

Post-Lyme disease syndrome

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Abstract

About 10% of patients with Lyme disease continue to experience musculoskeletal pain and cognitive dysfunction after recommended antibiotic treatment. This condition is called post-Lyme disease syndrome (PLDS) or post-treatment Lyme disease syndrome. These two terms are used interchangeably. The pathogenesis of PLDS has been controversial. The hypothesis that patients with PLDS may harbor hidden reservoirs of *Borrelia burgdorferi* after their initial antibiotic treatment is difficult to accept. The prospective, double-blind studies contradict this point of view. Also, recently published research applying xenodiagnosis to PLDS supports the opinion that PLDS most likely has an autoimmune background. Lengthy courses of antibiotics are not justified in patients with PLDS because of the lack of benefit, and they are fraught with hazards. Most patients with PLDS recover from persistent symptoms with time. However, it can take months before they feel completely well.

Key words: Lyme disease, *Borrelia burgdorferi*, xenodiagnosis, post-Lyme disease syndrome.

Most patients with Lyme disease are cured by a 3–4 weeks' course of antibiotics. However, a minority of them (about 10%) have prolonged somatic and neurocognitive symptoms, such as fatigue, difficulty in sleeping, arthralgia, myalgia, memory impairment, and headache [1, 2]. This condition is called post-Lyme disease syndrome (PLDS) or post-treatment Lyme disease syndrome (PTLDS). These two terms are used interchangeably. The initial term 'chronic Lyme disease' was rejected [3]. The latter would suggest that infection with *Borrelia burgdorferi* may become persistent in this group of patients despite antibiotic therapy. The present medical knowledge contradicts this point of view. However, rheumatologists and internists are now and again visited by patients receiving prolonged antibiotic therapy for many months in treating PLDS. Therefore there is an urgent need to clarify these controversies.

Post-Lyme disease syndrome – definition

In the initial studies on borreliosis the term PLDS was part of the catch-all term 'chronic Lyme disease'. Feder et al. classified patients diagnosed with chronic Lyme disease in four categories:

- category 1 – symptoms of unknown cause such as fatigue, night sweats, arthralgia, myalgias, sleep disturbance, depression, with no evidence of *B. burgdorferi* infection,
- category 2 – a well-defined illness other than Lyme disease, misdiagnosed as Lyme disease,
- category 3 – symptoms of unknown cause, no objective clinical findings that are consistent with Lyme disease, but with antibodies against *B. burgdorferi*,
- category 4 – post-Lyme disease syndrome.

Feder et al. assert that chronic Lyme disease is a misnomer. A more accurate label is post-Lyme disease syndrome (only patients who fall into category 4) [3].

In 2006 Wormser et al. published the following proposed criteria of PLDS [4]:

Inclusion criteria:

- A patient with a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention [5];
- After recommended treatment of the episode of Lyme disease, there is resolution or stabilization of the objective manifestation(s) of Lyme disease;
- Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and

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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, sleep disturbances.

The authors also listed many exclusion criteria which allow one to establish a precise diagnosis and to avoid embarrassing diagnostic mistakes.

Interestingly, the appearance of post-Lyme disease symptoms seems to correlate with disseminated disease, greater severity of illness at presentation, and delayed antibiotic treatment [6]. They do not correlate with the duration of the initial antibiotic treatment [7].

Post-Lyme disease syndrome – pathogenesis

The exact cause of PLDS is not yet known. The pathogenesis of PLDS has spawned one of the stormiest controversies in the history of medical research [8–10]. Some authors speak of ‘the Lyme wars’. The hypothesis that patients with PLDS may harbor hidden reservoirs of the spirochete *B. burgdorferi* after their initial antibiotic treatment is difficult to accept. Moreover, a very interesting, first-of-its-kind publication by Marques et al. has recently contradicted this hypothesis [11]. To examine the ‘boggling enigma’ of PLDS [8], in the study of Marques et al. pathogen-free larval *Ixodes scapularis* ticks were placed on the forearms of 36 volunteers: 10 symptomatic adults with C6 antibody index > 3 (C6 *B. burgdorferi* IgM and IgG [Lyme] ELISA) after a documented episode of Lyme disease received recommended therapy; 10 subjects with PTLDS; 1 subject with recent-onset erythema migrans on antibiotic therapy, 5 subjects recently treated for erythema migrans; and 10 seronegative healthy individuals residing in endemic areas.

Xenodiagnostic engorged ticks were collected 3–7 days after placement. They were used in two protocols. In protocol 1 nymphal ticks were fed on severe combined immunodeficiency (SCID) mice. Replete ticks were analyzed for infection and culture. Severe combined immunodeficiency mice were monitored for infection by culture and polymerase chain reaction (PCR) of punch biopsies from many mouse organs.

In protocol 2 recovered ticks were kept in a humidified chamber for 11–14 days. Then ticks were crushed and tested by PCR and injection of the lysate subcutaneously into SCID mice. Skin biopsies were tested by culture and culture PCR.

Xenodiagnosis was considered positive when any of the techniques demonstrated *B. burgdorferi* or its DNA in xenodiagnostic ticks or in tissue from the SCID mice injected with tick lysate or fed upon by nymphal ticks.

The authors found the presence of amplifiable *B. burgdorferi* DNA in xenodiagnostic ticks removed from only 2 individuals. The first patient had erythema migrans and had just started antibiotic therapy. The other patient suffered from PTLDS. The authors were unable to culture the spirochetes or to show their transmission to SCID mice. So viable *B. burgdorferi* was not ascertained in any subjects [11].

The critical opinions about that paper state that recovery of live spirochetes is the only reliable criterion for a positive xenodiagnosis. Detection of DNA is not tantamount to finding viable spirochetes. Critical opinions also state that in humans the bacteremia from *B. burgdorferi* is transient and the spirochetes do not reside in the skin as they do in mice, so a xenodiagnostic tick feeding on a person may not encounter bacteria [12].

Despite the reservations presented, the study of Marques et al. [11] refutes the arguments of the advocates of the theory of the persistence of viable spirochetes after a recommended course of antibiotic therapy. The study supports the opposing opinion that PLDS most likely has an autoimmune background, but does not solve conclusively ‘the conundrum’ of PLDS.

Post-Lyme disease syndrome – how to treat

So far there is no causative treatment of PLDS. The rational solution is application of antidepressants, pregabalin and gabapentin, analgesics, psychotherapy and even alternative medicine.

Post-Lyme disease syndrome – how not to treat

There is no proof that symptoms of PLDS reflect persistent infection with *B. burgdorferi*. None of the studies performed have shown that patients suffering from PLDS who received prolonged courses of antibiotics do better in the long run than patients treated with placebo. The study published by Klempner et al. [13] reported two parallel trials. Patients randomized to the treatment group received 30 days of intravenous ceftriaxone followed by 60 days of oral doxycycline. Patients randomized to the placebo group received a placebo infusion for 30 days followed by an oral placebo for 60 days. There was no significant difference in any outcome measure between the treatment and the placebo group. Interestingly, depression, anxiety and somatic complaints improved in both groups between baseline and the last day of the study, but there was no difference between the treatment and placebo group.

Other researchers who studied the efficacy of prolonged antibiotic therapy have found it of little or no

benefit [14, 15]. However, they emphasize the frequency of adverse events in such a regimen. Risks include the development of antibiotic-resistant infection, intractable diarrhea, kidney or liver damage, allergic reactions, gastrointestinal bleeding, venous thrombosis, etc. There have also been instances of death from inappropriate prolonged antibiotic therapy for PLDS [16, 17].

The assertion that prolonged antibiotic therapy for PLDS does more harm than good is well established and is in accordance with the assertion of the Infectious Disease Society of America (IDSA). Despite this, there are still contradictory opinions emerging. Recently two publications have been released which have raised a stir by questioning the assertion of IDSA [18, 19]. However, Klempner et al. made an accurate retort and emphasized that extended antibiotic treatment is not helpful in PLDS [20, 21].

Summary

Lengthy courses of antibiotics are not justified in patients with PLDS because of the lack of benefit, and they are fraught with hazards. Most patients with PLDS recover from persistent symptoms with time. However, it can take months before they feel completely well.

It is worth reminding doctors who are disappointed in the therapeutic opportunities in PLDS of the motto of medieval French medics:

*To cure – only sometimes
To alleviate suffering – often
To console – always.*

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