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Challenges and Limitations of Conventional Diagnostic Techniques in Central Nervous System Tuberculosis

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Abstract:
The extrapulmonary form of tuberculosis (EPTB) is one of the most devastating and life-threatening complications, with central nervous system tuberculosis (CNS-TB) causing high mortality and leaving neurological sequelae. The timely diagnosis is a key factor in patient's survival and therapeutic response. In spite of these, there are significant limitations in the sensitivity, specificity and turnaround time of the conventional diagnostic techniques such as smear microscopy of CSF, culture methods, biochemical analysis and radiological imaging. Due to the paucibacillary nature of CNS-TB, clinical overlap with other neurological diseases, and delayed laboratory confirmation, misdiagnosis and late diagnosis of CNS-TB occur. Although smear microscopy was reported to be less sensitive because of low bacillary load in CSF, culture techniques was reported to be the gold standard, but it was time consuming and result in delayed results that are not suitable for urgent clinical management. Likewise, imaging does not have any disease specific characteristics and may simulate fungal, bacterial, neoplastic or inflammatory lesions. Diagnostic challenges are exacerbated by the lack of sufficient laboratory services, availability of high-level diagnostic facilities and technical expertise, in resource-constrained environments. The major limitations of current methods of diagnosis in CNS-TB are critically reviewed and the implications for clinical decision making are emphasized. The importance of developing the diagnostic algorithms that combine rapid molecular technologies with standard ones to optimize early diagnosis and reduce disease burden is also discussed.

Keywords: Central nervous system tuberculosis, tuberculous meningitis, conventional diagnostics, smear microscopy, cerebrospinal fluid culture, diagnostic limitations, CNS-TB.

I. INTRODUCTION

Central nervous system tuberculosis (CNS-TB) is one of the most devastating and most lethal forms of extrapulmonary tuberculosis and is responsible for a considerable proportion of the neurological morbidity and mortality, globally [1]. It mainly involves tuberculous meningitis (TBM), intracranial tuberculomas, spinal arachnoiditis and tuberculous brain abscesses, of which tuberculous meningitis is the most common and most severe [2]. Although there have been significant developments in TB control programmes, CNS-TB remains a significant clinical problem especially in low and middle-income countries where TB prevalence is high and health services are poor [3].

The mechanism of spread of M. tuberculosis from a primary pulmonary or extrapulmonary focus to the CNS is hematogenous spread to the meninges or brain parenchyma [4]. When the subependymal and/or subpial tubercles rupture into the subarachnoid space, an acute inflammatory response ensues that results in meningeal exudates, vasculitis, hydrocephalus, infarction, and progressive neurological deterioration [5]. Often, delayed diagnosis and the start of treatment lead to serious complications like cranial nerve palsies, cognitive deficits, seizures, stroke, and permanent neurological dysfunction [6].

The diagnosis of CNS-TB is difficult with non-specific clinical symptoms and overlaps with bacterial, viral, fungal and autoimmune neurological diseases [7] particularly in the early stages. The onset of symptoms might be insidious, and differentiation with other central nervous system infections may be very difficult particularly for the presence of fever, headache, vomiting, neck stiffness, altered mental status, and focal neurological deficits [8]. Furthermore, the CSF is paucibacillary in most cases and it is very difficult to confirm it by conventional microbiological techniques, which makes microbiological confirmation difficult [9].Conventional In many health care facilities, the current diagnostic methods are still basing on smears microscopy, culture of CSF, biochemical analysis, cytological examination and neuroimaging [10]. The methods mentioned, however, have several drawbacks, including lack of sensitivity, low specificity, lengthy turnaround time and technical expertise requirements [11]. However, smear microscopy often shows very low detection rates due to the low bacillary load in CSF samples [12]. In the same way, culture methods, which are regarded as the gold standard in microbiology, can take several weeks to grow the bacteria and make important therapeutic decisions.

Radiological imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) may be helpful in diagnosis of CNS-TB but do not have pathognomonic features [14]. Abnormalities on imaging such as hydrocephalus, basal meningeal enhancement, infarctions and ring-enhancing lesions can also be seen in other disorders, such as fungal infections, malignancies, pyogenic meningitis and neurocysticercosis, making it difficult to make a diagnosis [15]. In addition, biochemical parameters of CSF like increased protein, decreased glucose and lymphocytic pleocytosis are not specific for the disease and can be present in many inflammatory neurologic diseases [16].

Conventional methods are also hindered by their diagnostic challenges, particularly when atypical presentations and altered immune responses occur in immunocompromised populations, HIV infected people and children [17]. However, in resource-poor environments, early detection and effective disease management is still limited due to poor laboratory facilities, poor training for laboratory personnel, and the absence of advanced diagnostic tools [18].

With all these significant constraints, traditional methods of diagnosis can often be inadequate to ensure timely and accurate diagnosis of CNS-TB. The impact of delayed diagnosis on mortality and neurological outcomes is very consistent [19]. Evaluation of the problems with the traditional diagnostic methods is therefore necessary to enhance the clinical decision making process and to make more sensitive molecular diagnostic technologies available in daily use [20].

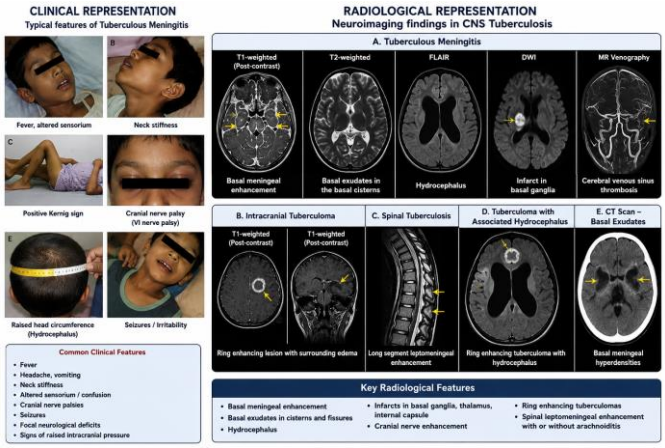

Fig 1: It shows the main clinical and radiological features of central nervous system tuberculosis with special reference to tuberculous meningitis. It points out the typical neurological signs and MRI/CT findings like basal meningeal enhancement, hydrocephalus, infarction, and ring enhancing tuberculomas, which help in diagnosis and evaluation of the disease.

II.CONVENTIONAL DIAGNOSTIC TECHNIQUES IN CNS TUBERCULOSIS

Central nervous system tuberculosis (CNS-TB) is one of the most difficult diagnoses to make in infectious neurology, due to its vague clinical presentation, low bacillary load and overlap with other neurological disease processes. Despite the emergence of new molecular diagnostic tools, conventional methods still remain a cornerstone of diagnosis and treatment of CNS-TB, especially in resource-constrained settings such as developing countries [1]. These include the smear microscopy of cerebrospinal fluid (CSF), culture methods, biochemical and cytological analysis, neuroimaging imaging and immunological tests. Despite their common use in routine clinical practice, each of the traditional methods has its own limitations in terms of sensitivity, specificity and time.Cerebrospinal Fluid (CSF) Smear Microscopy

One of the oldest and most widely used conventional smear microscopy techniques that can be used to detect Mycobacterium tuberculosis in CSF specimens is the Ziehl–Neelsen (ZN) smear microscopy [3]. It is based on the acid fastness of cell walls of mycobacteria which resist the action of the acid-alcohol solution. After staining, acid fast bacilli (AFB) will be bright red rods, surrounded by a blue background, under the microscope [4].

If the diagnosis of tuberculous meningitis is suspected, CSF is first centrifuged to concentrate the bacilli before taking a smear. Although not sensitive or expensive, smear microscopy shows very poor sensitivity in CNS-TB, which is a paucibacillary disease [5]. Bacilli may be too few in the CSF and there is a high false-negative rate. The sensitivity can be increased with repeated lumbar puncture and examination of larger CSF volumes, but this is not always feasible in patients with a critical illness [6].

Another drawback is that it is operator dependent. It is important to know that the quality of staining and interpretation of the microscopic appearance could significantly affect the outcome of the testing and that it can only be performed by experienced laboratory personnel who recognize acid fast bacilli. Moreover, smear microscopy is not able to distinguish between living and dead cells, and gives no resistance data [8].

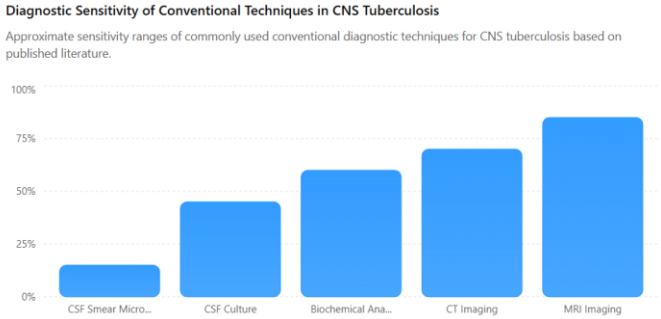

Figure 2 *Comparative diagnostic sensitivity of the conventional diagnostic techniques in central nervous system tuberculosis. The paucibacillary nature of CSF specimens results in the lowest sensitivity of CSF smear microscopy, while the characteristic neuroinflammatory changes seen on MRI result in relatively higher utility.*

A. Cerebrospinal Fluid Culture Techniques

Culture techniques are considered the gold standard in microbiologic diagnosis of tuberculosis infection because they enable direct isolation and identification of Mycobacterium tuberculosis [9]. The Lowenstein–Jensen (LJ) solid media and liquid culture systems like the Mycobacteria Growth Indicator Tube (MGIT) are conventional culture methods used [10].

Lowenstein–Jensen culture medium is used for slow growing mycobacteria; it takes 4-8 weeks for filaments to become visible [11]. The typical growth pattern of M. tuberculosis is rough, buff and dry appearance of the colonies. LJ culture is very specific but has a very long turnaround time, thus delaying initiation of treatment in CNS-TB where the early phase of treatment is important in reducing neurological complications [12].

To improve the speed of detecting mycobacterial presence in the system, the MGIT system was developed with fluorescent technology that detects respiration (oxygen consumption) during bacterial growth [13]. MGIT is more rapid and sensitive than LJ culture. But both methods have low bacillary concentration in CSF samples leading to low positivity rates [14].
Specialized biosafety laboratories and controlled incubation conditions are also needed, as well as trained microbiologists, for culture procedures. In many areas of the world with limited resources, it can be challenging to maintain these infrastructural needs, limiting the adoption of these systems on a broad scale [15]. The diagnostic yield can be further reduced if the specimens are contaminated during handling and before the initiation of any empirical anti-tubercular therapy [16].

B. Biochemical Analysis of Cerebrospinal Fluid

The CSF is processed routinely for biochemical markers which indirectly help evidence CM and is a necessary part of the evaluation of CNS-TB [17]. In CSF, there is a raised protein concentration, low levels of glucose, and a lymphocytic pleocytosis is typical [18].
CNS tuberculosis typically has high protein levels, due to the disruption of the blood–brain barrier and inflammatory exudation into the subarachnoid space [19]. Inflammatory cells and mycobacteria increase glucose consumption in CSF, leading to a decrease in CSF glucose concentration [20]. Chronic granulomatous inflammation (as seen in a TB infection) is associated with a predominance of lymphocytes which is termed as lymphocyte predominance [21].
These biochemical investigations are suggestive of CNS-TB, but not specific. The same type of abnormalities could be seen in fungal meningitis, bacterial meningitis, viral encephalitis, carcinomatous meningitis and autoimmune neurological diseases [22]. Thus, biochemical diagnosis alone should not be used for the definitive diagnosis.
Patient immune status may also also influence interpretation. Patients with HIV infections and/or immunocompromised patients often have abnormal CSF profiles and this decreases diagnostic accuracy [23]. In addition, the CSF parameters may be normal or slightly abnormal in the early stages of TB meningitis, making the diagnosis difficult [24].

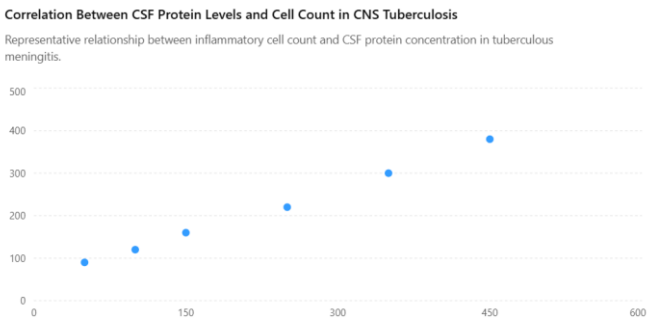

Figure 3 : The scatter plot shows that there is a positive correlation between the CSF protein concentration and the inflammatory cell count in CSFTB patients. The rising trend suggests that an association between increased cellular inflammatory response and increased CSF protein concentration, resulting from disruption of the blood–brain barrier and chronic meningeal inflammation exists.

C. Cytological Examination of CSF

Cytological analysis is the microscopic examination of the cell components of CSF, which is used to evaluate patterns of inflammatory response [25]. The CSF is usually lymphocytic pleocytic with neutrophilia sometimes occurring early in the disease [26].
The elevation of cells is variable from patient to patient, and can be related to the severity of the disease. In advanced tuberculous meningitis, there are often chronic inflammatory changes with the presence of activated macrophages [27].

Although supportive, the advantage of cytology is that similar cellular responses are observed in a variety of infectious and inflammatory conditions of the CNS [28]. Hence, a cytological diagnosis should be always relied upon along with the clinical presentation and further laboratory investigations.

D. Neuroimaging Techniques

Neuroimaging is an important ancillary diagnostic tool in the diagnosis of CNS tuberculosis. Structural abnormalities of tuberculous meningitis and intracranial tuberculomas are often detected with computed tomography (CT) or magnetic resonance imaging (MRI) [29].

Due to its speed and capacity to show hydrocephalus, cerebral oedema, infarctions and basal meningeal enhancement, CT scanning is often the first imaging test performed [30]. However, CT has a lower sensitivity than MRI for the early detection of meningeal inflammation and small lesions of the parenchymal tissue [31].

Due to its enhanced ability to visualize intracranial lesions and greater soft tissue resolution, MRI is regarded as the best imaging modality to evaluate CNS-TB. Basal meningeal enhancement, ring-enhancing tuberculomas, hydrocephalus, cerebral infarction, cranial nerve involvement and spinal leptomeningeal enhancement are characteristic MRI findings [33]. Although these benefits, radiological signs of CNS tuberculosis are not pathognomonic. The imaging changes in fungal infection, pyogenic abscess, metastatic tumor, sarcoidosis, and neurocysticercosis share some common features [34]. Thus, interpretation of neuroimaging should be made in combination with microbiological and clinical evidence and is not sufficient for diagnosis.

The other key challenge is accessibility and affordability. Even though there are growing MRI facilities in many rural and poor communities where TB burden is highest, they are still lacking in many places [35].Tuberculin Skin Test (TST)

The Tuberculin Skin Test (Mantoux test) is an immunological method used to detect prior sensitization to *Mycobacterium tuberculosis* antigens [36]. Purified protein derivative (PPD) is injected intradermally, and delayed hypersensitivity response is assessed after 48–72 hours [37]. A positive TST may support suspicion of tuberculosis exposure; however, it cannot differentiate active CNS disease from latent infection [38]. False-positive reactions may occur due to Bacillus Calmette–Guérin (BCG) vaccination or infection with non-tuberculous mycobacteria [39]. Conversely, false-negative results are common in malnourished individuals, HIV-positive patients, and severe CNS-TB cases because of impaired immune response [40].

Therefore, the clinical utility of TST in CNS tuberculosis remains limited and primarily supportive rather than confirmatory.

E. Interferon-Gamma Release Assays (IGRAs)

Interferon gamma release assays are blood tests that assess T-cell immune response to specific antigens of tuberculosis [41]. These assays are more specific than TST, and are not affected by previous BCG vaccination [42].

However, like with TST, IGRAs also fail to reliably differentiate between latent tuberculosis infection and active CNS-TB [43]. People with compromised immune systems and children are also less sensitive [44]. Further, it is very expensive and requires laboratory amenities that are not readily available in all health systems in low-resource settings [45].

TABLE II. DATA ANALYSIS TECHNIQUES

Analysis Stage	Technique / Method	Purpose / Description	Criteria / Threshold
Data Screening	Missing Value Analysis, Outlier Detection	Ensure data quality and suitability for analysis	No significant missing values; outliers treated
Descriptive Statistics	Mean, Standard Deviation	Summarize respondent characteristics and variable distribution	–
Reliability Analysis	Cronbach's Alpha	Assess internal consistency of constructs	$\alpha \geq 0.70$
Construct Reliability	Composite Reliability (CR)	Evaluate reliability in SEM	≥ 0.70
Convergent Validity	Average Variance Extracted (AVE)	Measure extent of variance captured by constructs	≥ 0.50
Discriminant Validity	HTMT Ratio / Fornell–Larcker Criterion	Ensure constructs are distinct from each other	HTMT < 0.85
Measurement Model	Confirmatory Factor Analysis (CFA)	Validate factor structure of constructs	Factor loading ≥ 0.70
Model Fit Assessment	CFI, TLI, RMSEA, Chi-square/df	Evaluate overall model fit	CFI/TLI ≥ 0.90, RMSEA ≤ 0.08
Structural Model	SEM Path Analysis	Test hypothesized relationships	Path significance ($p < 0.05$)
Mediation Analysis	Bootstrapping (5000 samples)	Test indirect effect (H3 = IV → DV)	Significant indirect effect
Moderation Analysis	Interaction Term (IV × EV)	Examine moderating effect of employee experience	Significant interaction effect
Conditional Process	Hayes Model 14 / SEM	Test moderated mediation effect	Conditional indirect effects

III. LIMITATIONS OF SMEAR MICROSCOPY

Smear microscopy is still one of the least sensitive tests used for diagnosis of CNS-TB. The main drawback is the low number of bacilli in CSF (often below the liminal value of microscopy).

The sensitivity of CSF smear microscopy has been shown to vary from 10% to 20% especially if small volumes of CSF are examined. Repeated lumbar punctures and a quantity of CSF may be necessary for accurate diagnosis—but this is not always possible when a patient is critically ill. Also, poor centrifugation procedures and staining quality have a substantial impact on the diagnostic yield.

The other big issue is that of operator dependence. The microscopic interpretation must be made by skilled laboratory staff and interobserver variation may be a factor. Lack of trained microbiologists and the lack of adequate laboratory equipment further compromise reliability in resource-limited health care environments.

Further, smear microscopy cannot differentiate between viable and nonviable bacilli and will not give information on drug resistance. This therefore makes it possible that a smear microscopy based diagnosis may be falsely negative and therapy may be delayed.

TABLE II. LIMITATIONS OF SMEAR MICROSCOPY

S. No.	Limitation	Description	Impact on Diagnosis
1	Low Sensitivity	Requires a high bacillary load ($\geq 10^4$ bacilli/mL) for detection.	Many true positive cases with low bacillary load are missed (false negatives).
2	Low Detection Rate in Paucibacillary Specimens	CSF and other extrapulmonary samples usually contain very few bacilli.	Smear is often negative in CNS tuberculosis and other paucibacillary forms.
3	Operator Dependency	Accuracy depends on the skill, experience and attention of the microscopist.	High inter-observer variability and possibility of human error.
4	Poor Specificity	Cannot differentiate *Mycobacterium tuberculosis* from non-tuberculous mycobacteria.	May lead to misinterpretation and inappropriate management.
5	Inability to Assess Viability	Detects both live and dead bacilli.	Cannot differentiate between active disease and past or treated infection.
6	Lower Sensitivity Compared to Culture and NAAT	Smear microscopy is less sensitive than culture and molecular methods.	Higher chances of false negative results compared to advanced techniques.
7	Requires High Quality Sample	Poor quality, insufficient or improperly collected samples reduce yield.	Increases false negative rate and reduces diagnostic reliability.
8	Non-uniform Distribution of Bacilli	Uneven distribution of bacilli in specimens may be missed in the examined smear area.	False negative results even in bacillary positive cases.
9	Biosafety Risk	Preparation and staining involve handling of infectious material.	Risk of laboratory-acquired infection if precautions are inadequate.
10	Limited Diagnostic Value in Early Disease	Bacillary load is often low in early or extrapulmonary disease.	Smear microscopy has limited value for early detection.

IV. CHALLENGES ASSOCIATED WITH CSF CULTURE

Culture methods are considered microbiological gold standard for tuberculosis diagnosis due to their high specificity. But their utility in the treatment of CNS-TB is severely restricted due to their prolonged turn around time and low sensitivity. The bacterial growth takes 4-8 weeks in Lowenstein–Jensen cultures and is a bit more rapid in the MGIT system but still takes several days to a couple of weeks. These delays are not clinically acceptable in CNS-TB as neurological deterioration can be rapid.

Another significant restriction is sensitivity. Culture positivity in tuberculous meningitis is not high even in optimal conditions due to low concentration of bacilli in CSF. Empirical ATT prior to commencing culture may further reduce culture yield. The potential for contamination is also a major concern. Culture integrity can be a problem if the specimens are not handled or stored properly, and if they are not transported safely, especially in peripheral laboratories without biosafety facilities.

In addition, these culture facilities are costly and in need of specially designed containment laboratories and are not available in many rural and low-resource areas with the highest burden of TB.

V. LIMITATIONS OF BIOCHEMICAL AND CYTOLOGICAL ANALYSIS

The biochemical parameter of CSF in routine analysis of CNS-TB usually shows signs of raised protein, low glucose and lymphocytic pleocytosis. These findings can aid in clinical suspicion but are very non-specific and share a large number of common features with many inflammatory and infectious neurological diseases. Fungal meningitis, bacterial meningitis, carcinomatous meningitis and viral encephalitis may have similar CSF disease profiles, for instance. As such, a biochemical analysis can not be used for a definite diagnosis.

There is also some intra-individual immune response variability, making the interpretation more complicated. Atypical CSF findings can occur with HIV-positive patients and immunocompromised persons, making diagnosis uncertain.

Moreover, none of the biochemical markers have sufficient sensitivity and specificity to confidently identify CNS-TB. Thus, the clinicians often have to rely on the routine CSF parameters in a situation of uncertainty.

VI. RADIOLOGICAL CHALLENGES IN CNS TUBERCULOSIS

Neuroimaging is of key importance in the diagnosis of structural abnormalities related to CNS-TB, but radiological features are seldom pathognomonic.

Basal meningeal enhancement, hydrocephalus, tuberculomas, and cerebral infarctions can also be seen on MRI in fungal infections, malignancies, neurosarcoidosis, and pyogenic meningitis. Likewise, ring-enhancing lesions that can be seen on a CT scan can be confused with metastatic tumors or neurocysticercosis. Radiologist expertise and clinical correlation may play a key role in interpreting imaging results. Diagnostic bias in endemic areas can result in either overtreatment or over-under treatment without microbiological diagnosis.

Another restriction is access. MRI facilities are still not available in many developing areas and high MRI cost becomes a challenge for the economically less well off population. Late diagnosis and poor prognosis are due to delayed imaging.

VII. DIAGNOSTIC DIFFICULTIES IN PEDIATRIC AND HIV-POSITIVE POPULATIONS

Even worse diagnostic tests have been shown in children and those with compromised immune systems. Suspicion of the disease is often late, as the children may have non-specific symptoms like irritability, poor feeders, fever, and altered consciousness. Collecting sufficient CSF samples in children is also difficult. HIV-positive people have abnormal inflammatory responses that cause abnormal CSF findings and decreased granuloma formation. Differential diagnosis is complicated by coinfections, like cryptococcal meningitis.

Conventional tests are thus found to be much less sensitive in these vulnerable groups, and lead to an increased risk of diagnostic delay and death.

VIII. FUTURE PERSPECTIVES & CONCLUSION

While conventional diagnostic tools still have a place in the diagnosis of CNS-TB, the shortcomings of these methods highlight the need for faster, more sensitive and specific methods. Molecular diagnostics using GeneXpert MTB/RIF, Xpert Ultra, line probe assays and next-generation sequencing have shown to have better diagnostic performance and shorter turnaround time.

Integrated diagnostic strategies incorporating clinical assessment, radiology, microbiology and molecular testing should be directed in the future. There is a special need for the development of low-resource friendly affordable point-of-care technologies.

In the near future, advances in imaging interpretation with artificial intelligence, in biomarker-based assays and in profiling host immune responses could further improve diagnostic accuracy. The current

diagnostic methods of C.S.Tb continue to have significant limitations and are still poorly effective in diagnosing the disease early and correctly. Smear microscopy has poor sensitivity, culture methods are time-consuming, biochemical tests are not specific, and the radiological appearances are often similar with other neurological disorders. These challenges are exacerbated in resource limited and pediatric and HIV populations.

While they remain in use in clinical practice, the conventional practice is not enough to deal with the complexity of the diagnosis of CNS-TB. Late diagnosis is a major cause of death, brain damage and long-term disability. Hence, it is important to enhance the diagnostic facilities to combine conventional and molecular rapid diagnostic methods to enhance the clinical outcomes and minimize the global burden of CNS TB.

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