POINT/COUNTERPOINT

How will research on neurologic Lyme disease need to change to identify better treatments?

Distinguish between clinical constructs.

Four clinical constructs are commonly attributed to nervous system Lyme disease, but only one of these actually represents nervous system infection with *Borrelia burgdorferi*, also known as neuroborreliosis. However, there are legitimate and important research questions for each construct.

Neuroborreliosis manifests as lymphocytic meningitis, multifocal inflammation of nerves and nerve roots, and – very rarely – multifocal inflammation of the CNS. This is probably the only one of these four constructs in which animal models, primarily nonhuman primates, can be informative.

Although antibiotics are curative for neuroborreliosis, it is virtually impossible (except in meningitis) to demonstrate spirochetes in involved tissue. Immune activation and amplification appear to play key roles in pathogenesis, but their mechanisms require clarification. Are there specific markers that predict which patients will develop neuroborreliosis and its particular form? Are there predictors of the rate or completeness of antimicrobial response? Do similarities between host and spirochete antigens cause antispirochete antibodies to attack the host?

JOHN J. HALPERIN, M.D.

Current diagnostic tools for neuroborreliosis are excellent. However, the sensitivity and specificity of cerebrospinal fluid (CSF) antibody measurement and polymerase chain reaction should be explored in well-defined populations with CNS infection. Measures of treatment response need improvement, be they nonspecific or specific. Although the currently recommended parenteral antibiotic regimens are highly effective, several European studies indicate that oral doxycycline is as effective as parenteral antibiotics for all but parenchymal CNS disease (Neurology 2007;69:91-102). This requires confirmation in U.S. patients.

A second clinical entity, referred to as Lyme encephalopathy, manifests as altered cognitive function in the setting of extraneurologic (but usually not nervous system) infection. Like patients with many other systemic inflammatory states, individuals with active Lyme disease often describe cognitive and memory difficulties, in the absence of CNS infection. An understanding of this disorder, which presumably is mediated by cytokines or other soluble molecules that are produced systemically and diffuse into the CNS, may well provide broad insights into the delirium seen in many other systemic infections. Studies should focus on the range of neuroimmunomodulators that are present in the serum and CSF of such patients, as well as microorganism characteristics. Then researchers can explore more specific therapeutic interventions.

Posttreatment Lyme disease syndrome (PLDS) manifests typically as fatigue, perceived cognitive and memory difficulty, widespread pain, sleep disorders, and other symptoms overlapping extensively with chronic fatigue syndrome, fibromyalgia, and similar states. These symptoms occur and persist for many months following usually curative treatment of patients with clear-cut Lyme disease. Identical symptoms have been observed following other infectious or inflammatory states.

Larger prospective studies are needed to establish whether PLDS occurs more frequently after Lyme disease than in control populations. If so, understanding its pathophysiology may be informative both for this state and for a broader range of similar, postinfectious states. Additional studies should focus on both who is affected and why. Work to date indicates that PLDS is not caused by ongoing infection, but rather appears to relate to pre-illness traits. Recovery seems to correlate best with patients' emotional resilience (Am. J. Med. 2009;122:843-50) and only inconsistently with psychiatric comorbidities.

Assays of markers of innate and acquired immunity both in serum and CSF could be performed to test whether or not there is ongoing immune stimulation in PLDS. A possible role of coinfections with other tick-borne infections such as flaviviruses can be assessed as well. The role of learned behavioral responses to stressors can be assessed by prospective studies using neuropsychological metrics and brain functional MRI or possibly PET scans. Treatment recommendations would follow from the demonstrated pathophysiology.

In other instances, individuals are diagnosed with and treated for "chronic Lyme disease" despite the absence of any evidence of their ever having had this infection. These symptoms are identical to PLDS and significantly impact quality of life in an estimated 2% of the general population (Med. Care 2005;43:1078-86), but often do not have an identifiable cause. Future studies should compare these patients to individuals believed to have PLDS to determine if there are any biological differences between the two populations. ■

DR. HALPERIN *is a professor of neurology at the Mount Sinai School of Medicine, New York, and is medical director of the Atlantic Neuroscience Institute and chair of the department of neurosciences at Overlook Hospital in Summit, N.J. He has served as an expert witness defending physicians accused of failure to diagnose nervous system Lyme disease.*

Make use of new detection, diagnostic methods.

Although progress has been made in our understanding of neurologic Lyme disease, important questions and unmet needs remain, particularly with respect to diagnostic tests and the cause and treatment of chronic sequelae.

The following five steps will further advance our understanding:

► **Conduct a large prospective study** of neurologic Lyme disease, which may clarify the incidence of chronic symptoms after standard treatment and identify risk factors that influence relapse vs. recovery.

► **Apply newly developed technologies** to identify better diagnostics and biomarkers and to examine the pathophysiology of chronic symptoms.

► **Create a national repository of clinical specimens** from patients at different stages of disease and recovery in order to apply this emerging technology rapidly. These patients need to be extremely well characterized across multiple disciplines via validated measures in order to bring maximal yield.

BRIAN A. FALLON, M.D.

► **Conduct a noninferiority, double-blind, randomized, controlled trial** to determine whether oral doxycycline is as good as IV ceftriaxone (as has been demonstrated in Europe) for acute neurologic Lyme disease.

► **Test nonantimicrobial therapies** to help patients who have chronic symptoms despite taking antibiotics.

This five-step approach will lead to better diagnostic tests, will help elucidate the prevalence and pathophysiology of chronic persistent symptoms, and will lead to more rational and effective treatment selection.

To determine whether unsuspected coinfections or uncommon strains of *Borrelia burgdorferi* are the culprits for persistent symptoms, many powerful techniques are now available to address such issues. Whole-genome sequencing has enabled the mapping of 13 additional U.S. strains of *B. burgdorferi* that should help to clarify whether distinct *B. burgdorferi* variants lead to different clinical manifestations and treatment responses. The combination of multiplex polymerase chain reaction with mass spectrometry (called MassTag PCR) can screen for multiple tick-borne pathogens using a single sample. This technology has revealed that 30% of ticks in New York state have a polymicrobial infection and that 2% carry the Powassan virus (Vector Borne Zoonotic Dis. 2010;10:217-21). Another technology, such as the Ibis T5000, uses broad-range PCR followed by electrospray ionization mass spectrometry to probe specimens for potential microbes in a nonbiased manner. It produces results within hours. Furthermore, "deep sequencing" technology can probe the entire microbial population in a single sample.

Advances in neuroimaging can help clarify the pathophysiology of chronic symptoms. Recent progress in the identification of radioligands that target the peripheral benzodiazepine receptor will allow PET scanning to determine whether patients with posttreatment Lyme disease syndrome (PLDS) have CNS microglial activation. Patients with PLDS often complain of multifocal pain, and many report diffuse hyperalgesia and/or allodynia. Could this result from central mechanisms that augment pain or attenuate activity in descending antinociceptive pathways, as has been demonstrated in fibromyalgia? The demonstration of abnormally activated central pain neural circuits in PLDS would suggest new directions in treatment. Such research could include peripheral tests of pain thresholds (pressure, heat, auditory), functional MRI studies of central sensory augmentation, and probing neurotransmitter activity via CSF and MR spectroscopy.

Recent animal and human studies also provide new directions. Could persistent symptoms among PLDS patients reflect the immune response to a small reservoir of persistent infection, as has been suggested by the finding of persistent *B. burgdorferi* in mouse and canine models after antibiotic treatment in U.S. and European studies? (These studies have led to a xenodiagnosis study in humans that is funded by the National Institute of Allergy and Infectious Diseases. It will test whether an uninfected tick feeding on a PLDS patient can attract *B. burgdorferi* even if *B. burgdorferi* was nondetectable in that human host by culture or PCR.) Do persistent symptoms reflect a persistently activated immune response with a persistent sickness syndrome, as has been suggested for many postinfectious illnesses? Recent studies demonstrate that approximately 50% of patients with PLDS have elevated antineuronal antibodies, with total antibody reactivity comparable to that seen among patients with systemic lupus erythematosus but far higher than among recovered controls (Brain Behav. Immun. 2010;24:1018-24). The pathophysiology underlying this immune abnormality and its relationship to clinical symptomatology deserve further study as it may suggest future immunologically based therapies. ■

DR. FALLON *is director of the Lyme and tick-borne diseases research center and is a professor of clinical psychiatry at Columbia University, New York. The center received a small grant last year from the Lyme Disease Association toward developing a repository for Lyme specimens.*