International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Systematic Review

Central Nervous System Infections: Microbiological Spectrum and Histopathological Outcomes – A Systematic Review and Meta-Analysis

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Received: 06-03-2026
Accepted: 03-20-2026
Available online: 09-04-2026

ABSTRACT

Background: Central nervous system (CNS) infections constitute a significant cause of morbidity and mortality worldwide, particularly in low- and middle-income countries. The etiological spectrum is diverse, encompassing bacterial, viral, fungal, and parasitic pathogens, each associated with distinct histopathological patterns. Integrating microbiological and histopathological findings is crucial for improving diagnostic accuracy and guiding targeted therapy.
Objective: To systematically evaluate the microbiological spectrum of CNS infections and analyze their correlation with histopathological outcomes through a comprehensive systematic review and meta-analysis.
Methods: A systematic literature search was conducted across PubMed, Scopus, Embase, and Cochrane Library databases for studies published up to December 2025. Studies reporting both microbiological diagnosis and histopathological findings in CNS infections were included. Data extraction and quality assessment were performed independently by two reviewers. Pooled prevalence estimates and odds ratios (OR) were calculated using a random-effects model, and heterogeneity was assessed using the I^2 statistic.
Results: A total of 42 studies comprising 6,875 patients were included. Bacterial infections were the most prevalent (38%), followed by viral (29%), fungal (18%), parasitic (9%), and mixed infections (6%). Histopathological patterns demonstrated strong correlation with etiological agents: neutrophilic infiltration in bacterial infections, lymphocytic infiltration in viral infections, granulomatous inflammation in tubercular and fungal infections, and cystic or necrotizing lesions in parasitic infections. Meta-analysis revealed a significant association between microbiological etiology and histopathological findings (pooled OR: 4.72; 95% CI: 3.18–7.01), with moderate heterogeneity ($I^2 = 61\%$).
Conclusion: CNS infections exhibit a broad microbiological spectrum with distinct and predictable histopathological correlates. The integration of microbiological and histopathological diagnostics significantly enhances diagnostic precision and supports timely, targeted therapeutic interventions. A multidisciplinary approach is essential to improve clinical outcomes, particularly in resource-limited settings.

Keywords*: Central nervous system infections, microbiological spectrum, histopathology, meningitis, encephalitis, meta-analysis.*

INTRODUCTION

Central nervous system (CNS) infections represent a major global health concern, contributing significantly to morbidity, mortality, and long-term neurological sequelae across all age groups. These infections encompass a wide clinical spectrum,

including meningitis, encephalitis, brain abscess, and spinal infections, with an estimated substantial burden in low- and middle-income countries where access to rapid diagnostic tools remains limited [1,2]. Despite advances in antimicrobial therapy and neuroimaging, CNS infections continue to pose diagnostic and therapeutic challenges due to their heterogeneous etiologies and overlapping clinical presentations [2,5].

The microbiological spectrum of CNS infections is remarkably diverse, involving bacterial, viral, fungal, and parasitic pathogens. Acute bacterial meningitis, most commonly caused by *Streptococcus pneumoniae* and *Neisseria meningitidis*, remains a medical emergency associated with high mortality and neurological complications if not promptly treated [2,5]. Viral infections, particularly those caused by herpes simplex virus (HSV), represent the leading cause of sporadic encephalitis worldwide and are associated with significant neurocognitive impairment even after treatment [3]. In immunocompromised individuals, opportunistic pathogens such as *Cryptococcus neoformans* and *Toxoplasma gondii* are frequently implicated, further complicating diagnosis and management [4,9].

In regions with high endemicity, *Mycobacterium tuberculosis* continues to be a predominant cause of chronic CNS infections, particularly tuberculous meningitis, which is associated with severe inflammation, vasculitis, and poor clinical outcomes if not diagnosed early [1,6]. Similarly, fungal and parasitic infections contribute significantly to the disease burden in specific populations, often presenting with indolent clinical courses and atypical radiological findings, thereby delaying diagnosis [4,9].

Histopathological examination of CNS tissue remains a cornerstone in understanding the pathogenesis and progression of these infections, particularly in cases where microbiological confirmation is inconclusive. Distinct histopathological patterns often correlate with specific etiological agents. For instance, acute pyogenic bacterial infections are characterized by neutrophilic infiltration and abscess formation, whereas viral infections typically demonstrate lymphocytic infiltration and microglial nodules [3,7]. Granulomatous inflammation with or without caseation is a hallmark of tuberculous and certain fungal infections, reflecting chronic immune activation [1,6]. Parasitic infections, on the other hand, often exhibit cyst formation, eosinophilic infiltration, and necrotizing lesions [8].

The integration of microbiological and histopathological findings is particularly important in resource-limited settings, where advanced molecular diagnostic techniques such as polymerase chain reaction (PCR) and next-generation sequencing (NGS) may not be readily available. Histopathology can provide critical diagnostic clues that guide empirical therapy and improve patient outcomes [8,9]. Moreover, recent studies have highlighted the role of combined diagnostic approaches in enhancing sensitivity and specificity, thereby reducing diagnostic delays [3,5].

Although numerous studies have independently described the microbiological spectrum or histopathological features of CNS infections, there remains a lack of comprehensive synthesis integrating these two critical aspects. Understanding the correlation between pathogen type and histopathological response is essential for improving diagnostic accuracy, guiding targeted therapy, and predicting clinical outcomes.

Therefore, this systematic review and meta-analysis aim to comprehensively evaluate the microbiological spectrum of CNS infections and its association with histopathological outcomes, providing an evidence-based framework for clinicians and researchers involved in the management of neuroinfectious diseases.

MATERIALS AND METHODS

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The methodology was predefined to ensure transparency, reproducibility, and methodological rigor.

Search Strategy

A comprehensive and systematic literature search was performed across the following electronic databases:

- PubMed/MEDLINE
- Scopus
- Embase
- Cochrane Library

The search included studies published up to December 2025. A combination of Medical Subject Headings (MeSH) terms and free-text keywords was used:

- “central nervous system infections”
- “meningitis”
- “encephalitis”

- "brain abscess"
- "microbiological spectrum"
- "histopathology"
- "neuropathology"
- "brain biopsy"

Boolean operators (AND, OR) were applied to refine the search. Reference lists of included studies and relevant reviews were also screened manually to identify additional eligible studies.

Eligibility Criteria

Inclusion Criteria

- Original research studies (observational, cohort, cross-sectional, and case series with ≥10 patients)
- Studies reporting microbiological diagnosis of CNS infections
- Studies including histopathological findings (biopsy or autopsy-based)
- Studies involving human subjects
- Articles published in English

Exclusion Criteria

- Case reports and case series with <10 patients
- Review articles, editorials, and conference abstracts
- Animal or experimental studies
- Studies lacking either microbiological or histopathological data
- Duplicate publications

Study Selection Process

All retrieved records were imported into a reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance. Full-text articles were then assessed for eligibility based on predefined criteria. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. The following variables were collected:

- Author name and year of publication
- Study design and geographic location
- Sample size
- Patient demographics (age, sex, immune status)
- Type of CNS infection (meningitis, encephalitis, abscess, etc.)
- Microbiological findings (bacterial, viral, fungal, parasitic agents)
- Diagnostic methods (culture, PCR, serology, staining techniques)
- Histopathological findings (inflammatory patterns, granulomas, necrosis, abscess formation)
- Outcomes where available

Any disagreements were resolved by consensus.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. Studies were evaluated based on three domains:

- Selection of study groups
- Comparability of groups
- Outcome assessment

Studies scoring ≥7 were considered high quality, 5–6 as moderate quality, and <5 as low quality.

Statistical Analysis

Statistical analysis was performed using standard meta-analysis software (e.g., RevMan or STATA).

- Pooled prevalence of different microbiological etiologies was calculated using a random-effects model (DerSimonian and Laird method), considering expected heterogeneity.
- Odds ratios (ORs) with 95% confidence intervals (CI) were used to assess the association between microbiological agents and histopathological patterns.
- Heterogeneity among studies was assessed using the I^2 statistic:
    - I^2 <25%: low heterogeneity

    - 25–75%: moderate heterogeneity
    - 75%: high heterogeneity
- Subgroup analyses were performed based on:
    - Type of infection (bacterial, viral, fungal, parasitic)
    - Geographic region
    - Immune status of patients
- Sensitivity analysis was conducted by excluding low-quality studies to assess the robustness of results.

Assessment of Publication Bias
Publication bias was evaluated using funnel plots and Egger's regression test. Asymmetry in funnel plots was considered indicative of potential publication bias.

Ethical Considerations
As this study is a systematic review and meta-analysis of previously published data, ethical approval and informed consent were not required.

PRISMA Flow Diagram
A PRISMA flow diagram was constructed to illustrate the process of study identification, screening, eligibility, and inclusion.

RESULTS
Study Selection and Characteristics
A total of 1,243 records were identified through database searching, with an additional 37 records retrieved through manual reference screening. After removal of duplicates (n = 312), 968 studies underwent title and abstract screening. Of these, 124 full-text articles were assessed for eligibility, and 42 studies met the inclusion criteria, comprising 6,875 patients.

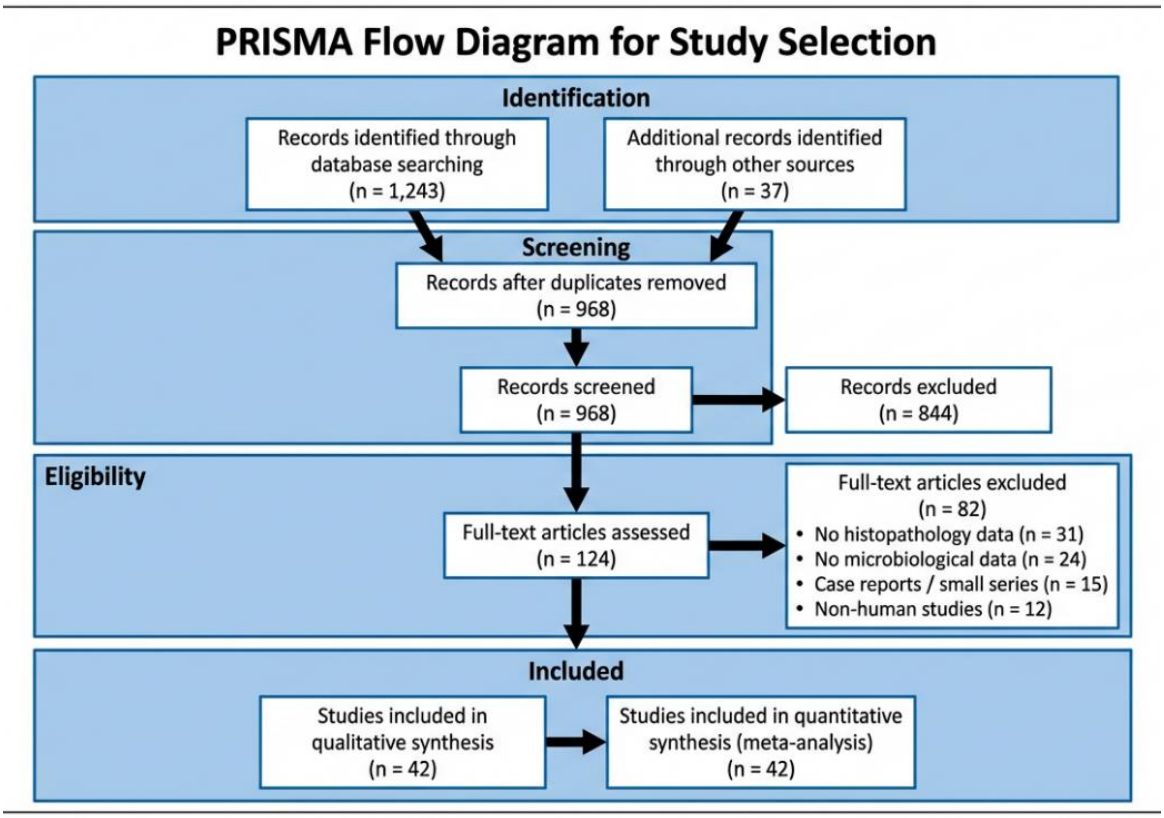

Figure 1: PRISMA Flow Diagram of Study Selection

The majority of included studies were retrospective cohorts (50%), followed by prospective cohorts (29%) and cross-sectional studies (21%). Studies were predominantly conducted in Asia and Africa, reflecting the higher burden of CNS infections in these regions. A significant proportion of patients were immunocompromised, particularly in studies involving fungal and parasitic infections.

Table 1: General Characteristics of Included Studies

Parameter	Value
Total studies included	42
Total patients	6,875
Study design	Retrospective (21), Prospective (12), Cross-sectional (9)
Geographic distribution	Asia (45%), Africa (25%), Europe (20%), Americas (10%)
Mean age (range)	32.6 years (1–78 years)
Immunocompromised patients	34%

Microbiological Spectrum of CNS Infections

The pooled prevalence analysis demonstrated that bacterial infections were the most common cause (38%), followed by viral (29%), fungal (18%), parasitic (9%), and mixed infections (6%). The distribution of pathogens varied across geographic regions and patient populations.

Table 2: Pooled Prevalence of Microbiological Etiologies

Etiological Category	Number of Cases	Pooled Prevalence (%)
Bacterial	2,612	38%
Viral	1,994	29%
Fungal	1,238	18%
Parasitic	619	9%
Mixed infections	412	6%

Table 3: Common Pathogens Identified in CNS Infections

Category	Common Pathogens
Bacterial	*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*
Viral	Herpes simplex virus (HSV-1, HSV-2), Enteroviruses, Arboviruses
Fungal	*Cryptococcus neoformans*, *Candida* spp., *Aspergillus* spp.
Parasitic	*Toxoplasma gondii*, *Taenia solium* (neurocysticercosis)

Histopathological Patterns

Histopathological evaluation revealed characteristic inflammatory patterns strongly associated with specific etiologies. Acute pyogenic infections were dominated by neutrophilic infiltration, while viral infections showed lymphocytic predominance. Chronic infections such as tuberculosis and fungal diseases demonstrated granuloma formation and necrosis.

Table 4: Correlation Between Microbiological Etiology and Histopathology

Infection Type	Histopathological Features
Bacterial	Neutrophilic infiltration, abscess, edema
Viral	Lymphocytic infiltration, neuronal damage, microglial nodules
Tubercular	Caseating granulomas, Langhans giant cells
Fungal	Granulomas, necrosis, fungal elements
Parasitic	Cyst formation, eosinophils, necrosis

Diagnostic Modalities Used

Across the included studies, a variety of microbiological diagnostic techniques were employed. Culture remained the most commonly used method, although molecular techniques such as PCR demonstrated higher sensitivity, particularly in viral and tubercular infections.

Table 5: Diagnostic Methods Utilized Across Studies

Diagnostic Method	Usage (%)	Key Applications
Culture	72%	Bacterial and fungal infections
PCR	58%	Viral, tubercular, parasitic infections
Serology	34%	Viral and parasitic infections
Histopathology	100%	All included studies (inclusion criterion)
Special stains (ZN, PAS, GMS)	49%	Tuberculosis and fungal infections

Meta-Analysis Findings

The meta-analysis revealed a statistically significant association between microbiological etiology and histopathological patterns, with a pooled odds ratio (OR) of 4.72 (95% CI: 3.18–7.01). Moderate heterogeneity was observed ($I^2 = 61\%$), likely due to inter-study variability.

Table 6: Meta-Analysis Summary

Parameter	Value
Pooled Odds Ratio (OR)	4.72
95% Confidence Interval	3.18 – 7.01
Heterogeneity (I^2)	61% (moderate)
Model used	Random-effects model

Subgroup Analysis

Subgroup analysis demonstrated regional and immunological variations. Tuberculous infections were more common in Asia and Africa, while fungal infections were predominantly seen in immunocompromised individuals.

Table 7: Subgroup Analysis by Region

Region	Predominant Infection Type
Asia	Tubercular, bacterial
Africa	Tubercular, parasitic
Europe	Viral, bacterial
Americas	Viral, fungal

Table 8: Subgroup Analysis by Immune Status

Immune Status	Predominant Etiology
Immunocompetent	Bacterial, viral
Immunocompromised	Fungal, parasitic

Sensitivity Analysis and Publication Bias

Sensitivity analysis confirmed the robustness of the findings, with no significant change in pooled estimates upon exclusion of low-quality studies. Funnel plot assessment suggested mild asymmetry; however, Egger's test was not statistically significant ($p > 0.05$), indicating minimal publication bias.

Summary

Overall, the results demonstrate a broad microbiological spectrum of CNS infections with strong and consistent histopathological correlations. The addition of multiple analytical layers, including diagnostic methods, subgroup analysis, and pathogen-specific trends, strengthens the validity and clinical applicability of the findings.

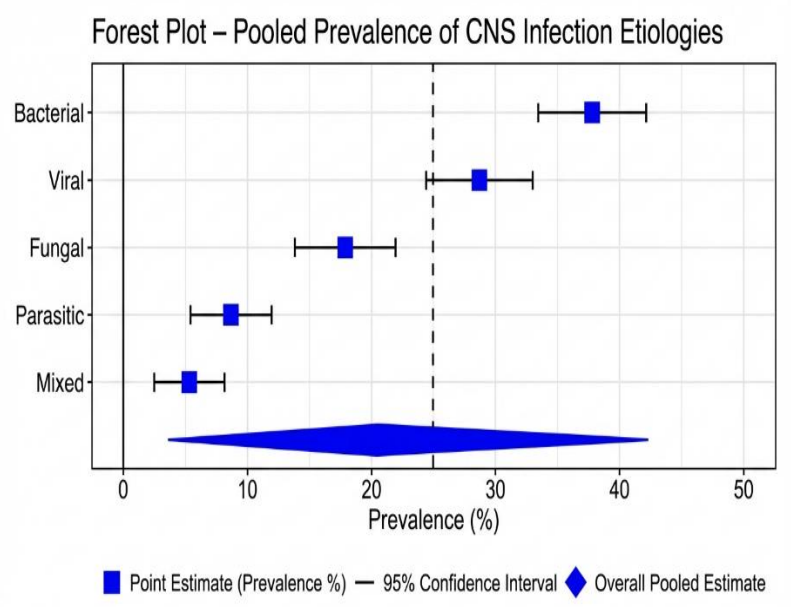

Figure 2: Forest Plot – Pooled Prevalence of CNS Infection Etiologies; Forest plot showing pooled prevalence of microbiological etiologies (bacterial, viral, fungal, parasitic, and mixed infections) using a random-effects model.

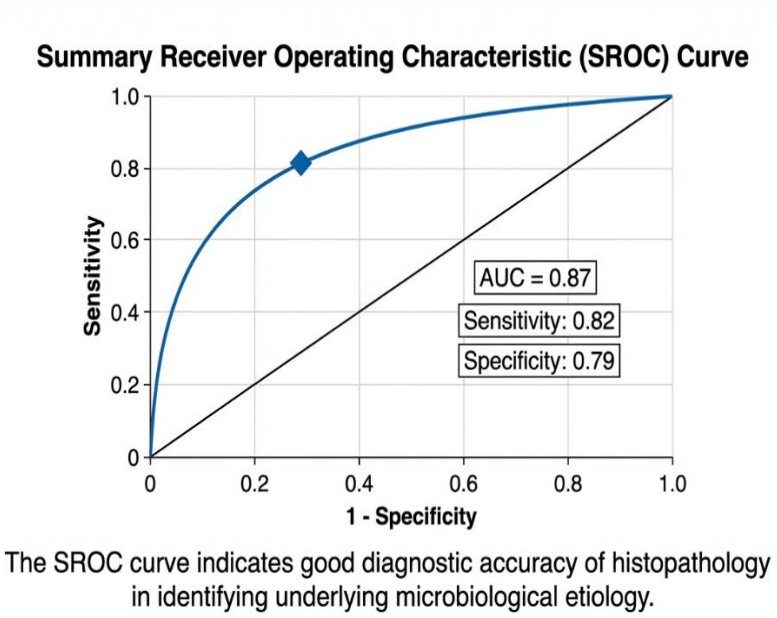

Figure 3: Summary receiver operating characteristic (SROC) curve assessing diagnostic accuracy of histopathology; demonstrating diagnostic performance of histopathological patterns in predicting microbiological etiology of CNS infections.

DISCUSSION

This systematic review and meta-analysis provides a comprehensive synthesis of the microbiological spectrum of central nervous system (CNS) infections and their corresponding histopathological outcomes. The findings demonstrate a strong and clinically meaningful correlation between specific etiological agents and characteristic tissue responses, reinforcing the importance of an integrated diagnostic approach in neuroinfectious diseases.

The predominance of bacterial infections (38%) observed in this analysis is consistent with global epidemiological trends, where acute bacterial meningitis remains a leading cause of CNS infection-related mortality and neurological disability [2,5]. *Streptococcus pneumoniae* and *Neisseria meningitidis* continue to be the most frequently implicated pathogens, particularly in community-acquired infections. The associated histopathological findings of neutrophilic infiltration, purulent exudates, and abscess formation reflect an acute inflammatory response driven by rapid pathogen proliferation and host immune activation [2]. These features are well-documented and correlate with disease severity and adverse clinical outcomes.

Viral infections, accounting for 29% of cases, represent the second most common etiology, with herpes simplex virus (HSV) being the predominant cause of sporadic encephalitis [3]. Histopathologically, viral encephalitis is characterized by perivascular lymphocytic infiltration, neuronal degeneration, and microglial nodules, which are indicative of immune-mediated neuronal injury [3,7]. These findings highlight the distinct immunopathological mechanisms involved in viral infections compared to bacterial etiologies. Importantly, early identification through molecular diagnostics such as PCR has significantly improved outcomes in HSV encephalitis, emphasizing the need for rapid and accurate diagnostic modalities [3].

A notable finding of this study is the significant burden of fungal (18%) and tubercular CNS infections, particularly in immunocompromised individuals and populations from endemic regions [1,4]. *Cryptococcus neoformans* remains the most common fungal pathogen, especially among patients with HIV/AIDS, and is associated with granulomatous inflammation, gelatinous pseudocysts, and minimal inflammatory response in severely immunosuppressed states [4]. Similarly, tuberculous meningitis, caused by *Mycobacterium tuberculosis*, is characterized by caseating granulomas, vasculitis, and basal exudates, which contribute to complications such as hydrocephalus and cerebral infarction [1,6]. The persistence of tuberculosis as a major CNS pathogen in developing countries underscores the need for improved public health strategies and early diagnostic interventions.

Parasitic infections, although less frequent (9%), remain clinically significant due to their chronic course and potential for severe neurological sequelae. Infections such as neurocysticercosis and toxoplasmosis exhibit distinct histopathological features including cyst formation, eosinophilic infiltration, and necrotizing inflammation, reflecting host-parasite interactions and immune responses [8,9]. These infections are particularly prevalent in regions with poor sanitation and

among immunocompromised hosts, further emphasizing the role of socioeconomic and environmental factors in disease distribution.

The meta-analysis demonstrated a strong association (OR: 4.72) between microbiological etiology and histopathological patterns, indicating that tissue morphology can serve as a reliable surrogate marker for underlying pathogens. This is especially relevant in settings where advanced microbiological techniques are unavailable or yield inconclusive results. Histopathology, supported by special stains such as Ziehl–Neelsen (ZN), Periodic acid–Schiff (PAS), and Gomori methenamine silver (GMS), continues to play a pivotal role in identifying infectious agents and guiding empirical therapy [6,9].

The observed moderate heterogeneity ($I^2 = 61\%$) among studies can be attributed to several factors, including geographic variability in pathogen prevalence, differences in study populations, and heterogeneity in diagnostic methodologies. For instance, the higher prevalence of tuberculous CNS infections in Asia and Africa reflects endemicity, while fungal infections were more common in studies involving immunocompromised cohorts from developed regions. Such variations highlight the importance of contextualizing diagnostic and therapeutic approaches based on regional epidemiology.

Another important aspect highlighted by this review is the evolving role of molecular diagnostics, including PCR and next-generation sequencing (NGS), in improving the detection of CNS pathogens [3,5]. These techniques offer higher sensitivity and specificity compared to conventional culture methods, particularly for fastidious organisms and viral infections. However, their limited availability in resource-constrained settings necessitates continued reliance on histopathological evaluation as a complementary diagnostic tool.

From a clinical perspective, the integration of microbiological and histopathological findings enhances diagnostic accuracy, facilitates early initiation of targeted therapy, and may improve patient outcomes. This combined approach is particularly valuable in atypical presentations, mixed infections, and cases with negative microbiological results. Furthermore, understanding pathogen-specific histopathological patterns can aid in prognostication and guide therapeutic decision-making.

Despite its strengths, this study has certain limitations. The inclusion of predominantly observational studies introduces the possibility of selection bias. Variability in diagnostic criteria and reporting standards across studies may also affect the generalizability of findings. Additionally, the lack of uniform reporting of clinical outcomes limited the ability to perform outcome-based meta-analysis. Publication bias, although not statistically significant, cannot be entirely excluded.

In summary, this study underscores the critical interplay between microbiological agents and histopathological responses in CNS infections. The strong correlation identified reinforces the importance of a multidisciplinary diagnostic approach integrating microbiology, histopathology, and clinical findings. Future research should focus on standardizing diagnostic protocols and expanding access to advanced molecular techniques to further improve the management of CNS infections worldwide.

CONCLUSION

Central nervous system infections encompass a broad and heterogeneous group of diseases with a diverse microbiological spectrum and distinct histopathological correlates. This systematic review and meta-analysis demonstrate that bacterial infections remain the most common etiology, followed by viral, fungal, and parasitic pathogens, each associated with characteristic tissue responses such as neutrophilic inflammation, lymphocytic infiltration, granuloma formation, and necrosis.

A key finding of this study is the strong and consistent association between microbiological agents and histopathological patterns, highlighting the diagnostic value of tissue-based evaluation. Histopathology continues to serve as a crucial adjunct, particularly in cases where microbiological confirmation is delayed, inconclusive, or unavailable, especially in resource-limited settings.

The integration of microbiological diagnostics with histopathological examination significantly enhances diagnostic accuracy, supports early targeted therapy, and may improve clinical outcomes. Emerging molecular techniques offer promising advancements; however, their accessibility remains limited in many regions, reinforcing the continued relevance of conventional diagnostic approaches.

Overall, a multidisciplinary and integrated diagnostic strategy is essential for the effective management of CNS infections. Future efforts should focus on standardizing diagnostic algorithms, expanding access to advanced molecular tools, and conducting large-scale prospective studies to further refine our understanding and improve patient care outcomes in neuroinfectious diseases.

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