



OPEN LETTER

REVISÉ Management of intracranial tuberculous mass lesions: how long should we treat for? [version 3; peer review: 3 approved]

Suzaan Marais ^{1,2}, Ronald Van Toorn³, Felicia C. Chow ⁴, Abi Manesh⁵, Omar K. Siddiqi ^{6,7}, Anthony Figaji ⁸, Johan F. Schoeman³, Graeme Meintjes⁹, Tuberculous Meningitis International Research Consortium

¹Department of Neurology, Inkosi Albert Luthuli Central Hospital and University of KwaZulu-Natal, Durban, 4091, South Africa

²Division of Neurology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, 7925, South Africa

³Department of Pediatrics and Child Health, Stellenbosch University, Cape Town, 7505, South Africa

⁴Weill Institute of Neurosciences and Department of Neurology and Division of Infectious Diseases, University of California, San Francisco, California, 94110, USA

⁵Department of Infectious Diseases, Christian Medical College, Vellore, 632004, India

⁶Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, 02215, USA

⁷Department of Internal Medicine, University of Zambia School of Medicine, Lusaka, Zambia

⁸Division of Neurosurgery and Neuroscience institute, University of Cape Town, Cape Town, 7700, South Africa

⁹Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, Department of Medicine, University of Cape Town, Cape Town, 7925, South Africa

v3 First published: 15 Oct 2019, 4:158 (<https://doi.org/10.12688/wellcomeopenres.15501.1>)

Second version: 31 Oct 2019, 4:158 (<https://doi.org/10.12688/wellcomeopenres.15501.2>)

Latest published: 26 Feb 2020, 4:158 (<https://doi.org/10.12688/wellcomeopenres.15501.3>)

Abstract

Tuberculous intracranial mass lesions are common in settings with high tuberculosis (TB) incidence and HIV prevalence. The diagnosis of such lesions, which include tuberculoma and tuberculous abscesses, is often presumptive and based on radiological features, supportive evidence of TB elsewhere and response to TB treatment. However, the treatment response is unpredictable, with lesions frequently enlarging paradoxically or persisting for many years despite appropriate TB treatment and corticosteroid therapy. Most international guidelines recommend a 9-12 month course of TB treatment for central nervous system TB when the infecting *Mycobacterium tuberculosis* (*M.tb*) strain is sensitive to first-line drugs. However, there is variation in opinion and practice with respect to the duration of TB treatment in patients with tuberculomas or tuberculous abscesses. A major reason for this is the lack of prospective clinical trial evidence. Some experts suggest continuing treatment until radiological resolution of enhancing lesions has been achieved, but this may unnecessarily expose patients to prolonged periods of potentially toxic drugs. It is currently unknown whether persistent radiological enhancement of intracranial tuberculomas after 9-12 months of treatment represents active disease, inflammatory response in a sterilized lesion or merely

Open Peer Review

Reviewer Status

	Invited Reviewers		
	1	2	3
version 3 (revision) 26 Feb 2020	 report		 report
version 2 (revision) 31 Oct 2019	 report	 report	 report
version 1 15 Oct 2019			

1 **Jerome H. Chin** , NYU Langone Health, New York City, USA

2 **Benedict Michael**, University of Liverpool, Liverpool, UK

revascularization. The consequences of stopping TB treatment prior to resolution of lesional enhancement have rarely been explored. These important issues were discussed at the 3rd International Tuberculous Meningitis Consortium meeting. Most clinicians were of the opinion that continued enhancement does not necessarily represent treatment failure and that prolonged TB therapy was not warranted in patients presumably infected with *M.tb* strains susceptible to first-line drugs. In this manuscript we highlight current medical treatment practices, benefits and disadvantages of different TB treatment durations and the need for evidence-based guidelines regarding the treatment duration of patients with intracranial tuberculous mass lesions.

Keywords

tuberculosis, central nervous system, treatment duration, management, imaging, tuberculous meningitis, tuberculoma, tuberculous abscess

3 **Julie Higashi**, Los Angeles County Department of Public Health, Los Angeles, USA
University of California, San Francisco, San Francisco, USA

Any reports and responses or comments on the article can be found at the end of the article.



This article is included in the [Wellcome Centre for Infectious Diseases Research in Africa \(CIDRI-Africa\)](#) gateway.



This article is included in the [Tuberculous Meningitis International Research Consortium](#) collection.

Corresponding author: Suzaan Marais (marais.suzaan@gmail.com)

Author roles: **Marais S:** Conceptualization, Project Administration, Resources, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Van Toorn R:** Writing – Original Draft Preparation, Writing – Review & Editing; **Chow FC:** Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Manesh A:** Writing – Original Draft Preparation, Writing – Review & Editing; **Siddiqi OK:** Writing – Original Draft Preparation, Writing – Review & Editing; **Figaji A:** Writing – Original Draft Preparation, Writing – Review & Editing; **Schoeman JF:** Writing – Original Draft Preparation, Writing – Review & Editing; **Meintjes G:** Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing;

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by the Wellcome Trust [098316 and 203135 to GM, 097254 to SM]. FCC was supported by National Institutes of Health/Fogarty International Center [R21TW011035]. OKS was supported by the National Institutes of Health [K23 NS084054-01]. AF was supported by the National Research Foundation SARChI Chair in Clinical Neurosciences. GM is also supported by the South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation (NRF) of South Africa [64787], NRF incentive funding [UID: 85858] and the South African Medical Research Council through its TB and HIV Collaborating Centres Programme with funds received from the National Department of Health [RFA# SAMRC-RFA-CC: TB/HIV/AIDS-01-2014]. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The opinions, findings and conclusions expressed in this manuscript reflect those of the authors alone. This work was supported by the Wellcome Trust through funding to the Tuberculous Meningitis International Research Consortium.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2020 Marais S *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Marais S, Van Toorn R, Chow FC *et al.* **Management of intracranial tuberculous mass lesions: how long should we treat for? [version 3; peer review: 3 approved]** Wellcome Open Research 2020, 4:158 (<https://doi.org/10.12688/wellcomeopenres.15501.3>)

First published: 15 Oct 2019, 4:158 (<https://doi.org/10.12688/wellcomeopenres.15501.1>)

REVISED Amendments from Version 2

Our revised manuscript includes several additional points of discussion. We mention the differential diagnoses of intracranial enhancing lesions that may be indistinguishable from tuberculous mass lesions by imaging and discuss the utility of diffusion weighted imaging/apparent diffusion coefficient values in tuberculous mass lesions. We include a cautioning remark that a lack of radiological response to TB treatment could indicate that the diagnosis of tuberculoma was incorrect. We describe a few additional immunomodulatory agents that have shown anecdotal benefit in paradoxical TB reactions affecting the central nervous system and emphasize the need for future studies investigating the utility of host-directed therapies in affected patients. We comment on the variability of follow-up practices in patients with intracranial tuberculous mass lesions as well as the lack of clear guidelines for timing of follow-up imaging in patients with persistent lesions. We reference case reports of patients with recurrent tuberculous mass lesions after completion of TB treatment and comment on the potential reasons for such recurrences, which includes paradoxical reactions. We include additional magnetic resonance and computed tomography images of intracranial tuberculous mass lesions.

Any further responses from the reviewers can be found at the end of the article

Disclaimer

The views expressed in this article are those of the author(s). Publication in Wellcome Open Research does not imply endorsement by Wellcome.

Introduction

Neurological tuberculosis (TB) manifests as meningitis, radiculomyelitis, bony spinal disease and tuberculoma/tuberculous abscess that may occur intracranially or within the spinal space¹. Similar to the other neurological TB manifestations, tuberculous mass lesions are common in settings with high TB incidence^{2,3}, and high HIV prevalence⁴⁻⁷, where this diagnosis accounts for a significant proportion of intracranial space occupying lesions. The diagnosis of intracranial tuberculoma is most often presumptive and based on radiological features, supportive evidence of TB elsewhere and response to TB treatment. However, the treatment response of tuberculomas is unpredictable and lesions may persist for many years despite appropriate TB treatment and adjunctive corticosteroid therapy⁸⁻¹². The optimal duration of TB treatment is unknown and clinical practice varies. In this manuscript we highlight current divergent clinical practice, benefits and disadvantages of different TB treatment durations and the need for prospective clinical trial data to determine the optimal treatment duration in patients with intracranial tuberculous mass lesions.

Pathogenesis and pathology

Hematogenous seeding after the primary infection is one proposed mechanism of central nervous system (CNS) involvement in TB¹³. Miliary disease may increase the risk of hematogenous spread to the CNS¹⁴. *Mycobacterium tuberculosis* (*M.tb*) may enter the CNS via direct infection of endothelial cells or trafficking through infected phagocytes^{15,16}, which is followed by the formation of tubercles, most commonly in the brain

cortex or meninges. Rupture of an adjacent tubercle into the sub-arachnoid space results in tuberculous meningitis (TBM), whilst tubercles that do not rupture may progress to form tuberculomas¹³. Tuberculomas show granulomatous inflammation with a central area of caseous necrosis surrounded by epithelioid histiocytes, Langerhan's giant cells, lymphocytes, astrocytes and vascular proliferation that evolves to develop a thick vascular connective tissue layer.

The mycobacterial burden in CNS TB is low. The impressive pathology and evolution of lesions during TB therapy highlights the role of the host inflammatory response in pathogenesis. Microglia in the CNS are infected by *M.tb* and activated microglia release many cytokines that play a crucial role in pathogenesis¹⁷. TNF- α is a central molecule in the control and mediation of inflammation in CNS TB. While TNF- α is involved in granuloma formation and control of disease, elevated levels are associated with markers of increased pathology such as cerebrospinal fluid leukocytosis, higher levels of other soluble inflammatory mediators, increased *M.tb* load and clinical deterioration¹⁸. Studies focused on the vasculature associated with tuberculomas have revealed significant vasculitis with proliferative changes in the basement membrane¹⁹.

Occasionally, tubercles may coalesce or continue to progress to form a tuberculous abscess, which is a large pus-filled encapsulated lesion containing bacilli^{20,21}. Histopathologically, the tuberculous abscess wall shows chronic vascular granulation tissue whilst lacking the granulomatous reaction of a tuberculoma.

Clinical presentation

The clinical features of tuberculomas depend on their anatomic location in the brain, related to local mass effect, obstruction of cerebrospinal fluid pathways, and/or seizures. Supratentorial lesions are common in adults while infratentorial involvement is slightly more common in children²². Patients usually present sub-acutely with symptoms and signs such as headaches, seizures, depressed level of consciousness, and focal neurological deficits^{12,23,24}. Infratentorial lesions commonly present with hydrocephalus. Pituitary apoplexy and movement disorders like chorea are rare manifestations of tuberculomas^{25,26}. If associated with TBM, meningeal symptoms and signs may dominate the clinical picture. Tuberculous abscesses have a more accelerated course, often presenting acutely with associated fever²¹.

Imaging findings

Neuroimaging is essential for identifying intracranial tuberculous mass lesions with findings determined by the composition of the lesion. Tuberculomas have classically been categorized as non-caseating, caseating solid, and caseating liquid, that can be differentiated on computed tomography (CT) and magnetic resonance imaging (MRI) (Figure 1)²¹. Multiple lesions are seen more often than isolated lesions though the latter is still common^{27,28}. Perilesional edema can be present or absent.

CT is the most frequent modality used to identify tuberculomas due to its wide availability though it has limitations in resolution. Tuberculomas typically appear as round or lobulated

nodules that are hypodense or isodense to the brain parenchyma. CT with contrast most commonly shows rim enhancement of lesions but nodular or homogeneous enhancement can also be seen¹².

MRI is the preferred modality for the identification of tuberculomas due to superior resolution and better visualization of the posterior fossa relative to CT. Non-caseating granulomas are hypointense or isointense on T1-weighted imaging (T1WI) and hyperintense on T2-weighted imaging (T2WI, “T2-bright”) with homogeneous contrast enhancement²¹. Caseating solid granulomas are hypointense or isointense on T1WI and hypointense on T2WI (“T2-black”) with rim enhancement. Caseating liquid granulomas, which are rare, are hypointense on T1WI and hyperintense on T2WI with rim enhancement. Tuberculous abscesses may be indistinguishable from tuberculomas with a liquid center on standard MRI settings, but they are usually larger (>3 cm in diameter) and thin-walled in appearance (Figure 1)²¹. Miliary tuberculomas appear as multiple, small (2–3 mm), scattered lesions that typically rim enhance with contrast administration and lack perilesional edema²⁹.

Evidence of a satisfactory radiological response on serial brain imaging after TB treatment initiation includes a reduction in perilesional edema, decrease in lesion size and calcification (seen on CT). Other findings supportive of improvement of liquified tuberculomas and abscesses on MRI are a decrease in T2 brightness and, subsequently, loss of T2 signal. Evolution of TB abscesses from early-stage “T2-bright” with edema to “T2-black” lesions may represent a marker for cure (Figure 2)³⁰. In our experience, the resultant homogeneous “T2-black” tuberculoma (with rim T1 contrast enhancement) may persist for many months in asymptomatic patients without relapse off TB treatment. CT of such lesions usually shows gradual calcification, which most often involves the capsule (Figure 3).

The differential diagnosis of enhancing brain lesions is vast and includes infective, neoplastic, inflammatory, demyelination and vascular conditions that may be indistinguishable from tuberculous mass lesions by CT and conventional MRI sequences^{31,32}. Although the presence of a “target sign” on CT, which consists of a rim enhancing lesion with central calcification, is highly suggestive of a tuberculoma^{33,34}, it is uncommon and other conditions

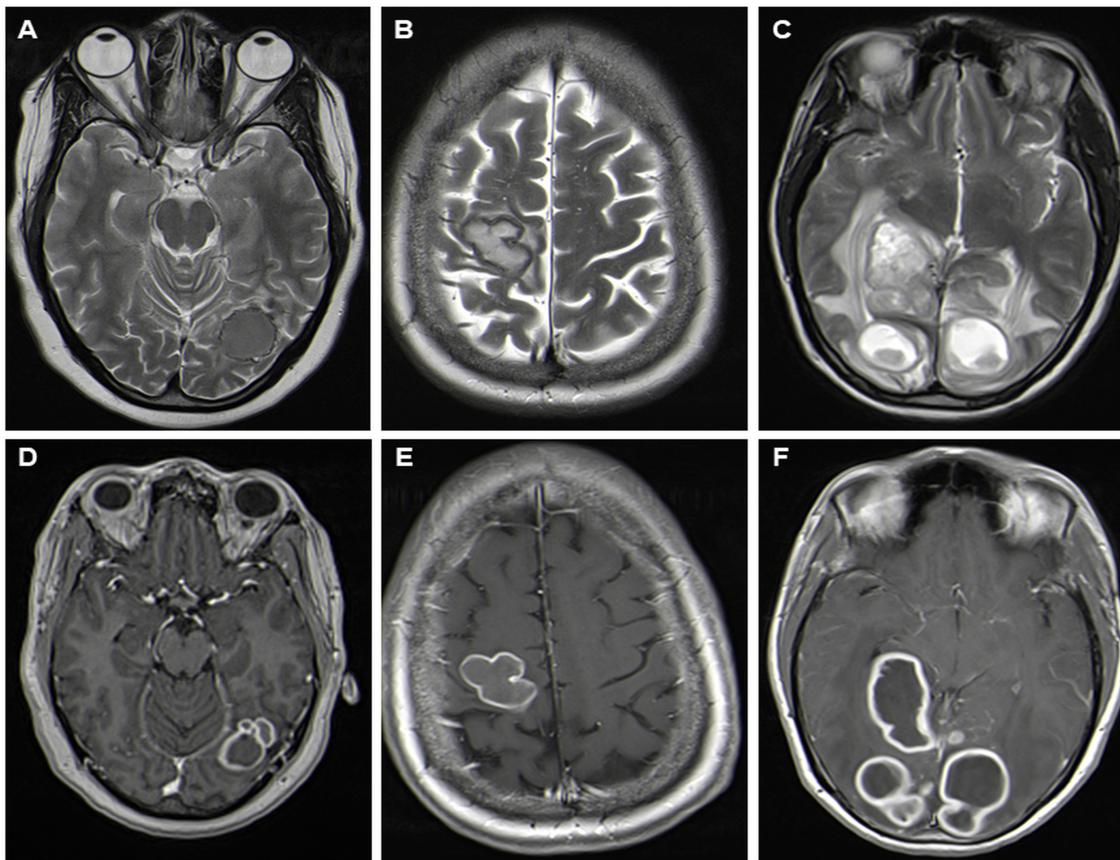


Figure 1. Magnetic resonance imaging of various categories of tuberculous mass lesions. Axial T2-weighted images (A, B and C) and corresponding T1-weighted post-contrast images (D, E and F) of caseating solid tuberculoma (A and D), caseating liquid tuberculoma (B and E) and tuberculous abscess (C and F).

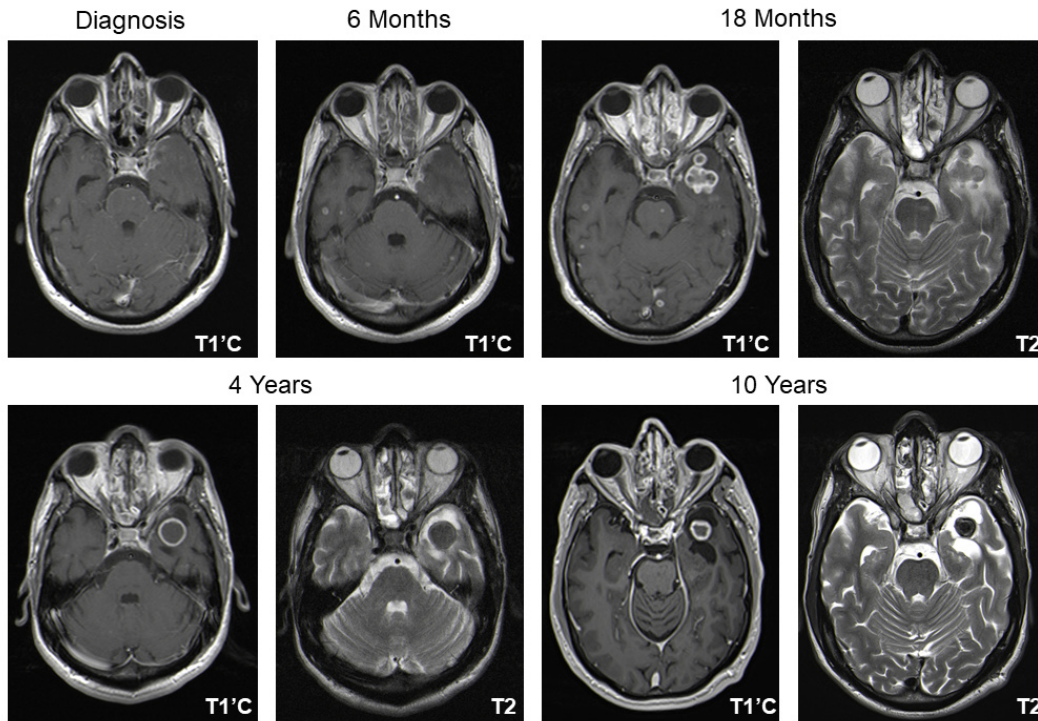


Figure 2. Serial magnetic resonance imaging of a patient with drug-susceptible central nervous system tuberculosis who received TB treatment for 4 years. Axial T1-weighted post-contrast (T1'C) images and T2-weighted (T2) images are shown. At diagnosis, a miliary pattern with focal meningeal enhancement of the left temporal lobe was noted, which persisted at 6-months follow-up. At 18 months, a lobulated rim-enhancing tuberculoma had developed in the left temporal lobe which was of mixed intensity on T2-weighted images with surrounding edema. Despite gradual reduction in lesion size and perilesional edema with associated atrophy, rim-enhancement persisted during the next 8.5 years of follow-up. Notably, the patient did not deteriorate clinically after cessation of TB treatment and the T2-signal of the lesion became increasingly hypointense (“T2-Black”) suggesting cure.

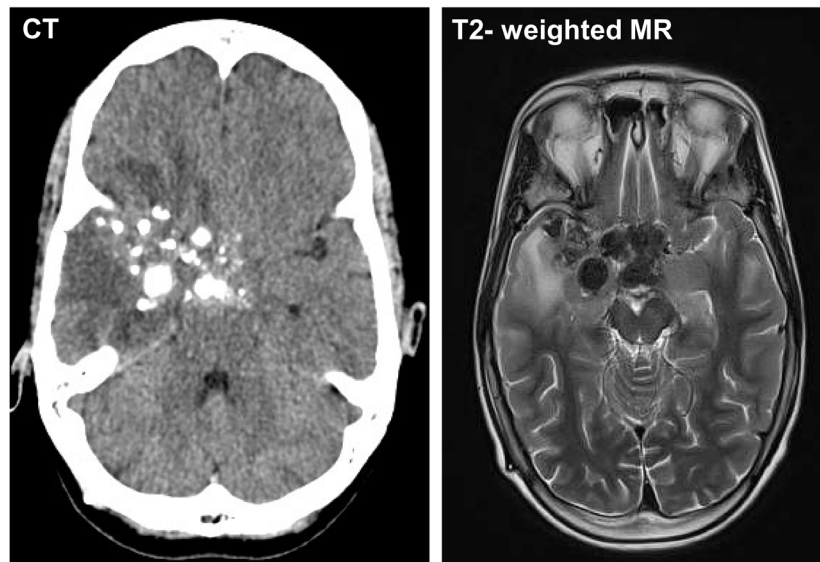


Figure 3. Corresponding magnetic resonance (MR) and computed tomography (CT) images of tuberculomas demonstrating calcification by CT imaging of lesions that appear hypointense (“T2-black”) by T2-weighted MRI.

may mimic these findings³⁵. MRI techniques such as diffusion weighted imaging (DWI) may improve the diagnostic accuracy of MRI for evaluating patients with intracerebral tuberculous mass lesions³⁶. DWI is a technique that characterizes tissues on the basis of the molecular motion of water contained within them. Tuberculous lesions that show hyperintense centers on T2WI (i.e. caseating liquid granulomas and tuberculous abscesses) frequently show increased signal intensity cores on DWI and have reduced apparent diffusion coefficient (ADC) values, which are consistent with restricted diffusion within the lesion^{37,38}. Conversely, caseating solid tuberculomas (hypointense centers on T2WI) most commonly show decreased signal intensity cores on DWI³⁷ and have significantly higher ADC values compared to T2 hyperintense lesions^{38,39}. As caseating liquid tuberculomas are rare, most tuberculomas do not demonstrate restricted diffusion. One of the main applications of DWI in tuberculous mass lesions is its ability to distinguish those with restricted diffusion from necrotic and cystic tumors, that typically show features consistent with free diffusion^{40,41}. However, tuberculous brain abscesses are indistinguishable from pyogenic abscesses that also typically show reduced diffusion^{36,41}. It may be possible to distinguish tuberculous lesions with restricted diffusion from other infections such as neurocysticercosis^{38,39}, cryptococcomas³⁶ and toxoplasmosis³⁶, that do not typically show restricted diffusion. However, DWI findings is variable in the vast majority of infective causes of intracerebral lesions³⁶ and results should therefore be considered in conjunction with clinical and other investigation findings. Other advanced MRI techniques such as MR spectroscopy (MRS), magnetized transfer (MT) imaging and susceptibility-weighted imaging (SWI) are also under investigation to improve the diagnostic yield of tuberculous brain lesions, but are beyond the scope of this article^{34,39}.

Paradoxical reactions

Paradoxical enlargement or the development of new intracranial tuberculomas or abscesses in patients with CNS or extraneural TB on appropriate treatment is well-described^{8,42-54}. Such reactions typically occur within the first six months after TB treatment initiation^{45,51,52,55}, but may rarely be delayed for a year or more^{10,55-57}. Paradoxical reactions are often identified when patients present with neurological deterioration during TB treatment, prompting brain imaging. In case series of predominantly HIV-uninfected patients with CNS TB, clinical deterioration due to paradoxical tuberculoma reaction has been described in 6–29%^{8,42-49}. However, many of these patients are asymptomatic during these episodes and the frequency of detecting paradoxical tuberculoma development or enlargement increases substantially (from 29% to 65%) if surveillance brain imaging is performed during the first six months of TB treatment⁴⁵. Paradoxical TB reactions are more common in HIV-infected patients, particularly in those who commence antiretroviral therapy (ART) after starting TB treatment, in which case it is referred to as paradoxical TB-immune reconstitution inflammatory syndrome (TB-IRIS)⁵⁸⁻⁶¹. The influence of HIV on the frequency of paradoxical tuberculoma reactions (separate from the effect of ART) has rarely been reported. One recent study of 47 HIV-infected and 14 HIV-uninfected adults with tuberculomas found no difference in the frequency of paradoxical reactions by HIV status (36% in each group)¹². The majority of HIV-infected patients were receiving ART prior to tuberculoma presentation or did not start

ART after diagnosis, precluding the development of TB-IRIS in this group. The pathogenesis of paradoxical reactions (including IRIS) remains unclear but is likely related to an aberrant immune response to TB antigens rather than failure of TB treatment^{52,62}. Clinical findings supporting this view are the observation that new or enlarging tuberculomas in TBM patients frequently appear in those known to be infected with drug-susceptible strains who show clinical and radiological improvement of other aspects of TBM (Figure 2)⁵³. Another argument is that anti-inflammatory drugs (corticosteroids and thalidomide) are effective in the prevention and management of paradoxical TB reactions, including tuberculomas^{53,63-65}. Anecdotal case reports describe patients who develop symptomatic intracranial tuberculoma months to years after completion of 12 months to four years of TB treatment for neurological TB^{9,30,66,67}. Whether some of these cases represent disease reactivation, an inadequate TB treatment duration or infection with a drug-resistant strain is uncertain and patients are often empirically recommenced on TB treatment, either with first-line drugs or a multidrug-resistant regimen, at time of deterioration^{9,30,66}. However, a delayed paradoxical response responsive to corticosteroids without additional TB treatment accounts for at least some of these cases⁶⁷.

Medical treatment

The mainstay of treatment of intracranial tuberculomas is similar to that of TBM and includes TB therapy and corticosteroids. The World Health Organization, Centers for Disease Control and Prevention of America and the British Thoracic Society recommend a 9–12 month course of TB treatment for CNS TB when the *M.tb* strain is sensitive to all drugs⁶⁸⁻⁷⁰. However, these guidelines are based on expert opinion rather than randomized controlled trials. Specifically, no studies have compared different treatment durations in patients with intracranial tuberculomas. The morphology of the lesion plays an important role in response to therapy and a one-size-fits-all approach may therefore be inappropriate in the decision regarding tuberculoma treatment duration. This is suggested by the almost invariably good response of miliary tuberculomas to TB treatment (presumably non-caseous) and the frequent persistence of caseous and liquified TB lesions (e.g. abscesses) despite TB treatment^{53,71}.

Some guidelines suggest adjunctive systemic corticosteroids in all forms of CNS TB, including those in whom a strong suspicion of tuberculoma exists⁷⁰. Corticosteroid therapy may be of particular value when there is significant perilesional edema (resulting in symptomatology) and in cases where there is paradoxical enlargement despite optimal TB therapy⁷². Corticosteroid duration should be tailored according to the radiological response of the tuberculoma and clinical wellbeing of the patient and balanced against side effects.

TB abscesses are often unresponsive to standard TB therapy with corticosteroids. Although no clinical trials exist, adjuvant thalidomide therapy (3–5 mg/kg/day) has been shown to be beneficial in patients who develop enlarging TB abscesses⁵³. In our experience, thalidomide can be stopped without relapse when clinical improvement is optimal or reached a plateau, regardless of whether radiological resolution has been achieved. Other immunomodulatory agents that have anecdotally been

beneficial in steroid resistant paradoxical TB reactions affecting the CNS include the TNF- α inhibitor infliximab⁷³ and interferon- γ ⁷⁴. The therapeutic benefit of these and other host-directed therapies aimed at reducing excessive CNS inflammation should be investigated in future prospective studies.

Surgical management

There are no controlled studies to determine the role of surgery in patients with intracranial tuberculous mass lesions. However, there are general principles from clinical practice and the existing literature that can be summarized^{10,75}. Biopsy for diagnosis is considered: 1) at the outset if the definitive diagnosis is unclear, and 2) for persistence or paradoxical growth of a presumed tuberculoma despite medical treatment (for diagnostics and drug sensitivity testing). Resection of the lesion may be considered: 1) to relieve symptomatic or potentially life-threatening mass effect and/or hydrocephalus, and 2) to treat medically refractory seizures. Drainage of abscesses is considered for symptomatic mass effect or hydrocephalus, especially when large and/or in the posterior fossa. However, surgery for tuberculous mass lesions is rarely performed in TB endemic settings as the clinical and imaging information is usually sufficient to make the diagnosis. Furthermore, risks associated with surgery, especially if the lesion is located in an eloquent or difficult to access brain area, and inadequate neurosurgical facilities usually combine to preclude surgical management.

Duration of TB treatment: what happens in practice?

There is variation in opinion and practice with respect to the duration of TB treatment in patients with intracranial tuberculomas or tuberculous abscesses. A major reason for this is the lack of prospective clinical trial evidence. In rare cases where a microbiological diagnosis is achieved, it is not feasible to access repeated clinical specimens from the site of disease to ascertain whether and when culture conversion has occurred, unlike pulmonary TB where sputum *M.tb* culture can be monitored and treatment duration adjusted accordingly. Monitoring is performed clinically and with brain imaging, with the frequency of both clinical and radiological follow-up being highly variable, depending on factors such as available resources, clinician's preference and individual patient characteristics¹².

The routine duration of TB treatment in intracranial tuberculoma cases include periods of 6⁷⁶, 9^{24,42,50,77}, 12⁷⁸, 15⁴⁹ and 18^{9,10,23,45,79,80} months depending on the clinician's preference. **Table 1** presents duration of treatment and outcome in tuberculoma studies published in English^{8,9,11,12,23,24,42,43,46,56,71,78,79,81–86}. Although some studies describe radiological resolution of tuberculoma in more than 80% of patients after 6–12 months of TB treatment^{43,76,78,83,84}, others have reported persistently enhancing lesions in the vast majority (71–82%) of cases after 9–12 months of treatment^{23,42}. Even after 24 months of therapy, tuberculomas may persist in 22%–46% of cases^{9,12,23} (**Figure 2**). Larger lesions (>2.5 cm) are significantly more likely to persist after 18 to 24 months of treatment^{9,12}. The medical management of patients with persistent intracranial tuberculoma after a “complete treatment course” (6–18 months) is particularly controversial. Some experts suggest continuing treatment until radiological resolution of enhancing lesions has been achieved^{23,87}, which may unnecessarily expose patients to potentially toxic

drugs for many years^{8,9,11,12,23,78,81,88}; in a study from South Africa, more than 50% of tuberculoma patients followed for 9 months or more (31/57) received TB treatment for more than 18 months (range 19–46 months)¹². Others are of the opinion that lesional persistence beyond 18 months does not reflect treatment failure, but rather represents a persistent immune response at the disease site that has been sterilized, hence extending TB treatment beyond this period will not add any benefit⁸⁹.

Rationale for using longer versus shorter regimens

It is currently unknown whether persistent radiological enhancement of intracranial tuberculomas after 9–12 months of appropriate treatment represents active disease, inflammatory response in a sterilized lesion or merely revascularization. Additionally, a lack of radiological response could indicate that the diagnosis of tuberculoma is incorrect, particularly if the patient did not respond clinically to TB treatment, and alternative diagnoses should be considered. The consequences of stopping TB treatment prior to complete radiological resolution of intracranial tuberculous mass has rarely been explored. These important issues were discussed at the 3rd International TBM Consortium meeting. Most clinicians were of the opinion that the continued enhancement does not necessarily represent treatment failure and that prolonged TB therapy (beyond 9–12 months) is not warranted in patients suspected of infection with or with proven *M.tb* strains susceptible to first-line drugs. This position is supported by the asymptomatic state of many patients and the paucity of AFB on staining and sterility of tuberculoma biopsy samples obtained prior to and following TB treatment initiation^{23,82}. Immunohistochemical staining of excised tuberculomas also demonstrates high expression of vascular endothelial growth factor (VEGF) in the lesions with intense positivity of inflammatory mononuclear cells as well as reactive astrocytes and fibrocytes⁹⁰. The VEGF-induced angiogenesis in the granuloma capsule may therefore contribute, in addition to inflammation, to the persistent and prolonged contrast enhancement frequently seen on serial brain imaging. Furthermore, one trial reports no clinical or radiological deterioration at 24 months follow-up in 20 patients with persistent intracranial tuberculomas after completion of 9 months' TB therapy²⁴.

A theoretical argument in favor of continuing treatment longer than 9–12 months is that drug penetration into the CNS is suboptimal and is likely even more suboptimal into the tuberculoma or tuberculous abscess. Drug penetration into cerebrospinal fluid is poor for rifampicin, the key sterilizing drug⁹¹. Tuberculous abscesses that, unlike tuberculomas, are teeming with bacilli may potentially act as an immune sanctuary protecting the bacilli from immune effector cells within pus²¹. The consequence of these factors may be that sterilization is not always achieved with 9–12 months treatment and that a longer duration may be required. The inability to obtain specimens to confirm sterilization make this an area of uncertainty. Pertinent, too, is that relapse of CNS TB could have catastrophic consequences. Furthermore, some patients need late re-initiation of immunomodulatory treatment and this should ideally be done while on TB treatment to avoid relapse resulting from iatrogenic immunosuppression. However, if treatment is continued because of residual lesions, when does the clinician stop therapy? Should this be until all

Table 1. Summary of reported medical management strategies and clinical and radiologic outcomes of intracranial tuberculoma case series.

Study, First author, year published, country	Study design	Patients, n (age group) ¹	Duration of ATT, Months: %	Steroid use,%	Favorable clinical outcome, %, (n/N) ²	Radiologic persistent tuberculoma(s), % (n/N): months F/U
Afghani ⁸¹ , 1994, multiple	Case report + review	41 (C + A)	10-24: 100	80 ³	68 (25/37)	N/A
Anuradha ⁴² , 2011, India	Retrospective observational	43 (C + A)	9: 100	100	26 (11/43)	79 (30/38): 9
Awada ⁴³ , 1998, Saudi Arabia	Retrospective observational	18 (C + A)	12-18: 100	67	N/A	100 (18/18): 12
Bayindir ⁸² , 2006, Turkey	Retrospective observational	23 (C + A)	12-18: 100	N/A	100 (15/15)	N/A
Gupta ⁸³ , 1990, India	Prospective observational	31 (C + A)	11-12: 97	N/A	N/A	14 (4/29): 12
Gupta ⁹ , 2003, India	Prospective observational	9 (C + A)	16: 11 18-34: 88	89	44 (4/9)	N/A
Harder ⁸⁴ , 1983, Saudi Arabia	Retrospective observational	20 (C + A)	12: 61 9-24: 39 ⁴	75	35 (7/20)	0 (0/10): 12 ⁵
Idris ⁷⁹ , 2007, Sudan	Retrospective observational	16 (A)	18: 100 ⁶	56	N/A	13 (2/16): 18
Li ⁸⁰ , 2012, China	Retrospective observational	6 (A)	18: 100	33	83 (5/6)	N/A
Man ⁴⁶ , 2010, France	Retrospective observational	23 (A)	9-18: 88 21: 12 ⁴	43	53 (10/19)	75 (12/16): 9-21
Marais ¹² , 2019, South Africa	Retrospective observational	66 (A)	≥9: 96% 19-46: 54 ⁴	76	37 (20/54)	49 (20/41): 18 33 (14/42): 24
Nair ⁹ , 2019, India	Retrospective observational	86 (C + A)	≥18: 100 >24-120: 22	N/A	N/A	22 (19/86): 24
Poonnoose ²³ , 2003, India	Retrospective observational	28 (C + A)	≥18: 100	54	68 (19/28)	69 (19/28): 18 46 (13/28): 24
Rajeswari ²⁴ , 1995, India	RCT	108 (C + A)	9: 100 ⁴	100	90 (97/108)	22 (20/91): 9 12 (11/89): 24
Ravenscroft ⁷¹ , 2001, South Africa	Prospective observational	34 (C)	≥6: 100 12: 6	N/A	N/A	44 (14/32): 6 ⁷
Shah, 2016 ⁷⁸ , India	Prospective observational	28 (C + A)	≥12: 100 18-24: 17 ⁸	79	N/A	17 (4/24): 12 13 (3/24): 24
Shah, 2019 ¹¹ , India	Case series	6 (C)	23-32: 100	83	83 (5/6)	83 (5/6): >24
Tandon ⁸⁵ , 1985, India	Retrospective observational	50 (C + A)	12-18: 98	N/A	78 (39/50)	40 (20/50): N/A
Wasay ⁵⁶ , 2004, Pakistan	Retrospective observational	102 (C + A)	9-12: 100 ⁴	79 ⁴	34 (17/50)	NA
Yaramis ⁸⁶ , 1998, Turkey	Retrospective observational	4 (C)	12: 100 24: 50	100	100 (4/4)	N/A

Abbreviations: n, number; ATT, antituberculous therapy; N, number with known data; F/U, follow-up, C, children; A, adults; N/A, data not available; RCT, randomized controlled trial

¹ All studies included HIV-uninfected patients or patients with unknown HIV status, except studies by Man *et al.*⁴⁶ and Marais *et al.*¹², that included 7, and 47 HIV-infected patients, respectively;

² The definition varies between studies and include descriptions such as “complete recovery”, “no neurological disability”, “asymptomatic” and unspecified “good clinical recovery”. Several studies included patients with co-existing tuberculous meningitis that might have influenced clinical outcomes.

³ Including 30 patients with available data

⁴ Including patients followed up for at least 9 months

⁵ Including patients treated medically without surgical intervention

⁶ Excluding 1 patient who died during therapy

⁷ “32” refers to number of meningeal tuberculomas in 25 patients

⁸ Including patients followed up for at least 12 months

contrast enhancing lesions have resolved – which can take years – or some arbitrary timepoint before then? A further question pertains to the timepoints at which repeat imaging should be performed, for which there are also no clear guidelines.

Conclusion

Intracranial tuberculoma represents a major health concern in developing countries. Routine practices often include prescription of TB therapy until lesional enhancement has resolved, which may expose some patients to an unnecessarily prolonged treatment course. Because of the lack of evidence-based guidelines and equipoise with respect to shorter versus longer duration regimens, further research is needed. In the first instance, a multi-country audit of existing practice and outcomes in terms of cure and relapse would help in defining the spectrum of current practice. Ultimately, a randomized controlled trial comparing a standardized duration of TB treatment with duration based on brain imaging would provide a definitive answer to this question.

Ethics statement

Images presented in [Figure 1](#) and [Figure 2](#) were obtained during a retrospective study of patients who presented with intracranial tuberculoma to Inkosi Albert Luthuli Central Hospital in Durban, South Africa. The Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal approved the study (BREC class approval number BCA325/15). Images presented in [Figure 3](#) were obtained during a retrospective study of patients with tuberculous meningitis at Tygerberg Hospital in Cape Town, South Africa. The Health Research Ethics Committee of the University of Stellenbosch approved the study

(N12/07/041). As these studies were retrospective folder reviews, and data were analyzed anonymously outside of the clinical settings, the ethics committees waived the requirement for informed consent and informed consent was not obtained.

Data availability

Underlying data

No data is associated with this article.

Acknowledgements

Tuberculous Meningitis International Research Consortium

Rob E. Aarnoutse; Suzanne T. B. Anderson; Nathan C. Bahr; Nguyen D. Bang; David R. Boulware; Tom Boyles; Lindsey H. M. te Brake; Satish Chandra; Felicia C. Chow; Fiona V. Cresswell; Reinout van Crevel; Angharad G. Davis; Sofiati Dian; Joseph Donovan; Kelly E. Dooley; Anthony Figaji; A. Rizal Ganiem; Ravindra Kumar Garg; Diana M. Gibb; Raph L. Hamers; Nguyen T. T. Hiep; Darma Imran; Akhmad Imron; Sanjay K. Jain; Sunil K. Jain; Byramee Jeejeebhoy; Jayantee Kalita; Rashmi Kumar; Vinod Kumar; Arjan van Laarhoven; Rachel P-J. Lai; Abi Manesh; Suzaan Marais; Vidya Mave; Graeme Meintjes; David B. Meya; Usha K. Misra; Manish Modi; Alvaro A. Ordonez; Nguyen H. Phu; Sunil Pradhan; Kameshwar Prasad; Alize M. Proust; Lalita Ramakrishnan; Ursula Rohlwick; Rovina Ruslami; Johannes F. Schoeman; James A. Seddon; Kusum Sharma; Omar Siddiqi; Regan S. Solomons; Nguyen T. T. Thuong; Guy E. Thwaites; Ronald van Toorn; Elizabeth W. Tucker; Sean A. Wasserman; Robert J. Wilkinson.

References

- Dastur DK, Manghani DK, Udani PM: **Pathology and pathogenetic mechanisms in neurotuberculosis.** *Radiol Clin North Am.* 1995; **33**(4): 733–52.
[PubMed Abstract](#)
- Dastur HM: **Diagnosis and neurosurgical treatment of tuberculous disease of the CNS.** *Neurosurg Rev.* 1983; **6**(3): 111–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Garg RK, Desai P, Kar M, *et al.*: **Multiple ring enhancing brain lesions on computed tomography: an Indian perspective.** *J Neurol Sci.* 2008; **266**(1–2): 92–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bhigjee AI, Naidoo K, Patel VB, *et al.*: **Intracranial mass lesions in HIV-positive patients—the KwaZulu/Natal experience.** *Neuroscience AIDS Research Group. S Afr Med J.* 1999; **89**(12): 1284–8.
[PubMed Abstract](#)
- Choe PG, Park WB, Song JS, *et al.*: **Spectrum of intracranial parenchymal lesions in patients with human immunodeficiency virus infection in the Republic of Korea.** *J Korean Med Sci.* 2010; **25**(7): 1005–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Modi M, Mochan A, Modi G: **Management of HIV-associated focal brain lesions in developing countries.** *QJM.* 2004; **97**(7): 413–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Smego RA Jr, Orlovic D, Wadula J: **An algorithmic approach to intracranial mass lesions in HIV/AIDS.** *Int J STD AIDS.* 2006; **17**(4): 271–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Gupta M, Bajaj BK, Khwaja G: **Paradoxical response in patients with CNS tuberculosis.** *J Assoc Physicians India.* 2003; **51**: 257–60.
[PubMed Abstract](#)
- Nair BR, Rajshekhar V: **Factors Predicting the Need for Prolonged (>24 Months) Antituberculous Treatment in Patients with Brain Tuberculomas.** *World Neurosurg.* 2019; **125**: e236–e247.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rajshekhar V: **Surgery for brain tuberculosis: a review.** *Acta Neurochir (Wien).* 2015; **157**(10): 1665–78.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Shah I, Shetty NS: **Duration of anti-tuberculous therapy in children with persistent tuberculomas.** *SAGE Open Med Case Rep.* 2019; **7**: 2050313X18823092.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Marais S, Roos I, Mitha A, *et al.*: **Presentation and outcome of patients with intracranial tuberculoma in a high HIV prevalence setting.** *Int J Tuberc Lung Dis.* 2020; [In press].
- Rich AR, McCordock HA: **The pathogenesis of tuberculous meningitis.** *Bull Johns Hopkins Hosp.* 1933; **52**: 2–37.
- Donald PR, Schaaf HS, Schoeman JF: **Tuberculous meningitis and miliary tuberculosis: the Rich focus revisited.** *J Infect.* 2005; **50**(3): 193–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jain SK, Paul-Satyaseela M, Lamichhane G, *et al.*: **Mycobacterium tuberculosis invasion and traversal across an in vitro human blood-brain barrier as a pathogenic mechanism for central nervous system tuberculosis.** *J Infect Dis.* 2006; **193**(9): 1287–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Krishnan N, Robertson BD, Thwaites G: **The mechanisms and consequences of the extra-pulmonary dissemination of Mycobacterium tuberculosis.** *Tuberculosis (Edinb).* 2010; **90**(6): 361–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Davis AG, Rohlwick UK, Proust A, *et al.*: **The pathogenesis of tuberculous**

- meningitis. *J Leukoc Biol.* 2019; **105**(2): 267–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Tsenova L, Bergtold A, Freedman VH, *et al.*: Tumor necrosis factor alpha is a determinant of pathogenesis and disease progression in mycobacterial infection in the central nervous system. *Proc Natl Acad Sci U S A.* 1999; **96**(10): 5657–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 19. Dastur DK, Dave UP: Ultrastructural basis of the vasculopathy in and around brain tuberculomas. Possible significance of altered basement membrane. *Am J Pathol.* 1977; **89**(1): 35–50.
[PubMed Abstract](#) | [Free Full Text](#)
 20. Kumar R, Pandey CK, Bose N, *et al.*: Tuberculous brain abscess: clinical presentation, pathophysiology and treatment (in children). *Childs Nerv Syst.* 2002; **18**(3–4): 118–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Bernaerts A, Vanhoenacker FM, Parizel PM, *et al.*: Tuberculosis of the central nervous system: overview of neuroradiological findings. *Eur Radiol.* 2003; **13**(8): 1876–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. Arseni C: Two hundred and one cases of intracranial tuberculoma treated surgically. *J Neurol Neurosurg Psychiatry.* 1958; **21**(4): 308–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 23. Poonnoose SI, Rajshekhkar V: Rate of resolution of histologically verified intracranial tuberculomas. *Neurosurgery.* 2003; **53**(4): 873–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Rajeswari R, Sivasubramanian S, Balambal R, *et al.*: A controlled clinical trial of short-course chemotherapy for tuberculoma of the brain. *Tuber Lung Dis.* 1995; **76**(4): 311–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Deogaonkar M, De R, Sil K, *et al.*: Pituitary tuberculosis presenting as pituitary apoplexy. *Int J Infect Dis.* 2006; **10**(4): 338–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Kalita J, Ranjan P, Misra UK, *et al.*: Hemichorea: a rare presentation of tuberculoma. *J Neurol Sci.* 2003; **208**(1–2): 109–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Azeemuddin M, Alvi A, Sayani R, *et al.*: Neuroimaging Findings in Tuberculosis: A Single-Center Experience in 559 Cases. *J Neuroimaging.* 2019; **29**(5): 657–668.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Sonmez G, Ozturk E, Sildiroglu HO, *et al.*: MRI findings of intracranial tuberculomas. *Clin Imaging.* 2008; **32**(2): 88–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Patkar D, Narang J, Yanamandala R, *et al.*: Central nervous system tuberculosis: pathophysiology and imaging findings. *Neuroimaging Clin N Am.* 2012; **22**(4): 677–705.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. van Toorn R, du Plessis AM, Schaaf HS, *et al.*: Clinicoradiologic response of neurologic tuberculomata in children treated with thalidomide. *Pediatr Infect Dis J.* 2015; **34**(2): 214–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Omuro AM, Leite CC, Mokhtari K, *et al.*: Pitfalls in the diagnosis of brain tumours. *Lancet Neurol.* 2006; **5**(11): 937–948.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. Garg RK, Sinha MK: Multiple ring-enhancing lesions of the brain. *J Postgrad Med.* 2010; **56**(4): 307–316.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. Gupta RK, Husain N, Kathuria MK, *et al.*: Magnetization transfer MR imaging correlation with histopathology in intracranial tuberculomas. *Clin Radiol.* 2001; **56**(8): 656–663.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Chaudhary V, Bano S, Garga UC: Central Nervous System Tuberculosis: An Imaging Perspective. *Can Assoc Radiol J.* 2017; **68**(2): 161–170.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. Kong A, Koukourou A, Boyd M, *et al.*: Metastatic adenocarcinoma mimicking 'target sign' of cerebral tuberculosis. *J Clin Neurosci.* 2006; **13**(9): 955–958.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Gasparetto EL, Cabral RF, da Cruz LC Jr, *et al.*: Diffusion imaging in brain infections. *Neuroimaging Clin N Am.* 2011; **21**(1): 89–113, viii.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Batra A, Tripathi RP: Diffusion-weighted magnetic resonance imaging and magnetic resonance spectroscopy in the evaluation of focal cerebral tubercular lesions. *Acta Radiol.* 2004; **45**(6): 679–688.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Gupta RK, Prakash M, Mishra AM, *et al.*: Role of diffusion weighted imaging in differentiation of intracranial tuberculoma and tuberculous abscess from cysticercus granulomas—a report of more than 100 lesions. *Eur J Radiol.* 2005; **55**(3): 384–392.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. Parry AH, Wani AH, Shaheen FA, *et al.*: Evaluation of intracranial tuberculomas using diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS) and susceptibility weighted imaging (SWI). *Br J Radiol.* 2018; **91**(1091): 20180342.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 40. Lai PH, Hsu SS, Ding SW, *et al.*: Proton magnetic resonance spectroscopy and diffusion-weighted imaging in intracranial cystic mass lesions. *Surg Neurol.* 2007; **68** Suppl 1: S25–36.
[PubMed Abstract](#)
 41. Alam MS, Sajjad Z, Azeemuddin M, *et al.*: Diffusion weighted MR imaging of ring enhancing brain lesions. *J Coll Physicians Surg Pak.* 2012; **22**(7): 428–431.
[PubMed Abstract](#)
 42. Anuradha HK, Garg RK, Sinha MK, *et al.*: Intracranial tuberculomas in patients with tuberculous meningitis: predictors and prognostic significance. *Int J Tuberc Lung Dis.* 2011; **15**(2): 234–9.
[PubMed Abstract](#)
 43. Awada A, Daif AK, Pirani M, *et al.*: Evolution of brain tuberculomas under standard antituberculous treatment. *J Neurol Sci.* 1998; **156**(1): 47–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Haris M, Gupta RK, Husain M, *et al.*: Assessment of therapeutic response in brain tuberculomas using serial dynamic contrast-enhanced MRI. *Clin Radiol.* 2008; **63**(5): 562–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 45. Kalita J, Prasad S, Misra UK: Predictors of paradoxical tuberculoma in tuberculous meningitis. *Int J Tuberc Lung Dis.* 2014; **18**(4): 486–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Man H, Sellier P, Boukobza M, *et al.*: Central nervous system tuberculomas in 23 patients. *Scand J Infect Dis.* 2010; **42**(6–7): 450–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 47. Ranjan P, Kalita J, Misra UK: Serial study of clinical and CT changes in tuberculous meningitis. *Neuroradiology.* 2003; **45**(5): 277–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Tai ML, Nor HM, Kadir KA, *et al.*: Paradoxical Manifestation is Common in HIV-negative Tuberculous Meningitis. *Medicine (Baltimore).* 2016; **95**(1): e1997.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 49. Unal A, Sutlas PN: Clinical and radiological features of symptomatic central nervous system tuberculomas. *Eur J Neurol.* 2005; **12**(10): 797–804.
[PubMed Abstract](#) | [Publisher Full Text](#)
 50. Vidal JE, Hernández AV, Oliveira AC, *et al.*: Cerebral tuberculomas in AIDS patients: a forgotten diagnosis? *Arq Neuropsiquiatr.* 2004; **62**(3B): 793–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 51. Lesprit P, Zagdanski AM, de La Blanchardiere A, *et al.*: Cerebral tuberculosis in patients with the acquired immunodeficiency syndrome (AIDS). Report of 6 cases and review. *Medicine (Baltimore).* 1997; **76**(6): 423–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
 52. Nicolls DJ, King M, Holland D, *et al.*: Intracranial tuberculomas developing while on therapy for pulmonary tuberculosis. *Lancet Infect Dis.* 2005; **5**(12): 795–801.
[PubMed Abstract](#) | [Publisher Full Text](#)
 53. Schoeman JF, Fieggen G, Seller N, *et al.*: Intractable intracranial tuberculous infection responsive to thalidomide: report of four cases. *J Child Neurol.* 2006; **21**(4): 301–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 54. van Toorn R, Rabie H, Dramowski A, *et al.*: Neurological manifestations of TB-IRIS: a report of 4 children. *Eur J Paediatr Neurol.* 2012; **16**(6): 676–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
 55. Jain SK, Kwon P, Moss WJ: Management and outcomes of intracranial tuberculomas developing during antituberculous therapy: case report and review. *Clin Pediatr (Phila).* 2005; **44**(5): 443–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 56. Wasay M, Moolani MK, Zaheer J, *et al.*: Prognostic indicators in patients with intracranial tuberculoma: a review of 102 cases. *J Pak Med Assoc.* 2004; **54**(2): 83–7.
[PubMed Abstract](#)
 57. Pauranik A, Behari M, Maheshwari MC: Appearance of tuberculoma during treatment of tuberculous meningitis. *Jpn J Med.* 1987; **26**(3): 332–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 58. Singh AK, Malhotra HS, Garg RK, *et al.*: Paradoxical reaction in tuberculous meningitis: presentation, predictors and impact on prognosis. *BMC Infect Dis.* 2016; **16**: 306.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 59. Narita M, Ashkin D, Hollender ES, *et al.*: Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med.* 1998; **158**(1): 157–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
 60. Brown CS, Smith CJ, Breen RA, *et al.*: Determinants of treatment-related paradoxical reactions during anti-tuberculosis therapy: a case control study. *BMC Infect Dis.* 2016; **16**: 479.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 61. Marais S, Meintjes G, Pepper DJ, *et al.*: Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis.* 2013; **56**(3): 450–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. Walker NF, Stek C, Wasserman S, *et al.*: The tuberculosis-associated immune reconstitution inflammatory syndrome: recent advances in clinical and pathogenesis research. *Curr Opin HIV AIDS.* 2018; **13**(6): 512–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. Schoeman JF, Van Zyl LE, Laubscher JA, *et al.*: Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome

- in young children with tuberculous meningitis. *Pediatrics*. 1997; **99**(2): 226–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Meintjes G, Wilkinson RJ, Morroni C, *et al.*: **Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome.** *AIDS*. 2010; **24**(15): 2381–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Meintjes G, Stek C, Blumenthal L, *et al.*: **Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS.** *N Engl J Med*. 2018; **379**(20): 1915–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Shah I, Borse S: **Paradoxical tuberculomas after completion of antituberculous treatment.** *Trop Med Health*. 2012; **40**(1): 15–17.
[PubMed Abstract](#) | [Free Full Text](#)
67. Machida A, Ishihara T, Amano E, *et al.*: **Late-onset paradoxical reactions 10 years after treatment for tuberculous meningitis in an HIV-negative patient: a case report.** *BMC Infect Dis*. 2018; **18**(1): 313.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
68. World Health Organization: **Treatment of tuberculosis guidelines.** Fourth edition. 2010; Accessed: Sept 09 2019.
[Reference Source](#)
69. Nahid P, Dorman SE, Alipanah N, *et al.*: **Official American Thoracic Society/ Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.** *Clin Infect Dis*. 2016; **63**(7): e147–e95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. Thwaites G, Fisher M, Hemingway C, *et al.*: **British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children.** *J Infect*. 2009; **59**(3): 167–87.
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Ravenscroft A, Schoeman JF, Donald PR: **Tuberculous granulomas in childhood tuberculous meningitis: radiological features and course.** *J Trop Pediatr*. 2001; **47**(1): 5–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
72. Donald PR, Van Toorn R: **Use of corticosteroids in tuberculous meningitis.** *Lancet*. 2016; **387**(10038): 2585–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
73. Blackmore TK, Manning L, Taylor WJ, *et al.*: **Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes.** *Clin Infect Dis*. 2008; **47**(10): e83–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
74. Coulter JB, Baretto RL, Mallucci CL, *et al.*: **Tuberculous meningitis: protracted course and clinical response to interferon-gamma.** *Lancet Infect Dis*. 2007; **7**(3): 225–232.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. Akhaddar A: **Surgical therapy.** In *“Tuberculosis Of The Central Nervous System: Pathogenesis, Imaging, And Management”* eds M. Turgut, A. Akhaddar, A.T. Turgut, R.K. Garg. Springer. 2017; 173–191.
[Publisher Full Text](#)
76. Schoeman JF, Van Zyl LE, Laubscher JA, *et al.*: **Serial CT scanning in childhood tuberculous meningitis: prognostic features in 198 cases.** *J Child Neurol*. 1995; **10**(4): 320–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
77. Thwaites GE, Macmullen-Price J, Tran TH, *et al.*: **Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study.** *Lancet Neurol*. 2007; **6**(3): 230–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
78. Shah IA, Asimi RP, Kawoos Y, *et al.*: **Tuberculomas of the brain with and without associated meningitis: a cohort of 28 cases treated with anti-tuberculosis drugs at a tertiary care centre.** *International Journal of Contemporary Medical Research*. 2016; **3**(12): 3484–7.
[Reference Source](#)
79. Idris MN, Sokrab TE, Arbab MA, *et al.*: **Tuberculoma of the brain: a series of 16 cases treated with anti-tuberculosis drugs.** *Int J Tuberc Lung Dis*. 2007; **11**(1): 91–5.
[PubMed Abstract](#)
80. Li H, Liu W, You C: **Central nervous system tuberculoma.** *J Clin Neurosci*. 2012; **19**(5): 691–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
81. Afghani B, Lieberman JM: **Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review.** *Clin Infect Dis*. 1994; **19**(6): 1092–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
82. Bayindir C, Mete O, Bilgic B: **Retrospective study of 23 pathologically proven cases of central nervous system tuberculomas.** *Clin Neurol Neurosurg*. 2006; **108**(4): 353–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
83. Gupta RK, Jena A, Singh AK, *et al.*: **Role of magnetic resonance (MR) in the diagnosis and management of intracranial tuberculomas.** *Clin Radiol*. 1990; **41**(2): 120–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Harder E, Al-Kawi MZ, Carney P: **Intracranial tuberculoma: conservative management.** *Am J Med*. 1983; **74**(4): 570–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
85. Tandon PN, Bhargava S: **Effect of medical treatment on intracranial tuberculoma—a CT study.** *Tubercle*. 1985; **66**(2): 85–97.
[PubMed Abstract](#) | [Publisher Full Text](#)
86. Yaramis A, Gurkan F, Elevli M, *et al.*: **Central nervous system tuberculosis in children: a review of 214 cases.** *Pediatrics*. 1998; **102**(5): E49.
[PubMed Abstract](#) | [Publisher Full Text](#)
87. Monteiro R, Carneiro JC, Costa C, *et al.*: **Cerebral tuberculomas - A clinical challenge.** *Respir Med Case Rep*. 2013; **9**: 34–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
88. Jinkins JR: **Computed tomography of intracranial tuberculosis.** *Neuroradiology*. 1991; **33**(2): 126–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Wasay M: **Central nervous system tuberculosis and paradoxical response.** *South Med J*. 2006; **99**(4): 331–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
90. Husain N, Awasthi S, Haris M, *et al.*: **Vascular endothelial growth factor as a marker of disease activity in neurotuberculosis.** *J Infect*. 2008; **56**(2): 114–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
91. Wasserman S, Davis A, Wilkinson RJ, *et al.*: **Key considerations in the pharmacotherapy of tuberculous meningitis.** *Expert Opin Pharmacother*. 2019; **20**(15): 1–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:   

Version 3

Reviewer Report 04 March 2020

<https://doi.org/10.21956/wellcomeopenres.17274.r38036>

© 2020 Higashi J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Julie Higashi

¹ Tuberculosis Control Program, Division of Dental and Medical Affairs, Los Angeles County Department of Public Health, Los Angeles, CA, USA

² Francis J Curry International Tuberculosis Center, University of California, San Francisco, San Francisco, CA, USA

I have reviewed the revised manuscript and appreciate the authors careful attention to my suggestions. I have no further comments. Thank you for bringing attention to the challenges of managing CNS TB.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB epidemiology, implementation, program evaluation, clinical education.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 28 February 2020

<https://doi.org/10.21956/wellcomeopenres.17274.r38037>

© 2020 Chin J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Jerome H. Chin

Department of Neurology, NYU Langone Health, New York City, NY, USA

The revised article provides an improved discussion of the neuroimaging features of tuberculomas and tubercular abscesses and the differential diagnosis of enhancing intracranial mass lesions.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Diagnosis and treatment of central nervous system infections including tuberculosis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 31 January 2020

<https://doi.org/10.21956/wellcomeopenres.17008.r37110>

© 2020 Higashi J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Julie Higashi

¹ Tuberculosis Control Program, Division of Dental and Medical Affairs, Los Angeles County Department of Public Health, Los Angeles, CA, USA

² Francis J Curry International Tuberculosis Center, University of California, San Francisco, San Francisco, CA, USA

The article presents the current clinical approach to the management of tuberculous intracranial mass lesions, which is variable because of limited data that inform treatment interventions that might optimize outcomes.

Overall, the article generally presents a helpful review of the status of this problem and I agree with the recommendations for management, but could be improved by the following:

While corticosteroids remain the mainstay of immunomodulatory therapy, other agents besides thalidomide may improve outcomes. There are few reports of other agents improving outcomes (e.g. infliximab - Blackmore (2008)¹, interferon gamma - Coulter (2007)²), and suggestion that other agents (anakinra) may be beneficial, but the future of immunomodulatory therapy with more targeted agents is an exciting new area. A line or two with references to this handful of case reports as another avenue of investigation would make the article more complete.

Please include recommendations regarding monitoring of patients post treatment (imaging frequency and duration of follow up) - and frequency of recurrent paradoxical response events or symptoms after treatment that are not thought to be treatment failure. Other clinicians with much experience treating CNS TB who have anecdotally describe patients having focal neurological deficits that don't represent relapse of TB, but immune response years after treatment completion. If this is something that the panel of experts have noted, even if infrequent, is worth mentioning.

References

1. Blackmore TK, Manning L, Taylor WJ, Wallis RS: Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes. *Clin Infect Dis*. 2008; **47** (10): e83-5 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Coulter J, Baretto R, Mallucci C, Romano M, Abernethy L, Isherwood D, Kumararatne D, Lammas D: Tuberculous meningitis: protracted course and clinical response to interferon-gamma. *The Lancet Infectious Diseases*. 2007; **7** (3): 225-232 [Publisher Full Text](#)

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB epidemiology, implementation, program evaluation, clinical education.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 Feb 2020

Suzaan Marais, Inkosi Albert Luthuli Central Hospital and University of KwaZulu-Natal, Durban, South Africa

While corticosteroids remain the mainstay of immunomodulatory therapy, other agents besides thalidomide may improve outcomes. There are few reports of other agents improving outcomes (e.g. infliximab - Blackmore (2008)¹, interferon gamma - Coulter (2007)²), and suggestion that other agents (anakinra) may be beneficial, but the future of immunomodulatory therapy with more targeted agents is an exciting new area. A line or two with references to this handful of case reports as another avenue of investigation would make the article more complete.

1. Blackmore TK, Manning L, Taylor WJ, Wallis RS: Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes. *Clin Infect Dis*. 2008; **47**(10): e83-5 [PubMed Abstract](#) | [Publisher Full Text](#)

2. Coulter J, Baretto R, Mallucci C, Romano M, Abernethy L, Isherwood D, Kumararatne D, Lammas D: Tuberculous meningitis: protracted course and clinical response to interferon-gamma. *The Lancet Infectious Diseases*. 2007; **7**(3): 225-232 [Publisher Full Text](#)

RESPONSE: We have added a brief description of some additional immunomodulatory agents that have shown anecdotal benefit in paradoxical TB reactions affecting the CNS and emphasized the need for future studies investigating the utility of host-directed therapies in these patients.

Please include recommendations regarding monitoring of patients post treatment (imaging frequency and duration of follow up) - and frequency of recurrent paradoxical response events or symptoms after treatment that are not thought to be treatment failure. Other clinicians with much experience treating CNS TB who have anecdotally describe patients having focal neurological deficits that don't represent relapse of TB, but immune response years after treatment completion. If this is something that the panel of experts have noted, even if infrequent, is worth mentioning.

RESPONSE: We have added a few sentences on the variability of follow-up practices in patients with intracranial tuberculous mass lesions as well as the lack of clear guidelines for timing of follow-up imaging in patients with persistent lesions. We reference case reports of patients with recurrent lesions after completion of TB treatment and comment on the various potential reasons for such recurrences, including paradoxical reaction.

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 December 2019

<https://doi.org/10.21956/wellcomeopenres.17008.r37112>

© 2019 Michael B. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Benedict Michael

Institute of Infection and Global Health, University of Liverpool, Liverpool, L69 7BE, UK

In this excellent and thorough overview, the authors accurately summarise the clinical presentation, neuroimaging findings, and pathogenesis of CNS TB, and focus on the data (and lack thereof) to guide the duration of TB therapy.

The manuscript would be strengthened if, in addition to the serial MRI scans in one patient, a figure was included to demonstrate the specific neuroimaging findings described in the text (Figure allowance permitting). This is of particular interest given that they describe, at least theoretical, rationale for cessation/continuing TB therapy based on the nature of the lesions.

The manuscript (space permitting) would also benefit from a more descriptive outline of the nature of the RCT investigating TB therapy duration proposed by these authors, who represent leaders in the field. For example, inclusion/exclusion, how to address HIV/ART status, imaging and clinical sub-group analyses, and controlling for corticosteroid use. This would be in the discussion as opposed to the conclusion.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 21 Feb 2020

Suzaan Marais, Inkosi Albert Luthuli Central Hospital and University of KwaZulu-Natal, Durban, South Africa

In this excellent and thorough overview, the authors accurately summarise the clinical presentation, neuroimaging findings, and pathogenesis of CNS TB, and focus on the data (and lack thereof) to guide the duration of TB therapy.

RESPONSE: We thank the reviewer for this comment.

The manuscript would be strengthened if, in addition to the serial MRI scans in one patient, a figure was included to demonstrate the specific neuroimaging findings described in the text (Figure allowance permitting). This is of particular interest given that they describe, at least theoretical, rationale for cessation/continuing TB therapy based on the nature of the lesions.

RESPONSE: We have added additional images showing various stages of intracranial tuberculous mass lesions (Figures 1 and 3).

The manuscript (space permitting) would also benefit from a more descriptive outline of the nature of the RCT investigating TB therapy duration proposed by these authors, who represent leaders in the field. For example, inclusion/exclusion, how to address HIV/ART status, imaging and clinical sub-group analyses, and controlling for corticosteroid use. This would be in the discussion as opposed to the conclusion.

RESPONSE: A RCT investigating TB therapy duration will, as the reviewer rightly points out, require careful consideration of multiple potential confounders. Such a detailed description is outside the scope of this manuscript but could be the subject of a future manuscript.


Competing Interests: No competing interests were disclosed.

Reviewer Report 19 November 2019

<https://doi.org/10.21956/wellcomeopenres.17008.r36913>

© 2019 Chin J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Jerome H. Chin 

Department of Neurology, NYU Langone Health, New York City, NY, USA

This manuscript reviews published studies of the diagnosis and treatment of intracranial tuberculomas and provides a consensus opinion on current practices and research needs.

The authors state “The diagnosis of intracranial tuberculoma is most often presumptive and based on radiological features, supportive evidence of TB elsewhere and response to TB treatment.” Since the diagnosis of intracranial tuberculoma rests in part on exclusion of other causes of intracranial mass lesions, it is necessary for the authors to discuss neuroimaging features (including DWI/ADC) that may or may not distinguish tuberculomas and tubercular abscesses from other causes of rim-enhancing and homogenous-enhancing lesions, including metastases, sarcoidosis, lymphoma, and bacterial, fungal and parasitic infections (e.g. staphylococcus, brucella, cryptococcus, aspergillus, toxoplasma gondii, taenia solium, schistosoma). Further, the authors should discuss the possibility that lack of radiological improvement after > 12 months of anti-tuberculosis treatment could indicate that the diagnosis of tuberculoma is incorrect and should prompt consideration of alternative diagnoses.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Diagnosis and treatment of central nervous system infections including tuberculosis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 Feb 2020

Suzaan Marais, Inkosi Albert Luthuli Central Hospital and University of KwaZulu-Natal, Durban, South Africa

The authors state “The diagnosis of intracranial tuberculoma is most often presumptive and based on radiological features, supportive evidence of TB elsewhere and response to TB treatment.” Since the diagnosis of intracranial tuberculoma rests in part on exclusion of other causes of intracranial mass lesions, it is necessary for the authors to discuss neuroimaging features (including DWI/ADC) that may or may not distinguish tuberculomas and tubercular abscesses from other causes of rim-enhancing and homogenous-enhancing lesions, including metastases, sarcoidosis, lymphoma, and bacterial, fungal and parasitic infections (e.g. staphylococcus, brucella, cryptococcus, aspergillus, toxoplasma gondii, taenia solium, schistosoma).

RESPONSE: We have added a paragraph that includes 1) a list of differential diagnoses for intracranial space-occupying lesions; 2) a finding on CT that is very suggestive of tuberculoma versus other etiologies; 3) a discussion of the utility of diffusion weighted imaging/apparent diffusion coefficient values in tuberculous mass lesions and 4) a note of other advanced imaging that are under investigation for tuberculous brain lesion diagnosis.

Further, the authors should discuss the possibility that lack of radiological improvement after > 12 months of anti-tuberculosis treatment could indicate that the diagnosis of tuberculoma is incorrect and should prompt consideration of alternative diagnoses.

RESPONSE: We have included a sentence cautioning that a lack of radiological response to TB treatment could indicate that the diagnosis of tuberculoma was incorrect.

Competing Interests: No competing interests were disclosed.