NEUROBORRELIOSIS IN ADULTS

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ABSTRACT

Neuroborreliosis is an infection of the central and peripheral nervous system caused by spirochetes of the genus *Borrelia*, possibly by certain genospecies, e.g. *B. burgdorferi*, *genospecies garinii*. The nervous system is first afflicted during the early stage of Lyme Borreliosis with dissemination; the main features include meningitis, radiculoneuritis and polyneuritis cranialis. Late Lyme Borreliosis presents as sensory polyneuropathy in association with acrodermatitis chronica atrophicans or as progressive *Borrelia* encephalomyelitis. The diagnosis is confirmed by the presence of intrathecally produced specific antibodies and positive culture or PCR respectively. The accepted treatment of neuroborreliosis is either by ceftriaxone, possibly also by penicillin or doxycycline.

KEY WORDS

neuroborreliosis, diagnosis, therapy

INTRODUCTION

Several species of the genus *Borrelia* are capable of infecting the central and/or peripheral nervous system, hence causing the clinical entity of neuroborreliosis (NB). This review of NB in adults does not deal with diseases caused by tropical *Borrelia* species (e.g. *B. recurrentis* or *B. duttoni*), but only with the neurologic manifestations of *B. burgdorferi* (*Bb*) infection.

In 1922 C. H. Garin and C. H. Bujadoux described a patient with meningoradiculitis following a tick bite and associated with erythema migrans (EM) (1). In a very extensive review A. Bannwarth tried to categorize this disease entity, assuming it to be a rheumatological disorder (2). It was only after the discovery of the causative agent (3) of Lyme arthritis (4) that the etiology of this nervous system disease was recognized as being spirochetal (5-7).

This disease, now known as Lyme Borreliosis (LB) is present in nearly every part of the world, showing focal clustering.

CLINICAL PRESENTATIONS

The course of adult NB is highly variable. In about 30% to 40% of patients the disease starts with a characteristic skin lesion, the so-called erythema

(chronicum) migrans, which appears days to weeks after a tick bite in an endemic area. Neurologic, cardiac, articular and chronic skin involvement develops later. A chronological approach, indicating a stage-like course of disease was emphasized in the early years after the discovery of the causative agent, *Bb*. Today LB is divided into following clinical entities: (i) early LB without dissemination (EM), (ii) early LB with dissemination, cardiac and neurologic manifestations, (iii) late LB, (iv) asymptomatic LB, (v) late Lyme encephalopathy.

Neurologic signs and symptoms can appear at any time within the early LB with dissemination and the late LB stages. Late Lyme encephalopathy still is a matter of discussion.

Only recently have different genospecies of *Bb* been delineated which are associated with distinct clinical manifestations of LB: *B. burgdorferi sensu stricto*, *B. afzelii*, *B. pacifica* and *B. garinii* (8-11); the latter being most frequently associated with neurologic disease.

EARLY LYME BORRELIOSIS WITH DISSEMINATION

The typical triad of this stage consists of lymphocytic meningitis, cranial neuropathy and radiculoneuritis (7), occurring either in combination or oligosymptomatic (12,13). A presentation resembling aseptic meningitis is more frequently seen in children and young adults and may take an acute, chronic or relapsing course (14).

Cerebrospinal fluid (CSF) analysis indicates mononuclear pleocytosis, predominantly lymphocytes and plasma cells (15). Within 4 weeks after the onset of the neurologic disease, intrathecal synthesis of specific antibodies (IgG, IgM and IgA (16,17)) as well as oligoclonal bands (17) may be seen. Myalgia, arthralgia and fatigue frequently precede or concur with this disease. Radiculoneuritis, the hallmark of Garin-Bujadoux-Bannwarth-Syndrome, usually starts with extremely severe radicular pains, characteristically accentuated during the night hours and almost unresponsive to analgesic drugs including morphine derivatives (14). Facial palsy frequently appears within days after the radicular signs and symptoms have started. However, the disease may present as pure polyneuritis cranialis (18). Neurophysiological examination reveals widespread peripheral axonal injury (19). A sural nerve biopsy shows an infiltration of the vasa nervorum by mononuclear elements (lymphocytes and plasma cells) without necrosis of the vessel walls (20).

Less frequently acute myelitis, encephalitis, focal nodular myositis and vasculitis are prominent features of disseminated NB (21-23).

LATE LYME BORRELIOSIS

In the late stage of the disease the peripheral and central nervous system may be involved.

(i) Peripheral nerve involvement: peripheral neuropathy has been associated with the chronic dermatological stage of the disease, acrodermatitis chronica atrophicans (ACA) (24,25). More than half of ACA patients develop this predominantly sensory neuropathy. Motor impairment is usually not present. Electrophysiological findings are consistent with a mild to moderate predominantly axonal neuropathy (25).

(ii) In very rare instances central nervous system involvement has been described by a chronic course of the disease; Ackermann et al. coined the term of progressive *Borrelia* encephalomyelitis (26). These patients present with a wide range of neurologic disorders including spastic paraparesis, ataxia, brainstem dysfunction, cognitive impairment, neurogenic bladder dysfunction, etc. The evolution is gradual, progressing over months and years. The CSF shows a typical mononuclear pleocytosis, increased protein content and intrathecal synthesis of IgG, IgM and IgA. This constellation definitely allows to distinguish this disease entity from multiple sclerosis (27). The latter should never be confused with progressive *Borrelia* encephalomyelitis. In Northern America CNS involvement has been reported rather frequently (28-30), observing a meningovascular form of NB resembling tertiary neurosyphilis (31).

ASYMPTOMATIC NEUROBORRELIOSIS

Pfister et al. reported on the detection of *Bb* in the CSF of an otherwise healthy individual (32). It is not known whether this is a frequent or infrequent finding. Moreover, its clinical implications have not yet been fully elucidated.

LATE LYME ENCEPHALOPATHY

A mild chronic encephalopathy with memory disturbances and sleep disorders has been found in patients with LB in North America (28,29,33). Usually the CSF shows a normal cell count and only a mild increase in protein content. In most cases, intrathecal synthesis of antibodies to *Bb* can be seen. A controlled trial, subjecting 20 patients (a mean of 57 months

after acute NB) and 20 matched control persons to a wide range of neuropsychological testings, revealed statistically significant memory and learning deficits in the group of patients having suffered from acute NB with dissemination almost 5 years earlier (34). Similar findings were reported earlier by Krupp et al. and Kaplan et al. (35,36) in noncontrolled series.

LABORATORY DIAGNOSIS OF NEUROBORRELIOSIS

A patient presenting with a typical history of a tick bite and EM as well as the classical clinical presentation and inflammatory CSF changes is beyond doubt in terms of diagnosis. Unfortunately a tick bite is frequently not remembered, EM by far not always present and the clincial presentation - in a rather high percentage - either oligosymptomatic or atypical. CSF changes are unspecific, however the presence of intrathecal IgG, IgM and IgA certainly raise the level of suspicion. Isolation of the spirochetes from the CSF has been accomplished, but this diagnostic golden standard is difficult and untimely. Improvements in the detection of antibodies to *Bb* have resulted in a reliable laboratory diagnosis (37). J. C. Garcia-Monco and J. L. Benach constructed an algorithm to evaluate serologic information to diagnose NB and consider clinical and treatment parameters (38). The demonstration of intrathecal specific antibody production has now become the golden standard procedure for the laboratory diagnosis of NB (39-41). An additional important finding in the CSF is a markedly increased IgM index; oligoclonal IgG bands in the CSF can be seen during the course of disease (39,40). Polymerase chain reaction (PCR) is a reliable adjunct to other laboratory tests, as it is more sensitive than bacterial cultures (38). Positive PCR findings have been obtained from the CSF of patients with a disease duration of less than 2 weeks (42) and 4 to 8 months (43).

THERAPY

Treatment is based on the administration of antibiotics, penicillin G (20-30 mill. U t.i.d.) or ceftriaxone (2g once daily) (44-46). However, complex pathogenetic mechanisms, not yet fully understood, may require future alternative therapies. The duration of treatment is at least 2 weeks or even longer depending on the response. Oral tetracyclines, e.g. doxycycline 200 mg daily for 2 weeks, can be administered to patients allergic to penicillin or cephalosporins and may prove as effective as an IV penicillin in patients with the classical triad of NB (47). At present corticosteroids are not recommended (38,48).

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