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Paradoxical reactions in central nervous system tuberculosis: Insights into pathogenesis, diagnosis, and clinical management

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Abstract

Paradoxical reactions are immune-mediated complications that can arise during the treatment of tuberculosis, particularly in central nervous system tuberculosis. These reactions are characterised by clinical or radiological deterioration in patients who are already receiving appropriate anti-tuberculous therapy, driven by an exaggerated immune response to residual mycobacterial antigens. Central nervous system tuberculosis, one of the most severe forms of extrapulmonary tuberculosis, presents a significant therapeutic challenge when complicated by paradoxical reactions. This review explores the underlying mechanisms of these reactions, the diagnostic challenges faced by clinicians, and current therapeutic approaches, including the use of corticosteroids, tumour necrosis factor-alpha (TNF-α) antagonists, and surgical interventions, while also addressing gaps in existing knowledge and practice.

KEYWORDS

Paradoxical reactions, immune reconstitution inflammatory syndrome (IRIS), central nervous system tuberculosis, optochiasmatic arachnoiditis, tumour necrosis factor antagonists

INTRODUCTION

Central nervous system tuberculosis (CNS TB), though rare, remains one of the most severe forms of TB, associated with high mortality and significant neurological morbidity. Before the introduction of anti-tuberculous therapy (ATT), CNS TB was almost invariably fatal. Despite advances in treatment, it continues to pose a substantial challenge. Representing approximately 1% of all TB cases, CNS TB is particularly concerning due to its diagnostic complexity and the severe long-term outcomes faced by survivors.[1]

One of the most challenging complications in the management of CNS TB is the occurrence of paradoxical reactions, also referred to as paradoxical worsening.[2] These reactions are defined as the deterioration of pre-existing tuberculous lesions or the appearance of new lesions in patients who initially showed clinical improvement and had been on anti-tuberculous therapy for at least 10 days.[3]

In human immunodeficiency virus (HIV)-positive patients, these reactions are termed 'immune reconstitution inflammatory syndrome' (IRIS), a condition where pre-existing infections worsen after the initiation of antiretroviral therapy (ART). Tuberculosis-associated IRIS is characterised by a recurrence or exacerbation of tuberculosis symptoms and imaging abnormalities following ART initiation, despite prior improvement with ATT.[3]

Paradoxical reactions following CNS TB in non-HIV infected patients appear to be relatively common, with an incidence comparable to or even exceeding that of TB-associated IRIS in HIV-infected individuals. A prospective study reported that 47% of HIV-infected patients with tuberculous meningitis (TBM) developed TBM-IRIS.[3] Similarly, another prospective study found that 50% of non-HIV-infected patients with CNS TB experienced paradoxical reactions.[4]

While paradoxical reactions are common in CNS TB, their pathogenesis remains poorly understood, and standardised

treatment protocols have yet to be established. Current theories suggest that these reactions result from an exaggerated immune response to mycobacterial antigens, though the precise mechanisms, particularly within the CNS, remain unclear.[5]

These reactions are especially concerning in CNS TB, where inflammation in critical areas such as the meninges or brain parenchyma can lead to severe complications, including hydrocephalus, vasculitis, infarctions, or permanent neurological damage.[2] Diagnostic uncertainty often compounds the challenge for clinicians, as the symptoms of paradoxical reactions can mimic drug resistance, alternative infections, or treatment failure.[3]

Given the critical importance of effectively managing paradoxical reactions, this review explores their underlying mechanisms, diagnostic challenges, and therapeutic strategies in CNS TB. The goal is to enhance clinicians' understanding of this complex phenomenon and to examine emerging treatments that may improve patient outcomes, including corticosteroids, TNF-α antagonists, and surgical interventions.

Epidemiology and risk factors

Paradoxical reactions are more common in CNS TB than in other forms of extrapulmonary TB. Studies indicate that 31.2% of patients with CNS TB experience these reactions, compared to the 10-15% reported in pulmonary or lymph node TB.[3,5]

A prospective cohort study involving 41 patients with TBM found that 56% developed paradoxical reactions, a rate notably higher than previously reported in the literature.[6]

The incidence of paradoxical reactions also varies geographically. In high TB-burden regions, such as South Asia and sub-Saharan Africa, the frequency of paradoxical reactions is elevated. This is attributed to the higher prevalence of extrapulmonary TB and HIV co-infection, which increases the likelihood of IRIS-related paradoxical reactions.[7]

Several risk factors, both host- and disease-related, predispose patients with CNS TB to developing paradoxical reactions. HIV infection, particularly in individuals starting ART, is the most significant risk factor, as immune reconstitution can intensify inflammatory responses.[3,5] Younger age, especially under 40 years, is also associated with a higher risk, possibly due to a more vigorous immune response in younger individuals.[7,8]

In HIV-negative patients, a low baseline lymphocyte count in blood at diagnosis, followed by a substantial increase in lymphocyte count (≥300 cells/µl) during paradoxical reactions, has been identified as a key risk factor.[5] Female gender has also been implicated, potentially due to hormonal or immune system differences, though the underlying mechanisms remain unclear.[3] Additionally, a shorter duration of illness prior to presentation and a more acute onset of symptoms before initiating anti-tuberculous therapy (ATT) are associated with an increased likelihood of paradoxical reactions.[3,7]

Timing of paradoxical reactions

The onset of paradoxical reactions in TB is highly variable and unpredictable, occurring at any point during or even after the completion of ATT. These reactions can emerge anywhere from a few weeks to several months following the initiation of therapy. Reviews suggest that the median time for paradoxical reactions across all TB sites is approximately 60 days, with pulmonary TB showing a median onset of 42 days and disseminated TB around 60 days. In CNS TB, however, paradoxical reactions typically have a longer latency period, with a median onset of approximately 63 days.[9]

In patients with TBM, the onset of paradoxical reactions has been reported to occur between 28 days and nine months.[6] This extended delay in CNS TB is thought to result from factors such as the limited penetration of anti-tuberculous drugs across the blood-brain barrier (BBB) and the longer duration required for mycobacterial clearance and immune recovery within the CNS.[9]

The variability in the timing of paradoxical reactions is influenced by several factors. In HIV-positive patients, particularly those experiencing IRIS after initiating ART, paradoxical reactions commonly occur within two to six weeks of starting ART. This period coincides with immune recovery, during which CD4+ T cells begin to recognise and react against mycobacterial antigens that were previously contained by the immune system. The rapid immune restoration in this group often leads to severe and early paradoxical reactions, especially involving the CNS.[10]

In contrast, HIV-negative patients typically develop paradoxical reactions later, around eight weeks into ATT.[3] Notably, paradoxical reactions in CNS TB can also arise after the completion of ATT, with cases reported months to as long as 10 years after treatment cessation.[11-16] Additionally, these reactions can recur in up to 30% of HIV-negative patients.[6] Figure 1 shows the median and range of onset for paradoxical reactions across various forms of tuberculosis.

Pathophysiology of paradoxical reactions in CNS TB

1. Mycobacterial antigen release triggering the excessive host immune response

The pathophysiology of paradoxical reactions in CNS TB is a complex interplay between the host's immune response, mycobacterial antigens, and the unique environment of the CNS. [17]

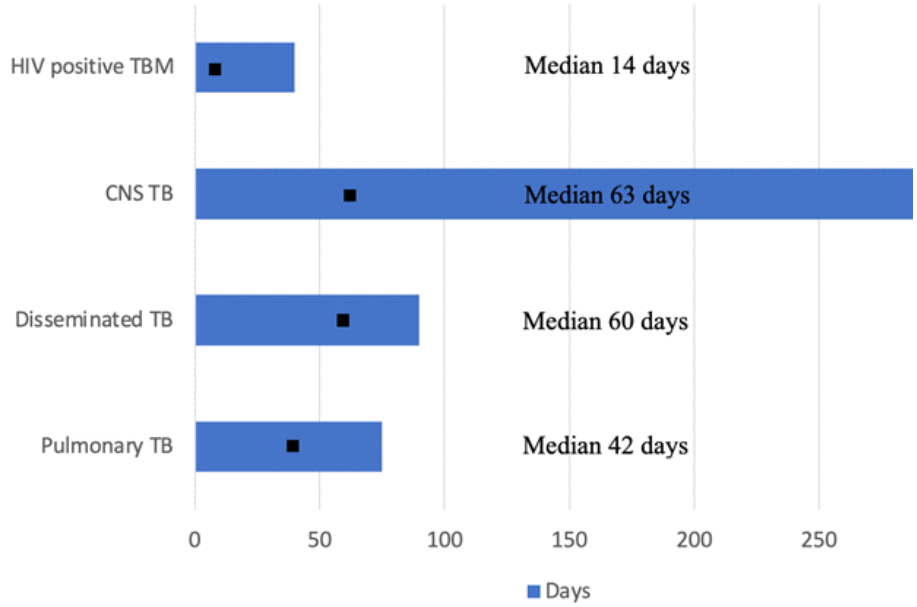

FIGURE 1 **Timeline of the onset of the paradoxical reaction in different TB manifestations.**

One proposed mechanism is that the rapid killing of bacilli by ATT releases a substantial load of microbial components, triggering an exaggerated inflammatory response. This process may be amplified in cases with higher baseline bacillary loads, increasing the likelihood of paradoxical reactions or IRIS. [6]

This concept is supported by the phenomenon of "immunologic paradox," where mycobacterium tuberculosis-specific T helper (Th) 1-cell activity in the cerebrospinal fluid (CSF) or peripheral blood rises after two to four weeks of ATT, even as clinical improvement is observed. Both humoral and cell-mediated immune responses are excessively activated by the release of antigens from bacterial destruction, further fuelling the inflammatory cascade.[6]

Recurrent paradoxical reactions lend support to the hypothesis that these immune responses are driven by local antigen release. The persistence of such reactions, even after prolonged treatment, suggests inefficient clearance of antigenic material from affected sites. Mycobacterium tuberculosis (MTB) contains lipid-rich, insoluble cell wall antigens, which strongly activate mononuclear phagocytes. The release of components like lipoarabinomannan and the 30-kDa antigen during bacterial destruction by ATT likely triggers a robust inflammatory host response.[6]

2. Role of immune reconstitution

Human studies highlight immune reconstitution as a critical factor in the pathogenesis of paradoxical reactions and IRIS. Active TB is associated with a suppression of delayed-type hypersensitivity responses. Mycobacterial protein derivatives increase interleukin-1 production, which suppresses immune responses and induces immunosuppressive levels of prostaglandin E2.[18] Additionally, the development of paradoxical reactions has been linked to the rapid recovery of peripheral blood lymphocytes following the initiation of antimycobacterial therapy, indicating that immune reconstitution is a significant component of the TB treatment response.[9,19,20]

3. The role of Th1 CD4+ cells

Th1 CD4+ T cell-mediated immune responses play a pivotal role in the development of paradoxical reactions and IRIS. Both conditions have been associated with the conversion of tuberculin skin tests from negative to positive after treatment initiation, demonstrating in vivo the reconstitution of cell-mediated immunity – a key factor in delayed-type hypersensitivity reactions.[21]

4. The role of TNF-α

TNF-α is a critical mediator in the pathogenesis of TBM, influencing disease progression through multiple mechanisms. It increases BBB permeability, promotes the release of additional cytokines, and correlates with disease severity in animal models. Post-mortem studies of TB granulomas reveal high levels of TNF-α at the interface between cellular and necrotic zones. In TBM-IRIS patients, elevated CSF TNF-α levels combined with low interferon (IFN)-γ levels have been identified as predictive markers of disease severity, underscoring the importance of TNF-α in the inflammatory processes underlying these reactions.[22]

Recent studies have highlighted the importance of a balanced TNF-α response in controlling disease progression. This concept, termed the "Goldilocks effect," demonstrates that

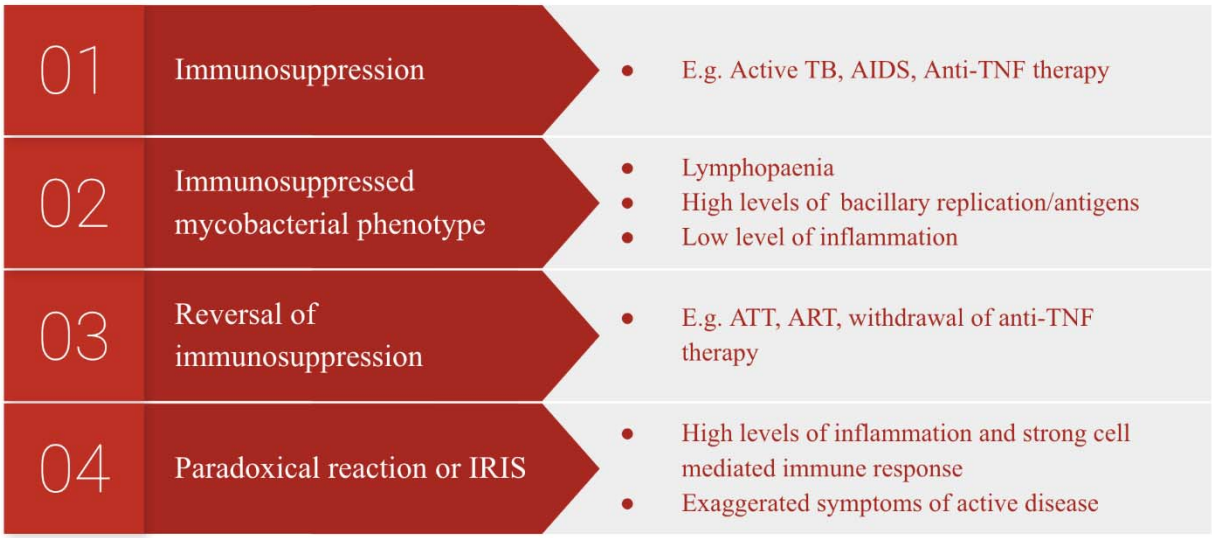

FIGURE 2 **Proposed common mechanism for pathogenesis in mycobacterial paradoxical reactions/IRIS.**[17].

both insufficient and excessive TNF-α production can exacerbate disease. Research in this model has shown that low or high TNF-α activity results in macrophage necrosis and uncontrolled bacterial replication, emphasising the need for a precise inflammatory balance.

This theory is supported by genetic studies in human TB and provides valuable insight into the dual role of inflammation in paradoxical reactions and IRIS. The excessive TNF-α production observed during paradoxical reactions in TB-IRIS patients likely contributes to the disease by driving heightened inflammatory responses, further complicating the clinical course.[17]

5. Risk factors

Higher baseline bacillary or antigen loads, coupled with baseline immunosuppression, are key factors in the pathophysiology of paradoxical reactions and IRIS. Studies have consistently supported the role of bacillary and antigen loads in driving these conditions. Patients with disseminated or extrapulmonary TB, who are presumed to have higher bacillary or antigen loads, are at an increased risk of developing paradoxical reactions and IRIS.[19-23,24]

The risk of IRIS is particularly pronounced when ART is initiated early during ATT, a period when bacillary loads are still near their peak. This finding has been validated by large randomized clinical trials designed to determine the optimal timing for ART initiation, underscoring the importance of managing bacillary burden and immune reconstitution carefully in these patients.[25,26]

Furthermore, studies indicate that patients with TBM who have MTB culture-positive CSF at diagnosis are at a higher risk of developing paradoxical TBM-IRIS.[27] Additionally, pre-treatment levels of the MTB antigen lipoarabinomannan in urine have been found to be elevated in patients who later develop TB-IRIS. These findings suggest that higher bacillary and antigen levels may serve as predictors for the development of paradoxical reactions and IRIS. However, the direct role of these factors in the pathogenesis of these conditions remains unclear.[18]

High baseline bacillary loads may also reflect an underlying immunodeficiency, which itself is an independent risk factor for paradoxical reactions and IRIS. This complicates the determination of whether high antigenic loads are a direct cause of the condition or merely a consequence of immunosuppression.[17]

The role of an immunocompromised state in the development of paradoxical reactions is particularly evident in HIV co-infection, widely recognised as the most significant risk factor. Similarly, in HIV-negative individuals, the importance of immune system functionality is underscored by findings that these patients often exhibit low baseline lymphocyte counts in the blood at the time of paradoxical reaction diagnosis, further emphasising the interplay between immune status and these conditions.[19]

HIV-seronegative patients undergoing anti-TNF-α therapy for autoinflammatory conditions are reported to have an increased risk of developing active TB due to immunosuppression. Additionally, these patients may experience a form of TB-IRIS when anti-TNF-α therapy is withdrawn.[28] This aligns with the proposed model (Figure 3), in which immunosuppression facilitates the formation of poorly inflamed, multibacillary TB lesions, followed by hyper-inflammatory disease upon the removal of immunosuppression.[29]

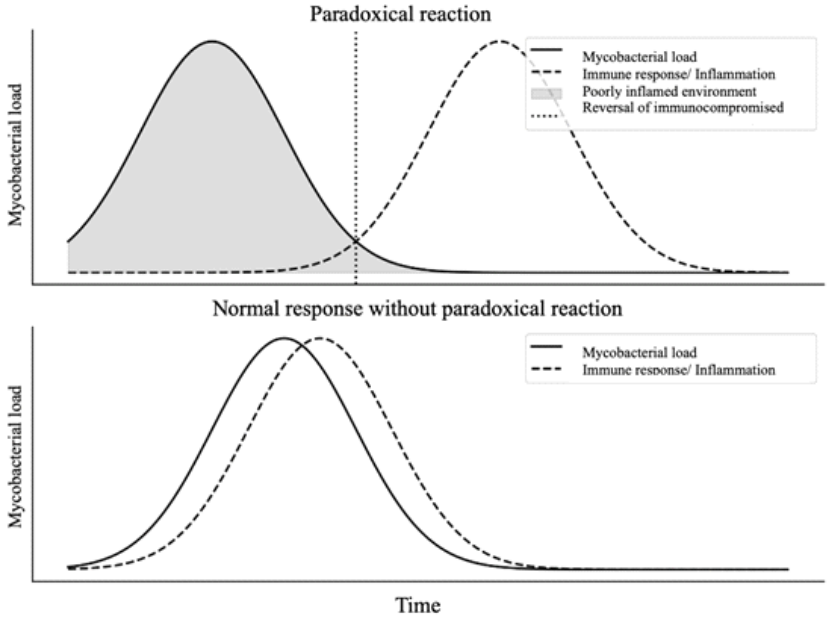

FIGURE 3 **Proposed pathogenesis of paradoxical reactions.**

Figure 3 illustrates the proposed pathogenesis of paradoxical reactions over time, highlighting changes in mycobacterial load and the immune response. In the lower section, the pathogenesis without paradoxical reactions/IRIS is shown, where the mycobacterial load and immune response/inflammation are synchronised. Here, inflammation and related clinical symptoms subside along with the mycobacterial burden once treatment begins. In contrast, the upper section shows the pathogenesis of paradoxical reactions/IRIS, where an immunocompromised state at baseline allows for uncontrolled mycobacterial growth in a low-inflammatory environment. When treatment is initiated and immunosuppression is reversed, paradoxical reactions/IRIS emerge, with symptoms occurring at a different time compared to those of the initial untreated infection.[17]

Clinical presentation

Paradoxical reactions in CNS TB can be categorised into three distinct types based on clinical manifestations, imaging findings, and CSF abnormalities.

Common clinical features of paradoxical reactions include fever, headache, altered sensorium, decreased vision, and seizures. Hemiparesis is frequently linked to the development of new infarcts, while cranial nerve palsies are associated with worsening leptomeningeal inflammation.[3]

In CNS TB, exudates predominantly accumulating in the interpeduncular, suprasellar, and Sylvian cisterns can result in optochiasmatic arachnoiditis, a condition commonly seen as a paradoxical reaction. This condition often leads to decreased visual acuity, with progression ranging from partial to total blindness.[30-32] Optochiasmatic arachnoiditis is more frequently observed in young adults, with female sex, younger age, and elevated CSF protein levels identified as significant predictors of its development.[30]

Paradoxical spinal involvement occurs in approximately 7% of patients with spinal TB, with most presenting with limb weakness, sensory abnormalities, and bladder or bowel dysfunction.[7]

On imaging, frequent paradoxical reactions in CNS TB include enhancing basal exudates, the appearance of new tuberculomata or enlargement of preexisting ones, infarcts, hydrocephalus, optochiasmatic arachnoiditis, and leptomeningeal enhancement.[3,6] Paradoxical angiographic abnormalities, such as vasculitis without vasospasm, may also be detected on repeat angiography.[6]

Tuberculomata are the most commonly observed imaging feature in CNS TB-IRIS, reported in 52% of cases in one study, often coexisting with meningitis. These lesions are typically supratentorial, moderately sized with a median diameter of 11 mm, and multiple in about half of the cases. They are frequently associated with surrounding oedema, although mass effect is uncommon. In patients with IRIS, the development of multiple lesions and more pronounced perilesional oedema is observed more frequently compared to the initial presentation of TBM.[33]

Magnetic resonance imaging (MRI) findings in optochiasmatic arachnoiditis typically reveal confluent enhancing lesions, most prominently located in the interpeduncular fossa, pontine cistern, and the perimesencephalic and suprasellar cisterns.[30]

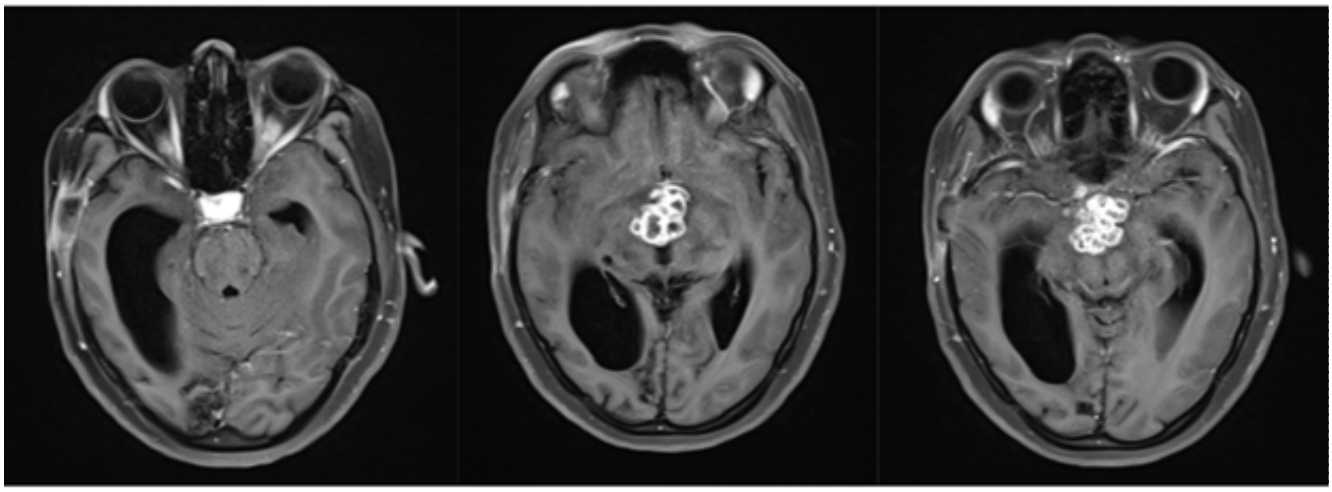

FIGURE 4 **MRI of the head showing multiple contrast enhancing lesions near the optic chiasm in optochiasmatic arachnoiditis.**

In spinal TB, MRI scans may demonstrate the development of spinal arachnoiditis or spinal tuberculomata, characterised by clumping of nerve roots or spinal cord involvement. Additional findings include leptomeningeal enhancement, TB myelitis with spinal cord oedema, and osteomyelitis of the spine.[6,7]

In paradoxical reactions, CSF findings typically reflect an inflammatory response corresponding to the clinical and imaging manifestations. A notable feature is the paradoxical shift in the CSF cellular profile, transitioning from lymphocytic predominance to polymorphonuclear predominance.[3,35] Interestingly, this shift may persist even in the absence of a rise in the total CSF cell count.[3] Other findings may include worsening CSF pleocytosis, elevated protein levels, and reduced glucose concentrations. However, specific thresholds for leukocyte count, protein levels, or glucose concentrations have not been firmly established.[3,6]

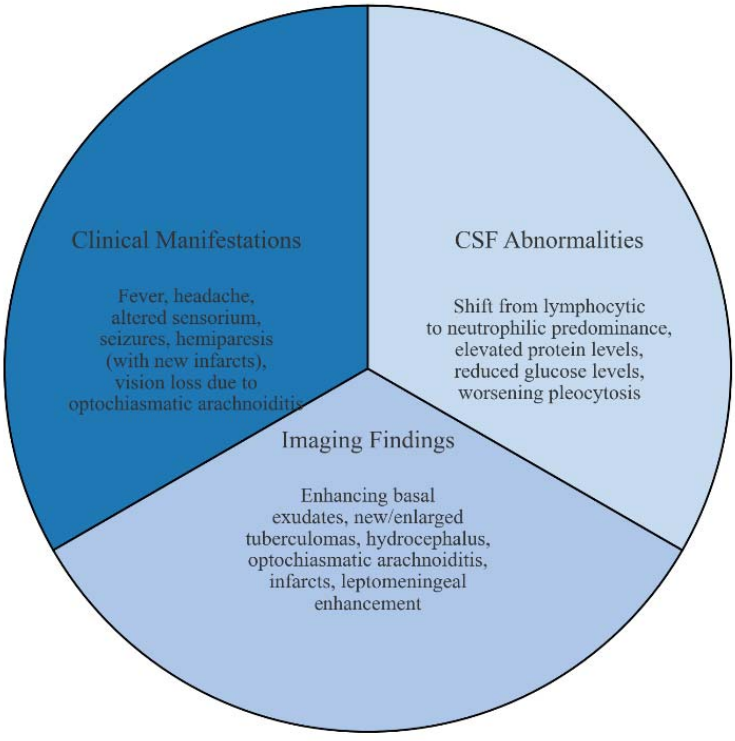

FIGURE 5 **Manifestations of paradoxical reactions in CNS TB.**

TABLE 1 **Diagnostic criteria of CNS TB paradoxical reactions**[5,19,36,37]

Presence of	Absence of
1) Initial improvement in TB-related symptoms and/or radiographic findings following an appropriate course of anti-TB treatment for a defined period.	3) Factors that might reduce the effectiveness of ATT, such as poor treatment adherence, drug malabsorption, drug resistance, or adverse effects from the treatment.
2) Subsequent paradoxical worsening of TB symptoms and/or radiologic abnormalities, either at the original site of infection or at new locations, during or after treatment.	4) Absence of other causes that could explain the clinical deterioration.

Diagnosis

The diagnosis of paradoxical reactions in patients with worsening TB remains a considerable challenge for clinicians globally. Despite advancements in understanding its definition and pathogenesis, there is still no rapid or reliable diagnostic test or biomarker available to confirm this clinical diagnosis.

Currently, paradoxical reactions are recognised based on widely accepted clinical criteria, as outlined in Table 1.

Differential diagnoses should be carefully considered based on the disease location, including tumours, secondary infections, or autoimmune conditions. In some cases, a biopsy may be required to differentiate between these possibilities.

Clinicians should remain vigilant for the diagnosis of a paradoxical reaction beginning two weeks after the initiation of ATT, with the likelihood of occurrence increasing significantly after two months of treatment.[5]

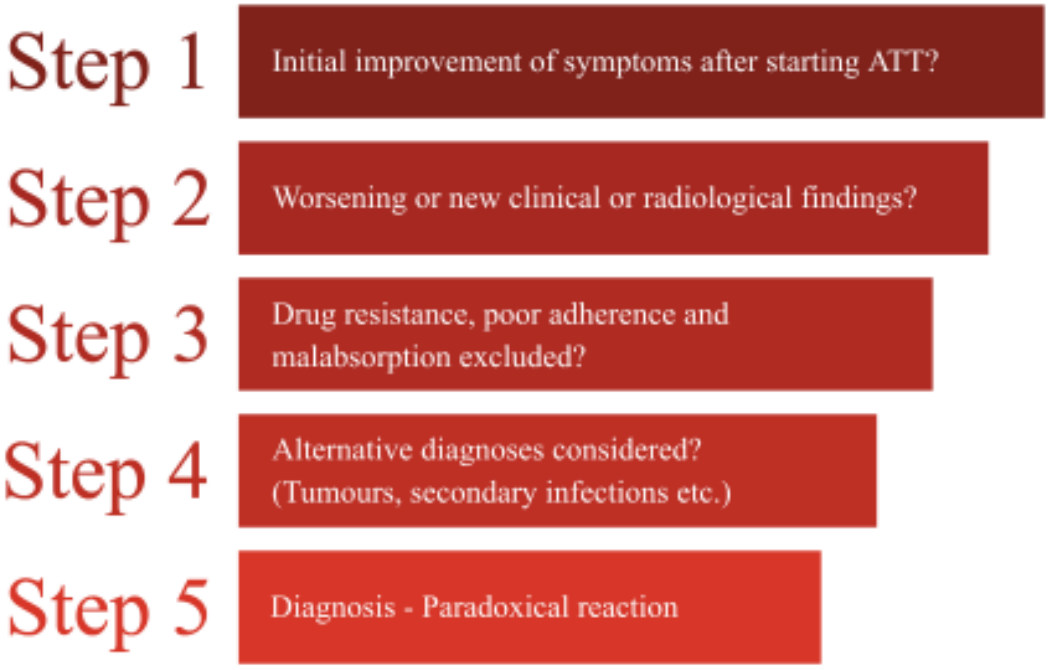

FIGURE 6 **Diagnosis of paradoxical reactions in CNS TB.**

Management of paradoxical reactions in CNS TB

Currently, there are no published guidelines for the treatment of paradoxical reactions in CNS TB patients. Although the literature often distinguishes between case reviews of HIV-positive and HIV-negative patients, the therapeutic approach for both groups remains essentially the same.[5]

1. Corticosteroids

In managing paradoxical reactions in TBM, high-dose corticosteroid therapy remains the cornerstone of treatment.[38] Corticosteroids play a critical role in controlling inflammation and are either continued or reinstated as needed.[39] The standard regimen initiated alongside ATT, as supported by numerous studies and guidelines, typically involves intravenous dexamethasone for four weeks. The dosage begins at 0.4 mg/kg/day during the first week, followed by a stepwise reduction to 0.3 mg, 0.2 mg, and 0.1 mg/kg/day in the subsequent weeks. This initial phase is then followed by oral corticosteroids for an additional four weeks, starting at 4 mg/day and tapering by 1 mg per week. [7,40,41]

Despite the widespread use of corticosteroids, robust evidence supporting their efficacy in managing paradoxical reactions in TBM is limited, as no randomised controlled trials (RCTs) specifically address this issue.[39] The optimal dosing regimen and tapering schedule remain undefined. Existing data suggest that lesions associated with late-onset paradoxical reactions are typically sterile and culture-negative, indicating that additional ATT may not be necessary in such cases. Overall, corticosteroids appear to be safe when used judiciously, particularly when the MTB strain is sensitive to first-line anti-TB medications and administered within a defined duration.[11]

Anecdotal evidence suggests that approximately 50% of patients with CNS TB experience symptom relief and reduced inflammation with corticosteroid therapy. However, a subset of patients presents with severe reactions that are resistant to corticosteroids, resulting in persistent or worsening symptoms.[11]

A case series involving adults with optochiasmatic arachnoiditis revealed that, despite receiving anti-tuberculous therapy and corticosteroids, the risk of blindness increased at the six-month mark.[42] While the adjunctive use of corticosteroids has been linked to reduced mortality in CNS TB patients, the incidence of paradoxical reactions or IRIS remains significant, ranging from 31.2% to 56.0% in non-HIV-infected individuals and up to 47% in those with HIV.[10] In such challenging cases, alternative anti-inflammatory treatments have been investigated.[11]

2. TNF-alpha antagonists

TNFα is essential for host defence against mycobacterial infections, and the use of TNF-α inhibitors, such as infliximab, significantly increases susceptibility to TB. Interestingly, the clinical deterioration of TB patients following the discontinuation of infliximab suggests that TNF-α also plays a role in the disease's pathology. [43]

The first documented use of infliximab for managing paradoxical reactions in TBM was reported in 2008,[44] with subsequent case reports supporting its efficacy in similar cases.[10, 45-49] Other TNF-α inhibitors, such as adalimumab and thalidomide, have also shown potential in managing paradoxical reactions in TBM.[10, 38, 46-51]

Although monoclonal antibodies generally do not cross the BBB, they may penetrate it under conditions of meningeal inflammation and barrier disruption. In animal studies of hepatic encephalopathy, infliximab has been shown to significantly reduce neuroinflammation, as demonstrated through immunohistochemical analysis.[50]

However, the optimal timing and duration of anti-TNF-α therapy, as well as the potential benefits of combining it with corticosteroids, remain unclear. Treatment duration may be guided by symptomatic improvement, reductions in inflammatory markers, and imaging changes observed on MRI or Positron Emission Tomography (PET) scans.[45]

A proposed approach for using infliximab in TBM involves administering 5 mg/kg at 0, 2, and 6 weeks, similar to the induction dosing recommended for patients with active psoriatic arthritis. Additional doses may be considered at 10-14 weeks, depending on the treatment response. However, infliximab has not been specifically studied for managing paradoxical reactions in tuberculosis.[50]

In adults, infliximab remains detectable in the serum for at least eight weeks following a single 5 mg/kg dose. In children aged two to six years, the median steady-state infliximab exposure may be approximately 40% lower than in adults. Infliximab is one of the most extensively reported anti-TNF-α agents for managing paradoxical reactions in adult TBM and has demonstrated a favourable safety profile in children when used to treat inflammatory bowel disease.[50]

Thalidomide is an alternative anti-TNF-α agent that has shown promise in observational studies involving children with complicated CNS TB, particularly when administered at low doses.[52]

An open-label study in South Africa demonstrated improved clinical and neuroimaging outcomes with escalating doses of thalidomide (6, 12, and 24 mg/kg/day) compared to historical controls, and the drug was generally well tolerated.[53] However, a subsequent randomised, double-blind, placebo-controlled trial using a 24 mg/kg/day dose was terminated prematurely due to adverse events and fatalities occurring exclusively in the thalidomide group. These findings led the authors to conclude that high doses of thalidomide are not suitable as adjunctive therapy for TBM in children.

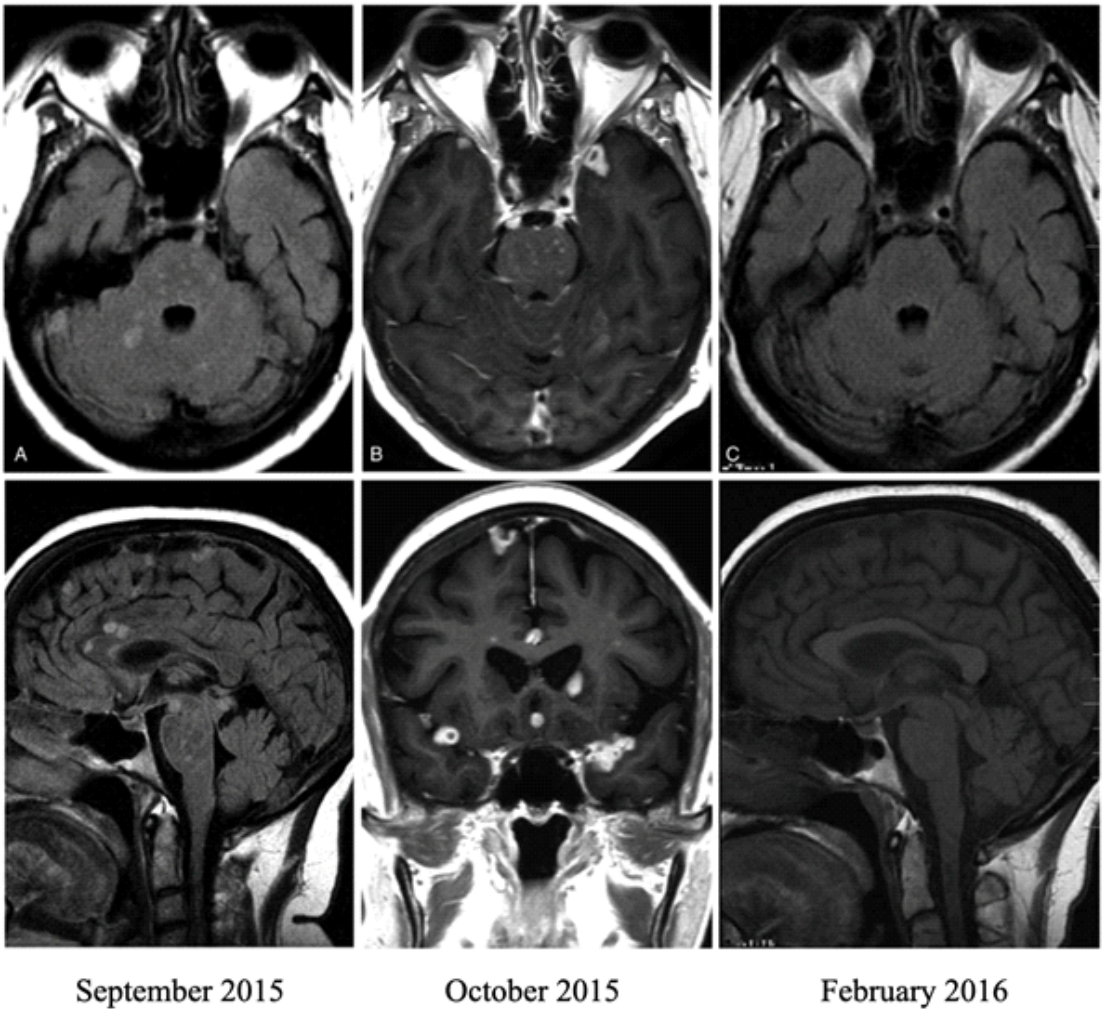

FIGURE 7 **Magnetic resonance imaging of the brain of a 53-year-old HIV-negative female microbiologically diagnosed with TBM in July 2015. Initial MRI of the brain without gadolinium contrast revealed no relevant findings. Axial and sagittal fluid-attenuated inversion recovery images without gadolinium (A) and axial and coronal T1-weighted images with gadolinium (B) performed five (September 2015) and eight weeks (October 2015) respectively after starting tuberculosis treatment, showing paradoxically developed multiple supra- and infratentorial lesions, distributed in the brain parenchyma and subarachnoid space. Axial and sagittal scans without gadolinium (C), taken after six weeks after receiving a three-dose course of infliximab, showing complete resolution of the tuberculomata.**[10]

Conversely, a case series involving 38 children treated with low-dose thalidomide (3-5 mg/kg), in addition to drug-susceptible anti-TB treatment and corticosteroids, reported favourable outcomes, further supporting the role of anti-TNF-α agents in managing paradoxical reactions.[54] Common adverse effects of thalidomide include maculopapular rash, peripheral neuropathy, elevated liver transaminases (without hepatic failure), and excessive sleepiness.[55]

A review of the literature involving 24 patients with paradoxical reactions in CNS TB found that TNF-α antagonists were generally well tolerated, with the exception of thalidomide. Severe adverse events occurred in 5.9% of patients treated with infliximab, primarily due to hypersensitivity, compared to 50% in those receiving thalidomide, mainly due to peripheral neuropathy. The high incidence of peripheral neuropathy, coupled with the difficulty of early detection in patients with existing neurological impairments, suggests that thalidomide is not suitable for managing severe paradoxical reactions.

Infliximab is therefore recommended as the preferred TNF-α antagonist for this indication. The favourable outcomes reported in most cases of paradoxical reactions, despite varying infliximab doses and treatment durations, suggest that effective control of these reactions does not require high doses or prolonged therapy.[56]

The duration of adjunctive anti-TNF-α therapy should be guided by clinical and radiological responses. In TBM, clinical improvement of mass lesions generally precedes radiological resolution, reflecting a reduction in perilesional inflammation.

Serial MRI studies using T2-weighted imaging have demonstrated that lesions progress from early-stage "T2 bright" abscesses with oedema to "T2 black" indicating a cure is underway.[57]

Although high-quality evidence is lacking, TNF antagonists are recommended by some experts for managing specific paradoxical reactions. These include corticosteroid-unresponsive optochiasmatic arachnoiditis causing visual impairment or optic disc pallor, enlarging TB abscesses despite corticosteroid therapy, large TB abscesses or tuberculomata in critical regions like the brainstem that are not amenable to surgical drainage and unresponsive to corticosteroids, and large dural-based TB abscesses causing focal-onset seizures. These recommendations are based on expert opinion and consensus. Treatment decisions should be individualised, guided by clinical judgment and tailored to the specific circumstances of each case.[58]

3. Cyclophosphamide

Cyclophosphamide, a potent immunosuppressive agent, effectively inhibits both humoral and cell-mediated immune responses. In guinea pigs immunised with mycobacteria, cyclophosphamide administration led to a temporary suppression of cutaneous hypersensitivity to tuberculin protein by significantly depleting lymphoid cells. In vivo cell transfer studies further demonstrated that cyclophosphamide-treated recipients exhibited transient unresponsiveness to purified tuberculin protein.[59]

Cyclophosphamide has shown potential in treating arachnoiditis involving the spinal cord and optic nerve/chiasm, particularly in cases unresponsive to other therapies.[60,61] In a case series of four patients, intravenous cyclophosphamide was administered at a dose of 500 mg/m² once a month for four months, resulting in significant clinical and radiological improvements in all cases.[60] However, its effectiveness in this context requires further validation due to concerns over its adverse effects, including the risk of TB reactivation as a potent immunosuppressive agent. A RCT is currently underway to evaluate its role in managing refractory arachnoiditis in CNS TB.[62]

4. Other Interventions

Intrathecal hyaluronidase

Intrathecal hyaluronidase (ITH) has been explored as a treatment for optochiasmatic and spinal arachnoiditis, although evidence is limited to two small case series and multiple case reports.[61]

Hyaluronidase works by breaking down glycosaminidase bonds in hyaluronic acid and other mucopolysaccharides in the extracellular matrix, thereby preventing the organised of exudates. In an early study from 1980, ITH was used as an adjuvant therapy for optochiasmatic arachnoiditis, with visual improvement observed in three out of seven patients.[63] However, the patients in this study were treated with older antitubercular drugs such as streptomycin, isoniazid, and thioacetazone.

More recently, a 2020 retrospective review reported outcomes for 11 patients with optochiasmatic arachnoiditis treated with adjuvant ITH at a dose of 1,500 IU weekly for 10 weeks. All patients demonstrated either complete or partial visual improvement.[64] These encouraging results suggest that ITH has potential as a therapeutic option, and its role warrants further investigation in prospective RCTs.

Surgery

The role of neurosurgery in managing paradoxical optochiasmatic arachnoiditis remains a subject of debate, as clinical deterioration may occur following initial temporary improvement. Surgical lysis of adhesions can be considered in cases where medical therapy proves ineffective or when there is diagnostic uncertainty.[30]

Different ATT regimens

Currently, there is no evidence to support that modifications to ATT – such as extending regimens, increasing doses, or employing alternative agents – reduce the risk of paradoxical reactions in CNS tuberculosis. Since these reactions are primarily driven by antigen load and immune reconstitution, such strategies are unlikely to be effective in prevention. Further research is required to better understand the underlying mechanisms and to develop more targeted interventions.[6]

5. Management of CNS TB – IRIS in HIV positive patients

Many immunomodulatory therapies have been investigated for the treatment of CNS TB-IRIS in HIV-positive patients; however, high-quality evidence remains scarce. Clinical trials for TB-IRIS often exclude patients with CNS involvement, creating a significant gap in robust data.[33]

An observational study reported that 18 out of 21 patients with CNS TB-IRIS treated with corticosteroids showed initial improvement within a median of 10 days. However, in a non-controlled cohort of 34 TB meningitis patients, prednisone at a dose of 1.5 mg/kg/day failed to prevent the onset of TBM-IRIS. [39]

The limited efficacy of corticosteroids in CNS TB contrasts with their greater effectiveness in non-CNS TB-IRIS, where they more successfully modulate peripheral immune responses.

This disparity suggests that CNS TB-IRIS may require stronger or more targeted immunomodulatory therapies, potentially due to differences in immune response dynamics or the difficulty of achieving therapeutic drug concentrations in the CSF.[33]

In severe cases where corticosteroids prove ineffective, TNF-α inhibitors such as infliximab and adalimumab have demonstrated success, as reported in several case studies. Thalidomide is generally reserved for the most severe corticosteroid-refractory cases.[65-68]

Outcomes and prognosis

Patients with CNS tuberculosis who develop paradoxical reactions often face increased mortality and significant long-term neurological deficits. These reactions, particularly in the context of CNS TB, can lead to severe complications such as hydrocephalus, brain infarctions, and spinal involvement, causing lasting damage even after the infection is managed. In a follow-up cohort study of TBM patients, 35% of those who experienced paradoxical reactions succumbed to the disease, while 18% were left with persistent neurological impairments.[6]

The prognosis of CNS tuberculosis complicated by paradoxical reactions is influenced by several factors, including the severity of the reaction, the timeliness of diagnosis, and the effectiveness of the treatment regimen. Delayed recognition or misdiagnosis can result in irreversible neurological damage. Additionally, the location and extent of CNS involvement – such as multiple lesions, cerebral oedema, or optochiasmatic involvement – are strong predictors of poor long-term outcomes.[5,6]

Long-term follow-up is critical for patients recovering from CNS TB-IRIS to monitor for relapses and manage residual neurological effects, which may require rehabilitation and supportive care. Further research is needed to develop more targeted therapies and reliable biomarkers for early detection of paradoxical reactions to improve patient outcomes and mitigate the long-term impact of CNS tuberculosis.

CONCLUSION

Paradoxical reactions in CNS TB present a significant clinical challenge, complicating treatment and contributing to high morbidity. Early diagnosis and timely administration of corticosteroid therapy are essential for mitigating their effects, while biologic agents such as TNF-α antagonists show promise for managing refractory cases. Despite these advances, robust evidence on the optimal management of paradoxical reactions remains limited, highlighting the urgent need for further research into their immunopathology.

The development of targeted therapies and personalised treatment strategies will be pivotal in improving outcomes for patients with CNS TB. Additionally, establishing evidence-based guidelines will equip clinicians with the tools needed to effectively navigate these complex and challenging cases.

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