RETROSPECTIVE ANALYSIS OF A COHORT OF INTERNATIONALLY CASE DEFINED CHRONIC FATIGUE SYNDROME PATIENTS IN A LYME ENDEMIC AREA

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ABSTRACT

Background: Chronic fatigue syndrome is a diagnosis of exclusion for which there are no markers. Lyme disease is the most common vector borne illness in the United States for which chronic fatigue is a frequent clinical manifestation. Intervention of patients with Lyme disease with appropriately directed antimicrobials has been associated with improved outcomes.

Methods: An arbitrary date was chosen such that all patients registered in the database of the practice of the PI, which is located in the Lyme endemic area of Northern Virginia area were reviewed. The diagnosis of clinically significant fatigue > 6 months was chosen. Inclusion criteria required fulfilling the International Case Definition for CFS.

Results: Of the total 210 included in the analysis, 209 or 99% were felt to represent a high likelihood of “seronegative Lyme disease.” Initiating various antimicrobial regimen, involved at least a 50% improvement in clinical status in 130 or 62%. Although not achieving the 50% threshold according to the criteria discussed, another 55 patients subjectively identified a beneficial clinical response to antimicrobials, representing a total of 188 or 88% of the total identified as having a high potential for seronegative Lyme disease.

Conclusions: A potentially substantial proportion of patients with what would otherwise be consistent with internationally case defined CFS in a Lyme endemic environment actually have a perpetuation of their symptoms driven by a persistent infection by Borrelia burgdorferi. By treating this cohort with appropriately directed antimicrobials, we have the ability to improve outcomes.
BACKGROUND

Chronic fatigue syndrome is a diagnosis of exclusion for which there are no markers (1). Lyme disease is the most common vector borne illness in the United States for which chronic fatigue is a frequent clinical manifestation (2) and for which the diagnosis may be challenging (3-6). Chronic Fatigue Syndrome represents a fatiguing symptom complex often including the co-morbidities of fractured nonrestorative sleep, endocrinopathies [such as decreased cortisol production], autonomic dysfunction [such as neurally mediated hypotension and postural orthostatic tachycardia] (7). It is the interpretation of the author that this “CFS like complex” represents a valid model for the management of many patients with chronic persistent Lyme infection (8).

The adverse societal impact of CFS was reported by Reynolds et al in 2004. Estimates were of a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS. The annual total value of lost productivity in the United States was $9.1 billion which represents about $20,000 per person with CFS or approximately one-half of the household and labor force productivity of the average person with this syndrome(9). The data presented in this treatise would suggest that we have the capacity to better characterize a substantial number of “CFS” patients as having “seronegative” persistent Lyme infection for which adjustments in intervention are shown to improve outcomes. Thus, we are attempting to provide evidence to the etiology of a cohort of patients with Chronic Fatigue Syndrome, while also providing input as to the clinical manifestation of persistent Lyme infection.

The management of Lyme disease regarding diagnosis and treatment unfortunately is wrought with controversy. There is one evidence based school of thought that Lyme disease is easily diagnosed and easily treated (10-11). This set of guidelines has had questions raised as to the quality of the evidence with which the recommendations have been generated: “…The IDSA guideline recommendations are primarily based on low-quality evidence derived from nonrandomized studies or expert opinion. These findings highlight the limitations of current clinical infectious diseases research that can provide high-quality evidence…” (12-14). There is an alternative, evidence based position that suggests that the diagnosis of Lyme disease is associated with insensitivities and that the management of those identified with this condition frequently have protracted, and relapsing courses. As such, following a patient’s clinical course including responses to appropriately directed antimicrobials, these complex, relapsing presentations often require prolonged courses of treatment (15). In essence, rather than arbitrary durations of therapy, clinical judgment is warranted at the point of care.

METHODS

An arbitrary date was chosen such that all patients registered in the database of the practice of the PI, which is located in the Lyme endemic area of Northern Virginia area were reviewed. The diagnosis of clinically significant fatigue > 6 months was chosen to filter the patients subsequently chosen. The charts of these individuals were reviewed to determine: Qualification for fulfilling the International Case Definition for CFS including (1,7): Appropriately guided causes of chronic fatigue have been ruled out [1] [including screening serologies for B burgdorferi, vis a vis the recommended “two tiered” system. (10) Secondary criteria: CFS symptom criteria [0-absent/10-profound] achieving at least 4 of the following 8 secondary criteria =>5 of 10 in a severity scale [0 being absent, 10
being most severe] impaired memory or concentration, sore throat, tender neck or axillary lymph nodes, myalgia, arthralgias, new headaches, unrefreshing sleep or post exertional malaise. Possibility of “seronegative” Lyme disease as determined by one or more of the following criteria: Seropositivity to ANY highly specific band to Bb IgM or IgG [23-25, 31, 34, 39, 83-93](16-20), and/or presence of any tick borne “co-infection” such as Babesia, Bartonella, or Ehrlichiosis species(21-32), and/or a low CD57 (33), and/or an elevated C4a (34), and/or an elevated C6 peptide (35-37).

Initiation of antimicrobial intervention for those suspected of having seronegative Lyme disease: Assessment of clinical course was determined by way of a symptom questionnaire attached. To assess construct validity, this metric was given to two independent clinical researchers with instructions to assign each item on the value of the question asked, for which there was agreement and thus felt to be validated. Completed contemporaneously at each office visit by the study patient, this questionnaire provided a numeric value of the patient’s complaints that could then be tracked serially with a high score representing a more symptomatic individual. Taking the highest score and comparing to the lowest score, we were able to determine the relative therapeutic impact of intervention employed. Antimicrobial intervention was varied but included such protocols as biaxin/omnicef and doxycycline/zithromax. Given that this was a retrospective analysis, antimicrobial management was not controlled, but chosen at the point of care. At least one visit after initiation of antimicrobials to allow for a relative assessment of therapeutic intervention. IRB approval: WIRB Study #1121119

RESULTS

All patients fulfilled the international case definition of CFS (1), including a negative Lyme disease serology. Of the total 210 included in the analysis, 209 or 99% were felt to represent a high likelihood of “seronegative Lyme disease.” Initiating various antimicrobial regimen [in conjunction with managing co-morbidities in this uncontrolled study], involved at least a 50% improvement in clinical status in 130 or 62%. Although not achieving the 50% threshold according to the criteria discussed, another 55 patients subjectively identified a beneficial clinical response to antimicrobials, representing a total of 185 or 88% of the total identified as having a high potential for seronegative Lyme disease.

<table>
<thead>
<tr>
<th>Analysis of PI patients</th>
<th>N</th>
<th>% total</th>
<th>% seronegative Lyme patients</th>
</tr>
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<tbody>
<tr>
<td>International Case Defined CFS</td>
<td>210</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>&quot;seronegative&quot; Bb screen, POSITIVE alternative criteria</td>
<td>209</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>equal to or &gt; 50% clinical improvement</td>
<td>130</td>
<td></td>
<td>62%</td>
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<tr>
<td>&lt;50% improvement but still clinically significant</td>
<td>55</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>total clinically significant improvement</td>
<td>185</td>
<td></td>
<td>88%</td>
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</table>
DEMOGRAPHICS

Seronegative Lyme patients:

<table>
<thead>
<tr>
<th>Ethnic background</th>
<th>women</th>
<th>men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>158</td>
<td>44</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>American Indian/Alaskan</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>other</td>
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<td>0</td>
</tr>
<tr>
<td>unknown</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>average age:</td>
<td>42</td>
<td>38</td>
</tr>
</tbody>
</table>

The one patient who did not fit the seronegative Lyme criteria was a 46-year-old Caucasian woman.

ANTIMICROBIALS EMPLOYED

Recognizing that the infectious process to which we are alluding is often polymicrobial [including *Borrelia, Babesia, Bartonella* species and others], several antimicrobials were often employed. In addition, there were frequently relapses in many cases when antimicrobials were entirely withdrawn. The duration of treatment was generally adjusted by the patient’s clinical response and was quite variable. Examples of regimen associated with at least a 50% clinical improvement include:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Duration [months]</th>
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</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>200mg bid</td>
<td>5</td>
</tr>
<tr>
<td>with Zithromax</td>
<td>500mg/d</td>
<td>9</td>
</tr>
<tr>
<td>Ceftin</td>
<td>1.0gm bid</td>
<td>8</td>
</tr>
<tr>
<td>with Ketek</td>
<td>400mg bid</td>
<td>7</td>
</tr>
<tr>
<td>Zithromax</td>
<td>250mg to 500mg/d</td>
<td>4</td>
</tr>
<tr>
<td>Mepron</td>
<td>750mg bid</td>
<td>2</td>
</tr>
<tr>
<td>Biaxin</td>
<td>500mg bid</td>
<td>12</td>
</tr>
<tr>
<td>Mepron</td>
<td>750mg bid</td>
<td>6.5</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>875mg bid</td>
<td>5.5</td>
</tr>
</tbody>
</table>
COMMENTS

Precedence exists in the literature regarding the need for prolonged antimicrobial management in certain infections: *Mycobacterium tuberculosis* treated for 6-18 months with multiple agents (38), Nontuberculous mycobacteria such as *Mycobacterium marinum* are likely to require at least 6 months of treatment (39) and disseminated *Mycobacterium chelona* treatment may involve a combination of oral and intravenous antibiotics administered for 6 to 12 months (40). Lastly, Hansen’s Disease [Leprosy] protocols are for up to 2 years (41-43).

DISCUSSION

It is our overarching hypothesis that a potentially substantial proportion of patients with what would otherwise be consistent with internationally case defined CFS in a Lyme endemic environment actually have a perpetuation of their symptoms driven by a persistent infection by *Borrelia burgdorferi*. By treating this cohort with appropriately directed antimicrobials, we have the ability to provide improved intervention. In essence, by improving our ability to characterize this cohort of individuals as having active Lyme disease and treating them accordingly, we are more likely to improve outcomes.

The concept of active seronegative Lyme disease is well established in the literature. The detection of DNA by PCR of *B. burgdorferi* is felt to be indicative of organism presence and active infection as described by Lebach, “Since isolation of *B. burgdorferi* from patients with Lyme borreliosis is laborious and often unsuccessful molecular typing methods based on PCR are recommended obviating the need for isolation by prior culture (44)

Chmielewski et al described “an analysis of 240 hospitalized patients presenting with various clinical symptoms suggesting Lyme borreliosis: 221 of the patients with neurological abnormalities and 19 with oligoarticular arthritis. Of that group, bacterial DNA by PCR were found in samples from 32 patients, including 28 patients with neuroborreliosis and 4 with Lyme arthritis. B. burgdorferi-specific IgM and/or IgG serum antibodies were detected in 14 of these patients.” (45) In essence, of the 32 patients with PCR detected Lyme, 18 were seronegative. Oksi et al described a group of “41 patients presenting with symptoms compatible with late Lyme borreliosis (LB)...Only patients with culture- or PCR-proven disease were enrolled in the study. ...7 patients were seronegative by ELISA.” (46) In their 2007 case study, Holl-Wieden et al described seronegative Lyme arthritis “diagnosed based on the detection of *Borrelia burgdorferi* DNA in synovial fluid. No humoral immune response to *Borrelia burgdorferi* was detectable before, at the time of diagnosis and up to 3 years.” (47)

Support of post treatment seronegative Lyme disease was described by Luft et al “This prospective study confirmed our previous observation that a subpopulation of patients treated promptly but ineffectively for erythema migrans may ultimately develop later manifestations of Lyme disease and be seronegative on ELISA tests for *B. burgdorferi* at the time of their relapse (48)

In addition, in his statement to the IDSA guideline review committee in 2009, former CDC guideline committee member David Volkman, Ph.D., M.D. alluding to a study in which he was a co-author (49) “....we described a group of 17 patients who all
suffered from either neurological or arthritic signs frequently attributed to chronic *borrelia* infection. These individuals lived in areas endemic for Lyme disease, all had had a pathognomonic erythema migrans (EM) rash, all had a course of antibiotics (tetracycline, erythromycin, or an abbreviated course of another antibiotic) early in their illness, all had T cell blastogenic responses consistent with exposure to borrelia, and curiously, all lacked detectable antibodies against *borrelia*. Although early antibiotic treatment abrogated antibody responses, it did not eradicate infection. When retreated, most of these chronic patients markedly improved within a month of completing a course of intravenous ceftriaxone, consistent with their problems being due to persistent, ongoing occult infection" (50)

There are multiple plausible explanations to explain this phenomenon of seronegativity using present technology in the diagnosis of Lyme disease. Recognizing that it is the organism’s immunogenicity to which the host amounts a response, any mechanisms that may alter this immunogenicity has the potential to decrease that response. In so doing, the sensitivities by which this serologic response could be detected would likely be diminished. *Bburgdorferi* has in fact evolved a number of mechanisms by which this is a likely occurrence. Adapting to changes in its environment, *Bburgdorferi* has been shown to have the capacity to change its physical characteristics, such as modulating the composition of its outer membrane. (51-56) Variable gene expressions have been well characterized. (57-60) Different structural forms of *Bburgorferi* have been described. Cystic structures (61,62) and “cell wall deficient spheroblasts and L-forms have been described (63-67)

Sanctuaries or areas of the body in which sequestered viable spirochetes reside, may lead to internal cycles of acute infection that evade the body’s immune response (68,69) This has been detected in the CNS.(70-73) as well as the synovium. (74) Residence in an intracellular location confers several survival advantages to *Bb* through protection from cellular and humoral responses. (75-78) Multiple researchers have demonstrated *in vitro* evidence of *Bb* within endothelial cells, myocardium, fibroblasts, ligamentous tissue, synovial cells, keratinocytes, lymphocytes, neurons and glial cells.(79-91)

Lastly, Stricker and Winger have characterized the potential decrease in a subset of NK cells in some with Lyme disease. (33) Thus, there is evidence for immune dysfunction to contribute to the attenuation of the aforementioned serologic response.

Questions have been raised that the therapeutic gain seen by the use of antimicrobials in the aforementioned setting is DUE to their anti-inflammatory affects. In addition to their antibacterial properties, it is clear that many antimicrobials also have anti-inflammatory effects. Examples would include tetracyclines (92,93), macrolides (94,95) and quinolones (96,97). With respect to the above clinical assessment, there may very well be a component of therapeutic gain, as likely seen in any other infectious process by the anti-inflammatory impact of some of these agents. However, we believe to suggest that the potential anti-inflammatory effect is the ONLY mechanism of action is a mischaracterization of this phenomenon. Virtually all patients with pain syndromes [including arthralgias/arthritis, headache, myalgias, etc] had already taken over the counter NSAIDS without adequate therapeutic gain. More importantly, if the mechanism of therapeutic impact of antimicrobials in this setting is strictly anti-inflammatory, how do we reconcile the development of post treatment Jarisch Herxheimer reactions? This frequently described phenomenon is felt to represent an increase in pro-inflammatory cytokines. (98,99) Associated with post antimicrobial exacerbation of symptoms (such as
headaches, arthralgias or fatigue) anti-inflammatory mechanisms of therapeutic impact should theoretically suppress this pro-inflammatory response, instead of actually being associated with a crescendoing increase of clinical activity.

POTENTIAL LIMITATIONS

This is a retrospective study which does not allow for control of confounding variables, such as treatment choice or management of co-morbid conditions such as fibromyalgia or fractured nonrestorative sleep. On the other hand, this sample may be more generalized to patients seen in actual practice as such patients were not excluded. Future research should assess for such variables so that they can be statistically controlled. The study sample represents those living in an endemic environment for Lyme disease and thus cannot be directly extrapolated to non-endemic regions. However, this must be qualified by recognizing that with our mobile society, it is quite conceivable that individuals not “living” in a Lyme endemic region that by vacationing, or other reasons, may very well have intermittent exposure to Lyme endemic regions. There may be a selection bias in seeking a clinician known to have expertise in chronic fatigue and Lyme disease management. In addition, although likely a lower relative risk regions that are not considered “endemic,” there is still likely some level of exposure risk. As such, consideration for this paradigm would still be appropriate.

As in any uncontrolled analysis the placebo effect must be considered as having some contribution to therapeutic gains. However, it is hard to believe that placebo effect is going to result in a normalization of profuse sweating or an improvement in the hemodynamics of blood pressure and heart rate in a patient with postural orthostatic tachycardic syndrome, as was seen in some of these respondents. In addition, as Brown et al described in relation to an assessment of hypothalamic-pituitary-adrenal axis, greater degrees of functional abnormalities are associated with a less robust response to placebo in depression. (100) The majority of those included in our analysis had moderate to severe disabilities and thus less likely to be impacted by placebo effects than those less ill. That being said, even if we were to discard inclusion of those with symptom scores improving by less than 50%, we would still be left with 62% respondents who improved by at least by 50% on antimicrobials.

Lastly, a cautionary caveat needs to be emphasized in relation to the potential of indiscriminant antimicrobial use. A careful analysis for the potential diagnosis of Lyme disease as characterized in this treatise ought to be obtained prior to the use of antibiotics. A careful risk/benefit analysis needs to be performed at the point of care with any intervention employed.

ADDITIONAL SUGGESTIONS FOR FUTURE RESEARCH

Obtain microarray analysis for Borrelia burgdorferi on the “seronegative” Lyme patients. Perform a prospective randomized placebo controlled trial for which a protocol and IRB are already in place and funding being pursued.
DISCLOSURES

The author has been a member of the International Association of Chronic Fatigue Syndrome since the early 90s and of the International Lyme and Associated Diseases Society since 2005.

No conflicts of interest are to be noted.

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Khalida Willoughby, MA
Debbie Repass

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## SYMPTOM QUESTIONNAIRE

**Symptom Questionnaire**

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<tr>
<td>unexplained fevers, sweats, chills or flushing</td>
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<tr>
<td>unexplained weight change [loss or gain]</td>
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<tr>
<td>fatigue, tiredness, poor stamina</td>
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<tr>
<td>unexplained hair loss</td>
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<tr>
<td>swollen glands</td>
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<tr>
<td>sore throat</td>
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<tr>
<td>testicular or pelvic pain</td>
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<tr>
<td>unexplained menstrual irregularity</td>
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<tr>
<td>irritable bladder or bladder dysfunction</td>
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<tr>
<td>unexplained milk production or breast pain</td>
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<tr>
<td>sexual dysfunction or loss of libido [sex drive]</td>
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<tr>
<td>upset stomach or abdominal pain</td>
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<tr>
<td>changes in bowel function-constipation and/or diarrhea</td>
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<tr>
<td>chest pain or rib soreness</td>
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<tr>
<td>shortness of breath or cough</td>
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<tr>
<td>heart palpitations or skipping heart</td>
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<tr>
<td>stiffness of the back</td>
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<td>muscle pain or cramps</td>
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<td>twitching of face or other muscles</td>
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<tr>
<td>headache</td>
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<tr>
<td>neck stiffness or pain</td>
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<tr>
<td>tingling, numbness, shooting pains and/or skin sensitivities</td>
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<tr>
<td>facial paralysis or Bell's Palsy</td>
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<tr>
<td>joint pain or swelling</td>
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<tr>
<td>vision problems-double, blurry, increased floaters and/or light sensitivity</td>
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<tr>
<td>ear or hearing problems-buzzing, ringing, ear pain, sound sensitivity</td>
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<td>motion sickness, vertigo and/or poor balance</td>
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<tr>
<td>lightheadedness, wooziness, unavoidable need to sit down</td>
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<tr>
<td>tremor</td>
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<tr>
<td>confusion and/or difficulty thinking</td>
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<tr>
<td>difficulty with concentration and/or reading</td>
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<tr>
<td>forgetfulness, short term memory loss, poor attention and/or problems absorbing information</td>
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<tr>
<td>disorientation, getting lost and/or going to wrong places</td>
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<tr>
<td>difficulty with speech, or writing or name blocking</td>
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<tr>
<td>mood swings, irritability and/or depression</td>
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<tr>
<td>disturbed sleep-too much, too little, frequent awakening and/or early awakening</td>
<td></td>
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</tbody>
</table>

As adapted from Burrascano, Jr. JJ Advanced Topics in Lyme Disease, Sixteenth edition October 2008
Chronic Fatigue Paradigm ©

Chronic Lyme Borrelia Complex

Chronic Fatigue in Lyme Disease
State of the Art Paradigm

Immune System
- UP regulation (eg. C4a and/or C6 peptide) AND DOWNregulation (eg. CD37)
  - Increased blood pressure and inotropic function
  - Decreased peripheral autonomic tone
  - Increased cerebral perfusion pressure
  - Postsynaptic/Hyperdysautonomia Tachycardia Syndrome
  - Decreased sympathovagal tone

CardioVascular System
- Decreased cardiac output
- Decrease in adenosine tone

Neurologic System
- Peripheral Autonomic
  - Decreased Neuron/Cognitive Function

Endocrine System
- Hypothalamic Disfunction
  - Decreased T4
  - Increased T3
  - Low T3
  - Thyroid-primed immune suppressive effect

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