Late and Chronic Lyme Disease: Symptom Overlap with Chronic Fatigue Syndrome & Fibromyalgia

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INTRODUCTION

Following the introduction of Borrelia burgdorferi into the skin by an infected tick, the organisms begin to spread both locally and systemically. Several days typically elapse before the appearance of the first sign of infection, i.e., erythema chronicum migrans (ECM), or other less typical rashes (29).

The rash occurs in fewer than 50% of patients with Lyme Disease (8,10), but the true incidence of Lyme Disease in the absence of a rash is unknown.

The occurence of multiple rashes is indicative of systemic spread of the organisms. Multiple rashes usually do not occur until 2-4 weeks following the initial tick bite. This is the same time period during which the organisms are being disseminated to their target tissues and cells. The incidence of multiple rashes was initially reported to occur in as many as 50% of cases, but has been much less common in the last two decades, probably because of frequent use of antibiotics. Approximately 4-6 weeks following the tick bite, the first systemic symptoms (other than multiple rashes) occur in some patients, usually in the form of "flu" (15). These symptoms include sore throat, severe headaches and neck aches, and severe fatigue. Rhinitis, sinusitis, and cough are not usually present, distinguishing this "flu" from other influenza-like illnesses. While the Lyme-flu symptoms can spontaneously resolve, patients can experience recurrent "flu".

Soon after the onset of Lyme-flu, fatigue, arthralgias and/or myalgias may begin. The arthralgias appear to primarily involve the large joints (i.e., knees, elbows, hips, shoulders), although smaller joints (e.g., wrists, hands, fingers, toes) may be involved(29). Some patients may have actual arthritis, often oligoarticular, more frequently in men than in women. Earlier estimates were that 50-75% of patients who developed late Lyme Disease had arthritis, but more recent analyses suggest that the incidence of actual arthritis in patients with late or chronic disease is closer to 25% (33).

Neck stiffness is common. The pains are described as severe, jumping from joint to joint, and may be present for only short periods of time. Pain in the teeth or in the temporal-mandibular joints is not uncommon. Rib and chest pains occur frequently, leading some patients to seek care in emergency rooms and urgent care centers for evaluation of possible cardiac disease. Frequently as well are paresthesias such as burning, numbness and tingling, and itching. Some patients experience crawling sensations, vibrations, or electric shock-like sensations. Rarely is there any actual palsy of the affected areas, making this much more of a neurosensory, rather than a motor, disease.

In addition to paresthesias, purely neurological symptoms and signs include headaches, an aseptic meningitis, facial nerve (Bell's) palsy, and encephalitis or encephalopathy that may be manifested by cognitive dysfunction, especially short-term memory loss, and psychiatric symptoms such as panic, anxiety, or depression (14). The aseptic meningitis and Bell's palsy tend to occur within the first few months following the tick bite, but may also occur as part of reactivation disease (9).

Other symptoms may include fevers (usually low grade, but may be high), sweats (which may be severe), visual dysfunction (described primarily as blurriness, but can include optic neuritis or uveitis), tinnitus, sensitivity to sounds, or hearing loss. Shortness of breath, palpitations and/or tachycardia, abdominal pains, diarrhea or irritable bowel, testicular or pelvic pain, urinary frequency or urgency, dysequilibrium, and tremors are also common symptoms. Some of the dysautonomia symptoms can be disabling.

Rarer symptoms may relate to panniculitis and hepatitis. Rarely as well are congenital and intrautero infection; when this occurs, it appears to be similar to toxoplasmosis and rubella, i.e., a primary infection during the first trimester. The occurrence of optic neuritis or uveitis raises other possibilities such as multiple sclerosis, but can be part of Lyme Disease.

The course of the disease can best be described as persistent, but with periods of worsening symptoms, often cyclical every few weeks or monthly. Especially disconcerting are persistent symptoms such as headaches and fatigue that can be exhausting. Some patients are more symptomatic than are others, which may reflect genetically- determined differences in responsiveness or extent of infection.

The disease does not appear to be progressive or destructive, as with cancer, nor is it fatal, but can be very debilitating.

The incidence of asymptomatic infection has not been adequately delineated. There appear to be substantial numbers of patients who remain asymptomatic, but reactivate their disease a number of months or years later, following trauma, pregnancy, a medical illness for which an antibiotic is prescribed, or other stresses, including psychological stresses (9). The Lyme OspA vaccine has appeared to reactivate Lyme Disease in a number of individuals who knew, but some who did not know, they had prior Lyme Disease (11). The mechanisms responsible for the reactivation of the disease have not been defined, but may include both molecular mimicry and underlying infection.

PATHOGENESIS

The pathogenesis of Lyme Disease remains to be defined. From the available studies, it would appear that the organisms are trophic for either the endothelial cells of the blood vessels that serve the nervous system or for the glial or neural cells themselves (4,24,26,31). Accumulating evidence supports the hypothesis of a persistent infection as the cause of the persisting or relapsing symptoms (26,31). Whether molecular mimicry is involved in the pathogenesis of some of the symptoms remains more speculative (18).

Although arthritis can occur in Lyme Disease, the organisms can only rarely be found in synovial tissue. And as many of the arthralgias that occur in the disease do not respond well to antiinflammatory agents, the disease is more of an infectious neuropathy than an actual invasion of synovial or bursal tissues. DIAGNOSIS

The diagnosis rests heavily on the clinical symptomatology. When there are clinical signs, e.g., rash, aseptic meningitis, optic neuritis, arthritis, an appropriate differential diagnosis must be pursued. On a clinical basis, "chronic fatigue syndrome" or "fibromyalgia" cannot be readily distinguished from chronic Lyme Disease. Indeed, accumulating experience suggests that Lyme Disease may be a frequent cause of fibromyalgia or chronic fatigue (8,12).

Other microbes have been proposed as causative agents of multisymptom disorders that are being termed chronic fatigue and fibromyalgia, especially more recently recognized mycoplasma species such as M.fermentans and M.genitalium, but definitive proof of cause and effect has not yet been established (6, 23). There has been an attempt to separate "late" Lyme Disease from "chronic" Lyme Disease, the former being manifested by objective signs of arthritis or neurological disease (32). Some have denied the existence of chronic disease, inferring that these patients suffer from psychiatric disorders; some have used the term "chronic" to mean post-treatment disease ("post-Lyme"), assuming that the infection has been treated, and the remaining symptoms are in the same realm as those patients who have "fibromyalgia" or "chronic fatigue" (27, 30).

These assertions are speculative and remain unproven. That chronic Lyme Disease actually exists, and is likely the most common form of the disease, is supported by epidemiologic studies demonstrating that 30-50-% of treated and untreated patients go on to develop a multisymptom disorder typical of, and indistinguishable from, fibromyalgia and chronic fatigue (1, 28). As with other multisymptom disorders, chronic Lyme Disease is a clinical syndrome consisting of fatigue, arthralgias and myalgias,and other nervous system dysfunction(7).

Furthermore, the results of treatment studies appear to support the hypothesis that persistent infection is responsible for the chronic symptoms. It is likely that Lyme Disease will serve as a useful model for other chronic multisymptom disorders. Whether the pathogenesis of "late" Lyme Disease differs from that of the chronic form of the disease remains to be established.

Routine laboratory tests are usually normal in Lyme Disease. The ESR is most often normal, distinguishing it from some of the inflammatory disorders such as rheumatoid arthritis or lupus. Culture of the borrelia is possible early in the disease, usually from biopsies of the erythema migrans rash; however, most laboratories are not capable of culturing the organisms.

The only currently available useful laboratory tests are the immunologically-based ELISA and Western blot assays. The recommendation was made in 1994 to have a two-tiered testing system in which the Western Blot would only be done on ELISA-positive samples (5). The recommendation was based primarily on the results obtained from patients with arthritis (13), did not take into account the chronic form of the disease, and was made despite the lack of consistent reproducibility of results between various laboratories (2, 16).

The ELISA has been shown to be an unreliable test in many patients with Lyme Disease, both in early infection and later disease (8, 10). Part of the reason for the lack of sensitivity of the ELISA is the use of whole organisms, resulting in a high amount of background absorbance.

After correction for the high background, only a small percentage of positives can be detected. Because Western blots separate the proteins of the borrelia, specific reactions can be visualized, and more accurate interpretations of the results made. Over 75% of patients with chronic Lyme Disease are negative by ELISA, while positive by Western blot (8, 10). Patients with oligoarticular arthritis may be more likely to have robust IgG responses and positive ELISA tests and IgG Western Blots (13).

By Western blot analyses, the first immunologic reactions in Lyme Disease are to the 41kd flagellar protein, and the 23kd OspC protein. Typically, at the time of the ECM rash, there will be an IgM reaction against the 23kd and 41kd proteins, and no IgG reactions. Within the next few weeks, the IgM reactions persist, sometimes accompanied by less specific reactions against 60kd and 66kd proteins, and IgG reactions are now visible against the 23kd and 41kd proteins. Thus, in the presence of an appropriate clinical picture, the immunoreactivity against the 23kd and 41kd proteins appear to be diagnostic of Lyme Disease.

Whereas the 41kd protein is not unique to B. burgdorferi, the 23kd protein appears to be unique. Also apparently unique proteins of B.burgdorferi are the 31kd (Osp A) and 34kd (Osp B) outer membrane proteins, and the 35kd, 37kd, 39kd, and 83/93kd proteins. Reactions to the 31kd proteins are not usually seen until after a year or more following the onset of disease. Not all patients with symptoms for more than one year, however, display reactions to the outer membrane proteins.

Most symptomatic patients have specific reactions on IgM Western blots (8,10). With resolution of the symptoms, the IgM reactions disappear or attenuate. IgG reactivity may continue to be present with resolution of symptoms, but it typically also disappears or attenuates with successful therapy. There are some patients (20%) who have symptoms, but whose Western blots are negative (8,10). If the borrelial organisms remain intracellular, with no extracellular reemergence once established, this could explain the absence of additional or persistent immune responses.

PCR (Polymerase Chain Reaction) is a highly sensitive means to detect microbial DNA or RNA, and it was hoped that this technique would find an important role in the diagnosis of Lyme Disease. Thus far, however, despite the specificity of this method, borrelial DNA or RNA has not been reliably detected in the blood, urine, or spinal fluid of patients with early or later forms of Lyme Disease, findings again supportive of an intracellular reservoir for the borrelia.

It should be possible to develop a better, highly specific ELISA for Lyme Disease, using recombinant 41kd, 23kd, 31kd and/or 34kd (and perhaps other B.burgdorferi-specific) proteins. Currently, however, the Western blot assay is the most reliable immunologic test.

TREATMENT

In vitro, B. burgdorferi is sensitive to several antibiotics (20,25). This assumption is complicated, however, because of the long incubation times needed to determine minimum inhibitory concentrations (MIC), as the borrelia have doubling times of 20-24 hrs. With these limitations, the results of a few studies show minimum bactericidal concentrations (MBC) to penicillin of 8ug/ml, ampicillin: 2ug/ml, tetracycline: 1-2ug/ml, doxycycline: 2ug/ml, ceftriaxone: 0.5ug/ml, cefotaxime: 0.5ug/ml, cefuroxime: 1-2ug/ml, cefixime: 8ug/ml,erythromycin: 0.5ug/ml, clarithromycin: 0.5ug/ml, azithromycin: 0.5ug/ml, and ciprofloxacin: 4ug/ml.

At the time of the first rash, any one of several antibiotics appear to be effective, if given for 2 weeks, according to several published studies. However, a number of patients so treated developed subsequent symptoms of arthralgias, fatigue, and paresthesias, with positive Western blots, who were then successfully treated with longer courses of antibiotics (8, 10). The recommendation at this time, therefore, is that tetracycline, doxycycline, or amoxicillin be used for 1 month if ECM is the only symptom of Lyme Disease.

Once any other symptoms appear, the treatment of Lyme Disease for only 2-4 weeks is associated with frequent failures and relapses (8, 10). Our initial experience suggested that a 3 month course of tetracycline was associated with a higher success rate(8).

In patients with symptoms present for more than six months, the treatment course may need to be more prolonged, or a retreatment course of varying length may be needed. In patients with symptoms for more than a year, 12-18 months may be needed for complete resolution of symptoms. The rationale for a longer treatment course is based on extensive observations (8,10), plus the analogy to the longer treatment courses required for tuberculosis, leprosy, Q fever, and certain fungal diseases.

With Lyme Disease, the slow growth rate and metabolic activity of the borrelia would seem to correlate with the need for longer treatment periods. Once treatment is initiated for patients beyond the earliest signs of infection, their symptoms frequently increase during the first several days, or even for the first several weeks of therapy. For patients with preexisting symptoms of more than a few months, relief of any of their symptoms may not occur until after 4-6 weeks of therapy (8, 10). Typically, there are short periods of relief, followed by relapsing or migrating symptoms; with continued therapy there are longer symptom-free periods. Some arthralgias may require 3 months or more to resolve, and fatigue may be the last symptom to disappear.

The preference for tetracycline evolved because of the large number of failures that were noted in patients who had been on ampicillin and doxycycline. Patients generally

had some response to doxycycline, but it was uaually not complete, nor long-lasting. Tetracycline may be more effective than doxycycline simply because of the greater dose, i.e., 100mg of doxycycline twice daily is not equivalent to 500mg of tetracycline three times daily; also, doxycycline is highly protein-bound, compared to tetracycline, which could limit the availability of free drug to diffuse into tissues and cells.

Some physicians use doxycycline at doses of 300-400mg daily to try to achieve a successful result. A strict comparison between doxycycline and tetracycline has not yet been made. Minocycline has also been used by some physicians, with varying success, but faces the same issues of dosage and protein binding.

Of the beta lactams used for the treatment of Lyme Disease, the most efficacious appears to be ceftriaxone. In limited comparitive trials, cefotaxime appears to be equally efficacious, and high-dose IV penicillin may also be effective.

In early Lyme Disease, oral amoxicillin is as effective as doxycycline. In later disease, many failures are noted, despite the use of up to 3 grams of amoxicillin daily, with probenicid. Cefixime would also not appear to be effective therapy. Cefuroxime axetil has been evaluated only in the treatment of early Lyme Disease, and appears comparable to doxycycline. Limited reports of its use in later Lyme Disease have not shown it to be efficacious.

The role of the newer macrolides in the treatment of Lyme Disease needs further assessment. Erythromycin has been regarded as ineffective, despite its good in vitro sensitivities. Azithromycin has been reported to be less effective in the treatment of early Lyme Disease than amoxicillin (21). Some physicians use clarithromycin and azithromycin in higher dosages and for longer periods of time, but there have been no reports of greater success with these drugs than with the tetracyclines or beta-lactams. In our experience, all macrolides are effective when combined with a lysosomotropic agent, especially hydroxychloroquine(see below)(10).

In evaluating the possible factors, it would appear that antibiotics that can achieve intracellular concentrations and activity are the most efficacious drugs. The results of studies in Klempner's laboratory using a tissue culture model of borrelia infection demonstrated that ceftriaxone was incapable of eradicating intracellular organisms (17); similar experiments in Raoult's laboratory using an endothelial cell model demonstrated that tetracycline and erythromycin were effective, but beta lactam antibiotics were not (3). These results are in line with our experience that the tetracyclines and macrolides achieve the greatest success.

In contrast to beta lactams, antibiotics of the tetracycline and macrolide classes are capable of good intracellular penetration. Experience with the macrolide antibiotics has been disappointing, however, when compared with its in vitro activities against the Lyme borreliae, and with the established efficacy of macrolides against other intracellular parasites such as chlamydia, legionella, mycobacterium-avium intracellulare, and toxoplasma. If, though, the Lyme borreliae reside in intracellular vesicles that are acidic, the macrolides' activity would be sharply decreased at the lower pH.

This is in contrast to the tetracyclines, which are active at acid pH; even so, the activity of doxycycline was shown to be further increased by increasing the pH. In a tissue culture model of ehrlichia infection, the use of lysosomotropic agents such as amantidine, NH4Cl, and chloroquine increased the killing of intracellular organisms by doxycycline (22).

Based on those studies, and the hypothesis that late Lyme Disease symptoms are due to persisting intracellular infection, we have been successfully treating patients using the combination of a macrolide and hydroxychloroquine (10). As regards "CNS" disease, there is no evidence that ceftriaxone is more successful than either the tetracyclines or the combination of macrolide and hydroxychloroquine; if our presumption that the pathogenesis of the disease involves the localization of the borrelia to the endothelial cells of the blood vessels serving the nervous system or to glial or neural cells is correct, then one would not need to have a drug that can cross the blood-brain barrier to be effective. Indeed, the tetracyclines can cross the blood-brain barrier to some extent, and were used when initially introduced into clinical medicine for the treatment of meningitis, with some success.

Macrolide antibiotics do not cross the blood-brain barrier, but have been effective in treating other CNS infections (e.g., toxoplasmosis), and in our experience have been effective in reversing the neuropsychiatric symptoms and signs (eg SPECT scans) of Lyme Disease (10). With regard to the issue of bactericidal vs bacteristatic effects, any such effect in vivo has not been demonstrated.

Finally, there have been no reports showing any change in antibiotic resistance patterns during the course of treatment. Ultimately, the determination of efficacy of therapy depends on the clinical response. FUTURE DIRECTIONS

The diagnosis and treatment of Lyme Disease have been hampered by less than adequate diagnostic tests and inadequate comparisons of antibiotic regimens. Specific antigen-based ELISA tests should result in greater specificity, but sensitivity of any tests based on measurements of the host immune response might still be of limited value if the borrelia remain intracellular. Most useful would be the development of tests that can determine the presence and extent of any residual borreliosis. In the therapy of Lyme Disease, double-blind, placebo-controlled and comparitive trials are needed to answer the questions relating to duration and class of antibiotic therapy.

The apparent failure of a regimen of one month of IV ceftriaxone, followed by two months or oral doxycyline, to improve the outcomes of patients with chronic Lyme Disease (19) was not surprising, based on prior observations that neither regimen used for a limited duration was capable of yielding patient improvement (8,10,33). Additional trials are needed to evaluate whether longer durations of treatment, using tetracycline itself, or the novel combination of macrolide and lysosomotropic agent, would be proven effective treatments.

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