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RESEARCH ARTICLE

The Neurological Renaissance: Elucidating the Complex Relationship between Syphilis and Neurodegenerative Disorders in the Contemporary Era

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Abstract

The global resurgence of syphilis has coincided with increasing evidence of complex interactions between *Treponema pallidum* infection and neurological disorders, extending beyond classical neurosyphilis manifestations. This perspective article synthesizes recent clinical and translational evidence on syphilis-associated neurological complications, focusing on (i) putative mechanisms linking infection to neurodegenerative trajectories (molecular mimicry and persistent neuroinflammation), (ii) clinical phenotypes that mimic autoimmune disease, and (iii) diagnostic challenges arising from atypical presentations and evolving biomarker strategies. Recent studies indicate that spirochetal infections may contribute to neuroinflammatory cascades associated with dementia, movement disorders, and psychiatric manifestations through molecular mimicry and persistent neuroinflammation. The increase in syphilis incidence, from 39.6 to 62.5 per 100,000 in the United States between 2019 and 2023, necessitates urgent reconsideration of screening protocols, particularly for populations presenting with unexplained neurological symptoms. We advocate for a paradigm shift toward comprehensive neurological evaluation in syphilis cases, enhanced surveillance for atypical presentations, and integration of advanced diagnostic biomarkers, including *Cerebrospinal Fluid* (CSF) CXCL13 and other emerging neuroinflammatory markers, with explicit attention to implementation barriers that limit global adoption.

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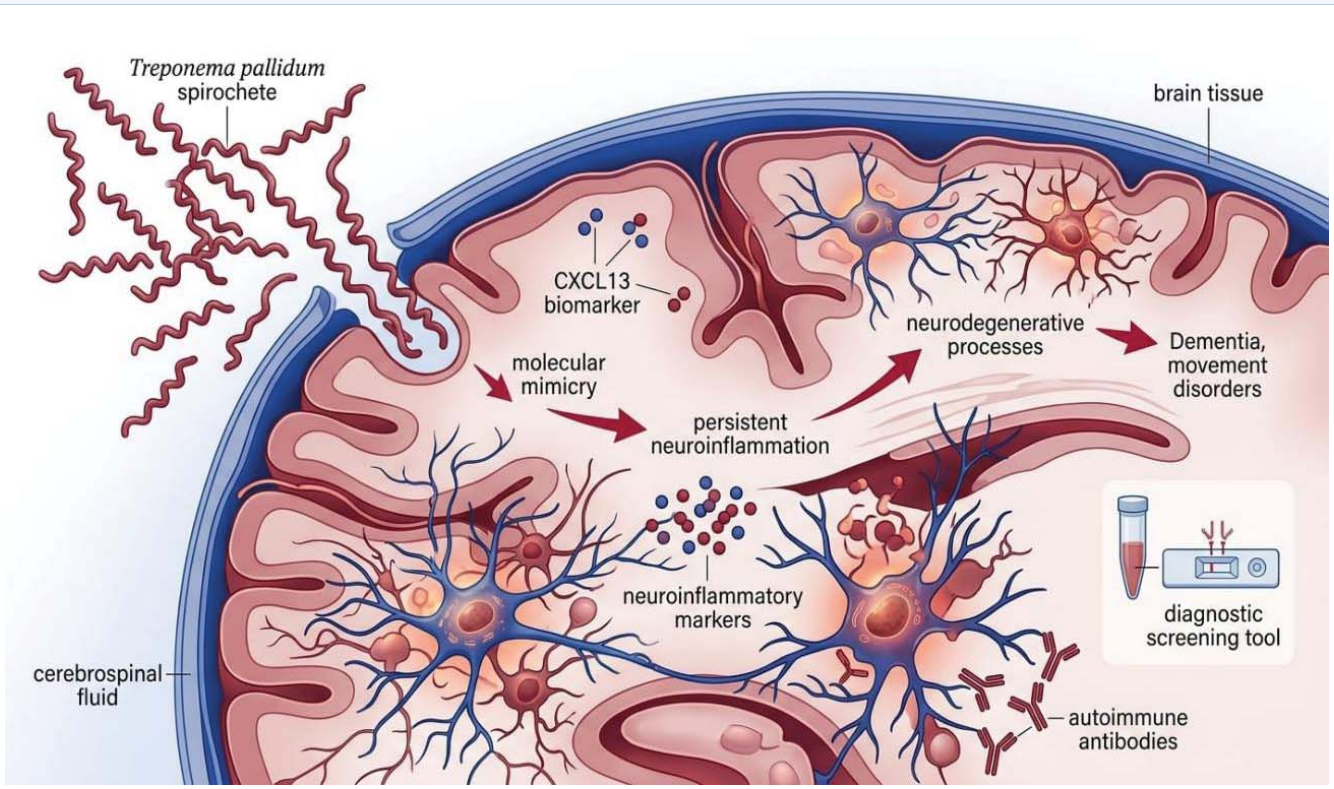

Introduction

Syphilis, historically termed "the great imitator," has re-emerged globally in parallel with substantial advances in neurology and neuroimmunology. Epidemiological data from the United States indicate a 58% increase in syphilis cases from 2019 to 2023 [1], representing both a public health resurgence and an evolving neurological challenge. This trend unfolds in the context of an aging global population in which neurodegenerative disorders are a growing health burden [2]. A central question emerges: is the return of syphilis merely coincident with this neurodegenerative burden, or does *Treponema pallidum* infection contribute to, trigger, or accelerate neurological deterioration in a subset of patients?

Multiple mechanistic hypotheses include molecular mimicry, in which treponemal antigens resemble host neural proteins and promote autoimmune-like responses, and persistent neuroinflammation. Systematic syntheses examining spirochetal infection and neurodegenerative outcomes support relationships extending beyond classical neurosyphilis categories [3], motivating the reconsideration of diagnostic and surveillance protocols.

The evolving spectrum of syphilis-associated neurological disorders

Beyond classical neurosyphilis: Traditional subtypes (asymptomatic, meningeal, meningovascular, *parenchymatous*) remain foundational [4,5], but do not capture the breadth of modern presentations.

Movement disorders: Systematic literature details syphilis-associated parkinsonism, dystonia, and chorea that can respond to antimicrobial therapy [6]. Such phenotypes challenge the assumption that neurosyphilis is mainly cognitive or sensory and underscore the risk of misclassifying treatable infection as primary neurodegeneration.

Autoimmune mimicry: Syphilis can clinically resemble multiple sclerosis, SLE,

and autoimmune encephalitides, complicating diagnostic accuracy and delaying infection-directed therapy [7].

Psychiatric manifestations: Psychiatric symptoms, including depression, psychosis, and cognitive impairment, may represent early neurological involvement, supporting low thresholds for syphilis testing in atypical neuropsychiatric syndromes [8].

Mechanistic pathways linking syphilis to neurodegenerative trajectories

Blood–brain barrier breach and neuroinvasion: *T. pallidum* may breach the BBB and trigger compartmentalized neuroimmune responses [9,10]. Key gaps include identifying which host and microbial factors govern CNS pathology and which biomarkers best reflect early neuroinvasion.

Persistent neuroinflammation: CSF proteomics reveal lysosomal and axonal protein dysregulation in neurosyphilis, suggesting ongoing cellular dysfunction [11]. Advanced neuroimaging can detect inflammatory lesions that are not apparent on conventional MRI [12].

Molecular mimicry: Autoimmune-like presentations may result from cross-reactivity between treponemal and neural antigens. Target antigens and immune mechanisms remain under investigation [7] (Figure 1).

This figure illustrates the hypothesized cascade of neurological damage initiated by *Treponema pallidum* infection. Following breach of the blood-brain barrier, two parallel cellular responses emerge: microglial activation and astrocytic response. These lead to neuroinflammation, blood-brain barrier dysfunction, molecular mimicry, and protein aggregation. The resulting autoimmune response and neurodegeneration converge into persistent neurological dysfunction. This model highlights the multifactorial nature of syphilis-associated neuroinflammatory damage and its potential role in chronic neurological disease.

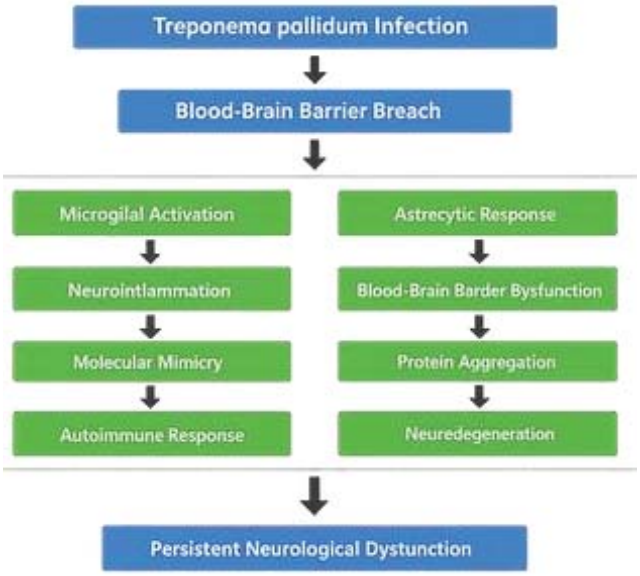

Figure 1 Proposed Pathogenic Pathways Linking Syphilis to Neurodegeneration.

Diagnostic revolution: Advanced biomarkers and implementation

Candidate biomarkers: CSF CXCL13 is a major diagnostic innovation, with meta-analytic evidence of sensitivity 89–95% and specificity 85–92% [13]. Other candidates: CXCL1/CXCL8 (inflammatory activity) [14], NFL/tau (neuronal injury) [15], IL-27/IL-17 (immune modulation) [16], and metabolomics (disease differentiation) [17] (Table 1).

Implementation barriers: Limited laboratory access, assay variability, regulatory challenges, and costs restrict routine adoption of CSF CXCL13 [13,18]. Solutions require harmonization, quality control, and pragmatic, resource-tiered protocols.

Practical diagnostic and follow-up considerations

- Testing: Include syphilis investigation in unexplained cognitive, neuropsychiatric, or movement presentations.
- CSF Evaluation: Use CXCL13 when indicated, especially with ambiguous findings [13,19].

Table 1: Novel diagnostic biomarkers for syphilis-associated neurological disorders.

Category	Marker	Use	Performance	Status
Chemokines	CSF CXCL13	Neurosyphilis diagnosis	Sensitivity 89 - 95%, specificity 85-92% [13]	Expanding clinical use
Inflammatory	CSF CXCL1, CXCL8	Disease activity	Under evaluation [14]	Research phase
Neuronal damage	CSF NFL, tau	Neurodegeneration	Initial findings [15]	Research phase
Immune regulation	IL-27, IL-17	Treatment response	Correlates with severity [16]	Research phase
Metabolomics	Multiple metabolites	Disease differentiation	~80 - 85% accuracy [17]	Research phase

- Follow-up: Baseline neurological assessment, followed by 6–12 month intervals post-treatment in the first two years, then annual reviews, adapting as clinically required.

Treatment and adjunct strategies

Penicillin remains first-line [20]. Observational data support corticosteroids for severe inflammatory responses [21]. Evidence to support neuroprotective adjuncts is preliminary [22].

Surveillance and health system preparedness

Scaling CXCL13 and similar diagnostics requires investment in laboratory and workforce infrastructure [18]. Surveillance must be updated to capture neurological syphilis and guide policy, especially for high-risk groups [23-25].

Conclusion

Modern syphilis must be recognized as producing a broad spectrum of neurological phenomena intersecting with neuroinflammation and degeneration. Translation of biomarkers into practice and an interdisciplinary approach are urgently needed to reduce avoidable neurological morbidity.

Author Contributions

All authors wrote sections of the manuscript, contributed to editing, and participated in the development, editing, and refinement of figures. A.K.J and V.A. conceived the central idea and coordinated manuscript development. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest

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