

## The Post-Lyme Disease Treatment Syndrome (PTLDS) A Review of its Origin and its Consequences in the Socio-Economic Sphere

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### Abstract

In the 90s patients treated for Lyme disease, caused by the bite's tick, which transmit the spirochete *Borrelia burgdorferi* began to show a set of signs and symptoms that started months after concluded the treatment; they began to reported by various scientists around the world and called Post Treatment Lyme Disease Syndrome (PTLDS), mainly characterized by cognitive deterioration, recurring headaches, fatigue, memory problems, musculoskeletal pain and many others. For some individuals the syndrome is clinically evident, while for others it has a psychosomatic element. In this research we will make a chronological description of post-Lyme syndrome, when it appeared, its symptoms and if it really deserves to be recognized by the World Health Organization (WHO) in the new ICD-11 codes. In addition to this aspect, clarify the meaning of this term and scope in medical and non medical practice. We will propose a management regimen for Lyme disease that could eliminate this bacterium that is causing so much deterioration in the affected population worldwide.

### Main Objective

Make a chronological description of the Post Treatment Lyme Disease Syndrome (PTLDS) from its beginnings to the present, its clinical characteristics in all affected age groups regardless of sex, age, race and nationalities.

### Secondary Objectives

- Determine if Post Lyme Syndrome is a scientific reality that should be:
- Considered within the new ICD-11 codes (International Classification of Diseases year 2018). ?
- They are cognitive symptoms after the treatment of Lyme disease?
- It's a term clearly defined?
- Lead to new alternative treatments for Lyme disease that would mainly cover the second, third and sequel of the disease.

### Methods

The methods to used include analysis of all the databases and articles published in this regard, both for or against Lyme disease post treatment syndrome (PTLDS), using the National Library of Medicine of the USA. (Pubmed, Medline). Scientific and technical literature on Health in Latin America and the Caribbean (LILACS), and Europe (SCOPUS, EMBASE); make a chronological description of the post-treatment syndrome of Lyme disease from the first time it was mentioned in the scientific literature to the present day, highlighting the most relevant. The objective was to determine if this syndrome is a clinical reality, a psychosomatic disease, or a spectrum of conditions needing better defining. In addition to that, we will explain why this term is causing so much controversy today, and we will propose a new treatment regimen that should be considered by the world health authorities for the treatment of Lyme disease.

In the chronology of Post-Treatment Lyme Disease Syndrome (PTLDS) we will highlight the most relevant ones in the timeline, describing the term first, by the health authorities, and by the scientists concerned in the study of these clinical manifestations.

Received date: January 29, 2019

Accepted date: February 22, 2019

Publish date: March 4, 2019

**Citation:** Trivedi, MK., et al. Wound Healing Activity of Consciousness Energy Healing Treatment on HFF-1 Cells and DMEM Using Scratch Assay (2019) Invest Demerol and Venereol Res 5(1): 1- 6.

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## Introduction

**Definition of the Term According to the Cdc:** The CDC defines Lyme disease as: “Lyme disease is an infection caused by the bacterium *Borrelia burgdorferi*. In the majority of cases, it is successfully treated with oral antibiotics. Physicians sometimes describe patients who have non-specific symptoms (like fatigue, pain, and joint and muscle aches) after the treatment of Lyme disease as having Post-Treatment Lyme Disease Syndrome (PTLDS) or Post Lyme Disease Syndrome (PLDS). The cause of PTLDS “is not known.”

The CDC also dismisses the use of the term “Chronic Lyme Disease” (CLD), arguing that this term is confusing in the scientific community and has been used at times to describe symptoms in patients who “never had actual or past contact” with *Borrelia burgdorferi* infection<sup>[1]</sup>.

**In summary:** For the CDC, Post-treatment of Lyme disease syndrome (PTLDS) is of “unknown cause” and in addition the term “Chronic Lyme Disease” (CLD) should not be used.

**Definition of the term According to the researchers:** Lyme disease is caused by a bacterium *Borrelia Burgdorferi*. Some patients show persistent neurological and organic symptoms (Post-Treatment Lyme Disease Syndrome (PTLDS), even after proper antibiotic therapy. The PTLDS symptoms include: cognitive changes: memory loss, verbal flexibility, association changes, speeds of thought, fatigue, musculoskeletal pain, weakness. It is thought that the cause of this is a chronic encephalopathy caused by the *Borrelia burgdorferi* when it reaches the brain<sup>[2,9-15]</sup>.

Also many, perhaps most researchers recognize the term “Chronic Lyme Disease (CLD), widely described in the literature<sup>[2]</sup>, and could be considered the same Post-Treatment Lyme Disease Syndrome (PTLDS). In addition, it is considered that in many cases the diagnosis was made late due to failures in the blood tests and resistance to the treatment with antibiotics.

**In summary:** for the scientific community, the term “post-treatment of Lyme disease syndrome (PTLDS)” is a reality and, in many cases, the cause of this is a chronic encephalopathy that causes the symptoms. The failure of the treatment with antibiotics, or the late establishment of it by misdiagnoses, could contribute to the symptomatology.

## Chronologic Evolution

### Decade from 1990 to 2000

In the year 1991 Krupp et al<sup>[3]</sup>; describes 15 patients treated for Lyme disease who complained of persistent cognitive difficulty after 6 to 7 months of treatment with antibiotic therapy; they were compared with 10 healthy controls. Post-Lyme patients showed a marked deterioration in cognitive tests: memory loss mainly in selective recognition. Memory deterioration did not correlate with anti-*Borrelia burgdorferi* antibodies titers in the blood or cerebrospinal fluid. No evidence of alterations in the magnetic resonances was found in the affected patients, also symptoms of depression. The authors conclude that it is an encephalopathy of unknown cause, where factors such as the sequel of systemic infection by *Borrelia* and other toxic metabolic factors may be partly responsible for these symptoms<sup>[3]</sup>.

Perhaps this represents the first study in Post-Treatment Lyme Disease Syndrome (PTLDS), or Post-Lyme Syndrome (PLS) because patients were evaluated months after receiving treatment and presented neurological damage symptomatology in this case chronic encephalopathy<sup>[3]</sup>.

**Note:** In all the previous studies of Lyme disease the term Post-Lyme Treatment Syndrome (PLTDS) is not mentioned; they describe chronic manifestations as part of the second or late phase of Lyme disease, but not this term until 1991 where these researchers publish the study<sup>[2-3]</sup>.

**1995:** After the description of Krupp et al., another scientists: Benke, et al.[4], in the year of 1995, published a study on 20 patients with Lyme Borreliosis previously diagnosed several years earlier, with an average of 4.3 years after the acute phase of Lyme, compared with a control group; This study revealed that patients with Lyme revealed deficits in verbal memory, mental flexibility, verbal associative functions and vocal articulation. The authors suggest that these findings are similar to those reported by Krupp et al. in 1991 and reaffirm that it is an encephalopathy associated with a long-term neuropsychological deficit that predominantly affects internal functions<sup>[4]</sup>.

**1996:** One year later Bujak, et al. in 1996 published a study of 23 patients after had Lyme positively tested with ELISA, and previously treated with standard antibiotic regimens for the disease; neurocognitive impairment, persistent arthralgia, fatigue and memory loss were evaluated, finding the following facts: 7 patients (30 %) had fibromyalgia, 3(13 %) had chronic fatigue syndrome and 22 of 23, they complained about memory problems or decreased concentration. The scores for the attention scale, verbal memory, visual memory, sleep problems, mood swings and depression symptoms were higher for Post Lyme patients (PLS) than the normal.

The authors conclude that despite treatment with appropriate antibiotics for Lyme disease, sequelae mainly neurocognitive disorders, persistent arthralgias and fatigue can arise<sup>[5]</sup>.

**1997:** In this year, Gaudino, et al. published a study to evaluate the differences and similarities between chronic fatigue syndrome (CFS) and post-Lyme syndrome (PLS) studying 25 patients with chronic fatigue syndrome (CFS) with exclusion criteria for Lyme disease, 56 healthy controls and 38 patients with Post Lyme syndrome (PLS), seropositive for *Borrelia burgdorferi* with positive criteria by the CDC for Lyme, who presented symptoms of severe fatigue 6 months after having complied with the treatment of antibiotics for Lyme disease. All the patients underwent structured psychiatric interviews, evaluating: attention tests, verbal memory, verbal fluency and motor speed. Patients with chronic fatigue syndrome (CFS) and Post Lyme syndrome (PLS) were similar in several somatic symptoms and in the psychiatric profile. Patients with PLS had a worse performance on cognitive tests compared to healthy controls.

The authors conclude that despite the overlap of symptoms, patients with Post Lyme Syndrome (PLS) show greater cognitive deficits than patients with Chronic Fatigue Syndrome (CFS) compared to healthy controls. This fact became more evident among patients with PLS who lacked premorbid psychiatric

disease<sup>[6]</sup>.

**1998:** Bloom, et al. studied 5 children from the neurocognitive point of view after having been diagnosed with Lyme. They were treated for 2 to 4 weeks with intravenous ceftriaxone and evaluated comprehensively including detailed neuropsychiatric tests. The main objective of the study was to consider the possibility that Lyme disease after treatment left a sequel in children as well, as it had already been demonstrated in adults.

The 5 children were followed up for a period of 2 to 7 years after the treatment with antibiotic (ceftriaxone) and it was found that months after the treatment the children after having had the classic erythema migrans, cranial neuropathy or Lyme arthritis, developed behavioral changes, forgetfulness, decreased school performance, headache, fatigue and in two cases complex seizure disorders.

The five patients were found IgG antibodies against *Borrelia burgdorferi* in serum, intrathecal IgG antibodies and two of them pleocytosis of the Cerebro Spinal Fluid (CSF). Despite normal intellectual functioning, the five children had mild to moderate impairments in auditory or visual sequential processing.

The authors conclude that children can develop neurocognitive symptoms together with or after the classic manifestations of Lyme disease, and attribute it to an infectious or postinfectious encephalopathy related to *Borrelia burgdorferi*, confirming previous studies in adults<sup>[7]</sup>.

In this study it was demonstrated that the Post-Treatment Syndrome of Lyme Disease (PTLDS) not only affects adults, but also children, and it is reaffirmed that the cause of it is an encephalopathy caused by the infection by the *Borrelia burgdorferi*.

**1999:** In the year of 1999 Elkins et al. published a work on 30 patients with Post Lyme Syndrome (PLS), who were surveyed to determine the neuropsychological status found as a fundamental aspect: the mood of PLS participants was characterized by reduced levels of positive affect (PA) and typical levels of negative affect. Authors conclude that these symptoms are the most useful markers in patients with Post Lyme Syndrome (PLS)<sup>[8]</sup>.

That same year Kaplan, et al. conducted a study where they claim that a small group of patients with Lyme develop encephalopathic symptoms months to years after diagnosis and treatment. The most common symptoms reported were fatigue, memory loss, sleep disorders and depression with a controversial etiology of the syndrome (PLS). The study was done comparing patients with Lyme and abnormal Cerebro Spinal Fluid (CSF), patients with Lyme and normal CSF and healthy controls. Both groups with Lyme showed memory deficits, but more accentuated and measurable in those with abnormal CSF; they also showed higher score in the depression in relation to healthy controls<sup>[9]</sup>.

**2000-2001:** In 2001 Klempner, et al. conducted a study to test the efficacy of antibiotic treatment in Lyme-positive patients with persistent symptoms and a history of Lyme disease. Two groups of patients were studied: 78 seropositive patients and 51 seronegative patients for *Borrelia burgdorferi*. Patients received intravenous ceftriaxone, 2 g daily for 30 days, followed by oral

doxycycline, 200 mg daily for 60 days, or corresponding oral and intravenous placebos. Each patient had well documented and treated Lyme disease, and had persistent musculoskeletal pain, or dysesthesia associated with fatigue. The authors conclude that there is a considerable deterioration in health-related quality of life among patients with persistent symptoms despite prior treatment for acute Lyme disease. In these two trials treatment with oral or intravenous antibiotics for 90 days did not improve symptoms more than placebo<sup>[10]</sup>.

Morgen, et al. performed a brain Magnetic Resonance (MR) study in 27 patients with post-treatment Lyme disease syndrome to try to help identify the pathological mechanisms of the disease. Of the total, four (4) patients had focal neurological deficits, recurrent remitting disease and lesions in a typical electron microscopy (EM) distribution; 23 (85 %) patients presented non-focal symptoms, such as fatigue, subjective memory deficiencies and mood disorders. Twelve of these patients (44%) had normal magnetic resonance imaging (MRI); 10 (37 %) had mainly punctate and subcortical lesions, and one patient had multiple periventricular lesions.

The authors concluded that in a portion of patients with Lyme disease syndrome after treatment, hyperintensities of the white matter tend to occur in subcortical arteriolar watershed areas and are not-specific<sup>[11]</sup>.

These last two studies show:

- Many patients do not improve with long-term antibiotics after presenting chronic symptoms post Lyme and
- It is demonstrated that there are obvious findings of the damage of the cerebral white matter in post-Lyme patient's treatment, found by means of Magnetic Resonance Imaging (MRI).

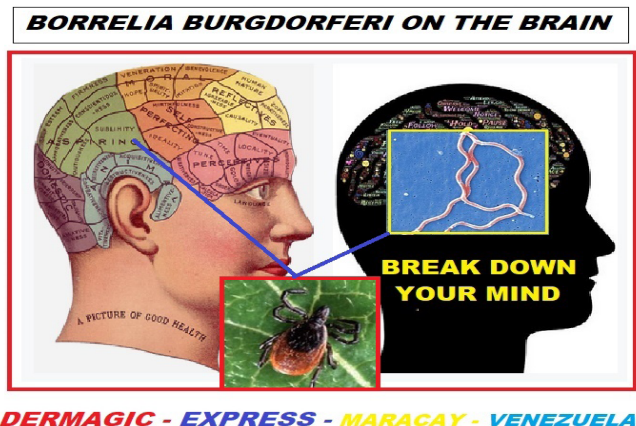
This means that in the line of time and for the 90s and the beginning of the 2000s, a harsh reality is uncovered: Lyme disease is an illness that in many cases becomes chronic, months or years after symptoms begin, even after having disappeared with proper treatment.

The most frequent symptoms of Chronic Lyme Disease (CLD) or Post-Treatment Lyme Disease Syndrome (PTLDS): 2001-2018

**Chronic Lyme Disease Symptoms:** Fatigue and lack of resistance; Nocturnal sweating; Pale, dark circle under the eyes; Abdominal pain; Diarrhea or constipation; Nausea; Cardiac anomalies; Lyme carditis; Orthopedic disorders: sensitivity, spasms and generalized muscle pain, rigidity and / or retarded motion; Respiratory infections of the superior tract and otitis; Arthritic disorders and painful joints; Neurological disorders: Headache Drowsiness, Loss of memory, Convulsions, Facial paralysis, Irritability, Bad mood; Suicidal thoughts; Anxiety; Anger or rage; Hallucinations; Earning disorders and humor changes: Cognitive speaking, Speech delay, Reading-writing problems, Problems of vocal articulation, Auditory / visual processing problems, Word selection problems, Dyslexia; Aggression or violence; Irritability; Emotional disorders; Depression; Hyperactivity; Photophobia; Gastroesophageal reflux with vomiting and coughing; Secondary eruptions; Other eruptions; Ocular problems: posterior cataracts, myopia, stigmatism, conjunctive erythema (Lyme

eyes), optical nerve atrophy and / or uveitis; Sensitivity of skin and noise (hyperacuity)<sup>[12-45]</sup>.

Probably there are more, the evidence is that there really are chronic symptoms in Lyme disease, with or without adequate treatment.



## Conclusions

It is demonstrated that the chronic symptoms of Lyme disease are a reality, referred to as:

Chronic Lyme disease (CLD); or  
Syndrome- Post-treatment of Lyme disease (PTLDS).

As we said at the beginning, the CDC does not recognize the term Chronic Lyme Disease (CLD) because it is confusing<sup>[1]</sup>.

With respect to this, we conclude that the CDC is wrong because data demonstrated that months or years after adequate treatments with antibiotics, patients can have the same or worse symptoms, which gives truth to the term: chronic Lyme disease (CLD).

On the other hand, the CDC alleges that the term Post-treatment of Lyme disease syndrome (PTLDS) is used by some scientists to define symptoms after the treatment of the disease and that it is due to “unknown cause”:

With regard to this aspect, the “so called” Post-treatment of Lyme disease syndrome (PTLDS), is the same chronic Lyme disease, consisting of:

- Lyme positive patients who were never treated.
- Positive Lyme patients who after treatment in acute phase relapsed months or years later, and reached the secondary or late stage with symptoms equal or more severe than at the beginning. Patients who were misdiagnosed due to lack of effective diagnostic tests and reached the chronic stage. Today the CDC recognizes that its diagnostic tests are not 100% effective.

Well-diagnosed Lyme patients who never responded to the treatments recommended by the CDC.

- We also disagree with the CDC about the definition of “unknown cause” when most studies and research show that it is a chronic encephalopathy produced by *Borrelia burgdorferi*, either by:
- Its persistence in the bloodstream, cerebrospinal fluid and tissues due to resistance to treatment, under the well-known mechanism of “Biofilm”.
- Generation of neurological damage due to the persistence of *Borrelia burgdorferi* in tissues that do not regenerate, such as

the nerve cells.

- An inflammatory process that remained in the nervous system and tissues after eliminating the causative agent.

In some patients, the coexistence of other diseases such as *Erlchiosis*, *Babesiosis* and *Bartonellosis*, which worsen the symptoms and obstruct the treatment.

We find with an unprotected society, the reality is that thousands of patients are discarded as positive Lyme after 4 months of treatment, because the treatment guidelines of the CDC say that in that time or less you will be cured, which we prove is false in a good proportion of patients.

In 2019 May, is the limit for the recognition of ICD-11 *Codes of Lyme disease* (International classification of diseases), and the WHO refuse to recognize them all, which will cause patients without coverage for their treatments. One of the unrecognized codes is congenital Lyme<sup>[46-54]</sup>.

The global community of patients with Lyme must organize well and adequately claim from health authorities such as the World Health Organization (WHO) to recognize the entire Lyme codes, and ensure coverage of their treatment at all levels.

The Syndrome post-treatment of Lyme disease (PTLDS), which is nothing more than the “chronic symptoms” of the disease, is being used perversely to cover the reality of this disease, avoid coverage by health insurance, and tell patients: “you have nothing, go to a psychologist ... when their blood and brain are sailing in a sea of *Borrelia*s.

## Comments

With regard to the proposal of new treatment guidelines for Lyme disease, we prefer to wait for what the health authorities at the world level will propose; then we will make a new publication about it.

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## Acknowledgments

To the Lyme world community that fights for its rights to be treated as real patients and not as psychiatric patients.

To my son J. Miguel MD, for his logistical support and co-author.

To all patients with Lyme especially Stacy Cellier Gomez whose story was quite motivating.

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