

blood –brain barrier / why it isn't always easy to cure Lyme disease

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" Scientific reasoning is a kind of dialogue between the possible and the actual, between what might be and what is in fact the case."

Sir Peter Medawar

".....Neither the clinical presentation nor routine laboratory tests accurately predicted which patients had *B. burgdorferi* DNA in their CSF

.....Our findings demonstrate that *B. burgdorferi* can disseminate to the CNS very early on in the course of the infection with little or no clinical evidence of CNS involvement....."

".....This raises the possibility that the CNS may act as a sanctuary for *B. burgdorferi*, protecting it from the action of systemic anti–biotics and immunity and thereby allowing it to reseed the periphery intermittently..."

from: Invasion of the Central Nervous System by *Borrelia burgdorferi* in Acute Disseminated Infection

JAMA. 1992;267:1364–1367

authors: Benjamin J. Luft,Raymond J. Dattwyler

".....In this prospective study of unselected patients, we found two thirds of the patients with disseminated infection had *B. burgdorferi* DNA in their CSF. Although the presence of spirochetal DNA does not necessarily mean that viable *B. burgdorferi* were present in the CNS of these patients, this is very likely, given the fact that these patients had evidence of active clinical infection. The parameters have been used in the past to diagnose acute CNS infection may have greatly underestimated the true incidence of CNS involvement in this group of patients. Neither the clinical presentation nor routine laboratory tests accurately predicted which patients had *B. burgdorferi* DNA in their CSF

.....Our findings demonstrate that *B. burgdorferi* can disseminate to the CNS very early on in the course of the infection with little or no clinical evidence of CNS involvement. Acute primary and secondary infections due to *Treponema pallidum* (syphilis) are also associated with a high rate of

dissemination to the CNS.....This study has important therapeutic implications as well. In the past, the recommended treatment of acute Lyme disease consisted of low doses of oral tetracycline or penicillin, even in patients with signs and symptoms of systemic and therefore potential meningeal involvement...an inordinately high failure rate....when ceftriaxone, an antibiotic that is highly active against *B. burgdorferi*, achieves high CSF levels, and has a prolonged half–life, was compared with penicillin for the treatment of late Lyme disease, ceftriaxone had a significantly higher success rate.....Among four patients with chronic Lyme arthritis, *B. burgdorferi* was found in the CSF of one patient with relapsing arthritis. This patient had no clinical evidence of CNS involvement and no intrathecal antibody production . This raises the possibility that the CNS may act as a sanctuary for *B. burgdorferi*, protecting it from the action of systemic anti–biotics and immunity and thereby allowing it to reseed the periphery intermittently. This finding is especially important when considering the appropriate treatment of the chronic phase of this disease and whether the use of oral antibiotics alone, as suggested by some for chronic arthritis, is appropriate."

".....persistence of brain infection after treatment with antibiotics that do not readily penetrate the blood–brain barrier..."

Neuroborreliosis during relapsing fever: review of the clinical manifestations, pathology, and treatment of infections in humans and experimental animals.

Clin Infect Dis 1998 Jan;26(1):151–64 (ISSN: 1058–4838)

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The spirochetal disease relapsing fever is caused by different *Borrelia* species. Relapsing fever is well recognized as an infection of the blood, but little is known about its predilection for the nervous system and the eyes. To investigate neurological and ocular involvement during relapsing fever, we reviewed the clinical manifestations, pathology, and treatment of relapsing fever of humans and experimental animals. The results indicate that *Borrelia turicatae* and *Borrelia duttonii*, the agents of tick–borne relapsing fever in southwestern North America and sub–Saharan Africa, respectively, cause neurological involvement as often as *Borrelia burgdorferi* in Lyme disease. Evidence of this is the frequent occurrence of lymphocytic meningitis and peripheral facial palsy in human disease; the identification of spirochetes in the brain and other nervous tissues of humans, animals, and arthropod vectors; and the persistence of brain infection after treatment with antibiotics that do not readily penetrate the blood–brain barrier.

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from: A Perspective on the Treatment of Lyme Borreliosis

authors: Benjamin J. Luft, Gorevic, Halperin, Volkman, and Raymond J.

Dattwyler

source: Reviews of Infectious Diseases Vol. II

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".....It is apparent that *B. burgdorferi* disseminates hematogenously in a sizable group of patients ...and that high tissue levels of antimicrobial agents may be needed to eradicate the infection.....If CNS involvement is discovered or there is significant compromise of an organ system as a result of infection, the patient should receive parenteral therapy so that adequate CNS drug levels are attained.Recently, Weber et al reported the congenital transmission of *B. burgdorferi* to an infant whose mother had been treated with 1 million units of oral penicillin for 7 days. Given the significant failure rate described by Steere et al. in patients treated with 250 mg of oral penicillin (more than 50% of whom developed 'minor'and 'major' disease), it would seem reasonable to administer more vigorous.....to pregnant patients with acute EM. No study has established the optimal treatment in this instance;Further studies must establish the duration of therapy necessary to eradicate this infection and thus to prevent congenital transmission..."

".....We do not believe this high incidence to be an artifact of patient selection, since these patients were all studied before this neurologic syndrome was widely appreciated, and since all were initially referred by a rheumatologist, not a neurologist..."

".....However, following treatment the most distal portion of nerves seemed to improve first—even in nerves that were initially apparently normal—suggestive of a dying back neuropathy...."

".....we have been unable to identify either spirochetes or evidence of active inflammation in the nerve, nor have we been able to demonstrate antibody compliment, or immune complex deposition. However, we have been struck by the rapid clinical and neurophysiologic recovery following antibiotic treatment as well as to treatment with other agents known to cross into the nervous system....."

"....This resolution of symptoms has occurred before there has been any appreciable drop in antibody titer, suggesting the problem is a direct effect of infection with spirochetes and not a purely immune-mediated phenomenon..."

....."Of the many patients we have seen with chronic Lyme disease (most of whom had worsened despite treatment with recommended oral antibiotics)..."

".....Our observations led us to conclude that many patients with Lyme disease have significant abnormalities of the peripheral nervous system, not attributable to other causes, and that many of these abnormalities can resolve following APPROPRIATE antibiotic treatment....."

".....This syndrome clearly may evolve despite treatment with currently recommended antibiotic regimens....."

".....the use of sequential studies in affected patients emphasizes the utility of using patients as their own "controls....."

Lyme Disease: Cause of a treatable peripheral neuropathy
Authors: Halperin, Little, Coyle, Dattwyler
Neurology 1987;37:1700

".....Of the many patients we have seen with chronic Lyme disease (most of whom had worsened despite treatment with recommended oral antibiotics) many have noted intermittent tingling paresthesias of their extremities, yet had no demonstrable neurologic deficits. These symptoms were distinctly different from, and more commonplace than, those described in the literature, leading us

to study this population in greater detail.....

Materials and methods. Subjects. Between October 1985 and March 1986, 36 patients with proven late Lyme disease were evaluated in the Lyme Disease Clinic at University Hospital, SUNY, Stony Brook. All patients had clinical histories consistent with diagnosis and had immunologic evidence of reactivity to B.

burgdorferi.....Three of the 22 patients with clinical and immunological evidence of Lyme disease but without the typical history of limb paresthesias also underwent neurophysiologic testing to determine if similar abnormalities occurred in asymptomatic patients. One of these patients, a carpenter, had a history suggestive of carpal tunnel syndrome at the time his arthritis had been most active, but these symptoms were no longer present. Another, a mechanic, had a history of left arm tingling and back pain since a driving accident in which several cervical vertebrae had been fractured. The third had no paresthesia of any sort.....

.....Discussion. Several distinct syndromes involving the peripheral nervous system have been described in patients with Lyme disease. Although we see large numbers of patients with Lyme disease, we have only rarely observed these syndromes. None of our patients had severe radicular pain, brachial neuritis, or obvious mononeuropathy multiplex. Only one had electrophysiologic findings suggestive of a Gullian–Barre–like syndrome.

..... the electrophysiologic testing failed

to reveal any more subtle evidence of cranial nerve dysfunction. Yet, almost one half of the patients we have seen with late Lyme disease have had neurologic difficulties, the most common of which has been the presence of intermittent paresthesias. Therefore, we believe this syndrome to be a very common entity, but one quite different from those previously described. We do not believe this high incidence to be an artifact of patient selection, since these patients were all studied before this neurologic syndrome was widely appreciated, and since all were initially referred by a rheumatologist, not a neurologist.

The reason that this syndrome has not been previously recognized may be that the neurologic examination is usually not strikingly abnormal in these patients. In the few previous reports of neurophysiologic testing in this disease, this was performed on patients with clinical abnormalities. Because of the consistent and persistent subjective symptoms, and in spite of the normal clinical examinations, we chose to study these patients neurophysiologically.

.....Our observations led us to conclude that many patients with Lyme disease have significant abnormalities of the peripheral nervous system, not attributable to other causes, and that many of these abnormalities can resolve following appropriate antibiotic treatment. This syndrome clearly may evolve despite treatment with currently recommended antibiotic regimens.....However, it is striking that several patients have responded to more prolonged or higher dose penicillin regimens, as well as to treatment with other agents known to cross into the nervous system.....

The pathogenesis of this peripheral neuropathy remains unclear. It appears to be quite separate from the CNS manifestations of Lyme disease—its occurrence does not coincide with the acute meningoencephalitis, nor does its response to treatment necessarily parallel that of encephalopathy. The neurophysiologic

abnormalities are multifocal in nature such as might be seen in mononeuritis multiplex. However, following treatment the most distal portion of nerves seemed to improve first—even in nerves that were initially apparently normal—suggestive of a dying back neuropathy.....Finally, we have been unable to identify either spirochetes or evidence of active inflammation in the nerve, nor have we been able to demonstrate antibody compliment, or immune complex deposition. However, we have been struck by the rapid clinical and neurophysiologic recovery following antibiotic treatment. This resolution of symptoms has occurred before there has been any appreciable drop in antibody titer, suggesting the problem is a direct effect of infection with spirochetes and not a purely immune-mediated phenomenon.

This study leads to two very different but equally important sets of conclusions. First, it serves to emphasize the sensitivity and utility of neurophysiologic testing, making possible the demonstration significant abnormalities of peripheral nerve function in clinically normal patients. Furthermore, the use of sequential studies in affected patients emphasizes the utility of using patients as their own "controls," demonstrating significant changes where values before and after were both well within the rather broadly defined "normal range".

Second, these techniques have enabled us to characterize a clinical syndrome quite distinct from those previously described in Lyme disease and to demonstrate that it is one of the small number of neuropathies that is readily reversible. Since the neurophysiologic abnormalities improve with effective treatment, they have provided a quantitative, objective assessment of the efficacy of different antibiotic regimes in this disease. Since the best antibiotic regime to treat Lyme disease remains to be determined, having such a means of objectively comparing different agents will be invaluable."

".....; the identification of spirochetes in the brain and other nervous tissues of humans, animals, and arthropod vectors; and the persistence of brain infection after treatment with antibiotics that DO NOT READILY PENETRATE THE BLOOD–BRAIN BARRIER..." i.e. IV or IM

Neuroborreliosis during relapsing fever: review of the clinical manifestations, pathology, and treatment of infections in humans and experimental animals. Cadavid D, Barbour AG
Clin Infect Dis 1998 Jan 26;1 151–64

Abstract

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