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REVIEW

Chronic Diseases® and Translational Medicine

Posttreatment Lyme disease syndrome and myalgic encephalomyelitis/chronic fatigue syndrome: A systematic review and comparison of pathogenesis

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Abstract

Lyme disease is the most common vector-borne illness in the United States and has been causing significant morbidity since its discovery in 1977. It is well-documented that about 10% of patients properly treated with antibiotics never fully recover, but instead go on to develop a chronic illness dubbed, posttreatment Lyme disease syndrome (PTLDS) characterized by severe fatigue, cognitive slowing, chronic pain, and sleep difficulties. This review includes 18 studies that detail the symptoms of patients with PTLDS and uses qualitative analysis to compare them to myalgic encephalitis/chronic fatigue syndrome (ME/CFS), a strikingly similar syndrome. In the majority of the PTLDS studies, at least four of the six major symptoms of ME/CFS were also noted, including substantial impairment in activity level and fatigue for more than 6 months, post-exertional malaise, and unrefreshing sleep. In one of the included PTLDS articles, 26 of the 29 ME/CFS symptoms were noted. This study adds to the expanding literature on the post-active phase of infection syndromes, which suggests that chronic illnesses such as PTLDS and ME/CFS have similar pathogenesis despite different infectious origins.

KEYWORDS

chronic fatigue syndrome, Lyme disease, myalgic encephalitis, posttreatment Lyme disease syndrome, systematic review

Key points

- This systematic review uses qualitative analysis to compare posttreatment Lyme disease syndrome to myalgic encephalitis/chronic fatigue syndrome, both of which are post-active phases of infection syndromes.
- The result of this review suggests that chronic illnesses such as PTLDS and ME/CFS have similar pathogenesis despite different infectious origins.

1 | INTRODUCTION

Lyme disease is a rapidly spreading tick-borne illness caused by *Borrelia burgdorferi* endemic to much of the United States. There have been at least 30,000 reported cases annually since its discovery in 1977, and the CDC published 275,589 reported cases from 2008 to 2015.[1] The earliest stage of Lyme disease is characterized by erythema migrans with or without constitutional symptoms, which resolves 90% of the time with antibiotics.[2] However, 10%–20% of patients go on to develop debilitating fatigue, myalgias, arthralgias, headaches,

sleep difficulties, cognitive slowing, and paresthesia.[3] Oftentimes, these severe symptoms render patients unable to work or care for their loved ones.[4] This collection of severe, continued Lyme disease symptoms, dubbed posttreatment Lyme disease syndrome (PTLDS) can persist for months to years. Although we have less knowledge about this syndrome, it is distinct from other Lyme disease sequelae, such as late-stage Lyme disease, Lyme neuroborreliosis, and antibiotic-refractory Lyme arthritis. The underlying pathophysiology of PTLDS is unknown and the validity of the diagnosis is often questioned in the medical community.[2,3] This review seeks to compile and comprehensively review evidence that validates that PTLDS is not only a true chronic disease, but that its symptoms and timeline are strikingly similar to other chronic illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long coronavirus disease (COVID).

PTLDS follows a similar pattern to a more recently prevalent disease, long COVID, a condition in which patients appear to have cleared COVID-19 according to objective lab results yet continue to suffer from subjective symptoms including disabling fatigue, post-exertional exhaustion, shortness of breath, and generalized malaise.[5] Long COVID itself has been linked to ME/CFS as many long COVID patients are satisfying the Institute of Medicine criteria for ME/CFS.[5] ME/CFS is characterized by fatigue, cognitive slowing, headaches, flu-like symptoms, arthralgias, and myalgias.[5] ME/CFS is a diagnosis of exclusion and requires the presence of severe fatigue interfering with daily life for greater than 6 months and moderate, severe, or substantial intensity of symptoms at least half of the time. Patients must have the following: (1) new onset inability/reduction in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that last greater than 6 months and are not relieved with rest or caused by excessive activity; (2) worsening of these symptoms after prolonged physical or mental exertion; (3) unrefreshing sleep; and (4) cognitive impairment and/or orthostatic intolerance.[5,6] The standard of care for ME/CFS is supportive treatment, often with the same medications used to treat fibromyalgia, although in most cases there is little improvement in symptoms.[6] Accepted treatment for long COVID is similar; it includes evaluation of chronic symptoms with supportive care on a case-by-case basis.[5]

Like long COVID and ME/CFS, the exact pathophysiology of PTLDS is still unknown. Several studies have documented elevations of pro-inflammatory markers and disturbances in energy production/metabolic functions. A case–control study by Fitzgerald et al.[7] identified metabolic differences between healthy controls and those with PTLDS. These findings are similar to results that have been seen with ME/CFS, which have a major effect on energy production and provide a possible mechanism for patients' chronic fatigue.[8] Other hypotheses point to antibiotic-refractory Lyme arthritis as an example of *Borrelia burgdorferi* causing a localized pro-inflammatory state in joints after the infection has cleared.[9] One study by Steere et al.[10] found that patients with HLA-DR alleles, which are linked to autoimmune diseases, are more likely to develop Lyme arthritis. Another study from Uhde et al.[11] found that patients with PTLDS and antibiotic-refractory Lyme arthritis both have elevated C-reactive protein levels. Other potential markers including IL-23, CCL19, and anti-neural antibodies have been found to be elevated in patients with PTLDS.[12–14] This further strengthens arguments that these chronic symptoms could be due to immune dysregulation.

Although there are over one million patients suffering from PTLDS in the United States, there is still a paucity of potential treatments.[15] ME/CFS has a larger body of research, and if found to have similar pathophysiology to PTLDS, that research could potentially improve the lives of these patients. This systematic review seeks to compare documented symptoms of ME/CFS to PTLDS to reveal similarities between the two conditions and propose that Lyme disease is yet another way to develop a post-active phase of infection syndrome. To uphold this argument, this study uses a qualitative approach to the systematic review to present the symptoms of PTLDS and compare them to the most common symptoms of ME/CFS.

2 | METHODS

PubMed and MEDLINE/Ovid were the primary databases used to search for articles that documented the symptoms of PTLDS. Articles were included up until November 15, 2022. There is no standardized name for PTLDS, so alternative search phrases of "chronic Lyme disease" and "posttreatment Lyme disease" were both used. This process followed the PRIMSA guideline for systematic review.[16]

On PubMed, "chronic Lyme disease" yielded 1415 results, and "posttreatment Lyme disease" yielded 327 results. On Medline, "posttreatment Lyme disease" yielded 50 results, and "chronic Lyme disease" yielded 231 results. Titles and abstracts of the resulting articles were reviewed, and articles that documented the individual symptoms of patients diagnosed with PTLDS were selected. To fit these criteria, patients in the article had to be diagnosed with Lyme disease and treated with antibiotics according to the standard of treatment with no relief from their symptoms. Ideally, articles included only documented patients who suffered from PTLDS symptoms for at least 6 months to correlate well with ME/CFS diagnostic inclusion criteria. However, this search returned too few articles. Therefore, articles were included that documented PTLDS symptoms in patients for at least 3 months posttreatment with antibiotics. All articles regarded PTLDS as a diagnosis of exclusion and symptoms could not be related to another ailment.

Articles were excluded if they did not describe the symptoms of the study participants or other related conditions such as Lyme arthritis or late-stage Lyme disease without antibiotic treatment. The chart displayed is adopted from a study by Lim and Son[17] and used previously in a study by Wong and Weitzer[5] to compare ME/CFS to long COVID.[5,17]

3 | RESULTS

The initial search criteria resulted in 2023 articles. Using the above search criteria and removing duplicate and unrelated articles, 52 articles remained. The full texts of the remaining articles were examined, and articles that did not report the PTLDS symptoms of the participants were excluded. For example, exclusion criteria impeded the authors from including a study by Vargas et al.[18] published in 2021 due to its inclusion of one participant who had confirmed antibiotic-refractory Lyme arthritis. A study by Uhde et al.[19] that examined the level of C-reactive protein elevation in patients with ME/CFS in comparison to those with PTLDS was excluded because it did not list the clinical symptoms of its participants. After an exhaustive search for articles that fit the criteria, the systematic review included 18 articles.

The 18 PTLDS articles are described in Table 1, which includes the total number of patients, the location of study, the time elapsed since initial antibiotic treatment, how results were gathered, the percentage of patients with confirmed PTLDS who reported each specific symptom, and the risk of bias. The articles are organized from the largest to smallest sample size. Sample sizes smaller than 50 participants were documented in 50% of the included articles. Small sample sizes in each individual study are recognized to be the largest threat to the integrity of the data as a whole.

In Table 2, reported ME/CFS symptoms are compared with reported PTLDS symptoms. The symptoms that are well-established and a requirement for diagnosis are documented as the primary symptoms, and the remaining symptoms attributed to ME/CFS are listed below the primary.[5,6,17] Out of the 18 included studies, 15 documented the symptoms as lasting greater than 6 months. The other three studies recognized that most of their patients had been suffering for over 6 months but chose not to require 6 months of symptoms for study inclusion. Each of the symptoms attributed to ME/CFS were reported by at least one study in the setting of PTLDS except three: lymphadenopathy, susceptibility to viruses, and food sensitivities. These were the same symptoms that were not reported by any patients with long COVID as documented in the systematic review by Wong and Weitzer.[5] Symptoms that appeared to be unique to PTLDS included paresthesia, tremor, and stiff neck, with paresthesia being the most common.

The most common overlapping symptoms included fatigue and brain fog. Both symptoms were reported by participants in 15 studies, followed by arthralgia, myalgia, and memory difficulties which were seen in 11 studies. It should be noted, however, that three of the studies were focused only on cognitive issues. Although they did not assess any other symptoms in their patients who met PTLDS criteria, it is quite possible that the patients were also suffering from fatigue and other symptoms. In the study by Nilsson et al.,[20] all of the participants satisfied the diagnostic criteria of ME/CFS if not for their documented PTLDS.

4 | DISCUSSION

The purpose of this systematic review is to fill a recognized gap in data on PTLDS by comparing it to ME/CFS. Both syndromes were defined in the last 30 years and have different inciting factors. However, as the evidence in this review suggests, the resulting chronic syndromes are largely the same.

As seen in Table 2, the symptoms of ME/CFS outlined by Wong and Weitzer in 2021 are comparable to the PTLDS symptoms described by participants in the 18 included articles. Of the 29 ME/CFS symptoms, all but three (lymphadenopathy, susceptibility to viruses, and food sensitivities) were reported in at least one included article as experienced by their participants. Of the six major diagnostic symptoms, over half of the articles reported at least four. The most shared characteristics are symptoms lasting greater than 6 months, fatigue, sleep difficulties, and brain fog. Although post-exertional malaise, part of the major criteria for ME/CFS, was not cited as often, it is possible that this criterion was included with fatigue/malaise for most of the articles. Other similar symptoms included arthralgias, myalgias, memory difficulties, and headaches. The overlap of symptoms makes a compelling argument that PTLDS and ME/CFS are very similar.

These symptoms are highly characteristic of global inflammatory processes. Additional research links the two syndromes even more tightly as inflammatory conditions with an infectious nidus. A study of children with ME/CFS found elevations of IL-23 which is an inflammatory marker also found to be elevated in patients with documented PTLDS.[14,37,38] Elevation in pro-inflammatory cytokines in ME/CFS is well-documented and increasing evidence compiled on PTLDS has also identified elevated inflammatory markers including C-reactive protein, IL-23, CCL19, and anti-neural antibodies.[11–14] A study by Fitzgerald et al.[7] also documented metabolic differences between healthy controls and patients diagnosed with PTLDS. This finding was very similar to results in patients with ME/

TABLE 1 Studies included in the review.

Authors	No. of patients	Location	Time at assessment	Methodology	Key findings	Other findings
Hill et al.[4]	82	USA	>6 months	Questionnaires	Physical functioning issues, social functioning issues, low energy	Increased pain, psychiatric issues
Nilsson et al.[20]	85	Sweden	>6 months	Interview	Fatigue (66%), neurocognitive symptoms (59%), dizziness (38%), sleep disturbance (36%), reduced endurance (33%)	Neurological issues (84%), musculoskeletal issues (78%), malaise (76%), arthralgias (53%)
Horowitz et al.[21]	165	USA	>6 months	Survey/interview	Fatigue (88%), memory issues/brain fog (77.6%), sleep issues (63.7%), speech/writing difficulties (53.4%)	Myalgia/arthralgias (74%), headache (44.8%), paresthesias (49.1%), sweats/flushing (48.5%)
Berende et al.[22]	280	USA	>4 months	Questionnaires	Fatigue (95%), neurocognitive issues (86%)	Arthralgia (90%), myalgia (80%), sensory issues (76%), neuralgia (15%)
Klempner et al.[23]	129	USA	>6 months	Questionnaires	Fatigue/malaise (90%), neurocognitive symptoms (72%), sleep disturbance (51%)	Arthralgia/myalgia (92%), dysthesia (70%), headache (42%)
Baarsma et al.[24]	15	Netherlands	>6 months	Focus group/interview	Fatigue (87%), cognitive problems (53.3%)	Myalgia/arthralgia (47%), impaired coordination (33%), visual/auditory impairments (33%), feeling feverish/chills (33%)
Aucott et al.[25]	234	USA	6 months–1 year	Questionnaires	Fatigue, difficulty focusing/difficulty finding words/memorydifficulty, difficulty sleeping	Muscle pain, joint pain/swelling, paresthesias, depression/anxiety/irritability, headache, chills/sweats, fevers, photophobia/visual clarity, tinnitus, dizziness, sore throat, diarrhea
Rebman et al.[26]	212	USA	Median 1.67 years	Questionnaires	Fatigue, memory issues, difficulty focusing, word-finding difficulties, difficulty sleeping	Myalgias, arthralgias/joint swelling, headache, paresthesias, photophobia, vision issues, fever/chills/sweats, nausea, depression, anxiety, irritability
Touradji et al.[27]	124	USA	>6 months	Questionnaires	Cognitive complaint (91.7%)	Depression (22%), anxiety (9%)
Krupp et al.[28]	55	USA	>6 months	Interview and Questionnaires	Severe fatigue, cognitive slowing	
Aprielle et al.[29]	42	USA	>2 years	Questionnaires	Fatigue (64%), sleep disturbance (45%), poor memory (38%), poor concentration/word finding (33%)	Myalgia (67%), arthralgia (55%)
Murray et al.[30]	29	USA	>6 months	Questionnaires	Fatigue, low physical functioning, cognitive difficulties	Chronic pain, depression
Musonera et al.[31]	27	Canada	Not documented	Patient chart review	Fatigue (70%), insomnia (19%), difficulty concentrating (15%)	Headache (70%), arthralgia (59%), myalgias (48%), paresthesias (26%), tremor (15%)

TABLE 1 (Continued)

Authors	No. of patients	Location	Time at assessment	Methodology	Key findings	Other findings
Turk et al.[32]	15	USA	>12 months	Questionnaires	Fatigue (87%), concentration/memory issues (73%), word-finding difficulties (40%), sleep disturbances (33%), dizziness/lightheadedness (7%)	Arthralgias (33%), mood disturbance (33%), headache (27%), paresthesia (27%), myalgias (20%), stiff neck (20%), tinnitus (7%)
Weitzner et al.[33]	14	USA	>6 months	Questionnaires/interviews	Fatigue (79%), memory/concentration impairment (27%), dizziness (35%)	Headache (50%), arthralgia (50%), feverish (43%), stiff neck (43%), anorexia (36%), myalgias (35%), paresthesia (27%), prolonged PR on EKG (15.4%), cough (14.3%)
Coyle et al.[34]	12	USA	>6 months	Interview	All 12 patients met CFS criteria, 6 met minor criteria	
Marvel et al.[35]	12	USA	>9 months	Questionnaires	Cognitive decline	Slower working memory
Novak et al.[36]	10	USA	>6 months	Neurological evaluation/Questionnaires	Orthostatic drop (70%), lightheadedness (80%)	Autonomic dysfunction (80%), aching pain (100%), paresthesia (80%), GI upset (40%)

CFS from a previous study, with both articles showing changes in glycerophospholipid, aromatic and branched-chain amino acid, carnitine, bile acid, fatty acid, and sphingolipid metabolism.[8] As there is no standardized test for ME/CFS or PTLDS, developing diagnostic biomarkers is the key to streamlining diagnosis.[12,13]

In addition to documenting the symptoms of their participants, studies have also hypothesized the pathophysiology of PTLDS. Although there is currently no evidence that *Borrelia burgdorferi* remains in human tissue after adequate treatment, several studies have shown improvement in fatigue after long-term intravenous antibiotics.[3] A retrospective chart review by Horowitz and Freeman[21] which followed 200 patients showed that Dapsone combination treatment for 6 months was statistically significant in reducing the severity of eight major PTLDS symptoms. However, two studies published in the *New England Journal of Medicine* in 2001 and 2016 showed no statistically significant differences in those treated by antibiotics in comparison to placebo.[22,23] In consequence, it is not the standard of care to treat PTLDS with additional antibiotics.[2,39] Depending on the chronicity of their Lyme disease upon diagnosis, patients are treated with one finite antibiotic regiment.[2] Early-stage patients receive 10 days of Doxycycline and late-stage cases with neurologic manifestation receive intravenous Ceftriaxone for 28 days; any further antibiotic regimens are not recommended.[2] Patients can choose to participate in research studies that explore if long-term antibiotic treatment would improve their chronic PTLDS symptoms.[21] It is important to note that PTLDS still carries a degree of stigma in the medical community. Many practitioners argue against its existence and others struggle to diagnose it without a standardized test.[24,40] Due to these factors, patients who satisfy the criteria for PTLDS may have had negative experiences in the healthcare field and experienced discrepancies between symptom onset and diagnosis. This may affect data in patients who may exaggerate symptoms to obtain care or conversely may be the reason for the smaller sample sizes in the included articles. This may also contribute to many patients with the disease remaining undiagnosed.

Limitations for most of the articles in this review include a small sample size and homogeneous participant population, with a great majority of the patients being of a higher socioeconomic status and White race. Many of the studies also relied on patients volunteering themselves or being referred by other clinicians which may have skewed the results. For future literature, it would be encouraging to see more studies comparing ME/CFS and PTLDS responses to different treatments to find even more similarities.

TABLE 2 Comparison of compiled ME/CFS symptoms to reported PTLDS symptoms.

Items	ME/CFS criteria symptoms	Reference number of PTLDS studies with matching symptoms	Non-ME/CFS criteria symptoms
Major ME/CFS criteria	Duration ≥6 months	4, 20, 23, 25, 27, 29, 30–34, 36–38, 40	
	Fatigue/reduced daily activity	4, 20, 23–25, 27, 29, 30, 32–38	
	Post-exertional malaise	4, 20, 32, 38	
Neurologic/pain	Sleep difficulties	20, 23, 25, 29, 30, 33, 35, 36, 38	
	Myalgia	20, 23–25, 27, 29, 30, 33, 35–37	
	Muscle weakness	20	
	Motor disturbance	20, 27	
	Generalized hyperalgesia(increased pain)	4, 20, 24, 25, 27, 34, 40	
	Joint pain/arthralgia	20, 23–25, 27, 29, 30, 33, 35–37	
	Headaches	20, 23, 25, 29, 30, 35, 36	
	Hypersensitivity to noise/light	29, 30	
	Tinnitus, double vision	20, 24, 27, 29, 30, 36	
		20, 23, 24, 29, 35, 36, 37, 40	Paresthesias
		36, 37	Stiff neck
		35	Tremor
Neurocognitive/psychiatric	Cognitive slowing/brain fog	20, 23, 24, 25, 27, 29, 30–37, 39	
	Memory difficulties/forgetfulness	20, 23, 24, 27, 29–31, 33, 34, 36, 37	
	Attention difficulties	29, 30, 33, 35–37	
	Psychiatric issues (depression, anxiety, etc.)	4, 20, 29, 30, 31, 34, 36	
Neuroendocrine			
	Thermostatic instability	20, 23, 27, 29, 30, 37, 40	
	Anorexia	37	
Autonomic	Orthostatic intolerance/dizziness	20, 24, 29, 36, 37, 40	
	Cardiovascular (palpitations, chest pain, *etc.*)	20	
	Respiratory (dyspnea, etc.)	20	
	Gastrointestinal (nausea, vomiting, diarrhea)	20, 29, 30, 40	
	Incontinence	20, 40	
Immune system	Fever/chills	27, 29, 30	
	Flu-like symptoms	29	
	Sore throat	29	
	Lymphadenopathy		
	Susceptibility to viruses		
	Food sensitivities		

Abbreviations: ME/CFS, myalgic encephalitis/chronic fatigue syndrome; PTLDS, posttreatment Lyme disease syndrome.

5 | CONCLUSIONS

This systematic review seeks to highlight the similarities between ME/CFS and PTLDS. From a vast literature review, 18 articles that document the symptoms of patients with PTLDS were chosen. The 18 PTLDS studies cited all but three of the 29 ME/CFS symptoms and most of the articles documented four of the six major ME/CFS symptoms. Both syndromes begin after an infectious event from which approximately 10% of patients never

truly recover. Pro-inflammatory states and changes in metabolism are the foremost hypotheses to explain the pathophysiology of each illness. This review uses qualitative data to make an argument that ME/CFS and PTLDS are similar in nature. It remains to be seen whether either illness will have a diagnostic test or effective treatment to improve the lives of the patients who are currently suffering.

AUTHOR CONTRIBUTIONS

Natalie A. Bai reviewed the literature. Natalie A. Bai and Christie S. Richardson contributed equally to writing and revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in this article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Not applicable.

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