Is There a Link between Lyme Disease and Chronic Fatigue Syndrome?

by

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9th International IACFS/ME Conference
Reno, Nevada
March 12-15, 2009

Introduction and Background

There are currently two prominent case definitions for chronic fatigue syndrome (CFS): the international research case definition of 1994, sponsored by the Centers for Disease Control and Prevention (CDC) [1], and the Canadian myalgic encephalomyelitis/chronic fatigue syndrome clinical working case definition of 2003 [2], which is intended to be used in clinical diagnosis.

The diagnosis of chronic fatigue syndrome is not always clear-cut when either of these definitions is used, because there is no accepted diagnostic test. Rather, the diagnosis is made on the basis of clinical judgment as to whether the specified symptom-based criteria are satisfied, after the exclusion of other known disorders that could account for the symptoms. Active Lyme disease is specified as one of the exclusionary disorders in both these case definitions for CFS. However, there is considerable overlap between the symptoms of CFS and those experienced by patients with Lyme disease. According to the guidelines of the International Lyme and Associated Diseases Society, "The clinical features of chronic Lyme disease can be indistinguishable from fibromyalgia and chronic fatigue syndrome [3]."

The diagnosis of Lyme disease is not always clear-cut, either, and the appropriate diagnostic criteria for it continue to be a subject of controversy. On the one hand, there are the criteria recommended by the Centers for Disease Control and Prevention (CDC) [4], which are in agreement with a set of guidelines established by the Infectious Disease Society of America (IDSA) [5], and on

the other hand, there is the set of criteria recommended by the International Lyme and Associated Diseases Society (ILADS) [3]. In some cases the onset of Lyme disease is accompanied by a characteristic rash (erythema migrans), and there is general agreement that when it is present, it establishes the diagnosis. History of having a tick bite is also an important factor in diagnosis. However, the rash does not occur in all the cases (The ILADS estimates less than 50%, while the IDSA offers a higher estimate), and many patients with Lyme disease do not recall having had a tick bite. When the rash and memory of a tick bite are not present and Lyme disease is suspected, serological testing is performed. Unfortunately, the available tests lack sensitivity, and there is also disagreement between these guidelines over which tests and which criteria for interpreting them should be used.

This difficulty in differential diagnosis has resulted in the situation that many patients who were initially diagnosed as having CFS have later (in many cases several years later) been found by serological testing to have Lyme disease. This is regrettable, because unrecognized and untreated Lyme disease can be progressive and can have very serious consequences.

In addition, in cases in which Lyme disease has been recognized and treated, some of the patients have continued to experience symptoms. There is a disagreement within the medical community as to whether these patients continue to be infected with Borrelia burgdorferi (Bb), the bacteria that causes Lyme disease, and/or with one or more of the tick-borne coinfections, and thus are suffering from "chronic Lyme disease [3]," or whether the bacteria have been

eradicated, and the patients are therefore suffering from "post-Lyme disease syndrome [5]."

Two years ago the present author proposed a hypothesis for the etiology and pathogenesis of CFS, called the Glutathione Depletion—Methylation Cycle Block (GD-MCB) hypothesis [6]. This hypothesis has been found to be consistent with the results of a clinical study of a treatment based upon it [7]. The GD-MCB hypothesis proposes that a variety of stressors that place demands on glutathione can bring about the onset of CFS in genomically predisposed individuals.

The present paper elaborates the GD-MCB hypothesis by describing a specific biochemical link between Lyme disease and CFS, such that patients who are genomically predisposed to developing CFS can and do progress into CFS when they have contracted Lyme disease. They thus suffer from Lyme disease and CFS simultaneously (in spite of the artificial exclusion of active Lyme disease in the case definitions for CFS). If they are successfully treated for Lyme disease, this hypothesis holds that a significant fraction of them can and do continue to suffer from CFS, which must also be specifically treated. Another paper at this conference describes a clinical study of a treatment for CFS that appears to be promising [7].

<u>Summary of the CDC-sponsored international research case definition for chronic fatigue syndrome</u> [1]

This definition excludes other known conditions that could account for the symptoms, and then defines a case of CFS as involving the presence of the following:

“1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion, is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social or personal activities; and 2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain; multijoint pain without joint swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep; and postexertional malaise lasting more than 24 hours.” Having had Lyme disease that was “treated with definitive therapy before development of chronic symptomatic sequelae” does not exclude a patient from the diagnosis of CFS under this definition.

<u>Summary of the Canadian ME/CFS clinical working case definition</u> [2]

This definition specifies that a patient with ME/CFS will meet criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain; will have two or more neurological/cognitive manifestations and at least one symptom from two of the categories of autonomic, neuroendocrine and immune manifestations. In addition, the illness must have persisted for at least six months.

Symptoms in the various categories are delineated in detail in the definition. In this definition, active Lyme disease is listed among the infectious diseases to be excluded during diagnosis, but the definition also states, "If the potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if the patient meets the criteria otherwise."

<u>Summary of the IDSA Guidelines for diagnosis of Lyme disease</u> [5]

If erythema migrans rash is present, clinical diagnosis of Lyme disease can be made without laboratory confirmation. If not, evidence from laboratory testing is required.

These guidelines specify two-tier testing: First, a polyvalent enzyme-linked immunosorbent assay (ELISA) is to be performed. If the ELISA is positive or equivocal, it is to be followed with IgM and IgG western blots as specified by the CDC [4]. These are considered positive if 5 out of 10 IgG bands or 2 out of 3 IgM bands are positive.

<u>Summary of the IDSA proposed definition for "post-Lyme disease syndrome"</u> [5]

According to the IDSA, in order for a case to be diagnosed as "post Lyme disease syndrome," there must have been a documented episode of early or late Lyme disease, using the above criteria, and there must have been a generally accepted treatment regimen that resolved or stabilized the objective manifestations of Lyme disease. In addition, there must have been onset of any of the following symptoms within 6 months of the

diagnosis of Lyme disease, and persistence of continuous or relapsing symptoms for at least a 6-month period after completion of antibiotic therapy:

Fatigue
Widespread musculoskeletal pain
Complaints of cognitive difficulties

These symptoms must be of such severity that, when present, they result in substantial reduction of occupational, educational, social or personal activities.

There are a number of exclusions in this proposed definition, among them being a diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease.

<u>Summary of the ILADS guidelines for diagnosis of Lyme disease</u> [3]

The position of the ILADS on diagnosis of Lyme disease is different from that of the IDSA.

The ILADS maintains that Lyme disease is a clinical diagnosis, which includes a consideration of symptoms, and tests should be used to support rather than supersede the physician's judgment. Burrascano, an ILADS board member, has presented a list of 60 symptoms found in Lyme disease [8].

Erythema migrans rash is diagnostic, but is absent in over 50% of cases.

Diagnosis of Lyme disease by the two-tier confirmation fails to detect up to 90% of cases.

Sensitivity and specificity for both the IgM and IgG western blots range from 92 to 96% when only two specific bands are positive.

Overlap in symptoms between Lyme disease (including "chronic Lyme disease" and "post-Lyme disease syndrome") and CFS

A comparison of Burrascano's symptoms list for Lyme disease [8] with the discussion of symptoms in the Canadian criteria for CFS [2] reveals that these two disorders have a large number of symptoms in common, and very few if any that are specific to one or the other of these disorders. Similarly, a comparison of the IDSA proposed definition for "post-Lyme disease syndrome" [5] and the Canadian criteria for CFS [2] shows that the symptoms specified in the former are also prominently found in the latter.

Etiology of Lyme disease

It is well-established that the Borrelia burgdorferi bacterium is responsible for causing Lyme disease [9], and that there are several other tick-borne diseases that can be present with Lyme disease as coinfections [5,8].

Etiology of CFS, and the Glutathione Depletion—Methylation Cycle Block (GD-MCB) hypothesis for CFS

The etiology of CFS is not agreed upon. As noted above, the present author has proposed a hypothesis for CFS called the Glutathione Depletion—Methylation Cycle Block hypothesis [6], which proposes that the etiology of CFS consists of genetic predisposition

combined with the effects of some combination of a variety of stressors (physical, chemical, biological and/or psychological/emotional) that lead to the depletion of glutathione, which in turn causes a partial block in the methylation cycle. A updated review of the GD-MCB hypothesis follows:

- **An individual inherits a genomic predisposition (polymorphisms in several of certain genes) toward developing CFS. (This genomic factor is more important for the sporadic cases than for the cluster cases of CFS.)**

- **The person then experiences some combination of a variety of possible stressors (physical, chemical, biological, and/or psychological/emotional) that place demands on glutathione. [As will be discussed later, this is the point at which Lyme disease can come into this pathogensis.]**

- **Glutathione levels drop, producing oxidative stress, removing protection from cobalamin (vitamin B12) and allowing toxins to accumulate.**

- **Toxins react with cobalamin, lowering the rate of formation of methylcobalamin.**

- **Lack of sufficient methylcobalamin inhibits the activity of methionine synthase, placing a partial block in the methylation and folate cycles.**

- **Sulfur metabolites drain excessively through the transsulfuration pathway to form cysteine.**

- **Much of the cysteine is oxidized to cystine because of the state of high oxidative stress, and is therefore not available for the synthesis of glutathione. An alternative pathway initiated by cystathionine gamma lyase diverts the cystine into formation of hydrogen sulfide and thiosulfate, and the latter is excreted in the urine.**

- **An interaction (vicious circle) is established between the partial block in the methylation cycle and the depletion of glutathione, and this is what causes the disorder to become chronic.**

- **A wide range of symptoms results from these chronic abnormalities in the basic biochemistry of the cells.**

- **The dysfunction of the detoxication system and the immune system that results from this vicious circle mechanism allows toxins and infections to accumulate over time, which increasingly produce effects of their own.**

- **Treatment should be directed primarily at increasing the activity of methionine synthase. The resulting normalization of the methylation cycle, the folate metabolism and glutathione levels will restore function to the immune system and the detoxication system as well as to a wide range of other parts of the overall biochemistry.**

- **It can be expected that die-off of pathogens and mobilization of stored toxins will initially produce some exacerbation of symptoms, but improvements will be experienced as the body burdens of toxins and active infections are decreased.**

Included among the biological stressors that place demands on glutathione are infections, such as that produced by Borrelia burgdorferi. In other words, the possibility that Lyme disease could lead to CFS was part of the GD-MCB hypothesis as proposed. The biochemical mechanism of the proposed link between Lyme disease and CFS is elaborated in more detail below.

Hypothesis for a link between Lyme disease and CFS

The present author proposes that Lyme disease can lead to CFS in individuals who are genomically predisposed to developing glutathione depletion and a partial block in the methylation cycle under the influence of stressors. This occurs because the Borrelia burgdorferi bacterium depletes glutathione in its hosts. In such cases, Lyme disease and CFS exist together as comorbid conditions, so that CFS is a component of what has been called "chronic Lyme disease." If the Lyme disease is successfully treated, the CFS continues to be present chronically unless specifically and effectively treated, because of the ongoing vicious circle interaction between glutathione depletion and the partial methylation cycle block. The resulting condition then constitutes what has been called "post-Lyme disease syndrome," which falls into the category of the post-infective fatigue syndromes.

<u>Evidence in support of this hypothesis</u>

Sambri and Cevenini [10] found in culture experiments that Borrelia burgdorferi (Bb) requires that cysteine be supplied exogenously, and is not able to make use of either methionine or cystine as a cysteine source. They also found that cysteine diffuses passively into Bb, i.e. there is no active transporter protein. This requirement of Bb for exogenous cysteine is important, because it means that Bb must take cysteine from its host. Cysteine is the rate-limiting amino acid for the synthesis of glutathione in human cells, and if it becomes depleted, this synthesis will be inhibited [11].

It has been found that Bb uses cysteine in the synthesis of several of its essential proteins: outer surface protein

A (OspA), outer surface protein B (OspB), coenzyme A, a hemolysin and others [10,12]. Bb does not use glutathione for its control of its redox potential, as do human cells. Instead, it uses reduced coenzyme A (CoASH) [13].

Pancewicz et al. have found that Bb does in fact lower the cysteine and glutathione levels in its human host, and also inhibits the activity of glutathione peroxidase [14]. Because glutathione peroxidase, with the help of glutathione, normally converts hydrogen peroxide to water, thus eliminating its contribution to oxidative stress, low glutathione and low activity of glutathione peroxidase will allow a rise in hydrogen peroxide concentration and a rise in oxidative stress [15].

Although Bb appears to be more resistant than other bacterial pathogens to reactive oxygen species, it does incorporate unsaturated fatty acids in its membranes, and these are vulnerable to oxidative attack [16]. It has been observed that elevation of hydrogen peroxide causes Bb to assume its cyst form [17], in which it is less vulnerable to environmental threats [18], including antibiotics [19]. Perhaps this self-actuated mechanism serves to promote the survival of Bb in its host.

It is known that the immune system is dysfunctional in CFS, and the GD-MCB hypothesis [6] suggests that this results from glutathione depletion and disruption of the folate metabolism. Glutathione is particularly important for the function of the T lymphocytes [20], and folate is needed in the synthesis of DNA and RNA, necessary for the proliferation of T cells [21]. Thus, the biochemical mechanism suggested in the GD-MCB hypothesis can be expected to have a deleterious effect on the cell-

mediated (Th1) immune response, which is needed to counter intracellular pathogens. Bb has been found to be able to reside intracellularly [18], and it has been shown that Th1 types of responses are required for optimum eradication of Bb [22]. Therefore, this immune dysfunction may help Bb to continue to survive in the body of the host, which is relevant to chronic Lyme disease.

The major overlap in symptoms between CFS on the one hand, and both chronic Lyme disease and post-Lyme disease syndrome on the other, as described earlier, is also evidence that supports this hypothesis.
In this regard, a study was performed by Gaudino et al. [23] that compared a group of patients judged to have post-Lyme disease syndrome (though the authors acknowledged that the possibility of ongoing infections could not be ruled out) with a group who met the research case definition for CFS [1] but did not have histories suggestive of Lyme disease. The authors found that both groups experienced severe fatigue, myalgia, headaches, and perceived cognitive problems. Eighty-four percent of the post-Lyme patients also met the research case definition for CFS. They did not find significant differences between the two groups in terms of psychiatric illness.

Despite the overlap in symptoms, they did find that some symptoms distinguished the two groups. Fever, sore throat, tender lymph nodes and unrefreshing sleep were found to be significantly more common among the patients with CFS. They also found that post-Lyme patients showed more global cognitive impairment.

It should be noted that the CFS research case definition [1] described earlier, which was used for patient selection in this study, specifically lists sore throat, tender lymph nodes and unrefreshing sleep among eight symptoms, four of which must be present to diagnose CFS. The more recent Canadian diagnostic case definition for ME/CFS [2] specifies a broader definition for sleep dysfunction and combines sore throat and tender lymph nodes together under "immune manifestations." The immune manifestations are then grouped together with two other categories of symptoms, and the definition requires only that at least one symptom from two of these three categories must be present. Since there are 21 symptoms listed in these three categories, it is likely that patients in a group selected using the Canadian criteria for CFS would be less likely to exhibit sore throat, tender lymph nodes and unrefreshing sleep than a group selected using the CFS research case definition. In view of this, the differences found in this study between these symptoms in post-Lyme disease syndrome and CFS do not appear to be very robust. In addition, while this study found little cognitive deficit in the CFS patients, an earlier study in CFS reported poor performance on reaction time and attention [24], in disagreement with this study. It therefore appears that CFS and post-Lyme disease syndrome are essentially indistinguishable on the basis of comparison of symptoms.

<u>Implications for the debate concerning "chronic Lyme disease" vs. "post-Lyme disease syndrome"</u>

In view of the hypothesized link between Lyme disease and CFS, it seems possible that either chronic Lyme disease or post-Lyme syndrome could be present in a

given case that began with Lyme disease and progressed into CFS, depending on whether or not Borrelia burgdorferi had subsequently been eradicated. If Bb were still present, the condition would properly be called chronic Lyme disease. If Bb had been eradicated, the patient would still have CFS, which would persist because of the vicious circle mechanism described in the GD-MCB hypothesis. Therefore, the patient would have post-Lyme disease syndrome, which is a post-infective fatigue syndrome, a recognized category within CFS [25].

Testing this hypothesis

This hypothesis can readily be tested by means of the commercially available methylation pathways panel [26], which is increasingly being used in CFS and autism. This panel measures metabolites in the methylation cycle and the folate metabolism, as well as the reduced and oxidized forms of glutathione, and will reveal whether glutathione depletion and/or a partial block in the methylation cycle are present. This panel could be used on patients believed to have either chronic Lyme disease or post-Lyme disease syndrome, to find out whether this hypothesis is valid for these patients.

Implications for treatment

If this hypothesis is valid, it suggests that treatment of "chronic Lyme disease" or "post-Lyme disease syndrome" should include treatment to lift the partial methylation cycle block. Such treatment of patients with combined diagnoses of chronic fatigue syndrome and fibromyalgia has been subjected to a clinical

research study, and the results are reported in another paper at this Conference [7].

Summary

A link has been hypothesized between Lyme disease and chronic fatigue syndrome (CFS). This link is based on the Glutathione Depletion—Methylation Cycle Block (GD-MCB) hypothesis for CFS [6]. The GD-MCB hypothesis proposes that in a person who is genomically predisposed, stressors that place demands on glutathione can cause it to become depleted, and can lead to a partial block in the methylation cycle. The resulting vicious circle interaction maintains CFS as a chronic condition. The present paper suggests that Lyme disease is one of the stressors that can produce this vicious circle interaction in the body of a person who is genomically predisposed. It is suggested that this leads to chronic Lyme disease. If the Borrelia bacteria are subsequently eliminated by treatment, the patient then has post-Lyme disease syndrome. Post-Lyme disease syndrome is one of the post-infective fatigue syndromes, a category of disorders within chronic fatigue syndrome [25]. A commercial test panel is available to test this hypothesis [26], and treatment to lift the methylation cycle block and to restore glutathione is available [7] if these are found to be present.

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26. The methylation pathways panel is available in the U.S. from Vitamin Diagnostics, Inc., Cliffwood Beach, NJ (phone: (732-583-7773) and in Europe from the European Laboratory of Nutrients in the Netherlands.