Original Paper

Clinical perspectives into the use of thalidomide for central nervous system tuberculosis.

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Word count: 2590

Abstract word count: 250

Figures: 1 **Tables:** 3

Keywords
Central nervous system, CNS, tuberculosis, TB, tuberculosis, thalidomide.

Disclosure of Conflict of Interest
None

Abstract

Background

Central nervous system (CNS) tuberculosis (TB) accounts for over 4% of all TB notifications in the United Kingdom, and causes death or significant disability in over half of those affected. TNF-alpha is a critical cytokine involved in the neuropathogenesis of CNS TB. Thalidomide has been trialled in CNS TB due to its immunomodulatory and immune reconstitution effects, through inhibition of TNF-alpha. Despite animal models demonstrating dramatic improvement in survival, studies in paediatric patients have been associated with higher levels of mortality. The effects of thalidomide have not yet been studied in adults with CNS TB.

This narrative case series guides clinicians through a range of CNS TB clinical cases seen in a large London teaching hospital, serving a region with a high TB incidence of 32 per 100,000, with 55% of TB manifesting as extrapulmonary disease. We aim to illustrate our experiences of using thalidomide to treat a range of severe CNS TB complications.

Methods

Five inpatients at the Royal London Hospital, London, UK treated with thalidomide in addition to standard TB treatment are described in detail. The rationale for treatment initiation with thalidomide is explained.

Results

The case examples are used to guide our reflections and lessons learnt regarding the use of thalidomide. Responses to treatment and functional outcomes suggest thalidomide may be a useful adjunct to standard TB therapy in selected adult cases.

Conclusions

The experience gained from using thalidomide in this small case series may provide evidence towards more research into using thalidomide to treat severe CNS TB.

Introduction

Central nervous system (CNS) tuberculosis (TB) accounts for over 4% of all TB notifications in the United Kingdom, and causes death or significant disability in over half of those affected (1). Thalidomide treatment has been trialled in CNS TB due to its potential immunomodulatory and immune reconstitution effects (2–8). The use of thalidomide in the context of CNS TB in clinical practice is controversial. Animal models studying adjunctive thalidomide use compared to standard CNS TB treatment have demonstrated dramatic improvement in survival (9,10). Initial safety studies in children displayed promising improvement in clinical outcome with minimal side effects(4,5), but a further randomised controlled study in 47 children demonstrated higher levels of mortality compared to controls, and therefore thalidomide was not recommended in routine practice (3). Current British Infection Association guidelines suggest that thalidomide could be considered in tuberculomas that are not responding to standard treatment or high-dose corticosteroids (11). A literature review of thalidomide treatment in CNS TB described four case reports, one clinical trial and one placebo-controlled trial that demonstrated benefit to the use of thalidomide in CNS TB not responding to standard therapy (8). It is difficult to explain such contrasting results obtained by the only randomised trial compared to data from other animal and clinical studies. It is clear that clinical equipoise exists around the use of thalidomide in CNS TB, and that its effects have not been fully studied in adults.

This paper aims to report our experiences of using thalidomide to treat severe CNS TB in five cases. The decision to use thalidomide in the treatment of CNS TB should be taken with extreme caution, and by clinicians highly experienced in TB and CNS inflammation. The decision to use thalidomide in each case below was taken after considerable discussion

between TB experts, when the predicted mortality for the patient was deemed to be extremely high, and very unlikely to respond to standard CNS TB treatment. The presenting features, rationale for selecting thalidomide and resulting clinical outcomes are discussed below as a means of sharing our experiences with the wider TB community.

Ethics board review was not required for this case series. All patients included in this study (or their next of kin where appropriate) provided signed consent forms for their information to be published anonymously in medical journals and associated websites.

Case one

A 40-year-old female of Indian origin on treatment for pulmonary TB for six months presented with headache, vomiting and confusion. Glasgow Coma Scale (GCS) score was 14 at presentation, and no focal neurology was detected on examination. Magnetic Resonance (MR) imaging demonstrated an abscess with significant oedema, midline shift and contralateral hydrocephalus. The patient underwent emergency craniectomy and postoperatively commenced IV Rifampacin, Isoniazid, Moxifloxacin and Dexamethasone (8mg BD). The abscess was smear-positive for acid-fast bacilli (AFB); TB culture was negative. PCR confirmed Mycobacterium tuberculosis with no mutations associated with rifampicin resistance. She was discharged after five days following craniectomy on oral Rifater, Ethambutol and Pyridoxine.

She re-presented two months afterwards with headaches and vomiting. MR imaging demonstrated recurrence of the collection and a second lesion in the right temporal lobe. A second craniectomy and abscess drainage was performed. The worsening appearance was

felt to be secondary to paradoxical immune reconstitution inflammatory syndrome (IRIS) due to steroid reduction. Thalidomide was chosen as a steroid-sparing agent and was continued for one year without significant reported side effects. TB antimicrobial treatment was discontinued after two years.

Outcome: Mild memory impairment, back in full-time employment. Peripheral neuropathy.

Learning points: Reducing steroids risks potentiating the immune reconstitution syndrome and worsening of clinical status. Thalidomide may have a role in allowing safe reduction of steroids whilst preventing immune reconstitution. Thalidomide can induce a dose-dependent sensorimotor length-dependent axonal neuropathy and therefore close monitoring is advised.

Case two

A 37-year-old Senegalese male presented with headache, fever and confusion. GCS was 14 and no focal neurology was identified. MR imaging demonstrated multiple enhancing lesions with leptomeningeal enhancement and an intramedullary spinal lesion from the craniocervical junction to T2, with two further lesions at T3 and T11-12. He deteriorated despite IV antituberculous therapy and IV dexamethasone 8mg TDS. It was unclear whether this was due to resistance or due to paradoxical IRIS. Bronchial washings were smear positive for acid-fast bacilli and a fully sensitive organism grew on culture, which made the diagnosis of IRIS more likely. Therefore, the steroid dose was increased and thalidomide initiated.

After one month of clinical and radiological stability, the steroid dosage was reduced

(Dexamethasone 8mg tds to 8mg bd). Following this change, there was a sudden deterioration of GCS with fixed and dilated pupils. Computerised Tomography (CT) scan showed a dilated fourth ventricle and multiple parenchymal lesions causing crowding of the foramen magnum with tonsillar descent. An emergency extra ventricular drain was inserted, but unfortunately soon after the patient suffered a cardiac arrest and died.

Outcome: Patient deceased.

Learning Points: Attenuation of the inflammatory response in CNS TB appears to improve survival by reducing the likelihood or severity of neurologic complications (5,8). The British Infection Society guidelines for the diagnosis and treatment of CNS tuberculosis recommend starting dexamethasone at 0.4mg/kg/day IV, with a tapering dose to 0.3mg/kg/day at week two, 0.2mg/kg/day at week three, 0.1mg/kg/day at week four to 4mg total dose/day orally before stopping at week eight (11). Trials have not been conducted to ascertain the optimum starting dose or tapering regime of steroids. The recommended dose and length of treatment may not reflect the severity or extent of TB-related CNS inflammation. We tend to use 16-20mg dexamethasone/ day IV, with a far more protracted reduction in severe cases, until clinical stability is clearly demonstrated. Similar to the previous case, this patient appeared to develop IRIS related to early steroid reduction. Thalidomide was initiated five weeks following acute deterioration. It may be that thalidomide needs to be started early in patients with poor prognostic factors to prevent CNS inflammation rather than as 'rescue medication'.

Case three

A 50-year-old Somali male presented with bilateral lower limb weakness and urine retention for 48 hours. Examination revealed a flaccid paraparesis with preserved sensation. MR imaging revealed abnormal signal in the brainstem with associated meningeal thickening and enhancement, and a radiculomyelitis affecting the cervical, thoracic and lumbar cord with relative sparing of the conus, suggestive of TB (see figure 1). Two cerebrospinal fluid (CSF) examinations performed a week apart demonstrated high protein (1-1.4g) and high lymphocyte counts (15-45/microliter). Samples were negative for AFBs, TB culture and TB PCR.

The patient was empirically started on antimycobacterial therapy and prednisolone 120mg daily. The extent of spinal cord swelling and risk of cord compression was felt to justify the simultaneous initiation of thalidomide in an attempt to maximally supress inflammation. He remained an inpatient for four months, for treatment and rehabilitation. There were no reported side effects from thalidomide.

At six months the patient had regained continence, with improved lower limb tone but no improvement in power. MR imaging displayed radiological improvement, with regression of the abnormal brainstem signal and basal leptomeningeal enhancement, and resolution of spinal cord and leptomeningeal enhancement despite persistent cord signal change (see figure 1) .

Outcome: The patient remained wheelchair bound, but regained continence.

Learning Points: Thalidomide was initiated at the onset of antitubercular therapy with high dose steroids in an attempt to maximally supress secondary inflammation.. It is unclear

whether thalidomide can reverse the effects of established spinal cord tuberculosis Thalidomide is thought to supress secondary TB associated vasculitis and tuberculoma formation through immune modulation (8,10). It is not clear whether initiation of thalidomide early in the disease process helps prevent secondary complications, or whether it should be reserved for use only once secondary complications are established, suggesting the need to escalate treatment.

Case four

A 41 year old Congolese female presented with a thunderclap occipital headache. CSF was heavily blood-stained, with protein of 2.2g/dL, CSF Glucose 4.0 mmol/L, Serum Glucose 5.9 mmol/L, WCC 270/ microliter (70% neutrophils); no organisms were seen. The patient's GCS dropped to 9 within 24 hours, and repeat CT head demonstrated hydrocephalus, for which an EVD was inserted. An MRI brain demonstrated meningeal enhancement around the brainstem. The patient was commenced on Rifampicin, Isoniazid, Pyrazinamide, Moxifloxacin and Dexamethasone 15mg BD for presumed CNS TB. Moxifloxacin was selected instead of Ethambutol due to its risk of optic neuropathy and the inability of being able to examine visual acuity due to the patient's low conscious state, as well as its superior CNS penetration properties.

An interval MRI performed a week later demonstrated small foci of restricted diffusion involving the cerebellum, midbrain and pons secondary to an underlying vasculitis. The finding of associated vasculitis prompted initiation of thalidomide 50mg BD.

A ventriculoperitoneal shunt was inserted and the EVD was removed. In the days following initiation of thalidomide, the patient became more responsive, albeit confused with

inappropriate speech. She was able to follow simple one stage commands, moving all four limbs.

Three weeks later she deteriorated with further infarcts. The thalidomide dose was increased to 100mg BD with addition of Prothionamide due to its effective CNS penetration (8).

During this time the patient developed a brief transaminitis and episodes of bradycardia, which were thought to be secondary to the increased dose of thalidomide. After four months of prolonged high dose steroids, the thalidomide dose was increased to 150mg BD as a 'steroid sparing' agent. Upon increase, there were frequent episodes of profound bradycardia (HR<40), which prompted a change of dosing to 100mg TDS. The dexamethasone was subsequently weaned by 2mg each week. The patient gradually improved and was able to follow more complex three-stage motor commands, could feed herself and was able to have short conversations in her native language. An interval MRI showed on-going meningeal enhancement but no new ischaemic lesions.

Outcome Severe cognitive-communicative impairment, walking with frame and assistance.

Learning Points: This demonstrates the rapid deterioration that can occur in vasculitis despite maximal standard TB therapy and high dose steroids. Thalidomide was initiated in an attempt to prevent further infarcts. Despite this the patient had a further area of infarction three weeks after treatment initiation. Little is known regarding how quickly thalidomide takes effect or the optimum dose required to prevent vasculitis, but it seems increasing the dose to 100mg BD may have contributed to attenuating the inflammatory response. Hepatitis and bradycardia were side effects but were easily mitigated with dose

alteration.

Case five

This 37-year old Polish gentleman with a background of crack-cocaine use was admitted confused and combative with a GCS of 10. Initial CT head and chest showed a small thalamic bleed and evidence of miliary TB. He was initiated on standard TB therapy, but became increasingly drowsy over the next 24 hours. A repeat CT showed diffuse cerebral oedema and hydrocephalus. He was intubated, ventilated, and a right frontal EVD was inserted. EVD CSF revealed a protein of 1.2g and 20 WCC mm^3 (85% lymphocytes). Due to a high index of concern for the potential for MDR-TB in a high-risk patient, Levofloxacin and Amikacin were added to standard TB therapy with dexamethasone 16mg BD.

Bronchial lavage was positive for acid-fast bacilli. GeneXpert analysis demonstrated no rifampicin resistance.

An interval CT head at four weeks demonstrated bilateral thalamic infarcts. This prompted a neurology review and initiation of thalidomide 50mg BD. An interval MRI at 13 weeks demonstrated on-going disseminated intracranial tuberculosis with multiple tuberculomata but no further infarction. Thalidomide was increased gradually to 200mg BD.

Sequential imaging demonstrated stable disease, but the development of hydrocephalus despite ICP measurements being normal. This led to a diagnosis of normal pressure hydrocephalus. A VP shunt was inserted leading to significant neurological improvement. After 8 months the patient is able to hold simple conversations, sit out in a chair, transfer independently and feed himself.

Outcome: Severe cognitive impairment. UL and LL power improving.

Learning point: The introduction of thalidomide appeared to prevent further ischemic infarcts, suggesting its efficacy at dampening inflammation. There are case reports describing successful treatment of cerebral tuberculomas with thalidomide (4,6,8).

Discussion

Infarctions as a result of CNS TB associated vasculitis occur in approximately 20-30% of patients (12,13) and is a devastating complication of advanced infection and an important determinant of outcome. Patients who develop CNS TB associated infarction are three times more likely to die than those without infarction (12). CNS TB associated vasculitis is thought to be caused by two processes; direct invasion and immunologic injury. Direct invasion occurs through basal exudates causing inflammatory changes in the vessels of the circle of Willis, causing vessel lumen inflammation and thrombus formation. Immunologic injury occurs through tuberculoprotein immune complexes forming in vessels (13). Anti-tuberculous chemotherapy appears to be relatively ineffective in preventing vascular complications, perhaps suggesting an underlying immune mechanism (14).

Immunomodulatory treatment with thalidomide through the inhibition of TNF-a has been studied experimentally and clinically. TNF-a in the CSF produced during TBM has been shown to correlate with disease activity in studies using rabbits (15). Moreover, when animals were infected with high doses of CNS mycobacterium, 50% died when treated with standard TB medication. Only the combination of anti-TB drugs with thalidomide resulted in a dramatic improvement in survival to 100% (10). A randomised controlled trial of

thalidomide for paediatric TBM cases had to be stopped early due to deaths (4/30) and adverse events occurring in the treatment arm. This study may have been biased; the small number of thalidomide treated patients that died had very severe neurological impairment at presentation compared to the standard treatment group. Motor outcome after six months of treatment was similar in the two groups despite this (3). Regardless of potential flaws in methodology, this research finding halted on-going studies into thalidomide as an adjunctive treatment in CNS TB. As discussed above, a literature review into thalidomide treatment for CNS TB has shown favourable results in selected cases (8). This case series appears to demonstrate a trend in preventing on going complications in well-selected patients without serious side effects. In the cases presented, thalidomide was potentially effective in reducing morbidity in cases or paradoxical IRIS, as well as TB associated vasculopathy. Further randomised controlled trials would need to be conducted to ensure the efficacy of thalidomide in clinical practice compared to best standard therapy.

The efficacy of thalidomide in CNS TB in laboratory controlled animal studies contrasts that seen in previous clinical trials. Questions remain unanswered regarding the potential use of thalidomide to treat CNS TB. Firstly, the safety of thalidomide has not been studied in adults. No consensus has been agreed regarding the indications for, timing or duration of treatment of thalidomide in CNS TB. Concurrent use and dosage of steroids may also influence outcome. Once considered a 'last-ditch' medication provided to patients in extremis, our experience suggests initiation of treatment early in disease onset may prevent immune mediated responses developing, and the disabling sequelae that follows. Without more novel therapeutics in production, thalidomide may be one more weapon in the arsenal against this notoriously difficult to treat, severely disabling neurological condition.

Declaration of conflicts of interest

None

Funding

None

Authorship contributions

All authors to this paper have contributed in the following ways to the production of the journal

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table I- Demographics and presenting features of patients with CNS TB treated with thalidomide.

Case	Sex	Age	Ethnicity	TBM	Tuberculoma	Spinal tuberculosis	Presenting GCS	MRC TB grade	HIV status	Presenting features	Extra CNS TB
1	F	40	Indian		Y		14	I	-ve	Headache, vomit, confusion	Miliary
2	M	37	Black British African	Y	Y	Y	14	II	-ve	Fever, headache, confusion	Pulmonary
3	M	50	Black British African	Y		Y	15	III	-ve	Bilateral lower limb weakness	No
4	M F	41	British African	Y		Y	9	III	-ve	Low GCS, headache	No
5	M	37	White Polish	Y	Y		10	III	-ve	Low GCS, agitation	Pulmonary

* Grade I= non-specific symptoms, minimal signs of meningitis, Grade II= drowsy or focal neurological signs, Grade III= deep stupor or comatose

Table II- Investigation findings of CNS TB cases treated with thalidomide

Case	LP protein (g/dL)	LP WCC (mm^3)	LP lymphocyte %	LP AFB	LP MC&S	LP glucose CSF: Serum	TB +ve samples	MRI findings
1	ND	ND	ND	Positive	Negative	ND	Tuberculous abscess aspirate +ve for AFB and PCR	Tuberculous abscess in the right superior temporal lobe with associated meningitis + oedema with midline shift and some early contralateral hydrocephalous
2	1.12	1	NA	Negative	Negative	2.8 : 6.4	Bronchial washings AFB and PCR +ve	Multiple enhancing parenchymal lesions, leptomeningeal enhancement. Spinal intramedullary lesion
3	1.47	45	70	Negative	Negative	2.3 : 9.7	Nil	Basal leptomeningeal enhancement Myelitis from T7 to conus, radiculomyelitis
4	2.22	40	99	Negative	Negative	4.0 : 5.9	Nil	Meningitis, parenchymal enhancing lesions, ischemic lesion Myelitis
5	1.20	8	90	Negative	Positive	0.9 : 6.6	Bronchial sample +ve AFB, culture, genxpert*	Meningitis, parenchymal involvement, ischemic lesion

ND= Not done, WCC= White Cell Count, AFB= Acid Fast Bacilli, PCR= Polymerase Chain Reaction

* Is a nucleic acid amplification test that can identify Mycobacterium tuberculosis DNA and resistance to rifampicin.

Table III- Treatments and outcomes of CNS TB cases treated with thalidomide

Case	Antimicrobials	Initial steroid and dose	Decision to give thalidomide	Thalidomide initiation from presentation (weeks)	Surgical intervention	MRS* at follow up	Follow up duration (months)
1	Ri, Z, E	Dexamethasone 8mg BD	IRIS – steroid sparing	15	Craniectomy, abscess drainage x2	2	33
2	Ri, Z, M	Dexamethasone 8mg TDS	Drug resistant disease	6	EVD	6	24
3	Ri, E, M	Prednisolone 60mg	Aggressive disease	2	Nil	4	12
4	R, H Z, M	Dexamethasone 15mg BD	Associated vasculitis	3	EVD, VP shunt	4	9
5	R, H, Z, E	Dexamethasone 8mg BD	Associated vasculitis	8	ICP bolt, EVD, VP shunt	4	8

BD= twice daily, TDS= three times daily
EVD= Extra Ventricular Drain, VP= Ventriculo-peritoneal, Ri=Rifinah, R= Rifampicin, H=Izoniazid, Z=Pyrazinamide, E=Ethambutol, M=Moxifloxacin
*MRS= Modified Rankin Scale 0=no symptoms, 1=no significant disability, able to carry out usual activities despite symptoms, 2= Able to look after own affairs without assistance but unable to carry out previous activities, 3=requires help but able to walk unassisted, 4=unable to attend to own bodily needs, unable to walk unassisted, 5=requires constant nursing and attention, bedridden, incontinent, 6=dead