Tc-99m HMPAO Brain SPECT Imaging in Chronic Lyme Disease

Jeffery J. Plutchok, MD; Ronald S. Tikofsky*‡, PhD; Kenneth B. Liegner§, MD; Janice M. Kochevar§, FNP-C; Brian A. Fallon†, MD; and Ronald L. Van Heertum*, MD*

ABSTRACT

Patients with Lyme disease may experience neuropsychiatric problems that persist even after standard courses of antibiotic therapy. Objective detection of neuroimaging brain abnormalities can be helpful to the clinician by demonstrating either focal or diffuse deficits, thereby supporting a CNS origin to the neuropsychiatric problems. To examine the potential utility of SPECT brain imaging in the evaluation of chronic Lyme disease (CLD), two questions were addressed: 1) Are SPECT brain scans abnormal in CLD patients with neuropsychiatric findings? and 2) If abnormal, are the perfusion abnormalities specific for CLD?

SPECT brain scans of 19 patients with CLD and 14 non-CLD patients with other neurological diagnoses resulting in perfusion abnormalities were evaluated in a blinded read without reference to clinical status. Scans were randomly ordered for interpretation by three experienced SPECT readers. Final interpretation was arrived at by consensus. Scans were interpreted as normal, abnormal-focal hypoperfusion, or abnormal-diffuse hypoperfusion. Hypoperfusion was described as homogenous or heterogenous. Results were analyzed as percent normal or abnormal and pattern of abnormality.

CLD SPECT scans were interpreted as abnormal in 14 of 19 (74%) scans, each characterized as heterogeneous with or without globally decreased perfusion. One CNSLD scan showed a focal lesion. CLD patterns could be distinguished from non-LD patients with a diagnosis of Alzheimer's or Moya-Moya disease but not from non-LD patients with a diagnosis of Creutzfeldt-Jacob disease, Lupus, cerebral vasculitis, or chronic fatigue syndrome. Of the 14 patients who had brain MRI scans, only 2 (14.3%) were abnormal, revealing white matter hyperintensities.

These findings suggest that brain SPECT may be a more sensitive tool than MRI for identifying brain abnormalities in CLD, but that the heterogenenous pattern is not specific to CLD.

Key words: Lyme disease, SPECT, brain imaging, profusion

INTRODUCTION

Patients with chronic Lyme disease (CLD) may have persistent neuropsychiatric signs and symptoms.[1-3] The identification of objective markers of brain involvement in this patient population is critical: a) to support the hypothesis that the neuropsychiatric problems are related to a diffuse brain disease; and b) to provide evidence of physiologic change that may correlate with reduced symptoms following treatment. A variety of imaging modalities including CT and MR have had limited value in the evaluation of CLD patients. SPECT brain imaging is a potential tool for establishing the presence of brain changes in these patients. In particular, if SPECT brain scans reveal perfusion abnormalities, then such findings would be helpful in establishing the physiological basis for the clinical presentation. Preliminary reports suggest that brain SPECT studies of patients with CLD who present with neurological and/or psychiatric complaints[4-6] are often abnormal.

To examine the potential utility of SPECT brain imaging in the evaluation of the patient with CLD, we performed a retrospective study to address two questions.

*From the *Departments of Radiology and †Psychiatry, New York-Presbyterian Medical Center, New York, New York; ‡Department of Radiology, Harlem Hospital Center, New York, New York; §Private Practice in Armonk, New York; and Department of Radiology, St. Joseph's Hospital and Medical Center, Paterson, New Jersey.*

Address correspondence to Ronald L. Van Heertum, MD, Division of Nuclear Medicine, Department of Radiology, New York-Presbyterian Medical Center, New York, NY 10032.

First, do CLD patients with neurological and/or psychiatric findings have abnormal SPECT brain scans? Second, if SPECT scans are interpreted as abnormal, are the perfusion abnormalities specific for CLD?

MATERIALS AND METHODS

Subjects

Lyme disease patients. SPECT brain scans of 19 patients (mean 35.6 years, SE 2.8, 9M/10F) with a diagnosis of CLD who were referred to the Nuclear Medicine Division, Department of Radiology, New York Presbyterian Medical Center prior to 11/19/96 were evaluated in a blind read. The clinical work-up and diagnosis of CLD was made by the referring physicians.

Based on clinical records and examination the diagnosis of CLD was confirmed by ensuring that all patients met the following criteria: a) a multisystem illness affecting the neurologic, articular, cardiac, and/or dermatological systems; b) a positive Western blot (IgG or IgM) for Lyme disease; and c) exposure to a Lyme endemic area. Patients in this sample had Western blot assays performed at one or both of the following two laboratories: BBI Clinical Laboratories (New Britain, CT) and/or University Medical Center Health Sciences Center, State University of New York at Stony Brook (Stony Brook, New York). The standard for Westem blot interpretation varied depending upon the individual laboratory.

Chart review showed that each patient had constitutional, musculoskeletal, and neuropsychiatric symptoms. The most prominent complaints among the 19 patients were:

Constitutional—fatigue (100%), insomnia (52.6%), night sweats (26.3%).

Musculoskeletal—migrating large joint pains (84.2%), neck pain (52.6%), arthritis (15.8%).

Neuropsychiatric—cognitive complaints (eg, memory, attention) (94.7%), headache (89.5%), paresthesias (57.9%), tinnitus (57.9%), depression (52.6%), blurry vision (52.6%), photophobia (26.3%).

It was documented in the physician's chart that 31.6% of the patients had an erythema migrans rash. Only 26.3% of the patients recalled a tick bite. All CLD patients in this study had undergone prior antibiotic treatment for Lyme disease. The majority of patients had been ill for more than a year before Lyme disease was diagnosed and treated (median 88 weeks).

MRI, EEG, CSF, and neuropsychological test data were available on some of the patients: 2 of 14 patients (14.3%) had abnormal brain MRIs (white matter hyperintensities); 1 of 8 patients had an abnormal EEG; 6 of 11 patients (54.5%) had abnormal spinal fluid (elevated protein, lymphocytosis, *Borrelia burgdorferi* PCR, and/or elevated Lyme titer). None of these 6 patients met criteria for intrathecal antibody production; 10 of the 19 patients had a battery of neuropsychological tests with each of the 10 individuals demonstrating clinically significant cognitive deficits.

Non-Lyme disease patients. SPECT brain images of 14 non-LD patients were selected from among the recent scans performed in the Nuclear Medicine Laboratory of the Nuclear Medicine Division of the Radiology Department at the New York-Presbyterian Hospital. These scans were interspersed among the scans obtained on the CLD patients as described below. Non-LD patients ranged in age from 29-47 years (mean 46 yrs). Clinical diagnoses in these patients were: presumed Alzheimer's disease-2; cerebral vasculitis-4; chronic fatigue syndrome-3; Creutzfeldt-Jacobs disease (pathologically confirmed)-l; Lupus-2; and vascular insufficiency-2. The 3 patients with chronic fatigue syndrome were seronegative for Lyme disease according to the referring physician. Because this was a clinical series of scans, the medical work-up of these other 11 patients with other neurologic illnesses was unknown to us. In other words, we do not know whether or not these patients had been tested for Lyme disease.

SPECT Imaging Studies

Prior to their SPECT examination, LD patients were told not to use caffeine and nicotine for at least 2 hours prior to the study. Patients were administered an IV injection of Tc-99m-hexamethlypropyleneamine (Tc-99m-HMPAO) in doses ranging from 555 to 814 megabecquerel (15-22 millicuries) while in a supine position with eyes open in a low-stimulation environment. Imaging was begun 40 minutes post injection.

Images were acquired on a triple-headed SPECT camera (Picker Prism 3000, Cleveland, OH) following a previously validated rapid acquisition sequence (RAS) imaging protocol.[6] The details of image acquisition and processing are described in the Appendix. Axial, coronal, and sagittal Picker light box images were reviewed using the Picker step-10 color scale. Studies were normalized to mean cerebellar counts. Background counts were set to the scalp activity (approximately 10% background subtraction). If cerebellar disease was evident then the study scale was normalized to the deep grey matter. The color scale was consistent across all patients.

Image Interpretation

The 33 SPECT brain scans (19 CLD and 14 non-LD patients) were randomly ordered for a blinded interpretation by 3 experienced SPECT readers (RVH, RST, JJP). Final interpretation was arrived at by consensus. No clinical information was available to the readers when the

images were subjected to interpretation. Scans were interpreted as normal if there were no areas of hypo/hyperfusion. An area of abnormal perfusion was defined as nonanatomic cerebral hypoperfusion that was ≤ 60% of the cerebellar or deep grey matter perfusion. Perfusion abnormalities were defined as: a) focal if the hypoperfusion was confined to one brain lobe, or b) diffuse if more than one lobe showed hypoperfusion. Patterns of hypoperfusion are described as either homogenous or heterogenous. A homogeneous pattern was defined as diffuse hypoperfusion throughout the cerebrum. A heterogeneous pattern was defined as multiple or diffuse areas of hypo perfusion interspersed with areas of normal perfusion.

Data Analysis

Results of the consensus read of the SPECT scans were subsequently analyzed to determine the percent of scans interpreted as normal or abnormal and types of abnormal patterns observed.

RESULTS

SPECT scans were interpreted as abnormal in 14 of the 19 (74%) patients with CLD. In 13 of the 14 patients, a SPECT scan pattern was characterized by diffuse cortical heterogeneity with or without globally decreased perfusion. A focal lesion was seen in 1 abnormal scan. The patterns in the CLD scans could not be accurately distinguished from the scan patterns observed in patients with Creutzfeldt-Jacobs disease (1/1 incorrect), Lupus (1/2 incorrect), cerebral vasculitis (2/4 incorrect), and chronic fatigue syndrome (3/3 incorrect). This heterogeneous pattern was not seen in the 2 Alzheimer's patients and the patient with Moya-Moya disease. Representative SPECT scans for CLD and non-LD patients are shown in the Figure.

Of the 11 patients on whom CSF results were available, 6 had an abnormal CSF of whom 4 also had an abnormal SPECT, and 5 had a normal CSF of whom 4 had an abnormal SPECT. Of the 10 patients who had neuropsychological testing and who demonstrated cognitive deficits, 6 of the 10 had abnormal brain SPECT scans. Of the 14 patients on whom MRI results were available, 12 had normal brain MRIs but 9 of these 12 had abnormal SPECT scans.

DISCUSSION

Lyme disease is the most common vector-borne infectious disease in the United States. It is caused by the bacterium, *Borrelia burgdorferi,* a spirochete.[7] The disease may cause acute-subacute (days to weeks), and chronic (months, years, and even decades) bouts of insidious, multisystem signs and symptoms of infection. The most commonly reported symptoms are musculoskeletal, dermatologic, neurologic, psychiatric, and cardiac.[8]

Neurologic/psychiatric signs and symptoms may occur in up to 40% of patients shortly after infection. Neurologic findings may include Bell's palsy, acute meningitis, acute encephalitis, or motor or sensory peripheral nervous dysfunction. Memory loss, inattention, slow processing speed, anxiety, depression, paranoia, and severe mood swings have been reported as neuropsychiatric manifestations of central nervous system involvement.[3]

Reports suggest that not all patients with Lyme infection become seropositive.[9,10] There is a need for "objective" tools to aid in diagnosis, and to gauge the efficacy of antibiotic therapy in patients with neuroborreliosis. Such tools include neuropsychological testing and noninvasive imaging procedures. MR imaging in CLD reveals a wide variety of noncortical abnormalities. Reports show that the percent MR abnormalities vary between 10% and 40% in LD patients with neurologic signs and symptoms.[3,11,16] In our sample, 14.3% had abnormal MR scans, each demonstrating white matter hyperintensities. Although not a sensitive test in detecting abnormalities among patients with CLD, MRI is a very useful technique for excluding other diseases such as neoplasms, vascular or congenital malformations, and chronic extra-axial bleeds that could result in clinical presentations like those of CLD.

SPECT brain imaging is another noninvasive imaging modality that may have utility for assessing CNS involvement associated with Lyme disease. Das et al reported that 51.4% of 35 suspected CNS Lyme disease patients showed SPECT abnormalities.[4] The pattern described was that of heterogenous decreased cortical perfusion in 83% of cases with abnormal scans. We report a similar finding, with 14/19 scans (74%) being abnormal. The most prominent pattern was that of a diffuse heterogenous reduction of cortical perfusion. At the present time there is no satisfactory explanation for the pattern observed in LD. The cortical abnormalities seen on SPECT scans may represent a secondary response to involvement of subcortical white matter. These abnormalities may also be caused by vasculitis.[16] Logigian et al,[5] using quantitative brain SPECT analysis, reported multifocal white matter perfusion abnormalities in patients with LD.

The pattern of diffuse cortical heterogeneous hypoperfusion reported in the present study is similar to that seen in patients with Creutzfeldt-Jacob disease, primary cortical vasculitis, Lupus, and chronic fatigue syndrome. This pattern has also been reported for patients with AIDS infection and polysubstance abuse.[17,21] However, the pattern is distinct from that of Alzheimer's disease or the watershed hypoperfusion in Moya-Moya disease. In Alzheimer's disease, for example, we would typically see decreased perfusion in the temporo-parietal regions of the brain in both hemispheres with sparing of the sensory-motor strip.

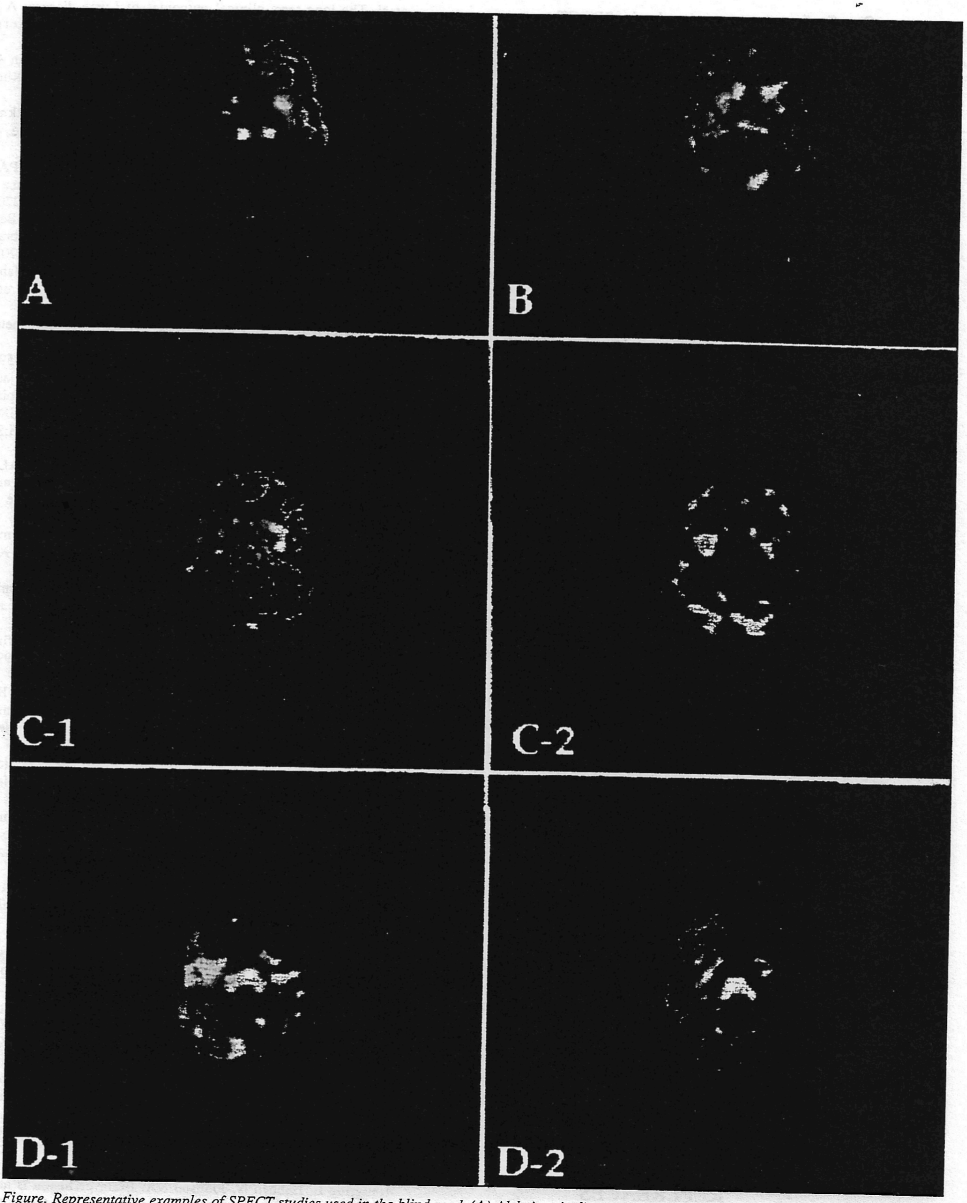

Figure. Representative examples of SPECT studies used in the blind read. (A) Alzheimer's disease; (B) cerebral vasculitis; (C-1) baseline—Lyme disease patient; (C-2) same patient after treatment showing improvement; (D-1) baseline—Lyme disease patient; and (D-2) same patient after treatment whose condition worsened.

Our findings suggest that brain SPECT scans may be an objective and useful tool for visualizing the cortical changes that may be correlated with the central nervous system manifestations of Lyme disease. It must, however, be emphasized that the finding of a "normal" brain SPECT scan is not sufficient to "rule out" the presence of CNS Lyme disease. Likewise, an abnormal SPECT scan by itself does not suffice to establish a diagnosis of Lyme disease, but with other clinical and laboratory data may point to CNS involvement when the diagnosis of Lyme disease cannot be established by other means. Abnormalities revealed in the SPECT scans are not typically seen with standard anatomic imaging procedures such as MRI or CT.

Although a significant number of scans of the CLD patients revealed abnormalities, these abnormalities could not be distinguished from other disease entities that show diffuse heterogenous hypoperfusion. Our findings, therefore, demonstrate that SPECT brain imaging can be helpful in identifying the presence of a disease process that affects the brain diffusely, but the lack of specificity in the heterogeneous pattern limits its usefulness in distinguishing one diffuse brain disorder from another. Our study does not answer the question of whether brain SPECT scans can be used to differentiate patients with primary psychiatric disorders from patients with Lyme disease accompanied by secondary psychiatric disorders because none of our control patients had a primary psychiatric disorder as the main diagnosis.

This study by nature of its retrospective design has limitations that preclude definitive conclusions. For example, although we presumed that the non-Lyme disease patients did not have Lyme disease based on the referring physician's clinical information, this is not certain given that we did not conduct Lyme tests on these patients. This issue is particularly problematic regarding patients with chronic fatigue syndrome whose symptom constellation is quite like that of patients with CLD. Although the referring physician assured us that patients with chronic fatigue syndrome had negative Lyme serologies, we still could not be certain that they did not have Lyme disease as the trigger to their chronic fatigue given the problems with serologic sensitivity in Lyme disease.

Further research, combining systematic neurologic/neuropsychologic testing with serial SPECT scanning is needed to further elucidate the role of SPECT scanning in Lyme disease and to assess the effects of various therapeutic interventions for CLD.

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APPENDIX

SPECT images were obtained by acquisition of four RAS data sets with a Leuhr-Fan beam collimators (Picker). Each data set was a 360° continuous mode. Acquisition was comprised of 120 total projection images (40 projection images per detector). The radius of rotation was equal to or less than 14 cm, with a hardware zoom-magnification factor of 1.0. Each projection image was 7.5 seconds with a total acquisition time of approximately 20 minutes. Axial images were aligned parallel with the canthomeatal line and the corona/sagittal planes were aligned perpendicular to the axial rotation of the camera. Images were acquired into a 128 × 128 digital computer matrix. The four rapid acquisitions sequences were subsequently summed together and reconstructed with filtered backprojection and attenuation correction of 0.11 (Picker). A low-pass (Butterworth, Picker) filter was used with a fifth order slope and the cut-off frequency of .35–.45 cycles per pixel. Single pixel width transaxial images were used to reconstruct the coronal and sagittal planes. All image planes were displayed as 3 pixel width (6.6 mm) thick slices. The SPECT system spatial resolution was 0.78 cm (FWHM).