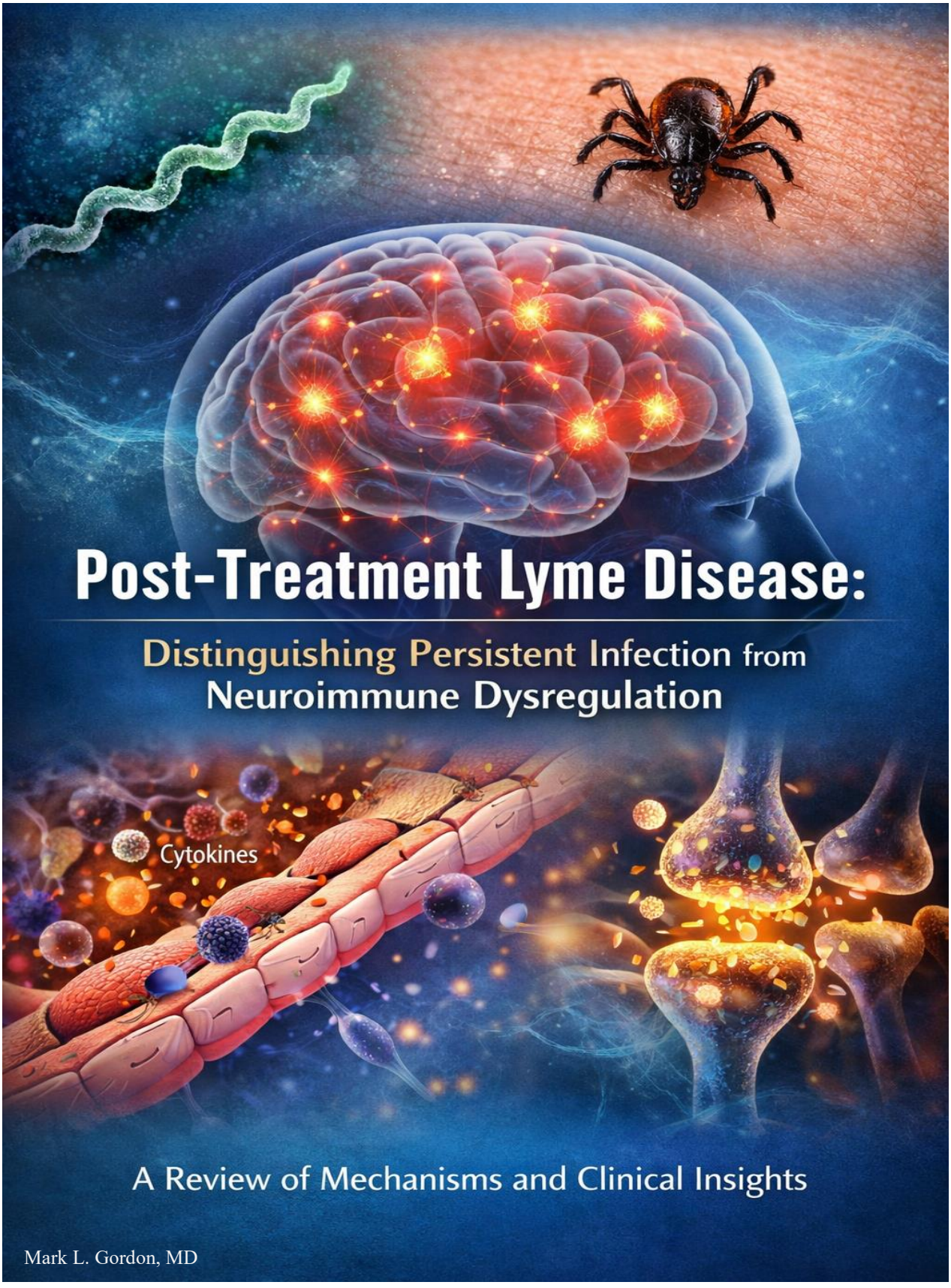

Post-Treatment Lyme Disease:
Distinguishing Persistent Infection from Neuroimmune Dysregulation
Cytokines
A Review of Mechanisms and Clinical Insights
Mark L. Gordon, MD

Post-Treatment Lyme Disease: Distinguishing Persistent Infection from Neuroimmune Dysregulation

Introduction

Lyme disease, caused primarily by the spirochete *Borrelia burgdorferi*, remains the most common vector-borne infection in North America and Europe. In its early stages, the condition is typically responsive to appropriately selected antimicrobial therapy, and the majority of patients experience full clinical recovery. However, a meaningful subset of individuals report persistent symptoms that continue well beyond completion of antibiotic treatment. These lingering effects, often characterized by cognitive slowing, impaired executive function, emotional volatility, heightened anxiety, disrupted sleep architecture, and pervasive fatigue, are collectively referred to as **Post-Treatment Lyme Disease (PTLD)**.

For many patients, these symptoms are not subtle. Individuals frequently describe difficulty concentrating, a diminished ability to multitask, increased sensitivity to stress, and fluctuations in mood that feel unfamiliar or disproportionate to circumstance. Physical stamina may also decline, with exertion leading to disproportionate exhaustion. Importantly, these experiences occur despite prior antimicrobial therapy deemed appropriate by contemporary standards and, in most cases, without objective evidence of ongoing infection.

The scientific discussion surrounding PTLD has historically centered on two competing interpretations. One perspective proposes that persistent symptoms are driven by ongoing microbial infection that has evaded eradication. The other posits that the initiating infection has been cleared, but the immune response it triggered has left behind a state of sustained neuroimmune dysregulation. In this latter model, the body's inflammatory and stress-regulation systems remain activated beyond their intended purpose, resulting in ongoing alterations in brain chemistry and physiological balance.

Since 2010, accumulating mechanistic research has increasingly supported the second explanation for most appropriately treated individuals. Rather than demonstrating consistent evidence of active bacterial proliferation, studies have identified patterns of immune activation, inflammatory signaling, and altered neurobiological function that can persist after microbial clearance. In this framework, PTLD represents a post-infectious neurobiological state, one characterized not by continued infection, but by immune-mediated remodeling of neural and endocrine systems.

This distinction is far more than academic. Whether persistent symptoms are attributed to ongoing infection or to neuroimmune dysregulation fundamentally shapes clinical decision-making. It influences the appropriateness of prolonged antibiotic therapy, guides the selection of diagnostic testing, informs risk stratification, and determines how patients are counseled regarding prognosis and recovery. A clear and biologically grounded understanding of PTLD is therefore essential—not only to advance scientific clarity, but to ensure that patient care is rational, evidence-based, and aligned with underlying pathophysiology.

Microbial Versus Persistent Infection

Following completion of standard, guideline-directed antibiotic therapy, convincing evidence for ongoing, viable *Borrelia burgdorferi* infection in immunocompetent patients remains limited. Although experimental animal models have demonstrated the presence of residual antigenic fragments or non-cultivable spirochetal remnants after treatment, these findings do not consistently translate into demonstrable, replicating infection in human subjects. The presence of bacterial debris or persistent antigenic material does not necessarily imply that the organism remains alive or capable of propagation. Rather, such remnants may continue to interact with the immune system even after microbial eradication.

In human studies, the more consistent and reproducible findings following appropriate treatment involve markers of immune activation rather than evidence of active bacterial proliferation. Patients with persistent

symptoms have been shown to exhibit elevations in inflammatory mediators, including cytokines and chemokines associated with innate immune activation. Alterations in immune cell phenotypes have also been observed, suggesting that the immune system may remain in a primed or sensitized state. In some cohorts, sustained cytokine expression patterns have been documented months after antimicrobial therapy, even in the absence of objective microbiologic evidence of ongoing infection.

Clinically, these immunologic patterns correlate with a continued burden of symptoms despite apparent microbiologic resolution. Patients may remain functionally impaired, experiencing cognitive inefficiency, fatigue, or emotional instability long after the initial infection has been treated. This dissociation, between the absence of demonstrable infection and the persistence of symptoms, favors an immune-mediated model of ongoing symptomatology rather than a model centered on uncontrolled microbial replication.

The emerging framework aligns PTLD with other recognized post-infectious syndromes, in which the inciting pathogen has been cleared but immune signaling pathways remain activated. In such conditions, the host response, not the microbe itself, becomes the primary driver of persistent dysfunction. The immune system, initially mobilized as a protective mechanism, may fail to fully return to baseline equilibrium. The resulting state of sustained inflammatory signaling can influence neural circuits, endocrine balance, and cellular energy metabolism, thereby perpetuating symptoms in the absence of active infection.

Understanding this distinction is critical. It shifts the clinical focus from antimicrobial escalation toward careful evaluation of immune, neurochemical, and neuroendocrine regulation. In doing so, it reframes persistent symptoms not as evidence of therapeutic failure, but as the downstream consequence of a biologically complex host response that may require a different therapeutic strategy altogether.

Neuroimmune Activation After *Borrelia burgdorferi* Exposure

During acute Lyme infection, *Borrelia burgdorferi* interacts directly with the innate immune system. One of the primary mechanisms involves engagement of Toll-like receptors, particularly TLR2, located on microglia within the central nervous system as well as on peripheral immune cells such as macrophages and dendritic cells. These receptors function as early warning sensors, recognizing structural components of invading pathogens. Once activated, they initiate intracellular signaling cascades designed to mount a defensive inflammatory response.

Among the most important downstream pathways triggered by TLR2 activation is the nuclear factor kappa B (NF-κB) signaling pathway. NF-κB acts as a transcriptional regulator, entering the cell nucleus and promoting the expression of multiple pro-inflammatory genes. This process results in the production and release of key inflammatory mediators, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). These cytokines serve essential protective roles during acute infection by enhancing immune recruitment and coordinating pathogen clearance. However, their activity also has direct consequences for neural tissue.

Within the brain, microglia, its resident immune cells, shift from a surveillant state (M0) to an activated phenotype (M1) during infection. Activated microglia influence synaptic regulation, modulating neurotransmitter release and receptor sensitivity. Sustained inflammatory signaling can promote an excitatory bias within cortical and limbic circuits, increasing glutamatergic tone and altering inhibitory balance. Clinically, such changes may manifest as heightened anxiety, emotional reactivity, cognitive inefficiency, or disrupted sleep patterns.

Importantly, emerging research suggests that this immune activation does not always fully resolve once the pathogen has been cleared. Microglia can remain in a “primed” state, meaning they respond more robustly to subsequent stressors or immune triggers. In this primed phenotype, even minor physiological challenges may provoke exaggerated inflammatory responses. Additionally, patterns of cytokine transcription may remain elevated beyond the acute infectious phase, indicating that inflammatory gene expression programs have not entirely returned to baseline. Peripheral immune dysregulation may further reinforce central

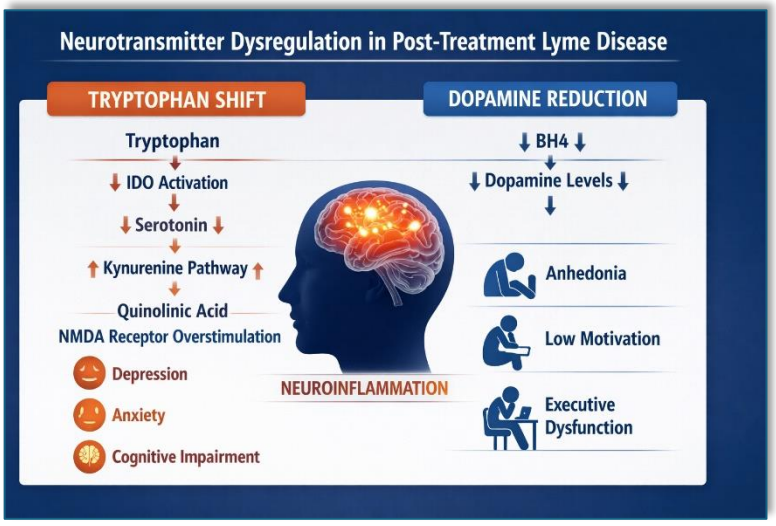
immune signaling through bidirectional communication pathways between the systemic immune system and the brain.

The result is a sustained, low-grade neuroinflammatory environment. While far less intense than the acute inflammatory response, this chronic signaling can subtly but persistently alter neurochemical equilibrium. Synaptic efficiency may decline, neural network connectivity may become less synchronized, and cognitive processing speed may be reduced. Over time, these changes can translate into the persistent neuropsychiatric symptoms reported by some individuals following otherwise appropriate antimicrobial treatment.

In this context, the immune system's protective response to infection may inadvertently transition into a prolonged state of dysregulation, with the brain remaining influenced by inflammatory signals long after the inciting organism has been eliminated.

Cytokine Signaling and Neurotransmitter Remodeling

Inflammatory signaling does not remain confined to the immune system. Pro-inflammatory cytokines exert direct and measurable effects on neurotransmitter pathways, altering the delicate chemical balance that supports mood regulation, cognitive clarity, motivation, and emotional resilience. In the context of post-treatment Lyme disease, sustained low-grade inflammation may therefore translate into persistent neuropsychiatric symptoms through well-characterized biochemical mechanisms.



One of the most studied pathways linking inflammation to mood and cognition involves the tryptophan–kynurenine metabolic shift. Under normal conditions, tryptophan serves as a precursor for serotonin synthesis. However, inflammatory cytokines such as interferon-gamma, interleukin-6, and tumor necrosis factor-alpha activate the enzyme indoleamine 2,3-dioxygenase (IDO). When IDO activity increases, tryptophan is preferentially diverted away from serotonin production and instead metabolized into kynurenine and its downstream metabolites.

This biochemical rerouting has several important consequences. Serotonin availability may decline, contributing to mood instability and heightened anxiety. At the same time, kynurenine metabolites such as quinolinic acid can accumulate. Quinolinic acid is an agonist at the N-methyl-D-aspartate (NMDA) receptor and promotes excitatory glutamatergic signaling. Excessive activation of this receptor system can create an excitotoxic bias within neural networks, particularly in cortical and limbic regions involved in memory, mood, and executive processing. Clinically, this inflammatory shift has been associated with depressive symptoms, anxious phenotypes, slowed information processing, and reduced cognitive flexibility. These relationships are well documented in broader models of infection-associated depression and inflammatory neuropsychiatric illness.

Inflammation also influences dopaminergic pathways. Dopamine synthesis depends on the availability of tetrahydrobiopterin (BH4), a critical enzymatic cofactor. Pro-inflammatory cytokines increase oxidative stress and reduce BH4 availability, thereby impairing dopamine production. Reduced dopaminergic tone can manifest as diminished motivation, reduced reward sensitivity (anhedonia), impaired concentration,

and executive dysfunction. In practical terms, individuals may describe feeling mentally slowed, less driven, or unable to sustain focus on complex tasks.

These cytokine-driven alterations in serotonin and dopamine systems help explain why persistent inflammation can produce neuropsychiatric symptoms even in the absence of ongoing infection. The immune system, through its chemical mediators, effectively reshapes neurotransmitter availability and receptor signaling.

Neurosteroid Vulnerability

In addition to classical neurotransmitters, inflammation also affects neurosteroid synthesis. Neurosteroids such as pregnenolone, allopregnanolone, and dehydroepiandrosterone (DHEA) play critical roles in modulating neuronal excitability, stress responsiveness, and emotional regulation. These molecules are synthesized within the brain and peripheral endocrine tissues and act locally to stabilize neural circuits.

Inflammatory cytokines interfere with neurosteroid production at multiple levels. They suppress the activity of steroidogenic acute regulatory protein (StAR), which is responsible for transporting cholesterol into mitochondria, the first step in steroid hormone synthesis. By impairing mitochondrial cholesterol transport, inflammation reduces the availability of downstream neurosteroids.

Allopregnanolone is particularly important in this context. It functions as a potent positive allosteric modulator of the gamma-aminobutyric acid type A (GABA-A) receptor, enhancing inhibitory signaling in the brain. Adequate allopregnanolone levels support emotional stability, stress tolerance, and restorative sleep. When inflammatory processes diminish its synthesis, inhibitory tone decreases. The result may be heightened limbic reactivity, increased anxiety, fragmented sleep, and a persistent state of hyperarousal.

This interaction between inflammation and neurosteroid depletion creates a self-reinforcing loop. Inflammatory signaling reduces neurosteroid support, weakening inhibitory buffering within neural circuits. Reduced inhibitory control increases stress reactivity and sympathetic activation, which in turn can further stimulate inflammatory pathways.

In the setting of post-treatment Lyme disease, neuroinflammation does not merely produce transient immune activation. It has the potential to recalibrate neurotransmitter systems and diminish neurosteroid-mediated stabilization, contributing to ongoing emotional volatility, cognitive inefficiency, and stress sensitivity. Recognizing these interconnected mechanisms allows for a more comprehensive understanding of persistent symptoms and underscores the importance of evaluating immune, neurochemical, and neuroendocrine dynamics together rather than in isolation.

HPA-Axis Dysregulation

The hypothalamic-pituitary-adrenal (HPA) axis serves as one of the body's primary regulatory systems for stress adaptation and immune modulation. Under normal circumstances, this axis operates with remarkable precision. The hypothalamus releases corticotropin-releasing hormone (CRH) in a pulsatile pattern, stimulating the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn signals the adrenal glands to produce cortisol. Cortisol follows a distinct circadian rhythm, rising sharply in the early morning to promote alertness and gradually declining throughout the day. Beyond its role in energy regulation and stress adaptation, cortisol exerts potent anti-inflammatory effects, helping to restrain excessive immune activation.

Inflammatory signaling, however, has a profound impact on this finely tuned system. Chronic exposure to pro-inflammatory cytokines can disrupt CRH pulsatility, alter ACTH responsiveness, and flatten the normal diurnal rhythm of cortisol secretion. Rather than demonstrating a robust morning rise and appropriate daytime modulation, cortisol output may become blunted, erratic, or insufficient relative to physiological demand. Even subtle deviations from normal rhythmicity can influence mood stability, cognitive clarity, and resilience under stress.

Research on post-infectious syndromes more broadly has documented several recurring patterns. One of the most frequently observed findings is a blunted cortisol awakening response, in which the expected early-morning surge is diminished. Individuals with this pattern often report reduced stamina, slower cognitive activation upon waking, and heightened vulnerability to stressors throughout the day. Altered glucocorticoid receptor sensitivity has also been described, meaning that even when cortisol is present, tissues may respond less effectively to its regulatory signals. This impaired responsiveness weakens cortisol's capacity to dampen inflammatory pathways.

When cortisol dynamics become suboptimal, the body's ability to contain inflammation is compromised. Inadequate anti-inflammatory signaling allows cytokine activity to persist longer than intended, perpetuating low-grade immune activation. At the same time, sustained inflammation further disrupts HPA-axis regulation, creating a bidirectional feedback loop. The immune system and stress axis, normally partners in maintaining equilibrium, instead reinforce one another's dysregulation.

Within the framework of post-treatment Lyme disease, this interplay offers a biologically coherent explanation for chronicity. Persistent cytokine signaling may recalibrate the stress axis and altered cortisol regulation may fail to adequately suppress inflammatory activity. The result is a self-perpetuating cycle in which immune activation and stress dysregulation sustain each other, contributing to ongoing fatigue, cognitive inefficiency, emotional volatility, and reduced stress tolerance long after the initial infection has resolved.

Mitochondrial and Bioenergetic Impairment

The brain is one of the most energy-dependent organs in the human body. Neurons require a constant and substantial supply of adenosine triphosphate (ATP) to maintain membrane potentials, propagate action potentials, recycle neurotransmitters, and sustain synaptic plasticity. Even subtle reductions in cellular energy production can therefore translate into noticeable changes in cognitive performance, emotional stability, and sensory processing. In the context of persistent neuroinflammation, mitochondrial function becomes particularly vulnerable.

Inflammatory activation increases the production of reactive biochemical species, including nitric oxide, reactive oxygen species (ROS), and peroxynitrite. While these molecules play useful roles in acute immune defense, excessive or prolonged generation can disrupt normal cellular physiology. Within mitochondria, these reactive species interfere with components of the electron transport chain, the enzymatic system responsible for ATP generation through oxidative phosphorylation. Damage or functional inhibition of these complexes reduces the efficiency of energy production and increases oxidative stress within the cell.

As mitochondrial efficiency declines, neurons operate under conditions of relative energy insufficiency. This state does not necessarily produce overt structural damage, but it can impair network performance. Patients may experience cognitive fatigue, characterized by diminished mental endurance and reduced processing speed after sustained concentration. Tasks that were previously routine may require disproportionate effort. Additionally, some individuals report post-exertional symptom exacerbation, in which physical or mental activity leads to delayed worsening of fatigue, cognitive fog, or emotional instability. Sensory hypersensitivity, including heightened sensitivity to light, sound, or environmental stimuli, may also reflect impaired energy buffering within neural circuits that normally modulate sensory input.

Mitochondrial vulnerability also feeds back into the broader neuroimmune environment. Impaired oxidative phosphorylation increases oxidative stress, which can further stimulate inflammatory pathways. In turn, ongoing inflammation continues to challenge mitochondrial integrity. This reciprocal relationship creates another reinforcing cycle: inflammation impairs bioenergetics, and bioenergetic compromise sustains inflammatory signaling.

Within the framework of post-treatment Lyme disease, mitochondrial dysfunction provides a plausible mechanistic bridge between immune activation and the lived experience of persistent fatigue and cognitive

inefficiency. It underscores the concept that ongoing symptoms may arise not from active infection, but from sustained alterations in cellular energy metabolism driven by prior inflammatory stress.

Cytokine Monitoring and Biomarker Considerations

Given the central role of immune signaling in post-treatment Lyme disease, thoughtful laboratory evaluation can provide valuable context when persistent symptoms are present. While no single laboratory marker defines PTLD or conclusively distinguishes it from other post-infectious conditions, patterns of immune and neuroendocrine imbalance may offer objective insight into the biological terrain underlying ongoing symptoms.

From an immunologic perspective, assessment often includes measurement of circulating inflammatory mediators. Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are among the most studied cytokines in post-infectious syndromes and serve as indicators of innate immune activation. Interferon-gamma may reflect ongoing Th1-mediated immune signaling. High-sensitivity C-reactive protein (hs-CRP), while nonspecific, provides a global index of systemic inflammatory tone and can help contextualize other findings. Elevations in these markers, particularly when persistent or fluctuating in parallel with symptoms, may support the presence of sustained inflammatory activity even in the absence of active infection.

Equally important is the evaluation of stress-axis and neurosteroid dynamics. Because inflammatory signaling can disrupt hypothalamic-pituitary-adrenal (HPA) regulation, assessment of cortisol rhythms, rather than a single random cortisol value, may be more informative. Measurement of morning cortisol, diurnal salivary cortisol patterns, or cortisol awakening response can reveal whether the stress axis is functioning with appropriate amplitude and circadian integrity.

Neurosteroid-related markers such as dehydroepiandrosterone sulfate (DHEA-S) and pregnenolone may also provide indirect insight into steroidogenic capacity and neuroendocrine resilience. Reductions in these precursors can reflect inflammatory suppression of steroidogenesis and may correlate with symptoms of fatigue, stress intolerance, mood instability, or sleep disturbance.

It is important to emphasize that PTLD is not defined by any single abnormal laboratory value. Rather, clinicians often look for constellations of findings, subtle elevations in inflammatory markers combined with evidence of altered cortisol dynamics or diminished neurosteroid support. The integration of these domains offers a more comprehensive picture than isolated measurements.

Longitudinal monitoring is frequently more informative than a single time-point assessment. Inflammatory and neuroendocrine systems are dynamic, and patterns over time may reveal trends that static values cannot. Observing whether cytokine levels normalize, remain persistently elevated, or fluctuate in response to stressors can help clarify the degree of ongoing immune activation. Similarly, tracking cortisol or neurosteroid patterns over months may demonstrate gradual recalibration or persistent dysregulation.

Within this framework, biomarker evaluation serves not as a diagnostic shortcut, but as a biologically grounded tool to better understand the interplay between immune activation and neuroendocrine function. When interpreted cautiously and in clinical context, these measurements can help objectify aspects of symptom persistence and guide a more rational, systems-based approach to care.

Clinical Differentiation Framework

Distinguishing persistent infection from post-infectious neuroimmune dysregulation is one of the most important, and often misunderstood, clinical challenges in post-treatment Lyme disease. While both hypotheses attempt to explain ongoing symptoms, careful clinical assessment frequently reveals patterns more consistent with immune-mediated dysregulation than with active microbial proliferation.

One of the most reassuring findings in favor of a neuroimmune model is a stable neurologic examination over time. In cases of uncontrolled or progressive infection, clinicians would expect evolving objective

deficits, worsening focal weakness, progressive cranial nerve abnormalities, new sensory loss, or measurable decline in coordination. In contrast, many individuals with PTLD demonstrate a neurologic examination that remains stable, even though they report significant subjective cognitive or emotional symptoms. This stability argues against an ongoing destructive infectious process.

Similarly, the absence of progressive structural or objective deterioration supports a post-infectious framework. Patients often describe persistent cognitive fog, mood instability, or fatigue, yet serial evaluations do not reveal accumulating neurologic damage. The symptom burden may be substantial, but it does not follow the pattern typical of an advancing infection.

Another distinguishing feature is the fluctuating nature of symptoms. Individuals with neuroimmune dysregulation frequently report that their condition varies with stress levels, sleep quality, or other physiological stressors. Periods of adequate rest may yield partial improvement, while emotional strain, sleep disruption, or intercurrent illness may provoke temporary worsening. This variability aligns more closely with immune and stress-axis sensitivity than with steady bacterial replication.

The fatigue pattern itself also offers diagnostic clues. Many patients describe a form of central fatigue characterized by diminished cognitive stamina, slowed information processing, and disproportionate exhaustion following mental or physical exertion. This presentation resembles other inflammatory or post-infectious states rather than the progressive weakness or tissue damage expected in untreated infectious disease.

Perhaps most telling is the lack of sustained improvement with prolonged or repeated antibiotic therapy. If persistent symptoms were driven primarily by ongoing microbial replication, additional antimicrobial treatment would be expected to yield consistent and durable benefit. In most appropriately treated individuals, however, extended antibiotic courses do not produce reliable resolution of cognitive or neuropsychiatric symptoms. This observation further supports the interpretation that the underlying driver is immune-mediated neurobiological remodeling rather than uncontrolled infection.

Taken together, these clinical patterns reframe PTLD not as an active infectious process, but as a post-infectious neurobiological syndrome in the majority of treated cases. Recognizing this distinction allows clinicians to shift the therapeutic focus away from repeated antimicrobial escalation and toward careful evaluation of immune regulation, stress-axis dynamics, neurochemical balance, and bioenergetic function. In doing so, the approach becomes more aligned with underlying physiology and more responsive to the lived experience of patients navigating persistent symptoms.

Conclusion

Post-Treatment Lyme Disease is best understood as a biologically mediated, post-infectious neuroimmune state rather than as evidence of uncontrolled infection in most appropriately treated individuals. The clinical picture that emerges from mechanistic research over the past decade reflects sustained immune activation and downstream neurobiological consequences rather than ongoing microbial proliferation.

At the core of this framework is persistent cytokine signaling. Even after the inciting pathogen has been eradicated, inflammatory mediators may remain elevated or dysregulated, subtly influencing neural function. These cytokines interact directly with neurotransmitter systems, reshaping serotonin, dopamine, and glutamate pathways in ways that can produce mood instability, cognitive slowing, and diminished motivation. Simultaneously, inflammation interferes with neurosteroid synthesis, reducing protective modulators such as allopregnanolone and weakening inhibitory buffering within limbic circuits.

The hypothalamic-pituitary-adrenal axis, highly sensitive to immune signaling, may also become dysregulated. Altered cortisol rhythms and impaired stress responsiveness reduce the body’s ability to restrain inflammatory cascades, allowing immune activation to persist. In parallel, inflammatory mediators disrupt mitochondrial function, compromising cellular energy production and contributing to cognitive fatigue, exertional intolerance, and sensory hypersensitivity.

Taken together, these processes form an interconnected network of immune, neurochemical, neuroendocrine, and bioenergetic alterations. The resulting symptom complex reflects a state of neurobiological remodeling initiated by infection but sustained by host immune dynamics.

Distinguishing persistent infection from neuroimmune dysregulation is therefore essential for rational clinical management. Misattributing immune-mediated symptoms to ongoing infection may lead to unnecessary or prolonged antimicrobial exposure without addressing the underlying physiology. Conversely, recognizing the post-infectious neuroimmune model allows clinicians to evaluate inflammatory tone, stress-axis regulation, and metabolic resilience in a more targeted and biologically coherent manner.

The cumulative mechanistic literature since 2010 increasingly supports this immune-driven model of persistent symptomatology in appropriately treated patients. While ongoing investigation remains necessary, current evidence suggests that, in most cases, the enduring effects of Lyme disease represent not continued microbial persistence, but the complex and sometimes prolonged recalibration of the immune, brain interface.

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