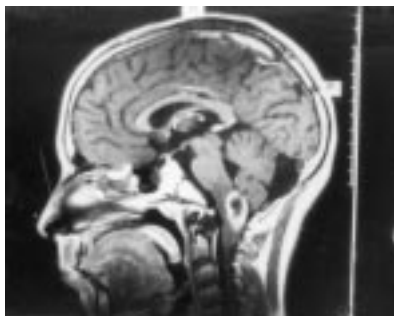
### Case report: disseminated tuberculosis

A 30-year-old woman presented with headache, vomiting and fever (104°F) of 6 days duration. She was conscious, oriented and attentive, and had bilateral lateral rectus palsy along with bilateral papilloedema. Left plantar was extensor. Neck rigidity and Kernig's sign were present. Other systemic and general examinations were normal. All haematological and serum biochemical parameters, including liver function tests, were normal. Chest X-ray showed miliary shadows in both lungs (figure 3B). CSF revealed elevated opening pressure, proteins 248 mg/dl, sugar 34 mg/dl (corresponding blood sugar was 98 mg/dl); 204 cells/ml, 15% polymorphs rest lymphocytes. CT head showed multiple small enhancing lesions in brain parenchyma (figure 3A). The patient was given antituberculous treatment and corticosteroids. She showed significant improvement in all her symptoms after 15 days.

#### Box 4



**Figure 4** T2-weighted MRI of brain showing a large caseating tuberculoma in the parasagittal area of the left parietal lobe



**Figure 5** Sagittal T2-weighted cranial MRI showing a caseating tuberculoma in the medulla oblongata

supratentorial tuberculomas. Intratentorial tuberculomas are more common in children and may present with brainstem syndromes, cerebellar manifestations, and multiple cranial nerve palsies.<sup>23-25</sup>

On CT, tuberculomas are characterised as low- or high-density and rounded or lobulated masses and show intense homogenous or ring enhancement after contrast administration. They have an irregular wall of varying thickness. Moderate to marked perilesional oedema is frequently present. Tuberculomas may be single or multiple and are more common in frontal and parietal lobes, usually in parasagittal areas. On CT, the 'target sign', a central calcification or nidus surrounded by a ring that enhances after contrast administration, is considered pathognomonic of tuberculoma.<sup>26</sup> In developing countries like India, tuberculomas are frequently confused with cysticercus granuloma. Rajshekhar *et al*<sup>27</sup> used CT features to differentiate between these two conditions after establishing definite diagnoses by stereotactic brain biopsy. On CT scanning, tuberculoma measure more than 20 mm in diameter, are frequently irregular in outline, and are always associated with marked cerebral oedema (leading to midline shift) and progressive focal neurological deficit. The MRI features of tuberculoma depend on whether the lesion is non-caseating, caseating with a solid centre, or caseating with a liquid centre. The non-caseating granulomas are hypointense on T1-weighted images and hyperintense on T2-weighted images; after contrast administration the lesion usually shows homogenous enhancement. The second type of tuberculoma are hypointense or isointense on T1-weighted images and also on T2-weighted image. After contrast administration there is ring enhancement. These types of granuloma have variable degree of perilesional oedema. The tuberculoma with central liquefaction of the caseous material appears centrally hypointense on T1- and hyperintense on T2-weighted images with a peripheral hypointense ring which represents the capsule of tuberculoma (figures 4 and 5). Images after contrast administration show ring enhancement.<sup>21</sup> Stereotactic diagnostic biopsy can help in establishing an accurate diagnosis.<sup>24</sup>

#### Intracranial tuberculous abscess

Tuberculous brain abscess is a condition distinct from CNS tuberculoma. In developing countries tuberculous abscesses have been reported in 4% to 7.5% of patients with CNS tuberculosis. The histopathological diagnosis of tuberculous brain abscess depends on the following criteria: microscopic evidence of pus in the abscess cavity, microscopic changes in the abscess wall, and isolation of *M tuberculosis*.<sup>11 28</sup> Abscesses are usually solitary and larger and progress much more rapidly than tuberculomas. CT and MRI pictures of a tuberculous abscess show a granuloma with a liquid centre, however, they are much larger and frequently multiloculated and with marked surrounding oedema. Clinical features include partial seizures, focal neurological deficit, and raised intracranial tension.<sup>28</sup> Surgical exploration and drainage of pus may produce excellent long-term results.

#### Pott's spine and Pott's paraplegia

It is estimated that involvement of the spine occurs in less than 1% of patients with tuberculosis. It is a leading cause of paraplegia in developing nations (box 5). Infection in the vertebral bodies usually starts in cancellous bone adjacent to an intervertebral disc or anteriorly under the periosteum of the vertebral body; the neural arch is rarely affected. Vertebral destruction leads to collapse of the body of the vertebra along with anterior wedging. Spinal cord compression in Pott's spine is mainly caused by pressure from a paraspinal abscess which is retropharyngeal in the cervical region (figure 6), and spindle shaped in thoracic (figure 7) and thoracolumbar regions. Neurological deficits may also result from dural invasion by granulation tissue and compression from the debris of sequestered bone, a destroyed intervertebral disc, or a dislocated vertebra. Rarely, vascular insufficiency in the territory of the anterior spinal artery has also been suggested. Neurological involvement can occur at any stage of Pott's spine and even years later, when there has been apparent healing, because of stretching of the cord in the deformed spinal canal. The thoracic spine is involved in about 65% of cases, and the lumbar, cervical and thoracolumbar spine in about 20%, 10% and 5%, respectively. The atlanto-axial region may also be involved in less than 1% of cases. Males are affected more often than females in most series, and the disease generally affects young persons.<sup>29-31</sup>

Typically, there is a history of local pain, tenderness over the affected spine or even overlying bony deformity in the form of gibbus. Paravertebral abscess may be palpated on the back of a number of patients. These patients usually have acute or subacute, progressive, spastic type of sensorimotor paraparesis. The incidence of paraparesis in patients with Pott's spine varies from 27% to 47%.



**Figure 6** X-ray of cervical spinal showing retropharyngeal abscess along with destruction of C6–7 vertebra



**Figure 7** A lumbar myelogram showing spinal block at the level of T9 vertebra. A fusiform paravertebral swelling and destruction of T8 and T9 vertebra are also seen

Conventional spinal X-rays are usually adequate to demonstrate the destruction of adjacent vertebral bodies and intervening disc spaces. However, superior investigative modalities used for the diagnosis of Pott's paraplegia include myelography (figure 7), CT scan (figure 8), MRI (figure 9) and CT-guided needle biopsy. These help to define precisely the level of spinal involvement, amount of bone destroyed, morphology and extent of the paravertebral abscess and cord compression. Vidyasagar and Murthy,<sup>31</sup> who used only plain radiography, myelography and CT scan, showed that myelography gave the best indication for spinal cord compression even when other superior investigative facilities were available. They found CT-guided needle biopsy to be very useful in establishing the aetiological diagnosis in their cases, picking up unexpected tumour metastases in several cases. A combination of surgical decompression and treatment with antituberculous drugs is needed for the majority of patients with Pott's paraplegia. A period of 12 months of postoperative antituberculous therapy is adequate.<sup>29–32</sup>

### Non-osseous spinal cord tuberculosis

Non-osseous spinal cord tuberculosis can occur in the form of tuberculomas. Dastur<sup>33</sup> reviewed 74 cases of tuberculous paraplegia without evidence of Pott's disease and observed that extradural tuberculomas occurred in 64% while arachnoid lesions without dural involvement, and subdural/extradural lesions occurred in 8% of patients in each group. Intramedullary tuberculomas are extremely rarely reported, reports from developing countries have also been sporadic. The clinical features are indistinguishable from those of any extramedullary or intramedullary tumour, although acute worsening may occur. Intramedullary lesions are frequently located in the thoracic region. More than one site in the spinal cord may also be affected. One case with conus medullaris syndrome has been described. Non-osseous spinal cord tuberculomas may increase in size while the patient is on antituberculous therapy. MRI is the investigation of choice for these lesions.<sup>33–36</sup>

### Spinal tuberculous meningitis

A predominantly spinal form of tuberculous meningitis may result from rupture of Rich's focus into the spinal arachnoid space rather than the basal meninges. The acute form presents with fever, headache, and radiating root pains, accompanied by myelopathy. The chronic form, usually localised to a few segments, presents with progressive spinal cord compression and may suggest a spinal cord tumour. The characteristic MRI features include CSF loculation and obliteration of the spinal subarachnoid space with loss of outline of spinal cord in the cervico-thoracic region and matting of nerve roots in the lumbar region. Spinal forms of tuberculous meningitis may be associated with syrinx formation.<sup>11 21 37</sup>

### Tuberculous arachnoiditis

Tuberculous arachnoiditis is a relatively common cause of myeloradiculopathy in countries endemic for tuberculosis. The inflammatory exudate surrounds, but does not infiltrate, the spinal cord and nerve roots. Frequently, there is vascular involvement with peri-arteritis and occlusion of small vessels. Neuronal structures are damaged by direct compression as well as by ischaemia. The changes of arachnoiditis may be focal, multifocal, or diffuse. In tuberculous arachnoiditis features of spinal cord or nerve root involvement may predominate but most often there is a mixed picture. Frequently, there is clinical evidence of multifocal radiculomyelopathy, but even when meningeal involvement is widespread, symptoms may arise from a single level. The hallmark of diagnosis is the characteristic myelographic picture, showing poor flow of contrast material with multiple irregular filling defects, cyst formation, and sometimes spinal block. Rarely, myelography may be normal. The CSF changes are those of a chronic meningitis, frequently CSF sugar concentration is normal. Occasionally lumbar tap may be dry. These patients need adequate antituberculous treatment for at least one year. The role of corticosteroids is uncertain, but there are several reports of apparently marked improvement following corticosteroid administration. If the patient does not respond to medical treatment, surgery may be required.<sup>37 38</sup>

### CNS tuberculosis in HIV infected persons

*Mycobacterium tuberculosis* and atypical tubercle bacilli *Mycobacterium avium intracellulare* infection have been described as uncommon CNS manifestations of

### Causes of paraplegia in CNS tuberculosis

- Pott's paraplegia
- non-osseous compressive myelopathies (tuberculoma): extradural, intradural, extramedullary, intramedullary
- transverse myelitis
- spinal meningitis
- spinal tuberculous abscess
- tuberculous arachnoiditis (myeloradiculopathy)
- syrinx formation

#### Box 5



**Figure 8** CT-myelogram showing extensive destruction of T9 vertebra, a paraspinal abscess producing spinal block



**Figure 9** Sagittal T1-weighted MRI of two patients showing vertebral collapse of C6 and 7 vertebra along with posterior wedging and paraspinal abscess compressing the spinal cord

AIDS. The clinical spectrum of CNS tuberculosis with HIV infection includes meningitis, cerebral abscesses and tuberculomas. CNS involvement occurs in 10–20% patients with AIDS-related tuberculosis, and in these patients mortality is high. HIV-infected intravenous drug abusers are, in particular, at high risk of developing focal CNS tuberculosis. Clinical features, including imaging characteristics, are similar to those seen in patients without HIV infection (box 6). In patients with *M avium intracellulare* infection, single or multiple mass lesions appear to be more than twice as common as meningitis. Every effort should be made to establish the correct diagnosis as most types of CNS tuberculosis in HIV-infected patients are responsive to treatment.<sup>28 39 40</sup>

### Treatment of CNS tuberculosis

In contrast to the rapid advances in the management of pulmonary tuberculosis, there have been only a few clinical studies in patients with CNS tuberculosis, including tuberculous meningitis. There is currently no general consensus about the form of chemotherapy or optimal duration of treatment.

#### PENETRATION OF ANTITUBERCULOUS DRUGS INTO CSF

There is some evidence that the majority of current antituberculous drugs penetrate into the CSF. In the presence of meningeal inflammation, the CSF concentrations of these drugs are at least equal to or higher than those in non-inflamed meninges; intrathecal administration of these drugs is therefore not indicated. Isoniazid diffuses readily into the CSF in the presence or absence of meningeal inflammation. The CSF concentrations obtained are approximately 20–90% of serum levels. Levels of isoniazid in the CSF are lower in fast acetylators of the drug. Rifampicin achieves high serum levels after oral administration, and CSF levels are approximately 20% of serum in the presence of meningeal inflammation. Little or no ethambutol is detectable in the CSF of persons with normal meninges, however, in patients with meningeal inflammation, the ethambutol level approaches 10–50% of serum levels. Similarly, streptomycin is not detectable in normal meninges, while in patients with meningitis CSF levels may reach up to 20% of serum concentrations. Pyrazinamide, ethionamide and cycloserine penetrate well into the CSF, both in patients with meningeal inflammation, and in those with normal meninges.<sup>41 42</sup>

#### TREATMENT REGIMENS

The Centres for Disease Control recommend<sup>43</sup> that treatment is started with isoniazid (10–20 mg/kg/day up to 300 mg), rifampicin (10–20 mg/kg/day, up to 600 mg/day) and pyrazinamide (15–30 mg/kg/day, up to 2 g a day). Patients should be monitored for hepatotoxicity from rifampicin which is seen in up to 20% of patients. Ethambutol or streptomycin may be added if the response is not satisfactory. The duration of therapy should be at least 6 months and in some instances up to 12 months treatment is required. The World Health Organization (WHO)<sup>44</sup> put CNS tuberculosis under TB treatment Category 1, and recommend initial phase therapy (for 2 months) with streptomycin, isoniazid, rifampicin and pyrazinamide, followed by a 7-month continuation phase with isoniazid and rifampicin. However, a number of other studies report varying experiences with short-course (6 months) treatment. As the emergence of neurological deficit has been seen in some of these studies, a minimum of 12 months of treatment would be worthwhile.<sup>10</sup> A similar drug regimen has been recommended for all forms of CNS tuberculosis. The optimal regimens for the treatment of CNS tuberculosis due to atypical mycobacteria in persons with HIV infection have not been finally established, although a four-drug regimen is needed to treat *M avium intracellulare* infection. Current recommendations include using azithromycin (500–100 mg/day) and clarithromycin (500 to 1000 mg/day) in combination with ethambutol (15 mg/kg/day) or clofazimine (100 mg/day). Alternative regimens include the use of ciprofloxacin and rifampicin. A significant increase in the frequency of adverse reactions to antituberculous therapy has been observed in patients with HIV infection.<sup>7 45 46</sup>

#### ROLE OF CORTICOSTEROIDS

One of the controversial aspects of treatment of tuberculous meningitis is the use of corticosteroids.<sup>47</sup> The response to steroids may be dramatic with rapid clearing of sensorium, regression of abnormalities of CSF, defervescence and relief of headache.<sup>7</sup> It was believed that corticosteroids had no place in the management of tuberculous meningitis because the drug did not alter the clinical outcome, however, more recent studies have shown that corticosteroids improved both survival rate and neurological outcome in patients with tuberculous meningitis.<sup>47–49</sup> Schoeman *et al* confirmed the useful role of corticosteroids in

**CNS tuberculosis in AIDS: features**

- CNS involvement in 10–20% of AIDS-related tuberculosis
- high mortality rate
- increased risk of tuberculous meningitis
- granulomas are less common than meningitis
- intravenous drugs abusers are at higher risk
- does not appear to alter the clinical course, response to therapy or prognosis
- infection with atypical mycobacteria is common

**Box 6****Indications for corticosteroids in tuberculous meningitis**

- altered sensorium
- focal neurological deficit
- spinal fluid pressure in excess of 300 mmH<sub>2</sub>O
- spinal block (CSF protein > 400 mg/dl)
- presence of tuberculomas
- basilar exudates

**Box 7****MRC staging of tuberculous meningitis<sup>53</sup>**

Stage I: prodromal phase with no definite neurological symptoms  
 Stage II: signs of meningeal irritation with slight or no clouding of sensorium and minor (cranial nerve palsies), or no neurological deficit  
 Stage III: severe clouding of sensorium, convulsions, focal neurological deficit and involuntary movements

**Box 8****Worst prognostic factors for tuberculous meningitis**

*Most important*  
 Stage III (mortality 50–70%)

*Others*

- extreme of ages
- malnutrition
- presence of miliary disease
- presence of underlying debilitating disease, eg, alcoholism
- hydrocephalus
- focal neurological deficit
- low CSF glucose levels
- markedly elevated CSF protein

**Box 9**

young children. They observed that, in addition to survival, corticosteroids significantly improved intellectual outcome and enhanced resolution of the basal exudates and intracranial tuberculoma were shown by serial CT scanning. Prednisolone treatment (60 mg/day in adults and 1–3 mg/kg/day in children) is suggested in patients with tuberculous meningitis with one or more of the indications listed in box 7. The dosage may be reduced by 50% in the second and third week and then be tapered gradually over the next 4 weeks. There is no need for intrathecal corticosteroids.<sup>47</sup> The main argument against using corticosteroids is that they decrease meningeal inflammation and, in turn, can affect CSF penetration of antituberculous drugs. In a clinical trial<sup>50</sup> in which eight patients were treated with isoniazid, rifampicin, streptomycin and pyrazinamide, in combination with corticosteroids (dexamethasone, 5 mg intravenously hourly during the first week, followed by oral prednisolone, 60 mg daily), the use of corticosteroids did not reduce the CSF concentration of any of the antituberculous drugs.<sup>48</sup>

**PARADOXICAL WORSENING**

It has been observed frequently that intracranial tuberculomas appear or paradoxically increase in size while patients are being treated for tuberculous meningitis. These lesions are usually discovered accidentally when follow-up CT scan is performed routinely or when new neurological signs develop during the course of antituberculous therapy.<sup>51 52</sup> A recent study<sup>48</sup> noted that about 8% of patients developed asymptomatic tuberculoma during the first month of treatment. Concomitant steroid therapy probably has a preventive role against these focal lesions. Paradoxical enlargement has also been observed in isolated intracranial tuberculoma while the patient was on antituberculous therapy. However, with continued treatment, eventual resolution of these tuberculoma occurs.<sup>51 52</sup>

**SURGERY**

Surgical procedures in patients with tuberculous meningitis are primarily directed to the treatment of hydrocephalus.<sup>47</sup> Serial lumbar punctures, together with diuretics and osmotic agents are useful as a temporary measure to relieve elevated intracranial pressure, thus probably preventing the progression of hydrocephalus. If these temporary steps fail, ventriculo-peritoneal or ventriculo-atrial shunting may relieve the signs and symptoms of hydrocephalus, and may bring considerable improvement in sensorium and neurological deficit. Shunts in these individuals may require revision because the high protein content of CSF causes blockage. As it is generally agreed that shunts can safely be inserted even in the presence of active disease, early shunting with drug therapy may offer the best therapeutic outcome.<sup>7 12</sup>

Intracranial tuberculomas that act as single space-occupying lesions with midline shifts and increased intracranial pressure, and that fail to respond to chemotherapy should be surgically removed. If the tuberculoma is totally removed, about 80% of patients will enjoy long-term recovery, particularly if they were treated in the early stage of the disease.<sup>25 26</sup>

**PROGNOSIS AND SEQUELAE**

The single most important determinant of outcome, for both survival and sequelae, is the stage of tuberculous meningitis<sup>47 53</sup> at which treatment has been started (box 8). If treatment is started in stage I, mortality and morbidity is very low, while in stage III almost 50% of patients die, and those who recover may have some form of neurological deficit (box 9).<sup>47</sup> About 20% to 30% of survivors manifest a variety of neurological sequelae, the most important of which are mental retardation, psychiatric disorders, seizures, blindness, deafness, ophthalmoplegia and hemiparesis. Endocrinopathies may become evident months or year after recovery. The endocrinopathies are most probably due to progressive damage of either the hypothalamus itself or adjacent basal cisterns. Obesity, hypogonadism, Frolich syndrome, sexual precocity, diabetes insipidus, and growth retardation have been reported. Intracranial calcification develops in 20% to 48% of patients with tuberculous meningitis, usually becoming detectable 2 to 3 years after the onset of the disease.<sup>5 54</sup>

**Conclusion**

The varied manifestations of CNS tuberculosis, a common neurological disorder in developing countries, have now become relevant for other parts of the world, as the whole spectrum of these disorders is now being reported worldwide. The increasing problem of drug resistance has added a new challenge. The early recognition and timely treatment of the disease is critical if the considerable mortality and morbidity associated with the condition is to be prevented.

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