

Diagnostic accuracy of imaging findings in tuberculous meningitis

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Abstract

Background

Tuberculous meningitis (TBM) is difficult to diagnose because of its variable clinical presentation, the absence of specific imaging or cerebrospinal fluid (CSF) biomarkers, and the lack of a single diagnostic test. Focal sulcal nodular enhancing lesion (FSNEL), the imaging correlate of the Rich focus, has been suggested to aid in diagnosis, but systematic data on its diagnostic accuracy are lacking. We aimed to determine the sensitivity, specificity, and predictive value of FSNEL for diagnosing TBM in patients with chronic meningitis.

Methods

In this diagnostic accuracy study conducted at a tertiary care center in Northern India, consecutive patients aged ≥ 14 years with clinically suspected chronic meningitis (headache for more than five days, with or without fever, nuchal stiffness, and constitutional symptoms) were screened on clinical grounds alone before neuroimaging or CSF results. Chronic meningitis and TBM were diagnosed using composite clinical, CSF, and imaging criteria. A radiologist, blinded to the final diagnosis, assessed FSNEL on post-contrast MRI. Diagnostic accuracy measures were calculated with 95% confidence intervals, including subgroup analyses restricted to patients without characteristic imaging findings.

Results

Of 146 patients screened, 113 had index test and reference standard available for analysis (91 with TBM, 22 with other chronic meningitides), yielding a TBM prevalence of 80.5%. FSNEL had a sensitivity of 39.6% (95% CI 29.5–50.4%), specificity of 86.4% (95% CI 65.1–97.1%), positive likelihood ratio of 2.90 (95% CI 0.98–8.56), negative likelihood ratio of 0.70 (95% CI 0.55–0.89), positive predictive value of 92.3% (95% CI 79.1–98.4%), and negative predictive value of 25.7% (95% CI 16.2–37.2%). In patients without parenchymal lesions ($n = 75$), the findings remained highly specific (89.5%) with lower sensitivity (32.1%). In a stricter subgroup without tuberculomas, hydrocephalus, or basal exudates ($n = 41$), specificity remained similar (88.2%) with lower sensitivity (12.5%).

Conclusion

FSNEL is a specific, noninvasive imaging marker for TBM with a modest rule-in value and remains useful even in the absence of parenchymal lesions. Given its limited sensitivity, this finding should be interpreted alongside clinical, CSF, and microbiological assessments rather than used alone. Larger multicentre studies are warranted to validate these findings.

Introduction

Tuberculous meningitis (TBM) is a paucibacillary infection of the central nervous system caused by *Mycobacterium tuberculosis*.¹ It is the most common cause of chronic meningitis in tropical countries, posing a major public health concern.² In developing countries, it is a cause of significant mortality and morbidity.³ The diagnosis of TBM is challenging due to its protean clinical features and the lack of specific imaging and CSF biomarkers, given its paucibacillary nature, which results in a limited number of CSF biomarkers. There is no single diagnostic test for TBM. Currently, the diagnosis is made using clinical composite criteria^{4–6} that consider multiple clinical and cerebrospinal fluid test results, as well as imaging findings. Often, the diagnosis is missed in the early stages, leading to a delay in starting therapy. In several instances, patients are treated empirically with anti-tuberculous drugs, and the response to therapy is considered part of the diagnostic criteria.⁷ Therefore, it is crucial to seek sensitive and specific imaging biomarkers to facilitate early diagnosis and timely initiation of therapy. The diagnosis is more straightforward when parenchymal lesions are identified, which can be seen in up to 25–50% of patients with TBM.^{3,8,9} In the remaining patients, however, the diagnosis must rely on subtler imaging clues. Some of these findings are uncommon. They may still be highly specific for TBM. Their diagnostic value remains largely unexplored. Focal sulcal nodular enhancing lesion (FSNEL) is one such finding. It is the imaging correlate of the Rich focus^{10–12} and may aid in diagnosing TBM even when parenchymal lesions are absent. Systematic data on the prevalence, predictive values, sensitivity, and specificity of imaging findings in patients with chronic meningitis are lacking.^{13–15}

Research in context

Evidence before this study

Tuberculous meningitis (TBM) is diagnosed using a combination of clinical, cerebrospinal fluid (CSF), and imaging criteria, since no single confirmatory test exists and microbiological confirmation is achieved in only a minority of cases. Established MRI features such as tuberculomas, hydrocephalus, and basal exudates support a diagnosis of TBM. However, the clinical and CSF criteria used to diagnose chronic meningitis are highly sensitive but lack specificity for an aetiological diagnosis, and specific imaging or CSF biomarkers for TBM are limited. Focal sulcal nodular enhancing lesions (FSNEL), the imaging correlate of the Rich focus, have been proposed as an additional imaging clue to TBM. However, no study has systematically quantified their diagnostic accuracy, including sensitivity, specificity, and predictive values.

Added value of this study

In a diagnostic accuracy study of 113 patients with chronic meningitis (91 with TBM, 22 with other chronic meningitides), we found FSNEL to have high specificity (86.4%) but moderate sensitivity (39.6%) for TBM, with a positive likelihood ratio of 2.90 and a positive predictive value of 92.3%. This study used real-world comparators with clinical differentials rather than healthy controls, and systematically assessed FSNEL's performance in subgroups lacking other classic TBM imaging features (parenchymal lesions and additionally hydrocephalus and basal exudates), where an alternative imaging marker is most needed. FSNEL retained high specificity in these subgroups, although its sensitivity was attenuated in the most stringent subgroup.

Implications of all the available evidence

FSNEL is a noninvasive, cost-effective, and highly specific MRI marker that may support a rule-in diagnosis of TBM, particularly in resource-limited, high-burden settings where alternative diagnostic tools are not readily available. However, given its limited sensitivity and the small comparator group in this study, FSNEL should be interpreted alongside clinical, CSF, and microbiological findings rather than used alone, and larger multicentre studies are needed to validate its diagnostic accuracy before it can be incorporated into formal diagnostic algorithms for TBM.

Methodology

This study was conducted at a tertiary referral center in Northern India, where patients aged ≥ 14 years, diagnosed with chronic meningitis according to the criteria described below, were recruited from July 2021 to October 2023. The study was designed and reported in accordance with the STARD¹⁶ (Standards for the Reporting of Diagnostic Accuracy) guidelines for diagnostic accuracy studies. The study was approved by the Institutional Review Board, and written informed consent was obtained from all patients or their legally authorized representatives.

The study population comprised consecutive patients with suspected chronic meningitis, including both TBM and its principal mimics. The index test was the presence of FSNEL on MRI as defined below. The reference standard was the composite clinical diagnosis of TBM or an alternative diagnosis, established over follow-up as described in detail in the following text, independently of the index test.

Consecutive patients with clinically suspected chronic meningitis (headache for more than five days, fever, nuchal stiffness, and constitutional symptoms) were first identified and screened on clinical grounds alone, prior to the acquisition of neuroimaging or CSF findings, in order to avoid circular

reasoning in the subsequent diagnostic accuracy evaluation of imaging parameters. Following screening, all patients underwent brain imaging, CSF analysis, and other diagnostic tests as part of the standard diagnostic work-up. This sequence ensured that the imaging and CSF findings analyzed in this study were obtained independently of the initial decision to screen a patient as a case of suspected chronic meningitis, rather than having the index imaging finding incorporated into the enrolment criteria for the diagnostic accuracy study.

Case definitions

Chronic meningitis was defined as the presence of headache for more than five days, with or without fever, nuchal stiffness, and constitutional symptoms, together with either [cerebrospinal fluid (CSF) findings suggestive of meningitis (pleocytosis ≥ 20 cells/ μ L with lymphocyte predominance ($> 50\%$), a protein concentration exceeding the age-specific normal value (> 40 mg/dL), or a glucose concentration less than 60% of the corresponding blood glucose concentration), or magnetic resonance imaging evidence of meningeal enhancement on contrast-enhanced T1-weighted sequences] established based on composite clinical criteria, imaging findings, and the natural history of the illness, were considered for inclusion. If the clinical and CSF criteria were met, patients were defined as having chronic meningitis, irrespective of leptomeningeal enhancement. In addition, the treating physician was required to determine whether the clinical syndrome was consistent with chronic meningitis. Patients who were seropositive for HIV and pregnant women were also eligible for inclusion.

TBM was diagnosed using clinical composite diagnostic criteria adapted from Ahuja et al.⁴ and Marais et al.⁶ (Box 1). The patients were classified as having TBM if they met the criteria for definite, probable, or possible TBM.

Box 1: Case Definition of Tuberculous Meningitis

Tuberculous Meningitis

In the setting of chronic meningitis as described above, one or more of

- CSF culture positivity, AFB positivity on microscopy, TBPCR or GeneXpert positivity in CSF
- Sputum AFB positivity, culture positivity for M.tuberculosis, GeneXpert or TBPCR from sputum, tracheal aspirates, or pulmonary samples obtained by bronchoscopic or transthoracic biopsies
- Culture, microscopy, or PCR from extra CNS tissue, such as biopsies of lymph nodes, intestinal biopsy, liver, or other tissue biopsies
- (Reasonable clinical certainty OR allied investigations such as CXR/CECT chest/abdomen/PET CT as per clinical indication suggestive of tuberculosis) AND (Other relevant investigations like CSF analysis not suggestive of alternative diagnosis such as neurocysticercosis/cryptococcal/other fungal infections/other causes of chronic meningitis such as brucella/ nocardia/ syphilis/recurrent viral meningitis/ carcinomatous/ lymphomatous meningitis or non-infective causes such as sarcoidosis/sub-arachnoid hemorrhage, etc.)

AND

- No other diagnosis can explain the syndrome better

Patients who develop features or test results suggestive of an alternative diagnosis with reasonable certainty during the course of treatment will be considered not to be due to tuberculous meningitis.

For investigating various etiologies, investigations including AFB on CSF staining; India ink stain or CSF cryptococcal antigen positivity on lateral flow assays or culture positivity for cryptococcosis, cultures, brain biopsy, PCR and other microbiologic tests suggestive of chronic bacterial or fungal infections such as brucellosis, nocardiosis, melioidosis, syphilis, aspergillosis, histoplasmosis, etc., CSF cytology positivity for leukemic, lymphomatous or carcinomatous cells, aseptic chronic meningitis in the setting of connective tissue diseases such as SLE, Sjogren's syndrome, Behcet's disease, etc. were done as the clinical situation demanded, with the final diagnosis at follow-up considered the reference standard. The ATT regimen and treatment duration, as well as follow-up imaging and diagnostic revision, were determined by the treating physician. Patients were followed up for up to 6 months after discharge for any changes in diagnosis.

The reference standard for TBM rested on one of three pathways: (1) microbiological confirmation in CSF (culture, AFB smear, TB-PCR, or GeneXpert); (2) microbiological or histological confirmation at a non-CNS site; or (3) reasonable clinical certainty combined with systemic imaging (chest radiograph, chest/abdomen CT, or PET-CT) and exclusion of alternative diagnoses. The entry criterion for chronic meningitis, CSF abnormalities or leptomeningeal enhancement on MRI was applied equally to the TBM and comparator groups and did not itself distinguish between them. Clinicians assigning the reference standard diagnosis were unaware of the FSNEL status on brain MRI. This kept the index test independent of the reference standard.

Magnetic resonance imaging was performed, and post-contrast sub-mm isovoxel 3D-FLAIR and 3D-T1 TSE sequences were used to detect FSNEL (index test).

The operational definitions of various MRI imaging findings were as described in Table 1. Imaging parameters were coded as present or absent; for graded parameters, Grade 0 was considered absent, and Grades 1–3 were considered present for diagnostic accuracy measures.

The imaging interpretation was performed by a neuroradiologist (AG) with more than 25 years of experience, who was blinded to the final diagnosis. The sensitivity and specificity of FSNEL for diagnosing TBM were estimated with 95% confidence intervals. The positive and negative predictive values of these findings were also estimated. To assess the diagnostic accuracy of this finding in patients without parenchymal lesions, a subgroup analysis was performed, excluding all patients with parenchymal lesions.

Statistical analysis

The sample size was calculated based on the expected diagnostic accuracy of FSNEL in TBM. Assuming a sensitivity of 70% (range, 60–80%) with 10% absolute precision, a minimum of 84 patients with TBM was required. Assuming a specificity of 80% (range, 70–90%) with the same precision, a minimum of 64 patients without TBM was required. Assuming a 70% prevalence of TBM among patients with chronic meningitis, a total sample size of at least 120 patients was required to yield 84 cases of TBM. The demographics, clinical features, and imaging parameters were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based application designed to support data capture for research studies hosted at the Institute. Data were exported and cleaned using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Descriptive statistics, including frequencies and percentages, were used to describe categorical variables. The mean and standard deviation were used for continuous variables with normal distributions, while the median and interquartile range were used for nonparametric data. For comparisons between groups, an independent samples t-test was used for normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. Dichotomous variables were compared using the Chi-squared test or Fisher's exact test. All statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA). A p-value of < 0.05 was considered statistically significant. Diagnostic accuracy measures were reported in percentages with 95% confidence intervals.

Table 1
Operational Imaging Definitions Used for CNS Tuberculosis Evaluation

Imaging Feature	Operational Imaging Definition	Key MRI Sequences	Scoring / Presence Criteria
Miliary Brain Lesions (Fig. 1)	Numerous (< 3–5 mm) uniformly enhancing intraparenchymal nodules, diffuse distribution, minimal edema.	T1 + C, T2, FLAIR	Present / Absent
Parenchymal Lesions (Fig. 2)	Focal (> 5 mm) brain granulomas with T2 hypointensity, ring/nodular enhancement, and variable edema	T1 + C, T2, FLAIR, DWI	Present / Absent
Subpial Lesions (Fig. 1)	Small enhancing nodules immediately beneath the pia, directly contacting the cortical surface	T1 + C, T2	Present / Absent
Focal Sulcal Nodular Enhancing Lesions-FSNEL (Fig. 1)	Discrete enhancing nodules located within a sulcus, subarachnoid origin	T1 + C, FLAIR	Present / Absent
Leptomeningeal Enhancement (Fig. 2)	Enhancement of pia–arachnoid, predominant in basal cisterns, Sylvian fissures, and sulci	T1 + C	Grade 0: none; Grade 1: ≤1 mm thin linear in ≤ 2 cisterns; Grade 2: 1–2 mm, continuous, ≥ 3 cisterns; Grade 3: >2 mm or nodular/plaque-like with cisternal obliteration
Basal Exudates (Fig. 2)	Enhancing soft-tissue replacing CSF in suprasellar, interpeduncular, prepontine, and ambient cisterns	T1 + C, FLAIR	Grade 0: none; Grade 1: ≤2 mm, cistern patent; Grade 2: 2–4 mm, partial cisternal effacement; Grade 3: >4 mm or > 50% cisternal obliteration.
Optochiasmatic Arachnoiditis (Fig. 2)	Enhancement/thickening surrounding optic nerves, chiasm; suprasellar cistern crowding	T1 + C	Grade 0: absent; Grade 1: ≤1 mm linear enhancement, cisterns open; Grade 2: 1–3 mm nodular/irregular enhancement, partial cisternal effacement; Grade 3: >3 mm thick encasing enhancement, chiasm engulfment, cisternal obliteration.
Parenchymal Lesions (Fig. 3)	Focal (> 5 mm) brain granulomas with T2 hypointensity, ring/nodular enhancement, and variable edema	T1 + C, T2, FLAIR, DWI	Present / Absent

Imaging Feature	Operational Imaging Definition	Key MRI Sequences	Scoring / Presence Criteria
Choroid Plexitis	Enlarged, thickened, nodular/irregularly enhancing choroid plexus	T1 + C, FLAIR	Grade 0: normal plexus without enhancement; Grade 1: thin (< 2 mm) linear or patchy enhancement with mild enlargement; Grade 2: 2–4 mm irregular or nodular enhancement with moderate enlargement and optional mild ependymal enhancement; Grade 3: >4 mm thick, mass-like or confluent enhancement with associated ventriculitis or intraventricular debris.
Infarcts	Restricted diffusion ± T2-FLAIR hyperintensity in perforator territories (BG, thalamus, brainstem)	DWI/ADC, FLAIR	Present/Absent
MRI sequences acquired included axial T2 TSE, 3D Sag T1, Ax DWI, 3D Sag FLAIR, Ax SWI, Post-gad 3D Sag T1, 3D TOF Circle-of-Willis.			

Results

We screened 146 patients and identified 137 who met the diagnostic criteria for chronic meningitis. We report 113 patients for whom the index test (MRI brain as per the defined protocol) and the reference standard assessment were available for diagnostic accuracy measures. Of these, 91 were due to TBM and 22 to other causes (Table 2). Since TBM is often diagnosed based on clinical, laboratory, and radiologic criteria, the diagnosis evolves over time. Through follow-up, we occasionally uncovered potential diagnostic clues that led to a revised diagnosis. Taking this into account, the 3-month follow-up was completed in 95 of 113 patients, of whom four had a change in diagnosis, and 14 were dead. In the 18 patients who were lost to follow-up, the initial diagnosis served as the reference standard. Further follow-up to six months was completed in 78 patients, of whom 11 were dead, and none had a change in diagnosis. Thus, the proportion of patients with TBM in this cohort of chronic meningitis was 80.5%.

The demographics and clinical features of the cohort are presented in Table 3. Sphincter dysfunction and quadriparesis were significantly higher in the TBM group. Clinical arachnoiditis was also significantly more common in TBM, reflecting greater meningeal inflammation. Other clinical symptoms, neurological deficits, and functional status measures did not differ significantly.

Table 2
Etiologic diagnosis of Chronic meningitis

Etiologic diagnosis	Number of patients
Tuberculous meningitis (Definite/Probable/Possible)	91
Other chronic Meningitides	22
• Fungal Meningitis	3
• Sarcoid	1
• Leptomeningeal lymphomatosis	6
• Leptomeningeal carcinomatosis	1
• Pyogenic meningitis (CSF Rhinorrhea/cribriform plate defect)	1
• Other immune-mediated meningoencephalitis (IgG4 RD-2; GFAP meningoencephalitis-1; Idiopathic hypertrophic pachymeningitis-1)	4
• Other infectious meningo-encephalitis (CMV-1; Toxoplasma-1; Nocardiosis-1; Leptospirosis-1; Scrub typhus-1; Herpes-1)	6

Table 3
Demography of patients with TBM and Chronic meningitis

Parameter	TBM (N = 91)	Other Chronic Meningitis (n = 22)	p-value
Age (years), mean (SD)	31.1 (14.0)	31.6 (13.9)	0.89
Male sex, n (%)	42 (46.2%)	12 (54.6%)	0.48
HIV positive, n (%)	0 (0.0%)	3 (13.6%)	0.01
Symptom duration (days), median (IQR)	60 (20–120)	37.5 (10–240)	0.82
Headache, n (%)	91 (100.0%)	22 (100.0%)	
Fever, n (%)	78 (85.7%)	16 (72.7%)	0.20
Constitutional symptoms, n (%)	24 (26.4%)	6 (27.3%)	0.93
Nuchal stiffness, n (%)	28 (31.5%)	6 (27.3%)	0.70
Seizures, n (%)	27 (29.7%)	8 (36.4%)	0.54
Visual impairment, n (%)	32 (35.2%)	6 (27.3%)	0.48
Diplopia, n (%)	17 (18.9%)	4 (18.2%)	1.00
Facial sensory loss, n (%)	4 (4.4%)	0 (0.0%)	1.00
Impaired hearing, n (%)	2 (2.2%)	0 (0.0%)	1.00
Dysphagia, n (%)	10 (11.0%)	3 (13.6%)	0.72
Dysarthria, n (%)	10 (11.0%)	1 (4.5%)	0.69
Tongue weakness, n (%)	2 (2.2%)	0 (0.0%)	1.00
Paraparesis, n (%)	10 (11.1%)	1 (4.5%)	0.69
Quadriparesis, n (%)	15 (16.5%)	0 (0.0%)	0.04
Hemiparesis, n (%)	12 (13.3%)	2 (9.1%)	0.73
Sphincter dysfunction, n (%)	20 (22.0%)	0 (0.0%)	0.01
Sensorium: Conscious alert, n (%)	63 (69.2%)	16 (72.7%)	1.00
Sensorium: Conscious, drowsy, n (%)	18 (19.8%)	4 (18.2%)	
Sensorium: Unconscious, n (%)	10 (11.0%)	2 (9.1%)	
Papilledema, n (%)	24 (26.4%)	5 (22.7%)	0.73
Cranial nerve palsies, n (%)	23 (25.3%)	4 (18.2%)	0.48
Reflexes: Normal, n (%)	67 (73.6%)	17 (77.3%)	1.00

Parameter	TBM (N = 91)	Other Chronic Meningitis (n = 22)	p-value
Reflexes: Hyporeflexia, n (%)	7 (7.7%)	2 (9.1%)	
Reflexes: Areflexia, n (%)	7 (7.7%)	1 (4.5%)	
Reflexes: Hyperreflexia, n (%)	10 (11.0%)	2 (9.1%)	
TBM Grade 1, n (%)	42 (46.7%)		
TBM Grade 2, n (%)	38 (42.2%)		
TBM Grade 3, n (%)	10 (11.1%)		
Clinical arachnoiditis, n (%)	52 (57.1%)	6 (27.3%)	0.01
mRS 0, n (%)	30 (33.0%)	11 (50.0%)	0.09
mRS 1, n (%)	10 (11.0%)	6 (27.3%)	
mRS 2, n (%)	12 (13.2%)	0 (0.0%)	
mRS 3, n (%)	2 (2.2%)	0 (0.0%)	
mRS 4, n (%)	8 (8.8%)	1 (4.5%)	
mRS 5, n (%)	29 (31.9%)	4 (18.2%)	

The cerebrospinal fluid analysis of these patients is listed in Table 4. None of the routine cerebrospinal fluid parameters demonstrated statistically significant differences between TB meningitis and other chronic meningitides. Opening pressure, total cell counts, lymphocyte and neutrophil proportions, CSF protein, glucose, and CSF–blood glucose ratio all showed substantial overlap without meaningful separation. The CSF was tested for a battery of investigations, including TB PCR, GeneXpert, AFB staining, cryptococcal antigen, PCR for viral, bacterial, and fungal etiologies, cytospin for malignant cells, serum MOG, NMO, and GFAP antibodies, as per the clinical profile and potential leads from other allied investigations, including chest imaging, PET-CT, etc.

Table 4
Findings of the Cerebrospinal Fluid Analysis

Parameter	N (TBM/Other)	TBM	Other Chronic Meningitis	p- value
Opening pressure (cmH ₂ O), mean (SD)	12/3	22.1 (9.6)	29.2 (9.5)	0.28
CSF TLC (cells/ μ L), median (IQR)	86/22	77.5 (20.0– 200.0)	45.0 (0.0–370.0)	0.45
Lymphocytes (%), median (IQR)	86/22	88.5 (60.0– 98.0)	84.0 (0.0–95.0)	0.28
Neutrophils (%), median (IQR)	86/22	10.0 (0.0– 30.0)	3.0 (0.0–12.0)	0.10
CSF protein (mg/dL), median (IQR)	84/22	141.0 (83.5– 215.5)	122.5 (34.0–246.0)	0.30
CSF glucose (mg/dL), median (IQR)	83/22	46.0 (32.0– 60.0)	54.0 (31.0–66.0)	0.34
CSF: Blood glucose ratio, median (IQR)	33/9	0.33 (0.28– 0.48)	0.39 (0.36–0.52)	0.20
CSF TB-PCR positive, n (%)	91	1 (1.1%)		
CSF GeneXpert positive, n (%)	91	11 (12.1%)		
CSF AFB staining positive, n (%)	91	1 (1.1%)		
CSF AFB culture positive, n (%)	91	0 (0.0%)		

Diagnostic Accuracy of Focal Sulcal Nodular Enhancing Lesions for TBM

Using FSNEL as an imaging marker for TB meningitis (TBM) shows moderate sensitivity and high specificity. The sensitivity of FSNEL was moderate at 39.6% (95% CI 29.5–50.4), indicating that fewer than half of true TBM cases demonstrated this feature. Specificity was high at 86.4% (95% CI 65.1–97.1), indicating that the sign was rarely present in non-TBM chronic meningitis. Three false positives were identified: one with sarcoidosis, one with cryptococcal meningitis, and one with recurrent pyogenic meningitis due to a cribriform plate defect. The positive likelihood ratio was 2.90 (95% CI 0.98–8.56), suggesting a modest rule-in value, whereas the negative likelihood ratio of 0.70 (95% CI 0.55–0.89) indicates limited rule-out capacity. The PPV was 92.3% (95% CI 79.1–98.4), indicating that when present, this feature strongly suggests TBM; however, the NPV was only 25.7% (95% CI 16.2–37.2), so its absence does not exclude TBM. Overall diagnostic discrimination (ROC area = 0.63; 95% CI = 0.54–0.72) was modest. In a subgroup analysis restricted to patients without parenchymal lesions (n = 75),

sensitivity was 32.1% (95% CI 20.3–46.0%) and specificity was 89.5% (95% CI 66.9–98.7%), with a positive likelihood ratio of 3.05 (95% CI 0.78–11.96), a negative likelihood ratio of 0.76 (95% CI 0.60–0.96), a PPV of 90.0% (95% CI 68.3–98.8%), and an NPV of 30.9% (95% CI 19.1–44.8%). In a further subgroup restricted to patients without tuberculomas, hydrocephalus, or basal exudates (n = 41: 24 TBM, 17 non-TBM), specificity remained similar at 88.2% (95% CI 63.6–98.5%), while sensitivity fell to 12.5% (95% CI 2.7–32.4%), yielding a positive likelihood ratio of 1.06 (95% CI 0.20–5.69), a negative likelihood ratio of 0.99 (95% CI 0.79–1.25), a PPV of 60.0% (95% CI 14.7–94.7%), and an NPV of 41.7% (95% CI 25.5–59.2%).

Diagnostic accuracy of imaging parameters

The sensitivity, specificity, positive and negative predictive values are reported with the 95% confidence intervals.

Table 5
Diagnostic accuracy measures

Parameter	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Leptomeningeal enhancement	82.4% (73.0–89.6%)	54.5% (32.2–75.6%)	88.2% (79.4–94.2%)	42.9% (24.5–62.8%)
Basal exudates	52.7% (42.0–63.3%)	95.5% (77.2–99.9%)	98.0% (89.1–99.9%)	32.8% (21.6–45.7%)
Parenchymal lesions	38.5% (28.4–49.2%)	86.4% (65.1–97.1%)	92.1% (78.6–98.3%)	25.3% (16.0–36.7%)
Miliary lesions	33.0% (23.5–43.6%)	81.8% (59.7–94.8%)	88.2% (72.5–96.7%)	22.8% (14.1–33.6%)
Subpial lesions	43.3% (32.9–54.2%)	76.2% (52.8–91.8%)	88.6% (75.4–96.2%)	23.9% (14.3–35.9%)
FSNEL	39.6% (29.5–50.4%)	86.4% (65.1–97.1%)	92.3% (79.1–98.4%)	25.7% (16.2–37.2%)
Choroid plexitis	5.5% (1.8–12.4%)	100.0% (84.6–100.0%)	100.0% (47.8–100.0%)	20.4% (13.2–29.2%)
MRI infarcts	28.6% (19.6–39.0%)	90.9% (70.8–98.9%)	92.9% (76.5–99.1%)	23.5% (15.0–34.0%)
Optochiasmatic arachnoiditis	49.5% (38.8–60.1%)	95.5% (77.2–99.9%)	97.8% (88.5–99.9%)	31.3% (20.6–43.8%)
Hydrocephalus	45.1% (34.6–55.8%)	90.5% (69.6–98.8%)	95.3% (84.2–99.4%)	27.5% (17.5–39.6%)

Discussion

Chronic meningitis is characterized by headache, with or without fever, nuchal rigidity, cranial nerve palsies, altered sensorium, and other focal neurologic deficits; none of these differed significantly between TBM and other causes, consistent with the clinical criteria's high sensitivity but limited specificity for an etiological diagnosis. Sphincter dysfunction and quadriparesis, however, were significantly more common in the TBM group. Clinical arachnoiditis, which is defined as symptomatic vision loss due to opticochiasmatic arachnoiditis or limb weakness and hypo/areflexia with or without sphincter involvement in the absence of parenchymal brain lesions, while also seen in both groups, was significantly more common in TBM, suggesting that symptomatic spinal meningitis and basal meningitis were more likely to be TBM as compared to competing diagnoses. The clinical criteria are very sensitive for detecting chronic meningitis but lack specificity for an etiologic diagnosis.

We found that the presence of FSNEL had a positive likelihood ratio of 2.90 (95% CI 0.98–8.56) and a low negative likelihood ratio of 0.70 (95% CI 0.55–0.89). The diagnostic accuracy of FSNEL is characterized by high specificity and low sensitivity, as is also associated with most diagnostic tools due to threshold effects. This makes it a useful rule-in finding, albeit one drawn from a small comparison group, and the absence of the finding does not rule out the diagnosis.

We could diagnose FSNEL on imaging as we used sub-mm isovoxel 3D FLAIR and T1-TSE sequences after contrast administration. High-resolution imaging enabled the detection of these tiny enhancing lesions, and T1 TSE ensured that we did not observe vascular enhancement.

The identification of FSNEL may not add diagnostic value in those with parenchymal lesions that are identified as tuberculomas. It is most useful in patients without parenchymal lesions, where an alternative imaging marker is most needed. In this subgroup, the finding remained highly specific (89.5%), albeit with lower sensitivity (32.1%) than in the overall cohort. In a stricter subgroup that excluded patients with parenchymal lesions, hydrocephalus or basal exudates ($n = 41$: 24 TBM, 17 non-TBM), specificity remained similarly stable at 88.2% (95% CI 63.6–98.5%), closely matching the 86.4% seen in the overall cohort. Sensitivity, however, fell sharply to 12.5% (95% CI 2.7–32.4%), which pulled the positive likelihood ratio down to 1.06 (95% CI 0.20–5.69) from 2.90 in the main analysis. FSNEL therefore remains an uncommon, specific finding even when these other classic imaging features are absent. However, its rule-in value is not preserved in this subgroup, driven by the drop in sensitivity rather than any loss of specificity. With only 41 patients and 5 FSNEL-positive results in total in this cohort, this estimate is hypothesis-generating rather than conclusive.

The study used robust methodology to reduce bias. We reduced selection bias by screening patients using an electronic screening log to ensure that they met the inclusion and exclusion criteria and by recruiting consecutive patients who did. The imaging protocol was clearly defined, MRI technicians were trained before the study began, and the procedure was standardized across all patients. The radiologist was blinded and interpreted the index findings of FSNEL with no knowledge of the diagnosis. The clinicians who made the diagnosis, pathologists, microbiologists, and others involved in patient care were unaware of the index findings. These measures avoided incorporation bias. The reference standard

was the diagnosis made using the clinical composite criteria at diagnosis or the revised diagnosis on longitudinal follow-up. Compared with several diagnostic accuracy studies that use healthy controls, we used real-world controls with diagnoses that closely mimic the condition of interest, which is a major strength of the study. This enhances the external validity of the study and reflects real-world diagnostic challenges in evaluating chronic meningitis. Contrast-enhanced MR imaging is already the standard of care^{13,17} in these patients, and this finding makes the investigation even more useful, as it is noninvasive and highly specific. It is accessible and cost-effective in the Indian setting, where next-generation sequencing is more expensive and has a longer turnaround time than imaging, making it a valuable decision-making tool.

Most TBM diagnoses in this cohort were reached through the clinical-certainty-plus-exclusion pathway rather than microbiological confirmation, which was uncommon (13 of 91 patients). Excluding competing diagnoses along this pathway draws on brain MRI appearances that differ from TBM in practice, so it is plausible, though not verifiable from the case definitions alone, that classic TBM-associated MRI features contributed to clinical certainty or to the exclusion of mimics in unconfirmed cases. We report this residual risk directly: choroid plexitis, which showed 100% PPV in our cohort, is the feature most likely to have supported a clinical impression of TBM in the absence of microbiological proof, and should be interpreted with caution.

Our study had a few limitations. Being a single-center study in a tertiary care institution, referral bias and the selective admission of sicker patients, who may not be representative of the general patient population, are possibilities. The cohort was also restricted to patients aged 14 years and above, so these findings may not generalize to pediatric TBM. Notably, no patient in the TBM group was HIV-positive; this most likely reflects a referral pattern rather than a true epidemiological absence, as HIV-positive patients with suspected CNS infections at our center are more often admitted under Medicine/Infectious Diseases rather than Neurology. The comparator group of Other Chronic Meningitis was also small and etiologically heterogeneous (n = 22, spanning fungal, sarcoid, lymphomatous, carcinomatous, pyogenic, and immune-mediated causes), limiting how precisely the observed false-positive pattern generalizes to any single competing diagnosis. The neuroradiologist has extensive experience in imaging neuroinfections, which may not be available in the community setting. This single neuroradiologist read all images. We did not assess inter-observer or intra-observer reliability. The reported diagnostic accuracy may not generalize to less experienced readers or to multi-reader settings. The same reader assessed the whole MRI, including exudates and hydrocephalus, while also scoring FSNEL. More overt TBM-associated findings on the same scan may have cued the reader to call FSNEL positive, rather than scoring FSNEL as a fully independent finding. However, our subgroup analyses retained the high specificity of FSNEL in patients without the characteristic imaging findings of TBM—namely, tuberculomas, hydrocephalus, and basal exudates. Since the reference standard diagnosis was made at baseline during admission, we had the index test and reference standards for all recruited patients. However, the 3-month follow-up was incomplete for a subset of patients, and the initial diagnosis served as the reference standard, potentially leading to diagnostic misclassification. Notably, the sample size calculation required at least 64 patients as true negative controls to estimate specificity

with adequate precision, but only 22 such patients were available for analysis. This shortfall in the specificity arm, rather than the sensitivity arm of the calculation (which was met), is the likely driver of the wide confidence intervals around specificity-dependent estimates such as the positive likelihood ratio (based on only three false positives) and the PPV of some individual imaging features; these estimates could shift substantially in a larger, adequately powered comparator group. We did not record the size, number, or distribution of FSNEL. We also did not assess its change with anti-tuberculous treatment. These data could clarify whether FSNEL burden or resolution adds further diagnostic or prognostic value. Imaging evidence of meningeal enhancement was itself an alternative entry criterion for chronic meningitis, so some patients qualified for enrolment partly on this basis. The diagnostic accuracy reported here for leptomeningeal enhancement specifically should be interpreted with this overlap in mind. Future studies could include microbiologically confirmed cases from larger cohorts to assess whether diagnostic accuracy remains consistent; we were unable to perform this sensitivity analysis here due to the limited sample size.

Given its high specificity, FSNEL is a promising rule-in sign. It may support a decision to initiate anti-tuberculous therapy, as it provides high diagnostic confidence and reduces delays. It would also help recruit patients for clinical trials, given its high positive predictive value. It may be incorporated into diagnostic algorithms and case definitions, leading to the development of new diagnostic criteria. It may also guide the development of new biomarkers. Since the finding is highly specific, it helps rule out viral, pyogenic, and fungal meningitis, thereby reducing exposure to antiviral and antifungal drugs, especially in fulminant disease, where several anti-infective medications are often simultaneously administered. However, the confidence interval around its positive likelihood ratio (2.90, 95% CI 0.98–8.56) crosses 1. Given its limited ability to rule out TBM, its value lies in confirmatory, triage, and research applications, not screening or exclusion. It becomes clinically meaningful when combined with clinical judgment, CSF profile, and microbiology, rather than when used alone.

Conclusion

FSNEL is highly specific for TBM, with a positive likelihood ratio of 2.90 (95% CI 0.98–8.56) and a low negative likelihood ratio of 0.70 (95% CI 0.55–0.89), making it a useful rule-in tool for TBM. Clinical features offer limited discriminatory value, whereas clinically symptomatic imaging-supported arachnoiditis may strengthen diagnostic suspicion. Given its noninvasive nature, accessibility, and high specificity, even in the absence of parenchymal lesions, this MRI finding is a promising rule-in tool. It can support clinical decision-making in resource-limited, high-burden settings. Because the confidence interval around its positive likelihood ratio crosses 1, it should not be used alone to guide treatment decisions. However, its limited sensitivity underscores the need to interpret it alongside clinical assessment, CSF analysis, and microbiological testing. Larger multicentre studies are warranted to validate these findings and inform future diagnostic algorithms.

Declarations

Conflicts of Interest

The authors do not report any conflict of interest.

Ethical review statement

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. All participants provided informed written consent to participate.

The study was reviewed and approved by the Institute Review Board of the All India Institute of Medical Sciences, New Delhi, India (IECPG-36/27.01.2022, OT-04/27.10.2022).

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Figures

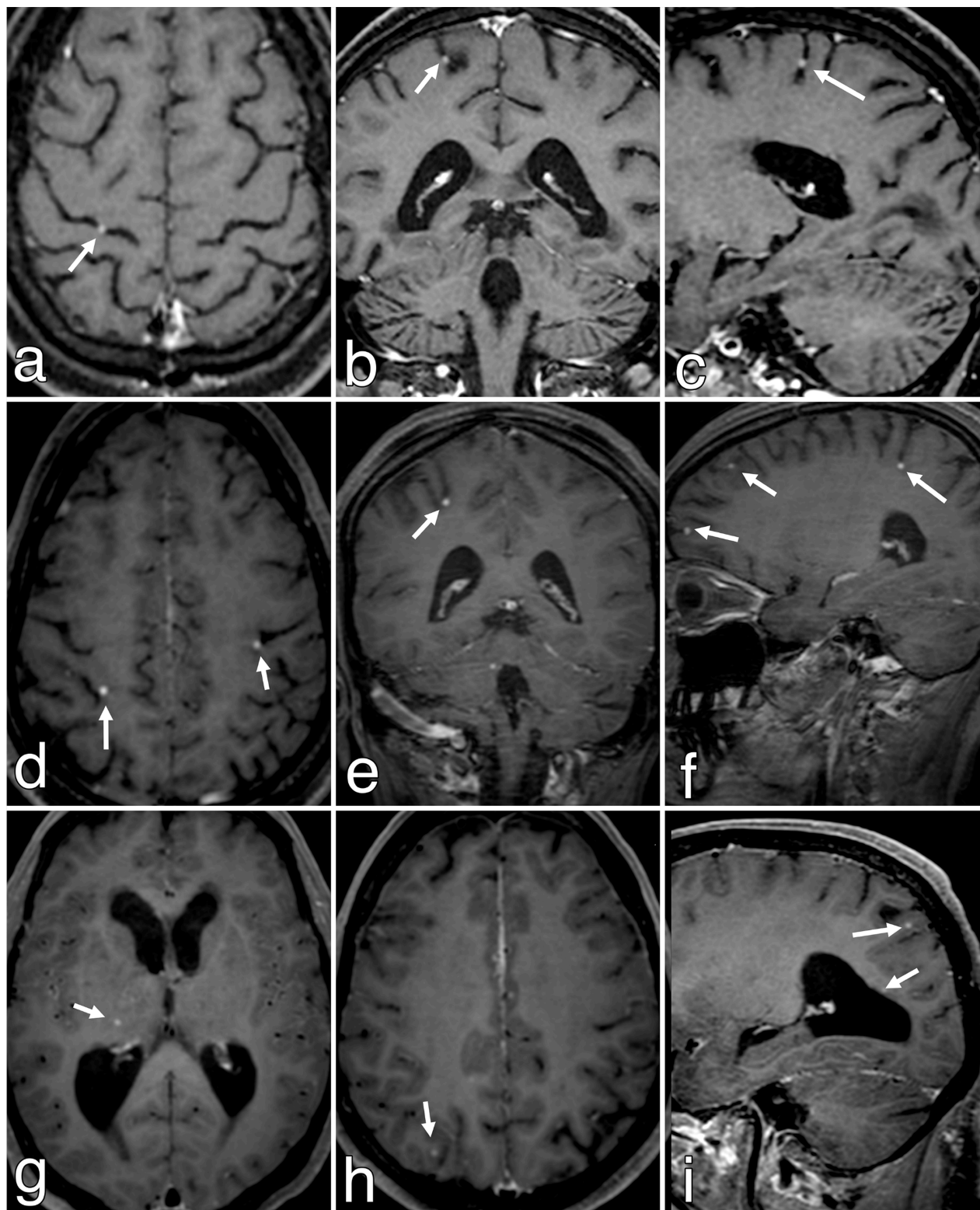


Figure 1

Spectrum of imaging findings in patients with chronic meningitis

enhancement patterns in intracranial tuberculomas on contrast-enhanced T1-weighted MRI. Each row represents a different patient.

(a–c) Sulcal nodular enhancing lesion. Axial (a), coronal (b), and sagittal (c) images show a small enhancing nodule within a cortical sulcus (arrows), following the sulcal contour without expansion of the adjacent gyrus. The sulcal location is better appreciated on the coronal and sagittal images.

(d–f) Subpial lesions. Axial (d), coronal (e), and sagittal (f) images demonstrate multiple small punctate and nodular enhancing lesions along the cortical surface, closely associated with the pial margins of the sulci and gyral crowns (arrows), with minimal or no surrounding oedema or mass effect.

(g–i) Miliary lesions. Axial (g,h) and sagittal (i) images show numerous tiny (≤ 1 mm) punctate enhancing foci involving the cortex, subcortical and deep white matter, and deep grey nuclei (arrows), consistent with miliary intracranial dissemination.

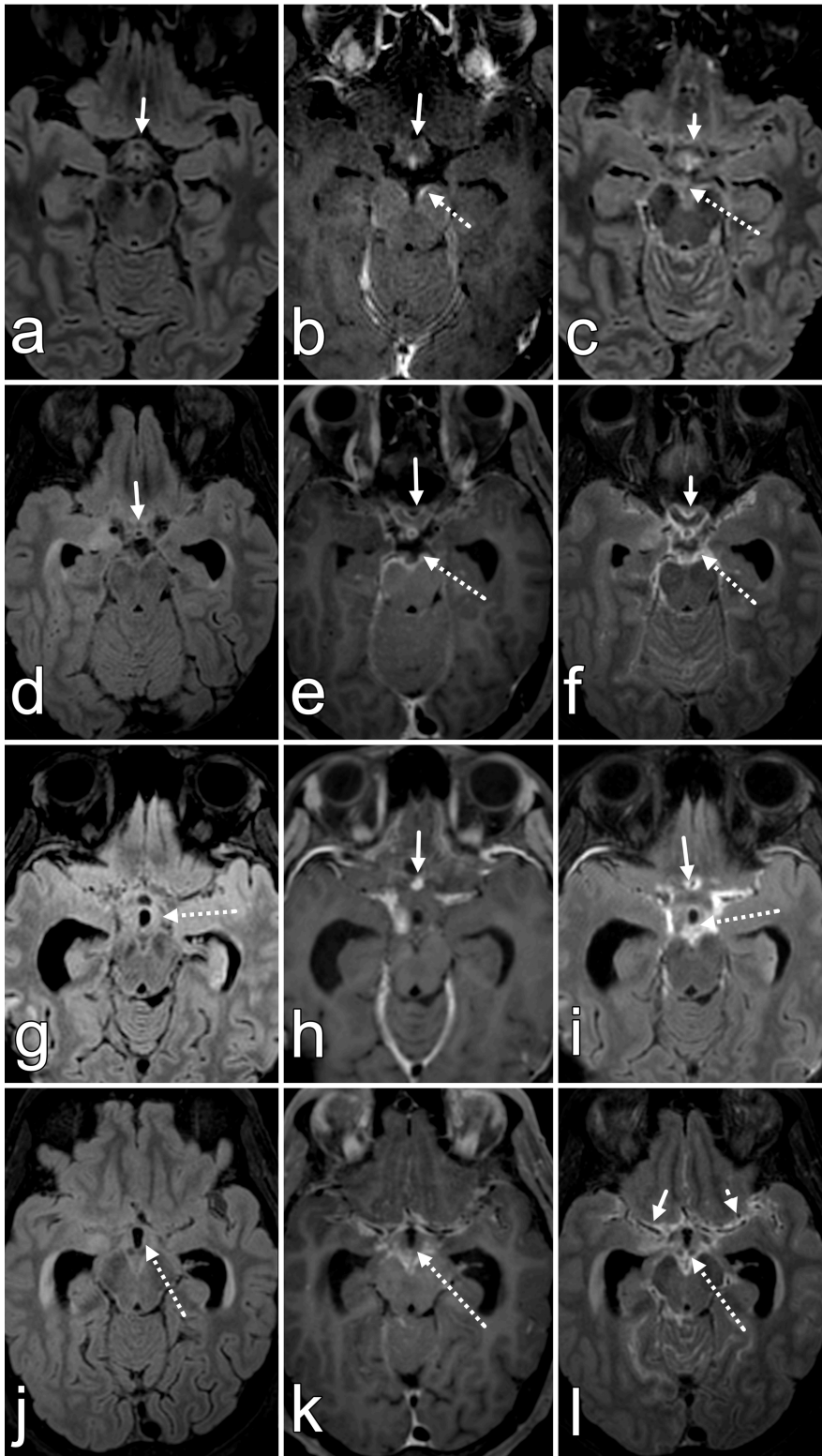


Figure 2

MRI spectrum of meningeal enhancement of increasing severity. For each patient, axial FLAIR (left column), post-contrast T1-weighted (middle column), and post-contrast FLAIR (right column) images at the suprasellar level are shown.

(a–c) Grade 1 (mild). FLAIR (a) shows subtle hyperintensity in the suprasellar cistern around the optic chiasm (arrow). Post-contrast T1-weighted (b) and post-contrast FLAIR (c) images show thin linear enhancement along the chiasmatic surface (solid arrows) with minimal adjacent cisternal enhancement (dotted arrows). Post-contrast FLAIR (c) also shows enhancement of the CSF surrounding the chiasm, reflecting contrast leakage into the CSF, which is not appreciable on post-contrast T1-weighted imaging.

(d–f) Grade 2 (moderate). FLAIR (d) shows more conspicuous hyperintense exudate with partial effacement of the suprasellar cistern (arrow). Post-contrast T1-weighted (e) and post-contrast FLAIR (f) images demonstrate thicker, partly nodular enhancing exudate encasing the chiasm (solid arrows), with extension into the interpeduncular and ambient cisterns (dotted arrows).

(g–i) Grade 3 (severe). FLAIR (g) demonstrates confluent hyperintense exudate filling the suprasellar cistern and obscuring the chiasm (dotted arrow). Post-contrast T1-weighted (h) and post-contrast FLAIR (i) images show thick, avidly enhancing exudate encasing the chiasm (solid arrows), with posterior extension within the basal cisterns (dotted arrows).

(j–l) Extensive leptomeningitis. FLAIR (j) and post-contrast images (k, l) show dense exudate involving the suprasellar and interpeduncular cisterns (dotted arrows), with extension into both sylvian fissures (arrow on the right and arrowhead on the left in l). The optic chiasm is no longer separately delineated.

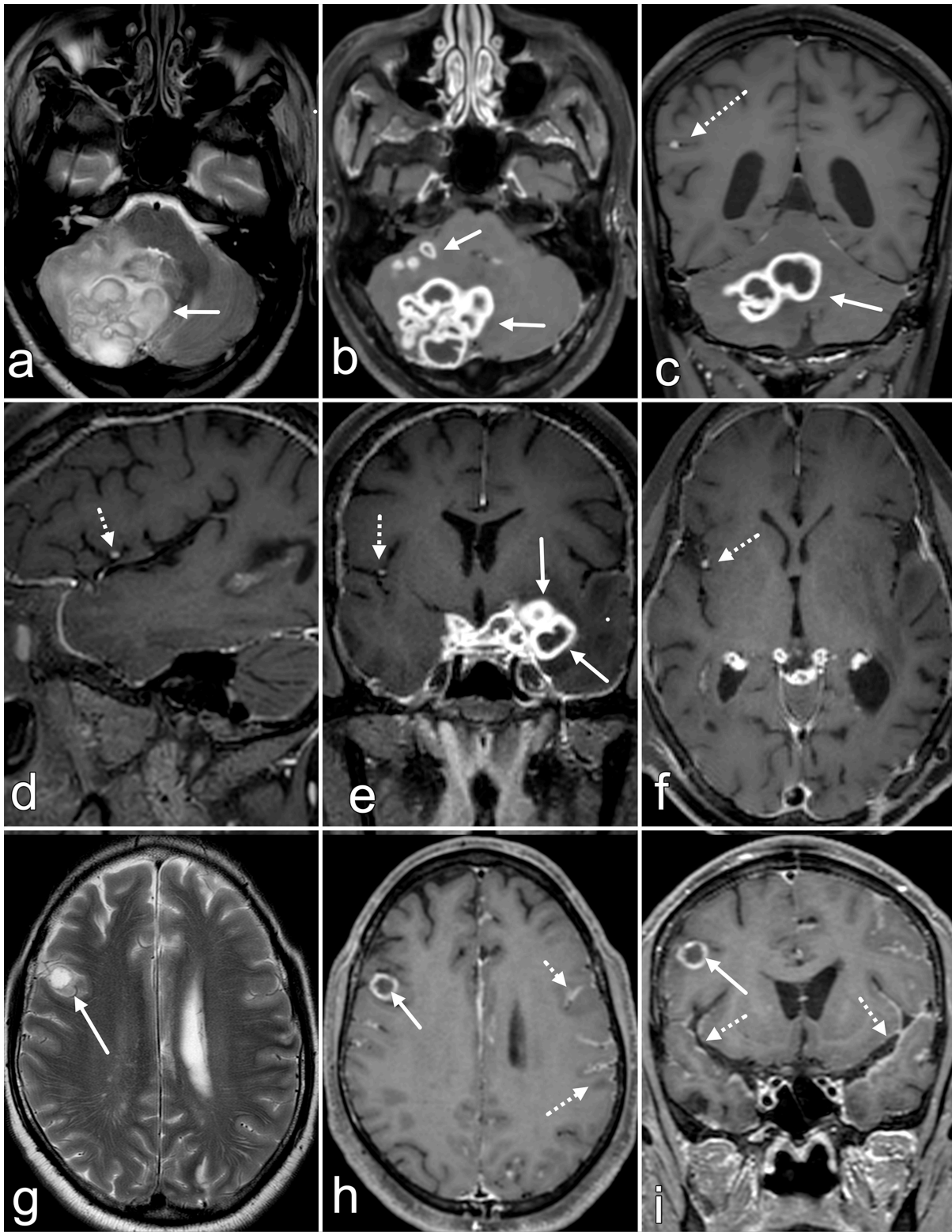


Figure 3

(a–c) Patient 1—cerebellar tuberculoma with a remote supratentorial sulcal tuberculoma.

(a) Axial T2-weighted image shows a conglomerate multiloculated lesion in the left cerebellar hemisphere, with T2-hypointense rims, central T2-hyperintense contents, and surrounding oedema (solid arrow). (b) Axial and (c) coronal post-contrast T1-WIs show corresponding conglomerate thick-walled

ring enhancement, producing a “cluster-of-grapes” appearance (solid arrows), with a smaller satellite ring-enhancing lesion anteriorly. A tiny additional nodular enhancing focus is seen within a right frontal sulcus (dotted arrow, c), representing a sulcal tuberculoma.

(d–f) Patient 2—temporal lobe tuberculomas with multiple sulcal (subpial) tuberculomas.

(e) Coronal and (f) axial post-contrast T1-weighted images show conglomerate ring-enhancing tuberculomas involving the temporal lobes and adjacent basal cisternal region (solid arrows), with associated basal leptomeningeal enhancement. The magnified post-contrast image (d), as well as (e, f), demonstrates multiple discrete small nodular enhancing foci along the pial surface within the cortical sulci (dotted arrows), consistent with subpial tuberculomas.

(g–i) Patient 3—parenchymal metastasis with leptomeningeal carcinomatosis: an imaging mimic.

(g) Axial T2-weighted image shows a right frontal lesion with a T2-hyperintense centre and surrounding oedema (solid arrow). (h) Axial and (i) coronal post-contrast T1-weighted images demonstrate thin, smooth ring enhancement of the parenchymal metastasis (solid arrows), accompanied by linear, sheet-like leptomeningeal enhancement extending along the depths of the cortical sulci and the sylvian and temporal surfaces bilaterally (dotted arrows). In contrast to the discrete nodular sulcal lesions in (d–f), the leptomeningeal enhancement here is predominantly continuous and linear, reflecting pia–arachnoid coating. This pattern may aid differentiation, although nodular leptomeningeal metastatic deposits can overlap in appearance; CSF cytology may be required for confirmation.

Screening	146 patients with Headache>5 days with or without [fever, neck stiffness, constitutional symptoms]
•11 patients excluded (Did not meet case definition of chronic meningitis based on CSF findings or MRI/CT leptomeningeal enhancement)	
Comprehensive evaluation	137 patients fulfilled inclusion criteria
•22 patients excluded because of lack of MRI in PACS (Diagnosed only based on CT scanning or MRI done from other centre and data missing) (Missing index test) •2 patients had no final diagnosis on file- Lost to follow up before comprehensive evaluation could be completed (Missing reference standard)	
Final analysis dataset	91 with TBM 22 with other chronic meningitis
•Sensitivity •Specificity •Positive Predictive value •Negative Predictive value	

Figure 4

STARD flow diagram of patient recruitment and diagnostic accuracy analysis

