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Myanmar Neurological Society

CNS Tuberculosis

1. Introduction
2. Pathogenesis
3. Different Clinical Presentation
4. Diagnosis
5. Treatment
6. Take home message

1. Introduction

- Tuberculosis remains a major global problem
- In recent times - a resurgence of tuberculosis in both developing and developed countries
- According to the WHO estimation, new TB cases are approximately 8.8 million every year until 2010, of which 1.45 million died
- CNS involvement – 5-10% of all extrapulmonary tuberculosis

Provoking factors for tuberculous infection

- Over-crowding in the urban population and insufficient areas of ventilation
- Poor nutritional status and unhygienic environment
- Increasing prevalence of HIV infection
- Appearance of drug-resistant strains of tuberculosis
- Anti-TB programme cannot cover effectively to the whole country

2. Pathogenesis

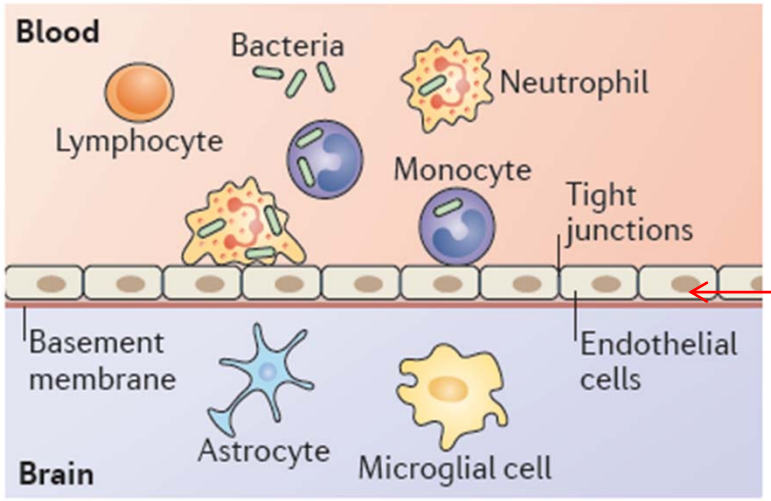
- *Mycobacterium tuberculosis*

- Transmission is airborne and, consequently, the first focus of infection is the lung

Following initial bacterial replication, the infection disseminates to the lymph nodes

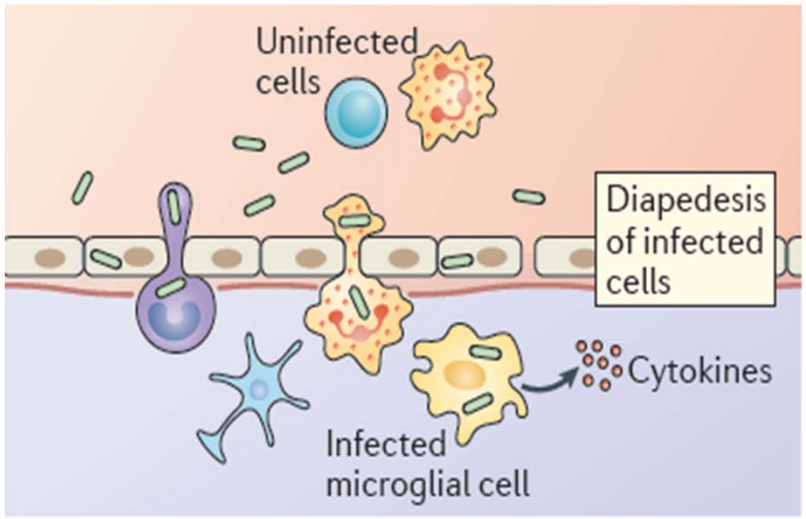
- Bacilli reach the CNS by the haematogenous route either via direct extension of local infection or via lymph nodes

- CNS tuberculosis develops in **two stages**
- First stage - small tuberculous lesions (Rich's foci) develop in the meninges, the subpial or subependymal surface of the brain or the spinal cord
- They remain dormant for years after initial infection
- Second stage - rupture or growth of one or more of these small tuberculous lesions (Rich foci)



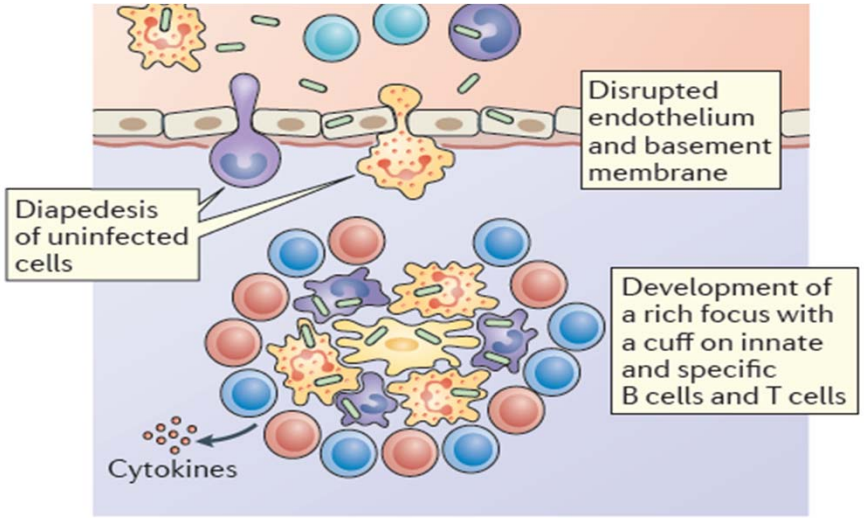
- Bacilli could reach brain blood capillaries within cells or as extracellular bacilli

(blood brain barrier)

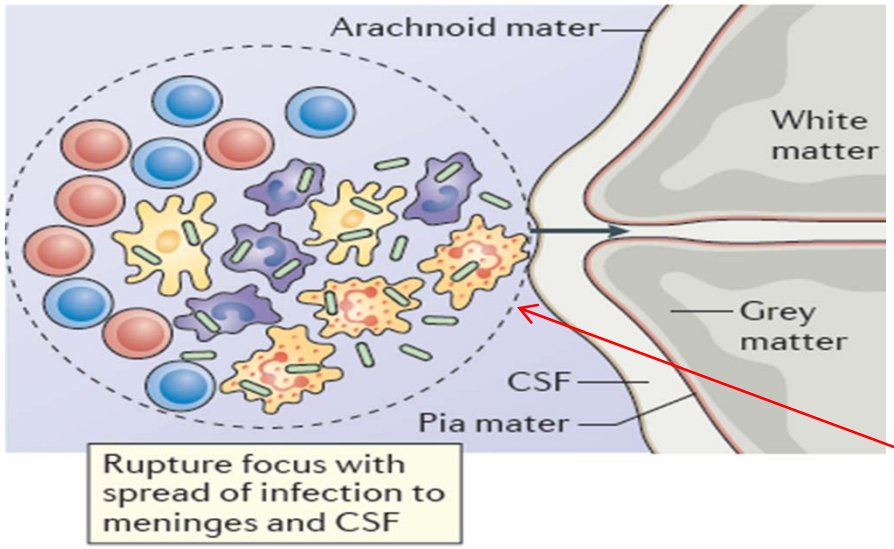


- The endothelium itself can be infected, or infected cells can adhere and undergo diapedesis (passage)
- Both processes result in breakdown of tight endothelial junctions and the basement membrane

Nature Review/Neurology



- Microglial cells can become infected, and these cells, together with infiltrating cells, produce inflammatory chemoattractants that result in further breakdown of the blood–brain barrier and influx of uninfected cells, including innate and specific T and B lymphocytes



- The formed granuloma might rupture via necrosis, leading to meningeal and intracerebral dissemination of infection

(granuloma)

Nature Review/Neurology

- Immunological mechanisms could play an important role for rupture or growth of Rich's foci

- Rupture into the subarachnoid space or into the ventricular system results in meningitis

- Type and extent of lesions depend upon the number and virulence of the bacilli, and the immune response of the host

3. Different Clinical Presentation

3.1. Intracranial

3.1.1. Tuberculous meningitis (TBM)

3.1.2. Tuberculous encephalitis and encephalopathy

3.1.3. Tuberculous vasculitis

3.1.4. Space-occupying lesions: tuberculoma (single or multiple)

3.1.5. Tuberculous brain abscess

3.1.1. Tuberculous meningitis (TBM)

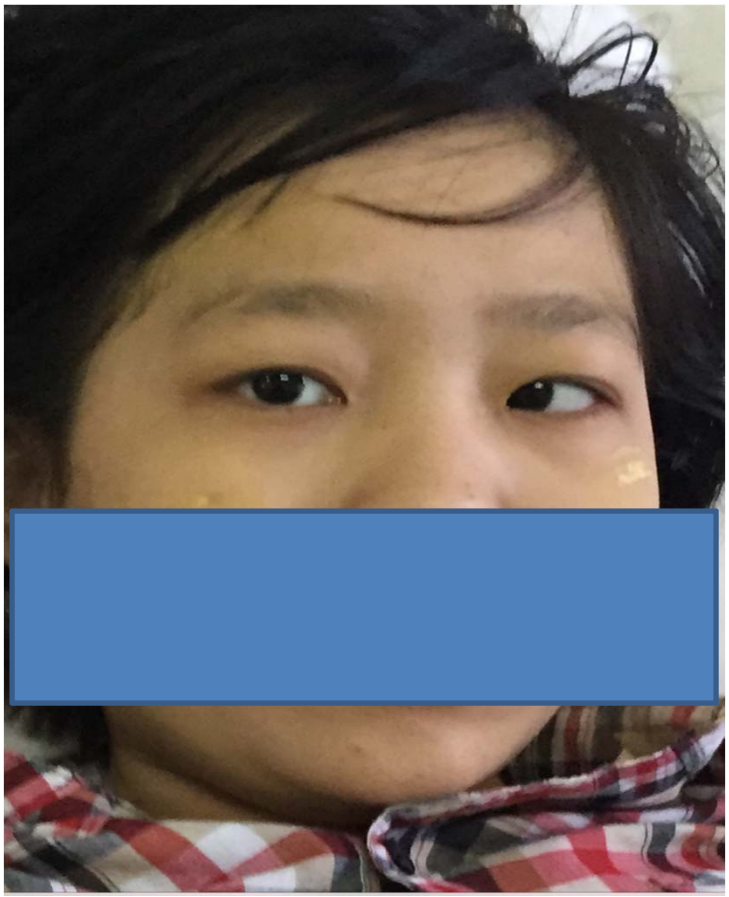
- Tuberculous infection of meninges which covers brain and spinal cord

Clinical features

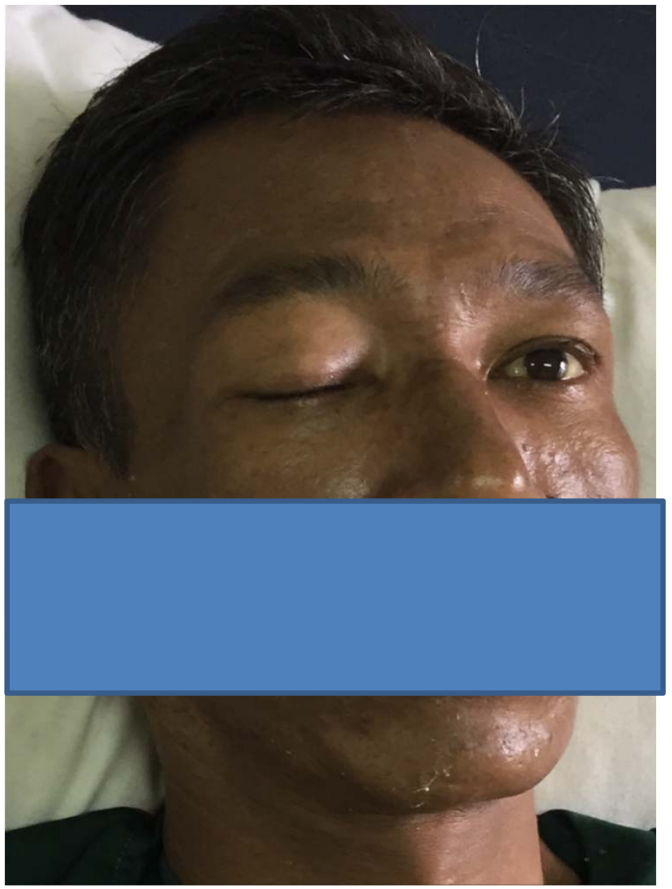
- Non-specific symptoms – malaise, anorexia, fatigue, fever, myalgia and headache occur 2–8 weeks prior to the development of meningeal irritation
- Neck stiffness - 25%
- Nausea, vomiting and altered sensorium may develop

- CRANIAL NERVE PALSY - in 20–30%
- May be the presenting manifestation because of basal meningitis
- Sixth cranial nerve - most commonly affected
- Vision loss due to optic nerve involvement may occasionally be a dominant and presenting illness
- Other cranial nerves III, IV, VII and VIII may be involved

Sixth cranial nerve palsy

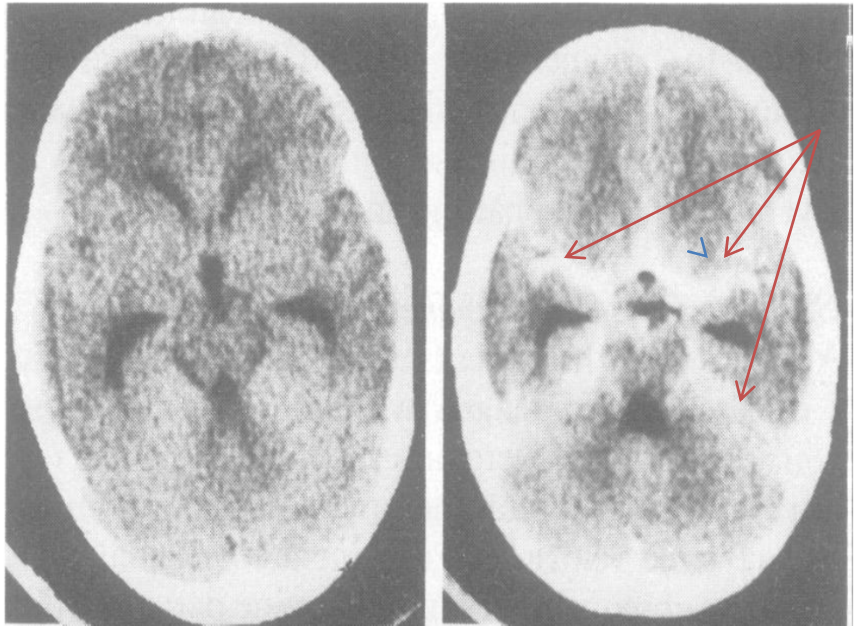


Third cranial nerve palsy



Basal Meningitis

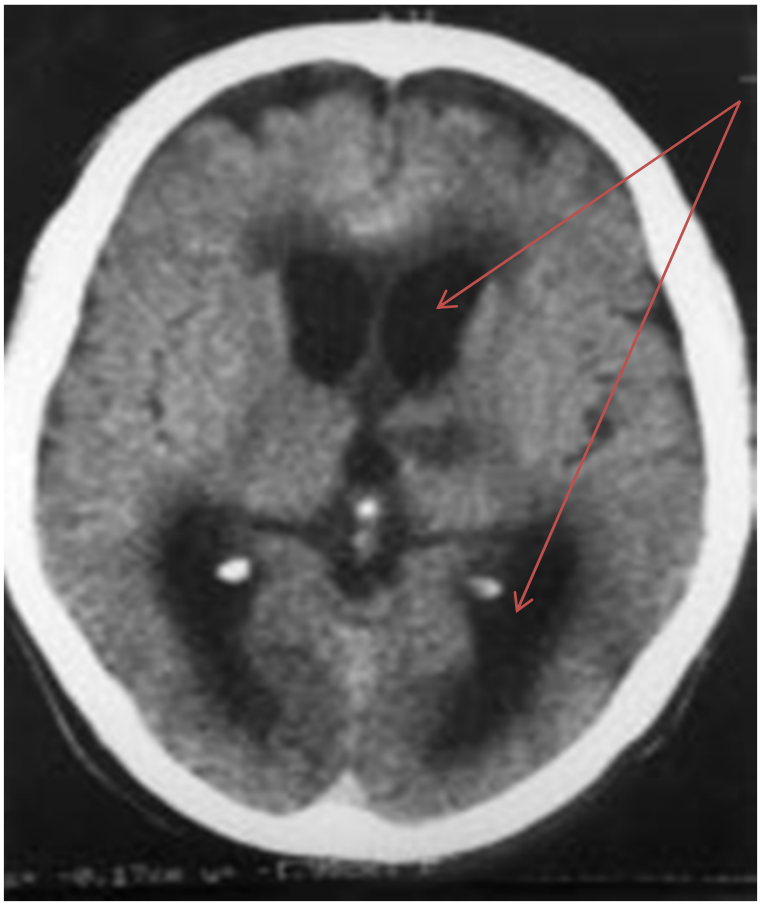
- A thick, gelatinous exudate around the sylvian fissures, basal cisterns, brainstem, and cerebellum



Plain CT scan and after contrast injection. There is diffuse enhancement of the basal meninges

Hydrocephalus

- Hydrocephalus may occur as a consequence of obstruction of the basal cisterns, outflow of the fourth ventricle, or occlusion of the cerebral aqueduct



CT (brain)

Medical Research Council tuberculous meningitis severity grade

In 1948, Medical Research Council investigators in the UK graded tuberculous meningitis for the first trial of streptomycin as:

- Early - no clinical signs of meningitis or focal neurology and fully conscious
- Medium - patient's condition falls between early and advanced
- Advanced - extremely ill, in a deep coma

Medical Research Council tuberculous meningitis severity grade

With the introduction of the Glasgow Coma Scale (GCS) in 1974, this classification was modified to:

- Grade I (GCS score 15; no focal neurological signs)
- Grade II (GCS score 11–14, or 15 with focal neurological signs)
- Grade III (GCS score ≤10)

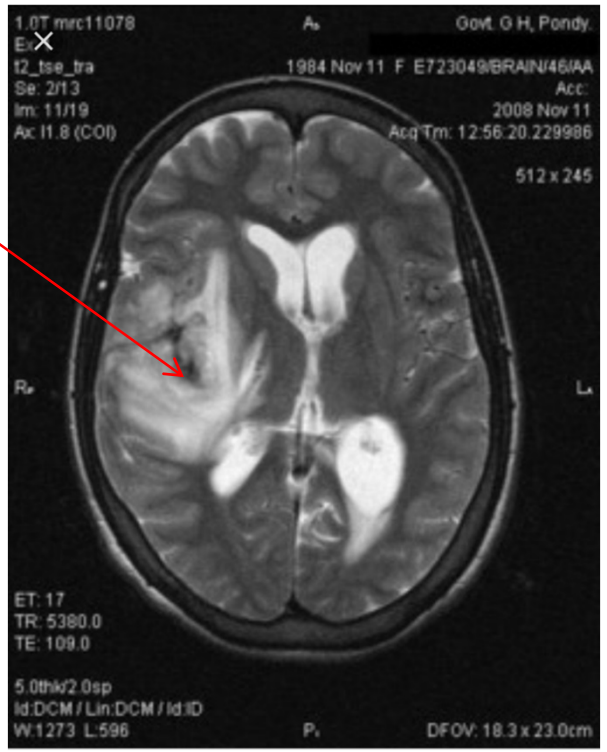
3.1.2.Tuberculous encephalitis and encephalopathy

Tuberculous encephalitis

- Tuberculous infection directly infects the brain resulting in encephalitis
- Focal or generalized seizures may occur
- Abnormal movements like choreiform or hemiballistic movements, athetosis , generalized tremors, myoclonic jerks and ataxia

MRI (brain)

Tuberculous encephalitis in right parietal lobe



Tuberculous encephalopathy

- A syndrome exclusively present in infants and children

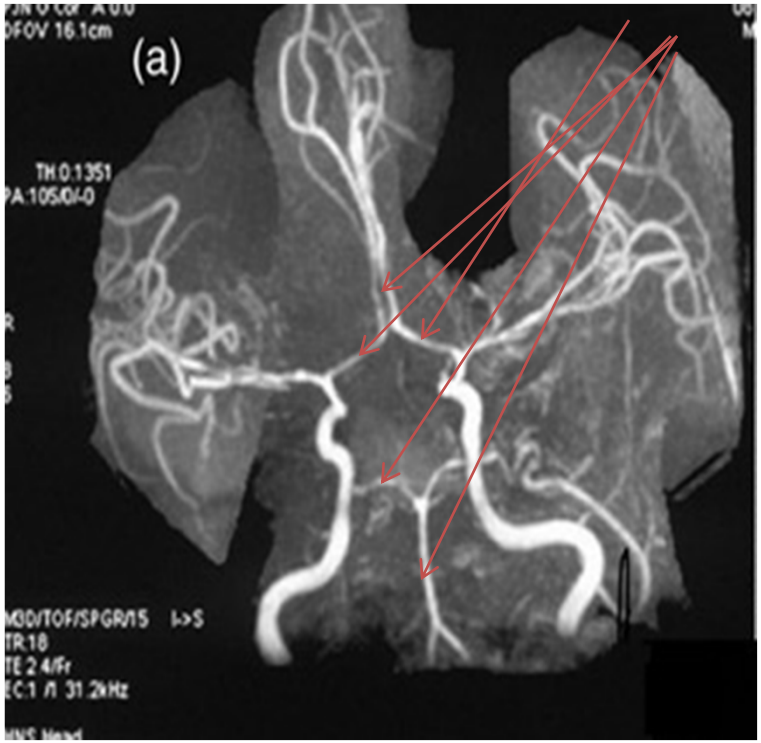
- Characteristic features -- development of a diffuse cerebral disorder in the form of convulsions, stupor and coma without signs of meningeal irritation or focal neurological deficit

3.1.3.Tuberculous vasculitis

- Brain tissue underneath the tuberculous exudate shows various degrees of oedema, perivascular infiltration, and a microglial reaction, a process known as ‘border zone reaction’
- Basal exudates are more severe in the vicinity of the circle of Willis, and cause inflammation of cerebral blood vessels mainly 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
- Hemiplegia or quadriplegia

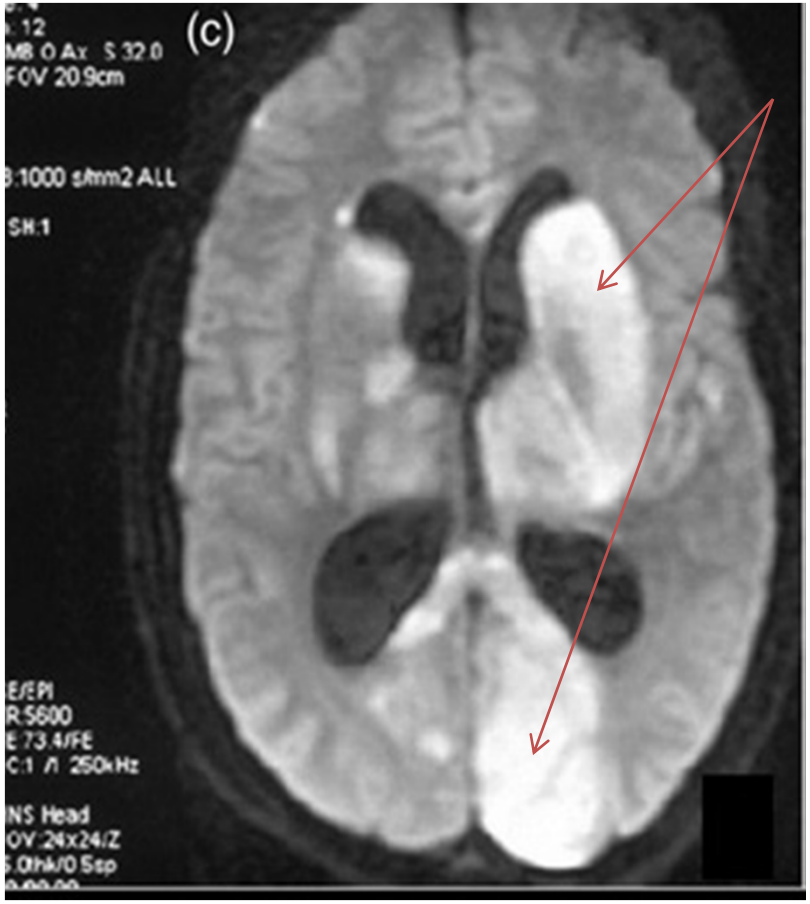
MRA(brain)

- Inflammatory changes in the vessel wall may be seen, and the lumen of these vessels may be narrowed or occluded by thrombus formation

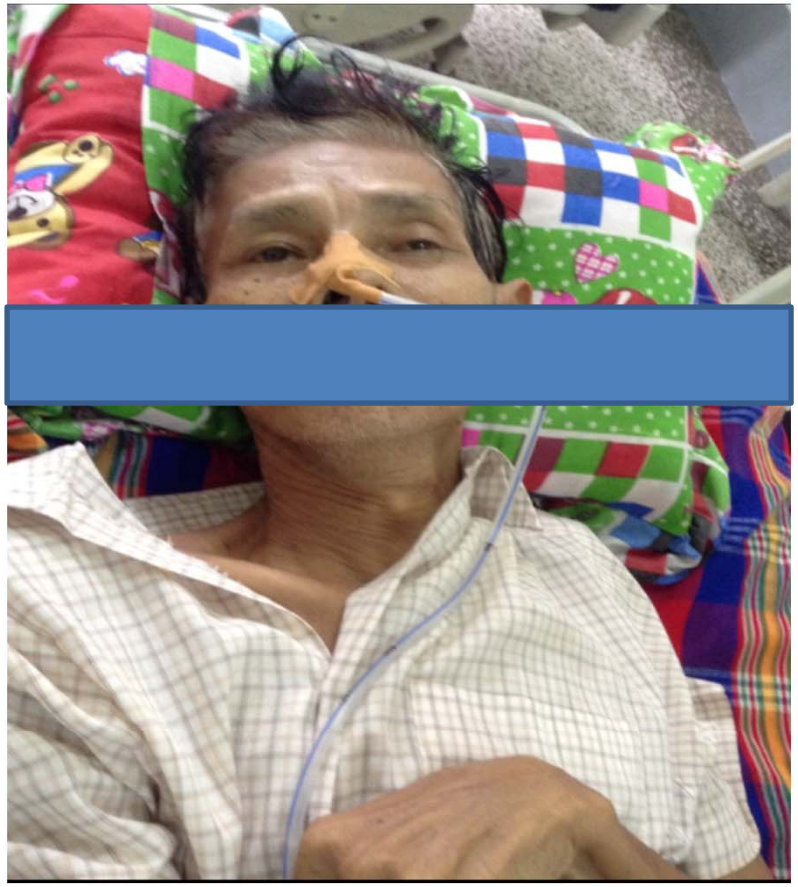


diffuse narrowing involving basilar, bilateral posterior cerebral, anterior cerebral, and middle cerebral arteries

Diffusion-weighted MRI



- restricted diffusion suggestive of acute infarct in left occipital cortex and bilateral basal ganglia



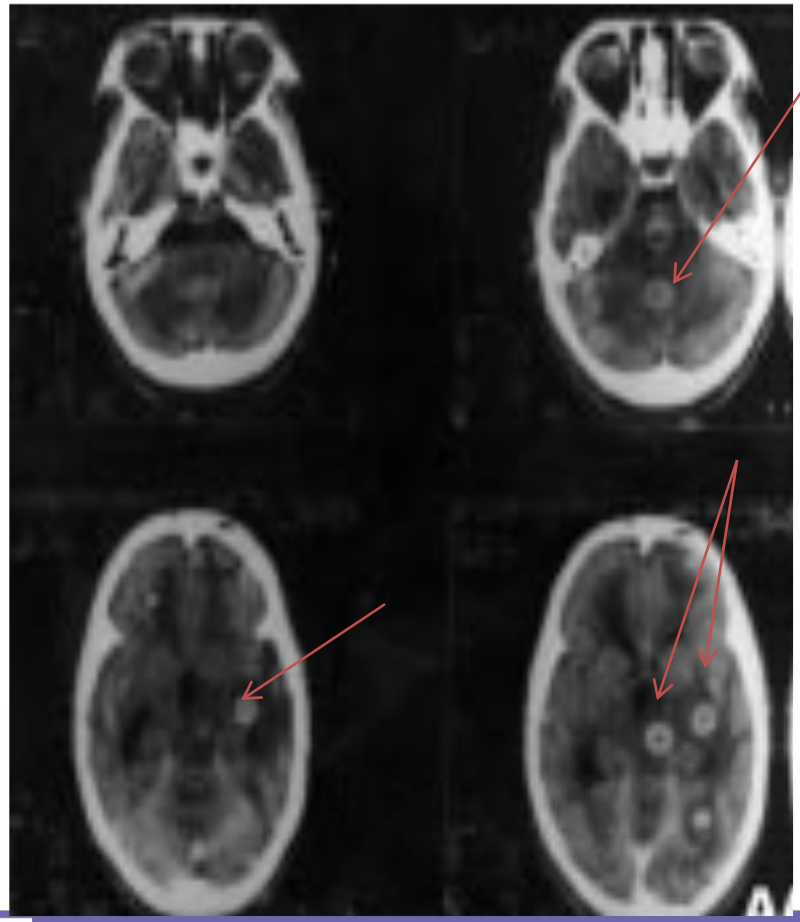
- Stroke due to tuberculous cerebral vasculitis

3.1.4.Intracranial tuberculoma

- Firm, avascular, spherical granulomatous masses, measuring about 2–8 cm in diameter
- Well defined from surrounding brain tissue which is compressed around the lesion and shows oedema and gliosis
- Inside of these masses may contain necrotic areas composed of caseous material, occasionally thick and purulent, in which tubercle bacilli can be demonstrated

- Symptoms are related to their location
- In developing countries, young adults and children are predominantly affected while in developed countries -- more common in older patients
- Low-grade fever, headache, vomiting, seizures, focal neurological deficit, and papilloedema are characteristic
- Infratentorial tuberculomas may present with brainstem syndromes, cerebellar manifestations, and multiple cranial nerve palsies

Contrast-enhanced CT scan of brain

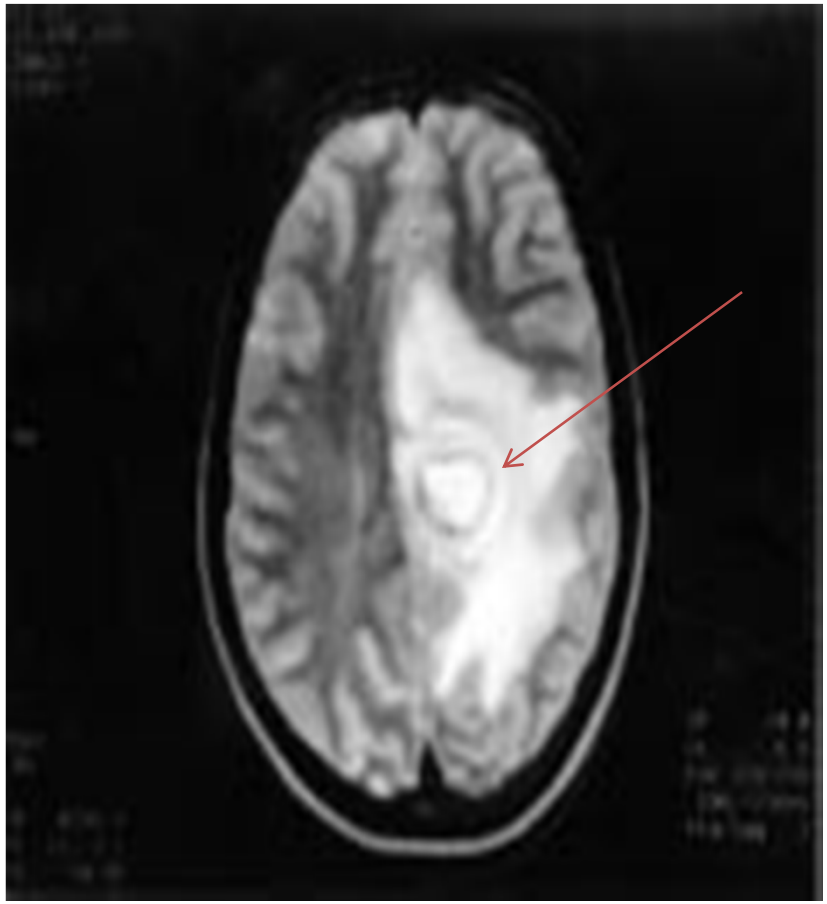


- multiple tuberculomas in a patient with tuberculous meningitis

3.1.5.Intracranial tuberculous abscess

- Distinct from CNS tuberculoma
- 4 - 7.5% of patients with CNS tuberculosis
- Usually solitary and larger and progress much more rapidly than tuberculomas
- Clinical features - partial seizures, focal neurological deficit, and raised intracranial tension
- Microscopic evidence of pus in the abscess cavity, microscopic changes in the abscess wall, and isolation of *M tuberculosis*
- Surgical exploration and drainage of pus may produce excellent long-term results

MRI (brain)



- A granuloma with a liquid centre with marked surrounding oedema

3.2. Spinal

3.2.1. Tuberculous myelitis

3.2.2. Spinal tuberculous meningitis

3.2.3 Tuberculous arachnoiditis (myeloradiculopathy)

3.2.4. Non-osseous spinal cord tuberculosis

3.2.5. Pott's spine and Pott's paraplegia

3.2.1. Tuberculous myelitis

- More common in young adults
- Direct infiltration of spinal cord
- Usually thoracolumbar spinal cord involvement
- Paralysis, sensory impairment , bladder and bowel dysfunction

3.2.2. Spinal tuberculous meningitis

- Result from rupture of Rich's focus into the spinal arachnoid space rather than the basal meninges
- Acute form - fever, headache, and radiating root pains, accompanied by myelopathy
- Chronic form - usually localised to a few segments, presents with progressive spinal cord compression

3.2.3. Tuberculous arachnoiditis

- Downward extension of intracranial exudates to spinal subarachnoid space – leads to inflammation of arachnoid mater causing spinal arachnoiditis

- 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
- 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

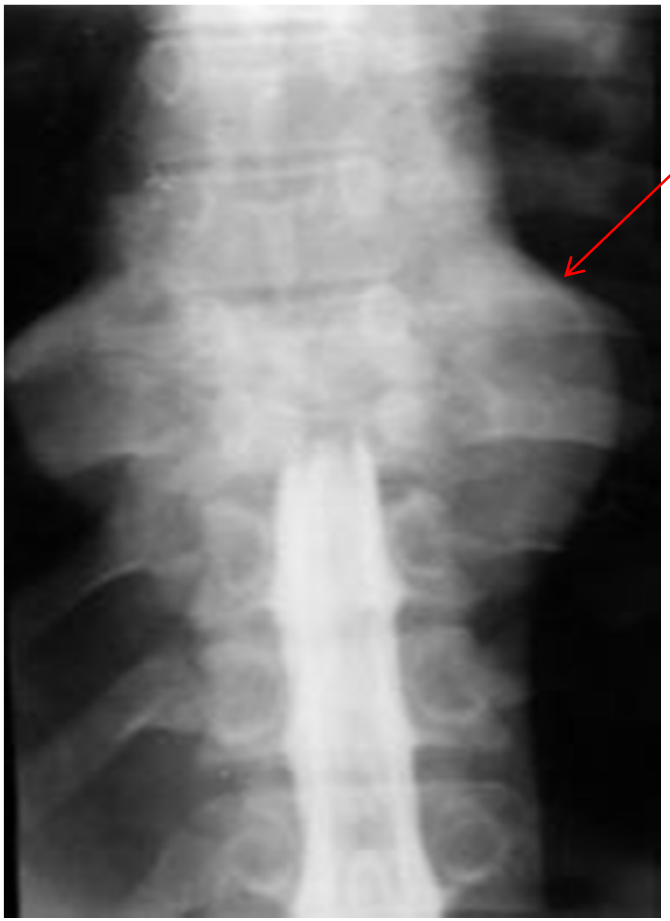
- Hallmark of diagnosis - characteristic myelographic picture, showing poor flow of contrast material with multiple irregular filling defects, cyst formation, and sometimes spinal block

- CSF changes are those of a chronic meningitis, frequently CSF sugar concentration is normal

- Occasionally lumbar tap may be dry

- Patients need adequate anti-tuberculous treatment for at least one year

A lumbar myelogram showing spinal block at the level of T9 vertebra



A fusiform paravertebral swelling and destruction of T8 and T9 vertebra

3.2.4. Non-osseous spinal cord tuberculosis

- Occur in the form of tuberculomas
- Usually - extradural tuberculomas
- Sometimes – intradural extramedullary lesions occured
- Intramedullary tuberculomas are extremely rare
- More common in thoracic region
- More than one site in the spinal cord may also be affected

4. Diagnosis

Diagnostic criteria for tuberculous meningitis are

1. *Mycobacterium tuberculosis* isolated from cerebrospinal fluid or
2. Clinical meningitis with negative gram and India ink stains, plus sterile bacterial and fungal cultures, plus one or more of the following:
   (a) cranial CT scan consistent with tuberculous meningitis (hydrocephalus, oedema, basal meningeal enhancement),
   (b) chest radiograph consistent with active pulmonary tuberculosis or
   (c) good response to antituberculosis chemotherapy

(Thwaites GE et al 2002)

4.1. Microbiological diagnosis

- Use of microscopy and Ziehl–Neelsen staining to detect of acid-fast bacilli in fluids or tissues from affected organs -- mainstay for the rapid diagnosis of tuberculosis
- 10-20 % sensitive
- Culture of *M. tuberculosis* from patient specimens is more sensitive than microscopy for diagnosis
- Gold standard
- Takes at least 10 days in liquid media and up to 8 weeks on solid media
- Sensitivity of around 60-70 %

4.2. Molecular assays

- Based on nucleic acid amplification to detect *M. tuberculosis*-specific molecules
- GeneXpert MTB/ RIF is a commercial, real-time PCR-based assay for the detection of *M. tuberculosis* in clinical specimens, and also detects mutations associated with rifampicin resistance
- Endorsed by the WHO in 2010, and is being adopted globally as a front-line diagnostic test
- 60% sensitive and nearly 100% specific

- Detection of lipoarabinomannan (LAM), a MTB cell wall lipopolysaccharide antigen, in urine is useful in the diagnosis of TB in HIV patients with advanced immunodeficiency

- CSF LAM for TBM diagnosis in immunosuppressed HIV-infected patients have shown improved diagnostic value (sensitivity 64% and specificity 69%) compared with smear microscopy

4.3. Diagnosis based on the host response

- IFNγ release assays depend on the ability of T lymphocytes from *M. tuberculosis*-infected individuals to produce IFNγ when stimulated with *M. tuberculosis*-specific antigens

- Sensitivities of blood and CSF IFNγ release assays are 78% and 77% respectively, with 61% and 88% specificity

- CSF levels of adenosine deaminase (ADA) in TBM - -
  - sensitivity (80 %) and specificity (80 – 90 %)

- Tuberculin skin test – sensitivity 47 % and specificity 86 %

4.4. Diagnostic imaging

- CT scan or MRI scan of the brain may reveal thickening and intense enhancement of meninges, especially in basilar regions
- Ventricular enlargement is present in a majority of patients
- Degree of hydrocephalus correlates with the duration of the disease
- Infarcts are another characteristic imaging feature

- Majority of infarcts are seen in thalamic, basal ganglion, and internal capsule regions

- Tuberculomas are infrequently seen

- Carotid or MR angiogram shows changes in vessels of the circle of Willis -- uniform narrowing of large segments, small segmental narrowing, irregular beaded appearance and complete occlusion

5. TREATMENT

Drug	WHO recommended daily dose		WHO recommended duration	CSF penetration (CSF/plasma concentration)	Important adverse effects
	Children	Adults			
First-line drugs for the treatment of drug-sensitive TBM					
Rifampicin	15 mg/kg (range 10–20 mg/kg); max. 600 mg	10 mg/kg (range 8–12 mg/kg); max. 600 mg	12 months	10–20%	Hepatotoxicity, orange urine, many drug interactions
Isoniazid	10 mg/kg (range 7–15 mg/kg; max. 300 mg	5 mg/kg (range 4–6 mg/kg); max. 300 mg	12 months	80–90%	Hepatotoxicity, peripheral neuropathy, lupus-like syndrome, confusion, seizures
Pyrazinamide	35 mg/kg (range 30–40 mg/kg)	25 mg/kg (range 20–30 mg/kg)	First 2 months	90–100%	Hepatotoxicity, arthralgia, gout
Ethambutol	20 mg/kg (range 15–25 mg/kg)	15 mg/kg (range 15–20 mg/kg)	First 2 months	20–30%	Dose-related retrobulbar neuritis, more common in renal impairment
Streptomycin*	15–30 mg/kg; max. 1 g IV or IM	15 mg/kg (range 12–18 mg/kg); max. 1 g	First 2 months	10–20%	Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity

Nature Reviews/Neurology

WHO recommends regimen

- 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol followed by 10 months of rifampicin and isoniazid, for all drug susceptible patients

Role of Corticosteroids

- Response to steroids may be dramatic with rapid clearing of sensorium, regression of abnormalities of CSF, defervescence and relief of headache

- Improved both survival rate and neurological outcome

PARADOXICAL WORSENING

- Intracranial tuberculomas appear or paradoxically increase in size while patients are being treated for tuberculous meningitis
- Discovered accidentally when follow-up CT scan is performed routinely or when new neurological signs develop during the course of antituberculous therapy
- However, with continued treatment, eventual resolution of these tuberculoma occurs

SURGERY

- Ventriculo-peritoneal or ventriculoatrial shunting may relieve the signs and symptoms of hydrocephalus
- Shunts may require revision because the high protein content of CSF causes blockage
- Intracranial tuberculomas with midline shifts and increased intracranial pressure, and that fail to respond to chemotherapy should be surgically removed

6. TAKE HOME MESSAGE

- CNS Tuberculosis causes death and disability
- Important risk factors for poor outcome are delayed diagnosis, delayed treatment, advanced disease, and antitubercular drug resistance
- Intracerebral and spinal pathology is mediated by a dysregulated inflammatory response that contributes to meningitis, tuberculoma formation, arteritis, obstruction of cerebrospinal fluid (CSF) flow, and vascular complications including stroke
- Multidrug antitubercular antibiotic therapy is the mainstay of treatment

THANK YOU