

REVIEW

Spinal cord involvement in tuberculous meningitis

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Objectives: To summarize the incidence and spectrum of spinal cord-related complications in patients of tuberculous meningitis.

Setting: Reports from multiple countries were included.

Methods: An extensive review of the literature, published in English, was carried out using Scopus, PubMed and Google Scholar databases.

Results: Tuberculous meningitis frequently affects the spinal cord and nerve roots. Initial evidence of spinal cord involvement came from post-mortem examination. Subsequent advancement in neuroimaging like conventional lumbar myelography, computed tomographic myelography and gadolinium-enhanced magnetic resonance-myelography have contributed immensely. Spinal involvement manifests in several forms, like tuberculous radiculomyelitis, spinal tuberculoma, myelitis, syringomyelia, vertebral tuberculosis and very rarely spinal tuberculous abscess. Frequently, tuberculous spinal arachnoiditis develops paradoxically. Infrequently, spinal cord involvement may even be asymptomatic. Spinal cord and spinal nerve involvement is demonstrated by diffuse enhancement of cord parenchyma, nerve roots and meninges on contrast-enhanced magnetic resonance imaging. High cerebrospinal fluid protein content is often a risk factor for arachnoiditis. The most important differential diagnosis of tuberculous arachnoiditis is meningeal carcinomatosis. Anti-tuberculosis therapy is the main stay of treatment for tuberculous meningitis. Higher doses of corticosteroids have been found effective. Surgery should be considered only when pathological confirmation is needed or there is significant spinal cord compression. The outcome in these patients has been unpredictable. Some reports observed excellent recovery and some reported unfavorable outcomes after surgical decompression and debridement.

Conclusions: Tuberculous meningitis is frequently associated with disabling spinal cord and radicular complications. Available treatment options are far from satisfactory.

Spinal Cord (2015) **53**, 649–657; doi:10.1038/sc.2015.58; published online 21 April 2015

INTRODUCTION

The spinal cord extends from the base of the skull up to the lower margin of the first lumbar vertebral body and consists of four major regions: the cervical, thoracic, lumbar and sacral. The spinal cord consists of 31 spinal cord segments. Each segment gives rise to a pair (ventral or anterior and dorsal or posterior) of spinal nerve roots. The ventral and dorsal nerve roots combine on each side to form the spinal nerves. The spinal nerves exit from the vertebral column through the neural foramina. Below the first lumbar vertebra, the spinal canal contains the lumbar, sacral and coccygeal spinal nerve roots that comprise the cauda equina. Tuberculous meningitis can affect each and every component of the spinal cord, but most predominantly it affects the spinal meninges and emerging nerve roots (Table 1).

Initial evidence of spinal cord involvement in tuberculous meningitis came from post-mortem examination. Subsequently, neuroimaging methods like conventional lumbar myelography, computed tomographic myelography and gadolinium-enhanced magnetic resonance-myelography contributed immensely. Most of the available information about spinal cord involvement in tuberculous meningitis is either in the form of isolated case reports or small case series.

Sir Victor Horsley, in 1909, first described arachnoiditis as 'chronic spinal meningitis'.¹ Later Cameron,² in 1919, provided early description of myelopathy with spinal subarachnoid obstruction secondary to

tuberculous arachnoiditis. He described a young girl who presented with acute weakness of the right lower limb. There was reflex asymmetry. Later child had florid manifestation of tuberculous meningitis. On post-mortem examination, authors noticed pathological findings suggestive of lumbar arachnoiditis—'there were giant-cell systems and foci of caseation among the issuing nerve roots of the lumbar enlargement'. Initially, this girl was considered to have poliomyelitis.² In 1947, Ransome and Montiero described four unusual cases of tuberculous meningitis encountered between 1938 and 1942. These four cases were dominated by lower motor neuron-type spinal cord manifestations. Cerebrospinal fluid (CSF) showed markedly raised protein and cells. After post-mortem, the description they provided was as follows—'It looked as if a yellow jelly had been poured into the subarachnoid space and had been allowed to set, but that this had been incomplete in the lower cervical areas. A few tubercles could be found in the meninges of the cord. The brain showed typical small tubercles in the arachnoid, in which acid-fast bacilli were demonstrated'.³

For this review, we have collected all available information on various aspects of spinal cord involvement in tuberculous meningitis. An extensive review of the literature, published in English, was carried out using the Scopus, PubMed and Google Scholar databases. The search terms included spinal cord and tuberculosis, spinal cord and

Table 1 Spectrum of spinal cord involvement in tuberculous meningitis

Early or initial
Paradoxical
Late or remote
<i>Vertebral</i>
Potts' spine (spondylitis) and Potts' paraplegia
<i>Spinal</i>
Tuberculous arachnoiditis (myeloradiculopathy)
Intradural, extramedullary tuberculoma
Intramedullary tuberculoma
Spinal tuberculous abscess
Acute myelitis
Longitudinal extensive transverse myelitis
Syringomyelia
Conus medullaris and cauda equina syndrome

tuberculous meningitis, spinal cord and meningeal tuberculosis, spinal cord and tuberculoma, tuberculous arachnoiditis and tuberculous myeloradiculopathy. Instances of extradural involvement (vertebral tuberculosis) were not included for the purpose of review. A total of 1078 articles/ reports published between 1947 and 2015 were short-listed for manual assortment. For the purpose of analysis, 70 publications were eventually utilized after assessment for relevance and completeness of information. (Supplementary file) Besides highlighting the number of patients affected by a specific complication, numbers of instances have been incorporated in view of co-occurrence of more than one complication in a single patient.

EPIDEMIOLOGY

According to a World Health Organization estimate, in 2013, among 5.4 million new cases notified in various National Tuberculosis Control programmes, 0.8 million patients had extrapulmonary tuberculosis including meningeal tuberculosis.⁴ In the European Union/European Economic Area, during the period from 2002 to 2011, 868 726 tuberculosis cases were reported and 167 652 (19.3%) had extrapulmonary tuberculosis. Meningeal tuberculosis was present in 5.8% of the pediatric cases, compared with 2.9% for all the other age groups combined.⁵ Of the 46 349 tuberculosis patients in the tuberculosis surveillance data from Germany between 2002 and 2009, 422 (0.9%) patients had meningitis.⁶ In USA, among 253,299 cases, 18.7% were extrapulmonary tuberculosis, including meningeal tuberculosis in 5.4% of patients.⁷ A study from New Zealand reported an incidence of myeloradiculopathy 3% among 104 patients with tuberculous meningitis.⁸ In a pediatric retrospective study with 554 patients, authors reported the presence of quadriparesis in 138 (24.9%) patients. However, exact figures about definite spinal cord involvement were not provided.⁹ In a recent study that included 55 HIV-positive patients of acute myelopathy or the cauda equina syndrome of tuberculous etiology (all adults), 9 patients had proven tuberculous meningitis. In four patients, tuberculous meningitis had been diagnosed prior to occurrence of spinal symptoms and they had concomitant intracranial imaging abnormalities as well.¹⁰

PATHOGENESIS AND PATHOLOGY

Tuberculous meningitis is caused by *Mycobacterium tuberculosis*. Tuberculous bacilli spread via blood to the meninges and brain

parenchyma from a primary site of infection (usually lung). Following bacteraemia, small tuberculous granulomas (Rich's focus) are formed in the subpial and subependymal surface of the brain and in the meninges. Later, rupture of one or more of these small tuberculous lesions releases the tuberculous bacilli in CSF spaces producing tuberculous meningitis.¹¹ Hallmark feature of tuberculous meningitis is the formation of thick gelatinous exudates. Exudates are relatively more copious in the basal regions of the brain. Other characteristic pathological changes are meningeal inflammation, vasculitis of the arteries of circle of Willis while traversing the basilar exudates and obstruction of the flow of cerebrospinal fluid resulting in hydrocephalus.^{12,13} Multiple small intracranial and spinal tuberculoma are frequent when tuberculous meningitis is part of the miliary tuberculosis.

In tuberculous meningitis, thick inflammatory exudates surround the spinal cord as well and produce a variety of spinal complications, like tuberculous radiculomyelitis, spinal tuberculoma, myelitis, syringomyelia, vertebral tuberculosis and very rarely spinal tuberculous abscess. Tuberculous arachnoiditis leading to myeloradiculopathy is the most characteristic spinal complication of tuberculous meningitis. Three different mechanisms had been suggested for the pathogenesis of the spinal cord involvement in tuberculous meningitis. Rupture of a tuberculous lesion present in the spinal meninges (during initial hematogenous spread) may produce local inflammatory changes, formation of exudates and subsequent tuberculous spinal arachnoiditis. Downward extension of intracranial exudates to spinal subarachnoid space may, alternatively, produce tuberculous spinal arachnoiditis. Finally, extension of spinal tuberculosis (from adjacent vertebrae disease to meninges) is a less likely mechanism. In patients with spinal tuberculous meningitis, the subarachnoid space between the spinal dura mater and the leptomeninges is usually filled with thick gelatinous exudate. In fact, there is partial or complete encasement of the spinal cord and emerging nerve roots. Exudate extends over several spinal segments. The exudate is particularly prominent posteriorly, probably due to lying in the supine position for a prolonged period. The nerve roots and spinal cord segments are inflamed and edematous.¹⁴⁻¹⁶ Myelitis often indicates the presence of inflammation of the spinal cord and is characterized by the presence of focal collection of inflammatory cells with varying amount of demyelination, varying amount of axonal injury and astroglial and microglial activation in the spinal cord parenchyma. Spinal blood vessels may also be involved by the necrotizing granulomas or by an inflammatory vasculitic process. Tuberculous vasculitis leading to thrombosis of the spinal vessels results in spinal cord ischemia.¹⁷

In late stages, the exudate gets organized, leading to matting of nerve roots in the cauda equina region; in addition, the inflamed roots may get atrophied. This condition is termed as tuberculous adhesive arachnoiditis. The subarachnoid space may be irregularly obstructed with the formation of CSF loculations.¹⁴⁻¹⁶ Syrinx is frequently a late complication of tuberculous meningitis, and exact pathogenesis of syrinx formation is not known. Several mechanisms have been proposed. In one such hypothesis, syrinx is considered to develop following an obliterative endarteritis causing ischemic injury or softening of spinal cord leading to cavitation in spinal cord parenchyma. Alternatively, it has been suggested that focal meningeal and spinal parenchymal scarring may lead to obstruction of the CSF flow, thus pushing CSF into the central canal of the spinal cord through Virchow-Robin spaces. Dilated perivascular Virchow-Robin spaces may, in fact, coalesce to form a syrinx in the spinal cord.^{18,19}

Classical histopathological feature of tuberculous meningitis is the formation of epithelioid cell granulomas consisting of Langhans giant cells, lymphocytic infiltrates and caseous necrosis.

CLINICAL FEATURES

A total of 147 patients with various complications associated with tuberculous meningitis have been reported. Among these, there were 181 instances of different forms in decreasing the order of occurrence—tuberculous radiculomyelopathy (38.7%), extramedullary-intradural tuberculoma (19.9%), syringomyelia (14.9%), intramedullary tuberculoma (9.4%), tuberculous myelitis (8.84%), tuberculous abscess (7.2%) and infarct (1.1%). The male-to-female ratio was 1.14 in favor of males. The age range for males was 0.5 to 61 years (mean: 28.6 years; median: 28.5 years), whereas that for females was 6 to 73 years (mean: 30.3 years; median: 28 years). Even though 17.1% patients with tuberculous meningitis had a concomitant complication, the median time for the development of any one of the complications was 3 months.

TUBERCULOUS RADICULOMYELOPATHY

Tuberculous radiculomyelopathy is the most common complication (38.7%) associated with tuberculous meningitis. Females are slightly more involved than males (females: males = 1.3), and their median age of presentation is 27 years and 28 years, respectively. It is characterized by subacute areflexic paraparesis, root pain, paraesthesias, bladder disturbance and muscle wasting. Paraparesis is the most frequent manifestation observed in 58.8% patients. In the lower limbs, there is hypotonia, and deep tendon reflexes are usually absent. There may be extensor plantar response. Tuberculous exudates present around the lumbosacral segments of spinal cord and lumbosacral nerve roots cause a picture similar to that of the cauda equina syndrome (Figure 1). The Cauda equina syndrome is clinically characterized by bladder disturbances, saddle shaped anesthesia and asymmetric paraplegia. Conus lesion, a lesion at the lower end of the spinal cord, can produce a mixture of upper and lower motor neuron signs in the legs, typically absent ankle reflexes (due to damage to the reflex arc) with extensor plantar responses (due to damage to the corticospinal tract). Weakness in the lower limbs is mild or absent, but there is profound sphincter disturbance and saddle anesthesia. In a study of 51 patients, bladder disturbances were present in one-third. Seven (28%) patients paradoxically developed new bladder abnormalities during follow-up. Majority of these patients had lumbosacral arachnoiditis.^{20–22}

Infrequently, spinal arachnoiditis may even be asymptomatic. In a study that included 16 patients with tuberculous meningitis of <1 month duration, spinal magnetic resonance imaging (MRI) revealed evidence of spinal arachnoiditis in 3 patients. High cerebrospinal fluid protein was a risk factor for development of spinal arachnoiditis.²³

Tuberculous radiculomyelopathy may evolve several years after the initial manifestation of tuberculous meningitis. It may be concomitant at the time of diagnosis or may appear as late as 30 years after tuberculous meningitis. As an associated manifestation or sequelae, syringomyelia may be present in ~22% patients and evidence of myelitis in about 13% patients with radiculomyelopathy. Kozłowski described two cases of adhesive arachnoiditis developing 7 and 9 years after tuberculous meningitis.²⁴ In a series by Chang *et al.*,²⁵ spinal manifestations were seen after a lapse of 14 and 17 years after occurrence of tuberculous meningitis.

TUBERCULOUS MYELITIS

Both acute transverse myelitis and longitudinal extensive transverse myelitis have been described in patients with tuberculous meningitis. These have been reported in 8.84% patients with an equal incidence in males (median age: 31 years), as well as females (median age: 27.5 years). Acute transverse myelitis is an acute inflammatory process that is characterized by a segmental inflammation manifesting as functional transection of the cord with motor, sensory and bladder dysfunction below the level of the lesion. Longitudinal extensive transverse myelitis is a condition that is characterised by a myelitis extending over three or more spinal segments. Tuberculous myelitis is usually associated with tuberculous intracranial involvement of the meninges or brain parenchyma or with tuberculous arachnoiditis of the spine (Figure 2). In majority (>80%) of patients, tuberculous myelitis affects more than one spinal segment, most commonly affected areas being the thoracic (62.5–81.3%) and cervical region (12.5%). Occasionally, imaging changes myelitis may affect the entire length of the spinal cord. More than half (56.3%) of the patients with myelitis show at least some evidence of arachnoiditis in their imaging studies. This much of extensive involvement is usually rare and associated with greater morbidity. An abnormal immune reaction against mycobacterial antigen is thought to be the main pathogenic mechanism.^{26,27}

SPINAL TUBERCULOMA

Other possible causes of paraplegia and quadriplegia in patients with tuberculous meningitis are extramedullary or intramedullary spinal cord tuberculoma. Intradural extramedullary tuberculous spinal granulomas without bony involvement and intramedullary spinal tuberculoma are, infrequently, a paradoxical manifestation of tuberculous meningitis. Intradural extramedullary tuberculomas have been reported with a higher frequency than intramedullary tuberculomas, 19.9% versus 9.4%, respectively. For undefined reasons, males outnumber females (3.25:1) in tuberculomas at intramedullary locations; they, however, occur at an equal frequency at intradural extramedullary location. The commonest presenting manifestations of spinal tuberculoma include progressive paraplegia, sensory deficits and bowel and bladder dysfunction. The majority of these lesions are localized to thoracic region (almost 50%), followed by cervical and lumbar regions. These tuberculomas may be observed at the time of presentation in approximately 18% patients with tuberculous meningitis but are usually evident at least 15 days (up to 2 years) from the time of diagnosis. In some cases intramedullary tuberculomas of the conus medullaris have also been reported; these patients present as the cauda equina syndrome.^{28–30}

SPINAL TUBERCULOUS ABSCESS

Spinal tuberculous abscess is a rare complication of tuberculous meningitis observed in 7.2% patients with tuberculous meningitis. Although a concomitant instance of abscess has been reported, it usually appears around a median period of 30 days. Following the trend of myelitis and tuberculomas, abscesses have most often been reported in the thoracic region (53.9%). Spinal subdural empyema usually presents with fever, spinal or root pain and a neurological deficit. According to the criteria of Whitener, tuberculous abscesses show pathological evidence of abscess formation within the brain parenchyma and should have microbiological confirmation. The abscess wall consists of vascular granulation tissue containing both acute and chronic inflammatory cells and *Mycobacterium tuberculosis*. Spinal tuberculous abscess can also involve subarachnoid, subdural or epidural space as well.^{31,32} Because of a variable intensity such lesions may be very difficult to diagnose correctly in the first instance. In a report of three atypical cases with intradural spinal tuberculous,

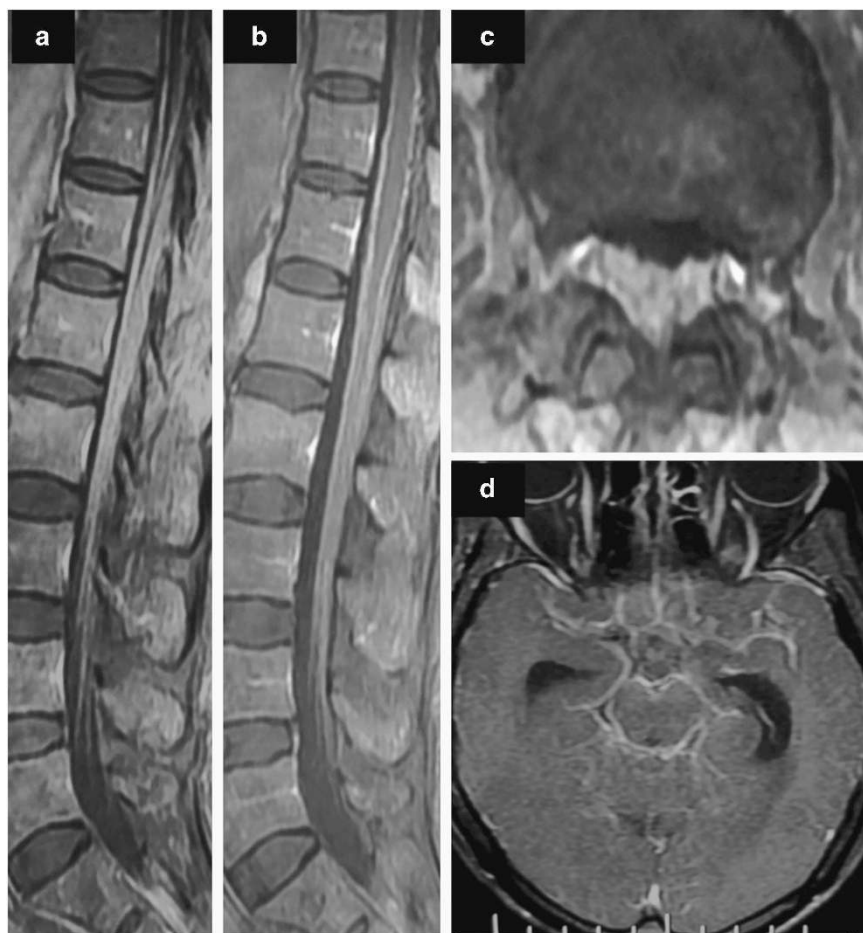


Figure 1 MRI of the spine of a 30-year-old gentleman depicts clumping of cauda equina nerve roots (sagittal T1-GAD, **a**); axial T1-GAD, **c**), along with leptomeningeal enhancement at the lower dorso-lumbar vertebral segments (sagittal T1-GAD, **b**). Basal exudates, as well as dilatation of the temporal horns, suggesting hydrocephalus, can be seen on MRI of the brain (axial T1-GAD, **d**).

histopathological confirmation of the diagnosis was warranted to aid definitive medical and surgical treatment. It was suggested that such masses may mimic neoplastic lesions and must be considered in the differential diagnosis of paraparesis for appropriate treatment.³³

SYRINGOMYELIA

Syringomyelia is usually a late complication of tuberculous meningitis observed in approximately 15% patients. Syrinx formation, usually, takes several years after patient has recovered from tuberculous meningitis. In several reports, syringomyelia had paradoxically and acutely developed when the patient was still receiving antituberculosis therapy.³⁴ Daif and co-workers reported two patients with tuberculosis meningitis who developed syringomyelia acutely. In these two patients, syringomyelia developed between 11 days and 6 weeks after tuberculous meningitis was diagnosed. Syringomyelia clinically manifests with progressive spastic paraparesis, often, with urinary disturbances.³⁵ The maximum reported duration between the diagnosis of tuberculous meningitis and that of syringomyelia is 30 years. The most common accompaniment of syringomyelia is tuberculous radiculomyelopathy that may be observed in about 55% patients.

VASCULITIS/INFARCT

Two females (14 and 73 years) with tuberculous meningitis have also been reported who developed infarcts in the spinal cord. The younger

patient had evidence of tuberculous radiculomyelopathy, as well as intradural extramedullary tuberculoma in the thoracic region, whereas the older one was diagnosed with an abscess. The latter patient succumbed after having subjected to surgical decompression of the cord.

INTRADURAL ARACHNOID CYST

Secondary intradural arachnoid cyst involving the spine is uncommon. Spinal intradural arachnoid cyst is usually secondary to trauma, hemorrhage, surgery or inflammation. Lolge *et al.*³⁶ reported two cases of treated tuberculous meningitis, both presented with gradual onset of quadriplegia and paraplegia, respectively, and MRI revealed intradural (cervical and thoracic) arachnoid cysts (ventral and dorsal to the spinal cord) with myelomalacic cord changes.

VERTEBRAL TUBERCULOSIS

The most common cause of myelopathy in patients with tuberculosis is vertebral body infection or Pott's disease. Spreading through the vertebral venous system, it involves predominantly anterior segments of thoracic and lumbar spine, leading to collapse of these vertebral bodies with secondary spinal root and cord injury. Most patients with vertebral involvement present with back pain, leg weakness and a gibbus deformity. Infection often starts in the anterior-inferior aspect of a vertebral body, spreads below the anterior longitudinal ligament



Figure 2 MRI of the spine of a 46-year-old gentleman, who presented with flaccid paraparesis, depicts clumping of cauda equina nerve roots (sagittal T1-GAD, **a**; axial T1-GAD, **c**) and hyperintense signals involving D4 to D6 dorsal cord segments (sagittal, T2-weighted, **b**). Multiple tuberculomas were noted on MRI of the brain (axial T1-GAD, **d**).

and can lead to disease in adjacent vertebral bodies. The lower thoracic and upper lumbar vertebrae are most often affected in spinal tuberculosis. Moreover, a vertebral abscess can spread along the psoas muscle causing retroperitoneal masses. The characteristic imaging features are destruction of the vertebral end plates and vertebral bodies, evidence of new bone formation and soft tissue abscess (Figure 3).³⁷

HIV INFECTION

HIV-infected patients are more likely to have disseminated tuberculosis and spinal cord involvement. The age of presentation (mean: 30 years; median: 27 years), time to development of complications, and outcome are apparently at par with the immunocompetent hosts. Many spinal complications like tuberculoma, arachnoiditis and epidural abscess can also be manifestations of the paradoxical tuberculosis-immune reconstitution inflammatory syndrome.³⁸ In a report of 190 patients with a diagnosis of the paradoxical tuberculosis-immune reconstitution inflammatory syndrome, 23 patients had the neurologic tuberculosis-immune reconstitution inflammatory syndrome: among these 3 had radiculomyelopathy. In another report, out of the 34 patients with tuberculous meningitis, 16 patients (47%) developed the tuberculous meningitis-immune reconstitution inflammatory syndrome and 3 patients had paraparesis. Magnetic resonance imaging of the spine was performed in two patients with paraparesis; both had features of radiculomyelitis.³⁹ Patients presenting with the

tuberculous meningitis-immune reconstitution inflammatory syndrome may have either polymorph or lymphocyte predominance in the CSF, and some patients have a very high CSF protein.⁴⁰

DISSEMINATED TUBERCULOSIS AND MILIARY TUBERCULOSIS

Tuberculous meningitis and spinal cord tuberculosis are often part of disseminated tuberculosis and miliary tuberculosis. For example, Shen *et al.*⁴¹ described a 30-year-old man with miliary tuberculosis of the lung. Patient had paraplegia due to tuberculomas in the thoracic spinal cord. In addition, MRI showed more tuberculomas in the cervical spinal cord, brain stem and cerebral and cerebellar hemispheres.⁴¹ Disseminated tuberculosis is defined as tuberculous involvement of more than two non-contiguous body structures. Disseminated tuberculosis is caused by widespread hematogenous dissemination of tubercle bacilli from an active caseous focus. Disseminated tuberculosis occurs frequently in HIV-infected patients with low CD4 counts and has a very high mortality rate.

Miliary tuberculosis is defined as a hematogenous spread of the tuberculous bacilli resulting in widespread caseous tubercle formations with bilateral diffuse millet-sized pulmonary nodules. Spinal cord may also be affected during miliary spread of mycobacteria. In this study, Garg and co-workers evaluated 60 consecutive miliary tuberculosis patients, who presented with neurological manifestations. In two patients, neuroimaging revealed a spinal tuberculoma. Nine (15%)

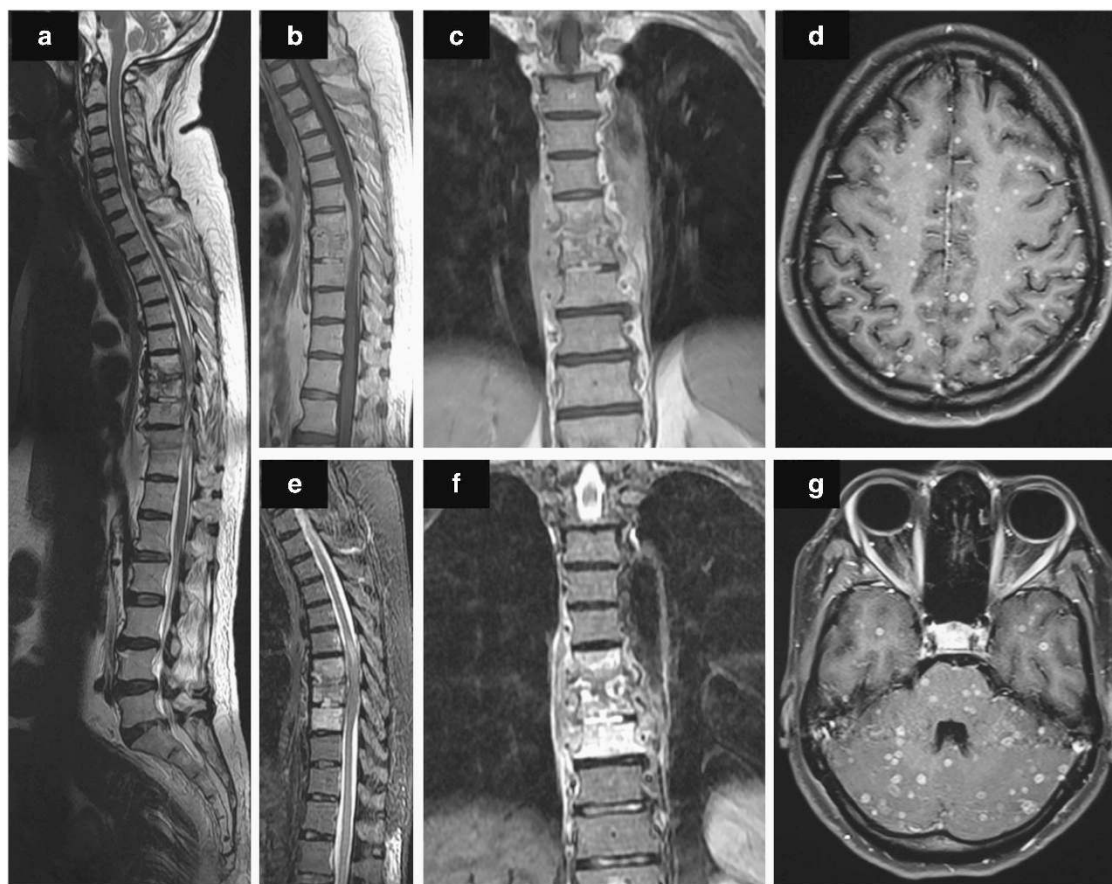


Figure 3 MRI of the spine of a 18-year-old boy depicts involvement of the D7 to D9 vertebrae, leading to paradiscal affliction with disk space reduction (Sagittal T2-weighted, **a**; Sagittal T1-GAD, **b**; Sagittal T2-weighted, **e**), and paraspinal abscess formation (Coronal T1-GAD, **c**; Coronal T2-weighted, **f**). Miliary tubercles were noted on the MRI of the brain (Axial T1-GAD, **d** and **g**).

patients presented with myelopathy. Three patients demonstrated Pott's paraplegia. Three patients presented with transverse myelitis (with normal neuroimaging). In three patients, the spinal MRI showed an intramedullary tuberculoma. Miliary central nervous system tuberculosis may remain asymptomatic but magnetic resonance evaluation shows numerous enhancing foci both in the brain and spinal cord (Figure 3).⁴²

MULTIDRUG-RESISTANT TUBERCULOUS MENINGITIS

Multidrug-resistant tuberculous meningitis is often associated with a high morbidity and mortality. The pathology, clinical features and the imaging appearances characteristics of drug-resistant tuberculous meningitis are the same as those of drug-responsive tuberculous meningitis.⁴³ Spinal cord involvement in the form of arachnoiditis and spinal tuberculoma are frequently part of florid extensive clinical manifestations.^{44–46}

PARADOXICAL SPINAL MANIFESTATIONS

In a patient with tuberculous meningitis spinal cord and radicular complications may occur paradoxically. Paradoxical reaction is defined as clinical worsening and/ or appearance of new lesions in computed tomography and MRI images of the brain and/ or spinal cord while the patient is receiving effective treatment of tuberculosis. Usually, paradoxical response and associated clinical deterioration occur several weeks after starting antituberculous therapy. Even though very few reports of paradoxical reaction in the spinal cord are available, it may

be interesting to note that the median period reported for the occurrence of paradoxical reaction (3 months) is exactly same as for the development of spinal cord complications in patients with tuberculous meningitis. This gives us the food for thought that these reactions are probably interlinked and not independent processes. Paradoxical response is thought to represent an exaggerated cell-mediated immune response against mycobacterial antigens. Possibly, a massive release of mycobacterial proteins into the core of tuberculoma and subarachnoid space leads to intense inflammation and expansion of existing tuberculous lesions. Many immuno-modulatory drugs, like tumor necrosis factor- α antagonists, thalidomide and interferon- γ , have been used in isolated cases with more severe forms of intracranial paradoxical reactions with varying success. Role of immuno-modulatory drugs in spinal paradoxical reaction is not known.^{47–50}

DIAGNOSIS

CSF examination is essential for the exact diagnosis of tuberculous meningitis. Typical CSF changes include lymphocytic pleocytosis, decreased glucose levels and elevated protein levels. The 'gold standard' for diagnosis confirmation is demonstration of *Mycobacterium tuberculosis* in the CSF. Bacteriological confirmation is performed either by smear examination after Ziehl-Neelsen staining or culture. In patients with arachnoiditis presenting with myeloradiculopathy, CSF examination often reveals a very high protein content (probably as a consequence of spinal block).⁵¹

Neuroimaging characteristics of tuberculous meningitis are leptomeningeal enhancement, hydrocephalus, infarcts and/ or tuberculoma. The basilar exudates, on imaging, manifest as intensely enhancing areas in the regions of basal cisterns and Sylvian fissure. Thick inflammatory exudates often obliterate the cisterns. Hydrocephalus, in course of illness, eventually develops in patients with tuberculous meningitis.

Magnetic resonance is an excellent imaging modality to evaluate spinal cord changes in tuberculous meningitis. The characteristic magnetic resonance changes indicative of spinal arachnoiditis include CSF loculations and obliteration of the spinal subarachnoid space, nodular, thick, linear, intradural enhancement and loss of outline of spinal cord in the cervico-thoracic region along with matting of nerve roots in the lumbar region.^{52–54} The myelitis is characterized by cord swelling with signal abnormalities. Tuberculous myelitis appears as hyperintense on T2, isointense to hypointense on T1-weighted images and shows segmental enhancement on post-contrast images.⁵⁵ Spinal tuberculomas are categorized as extradural, intramedullary or intradural extramedullary, according to their location. Tuberculomas show contrast-enhancing T1 hypointense rings with high T2 signal centrally. Contrast MRI reveals a ring-enhancing lesion with perifocal edema.⁵⁶ Extensive en plaque intradural extramedullary tuberculomas (along with multiple intracranial tuberculomas), as a manifestation paradoxical reaction, have been described in an unusual patient of tuberculous meningitis.⁵⁷ Tuberculous abscesses in comparison to tuberculoma are often of larger, thin walled, multiloculated and more frequently are single.⁵⁸ MRI in Pott disease reveals T1 hypointensity with T2 hyperintensity with contrast enhancement, progressing to vertebral body collapse and cord compression (Figure 1).

Chang and co-workers retrospectively studied myelograms, computed tomography myelograms and magnetic resonance images in 13 patients with spinal tuberculous radiculomyelitis. Eleven patients had intracranial tuberculous meningitis at the time of diagnosis or before. Conventional myelographic findings included a block of the CSF flow in the spinal cord (11/13), most commonly at the level of the conus medullaris. Almost all the patients had evidence of arachnoiditis. Two patients had intramedullary tuberculomas and one patient had cord infarction caused by vasculitis. In a more recent study, which included 51 patients of tuberculous meningitis and all were subjected to spinal MRI, 37 patients revealed spinal meningeal enhancement. Lumbosacral arachnoiditis was noted in 25, myelitis in 12 patients, CSF loculations in 6 and cord atrophy was seen in 5 patients.^{25,59}

In chronic adhesive arachnoiditis, the subarachnoid space is irregularly obstructed with formation of CSF loculations. The CSF loculations usually show normal CSF signal intensity on T1- and T2-weighted images and do not enhance on post-contrast images. CSF loculations may cause cord compression, necessitating surgical intervention. Late spinal cord changes include cord atrophy, syringomyelia, myelomalacia or spinal cavitation in the spinal cord. Syringomyelia, on MRI, presents as cord cavitation that typically demonstrates CSF intensity on T1- and T2-weighted images.⁵¹ Syrinx appears on imaging manifests with cord expansion with non-enhancing intramedullary fluid signal (isointense to CSF on both T1- and T2-weighted images) with or without loculations.

DIFFERENTIAL DIAGNOSIS

Myelitis and arachnoiditis can occur in many other central nervous system infections, as well as neoplastic, granulomatous, demyelinating and iatrogenic disorders. Tuberculous myeloradiculopathy is different from many other myeloradiculopathies as it frequently affects the

spinal cord, meninges and the nerve roots together along with intracranial manifestations.

The most important differential diagnosis of tuberculous arachnoiditis is meningeal carcinomatosis. Carcinomatous meningitis is defined as leptomeningeal infiltration by malignant cells. Carcinomatous meningitis is the result of seeding of the leptomeninges by malignant cells and is the most important differential diagnosis of spinal tuberculous arachnoiditis. Neoplastic meningitis is seen in approximately 5% of all patients with cancer. Tumor infiltration is most prominent at the base of the brain, on the dorsal surface of the spinal cord and, in particular, in the cauda equina. Patients with spinal neoplastic meningitis often present with areflexic paraparesis or quadriparesis. The presence of malignant cells in the CSF is diagnostic of neoplastic meningitis. Carcinomas of the breast and lung, melanoma, non-Hodgkin lymphoma and leukemia are the common causes of meningitis. Patients may present to an emergency department with cranial neuropathies, symptoms indicating involvement of cerebral hemispheres and symptoms of spinal cord or nerve root involvement.^{60–63}

However, the primary central nervous system lymphoma and toxoplasmosis are the most common space occupying lesions in the central nervous system in HIV-infected patients. Tuberculoma, which presents with mass lesion, is another differential diagnosis. All these lesions have also been described in spinal cord as well. Mohit and co-workers described a patient with a known HIV infection presenting with thoracic myelopathy who was initially diagnosed as having intramedullary primary central nervous system lymphoma after detection of Epstein–Barr virus DNA in the CSF. After failing to respond to radiotherapy, he underwent a spinal cord biopsy revealing intramedullary tuberculoma at T9.⁶⁴

TREATMENT

Anti-tuberculosis therapy is the main stay of treatment for tuberculous meningitis. The antituberculosis treatment needs to be continued for at least 9 to 12 months. Treatment is started with first-line antituberculous drugs, which include isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Tuberculous meningitis falls under category-1 of World Health Organization treatment category. For the patients of category-I, antituberculosis treatment regimen is divided into two phases: an intensive (initial) phase and a continuation phase. In intensive phase, antituberculous regimen include a combination of four first-line drugs: isoniazid, rifampicin, streptomycin and pyrazinamide. The intensive phase continues for 2 months. In continuation phase, a two drug regimen (isoniazid and rifampicin) is given for 7 or 10 months.⁶⁵

CORTICOSTEROIDS

In patients with tuberculous meningitis, corticosteroids should routinely be used. Corticosteroids significantly reduce death and disabling residual neurological deficit among survivors.⁶⁶ Previously, high-dose corticosteroids were reported effective in patients of tuberculous meningitis with spinal cord involvement. However, the precise role of corticosteroids in the treatment and prevention of spinal complications of tuberculous meningitis has not been addressed in the available literature. It would be worthwhile studying the same in a large multi-centric randomized controlled trial.

INTRATHECAL HYALURONIDASE

The enzyme hyaluronidase hydrolyzes the glucosaminidic bonds of hyaluronic acid and other degrades mucopolysaccharides of the intercellular ground substance of connective tissue. In earlier non-

randomized studies, its intrathecal use had been found beneficial in patients with tuberculous spinal arachnoiditis.⁶⁷ This form of treatment is no longer used and cannot be recommended.

SURGERY

In patients with intramedullary tuberculoma and intradural extramedullary tuberculoma surgical excision often results in remarkable improvement, 71.4% and 46.7%, respectively. Excellent results have also been observed in patients with tuberculous abscess where improvement has been observed in 81.8% patients. Even in cases with severe deficits, surgical intervention may be attempted for a good outcome.⁶⁸ In intramedullary tuberculoma, excision of lesion has been recommended if the patient deteriorates despite of medical treatment. In patients with tuberculous spinal arachnoiditis, surgical decompression is often indicated if arachnoiditis is localized or there is cord compression by a cyst. Surgery may also be carried out if pathological confirmation is required. Surgery is often unrewarding in patients with extensive chronic adhesive arachnoiditis. Decompressive laminectomy along with debridement is the most frequent surgical procedures employed in these patients. In patients with syringomyelia, and showing clinical deterioration, both syringo-subarachnoidostomy and syringo-peritoneal shunt have been attempted. It has been suggested that decent outcomes can be obtained with the syringo-peritoneal shunt procedure even in patients having a long-standing syrinx.⁶⁹

PROGNOSIS

The outcome of treatment in patients of tuberculous meningitis with spinal cord involvement is unpredictable. Some authors have reported excellent outcome, but of the reported instances improvement has been observed in 57.5% patients. In 14.2% patients sequelae developed, whereas no improvement/deterioration was noted in 10.6% patients; 17.6% patients die despite of the best available treatment option. Spinal cord atrophy, cavitation, multiple complications and formation of syringomyelia are often associated with poor outcome.

CONCLUSION

Spinal cord complications (myelopathy and radiculopathy) are an integral part of the symptom complex of tuberculous meningitis. Spinal cord complications frequently develop paradoxically. These complications, when ever present, adversely affect the prognosis. Disabilities are present even after otherwise successful antituberculous treatment and often severe in nature. Currently, no treatment option is available to prevent or treat them. Prevention of tuberculous meningitis and tuberculosis at large is the only option available.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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