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Review Article

Reconsidering Alzheimer's Disease Through the Lens of Neurospirochetosis: Historical Precedent, Biological Plausibility, and Structural Barriers to Paradigm Shift

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Abstract

The identification of *Treponema pallidum* as the cause of general paresis in 1913 fundamentally reshaped the understanding of infectious contributions to dementia. This precedent invites reconsideration of infectious hypotheses in contemporary neurodegenerative disorders. In 2011, Miklossy proposed that Alzheimer's disease (AD) may represent a chronic neurospirochetosis, potentially involving *Borrelia* species. Accumulating evidence implicates microbial agents in amyloid deposition, neuroinflammation, and biofilm formation. Despite biological plausibility and more than partial fulfillment of causative criteria, infectious models remain peripheral to mainstream Alzheimer's research, which has largely centered on amyloid and tau pathways. This perspective examines the historical basis for infectious dementia, evaluates current evidence supporting spirochetal involvement in AD, explores structural and economic factors that may influence research prioritization, and argues for expanded, methodologically rigorous investigation into antimicrobial and anti-biofilm strategies as potential therapeutic avenues.

Keywords: Alzheimer's Disease; Neurospirochetosis; Borrelia; Neuroinflammation; Infectious Hypothesis; Biofilms; Paradigm Shift; Neurosyphilis

Introduction

In 1913, Hideyo Noguchi demonstrated *Treponema pallidum* in the brains of patients suffering from general paresis of the insane (GPI), conclusively establishing a spirochetal cause of progressive dementia [1]. The eventual introduction of penicillin dramatically reduced the incidence of neurosyphilitic dementia.

This historical precedent is instructive: a condition once categorized as degenerative or psychiatric was ultimately shown to be infectious. Given this background, the possibility that modern neurodegenerative syndromes may contain infectious components warrants serious consideration.

In 2011, Judith Miklossy proposed that Alzheimer's disease (AD) may represent a chronic neurospirochetosis [2]. Her analysis evaluated spirochetal involvement in AD using Koch's postulates and Hill's criteria for causation. This proposal raises foundational questions regarding etiology and research direction.

Historical Precedent: Neurosyphilis as a model

General paresis was once a leading cause of institutionalized dementia. Noguchi's work provided pathological confirmation of spirochetal invasion of brain tissue [1]. Subsequent antibiotic treatment demonstrated therapeutic reversibility in early-stage cases [3].

Three principles emerge:

- Chronic spirochetes can invade and persist in neural tissue.
- Infection-induced neurodegeneration can mimic primary degenerative disorders.
- Paradigm shifts require decisive pathological and therapeutic validation.

These principles inform contemporary infectious hypotheses of AD.

Evidence supporting infectious contributions to Alzheimer's disease

Spirochetal detection in AD brains

Miklossy and colleagues reported detection of spirochetes in AD brain samples and demonstrated induction of amyloid-like deposits *in vitro* following exposure to *Borrelia* species [2,4]. The findings suggest biological plausibility.

Amyloid as antimicrobial peptide

Amyloid-β has been shown to exhibit antimicrobial properties [5]. This reframes amyloid deposition as a potential innate immune response rather than solely a pathological driver. If amyloid functions defensively, chronic infection may be upstream of plaque formation.

Polymicrobial associations

Additional pathogens implicated in AD include:

- Herpes simplex virus type 1 (HSV-1) [6]
- *Porphyromonas gingivalis* [7]
- Fungal elements in brain tissue [8].

These data suggest AD may be heterogeneous, with infectious triggers contributing in at least a subset of cases.

Neuroinflammation, biofilms, and chronic infection

Chronic infection may promote:

- Microglial activation
- Cytokine dysregulation
- Oxidative stress
- Biofilm formation [9]

Biofilms are particularly relevant, as spirochetes are capable of forming protective aggregates resistant to immune clearance and antibiotic penetration [10]. Persistent inflammatory signaling may drive progressive neuronal damage.

The concept of mixed infection—including bacterial, viral reactivation, and fungal components—complicates single-pathogen models but does not negate infectious contribution.

Methodological and paradigm barriers

Heterogeneity of Alzheimer's disease

AD likely represents a spectrum of etiologies converging on similar pathological endpoints. Infectious causation in a subset may be masked within aggregate data.

Funding structures and incentive alignment

Biomedical research ecosystems often prioritize patentable therapeutics. Antimicrobial agents effective against spirochetes (e.g., doxycycline, ceftriaxone) are largely off-patent. Large randomized trials investigating generic agents may attract less commercial funding.

This does not require intentional suppression; structural incentive alignment may suffice to influence research direction.

Entrenched research models

The amyloid hypothesis has dominated AD research for decades [11]. Grant structures, academic careers, and institutional frameworks are often built around prevailing paradigms, which can slow integration of disruptive hypotheses especially when fraud is in the mix.

Institutional trust and controversy

Debate surrounding chronic Lyme disease illustrates tensions between patient experiences and public health consensus [12]. Allegations of past pathogen manipulation research, including at facilities such as Plum Island, have circulated in public discourse.

The COVID-19 pandemic intensified scrutiny of gain-of-function research and institutional transparency. While distinct from Alzheimer's etiology, such events shape public perception of infectious disease governance.

Scientific evaluation must remain evidence-based while acknowledging that transparency deficits can influence societal trust.

Therapeutic implications and research directions

To evaluate infectious contributions rigorously, the following are needed:

- Multi-center, blinded pathogen detection studies
- Stratified cohort analysis identifying infectious biomarkers
- Randomized antimicrobial or anti-biofilm intervention trials in early-stage AD
- Integration of infectious, inflammatory, and metabolic models

If infectious involvement exists even in just a minority subset, early intervention could have substantial public health impact.

Hyperbaric oxygen therapy and potential synergy with antimicrobial strategies

If infectious processes contribute to Alzheimer's disease (AD) in even a subset of cases, adjunctive therapeutic modalities that enhance antimicrobial efficacy and modulate neuroinflammation warrant investigation. One such modality is hyperbaric oxygen therapy (HBOT).

Mechanistic rationale

HBOT involves the inhalation of 100% oxygen at pressures greater than atmospheric pressure, increasing dissolved oxygen levels in plasma and tissues. Elevated tissue oxygen tension has several biologically relevant effects:

- **Direct antimicrobial enhancement**: Increased oxygen tension can inhibit or impair anaerobic and microaerophilic organisms and may augment bactericidal activity of certain antibiotics [13].
- **Biofilm disruption**: Experimental data suggest that hyperoxia may reduce biofilm integrity and enhance antibiotic penetration [14].
- **Immune modulation**: HBOT has been shown to modulate inflammatory cytokine expression and reduce microglial activation in experimental models [15].
- **Mitochondrial support and neuroplasticity**: Improved tissue oxygenation may enhance mitochondrial function, angiogenesis, and neurogenesis [16].

Given that spirochetes such as *Borrelia* species can exist in biofilm-like aggregates and persist in low-oxygen microenvironments, increasing tissue oxygenation may alter local ecological conditions that favor persistence.

Evidence in neuroinflammatory and infectious contexts

HBOT has established indications for certain infectious conditions, including refractory osteomyelitis and necrotizing soft tissue infections, where it is used as an adjunct to antimicrobial therapy [17]. Its role in neurological disorders remains investigational.

In animal models, HBOT has demonstrated:

- Reduction in neuroinflammation
- Decreased oxidative stress markers
- Improved cognitive performance in ischemic and traumatic injury models [15,18].

In humans, studies have explored HBOT in mild cognitive impairment and post-stroke cognitive dysfunction, with mixed but suggestive findings [19].

Potential synergy with antimicrobial therapy

The hypothesis that HBOT may enhance antimicrobial therapy rests on several theoretical and experimental considerations:

- Increased oxygen tension may enhance reactive oxygen species-mediated bactericidal mechanisms.
- Improved perfusion and angiogenesis may facilitate antibiotic delivery to previously hypoxic or inflamed tissue.
- Biofilm destabilization may render previously sequestered organisms more susceptible to treatment.

If AD in a subset of patients involves chronic infection within hypoxic microenvironments or biofilm-protected niches, combined antimicrobial and hyperoxic therapy could theoretically improve microbial clearance and reduce inflammatory signaling.

Future research should consider:

- Stratifying participants by infectious markers (e.g., PCR, serology, biofilm indicators).
- Evaluating combined antimicrobial + HBOT protocols in early-stage disease.
- Measuring neuroinflammatory biomarkers and imaging correlates.
- Assessing long-term cognitive outcomes.

Such trials would require rigorous design and independent funding to avoid bias.

Discussion

The history of neurosyphilis demonstrates that infectious dementia can masquerade as degenerative disease. Contemporary data linking microbes to amyloidogenesis, neuroinflammation, and biofilm formation warrant expanded investigation.

The most parsimonious position is not that Alzheimer's is exclusively infectious, nor that current paradigms are entirely misguided. Rather, AD may represent a heterogeneous endpoint, with infection contributing variably across patients.

Failure to rigorously evaluate low-profit therapeutic avenues risks perpetuating incomplete models.

A disciplined expansion of research scope is the appropriate course.

Conclusion

Infectious mechanisms seem to contribute to Alzheimer's disease, so therapeutic approaches need to extend beyond conventional anti-amyloid strategies to include antimicrobial and adjunctive modalities such as hyperbaric oxygen therapy. Afterall, amyloid may be the result of the neuroimmune system dealing with an infection it can't resolve. The history of neurosyphilis demonstrates that infectious dementias can masquerade as degenerative disease.

Given the biological plausibility of microbial involvement and the theoretical synergy between antimicrobial agents and hyperbaric oxygen, systematic investigation is warranted. The burden of inquiry should be commensurate with the scale of the disease. As of this moment conventional medicine remains unburdened and that is meant in the most pejorative way possible.

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