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Differential Diagnosis and Treatment of Lyme Disease, with Special Reference to Psychiatric Practice

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Editor's Note

A few months ago, I was asked to see a patient in consultation who had a history of depressive episodes that had been effectively managed with sertraline. Although still on medication, the patient abruptly developed a severe depression. She did not respond to an increase in dosage, nor to a shift to another antidepressant. On careful questioning, I discovered that this episode was "not quite like previous ones." Suicidal ideation? Yes. A feeling of hopelessness? Yes. But she also experienced an unfamiliar exhaustion. Normally an active person, she found her state disabling, unbearable, depressing. I can't say exactly what made me suspicious, but I was. She did live in a semi-rural area where deer were abundant, but that was surely not enough. I strongly suggested she speak with her primary care physician and ask her to do tests for Lyme disease. The diagnosis was positive. Treatment with antibiotics led to a substantial improvement in her overall health and her depressive mood in particular.

An experienced clinician will have a "nose" for things that don't seem quite right, psychiatrically that is, when a physical illness may be contributing significantly to a state that manifests itself in mood or behavior. Lyme disease is one such condition, and in its late stage can involve an encephalomyelitis (rare) or encephalopathy, the latter being associated with symptoms that fluctuate from day to day—profound fatigue, sleep disturbance, new onset cognitive problems such as deficits in short-term memory or difficulty with performing and attending to multiple concurrent tasks.

The most common neuropsychiatric presentations of Lyme disease in adults are, in fact, fatigue and problems with memory and attention, along with mild to moderate mood swings. In children, headaches are often followed by behavioral, mood, and attentional problems. Concomitant fatigue, muscle and joint pains, neurologic symptoms and/or memory problems, onset following a flu-like illness, known history of a tick bite, tick exposure in a Lyme-endemic area, lack of response to psychotropic medication, should alert the physician to the possibility of Lyme disease. If the disease is suspected, a focused history and symptom inventory are in order, with referral to an internist or primary care physician for serologic testing and subsequent management. The laboratory assessments are critical, but often unclear, so that clinical assessment remains an essential tool in diagnosis.

For early localized or disseminated Lyme disease, a 3–4 week course of oral antibiotics is usually adequate, using, for example, doxycycline and other tetracycline derivatives, amoxicillin and other penicillin derivatives. In late-stage Lyme disease, and especially when the central nervous system is affected, intravenous antibiotics are the drugs of choice. *A timely diagnosis and effective treatment can save many patients from years of suffering and disability.*[1]

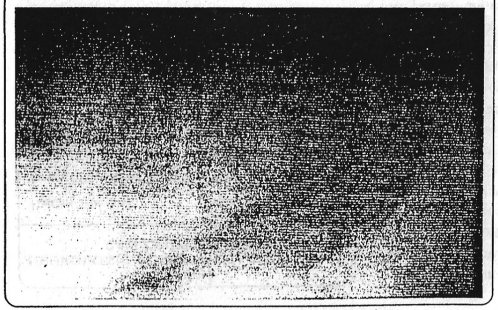
It is usually best to treat the patient with antibiotics alone, since the cognitive and mood disturbances will often improve as he or she recovers from Lyme disease. However, when the concomitant use of psychoactive medications is necessary, it must be done cautiously, considering drug-drug interactions with the antibiotics. If antidepressants are called for, SSRIs that are least reliant on Cytochrome P450 3A/4 enzymes for their metabolism are the safest choice, namely, sertraline, paroxetine, and fluoxetine.

Introduction

A wide array of infectious organisms are known to cause neuropsychiatric disorders, including: HIV, the agent of AIDS; treponema pallidum, the agent of syphilis; and now Borrelia burgdorferi, the agent of Lyme disease. Like syphilis, **Lyme disease can mimic a broad spectrum of psychiatric disorders**, so it behooves psychiatrists to become familiar with its phenomenology and diagnosis, especially since **psychiatric symptoms may be the presenting manifestation of the disease.** Furthermore, given the complexity of the psychological, psychosocial, and neurobiological ramifications of central nervous system Lyme disease, patients with known disease often seek psychiatric care.

Lyme disease was originally understood to be a tick-borne illness characterized by an erythema migrans rash and flu-like symptoms that, left untreated, might progress to disabling arthritis.[1] It is now known that early hematologic dissemination from the site of skin inoculation to multiple organ systems can result in multisystemic disease. Treated early, the course is usually benign, but late stage Lyme disease can become chronic, intensely disabling, and is most commonly and prominently a neuropsychiatric illness.[2] This lesson will provide an overview of the phenomenology, diagnosis, and treatment of neuropsychiatric Lyme disease, with special reference to those issues that are of significance to psychiatric practice.

Figure 1
A TYPICAL ERYTHEMA MIGRANS RASH



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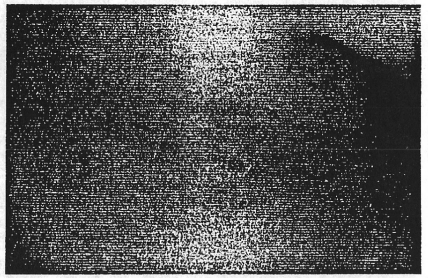
History and Epidemiology

Lyme disease is named for the town, Lyme, Connecticut, where the first known cases of Lyme arthritis were investigated and reported in the late 1970s.[3] Subsequently, **the disease was linked to a spirochete,[4] Borrelia burgdorferi, the causative agent of a number of previously-reported, prominently neurological syndromes in Europe known as Bannworth's syndrome, Garin-Bujadoux syndrome, and neuroborreliosis.[5–7] Whereas Lyme disease had been known in the United States mainly as a rheumatological disease, it is now recognized that the later stages of the disease manifest primarily as neurological and/or neuropsychiatric conditions.[8]** While the early neurological manifestations such as meningitis, cranial neuritis, and radiculitis have been widely reported, only recently have the late neuropsychiatric manifestations of Lyme disease become cause for rising concern and re-

search efforts. Many cases of late Lyme disease have thereby been missed on the basis of narrow clinical criteria which focused primarily on the rheumatologic and early neurologic manifestations.

Whereas the disease has been considered endemic to the East Coast, cases have now been reported throughout the United States as well as in Europe, Asia, and Australia. The most heavily affected areas include the Northeast (New York, New Jersey, Connecticut, Pennsylvania, Massachusetts, Rhode Island), the upper Midwest (Minnesota, Wisconsin), and the Pacific coastal region (California, Oregon). In 1996, the number of new cases of Lyme Disease reported to the Center for Disease Control totaled 16,461, representing an increase of 41% over the 1995 total.[9] The number of actual cases, including non-reported ones, is thought to be at least three times higher.

Figure 2
AN ATYPICAL ERYTHEMA MIGRANS RASH



Clinical Diagnosis

Despite the advances in laboratory testing over the last decade, Lyme disease remains a clinical diagnosis.[10] Hence, consideration of any given case must take into account the phenomenology of the disease as well as pertinent laboratory testing. Additional diagnostic aids are available for the evaluation of central nervous system Lyme disease and will be discussed in a separate section.

CLINICAL MANIFESTATIONS:

Staging for Lyme disease consists of three phases: *early localized* (erythema migrans rash), *early disseminated*, and *late stage*. Erythema migrans rash, although typically a bullseye red circular rash (see Figure 1), may have other shapes and colorations as well (see Figure 2). Early dissemination, when the spirochete is transported hematogenously, is typically marked by a flu-like illness characterized by fever, malaise, arthralgia, and myalgia. "Satellite" lesions similar in form to the erythema migrans rash are evidence of dissemination. Given that approximately one-third of patients do *not* recall a tick bite or a rash and because the initial flu-like illness may be mild, subsequent neurologic or neuropsychiatric manifestations may constitute the initial presentation. Invasion of the CNS can occur as early as a few weeks after inoculation.[2,11-13] The patient, however, may be asymptomatic for months to years, until the dormant CNS infection becomes active.[14]

In early disseminated neurologic disease, patients may experience headaches without any signs of inflammation in the cerebrospinal fluid (CSF).[15] **Meningitis, encephalitis, cranial neuritis, and/or motor or sensory radiculitis may then follow.**[16] Typical symptoms of meningitis include recurrent severe headaches, stiff neck, photophobia, and, less commonly, nausea and vomiting. When the brain parenchyma is involved, **other symptoms may include fluctuating disturbances of mood, concentration, memory, and sleep. It is at this stage or in the context of an ensuing encephalopathy that patients most typically seek psychiatric help, in some cases before the existence of a medical illness has been recognized. Cranial neuritis most typically affects the seventh cranial nerve, yet the resulting Bell's Palsy occurs in only 5%–10% of patients with neurologic Lyme disease.**[17] Other signs of **peripheral nerve involvement** include sensory or motor neuropathies: objective abnormalities may be evident on nerve conduction studies. Symptoms of peripheral neuropathy typically include sharp shooting pains, areas of numbness, paresthesias, weakness, or fasciculations. **Autonomic neuropathies may occur as well, presenting as localized piloerection, flushing, hypotension, syncope, resting tachycardia, and/or disturbances in sexual functioning.**

Table 1
NEUROLOGIC CONDITIONS LYME DISEASE CAN CAUSE OR MIMIC

Multiple Sclerosis	Multi-infarct dementia
Amyotrophic Lateral Sclerosis	Kline-Levin Syndrome
Guillain-Barre Syndrome	Strokes
Sydenham's chorea	Brain Tumor
Tourette's Syndrome	Epilepsy
Alzheimer's Disease	Tullio Phenomenon
Autonomic Dysregulation Syndrome	Neurally Mediated Hypotension

In the *late disseminated form* of Lyme disease occurring months to years after skin inoculation, the joints, eyes, heart, and/or CNS are typically affected. Left untreated, migratory arthralgias may develop into an inflammatory arthritis in 60% of patients, typically affecting the large joints, such as the knee.[18] Ophthalmologic involvement generally involves localized inflammation such as uveitis, iritis, or optic neuritis.[19,20] Symptoms may include photophobia, visual illusions such as flashing lights or shadows, visual distortions or, rarely, unilateral blindness.

Late central nervous system involvement consists of an encephalomyelitis or encephalopathy.[14,15,21] *Encephalomyelitis*, an uncommon manifestation of Lyme disease, may have quite severe and diverse presentations, including spastic paraparesis, hemiparesis, transverse myelitis, cerebellar syndromes, and movement disorders.[15,21] Because the symptoms of encephalomyelitis may wax and wane in intensity and **because the MRI lesions include white matter hyperintensities, patients may be misdiagnosed as having multiple sclerosis. Other neurologic presentations of Lyme disease may mimic (or include) amyotrophic lateral sclerosis, seizure disorders, Tullio phenomenon and Guillain-Barre syndrome** (see Table 1).[14,22-24]

Most common in late Lyme disease is an encephalopathy characterized by subtle to severe cognitive deficits and a polyradiculopathy,[14] **often without concomitant arthritis. Because the CSF and brain MRI scan may appear normal, establishing the diagnosis of Lyme encephalopathy is often helped by other adjunctive diagnostic aids, such as SPECT imaging and neuropsychological testing** (testing methods will be described below). **Patients with Lyme encephalopathy typically experience symptoms that fluctuate from day to day, most common of which are profound fatigue, sleep disturbance, and new onset cognitive problems, such as deficits in short-term memory or difficulty with performing and attending to multiple concurrent tasks. Other symptoms include photophobia, hyperacusis, irritability or emotional lability, word-**

Table 2
PSYCHIATRIC SYMPTOMS/DISORDERS ASSOCIATED WITH OR MIMICKED BY LYME DISEASE

ADULTS

Depression
Mood Swings/Atypical Bipolar Disorder
Panic Attacks
Anxiety
Depersonalization/derealization
Personality change (increasingly irritable, impulsive, or aggressive)
Conversion Disorders
Intermittent Explosive Disorders
Paranoia
Mania
Somatization Disorder
Posttraumatic Stress Disorder
Atypical psychoses
Schizophrenia
Schizoaffective Disorder
Dementia (misdiagnosed as Altheimer's disease or multi-infarct dementia)

CHILDREN & ADOLESCENTS

Attention-Deficit Disorder (Inattentive Subtype)
Oppositional Defiant Disorder
Mood Disorders
Phobias/Separation Anxiety Disorder
Obsessive Compulsive Disorder
Tourette's Syndrome
Anorexia Nervosa
Pseudo-psychotic disorders
Specific or Pervasive Developmental Delays
(In Parents): Munchhausen's by proxy

Table 3
WHEN CONSIDERING LYME DISEASE: HISTORY AND TEST

HISTORY
- *Exposure to a Lyme endemic area*
  - *Pets/Bird Feeder at home*
  - *Tick bite*
    - Ixodes Scapularis (not a dog tick)
    - Duration of attachment
    - Laboratory confirmation of B. burgdorferi within the tick

SYMPTOMS
- *Physician-diagnosed erythema migrans rash*
- *Severe flu-like illness: fever, arthralgia, myalgia*
- *Subsequent development of symptoms of disseminated Lyme disease (see Table 4)*

LABORATORY TESTS
- *ELISA, Western Blot, PCR (whole blood, urine, CSF)*
- *Evaluation of Prior Western blots: performed at a sensitive Lab? All bands reported?*
- *Experimental tests: antigen tests (urine, CSF), immune complex dissociation assays*
- *CSF analysis: routine assays, particularly opening pressure, protein, WBC, Lyme antibodies, PCR*
- *Neuropsychological testing*
- *Nerve Conduction Studies*
- *Structural Brain Imaging: T1- and T2-weighted MRI images with FLAIR sequences*
- *Functional Brain Imaging: SPECT or PET*

finding problems, dyslexic-like errors when speaking or writing, and spatial disorientation.[14,25] Because of the profile of persistent marked fatigue and cognitive deficits, patients with late-stage Lyme disease may be misdiagnosed as having chronic fatigue syndrome (CFS).[2] In one study of patients diagnosed with chronic fatigue syndrome after presumed adequate treatment for late Lyme disease, 50% were found to have ongoing evidence of *intrathecal antibody production to Borrelia burgdorferi.* This suggests that, at least in some cases, emergence of Chronic Fatigue Syndrome (CFS) following Lyme disease may in fact represent ongoing CNS infection[8] and that in some cases persistent symptoms may be responsive to antibiotics. Given that the symptoms which accompany encephalopathy include low energy, irritability, poor concentration, and sleep disturbance, it is readily apparent why **patients with Lyme encephalopathy initially may be misidentified as having primary depression alone.**

The most common neuropsychiatric presentations of Lyme disease in adults are fatigue, problems with memory and attention, and mild to moderate irritability. In children and adolescents, headaches are most common, followed by behavioral, mood, and attentional problems. However, the range of possible psychiatric presentations includes the entire spectrum of psychiatric disorders (see Table 2). Although psychiatric complications are most often a manifestation of late stage disease, psychiatric symptoms may occur as the presenting symptom. **The presence of concomitant fatigue, muscle and joint pains, neurologic symptoms and/or memory problems, onset following a flu-like illness, known history of a tick bite, exposure to a Lyme-endemic area, atypical psychiatric presentation or lack of expected response to psychotropic medication may alert the clinician to the possibility of Lyme disease** (see Tables 3 and 4).

If Lyme disease is suspected, the clinician should take a focused history and symptom inventory, order serologic testing, and, if indicated, refer to an internist, infectious disease specialist, neurologist, or rheumatologist. Three cases in which the initial presentation was psychiatric are described below. These cases will serve to illustrate important aspects of the clinical diagnosis of Lyme disease relevant to psychiatrists.

Table 4
SIGN AND SYMPTOM INVENTORY FOR LATE STAGE LYME DISEASE

SYSTEMIC
- Fatigue
- Fevers (typically low grade)
- Migrating arthralgias or arthritis
- Myalgia
- Sleep disturbance
- Anorexia

CARDIAC
- Cardiac conduction delay
- Pericarditis

CRANIAL or CENTRAL NEUROPSYCHIATRIC
- Headaches and Stiff Neck
- Cranial Nerves:
  - Optic Neuritis (II)
  - Extraocular Palsies (III,IV,VI)
  - Facial tingling/numbness (V)
  - Bell's Palsy (VII)
  - Hearing Loss, Tinnitus, Vertigo (VIII)
- Myoclonic jerks
- Cerebellar Disease
  - Intention Tremor
  - Dysmetria
  - Dysdiadochokinesia
  - Limb or Gait Ataxia
  - Feeling off balance: "as if on a rocking boat"
- Apraxia
- Altered spatial sense
- Visual: illusions, flashing lights
- Movement disorders: tic, chorea
- Sensory Hyperacuities:
  - Sound, Light, or Vibration
- Hemiparesis
- Transverse Myelitis

COGNITIVE
- Mental "fog"
- Short-term memory loss
- Inattention/easy distractability
- Slower mental processing
- Dyslexic changes
- Word-finding problems

PERIPHERAL NEUROLOGIC
- Sensory loss or weakness
- Sharp, stabbing, or lancinating pains
- Fasciculations
- Multifocal Paresthesias
- Burning pains
- Autonomic
  - Orthostatic dizziness
  - Sweating excess or deficit
  - Visual blurring
  - Resting tachycardia
- Bladder irritability leading to urinary frequency

Nota Bene: All symptoms may tend to fluctuate without apparent cause and/or to disappear entirely at intervals. The fluctuations may be from hour-to-hour, day-to-day, week-to-week or month-to-month. This list includes many nonspecific symptoms. Any case must be evaluated in light of the total clinical picture.

CASES WITH A PSYCHIATRIC PRESENTATION:

Case 1

A 45-year-old woman had been treated successfully with sertraline (Zoloft) for two successive depressive episodes, each following a significant life stressor. On both occasions, the medication had been tapered and then discontinued after several months of treatment, and the patient had remained symptom-free in the interval and for several years subsequently. During the autumn of her 44th year, she developed a recurrence of depressive symptoms, sleeplessness, and general malaise with intermittent headache, backache, and knee pain, which she attributed to stress and aging. **When retreated with sertraline, far from responding favorably as before, she developed severe anxiety and panic attacks which remitted on discontinuation of the drug.** A careful history revealed **she had suffered a bout of flu during the summer** when she had been on Cape Cod and had never quite regained her prior level of energy and well-being. She recalled no tick bite or rash, but had on several occasions found ticks on her 10-year-old twin daughters. Given her history of tick exposure in an endemic area, **her psychiatrist ordered Lyme serologies. The ELISA results were equivocal and the Western Blot was strongly positive. Referral was made to an internist who treated the patient with 6 weeks of oral antibiotics.** Both the physical and depressive symptoms remitted over the course of several months without any concomitant antidepressant medication. A later recurrence of depression without prominent physical symptoms was successfully treated with sertraline.

Case 2

A 42-year-old woman sought psychiatric treatment shortly after her move to a new town. She described the

new onset of panic attacks and mood swings. She admitted to being prone to anxiety, but insisted that she had always been upbeat. **She reported feeling "not myself," that her personality had changed, and that sometimes she had a strange sensation of not being inside her own body.** She felt as if she "must be going crazy." **Her history revealed childhood sexual abuse.** She had a "happy-go-lucky" temperament and had coped with past difficulties by "putting the bad things behind me." On mental status exam, she was engaging but emotionally labile, cheerful in overall demeanor, but bursting into tears on several occasions during the interview. There was no evidence of thought disorder, hallucinations, or delusions. **In passing, she remarked that she had been experiencing physical symptoms as well, which intensified the feeling of being "not herself,"** because she had always been a healthy person; **these symptoms fluctuated in intensity and severity**, present some days but not others. These symptoms included **muscle twitches, migrating arthralgia and myalgia, headaches, and episodes of extreme fatigue**. She reported **some difficulty with concentration and memory** as well, but indicated that she had always been "a bit scatter-brained." Despite the fact that depersonalization, somatization and anxiety symptoms seemed easily explicable on the basis of psychodynamic factors related to the patient's history, **the treating psychiatrist inquired further regarding her physical symptoms. Suspecting Lyme disease, he referred her for further medical evaluation.**

A work-up revealed a positive Western Blot, evidence of intrathecal Lyme antibody production in her CSF, cognitive abnormalities on neuropsychological testing, and a brain SPECT scan demonstrating diffuse heterogenously decreased uptake consistent with Lyme encephalopathy. She was then placed on 6 weeks of intravenous ceftriaxone.

Over the subsequent months, her physical symptoms and cognitive deficits remitted and there was a diminution in the frequency of her panic attacks. However, she began to experience nightmares relating to both her recent illness and to her past sexual abuse. She also remained somewhat anxious and labile, unable fully to regain her past emotional equilibrium. Psychodynamic psychotherapy, in addition to psychopharmacologic management (lorazepam[Ativan], 0.5mg p.r.n. up to t.i.d.), has helped her to better integrate early and recent experiences of vulnerability and physical violation resulting from both her recent illness and past abuse. She has been gradually stabilizing.

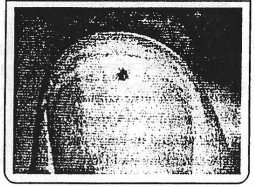
Case 3

A 22-year-old man was admitted to a psychiatric ward following his first psychotic episode. His roommates had noticed that he had been acting strange, staying up late at night, pacing, and making bizarre and elaborate plans for the future. One night the roommates came home and found him in a **highly agitated** state. **He accused them of stealing "classified" information and then began threatening them physically.** Recognizing him to be delusional, the roommates called 911. He was brought to the emergency room **violent and hallucinating** and was admitted to a psychiatric unit. **Multiple trials of antipsychotic and mood-stabilizing medication, although sedating, failed to produce remission of his psychosis.** He seemed to be **acutely sensitive to neurological side effects. His family history was negative for bipolar or other psychotic disorders, but at some point during the hospitalization, his parents mentioned that he had been diagnosed as having had Lyme disease 2 years previously for which he had been treated with 4 weeks of oral antibiotics with remission of his articular symptoms.** Although there were no current symptoms of joint pains, this patient did have recurrent headaches. **Serum ELISA was positive and the Western blot was highly suggestive with 4 of the 5 requisite CDC bands. Although CSF studies were negative, a brain MRI revealed two deep white matter hyperintensities and the brain SPECT revealed moderately decreased heterogeneous uptake.** The diagnosis of probable CNS Lyme disease was made. **This patient was treated with 8 weeks of i.v. ceftriaxone followed by several months of clarithromycin with a resolution of his headaches and psychosis, although he continued to have mild distractibility.** Follow-up MRI and SPECT scans both showed interval improvement.

CLINICAL DIAGNOSIS OF LYME DISEASE IN PATIENTS WITH PSYCHIATRIC PRESENTATIONS:

The diagnosis of Lyme disease may be relatively straightforward (as in case #1 above), **or it may be complicated by any of a number of factors. Such factors include: seronegativity; co-occurrence of both organic and psychogenic etiologic factors**(as in Case 2 above); **absence of objective physical symptoms** (as in Case 3 above); **and presentation in a child whose baseline personality, temperament, and intellectual capacity** are as yet undeveloped or unknown.

Figure 3
THE IXODES SCAPULARIS (DEER TICK)



Given a patient with a prominently psychiatric presentation, in addition to associated physical symptoms and serological test results, the following features, when present, can help in making or supporting the diagnosis of Lyme disease:

- Atypical features of the psychiatric disorder (e.g., absence of typical prodrome, unusually acute onset, uncharacteristic constellation of symptoms)
- Absence of family history of psychiatric disorders
- Presentation of a psychiatric disorder at an older or younger age than is typical (e.g. autistic behavior beginning at age 6, forgetfulness at age 35, first manic episode at age 45)
- Lack of expected response to psychotropic medication (e.g., Case 3)
- Adverse response to previously well-tolerated medication (e.g., Case 1)
- Lack of expected correlation of symptoms to psychological triggers (e.g., mood lability without apparent cause)
- A SPECT scan that demonstrates heterogeneously decreased radiotracer uptake
- Neuropsychological test findings consistent with Lyme encephalopathy

The difficulties of accurate differential diagnosis were well-documented recently in a case report of a young woman with atypical neuropsychiatric features. She was first diagnosed with chronic paranoid schizophrenia and narcolepsy, then PTSD, and finally neuropsychiatric Lyme disease based on positive serum and CSF titers, suggestive serum and CSF Western blots, and abnormal MRI and SPECT scan results.[26]

In addition to a standard medical and psychiatric history, **if Lyme disease is suspected, it is important to ask about exposure to ixodes scapularis** (deer) **ticks** (*not dog ticks*) (see Figure 3), **household pets and bird feeders, residence in or travel to an endemic area, and health of other family members and neighbors. For spirochete inoculation to occur, ixodes scapularis ticks generally need to be embedded for over 12 hours.** The evaluation should also include a **symptom inventory of both physical and psychiatric symptoms. Especially because symptoms typically fluctuate over time, involve multiple organ systems, and may be odd but not bothersome, patients may not consider them to be within the purview of a psychiatric examination or connect them in any way to their present distress.**

The psychiatrist should also inquire into both the precipitants of psychiatric symptoms and any correlation between the vicissitudes of physical and psychiatric symptoms. Episodes of anxiety may have been precipitated by sensory overstimulation, such as visiting a shopping mall. **Periods of increased irritability and depression may correlate with the presence of low-grade fevers.** Panic attacks that tend to occur in supermarkets may be mistakenly diagnosed as agoraphobia; the correlation of the same symptoms with nighttime driving and TV-watching may suggest instead a **sensitivity to fluorescent or strobe-like lighting occasionally seen in late-stage neurologic Lyme disease.**[25] Exposure therapy, as might be appropriate for agoraphobia, would only worsen the condition, as there is often a kindling-like intensification of Lyme disease-induced sensory hyperacuities with repeated or prolonged exposure.[27]

It is crucial to bear in mind during both evaluation and treatment that the clinical presentation may be multifactorial in origin and may be perpetuated, as in Case 2, **by both psychological and organic factors.** Patients with *borderline personality disorder* who develop Lyme-related mood swings and impulsivity may be particularly hard to diagnose and manage, especially as **once a medical diagnosis is made, some patients cling to it as the cause of all their problems,** driving their medical doctors to distraction and eschewing psychiatric help. On the other hand, **the medical diagnosis is easily missed in such patients** by virtue of their chaotic presentation and obvious psychopathology. Some patients may develop pseudo-neurologic symptoms on top of a genuine affliction with neurologic Lyme disease. As is the case with patients with pseudoseizures, a portion of whom are later found to have genuine neurogenic seizures,[28] **the presence of psychogenic neurological symptoms should not lead the clinician to dismiss the possibility of underlying organic disease. Patients with movement disorders may develop hysteroid elaboration of their movements** and thereby be easily dismissed as unbelievable. *Children may manifest behavioral problems or learning difficulties that vary radically from day to day. The correlation of such "bad" days with, for instance, heightened sensitivity to sound or light, headaches, and/or fasciculations may lend credence to the likelihood of an organic basis for such difficulties and help parents and educators evaluate and manage such fluctuations appropriately.* On the other hand, children are very suggestible and may be prone to psychogenic elaboration. Detailed questioning about the patterns and precipitants of symptom fluctuations is therefore essential.

Laboratory Testing

SEROLOGICAL TESTING:

The standard initial tests for suspected Lyme disease include the ELISA and the Western Blot. Both are indirect antibody tests and both should be ordered when evaluating a patient with suspected Lyme disease. **The ELISA, commonly used for screening purposes, may produce both false positive and false negative results.** For example, patients with oral gum disease might have false positive ELISA results due to cross-reactivity with normal non-pathogenic oral spirochetes. False negative results, both on the ELISA and Western blot, may arise in the context of an abrogated immune response due to early antibiotic treatment,[4] generalized immunosuppression, or testing too early in the disease process before antibodies have yet been made. The ELISA and Western Blot only detect free antibodies. Thus, patients with high levels of antigen may have falsely negative serologic results because the antibodies are present primarily or exclusively in circulating immune complexes. Because of the multiple factors that might produce false negative or false positive test results, **decisions about treatment should be based primarily on clinical features. Labs vary in their reliability, and there may be discrepancies in results even among good labs, so it is worth sending serum samples to more than one lab when there is significant uncertainty.**

When ordering a Western Blot, it is important to request that all positive bands (both the CDC-specific and the CDC-nonspecific) **be reported.** The CDC criteria for a positive Western Blot require the presence of 5 significant IgG bands and/or 2 significant IgM bands. The "significant" bands under consideration include the most commonly occurring bands in a sample of patients with early-stage Lyme disease as manifested by the characteristic bulls-eye rash. **Since psychiatric manifestations are most often indicative of late-stage disease, these criteria are not optimal for the population that typically comes to the attention of psychiatrists and may result in a test being falsely interpreted as negative when there is in fact ample evidence of infection.** In particular, the 31 and 34 Kd bands, which correspond to the late-expressing but highly specific OspA and OspB antigens, are not included among the CDC list of significant bands. In general, the presence of IgG reactivity is considered indicative of chronic infection and IgM reactivity of acute infection. Occasionally, however, there may be clinical evidence of late-stage disease and laboratory evidence of IgM reactivity only. The reasons for this are currently unknown. Lyme disease-specific bands as identified by the CDC include: IgM (23-25 kD, 39 kD, 41 kD) and IgG (18,23–25,28,30,39,41,45,58,66,93). The 41 kD band corresponds with a flagellar antigen common to other, including nonpathogenic, spirochetes, but is nevertheless included among the CDC criteria for

significant IgM bands as it tends to be among the first to become positive.

DIRECT TESTS:

Given the above-mentioned limitations of indirect antibody testing, several alternatives have been developed. These include **urine and cerebrospinal fluid** (CSF) **antigen tests and urine, serum, whole-blood or CSF Polmerase Chain Reaction** (PCR). **Both tests may give variable results as antigen shedding is sporadic and there may be very little spirochetal DNA in the circulation even in the context of clinically severe disease. It is best, therefore, to obtain several samples at intervals of a few days. One further mode is the immune-complex dissociation assay on paired samples of serum and CSF which can demonstrate the presence of antibody under conditions of antigen excess by dissociating the antigen-antibody complexes. This test can be extremely useful in confirming the presence of central nervous system infection.**[29]

PROBLEMS WITH TESTING:

It is not uncommon for patients who test negative initially to seroconvert in the course of treatment.[30] **In other infectious diseases, acute and convalescent titers can be helpful in monitoring the activity of the disease. This is less applicable to North American Lyme disease because titers are less reliable.** As noted in a recent FDA Public Health Advisory Statement,

> *"Assays for anti-Bb should be used only to support a clinical diagnosis of Lyme disease. A positive result does not necessarily indicate current infection with B. burgdorferi, and patients with active Lyme disease may have a negative test result."*[10]

There remains at present no surefire way to determine chronicity of infection based on lab testing, and indeed it is not clear whether or not it is possible to fully eradicate the infection once it has become entrenched.

In a demonstration of the problems with serologic testing among patients with Lyme encephalopathy, a recent study of 8 patients with CSF evidence of active CNS Lyme disease[31] demonstrated that 4 of the patients had equivocal serologic results and 2 of the patients were completely seronegative. This study highlighted the importance of multiple modalities in the evaluation of patients with Lyme encephalopathy, including CSF studies and SPECT imaging.

The one gold standard is to culture the organism from joint fluid or tissue samples, but this process has a notoriously low yield.

SPECIFIC AIDS TO THE DIAGNOSIS OF CNS LYME DISEASE:

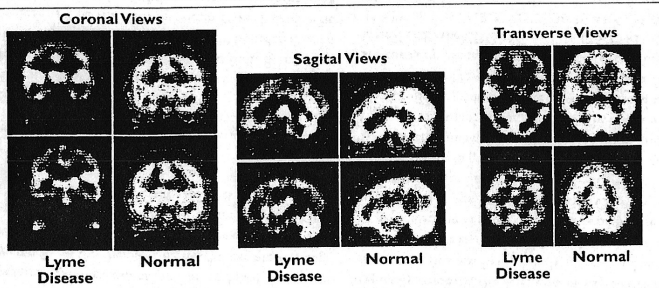
CSF Studies

In patients with suspected central nervous system infection, a lumbar puncture should be performed. Evidence of intrathecal antibody production is considered confirmatory. However, only in the phase of early meningitis or encephalitis is such production commonly found. In a study of 35 patients with late neurologic Lyme disease who had experimental evidence of B.burgdorferi Osp A antigen in their CSF, 43% had normal CSF antibody studies and 20% had no evidence of either Lyme antibodies or typical CSF abnormalities such as an elevated protein or a pleocytosis.[32] Direct detection methods, such as antigen analysis or PCR DNA assays, may be increasingly useful in the future when they are more widely available in commercial laboratories, but even these tests are not definitive. Therefore, **in both very early and late CNS involvement** (e.g., meningismus, encephalopathy, encephalomyelitis), **normal CSF results cannot be used to rule out CNS Lyme disease.**[15]

MRI Studies

In patients with Lyme encephalopathy, results of brain MRI studies are generally normal, although in some cases punctate white matter lesions may be demonstrable, similar to those seen in demyelinating disorders. To best visualize the white matter hyperintensities, the clinician should request T2 weighted images with FLAIR sequences. Because it may be impossible to distinguish the MRI hyperintensities in Lyme disease from those in Multiple Sclerosis, patients with possible Multiple Sclerosis for whom the diagnosis of Lyme disease is being considered should be followed with serial MRI studies. Often, after antibiotic treatment, the white matter lesions in Lyme patients resolve.

Figure 4
NEUROPSYCHIATRIC INDICATORS OF LYME DISEASE



These brain images present adolescents with and without encephalopathy linked to Lyme Disease.

Functional Brain Imaging

Functional brain imaging using SPECT or PET may reveal a pattern of diffuse heterogeneous hypoperfusion in cortical and subcortical areas in as many as 70% of patients with chronic Lyme disease, even among patients with normal CSF, MRI scans, and neuropsychological studies.[31,33-35] As is true for the MRI hyperintensities, improvement in the areas of hypoperfusion can be seen after antibiotic treatment, although scan improvement may not occur until several months after clinical improvement. When called upon to distinguish Lyme-related depressive symptoms from a primary psychiatric disorder, SPECT scans can be very helpful. With primary depression, one would most commonly expect to see decreased uptake in the left prefrontal cortex followed by decreased flow in the temporal lobes. If the pattern instead reveals diffusely decreased heterogeneous uptake throughout the cortex, then one can conclude that another process instead of, or in addition to, depression is involved. However, one cannot conclude that a pattern of diffuse heterogeneity is pathognomonic for Lyme disease, because such a pattern is also seen in other diseases such as vascular dementia, CFS, CNS Lupus, HIV encephalopathy, and chronic or acute stimulant abuse. But, in the absence of these other diseases, heterogeneity on functional imaging would support the diagnosis of neuropsychiatric Lyme disease (see Figure 4).

Neuropsychological Testing

Neuropsychological testing may be helpful in distinguishing Lyme encephalopathy from depression and in pinpointing and quantifying cognitive deficits for purposes of diagnosis, follow-up, and rehabilitation. Tests with multiple versions that are particularly useful include the following: short-term memory and retrieval, (e.g., Buschke Selective Reminding Test and Benton Visual Retention Test), attention/concentration (e.g., Continuous Performance Tests, Stroop), processing speed and complex visuomotor tracking (e.g., Trail Making, Symbol Digit Modalities), and verbal fluency (e.g., Controlled Oral Word Association Test). These tests cover the domains most commonly affected by CNS Lyme disease. Documentation of deficits and change after treatment can help patients obtain insurance coverage for needed antibiotic treatment and, if a relapse occurs after treatment, may be particularly useful when advocating on behalf of the patient to obtain additional antibiotic treatment. Given that there may be a dearth of objective findings on the neurological exam and in the CSF, **demonstrated worsening of SPECT scan and neuropsychological testing results**

Table 5
PSYCHOTROPIC MEDICATIONS OF POTENTIAL VALUE FOR LYME-RELATED SYMPTOMS

INDICATIONS	MEDICATIONS AND DOSAGE
Depression	**SSRIS, bupropion, TCAs, Venlafaxine, Nefazadone**
Bupropion may have fewer side effects in the medically ill. Patients with marked anxiety or mixed anxiety/depression may benefit from tricyclics at HS. Fluvoxamine may interact with the macrolide antibiotics and carbamazepine via its 3A4 Hepatic metabolism.	
Mood Swings	**Carbamazepine, Valproic Acid, Gabapentin**
Lithium should be avoided as it may result in greater organicity and impaired cognition.	
Fatigue and Inattention	**Bupropion, Stimulants**
Patients with seizures or significant myoclonus should avoid these medications as both lower the seizure threshold.	
Sleep Disturbance	**Trazadone, Doxepin, Zolpidem, Amitriptyline**
Rarely, trazadone may result in priapism among men. Low dosages of these medications are often adequate.	
Anxiety/Obsessionality	**SSRIs for obsessionality, Clonazepam, Alprazolam**
Obsessionality can be markedly reduced with high dose SSRIs, although therapy should start at lower doses to reduce the likelihood of precipitating panic attacks.	
Sensory Hyperacuities	**Clonazepam, Carbamazepine, Valproate**
Sound sensitivity in particular may be reduced.	
Pain	**SSRIs, Low dose tricyclics, esp. Amitriptyline. Carbamazepine, gabapentin**
Fluoxetine and paroxetine may decrease the efficacy of narcotic pain relievers via their 2D6 hepatic isoenzyme effects. High dose gabapentin may be particularly helpful for pain relief, however a subset of patients may experience worsening articular symptoms and confusion.	

may be the only available confirmation. Word, number, and letter reversals in speaking and writing are common, including in patients with no prior history of dyslexia. Paraphasias are common as well (e.g., crutches for chopsticks, map for calendar) as are parapraxes (e.g., putting the cereal box in the refrigerator and the milk on the cabinet shelf). Evidence of depression on neuropsychological testing should not be used as a basis for ruling out organic disease: co-occurrence is common. The MMPI is an unreliable test for patients with Lyme disease because the diversity of genuine symptoms will result in a high score on the hypochondriasis and depression subscales.

Microbiology Relevant To Diagnosis and Treatment

The microbiology of B. burgdorferi sheds light on why Lyme disease can be relapsing and remitting and refractory to normal immune surveillance and standard antibiotic regimens.[36-39] Like other species of Borrelia, B. burgdorferi is subject to significant antigenic variability[40,41] and therefore to variable serological patterns of antibody response in the host, variable clinical presentations, and fluctuating symptoms. **The organism has the capacity to become intracellular in Borrelia lymphocytes, macrophages, and fibroblasts,[42,43] thereby evading the immune response and/or antibiotic treatment. The intracellular location of some organisms lends protection from antibiotics the majority of which work only extracellularly.** Significant disease may occur in the presence of very few organisms, hence the notoriously low yield of attempts to culture the organism and to demonstrate its presence by PCR. **Like Mycobacterium tuberculosis, B. burgdorferi has a long replication time and therefore longer courses of treatment may be needed.** Intracellular organisms and/or organisms present in sequestered areas of the body such

as joint spaces, the anterior chamber of the eye, and the brain parenchyma may survive standard courses of antibiotic treatment; their emergence may be the cause for subsequent relapse. **The capacity of the organism to remain dormant in sequestered areas of the body for long periods of time raises the question as to whether eradication is possible in entrenched cases. Co-infection with other tick-borne organisms, in particular ehrlichia and babesia, may occur and should be tested for.** They will require the use of different antibiotics. Co-infection with babesiosis in particular tends to cause an illness with greater morbidity and chronicity among patients with Lyme disease.[44]

PREVENTIVE MEASURES:

Preventive measures include avoidance of highly tick-infested areas (e.g., wooded areas with dense underbrush), wearing of proper covering (preferably light-colored clothing with pant legs tucked into socks), tick checks, antibiotic prophylaxis and, most recently, the Lyme disease vaccine that has recently been recommended for approval by the FDA. In general, antibiotic prophylaxis is not recommended. In cases of a known tick bite, a low threshold should be maintained for serologic testing; treatment should be initiated should a rash appear, and should be strongly considered should flu-like or other symptoms suggestive of Lyme Disease emerge. Treatment of an asymptomatic tick bite may both be unnecessary and block the development of the immune response, thereby diminishing the value of subsequent laboratory testing. If the tick carries Borrelia burgdorferi, antibiotic prophylaxis should be considered.

The vaccine, which, if approved, will be marketed by SmithKline Beecham as LYMErix, is cause for cautious optimism. **LYMErix has been found in placebo-controlled studies to be about 80% effective after three doses, which are given over the course of two years. The vaccine, which contains the Osp A outer-surface antigen, stimulates the production of antibody** (corresponding to the 31 kD band on Western Blot) **in the recipient. The first two doses, given a month apart prior to tick season, confer approximately 50% protection. The third dose, given a year later, yields almost 80% efficacy, according to the studies. Despite these promising results, some significant limitations and safety concerns exist. The vaccine has not yet been adequately researched in children or the elderly. People under age 15, a group at high risk for Lyme disease, should not be given the vaccine until further data are available.** Case reports suggest that the vaccine may be associated with the development of chronic arthritis in patient with prior B. burgdorferi infection, therefore this population also is ineligible. As the vaccine is costly and requires three doses over a two-year period, it requires motivation and organization on the part of recipients to complete the regimen. Those who have received the full course of inoculation should continue to take safety precautions, as protection remains only partial. Lastly, and most importantly, the potential for long-term complications following vaccination, like those seen in late-stage disease, is at present unknown.

Treatment

ANTIMICROBIAL TREATMENT:

For early localized or early disseminated Lyme disease, a course of oral antibiotics is usually adequate. Some controversy exists regarding the duration of treatment, with recommendations ranging from **3–4 weeks. Effective agents include: doxycycline and other tetracycline derivatives, amoxacillin and other penicillin derivatives, ceftin, clarithromycin, and azithromycin.** Relapses may occur even with appropriate early treatment. When a relapse occurs, the physician may opt to retreat with the same drug, but for a longer duration and/or with a higher dose; alternatively, a different antibiotic may be tried. If the relapse includes a progression of symptoms to those seen in late stage disease and/or occurs after a significant time interval without evidence of reinfection or of another disease process, more aggressive treatment, as appropriate for late-stage disease, should be considered.

For late-stage Lyme disease and particularly for CNS Lyme disease, intravenous antibiotics are the treatment of choice. First line drugs include: *cefriaxone, cefotaxime,* and *penicillin derivatives.* Intravenous *doxycycline* may be effective as well. There is significant debate regarding the treatment of late stage Lyme disease, including: the relative benefits of intravenous versus oral administration, the need for oral follow-up antibiotics, and the need for repeated courses of treatment and/or treatment with multiple agents in some

cases. **The initial treatment recommendation is generally 4 to 6 weeks, but persistent or recurrent symptoms are quite common at this stage.** Symptoms that continue after antibiotic treatment may be due to persistent infection or to a post-Lyme syndrome. **Given that some patients do respond to repeated courses of antibiotics and that persistent infection has been demonstrated in animal models and human case reports, repeated empirical antibiotic treatment is warranted in some cases with response to treatment monitored by SPECT and/or neuropsychological tests.** For a full discussion of antimicrobial treatment recommendations, consult one of the reviews referenced.[45–47]

PSYCHOPHARMACOLOGIC TREATMENT:

In a patient with Lyme diseased-induced psychiatric symptoms, the question will arise as to whether and when to use psychotropic medication in addition to antimicrobial therapy. Where psychiatric symptoms pose a significant risk to the patient or others, there may be no choice but to medicate immediately. **If such risk is not severe, it may make sense for a patient to be treated initially with antibiotics alone.** The advantages of this approach include: the value of being able to assess clinical response to antibiotics with a minimum of confounding factors; the fact that **the patient may have paradoxical responses to psychotropic medication and a greater risk of side effects when the infection is as yet untreated; and that psychotropic medication may turn out to be unnecessary. On the other hand, psychotropic medication used concurrently with antimicrobial treatments may greatly alleviate symptoms of pain, depression, and insomnia and thereby hasten both physical and emotional recovery.** A list of the most commonly used psychotropic medications for late Lyme disease is included as Table 5.

Caution must be exercised regarding **drug interactions, especially for patients on clarithromycin, azithromycin, or other macrolide antibiotics. These drugs lead to increased levels of carbamazepine and increased risk of mania in conjunction with certain SSRIs. Those SSRIs least reliant on Cytochrome P450 3A/4 enzymes for their metabolism would be the safest choices** (e.g., sertraline [Zoloft], paroxetine [Paxil], fluoxetine [Prozac]). **There is an increased risk of dangerous side effects of some drugs (e.g., lithium, clomipramine [Anafranil], bupropion [Welbutrin]) in patients with an abnormal brain substrate. SSRIs are more likely to induce panic symptoms in untreated Lyme disease and may heighten sensory hyperacuities or illusions in untreated Lyme encephalopathy, but are generally well tolerated during or following effective antibiotic treatment. It is important to note as well that some antibiotics decrease the efficacy of oral contraceptives and, especially given the potential for both congenitally acquired Lyme disease and birth defects due to various antibiotics used to treat Lyme disease, adjunctive contraceptive measures should be used during treatment. Pregnant patients, on the other hand, may be safely treated with penicillin derivatives.**

INDIVIDUAL PSYCHOTHERAPY:

The purposes of individual psychotherapy include support, development of coping skills, and psychodynamic understanding. The last may prove necessary when illness and disability render a patient's previously adequate defensive repertoire ineffective. Sometimes (as in Case 2 above) psychotherapy provides the opportunity for a fruitful reworking of previously adequate but suboptimal defensive structures. Even where symptoms prove intractable, psychotherapy can greatly enhance life satisfaction. The inextricable interweaving of psyche and soma is clearly exemplified in such patients. An illustrative case follows.

CASE 4: AN EXPANDED CASE ILLUSTRATING THE COMPLEXITIES OF DIAGNOSIS AND TREATMENT:

Medical Background

A 14-year-old girl had been diagnosed with Lyme disease at age 9 and treated with a 21-day course of amoxacillin. At age 12, she developed arthritis in her left knee and was treated with a 14-day course of i.v. ceftriaxone. The arthritis resolved, but migrating arthralgias, myalgias, headaches, fasciculations, and fatigue persisted. These were attributed to post-Lyme syndrome, warranting no further treatment. She began to have frequent flu-like illnesses and sinus infections which

were treated with short courses of antibiotics, but none of this was deemed cause for concern. **Functionally, however, she was experiencing a significant decline.** Always an A student, her grades began to slip. She often missed school because of recurrent flus and sinus infections, and her teachers commented that she seemed inattentive and easily distractable. She tried to put in extra study time to make up for the decline, but when she stayed up late to study, her school performance only worsened. She said the classroom environment was difficult for her, as the slightest unexpected noise would startle her, and she found it difficult to focus. Even recess, typically a time to relax and seek the company of her friends, was overwhelming. Especially on one of her bad days, the hubbub was confusing and the noise hurt her ears. She became increasingly dependent on her parents, specifically her mother, for emotional and academic support.

Psychosocial Issues

By age 14, her problems had worsened. Her close circle of female friends had disbanded as they went their separate ways for high school. Those who were at the same high school with the patient had become interested in boys and began to sort themselves into various "cliques." The patient found it difficult to keep up with them. **Increasingly plagued by headaches and fatigue, she was often unable to participate in social activities and would have to cancel out at the last minute. When she felt well enough to attend parties, she found that the loud music and the strobe lighting made her dizzy, nauseated, and overwhelmingly anxious.**

At home, she was emotionally labile, anxious, and depressed. She began to lose weight. Her mother urged her to eat, saying that she needed to increase her strength in order to regain her health. There began to be increasingly heated mealtime scenes over this issue. Having been a slightly chubby but attractive preteen, the patient gradually became gaunt. Her father, withdrawing from the fray, began to spend more and more time at the office. Left to themselves, she and her mother became involved in nearly constant fights and power struggles.

Diagnosis

The pediatrician made the diagnosis of anorexia nervosa and made a referral to a psychiatrist. The psychiatrist confirmed the diagnosis, but, noting the patient's cognitive difficulties and history of medical illness, ordered some additional tests. Lyme serologies at this time were positive, including two IgM bands on Western Blot. One out of three serial serum PCRs was positive. **A brain SPECT scan revealed diffuse, patchy hypoperfusion of the temporal and parietal lobes bilaterally.** A spinal tap was recommended but declined. **Neuropsychological testing revealed significant impairments in short-term and "working" memory, verbal fluency, and mental processing speed consistent with a diagnosis of Lyme encephalopathy.**

Medical Treatment

The patient was treated with **6 weeks of i.v. ceftriaxone, with an initial worsening of symptoms followed by some improvement in her pain, mood, cognition, and energy level.** The anorexia, however, persisted, and she was admitted to a psychiatric unit. Under the protocol there, she began to gain weight and to modify some of her eating habits, but her fasciculations, pain, and fatigue as well as her emotional lability began to worsen again. **She was discharged to a day program for patients with eating disorders and placed on i.v. cefotaxime. The symptoms again began to clear.**

Psychotherapy

Having begun psychotherapy twice a week on discharge from the inpatient unit, **the patient began to uncover some of the antecedents of her anorectic behavior. She came from a classically weight-conscious family with high standards for academic achievement. She was used to feeling "in control" of her life. Finding herself ill and unable to keep up with her schoolwork had been devastating to her.** At a time when her friends were discovering the pleasures of the opposite sex, she was struggling with what felt like a traitorous and ravaged body. **Menarche was marked not by a joyful arrival, but by an ironic worsening of symptoms:** her pain worsened; she had muscle twitches and jerks that were embarrassing to her; her skin was hypersensitive to touch such that her clothes seemed to "burn" her skin; certain foods tasted unbearably sharp or bitter; sounds grated on her ears; and sunlight was painfully bright. Accustomed to being a model student, she felt confused,

inadequate, and left behind, both academically and socially.

She tried desperately to hide her inadequacy from both her friends and her family but, intensely frustrated and humiliated, repeatedly found herself falling back on her mother's help. **With so many other aspects of her life and body being out of control, she seized upon one aspect that she could control: her weight.** Weight loss gave her some feeling of accomplishment; it made her feel strong. It seemed also that both her moodiness and her physical pain were lessened somewhat when she was at a low weight.

Recognizing these elements as precipitants of her anorexia, she began, with her therapist's help, to seek more effective ways to build autonomy and healthier alternatives to her hostile-dependent enmeshment with her mother. In acknowledging her areas of cognitive and emotional difficulty, she began to find genuine sources of companionship and support, first in her therapist and gradually extending to teachers and a few close friends. With these new developments, some of the tensions between her and her mother began to recede, and her struggles with food and weight-related issues took less prominence in her psychological life.

Multimodal Approach to Diagnosis and Treatment

Treatment required a multimodal approach as, by the time she sought psychiatric consultation, both her Lyme encephalopathy and her anorexia nervosa were quite entrenched. She was given long-term antibiotics to sustain her recovery from Lyme disease. Some mild cognitive deficits persisted. Treatment of her anorexia involved an inpatient behavioral and refeeding program followed by a day program including behavior, group, and family therapy. Sertraline was helpful in reducing her moodiness and obsessionality. Ongoing psychotherapy focused both on psychodynamic issues related to her anorexia and on coming to terms with the subtle cognitive deficits and physical symptoms that would likely linger for a long time to come.

On first blush, this case appeared to the treating psychiatrist as a classic case of anorexia nervosa. Had he limited himself to that diagnosis, however, it is doubtful she would have made much improvement. Conversely, a view of her difficulties as "purely organic" and Lyme disease-related would have been inaccurate and fruitless. It was only in understanding and working with the complex interweaving of physical, emotional, neurobiological, and familial elements in this patient's presentation that a positive result could be achieved and maintained.

COUPLES WORK:

Like many chronic medical conditions, late Lyme disease may bring about changes in the balance of a marriage and necessitate a redefinition of roles. Many marriages falter under the pressure of these changes, as a result of the multiple losses and narcissistic injuries that illness and disability impose. Other couples find new and deeper connectedness through a joint commitment to coping with change. Like many medical conditions, Lyme disease tends to cause **decreased libido and/or diminished sexual pleasure** which can create or exacerbate marital tensions. It may be helpful to open this issue to discussion, thereby helping the partner to take it less personally. Partners suffering from the life-changes brought on by the illness may need permission to express their own concerns. **Because Lyme encephalopathy changes a patient's experience in a way that is invisible from the outside, it may be difficult for a spouse to comprehend how sick, exhausted, and confused the patient feels. Fluctuations in symptoms may be interpreted by the partner as evidence of psychogenicity or secondary gain.**

FAMILY WORK:

In some families, more than one member may have chronic Lyme disease. Unfortunately, the potential for children in such families to develop psychogenic symptoms is very high, leading to situations where the interplay of organic disease, conversion reactions, and family dynamics is enormously complex. Home i.v. infusion for a family member means changing the home environment and routine in ways to which children are acutely sensitive (e.g., presence of i.v. poles and tubing, medical equipment, visiting nurses, red sharps containers). A sick child may be envious of the well child's ability to go on with a normal life; the well child may feel cheated out of parents' time and attention. Children may be puzzled and alarmed by changes in a sick parent

who looks well, shows no external evidence of disease, and yet is behaving and functioning very differently from previously. Children with genuine disease often develop a functional overlay. In such cases, inpatient hospitalization in a high quality child unit with an emphasis on milieu treatment and family therapy may be enormously helpful both diagnostically and therapeutically: the child's behavior outside the family environment can be observed, family dynamics reworked, and the child taught new coping skills. The importance of maintaining an open mind and of not clinging to simplistic ways of understanding such situations cannot be overemphasized. As in Case 4 above, a multimodal approach is optimal.

ADJUNCTIVE THERAPIES AND TECHNIQUES:

Adjunctive therapies, such as cognitive remediation, physical therapy, biofeedback, massage, and yoga, may provide cognitive, emotional, and physical benefits. For example, for a patient who feels globally impaired, humiliated, and incompetent in the realm of mental functioning, cognitive remediation may help by breaking down the experience of a global impairment into specific deficits which may be compensated for. Knowledge of a patient's specific strengths and weaknesses can then be used to teach the patient alternative analytic, memorization, and learning strategies that may enhance the patient's cognitive functioning, sense of confidence, and hope for the future. Physical therapy may enable a patient to regain range of motion and rebuild muscle strength, reversing illness-related stiffness and muscular deconditioning. A personal moderate exercise regimen is also often very helpful in reducing pain, restoring a more normal sleep pattern, increasing strength and flexibility, and providing a sense of mastery that can further enhance emotional well-being. High-impact exercise should be avoided, and aerobic exercise should be attempted only after the patient is substantially recovered. Some patients may be inclined to pursue various relaxation techniques, including biofeedback, massage therapy, yoga, or meditation. Any of these modalities may be beneficial. Yoga has the particular advantage that it can build physical strength and flexibility while at the same time facilitating stress management and cultivating a calm state of mind. Patients with chronic disease and diminished functional capacity may need to be encouraged to make lifestyle changes for purposes of stress reduction, particularly as stress is known to exacerbate anxiety, depression, and sleep disturbance and may be disruptive to optimal immune system functioning as well.

LIAISON WITH PRIMARY CARE PHYSICIAN AND/OR WITH SCHOOLS:

Some primary care doctors are quite comfortable dealing with uncertainty and with anxious patients; others are not. Psychiatrists can be very helpful in negotiating the interplay of physical and psychiatric symptoms, treating anxiety and depression, and advocating for their patients for needed medical treatment. **Knowing that someone else is handling the psychiatric issues can in turn help internists attend to medical concerns more thoroughly and respectfully.** Liaison with schools may be very helpful in educating teachers and school psychologists regarding the illness, including the possibility of fluctuating symptoms, and in clearly delineating the particular nature of a given child's deficits. Some children benefit enormously from home tutoring and/or a reduced school day. Computor-assisted courses of study have made it possible for some homebound children to maintain their grade levels without extensive tutoring.

VALIDATION AND CLARIFICATION OF PATIENTS' EXPERIENCES:

The areas of controversy in the diagnosis and treatment of Lyme disease put the patient in the difficult position of having to evaluate conflicting advice from reputable sources and of feeling dismissed by some doctors as having an inconsequential or purely psychogenic illness. **Many patients, even those with a history of very severe disease, have said the most devastating aspect of their illness experience was not being believed by doctors or having their reality denied by those close to them.** Psychiatrists may be in an optimal position to help by providing validation and clarification of a patient's subjective experience and by helping the patient to sort out his or her options. Given the perplexity of coping with an illness involving fluctuating symptoms and bizarre neuropsychological manifestations, such clarification and validation may in themselves be vital to a patient's ability to endure and to function.

Summary and Conclusion

Lyme disease is epidemic in many areas of the USA and Europe. It has protean manifestations affecting multiple organ systems. Late stage disease is prominently neurological and neuropsychiatric and may become chronic. Prolonged or repeated courses of antibiotics may be needed to alleviate late-stage symptoms in some cases. A variety of laboratory tests is available to aid the clinician, but none is infallible; Lyme disease remains a clinical diagnosis. MRI, SPECT, and neuropsychological testing may be helpful in evaluating possible Lyme encephalopathy. Specific psychopharmacologic treatments may be used following or in conjunction with antibiotics for symptom management. A multimodal approach to late Lyme disease works best.

Work with patients suffering from late-stage Lyme disease calls upon the breadth of a psychiatrist's training and skills in a way most aspects of psychiatric practice do not. A comprehensive approach to this population includes the use of medical diagnostic skills, neuroimaging, psychopharmacology, liaison with nonpsychiatric physicians, and psychotherapy. In-depth work with this group of patients highlights in dramatic and sometimes unexpected ways the inexorable interweaving of biological and psychological factors in emotional life and requires a diversity of skills that is the unique purview of psychiatry. Further research is needed to optimize diagnosis and treatment of Lyme disease; it is hoped that such research may shed light not only on the workings of this complex disease but also on aspects of the interplay between the brain and behavior in ways relevant to other conditions.

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Questions Based On This Lesson

To earn CME credits, answer the following questions on your quiz response form.

37. Lyme disease:

A. If diagnosed and treated early, usually has a benign course.

B. Is most often chronically disabling, even with antibiotic treatment in the early stage of the disease.

C. Was originally thought to be caused by a spriochete, Borrela burgdorferi, but has been now shown to be primarily an autoimmune disorder.

D. Is most commonly found in Florida, Louisiana, and Arizona.

38. Which of the following symptoms is *not* among the most common neuropsychiatric presentations of Lyme disease in adults?

A. Fatigue

B. Problems with memory and attention

C. Somatic delusions

D. Mild to moderate mood swings

39. In the treatment of Lyme disease:

A. Antidepressants should never be combined with antibiotics because of potentially serious drug-drug interactions.

B. If possible, monotherapy with antibiotics is preferable, since the neuropsychiatric manifestations often clear up with recovery.

C. SSRIs that are least reliant on Cytochrome P450 3A/4 enzymes for their metabolism, such as sertraline, paroxetine, and fluoxetine, must be avoided in patients receiving antibiotic therapy.

D. Psychotherapy should *not* be done because it conveys to the patient the idea that the doctor considers all of his or her complaints as being entirely psychological and without a physical basis.