Clinical Reviews

Tuberculosis of the central nervous system: recognition, diagnosis and treatment in a low-prevalence country

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Abstract

Tuberculosis (TB) is one of the greatest threats to global public health, with 9.2 million new cases in 2006[1] and has become increasingly common in the UK. Central nervous system (CNS) infection with Mycobacterium tuberculosis (MTB) is relatively rare but is associated with a serious risk of neurological morbidity or death. Delays in diagnosis worsen prognosis and even with anti-tuberculous therapy up to 30% of tuberculous meningitis (TBM) patients may die.[2] TBM and tuberculomas can mimic other CNS pathologies. Careful analysis of the clinical features, CSF examination and pragmatic use of diagnostic tests can aid the diagnosis. Prolonged anti-tuberculous treatment is required and presumptive treatment should not be delayed for microbiological confirmation of the disease.

Keywords

Tuberculosis, Central nervous system, Tuberculous meningitis, Tuberculoma

Introduction

There are an estimated 9 million new cases of tuberculosis (TB) worldwide every year with over 8000 in the UK,[3] particularly in inner city areas where foreign migration and the spread of HIV are important contributing factors.[4]

Tuberculosis is predominantly a chest infection but also causes extrapulmonary disease including tuberculous lymphadenitis, infections of the abdomen, bone, joints, brain, meninges and skin. Involvement of the central nervous system can take two major clinical forms, tuberculous meningitis and tuberculomas with or without meningitis. Although relatively rare in low prevalence countries such as the UK,[4] CNS TB carries the risk of significant morbidity and mortality. In England and Wales from 1988 to 2001, the death to notification ratios for CNS TB varied widely from 4.9 to 42%, but were never greater than 10% for respiratory and other disease sites.[5]

New diagnostic tools have improved the ability to detect MTB infection but many have not been adequately validated for CNS involvement[6] and the UK NICE guidelines[7] for CNS TB are by no means exhaustive. Features are often non-specific, especially during the initial stages of infection with potentially catastrophic consequences if the diagnosis is delayed. Management of this disease remains challenging and requires good clinical skills and a pragmatic approach.

Epidemiology of TB and CNS TB in England and Wales

The rate of TB in England and Wales was 10.93 per 100,000 in 1998[4] and predominated in London with a rate of 31.6 per 100,000. By 2006 the tuberculosis rate in London had risen to 44.8 per 100,000,[3] reflecting the wider global epidemic and spread of HIV.

In England and Wales the disease is most common in black Africans and Indians, with the highest rates in those born in endemic areas, recently having entered the UK and aged between 15 and 34 years, although age distribution varies between ethnic groups.[4] CNS presentations are relatively rare in low-prevalence countries; in 2001 there were 161 CNS TB notifications in England and Wales compared with 4853 respiratory notifications[5] and CNS TB accounts for only a small proportion of extrapulmonary disease in developed countries.[8] In developing countries however, tuberculomas are significantly more common, accounting for up to 20% of brain lesions in India and especially affecting those below the age of 20.[9]

Pathogenesis of cerebral TB (see Figure 1)

Tuberculosis is acquired through inhalation of MTB-infected droplets from an infectious source. The dynamics of transmission are incompletely understood but it seems that some clear the bacillus without developing a lasting infection. Evidence suggests that 30–50% of household contacts exposed to sputum smear positive source cases develop an infection[10] although most will contain the infection as latent TB. A few develop active primary TB especially if cell-mediated immunity is poor, such as those who are HIV co-infected.

CNS involvement can occur during primary infection or following reactivation of latent disease. During primary infection, haematogenous spread may result in miliary TB with foci of infection in the meninges, which tends to have an aggressive course. Alternatively, infection may seed in end-organs including the brain and meninges, provoking a localised granulomatous containment of the bacilli which may reactivate at a later date.[11]

Latent TB represents a balance between the bacilli and the immune cells, resulting in the granuloma, consisting of epithelioid cells (differentiated tissue macrophages), multinucleated giant cells (fusions of tissue macrophages), dendritic cells, T cells and

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fibroblasts in constant turnover with the bacillus.[11,12] The disease process may reactivate at any time into pulmonary, intrathoracic (involving the mediastinal lymph nodes) or extrapulmonary disease. The risk of progression to active TB is estimated to be 5–10% per lifetime in those without other significant co-morbidities [11,13] but the relative risk in those who are HIV infected is almost 10 times greater.[11,13]

In the CNS, MTB can cause meningitis, which is usually sub-acute with less meningism and a more insidious onset that bacterial meningitis, basal arteritis, encephalopathy, abscesses and tuberculomas. Meningeal infection is principally due to haematogenous spread, the primary focus is usually the lungs but spread may occur from lymph nodes and has been described in 10–30% of patients with miliary TB.[14] The meninges, particularly the basal meninges, become inflamed with an intense exudative appearance. The meningeal arteries develop an endarteritis obliterans leading to infarction and the development of focal neurological signs.[8]

Tuberculomas may form from tubercles via local haematogenous spread, through dissemination or as a reaction to a tuberculous meningitis and basal arteritis.[9, 15] Reactivation of latent foci in the brain may also occur. The formation of tuberculomas may occur during treatment for TBM.[16] Tuberculomas consist of a central area of caseous necrosis encapsulated in a wall of fibroblasts, epithelioid cells, Langerhans' type giant cells and lymphocytes.[17] Initially the capsule is poor in collagenous tissue but eventually becomes strengthened with collagen, thus reducing inflammation and following a more indolent progression. Tuberculous abscesses may form from focal cerebritis or the liquefaction of tuberculomas, they consist of a wall of inflammatory cells surrounding a collection of pus, both of which may contain bacilli[15] and they have a more aggressive clinical course.

Clinical Features

The classic triad of fever, cough and weight loss seen in pulmonary TB is well characterised[18] but the clinical picture in CNS infection may range from a subtle presentation to a florid neurological emergency. The presence of HIV does not necessarily alter the neurological features but is likely to adversely affect survival outcomes.[19]

Tuberculous meningitis often has an insidious onset, with headache, neck stiffness and fever common presenting symptoms in 2 case series[20,21] and cranial nerve palsies especially of the abducens nerve are characteristic.[20] Discriminating TBM from other forms of meningitis is difficult however; a study comparing TBM with bacterial meningitis in Vietnam found that younger age, a history of 6 days or more, lower white blood cell count, lower CSF total white cell count and lower CSF neutrophil proportion were all predictive of tuberculous meningitis when combined as weighted diagnostic index scores. The authors developed a diagnostic rule for diagnosing TBM with 86% sensitivity and 79% specificity. This approach to diagnosis is relevant to similar areas of high TB- and low HIV prevalence but is difficult to extrapolate to areas with substantially different epidemiology such as the UK.[2]

Severe TBM can present with seizures, altered levels of consciousness and focal neurological signs.[16] Features relating to spinal infection depend on the level and extent of involvement and can include neurogenic bladder and paraparesis.[20] The fundi should be examined for signs of raised intracranial pressure or the presence of choroidal tubercles, indicative of miliary TB. Cerebral infarction has been reported in 21% of TBM cases[22] usually associated with late stage disease. Arterial occlusion can cause lacunar and non-lacunar territory infarctions and stroke may occur in the cerebellum, internal capsule, pons, basal ganglia, thalamus, cerebral cortex and pons. The basal areas of the brain are more vulnerable, due to the collection of inflammatory exudate and related vasculitis.

Isolated tuberculomas can behave as space-occupying lesions without classic TB symptoms. They cause focal epilepsy or generalised seizures in up to 85% of cases[9] and depending on their site may also cause cerebral, brainstem, cerebellar and extrayramidal signs. Tuberculomas may occur in the context of meningitis resulting in a complex clinical picture, including signs of meningism, cranial nerve palsies, raised intracranial pressure cranial or spinal mass lesions and spinal radiculopathies.

Differential diagnosis (See Tables 1 and 2)

The range of differential diagnoses varies with the patient's ethnicity, age and HIV status. Tuberculous meningitis may be difficult to distinguish from other lymphocytic meningitides and investigation should encompass differential diagnoses including viral, fungal and carcinomatous meningitis or encephalitis, listerial infection and autoimmune or inflammatory disease.[23] There is a myriad of infectious causes of encephalitis or meningo-encephalitis including, more commonly, herpes simplex virus type 2 and enteroviruses. Investigation of alternative infective agents should reflect epidemiological features and the patient's risk factors such as recent travel to an endemic area, immunosuppression or recent vaccination.[24] HIV testing is mandatory in all cases and cryptococcal meningitis should be excluded in HIV positive individuals with an Indian ink examination of the CSF and crypotococcal antigen testing.[25]

Metastatic disease, primary CNS tumours, bacterial abscesses and inflammatory conditions can resemble tuberculoma.[9] Neurocystercicosis, endemic in Latin America, Asia and Africa, has similar clinical and radiological features[26] and should be sought in patients from these areas. Sarcoidosis may mimic CNS TB as aseptic meningitis or cerebral granulomatous lesions.[27] In immunocompromised patients, toxoplasmosis, fungal infections such as aspergillosis, bacterial abscesses and lymphoma may all have similar clinical and radiological features to tuberculoma.

Diagnosis (See Table 3 & Figure 2)

The mainstay of diagnosis remains microscopy and culture of a suitable specimen, and CSF examination is advocated.[7] This method is flawed as CSF is paucibacillary and microscopic sensitivity is low, but can be increased by taking large and repeated CSF samples. The CSF usually has a clear appearance with a raised white cell count, initially consisting of polymorphs then becoming lymphocytic and a high opening pressure. The protein can be very high and a low CSF/serum glucose ratio is common.[11] CSF findings in HIV may not differ significantly from non-HIV

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Infections	Risk factors	Investigations
Neurocysticercosis[26]	Born in or recent travel to endemic area	Neuroimaging, immunoblot
Toxoplasmosis	HIV infection	Toxoplasma serology and PCR
Bacterial abscesses	History of IVDU, endocarditis, lung abscess, meningitis.	Neuroimaging, CSF examination, blood culture
Fungal infection e.g. candida, aspergillosis	HIV infection	Neuroimaging, CSF examination, fungal cultures
Syphilitic gumma	HIV infection, MSM	Syphilis serology on blood and CSF
Coccidyoidmycosis	Rare	
Cryptococcus	Rare (HIV infection)	
Inflammatory		
Sarcoidosis[27]	Evidence of sarcoid elsewhere, erythema nodosum, bilateral hilar lymphadenopathy	Neuroimaging CXR, BAL, Biopsy (lymph nodes, skin, lung, liver)
Vasculitides e.g. Wegener's granulomatosis		Vasculitis screen
Amyloidosis	Renal dialysis, chronic inflammatory conditions	Biopsy
Tumours		
Metastases	Smoking, age >50years, family history of breast, lung, prostate CA	CXR, PSA, CT chest/abdo/pelvis
Lymphoma	HIV	CXR, blood film, CT chest/abdo/pelvis
Meningiomas		Neuroimaging
Gliomas		Neuroimaging

Table 1. Differential diagnosis of CNS tuberculoma.

Infections	Risk factors	Investigations
Bacterial meningitis (especially partially treated)[2]	Young or elderly, history of exposure, recent head injury	Neuroimaging, CSF examination, blood culture
Viral meningitis[51]	Enteroviruses are the most common Herpes viruses and arboviruses should be considered Rare causes include mumps, lymphocytic choriomeningitis virus, herpes zoster, HHV6 and influenza virus	CSF examination Viral PCR Serology for viruses and other pathogens e.g. *Borrelia burgdoferi*
Cryptococcal meningitis[25]	HIV, especially severe immunosuppression	Indian ink examination of CSF Cryptococcal antigen (serum/CSF/BAL)
Encephalitis[24]	Season, recent travel, insect bites, animal contact, vaccination history	Neuroimaging Viral PCR Serology Antigen detection
Syphilis	Multiple sexual partners	Syphilis serology
Inflammatory		
Sarcoidosis (Hoitsma)	Evidence of sarcoid elsewhere, erythema nodosum, bilateral hilar lymphadenopathy	CSF examination
Vasculitides e.g. Wegener's		Vasculitis screen
Amyloidosis	Down's syndrome, chronic inflammatory conditions, familial	Tissue biopsy
Tumours		
Metastases	Smoking, age >50years, history of breast, lung, prostate carcinoma	CXR, PSA, CT chest/abdo/pelvis
Lymphoma	HIV	CXR, blood film, CT chest/abdo/pelvis

Table2. Differential diagnosis of TB meningitis.

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Test	Evidence in TBM
CSF Microscopy	Fast but low sensitivity[28]
CSF Culture	Remains gold standard but even newer methods can take >2 weeks
CSF IGRA	Promising early evidence[52]
CSF ADA	Limited evidence
CSF Bromide	Limited evidence
CSF NAAT	Useful to rule in diagnosis; sensitivity 58.6% specificity 96.2% but lots of heterogeneity[6]
Neuroimaging	Mainstay of diagnosis for tuberculoma but MRI images are heterogeneous.[30] May show enhancement of leptomeninges, hydrocephalus and infarction.

Table 3. Common and newer tests used in diagnosing CNS tuberculosis

patients[29] depending on the extent of immunosuppression, which may change the diagnostic features. Normal CSF chemistry and microscopy does not exclude TB and CSF should be cultured, which can be achieved in under 3 weeks using newer methods e.g. BACTEC.[6] Despite improved culture methods, presumptive treatment should not be delayed by awaiting microbiological confirmation, as untreated TBM is usually fatal.

A CT or MRI of the brain, brainstem and if necessary spinal cord, should be reviewed by an experienced neuroradiologist. Tuberculomas on CT can be single or multiple lesions, usually above 6mm in diameter, often with a ring-enhancing pattern.[30] The parietal and frontal lobes are frequently affected. MRI is more sensitive revealing a greater number of lesions than on CT[17] and meningeal enhancement on T1 weighted images. Infarcts and hydrocephalus associated with TBM are common especially in HIV patients.[16,20,21] Images may vary in HIV patients reflecting the altered immune response.

The tuberculin skin test is unreliable and often falsely negative in this setting, especially in HIV co-infected patients. The new IFN- gamma release tests (IGRA), when performed on peripheral blood cannot necessarily distinguish infection from disease, however ELISpot used directly on CSF had a sensitivity of 90% and specificity of 100% in a recent small study.[31] A different approach using ELISpot on CSF to detect anti-*Mycobacterium bovis* BCG IgG and IgM secreting cells reported a sensitivity of 84%.[32] The role of immunology-based tests will be defined as experience grows.

Nucleic acid amplification tests (NAAT) have a sensitivity of 58.6% and specificity of 96.2% for diagnosing TBM on CSF samples[6] and are useful to confirm a diagnosis of TBM but cannot rule it out.[28] Other tests such as the adenosine deaminase test and the bromide partition test have performed well in the diagnosis of TBM. The adenosine deaminase test, based on an enzyme produced by lymphocytes had 86.5% sensitivity and 90.5% specificity in but lack of specificity has been cited as a problem and there one report is still insufficient evidence to determine how either test should be used in clinical practice.

Thorough investigation of all sites should be undertaken, especially in HIV positive patients[29] including a chest x-ray, sputum microscopy and culture, and gastric washings in children. A CT scan of the chest can reveal subtle features of TB and a lymph node biopsy may yield tubercles especially if there are features of lymphadenitis.

In cases with substantial diagnostic doubt, a stereotactic brain biopsy of a tuberculoma is occasionally justified. Biopsy of a suspected tuberculoma yielded a histological diagnosis in the cases included in a study from Saudi-Arabia.[33] Risks of biopsy include hydrocephalus, bleeding and haematoma[33–35] with permanent morbidity in up to 5%. Mortality, usually around 1%, varies according to the site of the lesion.[36,37] Abnormal leptomeninges, identified on MRI with contrast, can be biopsied to aid the distinction of tuberculous meningitis from other aetiologies including neoplastic carcinomatous meningitis and sarcoid. Consideration of whether to perform a biopsy should not delay a trial of anti-tuberculous therapy.

Treatment

Early presumptive therapy based on clinical findings and imaging should not await culture confirmation of the diagnosis. Evidence regarding appropriate treatment regimes is limited, especially for tuberculoma.[9] Fully sensitive TBM requires upto 12 months of treatment with isoniazid, pyrazinamide, rifampicin and a fourth drug e.g. ethambutol for the first 2 months then isoniazid and rifampicin for the remaining months.[7] Ethionamide, isoniazid, prothionamide and pyrazinamide most effectively cross the blood-this may occur at any time during therapy, especially during the first 2 months.[38] Guidelines on the management of potential hepatotoxicity should be followed;[39] in essence, all patients should receive baseline liver function tests and modest pre-treatment abnormalities are common. Those with AST/ALT levels 2 or more times the upper limit of normal should have weekly and then fortnightly liver function tests until normal. Those with a lower level transaminitis should be monitored at 2 weeks and if levels have increased, regular monitoring continued. Similarly, those with known chronic liver disease or viral hepatitis should be regularly monitored. Patients should be informed of the symptoms of early hepatotoxicity including malaise, nausea, vomiting and jaundice and liver function tests repeated if any of these occur. Treatment should be stopped and advice sought in those whose bilirubin level rises, or whose liver enzymes rise to 5 times the upper limit of normal.

All patients starting ethambutol should have a baseline visual acuity test with a Snellen Chart and this drug avoided in those with poor acuity or who will be unable to detect visual deterioration.[38] Retrobulbar neuritis can be missed in unconscious patients and ethambutol should be initiated with caution in this instance. Pyridoxine should be given to patients who are more vulnerable to isoniazid-induced peripheral neuropathy, including those who are HIV positive, diabetic or alcohol dependent.

Toxicity has been reported to be more common in HIV positive patients.[38] In one UK study, persistent vomiting and peripheral neuropathy but not hepatotoxicity occurred more commonly in HIV positive

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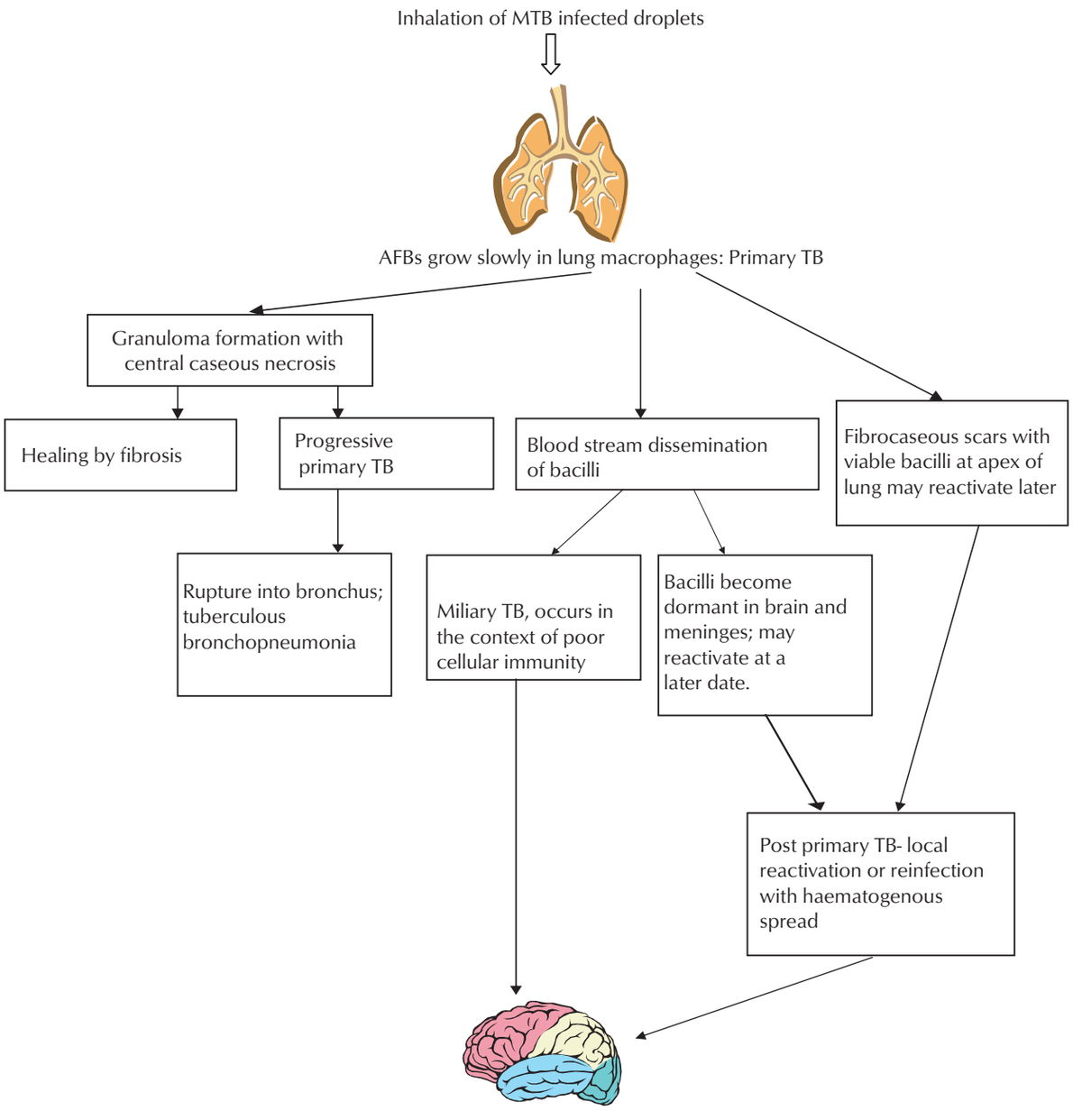


Figure 1. Pathogenesis of CNS TB Adapted from Lucas SB. Histopathology.[11]

patients,[40] but data from the US suggested the relative risk of developing drug-induced hepatitis was fourfold in HIV positive patients.[41] Other factors including age, sex and ethnicity, as well as concurrent drug therapies may also have a role to play in the development of toxicity.[40,41]

Use of steroids is discussed in recent treatment guidelines[7,38] although further research is needed. NICE recommends a glucocorticoid at the dose range in adults equivalent to prednisolone 20–40 mg if on rifampicin, or 10–20 mg prednisolone if not on rifampicin. A large randomised controlled trial from Vietnam[42] showed increased survival in TBM patients given dexamethasone but no significant difference in the primary outcome measure of death or severe disability. Patients with Grade I disease (GCS 15, no focal neurology) were prescribed 2 weeks IV therapy (dexamethasone 0.3mg/kg/day; week 1, 0.2 mg/kg/day; week 2) followed by 4 weeks oral therapy (0.1mg/kg/day; week 3, then 3mg/day, reduced by 1mg each week). Patients with Grade II disease (GCS 11–14 or GCS 15 with focal neurology) or Grade III disease (GCS less than or equal to 10) were given 4 weeks of IV dexamethasone (0.4mg/kg/day in week 1, reduced by 0.1mg/kg every week) then 4 weeks of oral therapy starting at 4mg/day and reduced by 1mg per week. Given the survival benefit shown in the Vietnam trial, dexamethasone

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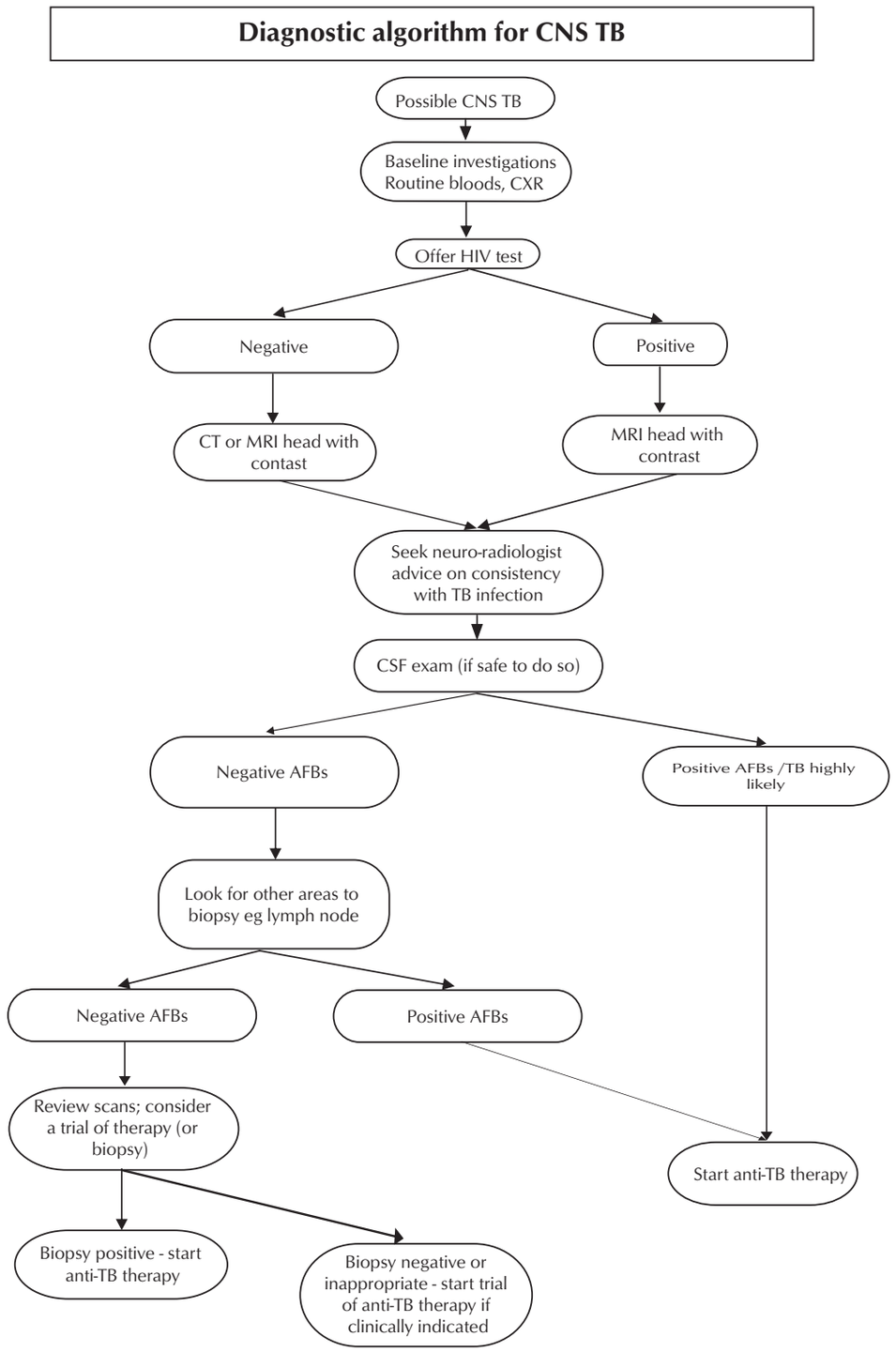


Figure 2. Diagnostic Algorithm for CNS TB.

in the doses outlined above should be considered in cases of TBM with or without tuberculomata.

The choice of treatment for secondary epilepsy is complicated by drug-drug interactions especially with the enzyme inducer rifampicin. Newer antiepileptics are less likely to have interactions than older drugs.[43] Antiretroviral treatment, especially protease inhibitors, is also affected in this way.[38] In both circumstances a multi-specialty approach is advocated. Drug resistance should be managed according to the sensitivities and specialist advice should be sought.

Prognosis

Clinical evaluation and serial neuroimaging are used to evaluate response to treatment. In one study, mortality from TBM was 24%, where lower CSF white cell count (especially neutrophils), higher CSF lactate levels and a lower CSF glucose: blood ratio were associated with

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death.[44] Partial or complete response has been reported in 62–88% of tuberculomas, no change in 0–8% and calcification in 7 to 33%.[9]

Paradoxical responses, where there is clinical and radiological progression of lesions following the initiation of anti-tuberculous therapy, have been described in CNS infection[45, 46] and tuberculomas can form during treatment for TBM. This does not necessarily indicate treatment failure if the organism is fully drug sensitive. Paradoxical response in HIV positive patients may occur as part of an immune reconstitution inflammatory syndrome (IRIS); where HIV viral suppression with antiretroviral therapy leads to rapid immune recovery and a dysregulated immune response to the TB pathogen.[47,48] Other potentially fatal differential diagnoses including multi-drug resistant TB or cerebral lymphoma must be excluded. Effective treatment for drug-sensitive tuberculosis can usually be continued and steroids are often prescribed although evidence is limited.

Surgical intervention such as ventriculoperitoneal shunt may be necessary in some.[49] For non-communicating hydrocephalus or persistent communicating hydrocephalus neuroendoscopic procedures can be effective in patients with TBM hydrocephalus and associated tuberculoma but success may be limited by complicating factors such as severe hyponatremia or tuberculosis dissemination.[50]

Case History 1

A 25-year-old woman from Somalia was admitted with a headache and seizures. There was no past medical history of note. Initial investigations revealed a mild microcytosis and lymphopenia with slightly raised CRP and normal urea and electrolytes. The chest X-ray was unremarkable.

Following an initial CT scan, a diagnosis of neurocysticercosis was postulated; however the cysticercosis immunoblot was negative. A follow-up MRI showed lesions in both cerebral hemispheres and right cerebellum. The larger lesions showed irregular enhancement with a thick wall and necrotic centre. There was no meningeal enhancement.

In the absence of an alternative focus for microscopy and culture, a brain biopsy was performed from the fronto-temporal lesion. This showed fragments of largely necrotic tissue, the variable areas consisting of chronic inflammatory infiltrates and numerous giant multi-nucleated histiocytes. Crucially, a single acid-fast bacillus was identified on ZN staining and a diagnosis of cerebral TB was made. She was started on anti-tuberculous therapy with prednisolone and has since been doing well with no recurrence of her initial symptoms.

Case History 2

A 17 year old Bangladeshi patient was admitted with a first fit; a generalized tonic-clonic seizure following a prodrome of right-sided parasthesiae. Her principal risk factor for TB was contact with a friend subsequently diagnosed with CNS TB. There was no other past medical history of note. Initial investigations showed a slightly raised white cell count (neutrophilia), mildly elevated inflammatory markers and a negative HIV antibody test.

A PA chest x-ray showed miliary nodular shadowing in both upper zones, more marked in the right apex, confirmed on CT chest. Biopsy of mediastinal and paratracheal lymph nodes was inconclusive and did not yield AFBs on culture or histology.

The initial CT brain showed 2 ring enhancing lesions in the left parietal lobe and a further lesion in the left temporal lobe with some enhancement in the pituitary fossa. The MR with contrast showed a cluster of ring enhancing lesions in the left parietal lobe, intraparenchymal, dural and leptomeningeal enhancement with small lesions in the frontoparietal lobe.

CSF was clear and colourless with a total protein of 0.23, normal glucose and no histological evidence of TB or lymphoma. Culture for AFBs was negative. Toxoplasma latex and cysticercosis immunoblot were both negative.

A presumptive diagnosis of CNS and possibly pulmonary TB was made and the patient was started on prednisolone, TB medications and anticonvulsants. Initially she progressed well but after one month she had a repeat episode of right-sided parasthesia without frank convulsions and was readmitted. A repeat CT and MR showed progression of the lesions despite adequate therapy but no leptomeningeal enhancement. The appearances were consistent with TB and medication was continued as before. The patient has remained well since and it is thought the change in MR and clinical appearance was due to a paradoxical reaction to TB treatment.

Key Learning Points

CNS TB is rare but potentially fatal	Prompt recognition and diagnosis are essential
Tuberculosis should be considered in at-risk populations	Consider in all those who are young (<36 years) and newly arrived from endemic areas e.g. sub Saharan Africa and Indian Sub Continent
Clinical features may be non-specific	Careful history and examination may elicit subtle features that suggest the diagnosis
An HIV test should be offered	The differential diagnosis and relative accuracy of diagnostic tests are affected by HIV
Neuroimaging is key	Consult a specialist neuroradiologist to aid differentiation from other lesions of the central nervous system
CSF examination	CSF examination should be performed early, however microscopy sensitivity is low and culture confirmation requires over 2 weeks
Consider newer diagnostic methods	NAAT or INF-gamma ELISpot on the CSF may aid diagnosis
Treat early and aggressively	Early and prolonged treatment is essential. Steroids may reduce mortality

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Conclusion

Tuberculosis continues to increase in the UK and whilst most cases are pulmonary, infection of the central nervous system is clinically significant due to the high risk of mortality or severe neuro-disability. Those most at risk of MTB infection are recently arrived in the UK from endemic areas and they may be young and/or HIV infected constituting a vulnerable patient group.

A small proportion of MTB infection will manifest as neurological disease. This may be due to post-primary dissemination or reactivation of latent disease and HIV co-infected patients are especially at risk. Tuberculous meningitis can be insidious, with subtle clinical findings, or may present with florid neurological symptoms, which is associated with a poor prognosis. The intense inflammatory exudate and resulting vasculitis causes complications including cranial nerve palsies, hydrocephalus due to blockage of cystic ducts and cerebral ischaemia and infarction. Tuberculoma may occur as a complication of TBM or occasionally as an isolated phenomenon with few distinguishing features to aid the diagnosis.

Microscopy and culture is the mainstay of diagnosis but microbiological confirmation should not delay the initiation of presumptive treatment. Newer tests such as Interferon-gamma ELISpot or NAAT on CSF appear promising in aiding the diagnosis but more clinical experience is required. Neuroimaging is key to investigating CNS TB and requires the collaboration of an experienced neuroradiologist to recognise the distinguishing features of TBM and tuberculoma.

Any patient with suspected TB should be offered an HIV test and in the context of CNS TB this will alter the most likely differential diagnoses and the treatment that should be offered. HIV patients may not have significantly different presenting symptoms or CSF findings but this varies according to the extent of immunosuppression. Disseminated tuberculosis infection is more common in this group and this should be investigated.

Treatment should be for at least 12 months starting with a four- drug regimen using at least one drug with good CSF penetration. Steroids should also be given when treatment is initiated as this may reduce mortality. Patients requiring treatment for epilepsy or HIV are more challenging due to the potential for drug interactions and a multi-speciality approach should be taken. Multi-drug resistance requires expert advice.

Mycobacterium tuberculosis infection of the CNS remains a frequently fatal disease and patients will require close monitoring for an extended period but with timely and effective intervention the prognosis is greatly improved.

References

1. WHO. Global tuberculosis control-surveillance, planning, financing. 2008; Available from: http://www.who.int/tb/publications/global_report/2008/en/
2. Thwaites GE, Chau TT, Stepniewska K, *et al*; Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet* 2002; **360**: 1287–92.
3. HPA. Available from: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1225354113418?p=1204186170287.
4. Rose AM, Watson JM, Graham C, *et al*; Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. *Thorax* 2001; **56**: 173–9.
5. Martineau AR, Lowey H, Tocque K, *et al*; Decreasing tuberculosis case fatality in England and Wales, 1988–2001. *Int J Tuberc Lung Dis* 2004; **8**: 737–42.
6. Dinnes J, Deeks J, Kunst H, *et al*; A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess* 2007; **11**: 1–196.
7. NICE. Clinical diagnosis and managment of tuberculosis and measures for its prevention and control. NICE; Available from: http://www.nice.org.uk:80/nicemedia/pdf/CG033FullGuideline.pdf.
8. Ormerod P: Non-respiratory tuberculosis, Davies PDO, Barnes PF, Gordon SB, editors: Clinical Tuberculosis. London, 2008, Hodder Arnold; Chapter. 10, p. 163.
9. Pagnoux C, Genereau T, Lafitte F, *et al*; Brain tuberculomas. *Ann Med Interne (Paris)* 2000; **151**: 448–55.
10. Schwander SK, Ellner JJ: Human immune response to *M. tuberculosis*, Davies PDO, Barnes PF, Gordon SB, editors: Clinical Tuberculosis, 2008, Hodder Arnold; Chapter 8, p. 121.
11. Lucas SB: Histopathology, Davies PDO, Barnes PF, *et al*, editors: Clinical Tuberculosis. London, 2008, Hodder Arnold; Chapter 7, p. 105.
12. Tufariello JM, Chan J, Flynn JL; Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection. *Lancet Infect Dis* 2003; **3**: 578–90.
13. Horsburgh CR, Jr.; Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004; **350**: 2060–7.
14. Sharma SK, Mohan A, Sharma A, *et al*; Miliary tuberculosis: new insights into an old disease. *Lancet Infect Dis* 2005; **5**: 415–30.
15. Vidal JE, Hernandez AV, Oliveira AC, *et al*; Cerebral tuberculomas in AIDS patients: a forgotten diagnosis? *Arq Neuropsiquiatr* 2004; **62**: 793–6.
16. Unal A, Sutlas PN; Clinical and radiological features of symptomatic central nervous system tuberculomas. *Eur J Neurol* 2005; **12**: 797–804.
17. Kim TK, Chang KH, Kim CJ, *et al*; Intracranial tuberculoma: comparison of MR with pathologic findings. *AJNR Am J Neuroradiol* 1995; **16**: 1903–8.
18. Brandli O; The clinical presentation of tuberculosis. *Respiration* 1998; **65**: 97–105.
19. Thwaites GE, Duc Bang N, Huy Dung N, *et al*; The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with Tuberculous meningitis. *J Infect Dis* 2005; **192**: 2134–41.
20. Lu CH, Chang WN, Chang HW; The prognostic factors of adult tuberculous meningitis. *Infection* 2001; **29**: 299–304.
21. Schutte CM; Clinical, cerebrospinal fluid and pathological findings and outcomes in HIV-positive and HIV-negative patients with tuberculous meningitis. *Infection* 2001; **29**:213–7.
22. Koh SB, Kim BJ, Park MH, *et al*; Clinical and laboratory characteristics of cerebral infarction in tuberculous meningitis: a comparative study. *J Clin Neurosci* 2007; **14**: 1073–7.
23. Kinirons P, Baily C, De Gascun C, *et al*; Lymphocytic meningitis: incidence, causes and outcomes over five years. *Ir Med J* 2005; **98**:238–40.
24. Tunkel AR, Glaser CA, Bloch KC, *et al*; The management of encephalitis:

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clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **47**: 303–27.

25. Bicanic T, Harrison TS; Cryptococcal meningitis. *Br Med Bull* 2004; **72**: 99–118.
26. Oncul O, Baylan O, Mutlu H, *et al*; Tuberculous meningitis with multiple intracranial tuberculomas mimicking neurocysticercosis clinical and radiological findings. *Jpn J Infect Dis* 2005; **58**: 387–9.
27. Hoitsma E, Faber CG, Drent M, *et al*; Neurosarcoidosis: a clinical dilemma. *Lancet Neurol* 2004; **3**: 397–407.
28. Pai M, Riley LW, Colford JM, Jr.; Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. *Lancet Infect Dis* 2004; **4**: 761–76.
29. Karstaedt AS, Valtchanova S, Barriere R, *et al*; Tuberculous meningitis in South African urban adults. *QJM* 1998; **91**: 743–7.
30. Wasay M, Kheleani BA, Moolani MK, *et al*; Brain CT and MRI findings in 100 consecutive patients with intracranial tuberculoma. *J Neuroimaging* 2003; **13**: 240–7.
31. Thomas MM, Hinks TS, Raghuraman S, *et al*; Rapid diagnosis of Mycobacterium tuberculosis meningitis by enumeration of cerebrospinal fluid antigen-specific T-cells. *Int J Tuberc Lung Dis* 2008; **12**: 651–7.
32. Quan C, Lu CZ, Qiao J, *et al*; Comparative evaluation of early diagnosis of tuberculous meningitis by different assays. *J Clin Microbiol* 2006; **44**: 3160–6.
33. Bouchama A, al-Kawi MZ, Kanaan I, *et al*; Brain biopsy in tuberculoma: the risks and benefits. *Neurosurgery* 1991; **28**: 405–9.
34. Field M, Witham TF, Flickinger JC, *et al*; Comprehensive assessment of hemorrhage risks and outcomes after stereotactic brain biopsy. *J Neurosurg* 2001; **94**: 545–51.
35. McGirt MJ, Woodworth GF, Coon AL, *et al*; Independent predictors of morbidity after image-guided stereotactic brain biopsy: a risk assessment of 270 cases. *J Neurosurg* 2005; **102**: 897–901.
36. Dammers R, Haitsma IK, Schouten JW, *et al*; Safety and efficacy of frameless and frame-based intracranial biopsy techniques. *Acta Neurochir (Wien)* 2008; **150**: 23–9.
37. Woodworth GF, McGirt MJ, Samdani A, *et al*; Frameless image-guided stereotactic brain biopsy procedure: diagnostic yield, surgical morbidity, and comparison with the frame-based technique. *J Neurosurg* 2006; **104**: 233–7.
38. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 1998; **53**: 536–48.
39. Ormerod LP, Skinner C, Wales J; Hepatotoxicity of antituberculosis drugs. *Thorax* 1996; **51**: 111–3.
40. Breen RA, Miller RF, Gorsuch T, *et al*; Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. *Thorax* 2006; **61**: 791–4.
41. Ungo JR, Jones D, Ashkin D, *et al*; Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. *Am J Respir Crit Care Med* 1998; **157**: 1871–6.
42. Thwaites GE, Nguyen DB, Nguyen HD, *et al*; Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; **351**: 1741–51.
43. Hachad H, Ragueneau-Majlessi I, Levy RH; New antiepileptic drugs: review on drug interactions. *Ther Drug Monit* 2002; **24**: 91–103.
44. Thwaites GE, Simmons CP, Than Ha Quyen N, *et al*; Pathophysiology and prognosis in vietnamese adults with tuberculous meningitis. *J Infect Dis* 2003; **188**: 1105–15.
45. AbdulJabbar M; Paradoxical response to chemotherapy for intracranial tuberculoma: two case reports from Saudi Arabia. *J Trop Med Hyg* 1991; **94**: 374–6.
46. Reiser M, Fatkenheuer G, Diehl V; Paradoxical expansion of intracranial tuberculomas during chemotherapy. *J Infect* 1997; **35**: 88–90.
47. Dautremer J, Pacanowski J, Girard PM, *et al*; A new presentation of immune reconstitution inflammatory syndrome followed by a severe paradoxical reaction in an HIV-1-infected patient with tuberculous meningitis. *AIDS* 2007; **21**: 381–2.
48. Lee CH, Lui CC, Liu JW; Immune reconstitution syndrome in a patient with AIDS with paradoxically deteriorating brain tuberculoma. *AIDS Patient Care STDS* 2007; **21**: 234–9.
49. Rao GP, Nadh BR, Hemaratnan A, *et al*; Paradoxical progression of tuberculous lesions during chemotherapy of central nervous system tuberculosis. Report of four cases. *J Neurosurg* 1995; **83**: 359–62.
50. Jha DK, Mishra V, Choudhary A, *et al*; Factors affecting the outcome of neuroendoscopy in patients with tuberculous meningitis hydrocephalus: a preliminary study. *Surg Neurol* 2007; **68**: 35–41; discussion -2.
51. Rotbart HA; Viral meningitis. *Semin Neurol* 2000; **20**: 277–92.
52. Kosters K, Nau R, Bossink A, *et al*; Rapid Diagnosis of CNS Tuberculosis by a T-Cell Interferon-gamma Release Assay on Cerebrospinal Fluid Mononuclear Cells. *Infection* 2008.

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