Screening for Neuroborreliosis in Patients With Stroke

Susanne Hammers-Berggren, MD; Ann Gröndahl, MD; Mats Karlsson, MD, PhD; Magnus von Arbin, MD, PhD; Anders Carlsson, MD; Göran Stiernstedt, MD, PhD

Background and Purpose: Borrelia burgdorferi, the etiologic agent of Lyme disease, can cause different neurological manifestations. We studied the prevalence of Lyme neuroborreliosis in patients with stroke.

Methods: During a 1-year period, sera from patients with cerebral thrombosis or transient ischemic attack without cardioembolism were investigated for antibodies against B burgdorferi.

Results: One of 281 patients had a positive serum immunoglobulin M titer and 23 of 281 (8%) had positive serum immunoglobulin G titers against B burgdorferi. One of the 24 seropositive patients, with a diagnosis of transient ischemic attack due to dysphasia, had a lymphocytic pleocytosis and intrathecal antibody production against B burgdorferi. The medical history revealed a 9-month period of general and neurological symptoms compatible with Lyme neuroborreliosis before the stroke-like incidents.

Conclusions: We conclude that Lyme neuroborreliosis may imitate stroke, but screening for antibodies against B burgdorferi seems to be of little value and may be replaced by a careful medical history. (Stroke. 1993;24:1393-1396.)

Key Words • cerebral ischemia, transient • cerebral thrombosis • Lyme disease

Lyme disease was first recognized in 1975 because of an epidemic of arthritis in the city of Lyme, Conn.1 The etiologic agent, Borrelia burgdorferi, discovered in 1982,2 is spread to humans by ticks of the genus Ixodes. The most common clinical pictures of the disease have been characterized. The spirochete may cause symptoms in the skin, nervous system, joints, and heart.1-6

The clinical manifestations of Lyme neuroborreliosis are usually meningitis, meningoradiculitis, or cranial neuritis.5-8 The frequency of recovery from neuroborreliosis is high even in patients not treated with antibiotics.9 In rare instances, however, neurological symptoms may progress in untreated cases, causing encephalomyelitis with symptoms like paraparesis, hemiparesis, dysphasia, and ataxia.7,8,10-12 Stroke-like manifestations of Lyme neuroborreliosis have been reported in a few publications.13-20 The clinical presentation in the published case reports of stroke-like manifestations in neuroborreliosis are characterized as transient ischemic attack (TIA) or cerebral infarction without cardioembolic source. The pathogenesis can be explained by a vasculopathy with a localized vasculitis that may cause focal neurological symptoms from the central nervous system (CNS) with a sudden onset.13-16,18,20 Angiographic changes of cerebral vessels compatible with vasculitis have been demonstrated in a few cases of Lyme neuroborreliosis with stroke-like symptoms.13-15

The aim of the present study was to investigate the prevalence of neuroborreliosis in patients with a diagnosis of cerebral thrombosis or TIA without cardioembolism who lived in a B burgdorferi–endemic area.

Subjects and Methods

During 1990, a serum sample was drawn from all of the 495 patients admitted to the Department of Internal Medicine, Danderyd Hospital, Stockholm, Sweden, with a diagnosis of stroke according to the International Classification of Diseases, Ninth Revision (ICD-9).21

The study population of 281 patients comprised 143 men and 138 women. Their ages varied from 22 to 99 (median, 74) years. Included were all cases with a diagnosis of cerebral thrombosis (n=176) or TIA without cardioembolism (n=105). Cerebral thrombosis was defined as an acute loss of focal cerebral function, with symptoms lasting longer than 24 hours, for which a cardioembolic source and cerebral hemorrhage were excluded. We defined TIA as an acute loss of focal cerebral or ocular function, with symptoms lasting less than 24 hours. Cardioembolism was defined as atrial fibrillation, organic heart defect, cardiac infarction within 3 months, cardiomyopathy, valve prosthesis, or bradytachyarrhythmia. Cerebral hemorrhage was excluded by computed tomography or lumbar puncture (LP).

Patients with a diagnosis of cerebral hemorrhage, cardioembolic stroke, or unspecified stroke were excluded from the present study.

The serum sample drawn at admission from the study patients (serum I) and a second serum sample drawn 6 weeks later (serum II) were analyzed with an indirect

Received November 20, 1992; final revision received March 10, 1993; accepted April 5, 1993.

From the Departments of Infectious Diseases (S.H.-B., M.K.) and Internal Medicine (A.G., M. von A., A.C.), Danderyd Hospital, Danderyd, and the Department of Infectious Diseases (G.S.), Huddinge Hospital, Huddinge, Sweden.

Reprint requests to Susanne Hammers-Berggren, MD, Department of Infectious Diseases, Danderyd Hospital, 182 88 Danderyd, Sweden.
immunoglobulin (Ig) M and IgG enzyme-linked immunosorbent assay (ELISA) using sonicated whole-cell *B. burgdorferi* spirochetes as antigen. The ELISA titer was expressed as the optical density multiplied by the serum dilution factor. The upper limit of normal values (cutoff) was defined as the 95th percentile among 200 healthy controls and was 500 for both IgM and IgG.

A previous study has shown that slightly elevated IgG antibody titers against *B. burgdorferi* are common among healthy individuals in the Stockholm area. Among 150 healthy persons (median age, 50 years) with no present history of Lyme borreliosis, 9% were seropositive against *B. burgdorferi* when the 95th percentile was used as the cutoff in ELISA. The same study has demonstrated that among 346 healthy individuals (median age, 59 years) living in a highly endemic area, 26% had elevated IgG titers against *B. burgdorferi*. Among 161 persons from this area older than 60 years, 39% were seropositive against *B. burgdorferi*. A previous Swedish study of patients with stroke has shown a mean age of 73 years in these patients. Because the percentage of healthy persons with positive antibody titers against *B. burgdorferi* increases with age in an endemic area and the mean age of patients with stroke was demonstrated to be 73 years, only patients with a positive IgM or IgG titer above the 98th percentile (IgM ≥700 or IgG ≥1000) in the first serum sample were selected for further investigation with an LP. Further, patients with a 50% titer change or more between serum I and serum II were also selected for LP.

The cerebrospinal fluid (CSF) was analyzed for leukocytes, albumin, glucose, lactate, and antibodies to *B. burgdorferi*. Intrathecal antibody production against *B. burgdorferi* was analyzed by calculating a spirochete titer index as follows: CSF titer/serum titer:CSF albumin/serum albumin. Index values of ≥1 were considered indicative of specific intrathecal IgM production, and index values of ≥2 were indicative of intrathecal IgG production against *B. burgdorferi*. If LP was indicated for other medical reasons in patients with stroke during the study period, the same analyses were performed.

Antibody titers (a.b.) against *Borrelia burgdorferi* (*B.b.*) in 281 patients with cerebral thrombosis or transient ischemic attack (TIA) without cardioembolism using an indirect enzyme-linked immunosorbent assay with cutoff value of 500 for immunoglobulin (Ig) M and IgG. LP indicates lumbar puncture.

**Results**

The study results are summarized in the Figure. During the 1-year study period, 495 patients with stroke were admitted to the Department of Internal Medicine. Included in the present study were 176 patients with a diagnosis of cerebral thrombosis and 105 patients with a diagnosis of TIA without cardioembolism.

The following patients were excluded: 29 with cerebral hemorrhage, 90 with cerebral embolism, 21 with TIA and cardioembolism, 18 with cerebral infarction without investigation of possible cardioembolism, and 56 with a diagnosis of cerebrovascular unspecified disease neither examined with cranial computed tomography nor investigated for cardioembolism.

**Serum**

In the first serum sample, serum I, 24 of the 281 (8%) patients had positive IgM or IgG titers against *B. burgdorferi* (Figure). One of the 24 patients had a slightly elevated IgM titer of 610 and a stationary titer value in serum II. This patient had a diagnosis of TIA. Twenty-three of the 24 patients (12 with TIA and 11 with cerebral thrombosis) had positive IgG titers in serum I.

Sixteen of the 23 patients (9 with TIA and 7 with cerebral thrombosis) had serum IgG titers between 500 and 990 in serum I. Twelve of the 16 patients had stationary IgG titers in serum II. In 2 of 16 patients, an LP performed due to IgG titers in the upper range in serum I (850 and 980, respectively) showed no pleocytosis or intrathecal antibody production against *B. burgdorferi*, and they were not followed up with a serum II. No serum II was obtained from the remaining 2 patients. The medical history of the 16 patients did not indicate previous or present Lyme neuroborreliosis.

Seven of the 23 patients with positive IgG titers in serum (3 with TIA and 4 with cerebral thrombosis) had IgG titers ≥1000. LP was not performed in 3 of these 7 patients because of death in 1 patient with a diagnosis of cerebral thrombosis and because of treatment with anticoagulants in 2 patients with TIA and cerebral thrombosis, respectively. In these 2 patients, three consecutive serum samples obtained during the 6 months
after the stroke incidents showed stationary IgG titers, and no symptoms of Lyme borreliosis appeared during follow-up.

Serum II was obtained from 163 of the 257 patients who were negative in serum I. No seroconversion was seen in these samples. Serum II was not obtained from the remaining 94 seronegative patients, 15 of whom died during the 6-week follow-up period.

Cerebrospinal Fluid

In 2 of 16 patients with IgG titers between 500 and 990 and in 4 of 7 patients with IgG titers ≥1000, LP was performed. In 5 of these 6 patients (1 with TIA and 4 with cerebral thrombosis), LP showed no pleocytosis and the spirochete titer index did not indicate intrathecal antibody production against *B burgdorferi*. The LP from the sixth patient showed pleocytosis with lymphocytic predominance and intrathecally produced antibodies against *B burgdorferi*. The initial diagnosis was TIA (see the following Case Report).

LP was performed in another 3 of the 281 patients in the study. In one, LP was performed to differentiate between hemorrhage and infarction. This patient was seronegative but had an elevated IgG titer against *B burgdorferi* in CSF without pleocytosis. A second LP performed 4 weeks later verified the results of the first LP, showing intrathecally produced IgG antibodies against *B burgdorferi* without pleocytosis. The serum sample from this patient remained negative for antibodies against *B burgdorferi*. Her medical history revealed no clinical symptoms of active or earlier neuroborreliosis, and the final diagnosis was that of hemorrhagic cerebral infarction without cardioembolism. In a second patient, LP was performed because of findings of polynuropathy simultaneously with the hemiparesis, and in a third patient LP was done because of high fever and hemiparesis at admission. These two patients were seronegative, and the CSF showed no pleocytosis or signs of intrathecal antibody production against *B burgdorferi*.

Case Report

A previously healthy 66-year-old woman started to suffer from headache and pain in her neck and shoulders and mandibular and lumbar regions in the spring of 1989. She consulted her dentist, who did not find any explanation for the mandibular pain. In the summer she developed vertigo, balance disturbances, intense pain in her arms, and tiredness. Examination at the local hospital and follow-up by her general practitioner showed normal clinical status, electrocardiogram, and routine blood tests.

From the end of August and during the following autumn, the patient suffered from headache, fatigue, weight loss of 10 kg, balance disturbances, and hand tremor. During December she developed blurred vision, and in January 1990 she consulted an ophthalmologist. Nothing pathological was found.

On January 27 she developed acute dysphasia that disappeared within a few hours, and no further symptoms appeared during 2 days of observation at the Department of Internal Medicine of Danderyd Hospital. Computed tomography of the brain, electrocardiogram, routine blood samples, and clinical status including blood pressure were normal. The patient did not smoke or have any other known risk factors for cardiovascular diseases. She was discharged with a diagnosis of TIA and included in the present study. Medication with 75 mg/d aspirin was initiated. Her medical history of general and neurological symptoms since 9 months was not found out during the 2 days in the hospital. After discharge, serology against *B burgdorferi* showed an elevated IgG titer of 1075 in serum I. An LP showed 74 × 10³ leukocytes/L (reference, ≤5 × 10³/L); 97% lymphocytes; protein, 1.9 (reference, ≤0.5 g/L); glucose ratio, 0.3 (reference, >0.5); and lactate, 3.4 mmol/L (reference, <3.0 mmol/L). The IgG titer against *B burgdorferi* in CSF was 66, and the albumin ratio was 0.028. Specific intrathecal IgG production against *B burgdorferi* was found in CSF. Syphilis serology was negative.

The patient was treated with 200 mg/d oral doxycycline for 14 days. The headache, neck pain, hand tremor, fatigue, and balance disturbances gradually disappeared. No further symptoms of dysphasia appeared, and she had a complete clinical recovery at follow-up after 1 year. The LP at follow-up was normal concerning cells, protein, glucose ratio, and lactate. She was then seronegative but had persistent intrathecal antibody production against *B burgdorferi*.

Discussion

Earlier publications have shown that Lyme neuroborreliosis can cause strokelike manifestations.13-20 This screening study performed during 1 year also demonstrates the possibility of neuroborreliosis mimicking stroke, but the frequency seems to be low. Among 281 patients with a diagnosis of cerebral thrombosis or TIA without cardioembolism, only one had strokelike symptoms due to chronic neuroborreliosis.

In the present study, we chose the 98th percentile as the cutoff in ELISA for IgM and IgG in serum I or a 50% titer change between serum I and serum II as a criterion to perform an LP. Neuroborreliosis cannot be completely excluded in the 18 seropositive patients in whom an LP was not performed. However, none of these patients had rising or declining antibody titers at follow-up. Also, none of the patients had any clinical symptoms compatible with neuroborreliosis before the diagnosis of stroke. The elevated antibody titers in these patients were probably caused by earlier exposure to *B burgdorferi*.

Previous studies have shown that patients with early neuroborreliosis may be seronegative (usually those with a disease duration of 6 weeks or less).22,25,26 Because serum II was negative at the 6-week follow-up of all patients with a negative serum I, it is unlikely that any of these patients had an undiagnosed active neuroborreliosis. Most case reports concerning patients with strokelike symptoms due to neuroborreliosis have described patients with disease durations of months.13,16,19,20 as in our case report. It therefore seems unlikely that patients with focal neurological symptoms from CNS and a negative serology against *B burgdorferi* suffer from neuroborreliosis.

The patient with a sudden onset of dysphasia and CSF findings with pleocytosis and intrathecal antibody production against *B burgdorferi* had a typical medical history of a chronic Lyme neuroborreliosis with symptoms of radicular pain, headache, weight loss, and so forth. Thus, we emphasize the importance of obtaining
a careful medical history for patients with stroke, especially those without a history of or risk factors for cardiovascular diseases.

The possibility that our patient with dysphasia suffered from two different diseases, Lyme neuroborreliosis and TIA due to arteriosclerosis, is unlikely because she had a typical medical history of ongoing chronic Lyme neuroborreliosis and CSF findings of chronic meningitis soon after developing stroke-like symptoms. She also responded promptly to antibiotic therapy and developed no further symptoms of stroke posttreatment. Previously published case reports of neuroborreliosis imitating stroke have also concerned younger patients in whom stroke-like symptoms due to arteriosclerosis would be unusual.13,15,17,18,20

One patient in the present study with a diagnosis of cerebral thrombosis had an intrathecal antibody production against *B. burgdorferi* but no signs of CSF inflammation or clinical picture of ongoing neuroborreliosis. A previous study12 has shown that intrathecal antibody production against *B. burgdorferi* can persist several years after clinical recovery from neuroborreliosis, and we believe that this patient had an earlier undiagnosed neuroborreliosis with a spontaneous recovery.

Computed tomography is one of the routine diagnostic methods used in evaluating stroke; LP is seldom performed. This study demonstrates the importance of performing LP in patients with a medical history of diffuse neurological and general symptoms before the onset of stroke-like symptoms.

Lyme neuroborreliosis may sometimes progress to a chronic disease, with a symptom duration of months or even years. At this stage of the disease, stroke-like manifestations may occur. However, the prevalence of neuroborreliosis among patients with a diagnosis of stroke seems to be low. We found only one patient with stroke-like symptoms due to neuroborreliosis among the 281 patients with a diagnosis of cerebral thrombosis or TIA without cardioembolism; thus, we conclude that screening with serology against *B. burgdorferi* seems to be of little value in these patients and may be replaced by a carefully gathered medical history.

References

Screening for neuroborreliosis in patients with stroke.
S Hammers-Berggren, A Gröndahl, M Karlsson, M von Arbin, A Carlsson and G Stiernstedt

*Stroke*. 1993;24:1393-1396
doi: 10.1161/01.STR.24.9.1393

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/24/9/1393

**Permissions**: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints**: Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions**: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/