Journal of Infection

Presentations and Outcomes of Central Nervous System TB in a UK Cohort: The high burden of neurological morbidity

--Manuscript Draft--

Manuscript Number:	YJINF-D-20-04006R1
Article Type:	Full Length Article
Section/Category:	Rest of the World Submissions
Keywords:	tuberculosis; Meningitis; tuberculoma; outcomes; hydrocephalus; Brain; neuroinflammation
Corresponding Author:	Derek Macallan St George's, University of London London, UNITED KINGDOM
First Author:	Clare Logan
Order of Authors:	Clare Logan
	Claire Mullender
	Miriam Mirfenderesky
	Nicholas Feasey
	Catherine Cosgrove
	Peter Riley
	Angela Houston
	Tom Harrison
	Tihana Bicanic
	Phil Rich
	Paul Hart
	Sile Molloy
	Derek Macallan
Abstract:	Objectives Most data for Central Nervous System Tuberculosis (CNS-TB) derive from high-incidence, resource-limited countries. We sought to determine the presentation, management and outcomes of CNS-TB in a low-incidence setting with accessible healthcare. Methods We undertook a retrospective, observational study of CNS-TB in adults at a single tertiary-referral London hospital (2001-2017). Cases were categorised as either TB meningitis (TBM) or TB mass lesions without meningitis (TBML), applying novel criteria for definite, probable, and possible TBML. Results We identified sixty-two cases of TBM (37% definite; 31% probable; 32% possible) alongside 14 TBML cases (36% definite; 29% probable; and 36% possible). Clinical presentation was highly variable. Among CSF parameters, hypoglycorrhachia proved most discriminatory for “definite” TBM. Neurosurgical intervention was required for mass-effect or hydrocephalus in 16%. Mortality was higher in TBM versus TBML (16% vs 0%) but overall morbidity was significant; 35% of TBM and 28% of TBML survivors suffered persisting neurological disability at 12-months. Hydrocephalus, infarct, basal enhancement and low CSF white cell count were independently associated with worse neurological outcomes. Conclusion Although mortality was lower than previously reported in other settings, morbidity was significant, highlighting the need for improved CNS-TB diagnostics, therapeutics and interventions to mitigate neurological sequelae.

RESPONSE TO REVIEWERS COMMENTS

We thank the reviewers for their time spent looking over our article and for their constructive comments which we believe have improved the quality of our manuscript.

Please see below our point-by point responses (in blue text) to Reviewers' comments and suggestions and how these have been addressed in the revision *(new text in Italics).*

Versions of the altered files showing changes as markup will be uploaded with the final resubmission.

REVIEWER #1:

This is a retrospective case series evaluating TBM and TB mass lesions, the latter which the authors are proposing as an entity. Descriptions are detailed, the paper well-written and the authors should be commended on the effort taken.

Methods:
1) ".. tuberculous mass lesion in the absence of meningitic clinical features". I would also add absence of CSF features indicating meningitis, or something along those lines, as readers would reflexively wonder whether CSF suggestive of meningitis are included. This is a strength of the paper, and can be further brought up.

We agree with this point and have clarified this further (see italics):

Page 3: The presence of radiological features consistent with a tuberculous mass lesion in the absence of meningitic clinical features *and if performed, absence of inflammatory CSF*, plus for:

- 'definite' - microbiologic evidence of TB infection in CNS pus/tissue (culture, PCR-positive or acid-fast bacilli (AFB) seen);
- 'probable' - evidence of extra-neural TB or granulomas (but not AFB-seen) on CNS histology;
- 'possible' - the presence of radiological evidence alone in an appropriate clinical context.

3) "Outcomes are worse for TBM compared to those with mass lesions". I would reserve this statement, until the authors have made statistical correction for time to presentation, which I shall elaborate later.

As this is not statistically significant (see change to text below) and time to presentation was not associated with worse outcomes we have removed this statement from the highlights.

Pg 8 first para: "... TBML appeared to have a more benign course with 70% having a favourable outcome...". This is not statistically significant, so the authors should phrase along the lines that there is "a trend towards a more benign course" and point out there it did not meet statistical significance in the text.

We agree that this needed to be clearer. We have added a statistical comparison of death rates and have rephrased the text (page 8):
For TBML, at 12-month follow-up, there were no deaths (p=0.19 versus TBM), but 4/14 (28%) suffered residual neurological disability (GOS 2-4). The rates of favourable outcome (GOS 5), 70% for TBML and 56% for TBM, were not statistically different (p=0.37) but comparisons are difficult given the discrepant and small cohort sizes. Our data does however suggest that the

hypothesis that TBML has a more benign course than TBM merits further exploration in larger adequately-powered studies.

Results

1) Clinical presentation

- The authors reported statistical significance in the symptom duration prior to presentation being longer in TBM compared to TBML (p=0.02). As a consequence, this may explain why the mortality and neurological morbidity may be more severe in the TBM group and should be adjusted for using a hypothetical cut off duration. If after adjustment that TBM mortality/morbidity is higher, then would it be worth mentioning as one of the key features, and highlights of the paper.

4) Univariable and multivariable analysis: Again should factor time to clinical presentation, since TBM presented later than TBML which might affect neurological morbidity and mortality

Table 5:

1) Include time to clinical presentation and adjust

We thank the reviewer for highlighting this. Subsequently, we have analysed if longer duration of symptoms (>7 days vs ≤7 days) was associated with worse outcome (GOS 1-4) for the whole cohort (TBM and TBML). We found virtually identical outcomes (40% vs 37%, p=0.99) with no statistical difference.

In order to enter into the multivariate analysis, a factor had to be significantly associated with TBM outcomes, not TBML outcomes given the small number of TBML cases. This did not apply to “time to presentation”. Even if we take significance for the whole cohort as a criterion for inclusion in the multivariate analysis, “time to presentation” does not merit inclusion (as above). We have therefore not included it in the multivariate analysis and have clarified the relationship between type of disease (TBML vs TBM) and outcomes in the text, as above

Diagnostics - Neuroradiology

1) ".. underwent neuro-imaging..." Are all these contrasted studies? Because contrast would help feature basal enhancement more prominently/ring enhancing lesions.

Unfortunately, we do not have the data as to whether these were all contrast studies or not but that would be our normal practice.

2) CSF findings - "...predominantly neutrophilic CSF in four patients". Are these immunocompromised in anyway, eg HIV? If so, this should be described in the text. Severely immunocomp/low CD4 counts are often associated with predominant neutrophilic CSF in CNS-TB patients.

In line with this comment and a comment from reviewer number #2, we have now clarified this and changed the text:

Page 6: *Of the definite TBM cases, 4 (17%) immunocompetent patients had a neutrophilic pleocytosis, which is recognised in the early phase of TBM. One case had isolated hypoglycorrhachia only.*

Discussion:

1) Page 11, first para: The authors postulated the pathophysiology behind the cellular response with high CSF neutrophil counts and greater mortality. Ong et al Journal of Neuroinflammation 2017 and Brilha et al Scientific Reports 2017 can be cited and commented on since neutrophils can drive bloodbrain barrier disruption in TBM.

We appreciate the reviewer directing us to these interesting papers regarding how neutrophils contribute to CNS-TB immunopathology which are now referenced and briefly discussed, although not discussed in detail given word count limitations.

Page 11: This observation is however consistent with data from large TBM cohorts in Vietnam where lower CSF lymphocyte counts predicted death regardless of HIV-status [31]. The type of cellular response may be critical as high CSF neutrophil counts appeared to predict greater mortality in an Indonesian TBM cohort [37], *and studies have proposed neutrophils mediate disruption of the blood-brain-barrier and tissue destruction in CNS-TB* [38, 39].

Table 3:

1) CSF values: include neutrophil count, since the authors had commented in their Discussion

Neutrophil count is now included in Table 3.

2) The authors might want to further clarify that these patients include the Confirmed, probable and possible cases i: In the rows, it would be devoting a section on how many of TBM, TBML are of each category.

We tried to reformat and repopulate the Table in this way, but it resulted in a table that was too ‘busy’, and very difficult to decipher so have not included this suggested revision.

REVIEWER #2:

This paper informs on clinical presentation and outcomes of CNS TB in a high resource setting. It is helpful in highlighting the variability of clinical presentation of such disease and the challenges posed by CNS TB diagnosis and management. Findings of substantial morbidity in CNS TB in high resource settings are in keeping with literature data (mostly arising from low resource settings) and therefore deemed to be of interest for publication. Prognostic indicators of persistent morbidity are proposed, although validity of those can be affected by small sample size and suggest commenting in the limitations.

We thank the reviewer for these comments and have expanded the study limitations to make this more explicit:

Page 11: *The study is limited by its single-centre, retrospective nature and small sample size, constraining statistical power; consequently, multivariable analysis results have large confidence intervals. Additionally, diagnostics and therapeutics have evolved during the timeframe of the study….*

Overall the text is clear although the results section could be improved in writing, especially looking for simplification and avoidance of redundancies.
In particular would suggest reviewing of:

1) In the results section: "Even in definite cases (Figure 2b), a number of individuals (5/23) had atypical patterns of CSF abnormalities, including a predominantly neutrophilic CSF in four patients (17%)." This statement is incorrect and should be rephrased as neutrophilic pleyocitosis is well described in TBM, especially in early phase of disease.

We agree with this comment and also comment by reviewer no. 1 and have changed the text: Of the definite TBM cases, *4 (17%) immunocompetent patients had a neutrophilic pleocytosis, which is recognised in the early phase of TBM.*

2) In the Microbiology findings: 'Despite overlap, all three modalities, smear, culture and PCR, added additional cases to the total microbiologically-proven caseload.' Would suggest rephrasing as smear, culture and PCR are all indicated in the investigation of TBM, one test does not substitute the others.

We agree with the reviewer and importance of this point. To simplify the results section, we have removed this sentence as it repeats itself in the discussion, and rephrased it as:

'Definite' (microbiologically proven) diagnosis accounted for 37% of cases, typifying the experience of other CNS-TB studies [20] and highlighting the limitations of the current diagnostic armamentarium of microscopy, culture and PCR. *In this cohort, all three tests added to the microbiologically-proven cases. Hence, one diagnostic modality does not substitute for another; all are indicated in the investigation of TBM to maximise diagnostic yield.*

Re: Tables and Figures - would suggest the following
Table 2 - to be reviewed- eg cough/weight loss/sweats could be listed perhaps clustered as systemic signs/extrapulmonary signs of disease

We have simplified and now clustered weight loss and night sweats together.

Figure 1 - would substitute legend A and B with TBM and TBML for simplification

We have substituted A and B with TBM and TBML.

Figure 2 - same as above and would remove figure 2 B as redundant

We have removed figure 2B.

REVIEWER #3:

This manuscript describes a retrospective review of TB meningitis (N=62) and TB brain mass lesions without meningitis (n=14) in a single centre in London over 16 years (2001-2017). It's a nicely written report that describes the presentation, treatment and outcome of the cases, with some analysis of the features associated with poor outcome. There is very little to object to about the report, other than its obvious limitations of being relatively small (although not for the UK), retrospective, observational, and single centre. These limitations reduce the impact of the findings on clinical practice. But the data will be useful to those practicing in well-resourced settings and they highlight the devastating consequences of central nervous system tuberculosis regardless of available resources.

We thank the reviewer for their positive comments; whilst we agree that this study will not change practice, it may help direct strategy. It is important to recognize that even in relatively well-resourced settings, outcomes remain poor and progress needs to be made to reduce the neurological burden on CNS-TB through the development of new therapeutic strategies. We also feel our paper makes a significant contribution to recognition of patterns of presentation of disease which have not been brought out in the same way in previous literature.

Title: Presentations and Outcomes of Central Nervous System TB in a UK Cohort: The high burden of neurological morbidity

Running title: Presentations and Outcomes of CNS-TB

Authors:

Clare Logan[a,b*], Claire Mullender[a*], Miriam Mirfenderesky[a,1], Nicholas Feasey[a,c], Catherine Cosgrove[a,b], Peter Riley[a], Angela Houston[a], Tom Harrison[a,b], Tihana Bicanic[a,b], Phil Rich[d], Paul Hart [e,f], Síle F Molloy[b], Derek C. Macallan[a,b]

* CL and CM contributed equally to the manuscript

Affiliations:

a. Infection Care Group, St George's University Hospitals NHS Foundation Trust, London, UK
b. Institute for Infection & Immunity, St George's, University of London, London, UK
c. Liverpool School of Tropical Medicine, Liverpool, UK
d. Department of Neuroradiology, St George's University Hospitals NHS Foundation Trust, London, UK
e. Department of Neurology, St George's University Hospitals NHS Foundation Trust, London, UK
f. Department of Neurology, Epsom and St Helier Hospital, Epsom, UK

[1.] Present address: North Middlesex University Hospital, London

For Correspondence:

Prof Derek C. Macallan,
Infection & Immunity Research Institute,
St George's, University of London, London SW17 0RE
Tel: (44)-20-8725-0283; Fax: (44)-20-8725-3487; Email: macallan@sgul.ac.uk

Word counts:
Abstract: 199
Main text: 3,496
Tables: 5
Figures: 2

KEYWORDS: tuberculosis; meningitis; tuberculoma; outcomes; hydrocephalus; brain; neuroinflammation

ABSTRACT

Objectives

Most data for Central Nervous System Tuberculosis (CNS-TB) derive from high-incidence, resource-limited countries. We sought to determine the presentation, management and outcomes of CNS-TB in a low-incidence setting with accessible healthcare.

Methods

We undertook a retrospective, observational study of CNS-TB in adults at a single tertiary-referral London hospital (2001-2017). Cases were categorised as either TB meningitis (TBM) or TB mass lesions without meningitis (TBML), applying novel criteria for definite, probable, and possible TBML.

Results

We identified sixty-two cases of TBM (37% definite; 31% probable; 32% possible) alongside 14 TBML cases (36% definite; 29% probable; and 36% possible). Clinical presentation was highly variable. Among CSF parameters, hypoglycorrhachia proved most discriminatory for “definite” TBM. Neurosurgical intervention was required for mass-effect or hydrocephalus in 16%. Mortality was higher in TBM versus TBML (16% vs 0%) but overall morbidity was significant; 35% of TBM and 28% of TBML survivors suffered persisting neurological disability at 12-months. In TBM, hydrocephalus, infarct, basal enhancement and low CSF white cell count were independently associated with worse neurological outcomes.

Conclusion

Although mortality was lower than previously reported in other settings, morbidity was significant, highlighting the need for improved CNS-TB diagnostics, therapeutics and interventions to mitigate neurological sequelae.

Graphical Abstract (for review)

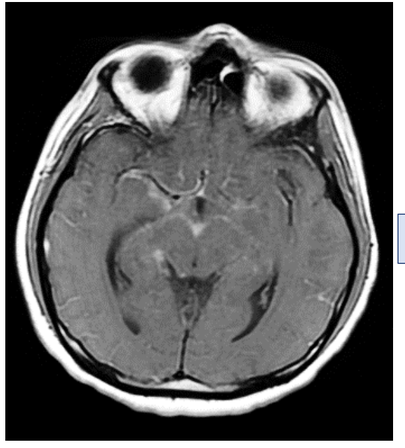
Spectrum of disease

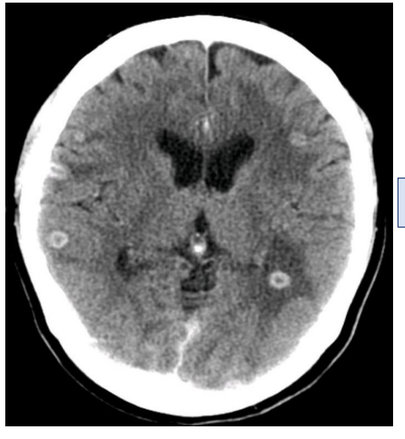
CNS-TB

TB Meningitis

TBM with mass lesions

TB mass lesions

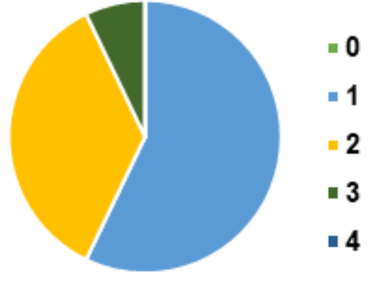




Clinical presentation

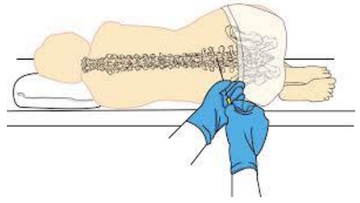
Number of symptoms

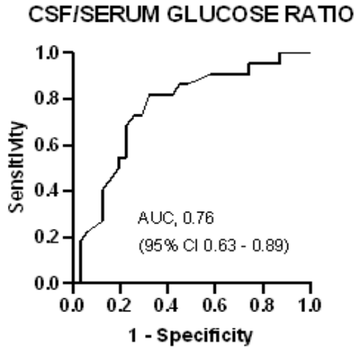
Mostly headache/fever



Mostly Seizures

CSF





Predictive value of CSF glucose

Outcomes

41% poor or death

Risk factors:
hydrocephalus, infarct, basal enhancement low CSF WCC

HIGHLIGHTS:

- Patterns of clinical presentation of TB meningitis are diverse
- Diagnostic criteria for possible, probable & definite TB mass lesions are proposed
- Seizures are a more frequent presentation in patients with TB mass lesions
- Neurological sequelae are common: occurring in about a third of CNS-TB survivors

INTRODUCTION

Central nervous system TB (CNS-TB) represents one of the most serious clinical manifestations of *Mycobacterium tuberculosis* (MTB) infection. There are two main patterns of disease presentation: (i) tuberculous meningitis (TBM) and (ii) intracranial tuberculous mass lesion(s) (TBML). Although CNS-TB only accounts for about 1% of TB cases [1], it contributes disproportionately to morbidity and mortality. Pathologically, CNS-TB arises from haematogenous seeding of *M. tuberculosis* to the brain following pulmonary infection. Small tuberculous foci (Rich foci) develop in the brain parenchyma or meninges [2]. Meningitis occurs when foci rupture into the subarachnoid space [3, 4]. Growth of the tubercules in the parenchyma generates mass lesions which may manifest as either solid, granulomatous lesions (tuberculoma) or, more rarely, as pus-filled cavities (tuberculous abscesses) [3]. Both processes may co-exist; mass lesions may occur in the absence of meningitis, and *vice versa*.

Recognition and diagnosis of CNS-TB are difficult given the variability in clinical presentation. Although a scoring system of diagnostic criteria has been established for research studies [5], it is not generally used in clinical practice where heightened clinical suspicion and prompt recognition are the crucial factors determining early diagnosis, timely treatment and hence better outcomes. Pathologically, the basal meninges are most affected. The consequent vasculitis of local and perforating blood vessels results in damage to cranial nerves, presenting as focal cranial neuropathies, and ischaemic parenchymal events. Obstruction to cerebrospinal fluid (CSF) flow is also common leading to hydrocephalus. Hence the importance of early diagnosis which creates a window of opportunity to treat before irreversible complications of hydrocephalus and/or ischaemic injury develop [6, 7]. Even with prompt treatment however, TBM is often a devastating disease; over half of patients die or suffer disabling neurological deficits [8–10]. Mortality is highest in those with HIV co-infection and in rifampicin-resistant or multi-drug resistant (MDR) TB [10]. Much less is known about TBML due to limited diagnostic criteria and the scarcity of outcome

data [11–14].

To date, most data for CNS-TB originate from studies in high incidence, resource-limited countries. The emergent picture reflects these settings and may not be generalisable. We sought to address this knowledge gap by investigating the progress of a cohort of TBM/TBML patients in the UK. The UK is considered a low-incidence setting for TB (<10 per 100,000 overall, but ~19 per 100,000 in London), with a low rate of HIV-TB co-infection (2.9% in 2018)[15], and a widely-accessible healthcare system [16]. In London, CNS-TB represents ~5% of all TB infections [15]. Hence, we performed this review of all patients with CNS-TB at a London teaching hospital (with on-site infectious disease, intensive care, neurology and neurosurgical facilities) to determine the clinical presentation, management and outcomes in such a setting.

Methods

Case identification

We performed a retrospective case-note review of adult patients (≥16 years) treated for CNS-TB at a single London tertiary referral centre between 2001-2017. Cases were identified from the London TB register and institutional records and designated as "TBM" or "TBML". TBM cases were included if they met consensus case-definition diagnostic criteria [5] and sub-classified as 'definite', 'probable' or 'possible' TBM on the basis of clinical features, CSF results, cerebral imaging and microbiology. Cases were excluded if TB treatment was discontinued in the context of an alternative diagnosis. To avoid duplication, cases with both a mass lesion and meningitis (either nuchal rigidity, inflammatory CSF or meningeal enhancement on imaging) were categorised as "TBM"; hence "TBML" in this context means a mass lesion without meningitis. Since 'TBML without meningitis' does not have a consensus case-definition, we developed novel criteria, defining TBML as:

The presence of radiological features consistent with a tuberculous mass lesion in the absence of meningitic clinical features and, if performed, absence of inflammatory CSF, plus for:

- 'definite' cases - microbiologic evidence of TB infection in CNS pus/tissue (culture, PCR-positive or acid-fast bacilli (AFB) seen);
- 'probable' cases - evidence of extra-neural TB or granuloma (but no AFB-seen) on CNS histology;
- 'possible' cases - radiological evidence alone in an appropriate clinical context.

Case note review

Routinely-collected demographic, clinical, radiological, microbiological, and outcome data were documented. Disease severity on admission was graded according to British Medical Research (MRC) criteria: grade I, Glasgow Coma Score (GCS) of 15 with no focal neurology; grade II, GCS 11-14, with or without focal neurological deficit or GCS of 15 with focal neurological deficit; grade

III, GCS ≤ 10, with or without focal neurological deficit [17]. Retrospective assessment of outcome was assessed from follow-up at ≥12-months using the Glasgow Outcome Score (GOS) [18], where 1 represents death; 2, vegetative state; 3, severely disabled (conscious but unable to live independently); 4, moderately disabled (able to live independently, but unable to return to work); 5, no disability (resumed most normal activities). Deaths were included in all-cause mortality data if they occurred within the routine 12-month follow-up period. The study was registered and approved by the St Georges University Hospital Audit & Clinical Effectiveness Unit. UK National Research Ethics Service guidance permits retrospective evaluation of routinely-collected anonymised clinical data without formal ethics approval.

Statistical analysis

To compare clinical presentation and outcomes between TBM and TBML, univariable analysis of categorical data was performed using Chi-squared or Fishers exact test, and Student t-test or Mann-Whitney *U* test for continuous data. Receiver-operator characteristic (ROC) curves to identify which CSF parameters predicted a 'definite' case were generated using Prism (Graphpad software, Version 8). For TBM cases with 12-month follow-up, we performed a complete-case analysis using multivariable logistic regression to evaluate associations between an 'unfavourable' outcome (GOS 1-4) and the following variables; age, MRC grade, HIV status, hydrocephalus, basal enhancement, presence of tuberculoma, cerebral infarct, CSF white cell count <50 cells/μL, CSF Protein ≥1g/L, and CSF glucose ≤2.2 mmol/L. Variables with a p-value ≤0.10 in univariable analysis were included in a multivariable model. Multivariable logistic regression was performed using a backward stepwise elimination approach to construct the final model using STATA (Statacorp Version 16).

RESULTS

Cohort characteristics

The cohort comprised 76 cases with CNS-TB (Table 1), including 62 with TBM, of whom 37% (23/62) were classified as 'definite'; 31% (19/62) 'probable'; and 32% (20/62) 'possible', by consensus criteria [5]. The remaining 14 cases were defined as TBML (without meningitis), including 36% (5/14) 'definite'; 29% (4/14) 'probable'; and 36% (5/14) 'possible' cases, according to the criteria proposed above. The age range was wide, from 16 (minimum for inclusion) to 77 years (median 38 years, IQR: 27-50). Both genders were equally represented (51% female). Most patients were born outside of the UK, but this was not a disease of new migrants; median time living in the UK prior to presentation was 10 years (IQR: 4-18 years). HIV co-infection was present in 26% (16/62) with TBM, but only 7% (1/14) of those with TBML (p=0.17). HIV-infected patients with CNS-TB tended to have advanced disease (median [range] CD4 cell count 81 [3-523] cells/uL) although CNS-TB also occurred in some patients with well-controlled HIV infection.

Clinical presentation

Clinical presentations of patients with CNS-TB were very diverse (Table 2). For those with TBM, the most common features were fever, headache, and altered consciousness/confusion. The presentation of TBML was quite distinct; seizures were the commonest presentation (in 64% versus 18% in TBM; p=0.01) and represented the only symptom in a third of cases (36%, 5/14). Conversely, fever was significantly less common in TBML (14% (2/14) versus 68% (42/62) in TBM; p=0.01). Reported symptom duration prior to presentation was significantly longer in TBM compared to TBML (median 14 versus 3 days; p=0.02), primarily because half of TBML cases presented with seizure without preceding symptoms. Most TBM cases (52%, 32/62) presented without impaired consciousness or focal neurology (MRC grade I), whilst 44% (27/62) presented with grade II, and 5% (3/62) grade III disease.

Since clinicians recognise diseases by symptom-complexes, not isolated symptoms, we examined how symptoms clustered in TBM and TBML. Selecting the three most frequent symptoms in TBM (headache, fever, and altered consciousness/confusion, Table 2) plus seizures, the most frequent in TBML, we analysed by co-presentation (Figure 1). The triad of the three most common TBM symptoms presenting together was only seen in about a quarter of TBM cases (27%, 17/62); almost two-thirds (60%, 37/62) presented with only one or two of the triad, most commonly headache plus fever (25%, 16/62). TBML, by contrast, most frequently presented with the 'seizure-only' clinical phenotype.

Diagnostics

Neuroradiology

All patients underwent neuro-imaging (CT 93%; MRI 90%; both CT & MRI 83%) (Table 3). In patients with TBM, basal enhancement was observed in 39% (24/62) and mass lesions were common (42%, 26/42). Hydrocephalus was found in 24% (15/62), more often in patients with MRC grade II or III disease (Hydrocephalus; MRC grade I: 9.3% (3/32) versus grade II/III: 40% (12/30), p=0.01). Cerebral infarction characterised 23% (14/62) of TBM cases. In TBML, conversely, hydrocephalus was only seen in 7% (1/14) and none had cerebral infarction. We reviewed the rate of resolution of mass lesions in all CNS-TB cases. 40 cases exhibited tuberculoma(s) on initial imaging (26/62 TBM plus 14/14 TBML); of these 22 (55%) had repeat imaging ≥ 9 months of follow-up. Tuberculoma(s) had resolved in 36% (8/22), were present but reduced in size in 41% (9/22), and had not changed in size in 23% (5/22).

Highlighting the importance of looking for TB outside the CNS, radiological features suggestive of extra-neural TB were identified in a third of patients with CNS tuberculosis (TBM 34%, 21/62; TBML 36%, 5/14), including pulmonary disease (18%, 14/76), miliary TB (7%, 5/76); and disease at other sites (9%, 7/76; discitis/paraspinal mass, osteomyelitis, liver, spleen, and lymphadenitis).

The extra-neural site yielded a positive culture in 22% (17/76) of cases (10 sputum; 5 lymph node; 1 pleural fluid; 1 liver biopsy, sputum & lymph node).

CSF findings

The classical triad of pleocytosis (with lymphocytic predominance), high protein and low glucose was the most commonly seen pattern of CSF abnormalities (Table 3 and Figure 2), but a third of patients (20/60) displayed alternative patterns. Of the definite TBM cases, 4 (17%) immunocompetent patients had a neutrophilic pleocytosis, which is recognised in the early phase of TBM. One case had isolated hypoglycorrhachia only. Notably, the absence of a raised CSF white cell count was not a rule-out (seen in 11 'all-TBM' and 4 'definite-TBM' cases). Assessing predictors of a 'definite-TBM' case by ROC analysis revealed that hypoglycorrhachia was the best discriminator (Figure 2). For TBML, CSF was obtained in four cases – all normal as per the TBML definition; in the remaining 10 cases, CSF examination was deemed clinically unnecessary or contraindicated.

Microbiology findings

TB was microbiologically confirmed in over a third of TBM cases (37%, 23/62). As expected, CSF direct smear examination was less sensitive than culture (AFB visualised in 11%, 7/61), although two cases on treatment at the time of LP were smear-positive but culture-negative. Cepheid Xpert® MTB/RIF PCR was introduced on-site in 2011; prior to this INNO-LiPA Rif.TB assay was performed by the TB Reference Laboratory. PCR was positive in 20% (5/25) of the cases in whom it was performed including one culture-negative case. 57% (8/14) TBML cases had drainage or biopsy procedures. Diagnostic yield was high; two-thirds confirmed TB (4 culture-positive; 1 AFB-seen) and 2 had histology consistent with TB (caseating/necrotising granuloma). Drug susceptibility testing of the cultured TB isolates (in TBM and TBML) demonstrated resistance in 18% (5/28); 4 INH mono-resistance; 1 INH and rifampicin resistance.

Management

Anti-tuberculosis chemotherapy for TBM and TBML closely followed contemporaneous local/national guidelines [4, 19], modified according to *in vitro* sensitivities. In the absence of known resistance, first-line therapy comprised ethambutol, isoniazid, rifampicin, and pyrazinamide (n=33) until 2008, when moxifloxacin largely replaced ethambutol (n=37). 8% (6/76) had alternative regimens due to drug-resistance or hepatic impairment. For both TBM and TBML, median (range) treatment duration was 12 (9–20) months (unascertained in 7 patients), being extended beyond 12 months in 11% (6/55) of TBM and 36% (5/14) of TBML cases for treatment interruptions or poor clinical response. Adjunctive steroid therapy was given in almost all cases (all CNS-TB, 95% 72/76; TBM 95%, 59/62; TBML 93%, 13/14).

Overall, 16% (12/76) had at least one neurosurgical intervention for mass-effect or hydrocephalus, including four craniotomy and excision/drainage procedures, four external ventricular drains, four ventriculoperitoneal shunts, and one lumbar drain. In total, 56% (9/16) of patients with hydrocephalus underwent surgical management. A further five patients, had neurosurgical intervention for diagnostic purposes only.

Clinical outcomes

12-month outcome data was available for 90% (55/62) of TBM cases (7 transferred or lost to follow up) and all TBML cases (14/14) (Table 4). Mortality was significant; 16% (9/55) in the TBM group died within 1-year of diagnosis. Deaths occurred both early and late; the median (IQR) time from hospital admission to death was 74 (54 – 80) days. In survivors, neurological sequelae were common; 33% (15/46) were left with an intermediate or severe neurological disability (GOS 2-4). For TBML, at 12-month follow-up, there were no deaths (p=0.19 versus TBM), but 4/14 (28%) suffered residual neurological disability (GOS 2-4). The rates of favourable outcome (GOS 5), 70% for TBML and 56% for TBM, were not statistically different (p=0.37), but comparisons are

difficult given the discrepant and small cohort sizes. Our data does however suggest that the hypothesis that TBML has a more benign course than TBM merits further exploration in larger adequately-powered studies.

In terms of predictors of outcome from TBM, ten variables were identified in univariable analysis as significantly associated with 'unfavourable' outcome, defined as death or neurological disability [GOS ≤4] (Table 5). Including variables with p ≤0.1 from the univariable analysis into a multivariable model, we identified hydrocephalus (Odds Ratio [95% Confidence Interval], 23.03 [2.92-181.35], *p*=0.01), cerebral infarct (OR 11.13 [1.36 – 91.94], *p*=0.03), basal enhancement (OR 5.66 [1.10-29.23], *p*=0.04), and a lower CSF WCC (OR 8.96 [1.51 – 53.16], *p*=0.02) as variables independently associated with an 'unfavourable' outcome (Table 5).

DISCUSSION

This retrospective review demonstrates the broad clinical spectrum of presentation of CNS-TB, the difficulties encountered in making a diagnosis and the frequency of complications, disability and mortality despite active management. This is the largest adult CNS-TB case series to date published in the UK and reveals some key insights.

Firstly, it is clear that identification of CNS-TB remains extremely challenging for the clinician, especially when trying to use clinical features to differentiate it from other causes of meningoencephalitis and/or space-occupying lesions. No one symptom-complex identifies TBM. Although fever, headache and altered consciousness were common, as described previously [20–24], 'classical' features such as neck stiffness were often absent. Indeed, analysing by symptom-complex (Figure 1), patients frequently presented with just one or two major symptoms, underscoring the need for a high degree of diagnostic suspicion. Similarly, the time-scale of TBM cannot be relied upon to discriminate it from other meningeal diseases. Classically TBM is described as subacute with a non-specific prodrome but, in our series, extremes of presentation were also seen; approximately a quarter presented within a week of symptom-onset.

Additionally, we have highlighted the contrasting presentations of TBM and TBML. TBML most commonly presents with isolated seizures, often without preceding symptoms or systemic features such as fever. Although headache and neurological manifestations were seen, depending on anatomic location, size and associated mass-effect, they were relatively uncommon. Importantly, the possibility that a space-occupying lesion might be TB should not be discounted because of the absence of systemic features.

Secondly, we have shown how even with good laboratory support, diagnostic confirmation of CNS-TB remains difficult. 'Definite' (microbiologically proven) diagnosis accounted for 37% of

cases, typifying the experience of other CNS-TB studies [20] and highlighting the limitations of the current diagnostic armamentarium of microscopy, culture and PCR. In this cohort, all three tests added to the microbiologically-proven cases. Hence, one diagnostic modality does not substitute for another; all are indicated in the investigation of TBM to maximise diagnostic yield. Measures to optimise diagnostic yield include using large volumes (>6ml) of CSF [25, 26], dedicating ≥20 minutes to microscopy [25], and centrifugation of CSF prior to PCR [27]. Cepheid Xpert® MTB/Rif Ultra may enhance detection of TBM compared to Cepheid Xpert® or culture in patients with low bacillary loads [28] and in HIV-infected patients [29], but the improvement is modest, and the negative predictive value (~75-93% compared to probable or definite cases) insufficient to exclude TBM [30]. In TBML, diagnostic opportunities may be limited by the location of the lesion and surgical risks. Given such difficulties, searching for TB elsewhere can be very useful as demonstrated in this study where extra-neural TB was found in over a fifth (22%) of CNS-TB patients.

Thirdly, we have demonstrated that even in relatively well-resourced healthcare settings with on-site critical care and neurosurgery, TBM continues to cause significant mortality and long-term neurological morbidity. In this study about one sixth of patients died and over a third (33%) were left with neurological sequelae (GOS 2-4 at 12 months). Our mortality data is lower than some other settings [8, 20, 31]. Although partly attributable to the relatively low HIV prevalence in this cohort, we surmise from the relatively high proportion of patients presenting with MRC grade I disease that accessible healthcare [16] favours early presentation leading to improved survival. This data thus supports the drive to ensure rapidly accessible diagnostic and therapeutic facilities for management of CNS-TB. In contrast, our morbidity data are comparable to other settings [8, 10]; a significant proportion of patients were left with functional impairment, possibly because some who might have died instead survived with morbidity, whilst a similar number did not suffer morbidity.

In terms of who suffered most morbidity, our finding in a multivariable model that individuals with hydrocephalus, cerebral infarction and basal enhancement are significantly more likely to have an 'unfavourable' outcome is consistent with previous literature [32–34]. Mitigating the impact of these adverse factors is one potential avenue to reduce neurological morbidity. Best practice for hydrocephalus management in CNS-TB remains unclear and differs between obstructive and communicating hydrocephalus, the latter being more common in TBM [35]. Over half of those with hydrocephalus in this study underwent neurosurgical intervention demonstrating the value of co-location of neuroradiology and neurosurgical services with CNS-TB facilities. Cerebral infarction and basal enhancement reflect neuroinflammation characterised by cerebral vasculitis [3]. The high morbidity seen in this and other studies reflects the paucity of proven treatments for TBM-associated neuroinflammation. Corticosteroids are of proven benefit [8] but other adjunctive non-surgical therapies discussed in the literature such as aspirin, thalidomide, infliximab and interferon [35, 36] have not yet been sufficiently evaluated. In view of the adverse impact of neuroinflammation, it is perhaps surprising that we observed an apparently protective effect of high CSF white cell counts (≥50 cells/per μL) against 'unfavourable' outcomes. This observation is however consistent with data from large TBM cohorts in Vietnam where lower CSF lymphocyte counts predicted death regardless of HIV-status [31]. The type of cellular response may be critical as high CSF neutrophil counts appeared to predict greater mortality in an Indonesian TBM cohort [37], and studies have suggested neutrophils mediate disruption of the blood-brain-barrier and tissue destruction in CNS-TB [38, 39]. Other cohorts have found HIV to be associated with poor outcomes [10, 20]; the lack of association in this study is likely due to the low HIV prevalence and smaller cohort size. Better understanding of the relationship between host immune response and TBM outcome is needed to inform which subgroups may benefit from which adjunctive immunomodulatory therapies.

Finally, in terms of the discussion around optimal treatment regimens [40], this study does not add any comparative data as all patients received very similar treatment regimens, closely following national guidelines [4, 19], but it does provide some reflections on treatment duration. Almost all patients completed at least a year of anti-tuberculous chemotherapy but some were treated for longer, especially those with TBML, about 40% of whom were received extended therapy (>1 year). This almost certainly relates to the persistence of radiologic abnormalities: 64% of cases with tuberculoma who had subsequent imaging still had persisting radiologic abnormalities at ≥9 months follow-up. Previous studies have similarly shown visible tuberculomas on imaging in ~22-75% of patients after 9-18 months of therapy [13, 41–43]; indeed, one serial MRI study in TBM showed that ~70% of patients developed new tuberculomas during treatment and >50% who had 'recovered' at 9 months had persistent lesions on MRI [44], suggesting this may be part of the normal radio-pathological response to treated infection. Radiological resolution may therefore represent a poor index of 'cure' in such patients.

The study is limited by its single-centre, retrospective nature and small sample size, constraining statistical power; consequently, multivariable analysis results have large confidence intervals. Additionally, diagnostics and therapeutics have evolved during the timeframe of the study. To avoid overinterpretation, we have restricted our conclusions to those validated by our own dataset and focussed on the generalisable clinical implications of our observations.

CONCLUSION

This case series highlights key practice points pivotal to prompt recognition, diagnosis and management of patients with CNS-TB. Even in relatively well-resourced settings with accessible healthcare, CNS-TB still carries a high burden of long-term neurological morbidity.

Declaration of competing interests

None

Acknowledgements

We are grateful to all the patients, and the clinical and laboratory staff who contributed towards the care of CNS-TB patients at St Georges Hospital.

Funding

This study received no external funding.

REFERENCES

1. Phypers M, Harris T, Power C (2006) CNS tuberculosis: A longitudinal analysis of epidemiological and clinical features. Int J Tuberc Lung Dis 10:99–103
2. Rich A, McCordock H (1933) The pathogenesis of tuberculous meningitis. Bull Johns Hopkins Hosp 5–37
3. Rock RB, Olin M, Baker CA, et al (2008) Central nervous system tuberculosis: Pathogenesis and clinical aspects. Clin. Microbiol. Rev. 21:243–261
4. Thwaites G, Fisher M, Hemingway C, et al (2009) British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 59:167–187. https://doi.org/10.1016/j.jinf.2009.06.011
5. Marais S, Thwaites G, Schoeman JF, et al (2010) Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis 10:803–812. https://doi.org/10.1016/S1473-3099(10)70138-9
6. Brancusi F, Farrar J, Heemskerk D (2012) Tuberculous meningitis in adults: A review of a decade of developments focusing on prognostic factors for outcome. Future Microbiol. 7:1101–1116
7. Hosoglu S, Geyik MF, Balik I, et al (2002) Predictors of outcome in patients with tuberculous meningitis. Int J Tuberc Lung Dis 6:64–70
8. Thwaites GE, Bang ND, Dung NH, et al (2004) Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults. N Engl J Med 351:1741–1751. https://doi.org/10.1056/NEJMoa040573
9. Prasad K, Singh MB, Ryan H (2016) Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst. Rev. 2016
10. Heemskerk AD, Bang ND, Mai NTH, et al (2016) Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. N Engl J Med 374:124–134.

https://doi.org/10.1056/NEJMoa1507062

11. Wasay M, Moolani MK, Zaheer J, et al (2004) Prognostic indicators in patients with intracranial tuberculoma: a review of 102 cases. J Pak Med Assoc 54:83–87
12. Rajeswari R, Sivasubramanian S, Balambal R, et al (1995) A controlled clinical trial of short-course chemotherapy for tuberculoma of the brain. Tuber Lung Dis 76:311–317. https://doi.org/10.1016/S0962-8479(05)80029-2
13. Marais S, Van Toorn R, Chow FC, et al (2020) Management of intracranial tuberculous mass lesions: how long should we treat for? Wellcome Open Res 4:158. https://doi.org/10.12688/wellcomeopenres.15501.3
14. Marais S, Roos I, Mitha A, et al (2020) Presentation and outcome of patients with intracranial tuberculoma in a high HIV prevalence setting. Int J Tuberc Lung Dis 24:224–232. https://doi.org/10.5588/ijtld.19.0386
15. Public Health England (PHE) (2019) Tuberculosis in England - 2019 Report
16. Fullman N, Yearwood J, Abay SM, et al (2018) Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: A systematic analysis from the Global Burden of Disease Study 2016. Lancet 391:2236–2271. https://doi.org/10.1016/S0140-6736(18)30994-2
17. Streptomycin in Tuberculosis Trials Commitee Medical Research Council . (1948) Streptomycin treatment of Tuberculous Meningitis. Lancet 251:582–96
18. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet (London, England) 1:480–4
19. National Institute for Clinical Excellence (NICE) . (2016) Tuberculosis Clinical Guidelines NG33
20. Marais S, Pepper DJ, Schutz C, et al (2011) Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting. PLoS One 6:e20077
21. Bang ND, Caws M, Truc TT, et al (2016) Clinical presentations, diagnosis, mortality and

prognostic markers of tuberculous meningitis in Vietnamese children: A prospective descriptive study. BMC Infect Dis 16:573. https://doi.org/10.1186/s12879-016-1923-2

22. Erdem H, Ozturk-Engin D, Tireli H, et al (2015) Hamsi scoring in the prediction of unfavorable outcomes from tuberculous meningitis: results of Haydarpasa-II study. J Neurol 262:890–898. https://doi.org/10.1007/s00415-015-7651-5
23. Yasar KK, Pehlivanoglu F, Sengoz G (2010) Predictors of mortality in tuberculous meningitis: a multivariate analysis of 160 cases. Int J Tuberc Lung Dis 14:1330–5
24. Thwaites GE, Duc Bang N, Huy Dung N, et al (2005) The Influence of HIV Infection on Clinical Presentation, Response to Treatment, and Outcome in Adults with Tuberculous Meningitis. J Infect Dis 192:2134–2141. https://doi.org/10.1086/498220
25. Thwaites GE, Chau TTH, Farrar JJ (2004) Improving the Bacteriological Diagnosis of Tuberculous Meningitis. J Clin Microbiol 42:378–379. https://doi.org/10.1128/JCM.42.1.378-379.2004
26. Heemskerk AD, Donovan J, Thu DDA, et al (2018) Improving the microbiological diagnosis of tuberculous meningitis: A prospective, international, multicentre comparison of conventional and modified Ziehl–Neelsen stain, GeneXpert, and culture of cerebrospinal fluid. J Infect 77:509–515. https://doi.org/10.1016/j.jinf.2018.09.003
27. Bahr NC, Tugume L, Rajasingham R, et al (2015) Improved diagnostic sensitivity for tuberculous meningitis with Xpert® MTB/RIF of centrifuged CSF. Int J Tuberc Lung Dis 19:1209–1215. https://doi.org/10.5588/ijtld.15.0253
28. Donovan J, Thu DDA, Phu NH, et al (2020) Xpert MTB/RIF Ultra versus Xpert MTB/RIF for the diagnosis of tuberculous meningitis: a prospective, randomised, diagnostic accuracy study. Lancet Infect Dis 20:299–307. https://doi.org/10.1016/s1473-3099(19)30649-8
29. Cresswell F V., Tugume L, Bahr NC, et al (2020) Xpert MTB/RIF Ultra for the diagnosis of HIV-associated tuberculous meningitis: a prospective validation study. Lancet Infect Dis

20:308–317. https://doi.org/10.1016/S1473-3099(19)30550-X

30. Donovan J, Cresswell F, Nguyen T, Boulware D, Thwaites G, Bahr N, Tuberculous Meningitis International Research Consortium . (2020) Xpert MTB/RIF Ultra for the Diagnosis of Tuberculous Meningitis: A Small Step Forward. Clin Infect Dis ciaa473:
31. Thao LTP, Heemskerk AD, Geskus RB, et al (2018) Prognostic Models for 9-Month Mortality in Tuberculous Meningitis. Clin Infect Dis 66:523–532. https://doi.org/10.1093/cid/cix849
32. Cantier M, Morisot A, Guérot E, et al (2018) Functional outcomes in adults with tuberculous meningitis admitted to the ICU: A multicenter cohort study. Crit Care 22:210. https://doi.org/10.1186/s13054-018-2140-8
33. Raut T, Garg RK, Jain A, et al (2013) Hydrocephalus in tuberculous meningitis: Incidence, its predictive factors and impact on the prognosis. J Infect 66:330–337. https://doi.org/10.1016/j.jinf.2012.12.009
34. Kalita J, Misra UK, Nair PP (2009) Predictors of Stroke and Its Significance in the Outcome of Tuberculous Meningitis. J Stroke Cerebrovasc Dis 18:251–258. https://doi.org/10.1016/j.jstrokecerebrovasdis.2008.11.007
35. Donovan J, Figaji A, Imran D, et al (2019) The neurocritical care of tuberculous meningitis. Lancet Neurol 18:771–783. https://doi.org/10.1016/S1474-4422(19)30154-1
36. Thwaites GE, van Toorn R, Schoeman J (2013) Tuberculous meningitis: More questions, still too few answers. Lancet Neurol. 12:999–1010
37. Van Laarhoven A, Dian S, Ruesen C, Hayati E, Damen M, Annisa J et al. (2017) Clinical Parameters, Routine Inflammatory Markers, and LTA4H Genotype as Predictors of Mortality Among 608 Patients With Tuberculous Meningitis in Indonesia | The Journal of Infectious Diseases | Oxford Academic. J Infect Dis 215:1029–1039
38. Ong CWM, Pabisiak PJ, Brilha S, et al (2017) Complex regulation of neutrophil-derived MMP-9 secretion in central nervous system tuberculosis. J Neuroinflammation 14:31.

https://doi.org/10.1186/s12974-017-0801-1

39. Brilha S, Ong CWM, Weksler B, et al (2017) Matrix metalloproteinase-9 activity and a downregulated Hedgehog pathway impair blood-brain barrier function in an in vitro model of CNS tuberculosis. Sci Rep 7:1–15. https://doi.org/10.1038/s41598-017-16250-3

40. Cresswell F V., Te Brake L, Atherton R, et al (2019) Intensified antibiotic treatment of tuberculosis meningitis. Expert Rev Clin Pharmacol 12:267–288. https://doi.org/10.1080/17512433.2019.1552831

41. Tandon PN, Bhargava S (1985) Effect of medical treatment on intracranial tuberculoma-a CT study. Tubercle 66:85–97. https://doi.org/10.1016/0041-3879(85)90073-X

42. Nair BR, Rajshekhar V (2019) Factors Predicting the Need for Prolonged (>24 Months) Antituberculous Treatment in Patients with Brain Tuberculomas. World Neurosurg 125:e236–e247. https://doi.org/10.1016/j.wneu.2019.01.053

43. Man H, Sellier P, Boukobza M, et al (2010) Central nervous system tuberculomas in 23 patients. Scand J Infect Dis 42:450–454. https://doi.org/10.3109/00365541003598999

44. Thwaites GE, Macmullen-Price J, Chau TTH, et al (2007) Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study. Lancet Neurol 6:230–236. https://doi.org/10.1016/S1474-4422(07)70034-0

TABLES

Table 1. Demographics, Diagnostic criteria and Severity of CNS-TB cases

Variable	Tuberculous Meningitis (n=62)	Tuberculous Mass Lesion (without meningitis) (n=14)
Age median (range) *years*	41 (16 – 77)	32 (19 - 60)
Female sex, n (%)	30 (48)	9 (64)
Place of Birth, n (%)		
Europe*	10 (16)	2 (14)
Africa	22 (35)	7 (50)
Asia	28 (45)	5 (36)
South America	2 (3)	0 (0)
HIV positive, n (%)	16 (26)	1 (7)
CD4 cells, median (range)	81 (3 – 523)	109 (NA)
Definition[a], n (%)		
Definite	23 (37)	5 (36)
Probable	19 (31)	4 (29)
Possible	20 (32)	5 (36)
Admission MRC grade[b], n (%)		
Grade I	32 (52)	9 (64)
Grade II	27 (44)	4 (29)
Grade III	3 (5)	1 (7)

Values are number (n) and percentage, except for age and CD4 where median (range) are shown. *All European cases were born in the UK, except for one. [a] Diagnostic categories according to consensus case definition for TBM (5) and criteria for TB Mass Lesions without meningitis defined in Methods. [b] Severity on admission was graded by Medical Research Council (MRC) criteria: Grade I indicates a Glasgow Coma Scale (GCS) of 15 with no neurological signs; Grade II, GCS 11-14, or 15 with focal neurological signs; Grade III, GCS of 10 or less. Abbreviations: CNS-TB, Central nervous system tuberculosis.

Table 2. Presenting Features in Tuberculous Meningitis (TBM) and Tuberculous Mass Lesions without meningitis (TBML)

Presenting symptoms	All CNS-TB (n=76)	TBM (n= 62)	TBML (n= 14)	*p*
Fever (%)	44 (58)	42 (68)	2 (14)	**0.01**
Headache (%)	48 (63)	41 (66)	7 (50)	0.36
Confusion / Altered consciousness (%)	32 (42)	29 (47)	3 (21)	0.13
Systemic symptoms (%)*	26 (34)	22 (35)	4 (29)	0.76
Nausea/vomiting (%)	20 (26)	18 (29)	2 (14)	0.33
Focal neurology (%)	22 (29)	18 (29)	4 (29)	0.99
Cranial Nerve Palsy (%)	17 (22)	15 (24)	2 (14)	0.72
Neck stiffness (%)	13 (17)	13 (21)	0 (0)	0.12
Seizures (%)	20 (26)	11 (18)	9 (64)	**0.01**
Cough (%)	12 (16)	11 (18)	1 (7)	0.45
Duration of symptoms, days	14 (7-28)	14 (7-42)	3 (1-25)	**0.02**

Frequencies of occurrence of each symptom ranked in descending order for TBM. Values are number (%) except for Duration which is median (IQR). P-values comparing TBM with TBML by Fishers-exact test.

* Includes night sweats and weight loss. Abbreviations: CNS-TB, Central nervous system tuberculosis; TBM, tuberculous meningitis; TBML, Tuberculous Mass Lesions without meningitis.

Table 3. Radiological and Laboratory Findings in Tuberculous Meningitis (TBM) and Tuberculous Mass Lesions without meningitis (TBML)

Variable	TBM (n=62)	TBML (n=14)
Neuroradiology, n (%)		
Tuberculoma/abscess	26 (42)	14 (100)
Infarct	14 (23)	0 (0)
Hydrocephalus	15 (24)	1 (7)
Basal enhancement	24 (39)	0 (0)
Extra-neural TB, n (%)		
Radiological changes suggestive of extra-neural TB	21 (34)	5 (36)
Suggestive of pulmonary TB	12 (19)	2 (14)
Suggestive of miliary TB	5 (8)	0 (0)
Other	4 (6)	3 (21)
TB positive[a] extra-neural sample, n (%)	15 (24)	2 (14)
Laboratory values, median (IQR)		
Serum CRP (mg/L)[b]	10 (4 – 38)	9 (5 – 15)
WCC ($x10^9$/L)	7 (6 – 9)	8 (6 – 8)
CNS specimen results, n (%)		
Patients with LP performed	61 (98)	4 (29)
Patients with tuberculoma pus/tissue taken	3 (5)	8 (57)
CSF values, median (IQR) [b]		
CSF total WCC (per µL)	75 (21 – 178)	3 (3 – 4)
CSF lymphocyte count (per µL)	60 (30 – 155)	…
CSF neutrophil count (per µL)	8 (2 - 28)	…
CSF protein (g/L)	1.5 (0.9 – 2.2)	0.3 (0.2 – 0.4)
CSF glucose (mmol/L)	2.1 (1.2 – 2.8)	3.3 (3.0 – 3.6)
CSF CSF:serum glucose ratio	0.3 (0.2 – 0.5)	0.6 (0.6 – 0.7)
CNS specimen microbiology , n (%)		
TB positive[a] CNS sample (CSF or tuberculoma tissue/pus)	23 (37)	5 (36)
Drug susceptibility[c] n/N (%)		
No resistance	16/23 (70)	4/5 (80)
INH monoresistance	4/23 (17)	-
MDR	1/23 (4)	-
Not available	2/23 (9)	1/5 (20)

[a] TB positive defined as either (1) positive CSF or tuberculoma tissue/pus culture for *M. tuberculosis*, (2) positive CSF or tuberculoma tissue/pus TB GeneXpert, or (3) AFB seen in CSF or tuberculoma tissue/pus. GeneXpert performed on 25/65 CSF samples, and 6/11 CNS tissue/pus samples; [b] Missing data: Serum CRP missing for 1 patient with TBM; CSF analysis; 1 patient had only CSF culture performed and missing WCC/lymphocyte/protein/glucose data; CSF/serum glucose ratio missing for 8 patients. [c] INH monoresistance, resistance to INH but not rifampicin; MDR, resistance to at least isoniazid and rifampicin.

Abbreviations: CNS, Central Nervous System; CRP, C reactive-protein; CSF, cerebrospinal fluid; INH, isoniazid; IQR, interquartile range; MDR, multi-drug resistant; n, number of patients; N, number of samples/investigations; TB, tuberculous; WCC, white cell count.

Table 4. 12-month Outcomes in Tuberculous Meningitis (TBM) and Tuberculous Mass Lesions without meningitis (TBML)

Group	n *	Neurological Outcome, n (%)			
		Good (GOS 5)	Intermediate (GOS 4)	Severe (GOS 2-3)	Death (GOS 1)
All CNS-TB	69	41 (59)	7 (10)	12 (17)	9 (13)
TBM	55	31 (56)	6 (11)	9 (16)	9 (16)
TBML	14	10 (70)	1 (7)	3 (21)	0 (0)

*Number of patients with 12-month outcome data. CNS-TB, Central Nervous System TB; GOS, Glasgow Outcome Score (18); GOS 1 represents death; 2, vegetative state; 3, severely disabled (conscious but unable to live independently); 4, moderately disabled (able to live independently, but unable to return to work); 5, no disability (resumed most normal activities).

Table 5. Univariable and Multivariable logistic regression analysis: Association between variables and an unfavourable outcome (GOS ≤ 4) at 12-months for TB Meningitis

Variable	Category	n	GOS I-IV	OR (95% CI), Univariable	*p*	OR (95% CI), Multivariable	*p*
Age	<40	25	36% (9)	1	0.26		
	≥40	28	54% (15)	1.02 (0.99 - 1.05)			
HIV	HIV-negative	42	43% (18)	1	0.49		
	HIV-positive	11	55% (6)	1.60 (0.42 - 6.08)			
MRC grade	Grade I	27	30% (8)	1	0.02*		
	Grade II/III	26	62% (16)	3.8 (1.21 -11.99)			
Hydrocephalus	Absent	39	31% (12)	1	0.01*	1	**0.01**
	Present	14	86% (12)	13.5 (2.61 - 68.88)		23.0 (2.92 - 181.4)	
Cerebral infarct	Absent	42	36% (11)	1	0.02*	1	**0.03**
	Present	11	82% (9)	8.1 (1.54 -42.48)		11.1 (1.36 - 91.9)	
Basal enhancement	Absent	33	33% (11)	1	0.03*	1	**0.04**
	Present	20	65% (13)	3.71 (1.15 - 11.96)		5.66 (1.10 - 29.2)	
Tuberculoma	Absent	29	38% (11)	1	0.24		
	Present	24	54% (13)	1.93 (0.64 - 5.80)			
CSF white cell count	≥50 cells/μL	35	31% (11)	1	0.10*	1	**0.02**
	<50 cells/μL	18	72% (13)	2.66 (0.83 - 8.57)		8.96 (1.51 - 53.16)	
CSF Protein	<1g/L	16	56% (9)	1	0.24		
	≥1g/L	37	41% (15)	0.53 (0.16 -1.73)			
CSF glucose	>2.2 mmol/L	23	48% (11)	1	0.75		
	≤2.2 mmol/L	30	43% (13)	0.83 (0.28 - 2.48)			

Complete case analysis – i.e. analysis included all subjects with no missing data, n=53. * Variables with a p-value ≤0.1 in univariable analysis were included in the multivariable analysis.

Figure 1. Patterns of Clinical Presentation in Tuberculous Meningitis (TBM) and Tuberculous Mass Lesions without Meningitis (TBML)

Patterns of clinical presentation in TBM *(n= 62),* and TBML *(n=14).* Histogram (i) demonstrates number of cases of presenting with combinations of headache (H), fever (F), altered consciousness (C), or seizure (S); Venn diagram (ii) shows number of cases with zero, one, two, three or four of these major symptoms.

Figure 2. Cerebrospinal Fluid (CSF) findings in Tuberculous Meningitis (TBM)

(a) Patterns of CSF findings in all cases of TBM with CSF analysis results *(n= 60),* Histogram (i) demonstrates number of cases of TBM presenting with combinations of cell count ≥10 cells/ul, protein ≥ 0.45 g/L, CSF/serum glucose ratio ≤0.5 or CSF glucose ≤2.2; inset Venn diagram (ii) shows number of cases with zero, one, two, or three of these major CSF findings.

(b) Receiver-operator characteristics for prediction of a “definite” case of TBM (versus possible or probable using definitions of Marais et al (5)) from protein (area under curve (AUC) 0.58, p=0.32), cell count (area 0.62, p=0.11), and glucose ratio (area 0.76, p=0.01). Maximizing Youden’s Index for glucose ratio gave a cut-off of 0.335 corresponding to a sensitivity of 81% and a specificity of 68%.

Figure 1

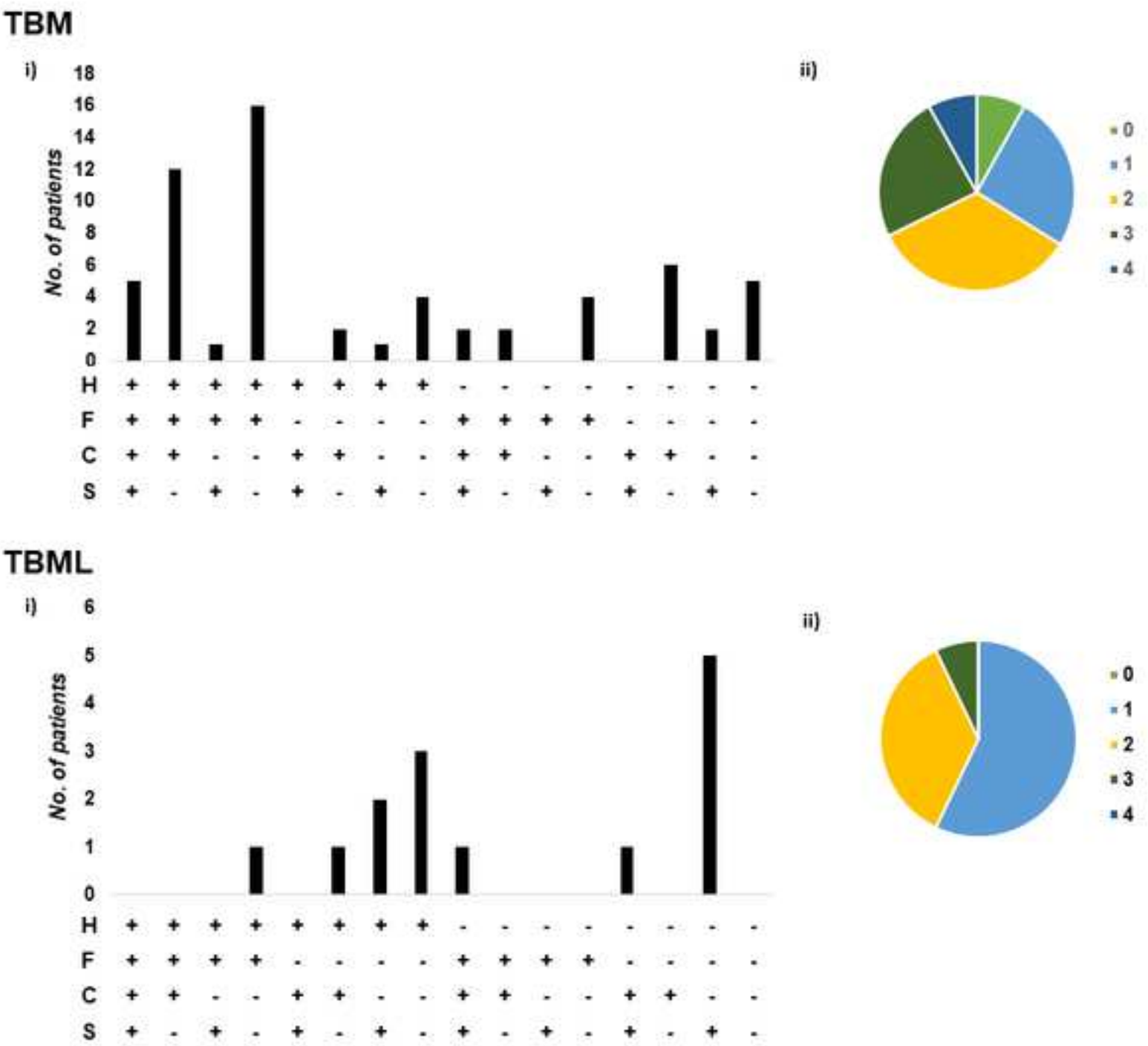
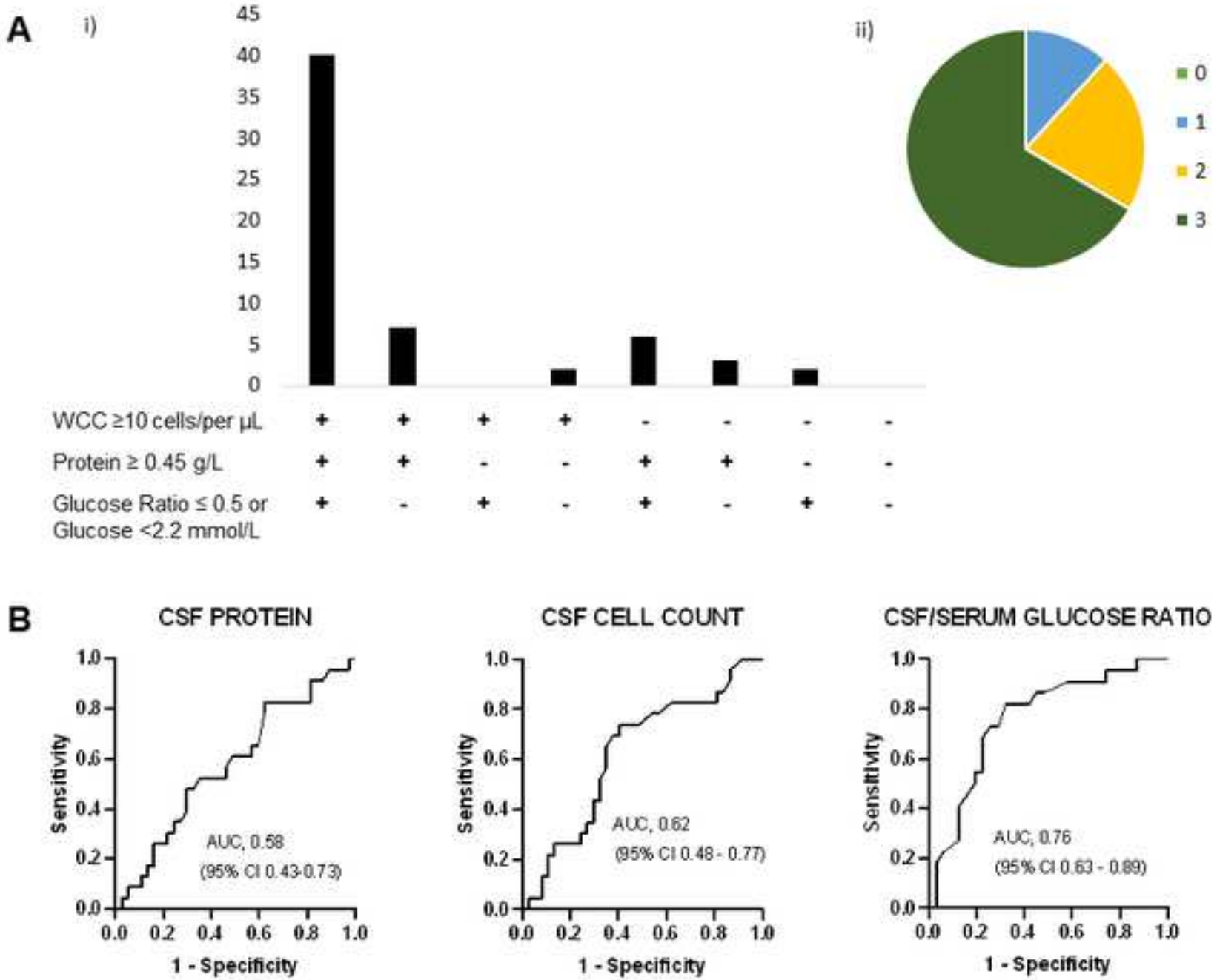


Figure 2



Tables with markup