Review of Lyme Neuroborreliosis CME

Disclosures

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Introduction

A series of 3 talks on the second day of the 13th Lyme Disease Conference examined the latest findings in the diagnosis and treatment of neurologic Lyme disease.

Brain Imaging in Lyme Disease

Structural and functional brain imaging can be useful to the clinician in the evaluation of patients with neurologic Lyme disease. Dr. Brian A. Fallon, Director of the Lyme Disease Research Program at the NYS Psychiatric Institute and Associate Professor of Clinical Psychiatry at Columbia University, New York City, presented a review of these brain imaging procedures in Lyme disease. This presentation reviewed published research and presented possibilities of how brain imaging can be used to answer important pathophysiologic and treatment questions about Lyme disease.

Structural brain imaging. MRI scans among patients with neurologic Lyme disease may demonstrate punctate white matter lesions on T_2-weighted images, similar to those seen in demyelinating or inflammatory disorders such as multiple sclerosis, systemic lupus erythematosus, or cerebrovascular disease. In Lyme disease, this is most often the case among patients with evidence of meningitis or encephalitis. In a report of patients with CSF-confirmed European Lyme disease with CNS symptoms, 50% of 14 patients had abnormal CT findings, most commonly hypodense areas corresponding with ischemic lesions caused by putative vasculitis. In each of the 3 studied cases, MRI revealed smaller, multiple sclerosis-like lesions and larger lesions also suspected to indicate vascular involvement. The authors concluded that, comparable to meningovascular and cerebrovascular syphilis, CNS micro- and macrovasculitis may cause both clinical symptoms and MRI changes in patients with CNS borreliosis.

The usefulness of MRI scans in American chronic Lyme encephalopathy is less clear. The general impression is that in chronic neurologic Lyme disease, brain MRI scans may be abnormal less often. In a report of a series of 24 patients with chronic neurologic abnormalities of at least 3 months' duration after Lyme disease, 4 (16.6%) had MRI abnormalities characterized as small round periventricular white matter lesions and 3 of these 4 patients had abnormal CSF studies. Among patients with Lyme encephalopathy in particular, the rate of MRI scans with white matter hyperintensities varied from 15% of 13 patients to 41% of 17 patients. In the latter study, when scans were repeated after treatment, half of the patients showed resolution of the signal hyperintensity. Among 8 children with neurologic Lyme disease, 25% had MRI abnormalities consisting of multiple focal areas of increased signal intensity in the white matter on long TR (both proton-density and T2-weighted) images.

In late-stage encephalomyelitis, MRI scanning often demonstrates focal areas of inflammation, most commonly in the white matter. In a series of 34 patients with acute or indolent encephalomyelitis, 26 (76.5%) had small multifocal hyperintense T2 signals, most commonly in the white matter and occasionally in the cortical and subcortical gray matter of the brain. Because encephalomyelitis clinically may result in prominent pyramidal, sensory, or cerebellar syndromes and because the MRI lesions resemble demyelination, patients with Lyme disease may be mistakenly diagnosed as having multiple sclerosis.

Despite the preponderance of evidence indicating a substantial rate of MRI hyperintensities in some patients with CNS Lyme disease, as of yet there have been no studies to examine the pathophysiology of these hyperintense areas (perfusion, reactivity to hypercapnia, metabolism) and whether they have prognostic significance. Do these hyperintensities represent demyelination or perivascular inflammation? Is the disease process underlying the hyperintensities primarily neuronal metabolic or vascular? These questions can be examined by a study that couples structural imaging with functional imaging, comparing cerebral blood flow and cerebral metabolic rate deficits. The more sensitive FLAIR sequence and magnetization transfer techniques can be used to maximize the yield on identifying white matter hyperintensities.

In other disease states, such hyperintensities have usually been attributed to ischemic cerebrovascular disease secondary to increased water content in perivascular space, axon and myelin loss, astrocyte proliferation (gliosis), and/or frank infarction. If the hyperintensities occur primarily in the arteriole-supplied watershed areas, then the most likely cause is vascular insufficiency, as these areas receive limited collateral supply. Risk factors that increase the likelihood of having hyperintensities include older age, hypertension, diabetes, coronary heart disease, and other vascular risk factors. The presence of hyperintensities has been shown to predict subsequent stroke, new-onset dementia, myocardial infarction, and vascular death.

Histopathologic studies of hyperintensities in neurologic and normal samples commonly show arteriolar hyalinization, ectasia, enlarged perivascular space, gliosis, spongiosis, and/or lacunar infarcts. Van Swieten found that white matter hyperintensities in the elderly were invariably accompanied by demyelination and gliosis, and less consistently with increased perivascular space. The demyelination was strongly associated with increased wall thickness of small arterioles. They concluded that arteriosclerosis in small arterioles (<150 microns) is the primary cause, leading to demyelination, and then cell loss with progression.

The hypothesis that MRI hyperintensities in Lyme encephalopathy are attributable to impaired blood flow (vascular insufficiency) in subcortical areas can be tested with in vivo perfusion imaging. In stroke samples, PET and SPECT studies consistently have shown correspondence between the identified areas of hypoperfusion and the structural abnormalities identified by CT, MRI, or pathology. The spatial extent of the perfusion deficit is typically larger than the areas of tissue necrosis defined by pathology or structural imaging, and remote functional changes may be observed (diaschisis).

Functional brain imaging. Single photon emission computerized tomography (SPECT) and positron emission tomography (PET) provide a dynamic picture of the brain's functioning: metabolism, blood flow, and chemistry. In comparison to SPECT scans, PET scanning is able to provide better spatial resolution images (4-6 mm vs 6-9 mm) and can be used to provide an absolute quantitative assessment of regional perfusion or metabolic abnormalities. SPECT has recently been reported to be a useful tool in the evaluation of patients with Lyme disease, showing multifocal areas of decreased perfusion in both the cortex and the subcortical white matter.

Logigian contrasted the brain perfusion patterns of 13 patients with definite Lyme encephalopathy (defined by objective memory deficits on cognitive testing and/or CSF with intrathecal Ab production or positive PCR), 9 patients with possible Lyme encephalopathy (no objective deficits), and 26 normal controls. Patients with definite Lyme encephalopathy had significantly more perfusion deficits than patients with possible Lyme encephalopathy, who in turn had significantly more deficits than normal controls. After the patients with definite Lyme encephalopathy were given 4 weeks of IV ceftriaxone, a partial reversal in brain perfusion deficits was observed. These results suggest that perfusion deficits are greater with more severe disease and that perfusion deficits may be seen in the absence of objective neuropsychological deficits.

Notably, although the treated patients did show improved perfusion, significant perfusion deficits remained. Several limitations of this study should be noted. First, because this study did not have age- and sex-matched controls, the results that suggested regions of deficit specific to Lyme encephalopathy (subcortical frontotemporal white matter and basal ganglia, frontal cortex, cingulate gyrus) need to be confirmed in a better-controlled investigation. Second, the relatively older control group did not have neuropsychological testing at baseline, thereby risking the inclusion of cognitively impaired individuals. This may explain why 4 of the 26 "normal" controls had perfusion deficits in the range of those seen in the Lyme encephalopathy patients. Third, because in this study 11 of the 13 treated patients with Lyme encephelopathy had never previously received a course of IV ceftriaxone of at least 3 weeks, the results of this study cannot be generalized to the larger group of patients with Lyme encephalopathy who have already received this standard course of treatment. The authors' impression that "patients with Lyme encephalopathy who have already been treated with oneor at most two 1-month courses of IV ceftriaxone rarely improve after further courses of ceftriaxone" needs to be tested in a carefully designed way. Fourth, patients did not undergo follow-up cognitive testing, thereby precluding objective investigation of the clinical significance of the improvement in perfusion.

Hypoperfusion defects visualized on SPECT scans may result from any process that alters the radiotracer distribution, including vascular delivery to neurons, transport of the tracer into the cells, and retention of the radioactive tracer in the cells. Problems may arise secondary to direct infection of neurons, from cellular dysfunction due to the indirect effects of neurotoxic immunomodulators such as cytokines, or from decreased perfusion through arterioles secondary to vasculitis. In other words, areas of hypoperfusion may result from a cellular-metabolic and/or a vascular problem. Although SPECT reports suggest that the use of imaging pre-and post-acetazolamide may be helpful in the indirect determination of a vascular from a metabolically induced area of hypoperfusion, only PET technology using glucose and oxygen studies is capable of addressing this question directly in a fully quantitative fashion.

In what ways, then, are functional imaging scans helpful in the diagnostic assessment? First, a scan with diffuse abnormalities may confirm that an objective abnormality is present in a patient considered to have a factitious disorder. Second, a normal scan in a patient with prominent neuropsychiatric symptoms may suggest that a psychiatric disorder is the primary cause of a patient's cognitive or emotional distress, and therefore may lead the clinician to recommend a re-evaluation of the patient's psychiatric treatment. Third, an improvement in a scan after treatment provides objective evidence of physiologic change.

It should be noted that one cannot conclude from a PET or a SPECT scan that a patient has Lyme disease, as similar patterns of abnormality may be seen with other diseases as well. A diffusely abnormal scan should alert the clinician to search for the presence of an organic etiology other than that which causes primary psychiatric disorders. Other disease processes that demonstrate a heterogeneous tracer uptake include vascular dementia, chronic fatigue syndrome, CNS lupus, HIV encephalopathy, and chronic or acute stimulant abuse.

There have been no metabolic imaging studies in Lyme disease; the limited data pertain to cerebral blood flow only. It remains to be determined how quickly the hypothesized perfusion and metabolic deficits improve and whether improvement in functional imaging is correlated with neuropsychological change. For example, it is known that metabolic or flow defects may persist after a stroke or trauma despite the presence of a normal neurologic exam. The Columbia Presbyterian Medical Center's clinical experience with Lyme disease patients indicates that improvement in SPECT abnormalities may occur rapidly or lag behind clinical improvement by many months.

Questions Raised by the Structural and Functional Imaging Data Studies of Chronic Lyme Encephalopathy. Several critical public health questions are raised. First, do patients with previously treated encephalopathy show an improvement in brain imaging (both functional and

structural) and cognition after repeated courses of antibiotic treatment? Second, are there patient variables that predict who is more likely to respond? Third, are there neuroimaging pretreatment variables that are associated with treatment response? Fourth, can structural or functional neuroimaging be used as an objective tool to monitor response to treatment? And finally, is there a subgroup of patients with possible Lyme encephalopathy who no longer respond to treatment because of cerebrovascular disease?

These questions will be addressed by a newly funded study of persistent Lyme encephalopathy being conducted at the Columbia Presbyterian Medical Center in New York City. Under the direction of Dr. Brian Fallon, this 4-year study will enroll 60 patients with cognitive deficits secondary to Lyme disease and 20 healthy controls. The 60 patients must have well-documented Lyme disease and must have received a total of at least 8 weeks of IV antibiotic therapy previously. Patients and controls will get baseline serologic, CSF, and imaging tests at baseline. The imaging tests include MRI and PET. The PET imaging includes a test of neuronal metabolism (FDG), a test of vascular flow (O15-water), and a test of vascular flow after a hypercapnic challenge. The hypercapnic challenge involves breathing in a small amount of CO_2-enhanced air which, in a person with normal blood vessels, would result in a broad increase in perfusion. In a patient with vasculitis with ischemia at which the vasculature may already be maximally dilated, however, the O15 PET scan after the hypercapnic challenge would reveal a relative deficiency of increased perfusion in the affected areas - thus providing a relative simple way of determining whether a patient's disease process involves vascular disease.

The treatment component of this new study (conducted at the patient's home) involves a placebo-controlled treatment with 10 weeks of IV ceftriaxone in which 40 patients get randomized to IV antibiotics and 20 patients get randomized to IV placebo. Patients will then be followed off antibiotics for 14 weeks, monitored both by cognitive tests and brain imaging 2 weeks after the end of treatment and 14 weeks after end of treatment. The aim is to determine whether patients who have persistent cognitive deficits despite considerable past IV antibiotic therapy benefit from a repeated course of intensive antibiotic therapy. This study should address questions regarding the time course of improvement cognitively and via imaging as well as whether the improvement between these 2 assessment modalities are closely correlated. Collaborators at other institutions will attempt to culture Borrelia organisms from the spinal fluid and examine the spinal fluid for markers of infection, such as matrix metalloproteinase, PCR, and *B burgdorferi*-specific immune complex. In addition, the investigation of multiple variables at baseline (serum, CSF, imaging, clinical) may help to identify markers that would predict who responds to treatment and who does not. Dr. Fallon concluded his talk by providing the phone number for physicians interested in referring patients to the study (212-543-5367).