

# Chronic Fatigue Syndrome in Patients with Lyme Borreliosis

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## Key Words

Lyme disease · Neuroborreliosis · Chronic fatigue syndrome

## Abstract

Several authors have reported a chronic fatigue-like syndrome in patients that have suffered from Lyme borreliosis in the past. To further investigate this suspicion of an association without sample bias, we carried out a prospective, double-blind study and tested 1,156 healthy young males for *Borrelia* antibodies. Seropositive subjects who had never suffered from clinically manifest Lyme borreliosis or neuroborreliosis showed significantly more often chronic fatigue ( $p = 0.02$ ) and malaise ( $p = 0.01$ ) than seronegative recruits. Therefore we believe it is worth examining whether an antibiotic therapy should be considered in patients with chronic fatigue syndrome and positive *Borrelia* serology.

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## Introduction

Lyme borreliosis is the most common vector-borne infection in the northern hemisphere with an annual incidence of 69 cases per 100,000 inhabitants [1]. Although the clinical course of borreliosis has been well described, data supporting the existence of a syndrome of chronic fatigue following infection is only just emerging [2].

Symptoms of the postinfectious chronic fatigue syndrome include persistent headaches, neuropsychological deficits and general malaise which can occur months or even years after infection and successful treatment of borreliosis [3–5]. This has been reported by Shadick et al. [5] in a population-based, retrospective cohort study showing a significantly higher incidence of fatigue (26 vs. 9%;  $p = 0.04$ ) and impaired ability to concentrate (16 vs. 2%;  $p = 0.03$ ) in patients that had been diagnosed with Lyme borreliosis when compared with an uninfected control population. In addition, Benke et al. [3] studied patients several years after they had been treated for Lyme borreliosis and compared their scores on various neuropsychological tests against an age- and education-matched control group. These patients showed deficits in memory, mental flexibility and articulatory and phonematic skills that were limited to a few memory functions and did not appear to be linked to a general mental decline.

In a recent clinical and serological follow-up study, Treib et al. [6] observed a significant reduction of neurological deficits 4.2 years after antibiotic treatment. However, more than half of the patients reported unspecific complaints such as headache as well as memory and concentration problems, similar to a chronic fatigue syndrome.

The association between Lyme borreliosis and chronic fatigue remains uncertain, however. It is also unclear whether an infection with *Borrelia* can lead to isolated neuropsychological deficits that resemble a chronic fatigue syndrome without the patient manifesting any other clinical signs of borreliosis or neuroborreliosis.

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We describe a double-blind comparison of the frequency of symptoms of chronic fatigue in infected and noninfected subjects. To reduce potential selection bias, we examined a cohort of young men without relevant medical disorders and without a history of Lyme disease. These individuals were screened for *Borrelia* exposure and symptoms of chronic fatigue.

## Methods

In a prospective, double-blind study, we examined a homogeneous sample of young men undergoing a thorough physical examination before entering their military service. Regarding regional origin, education and professional background they represented a cross section of German society. All were healthy young German men and assigned to units randomly. All of Germany is an endemic region for Lyme borreliosis, therefore all subjects were potentially exposed to *Borrelia burgdorferi* [7]. All subjects received an informational training session with lectures and slides carried out by a physician to increase their awareness and knowledge of Lyme borreliosis.

In addition to the serological tests, the subjects were also questioned about complaints or symptoms of fatigue using a standardized health questionnaire with simple yes/no questions. The questionnaire consisted of 5 pages. Page 1 contained the informed consent section, personal data about the subject, his family and his family physician. This data allows us to track down the individual in the future and conduct a very long-term follow-up at a later point in time in cooperation with the family physician. Page 2 records the history of tick bites: when and where (i.e. in which geographic region), complaints after tick bites, vaccination against tick-borne encephalitis (TBE), history of travel to regions where TBE is endemic and previous borreliosis or TBE infections. Page 3 is filled out by the physician and records any medical complaints the subject has, as well as any history of illness during the last year. A particular focus was on symptoms lasting longer than 1 month for which no other explanation could be found. Page 4 records hospital stays, medical treatments and procedures. Page 5 consists of questions relating to general well-being and complaints, symptoms corresponding to chronic fatigue, such as fatigue, malaise, weakness and pain. We used a relatively simple questionnaire where subjects only had to check a box, to keep the percentage of participation and overall compliance as high as possible.

The subjects were specifically asked by a physician about symptoms of Lyme borreliosis and whether a Lyme borreliosis had ever been diagnosed. Subjects with a known history of exposure or symptoms of Lyme borreliosis were excluded. Of the 1,416 subjects who were examined and questioned, 260 refused to participate in the study or were excluded due to a previous history or symptoms of Lyme borreliosis. Subjects with prior Lyme Borreliosis were excluded because our study focused on clinically silent infections.

A total of 1,156 healthy young men (mean age  $22.3 \pm 2.8$  years) were included in the study. They had provided their written informed consent to participate in the study and had agreed not to be informed about the results of the tests until after the end of their military service. Blood samples for our study were drawn during the standard procedure of blood group testing.

All subjects were tested for previous infection with Lyme borreliosis as determined by the presence of borreliosis antibodies in their

**Table 1.** Complaints of 505 recruits with tick bites, who were tested for *Borrelia* antibodies (%; significance computed with chi-square test)

	AB-positive (n = 42)	AB-negative (n = 463)	Significance
Fatigue	11.9	3.2	p = 0.02
Headache	7.1	3.4	n.s.
General malaise	11.9	2.4	p = 0.01
Fever	2.4	2.2	n.s.
Limb pain	7.1	1.4	p = 0.01
Joint pain	4.8	1.4	n.s.
Stiff neck	0	1.4	n.s.

serum. Serum was obtained from the recruits and tested double-blindly for IgG antiborrelia antibodies by ELISA. Positive and borderline ELISA results were confirmed by Western blot (both tests from Genzyme-Virotech, Rüsselsheim, Germany). Tests were evaluated according to the specifications of the manufacturer.

In addition to the serological tests, the subjects were also questioned about complaints or symptoms of fatigue using a standardized health questionnaire with simple yes/no questions. They were also asked about symptoms that occurred in connection with a tick bite, including especially severe symptoms lasting longer than 1 month for which no other explanation could be found.

## Results

A total of 505 (43.7%) recruits remembered a tick bite and 8.3% of them had serum that tested positive for *Borrelia* antibodies (another 2.5% tested as borderline positive). This is significantly more than the group of 645 recruits with no memory of a tick bite, where only 3.9% had detectable borreliosis antibodies in their serum (p < 0.01; all significances computed with chi-square test).

To obtain a homogeneous group, we analyzed the complaints of the 505 recruits with tick bites. They were differentiated into *Borrelia* antibody (AB)-positive and AB-negative recruits and reported the following frequencies of complaints and symptoms. Of the AB-positive patients, 11.9% reported fatigue, compared to 3.2% of AB-negative patients. The complaint headache was listed twice as frequently (7.9%) in the AB-positive group than in the AB-negative group. However, this difference was not significant. General malaise was named more than 4 times as often among AB-negative patients than in patients who were AB-negative (11.9% vs. 2.4%); 7.1% of the AB-positive patients complained of limb pain, compared to 1.4% of the AB-negative patients (table 1).

## Discussion

The well-known clinical symptoms of Lyme borreliosis include among others erythema migrans, chronic organ involvement (acrodermatitis, arthritis and carditis) as well as neurological symptoms such as meningoradiculoneuritis, meningitis and cranial neuritis [8, 9, 10]. In addition, nonspecific symptoms resembling chronic fatigue syndrome, such as reduced energy levels, fatigue and cognitive difficulties have been reported [6, 11–13].

Those subjects who tested positive for *Borrelia AB* by Western blot and who also had a history of previous tick bites showed a significantly higher frequency of fatigue and malaise than those who had a similar history of tick bites but tested negative for antibodies. Since the subjects were not aware of the results of the blood tests, it is unlikely that the increased occurrence of fatigue and malaise in the AB-positive group reflects a bias in sampling. Importantly, the outcome of the blood test had no influence on the military service, so that there was no incentive to falsely report symptoms of fatigue.

These results suggest that Lyme borreliosis is associated with fatigue and malaise, although the subjects did not suffer and had never suffered from a clinically manifest Lyme borreliosis or neuroborreliosis. Thus, our data is the first prospective, double-blind study to demonstrate a correlation between previous Lyme borreliosis infection and chronic fatigue and thereby suggests the existence of a post-borreliosis fatigue syndrome similar to that observed by Benke et al. [3].

## References

- 1 Berglund J, Eitrem R, Ornstein K, Lindberg A, Ringer A, Elmrud H, Carlsson M, Runehagen A, Svanborg C, Norrby R: An epidemiologic study of Lyme disease in southern Sweden. *N Engl J Med* 1995;333:1319–1324.
- 2 Haass A, Treib J: Neurological manifestations and classifications of borreliosis infection. *Infection* 1996;24:467–469.
- 3 Benke Th, Gasse Th, Hittmair-Delazer M, Schmutzhard E: Lyme encephalopathy: Long-term neuropsychological deficits years after acute neuroborreliosis. *Acta Neurol Scand* 1995;91:353–357.
- 4 Bujak DI, Weinstein A, Dornbush RL: Clinical and neurocognitive features of the post Lyme syndrome. *J Rheumatol* 1996;23:1392–1397.
- 5 Shadick NA, Phillips CB, Logigian EL, Steere AC, Kaplan RF, Berardi VP, Duray PH, Larson MG, Wright EA, Ginsburg KS: The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. *Ann Intern Med* 1994;121:560–567.
- 6 Treib J, Fernandez A, Haass A, Grauer MT, Holzer G, Woessner R: Clinical and serological follow-up in patients with neuroborreliosis. *Neurology* 1998;51:1489–1491.
- 7 Treib J, Woessner R, Grauer MT, Mueller-Reiland D, Haass A, Schimrigk K: Prevalence of antibodies to tick-borne encephalitis virus and *Borrelia burgdorferi* sensu lato in samples from patients with abnormalities in the cerebrospinal fluid. *Zentralbl Bakteriol* 1998;288:253–266.
- 8 Kaiser R: Neuroborreliosis. *J Neurol* 1998;245:247–255.
- 9 Steere AC: Lyme disease. *N Engl J Med* 1989;321:586–596.
- 10 Woessner R, Treib J, Haass A, Stoll M, Holzer G, Schimrigk K: Wertigkeit von Antikörpertitern für die Diagnose einer Neuroborreliose. *Nervenarzt* 1998;69:694–697.
- 11 Garcia-Monco JC, Benach JL: Lyme neuroborreliosis. *Ann Neurol* 1995;37:691–702.
- 12 Pachner AR, Duray P, Steere AC: Central nervous system manifestations of Lyme disease. *Arch Neurol* 1989;46:790–795.
- 13 Pfister HW, Wilske B, Weber K: Lyme borreliosis: Basic science and clinical aspects. *Lancet* 1994;343:1013–1016.
- 14 Halpertin JJ, Krupp LB, Golightly MG, Volkman DJ: Lyme borreliosis-associated encephalopathy. *Neurology* 1990;40:1340–1343.
- 15 Lightfoot RW Jr, Luft BJ, Rahn DW, Steere AC, Sigal LH, Zoschke DC, Gardner P, Britton MC, Kaufman RL: Empiric parenteral antibiotic treatment of patients with fibromyalgia and fatigue and a positive serologic result for Lyme disease: A cost-effectiveness analysis. *Ann Intern Med* 1993;119:503–509.

Bujak et al. [4] observed in a study with 23 patients suffering from post-Lyme syndrome that fatigue and neurocognitive impairment could probably be induced by Lyme disease, despite antibiotic treatment. In the past, antibiotic therapy of patients with chronic fatigue syndrome who are seropositive but have no autochthonous antibody production in the central nervous system has been considered unnecessary [14]. Lightfoot et al. [15] carried out a cost-benefit analysis that indicated that for the majority of patients with a positive Lyme antibody titer whose only symptoms are nonspecific myalgia or fatigue the risks and costs of empirical parenteral antibiotic therapy exceed the benefits. In light of these current results, we believe it is worth examining whether an antibiotic therapy should be considered in patients with chronic fatigue and positive *Borrelia* serology.

When encountering a patient with chronic fatigue syndrome one should therefore consider borreliosis as a possible cause, even if the patients seem otherwise healthy and have not previously suffered from clinically manifest borreliosis or neuroborreliosis.

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