MRI Findings and Clinical Outcomes in Tuberculous Meningitis: Insights into Paradoxical Reactions and Disease Progression

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Liam O'Halloran, Data collection and editor

DISCLOSURES
None

CONSENT
Written informed consent was obtained from patients for the submission of this manuscript.

HUMAN AND ANIMAL RIGHTS
This study adhered to ethical standards as per the Helsinki Declaration (1975, revised in 2000). Ethical approval was granted by the University Hospital Limerick ethics committee.

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ABSTRACT

Objectives: Cases series demonstrating the relationship between brain MRI findings and clinical characteristics, as well as outcomes of patients with tuberculous meningitis (TBM) treated with rifampicin-based regimens over an eight-year period.

Methods: This retrospective study included 87 participants aged ≥16 years who were diagnosed with TBM with MRI scans were performed at baseline and three months post-treatment initiation. Clinical outcomes were assessed using the Glasgow Outcome Scale (GOS). Paradoxical responses were defined and analyzed. Ethical approval was granted by the University Hospital Limerick ethics committee.

Results: Baseline MRI abnormalities were present in 94% of patients, with meningeal enhancement and tuberculomas being the most common findings. Paradoxical responses were observed in 82% of cases at two months, with new or worsening MRI findings, primarily miliary tuberculomas and meningeal enhancement. Paradoxical reactions did not correlate with six-month mortality.

Conclusions: MRI plays a critical role in diagnosing and monitoring TBM. Paradoxical MRI findings, although common, were not predictive of treatment failure or mortality.

Teaching Point: MRI findings such as meningeal enhancement and tuberculomas are prevalent in TBM. Paradoxical reactions highlight disease progression but do not indicate treatment failure.

CASE REPORT

BACKGROUND

Tuberculous meningitis (TBM) is a severe form of central nervous system tuberculosis characterized by significant morbidity and mortality. Magnetic Resonance Imaging (MRI) plays a crucial role in diagnosing TBM, monitoring treatment response, and identifying paradoxical reactions. This study investigates the relationship between MRI findings and clinical outcomes in patients with TBM, aiming to provide insights into disease progression and response to rifampicin-based treatment regimens over an eight-year period.

INTRODUCTION

Tuberculosis meningitis (TBM) is recognized as the most severe manifestation of TB, contributing to significant mortality and long-term complications in nearly half of affected individuals [1,2]. TB meningitis is due to the development of granulomatous lesions within the meninges or adjacent areas rupture into the subarachnoid space [3]. This can to complications such as stroke, hydrocephalus, and cranial nerve impairments. The clinical presentation and prognosis of TBM are heavily influenced by the location and severity of the inflammation [2,4].

Imaging plays a pivotal role in detecting the brain abnormalities associated with TBM. Unlike imaging methods that rely on ionizing radiation, MRI provides comprehensive visualization of brain structures. Notably, MRI surpasses computed tomography (CT) in identifying pathological changes in the meninges. Previous research has consistently highlighted a triad of MRI findings in TBM cases: basal meningeal enhancement, hydrocephalus, and infarction [5-7]. Patients often deteriorate both radiologically and clinically despite best treatment and management, the degree to which radiological deterioration corresponds to outcomes has not been clearly defined from previous research.

METHODS

Study Design, Participants, and Follow-Up

This was a retrospective study evaluating efficacy of rifampicin for tuberculous meningitis (TBM) study included patients over a 8 year period 2015-2023. Participants were adults and adolescents aged 16 years or older who presented with clinical signs of TBM. Inclusion criteria included a cerebrospinal fluid (CSF)-to-blood glucose ratio below 0.5 and a CSF leukocyte count of at least five cells/μL with either positive CSF India ink or Gram stain results. Inclusion criteria also required a baseline MRI brain with a repeat MRI brain performed within three months. Chart review was performed and inclusion criteria included patients that were on standard anti-TB treatment comprising rifampicin, isoniazid, ethambutol, and pyrazinamide for a minimum of six months as per local guidelines, with adjunctive dexamethasone administered in a tapering dose.

Patients were followed for 1 year with clinical outcomes categorized as death or severe disability. The Glasgow Outcome Scale (GOS) was used to evaluate recovery, with scores of 4 or 5 indicating a favourable outcome. For patients experiencing paradoxical worsening of symptoms, dexamethasone dosing was adjusted based on disease severity. Ethical approval was granted by the University Hospital Limerick ethics committee, Limerick, Ireland.

MRI Protocol

All scans were conducted using a 1.5 Tesla MRI system (Siemens Healthcare, USA) and included the following sequences:

- T1 spin echo
- Axial T2 turbo spin echo
- Axial T2 fluid-attenuated inversion recovery (FLAIR)
- Axial diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping
- Axial T2 gradient echo (GRE)
- Axial T1 3D with contrast

Gadolinium-based contrast agents (0.2 mmol/kg body weight) were administered intravenously to enhance imaging quality. The 3D MP-RAGE sequence produced 1-mm thick slices, facilitating high-resolution imaging and precise lesion localization. Identical imaging parameters were used for all axial-plane scans.

Infarction locations were categorized into cerebrum, cerebellum, or brainstem, with cerebral infarctions further divided into basal ganglia and non-basal ganglia regions.

Paradoxical Response

Follow-up MRIs were compared to baseline images to identify paradoxical responses, defined as the worsening of existing abnormalities or the development of new abnormalities. These included:

- New or worsening hydrocephalus
- New leptomeningeal enhancement
- Enlarging or new tuberculomas
- New infarctions

Clinical paradoxical responses involved the appearance of new neurological symptoms, such as cranial nerve palsy, motor deficits, seizures, or severe headaches, in patients previously showing improvement. Paradoxical responses were classified as "definite" if they arose more than four weeks after starting TB treatment.

Data Analysis

Continuous variables were summarized using medians, while categorical variables were presented as proportions. Baseline MRI findings and three-month paradoxical worsening were compared with six-month survival and functional outcomes. Statistical tests included Chi-square test for categorical data. Analyses were conducted using IBM SPSS Statistics version 24, with significance set at a p-value < 0.05.

RESULTS

Baseline MRI findings

A total of 87 participants (52% female, median age 30.5 years) were included. Of these, 48 patients underwent baseline MRI scans after a median of 2.5 days of initiating treatment. Most participants (90%) were diagnosed with MRC grade II TBM. Common presenting symptoms included headache (96%), neck stiffness (96%), fever (85%), loss of consciousness (83%), and motor impairments (56%). Pulmonary involvement was observed in 69% of cases, with 12% having miliary disease. All patients exhibited cerebrospinal fluid (CSF) abnormalities indicative of TBM, and 71% were confirmed microbiologically through microscopy, molecular methods, or culture.

MRI abnormalities were present in 94% of cases, with 83% displaying multiple brain lesions. The most prevalent finding was meningeal enhancement, particularly in the basal meninges and Sylvian fissures. Tuberculomas, predominantly miliary in nature, were the second most common abnormality, although only one pseudoabscess was reported. Acute brain infarctions were noted in 60% of patients, while 56% exhibited communicating hydrocephalus, characterized by features such as widened callosal angles, dilated temporal horns, and increased Evans' ratios. Cranial nerve abnormalities were observed in 19% of patients.

When stratified by the extent of MRI abnormalities (none, single, two, three, or four lesions), patients with greater numbers of lesions demonstrated longer illness durations, lower levels of consciousness, more severe motor deficits, higher rates of cranial nerve palsies, greater CSF abnormalities, and increased rates of positive CSF cultures. Due to the low proportion of HIV-positive participants (8%), further analysis by HIV status was not conducted. The median interval between the onset of neurological symptoms and baseline MRI was 19 days.

MRI Findings after Two Months of Treatment

In total 82% showed new or worsening MRI findings after two months of treatment. However, only 43% of these radiological changes were associated with clinical symptom deterioration. New cranial nerve abnormalities were the most frequent clinical manifestation.

Two patients experienced worsening symptoms without corresponding new MRI abnormalities: one developed facial and hypoglossal nerve palsy by day 30, while the other presented with ptosis. Among those with radiological progression, 76% exhibited either new or enlarged tuberculomas, while 76% had thickened or newly localized meningeal enhancement. New cranial nerve enhancements occurred in 24% of cases, one patient developed a new infarction, and two showed worsening hydrocephalus. Despite these findings, hydrocephalus improved in 32% of cases, even as other radiological abnormalities progressed.

Relationship between Neuroimaging Findings and Patient Outcomes

Baseline MRI abnormalities were not significantly associated with survival outcomes. Among patients exhibiting paradoxical responses at two months, 42% of those with clinical paradoxical changes died. No deaths occurred in the radiological paradoxical group, while 15% of those with combined clinical-radiological paradoxical reactions succumbed to the disease. Better recovery rates were observed in patients without paradoxical reactions or those with only radiological changes. However, the small sample size limited the robustness of statistical comparisons.

DISCUSSION

This study investigated neuroradiological patterns in a well-defined cohort of TBM patients in Ireland. Nearly all patients displayed some MRI abnormalities, with meningeal enhancement, tuberculomas, infarctions, and hydrocephalus being the most common. Patients with multiple MRI abnormalities exhibited more severe clinical symptoms and greater CSF abnormalities, indicative of advanced disease. Within the first two months of treatment, many participants developed new or worsening MRI findings, particularly miliary tuberculomas and meningeal enhancement. Baseline MRI findings were not significantly linked to paradoxical worsening, disability, or mortality during the study's follow-up period.

The high prevalence of abnormalities observed in this study is also seen in prior studies [8,9]. Advanced disease is characterized by thick basal exudates that compromise cranial nerves and arteries, as well as CSF absorption [10].

Our findings are consistent with earlier research showing that most TBM patients exhibit multiple baseline MRI abnormalities [5] particularly involving meningeal enhancement and tuberculomas. The basal subarachnoid cisterns were the primary sites of meningeal enhancement, consistent with the accumulation of dense gelatinous leptomeningeal exudates characteristic of TBM [1,2]. More extensive abnormalities correlated with indicators of severe disease, including lower Glasgow Coma Scale (GCS) scores, motor and cranial nerve deficits, pulmonary TB, microbiological confirmation, reduced CSF glucose, and elevated CSF protein levels.

The higher frequency of miliary tuberculomas in our study may be attributed to the enhanced sensitivity of the 3D MP-RAGE sequence, which enables the detection of smaller lesions and subtle meningeal enhancements through 1-mm slice thickness and gapless imaging.

Paradoxical reactions, characterized by worsening or new MRI abnormalities despite clinical improvement, were prevalent in this cohort. These reactions primarily involved miliary tuberculomas and meningeal enhancement, often without associated symptoms. This aligns with earlier studies reporting radiological paradoxical reactions within three

months of initiating anti-TB treatment [8,11]. Importantly, these reactions were not predictive of six-month mortality, supporting previous findings [11].

Our findings emphasize that paradoxical reactions should not be mistaken for treatment failure, drug resistance, or alternative diagnoses. Misinterpretation of these reactions could lead to inappropriate discontinuation of anti-TB therapy, potentially worsening patient outcomes.

CONCLUSION

MRI abnormalities were widespread among TBM patients in this study, with paradoxical reactions frequently observed despite the use of adjunctive steroids. These findings underscore the importance of MRI in diagnosing, monitoring, and understanding the disease progression of TBM. Moreover, MRI can aid in evaluating paradoxical reactions and exploring the immunopathology of TBM, providing valuable insights for clinical trials and the development of host-directed therapies.

QUESTIONS

Question 1: What is the most common MRI finding in TBM?

a. Hydrocephalus
b. Meningeal enhancement (applies)
c. Tuberculomas
d. Infarctions
e. None of the above

Explanation: Meningeal enhancement was observed in 94% of cases [Discussion Section, Clinical & Imaging Findings].

Question 2: What characterizes paradoxical reactions in TBM?

a. Worsening clinical symptoms
b. Development of new imaging abnormalities
c. Indicative of treatment failure
d. Both a and b (applies)
e. None of the above

Explanation: Paradoxical reactions involve new or worsening symptoms and imaging findings but are not linked to treatment failure [Discussion Section, Treatment & Prognosis].

Question 3: What imaging modality is superior in detecting TBM abnormalities?

a. CT
b. Ultrasound
c. MRI (applies)
d. PET scan
e. None of the above

Explanation: MRI provides superior visualization of TBM-related abnormalities, including meningeal enhancement and tuberculomas [Discussion Section, Clinical & Imaging Findings].

Question 4: Which of the following is a common feature of paradoxical reactions in TBM?

a. Miliary tuberculomas (applies)
b. Hydrocephalus resolution
c. Reduction in meningeal enhancement
d. Cranial nerve improvement
e. None of the above

Explanation: Paradoxical reactions frequently include the development or enlargement of miliary tuberculomas [Case Report, Follow-Up].

Question 5: What is the primary treatment for TBM?

a. Surgical intervention
b. Antifungal medication
c. Standard anti-TB regimen (applies)
d. MRI-guided therapy
e. None of the above

Explanation: The primary treatment for TBM includes a standard anti-TB regimen consisting of rifampicin, isoniazid, ethambutol, and pyrazinamide [Case Report, Management].

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TABLES

Table 1: Baseline Characteristics of the Study Population

Characteristic	Value
Total participants	87
Gender distribution	52% Female
Median age	30.5 years
HIV co-infection rate	8%
MRC grade II TBM	90%
Common symptoms	Headache (96%), Neck stiffness (96%), Fever (85%), Loss of consciousness (83%), Motor deficits (56%)
Pulmonary involvement	69% (12% with miliary disease)
CSF abnormalities (consistent with TBM)	100%
Microbiologically confirmed TBM	71%
Rifampicin-resistant TB (GeneXpert)	None

Table 2: Baseline MRI Findings

MRI Finding	Percentage of Patients Affected
Any MRI abnormality	94%
Multiple brain lesions	83%
Meningeal enhancement	Most common finding (basal meninges, Sylvian fissures)
Tuberculomas	Second most common (mainly miliary type)
Pseudoabscess	1 patient
Brain infarctions	60% (acute > chronic)
Hydrocephalus	56% (always communicating type)
Cranial nerve abnormalities	19%

Table 3: MRI Findings and Clinical Correlations

Number of MRI Abnormalities	Clinical Correlations
None	-
Single	Shorter illness duration
Two	Lower consciousness levels
Three	Greater motor deficits, higher cranial nerve palsy rates, more pronounced CSF abnormalities
Four	Higher rates of positive CSF cultures, longest illness duration

Table 4: MRI Findings After Two Months of Treatment

MRI Change	Percentage of Affected Patients
New or worsening findings	82%
Associated with symptoms	43%
New/enlarged tuberculomas	76%
Thickened/new meningeal enhancement	76%
Cranial nerve enhancement	24%
New infarction	1 patient
Worsening hydrocephalus	2 patients
Improved hydrocephalus	32%

KEYWORDS

Tuberculous meningitis; MRI; Rifampicin; Paradoxical reactions; Hydrocephalus

ABBREVIATIONS

TBM = TUBERCULOUS MENINGITIS
MRI = MAGNETIC RESONANCE IMAGING
CNS = CENTRAL NERVOUS SYSTEM
CSF = CEREBROSPINAL FLUID
PCR = POLYMERASE CHAIN REACTION
HIV = HUMAN IMMUNODEFICIENCY VIRUS
WHO = WORLD HEALTH ORGANIZATION
IRIS=IMMUNERECONSTITUTIONINFLAMMATORY SYNDROME