Cerebrovascular Events in Lyme Neuroborreliosis

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Background: Cerebrovascular events in neuroborreliosis are a rare condition described only in isolated or small case series. No specific clinical or radiological features have been identified, and diagnosis is based on very different criteria. *Methods:* We retrospectively describe cases diagnosed in the Stroke Unit of Nancy Hospital, located in the endemic area of the northeast of France. We also reviewed other cases found in the literature. *Results:* We identified 5 cases in our center and 57 other reported cases. Mean age was 39 years (range 5 to 77). Possible previous contact with *Borrelia burgdorferi* (*B burgdorferi*) was found in about half of cases. Additional neurologic symptoms (headache, cognitive impairment, and/or gait disturbance) were found in 44% of cases. Cerebral imaging revealed both ischemic (87%) and hemorrhagic lesions (13%) with a multiterritorial aspect in 22% of strokes, and signs of vasculitis in 71%. Analysis of cerebrospinal fluid (CSF) revealed lymphocytic meningitis in 90% of cases and elevated protein level in 86%. CSF/serum anti–*B burgdorferi* antibody index (AI) was positive in 91% of cases. Outcome was favorable after appropriate antibiotic treatment. Our 5 patients presented a modified Rankin scale score 0-1, without any stroke recurrence, after a median follow-up of 2.8 years. *Conclusions:* The diagnosis of Lyme neuroborreliosis should be considered for patients with cerebrovascular events without obvious cause living in an endemic area, in the presence of repeat multiterritorial strokes at short intervals, other neurologic symptoms, a history of *B burgdorferi* infection, and radiological signs of vasculitis. Diagnosis can be confirmed by CSF analysis with AI but with an incomplete sensitivity. **Key Words:** *Borrelia burgdorferi*—cerebrovascular diseases—cerebrovascular events—lyme vasculitis—neuroborreliosis—stroke.
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Introduction

Lyme disease is a multisystemic infection caused by *Borrelia burgdorferi* (*B burgdorferi*) with frequent neurologic manifestations. The incidence in France is estimated at 9.4 infected persons per 100,000 inhabitants and is increasing with a high regional disparity.[1] Cerebrovascular involvement, and especially stroke,[2] of Lyme disease seems to be a relatively rare complication and estimated to affect from 0.3% to 1% of patients in endemic areas.[3] Since the first reports in 1987, only single or small series case reports can be found in literature and these present a wide range of clinical and radiological features as well as diagnostic criteria,[4] so that studies have concluded it is not worthwhile systematically screening stroke patients for Lyme disease.[5] A more detailed description of signs and symptoms may help physicians to establish a diagnostic

strategy to identify neuroborreliosis as the cause of stroke. We therefore set out to define clinical, biological, and radiological presentations of cerebrovascular manifestations in Lyme neuroborreliosis. We retrospectively reviewed and described identified cases in a stroke unit of the Lorraine region, located in the northeast of France where the incidence of Lyme disease is estimated at 34 infected persons per 100,000 inhabitants,[1] and discuss previously reported cases.

Method

Cases of patients who presented neurovascular manifestations with identified neuroborreliosis between 2004 and 2013 in the Stroke Unit of the University Hospital of Nancy and reported cases in the literature were reviewed. A search was performed using the database MEDLINE/PubMed for articles published in the last 30 years with the key words "neuroborreliosis," " Lyme disease," "borrelia burgdorferi," "stroke," "cerebral infarction," and "cerebral vasculitis". Selected cases had to report symptoms and/or radiological signs of cerebral infarction (including retinal location and transitory ischemic attack), parenchymal hematoma, or subarachnoid hemorrhage (SAH). Patients with only radiological signs of cerebral vasculitis, and symptoms caused by inflammatory cerebral lesions were not included. Data from reports with demographic information, a possible history of contact with B burgdorferi (defined as tick bite and/or erythema migrans [EM]), presence of additional neurologic symptoms (defined as headache, cognitive impairment, and/or gait disturbance), type of stroke, associated vasculitis, positive anti–B burgdorferi antibodies on serum and cerebrospinal fluid (CSF), and CSF/serum anti–B burgdorferi antibody index (AI) were collected. Clinical history, and radiological and biological findings were detailed for each of our cases.

This was an observational study with no intervention on human subjects. Collection of data was retrospective from medical records. Written informed consent was obtained from all the patients, or their next of kin, described in this work.

Results

During the study period, only 5 patients with neurovascular manifestations attributed to neuroborreliosis were diagnosed, which represents less than 0.1% of the total number of strokes in our department. We found 57 cases reported in the literature.[5-40] The clinical, biological, and radiological features of all 62 cases are summarized in Table 1. In the whole population, 46% were male and the mean age was 39 years (range 5 to 77 years). Possible contact with B burgdorferi is described in about half of cases, with a reported interval before stroke onset varying from a few weeks to more than one year. Authors noticed

additional neurologic symptoms preceding stroke onset, not linked to the neurovascular events, in 44% of cases. Neurovascular events were ischemic infarcts in 87%, hemorrhagic strokes in 5%, and SAH in 8% of cases. Cerebral lesions were located in the anterior circulation in 48%, in the posterior in 30%, and were in multiple arterial territories in 22% of cases. Cerebral imaging showed sign of vasculitis in 71%. CSF analysis revealed lymphocytic pleocytosis in 90%, elevated protein level in 86%, and positive B burgdorferi serology in 93% with positive AI in 91% of cases. All our 5 patients presented a modified Rankin scale score of 0 or 1 (ie, no symptom or no significant disability) after a median follow-up of 2.8 years without any stroke recurrence.

Case 1

A 66-year-old man with a medical history of arterial hypertension was first admitted because of a sudden right hemiparesis. He had been experiencing headaches for several weeks. Brain magnetic resonance imaging (MRI) showed a left acute anteromedial pontine ischemic lesion with left vertebral artery occlusion on time-of-flight magnetic resonance angiography (TOF-MRA) confirmed by cervical ultrasonography. The electrocardiogram (ECG) and echocardiography were normal. Biological analysis found low-density lipoprotein (LDL)-cholesterol level at 1.33 g/L, a platelet count of 381 G/L, and a C-reactive protein (CRP) level under 5 mg/L. Clinical and radiological findings were compatible with an atherothrombotic ischemic stroke, and the patient was discharged to a rehabilitation center with a daily dose of aspirin, statin, and antihypertension therapy. However, 3 weeks later, he presented a left hemiparesis. Brain MRI revealed new acute ischemic strokes in the right pons, right lentiform, and caudate nuclei (Fig 1, A), with enhancement of vessel wall arteries compatible with vasculitis (Fig 1, B). CSF analysis showed lymphocytic meningitis (42 cells/µL), a high level of protein (219 mg/dL), and a normal glucose level. Borrelia burgdorferi serology (immunoassay, verified by immunoblot) and AI were positive, although there was no record of contact with B burgdorferi. The patient was initially treated with ceftriaxone for 21 days, and then 6 weeks later with doxycycline following persistence of a lymphocytic meningitis (40 cells/µL and protein level at 130 mg/dL). Three months later, CSF analysis was unchanged (47 cells/µL and protein level at 100 mg/dL), but the patient had achieved a complete recovery and has not experienced any neurologic deficits or headaches for 14 months.

Case 2

A 64-year-old woman, with a history of arterial hypertension, was admitted after a transient left hemiparesis, in a context of gradually worsening daily headaches. Brain computed tomography, ECG, and cervical ultrasonography were normal. Blood samples showed

Table 1. *Clinical, biological, and radiological data of reported cases with cerebrovascular events in neuroborreliosis*

Authors and references		5-40 + Wittwer et al
Reported cases (n)		62
Sex ratio F/M		−1.18
Age		
Range (y)		5-77
Mean age (y)		39
Contact with *Borrelia burgdorferi*		
Tick bite		50%
Erythema migrans		10%
Additional neurologic symptoms		44%
Headache ± cognitive impairment ± disturbance of gait		
CSF analysis		
Lymphocytic meningitis		90%
Elevated protein level		86%
Positive *Borrelia burgdorferi* serology		
Blood		71%
CSF		93%
Positive CSF/serum anti–*Borrelia burgdorferi* antibody index		91%
Type of stroke		
Ischemic	87%	TIA, 15%
		Territorial, 33%
		Multiterritorial, 35%
		Lacunar, 17%
Parenchymal hematoma		5%
Subarachnoid hemorrhage		8%
Stroke localization		
Anterior		48%
Posterior		30%
Multiple		22%
Cerebral vasculitis	71%	Anterior circulation, 38%
		Posterior circulation, 35%
		Both, 27%
		Stenosis/occlusion, 65%
		Enhancement of vessel wall arteries, 6%
		Aneurysms, 9%

Abbreviations: CSF, cerebrospinal fluid, F, female; M, male; TIA, transitory ischemic attack.

an LDL-cholesterol of 1.41 g/L, a CRP level under 5 mg/L, and a platelet count of 262 G/L. Her clinical condition worsened with onset of cognitive decline and gait disturbance. Fluid-attenuated inversion recovery MRI showed disseminated lesions, with diffuse meningeal and perivascular contrast enhancement suggesting inflammatory vasculitis (Fig 2, A), without anomaly of arterial caliber on TOF-MRA. CSF analysis showed lymphocytic hypercellularity (74 cells/μL) with high protein (77 mg/dL) and normal glucose levels. Blood and CSF *B burgdorferi* serologies were negative. However, a detailed interview revealed the patient had been bitten by a tick and experienced EM about 1 month before hospitalization. At that time, she received 4 days of oral amoxicillin. Despite negative serology, the combination of recent EM, lymphocytic meningitis, and radiological diagnosis of cerebral vasculitis led us to consider the likelihood of neuroborreliosis. The patient was then treated with intravenous ceftriaxone for 21 days, with rapid normalization of the clinical state, CSF, and brain MRI (Fig 2, B). She has not experienced any other neurologic deficit for 18 months.

Case 3

A 71-year-old woman, with a medical history of arterial hypertension, consulted because of progressive gait disturbance, tremor, memory disorder, and weight loss. The patient was not taking any anticoagulant or antiplatelet therapy. Interview did not find any contact with *B burgdorferi*. Neurologic examination showed bilateral pyramidal syndrome and cerebellar and proprioceptive ataxia. Cerebral and medullar T2*-weighted gradient-recalled echo MRI revealed disseminated microbleeds, especially in the left thalamus, the posterior fossa, and the cervical spinal cord in accordance with clinical signs (Fig 3, A,B). Diffusion-weighted, FLAIR MRI and TOF-MRA did not reveal anything else. Blood samples showed a platelet count
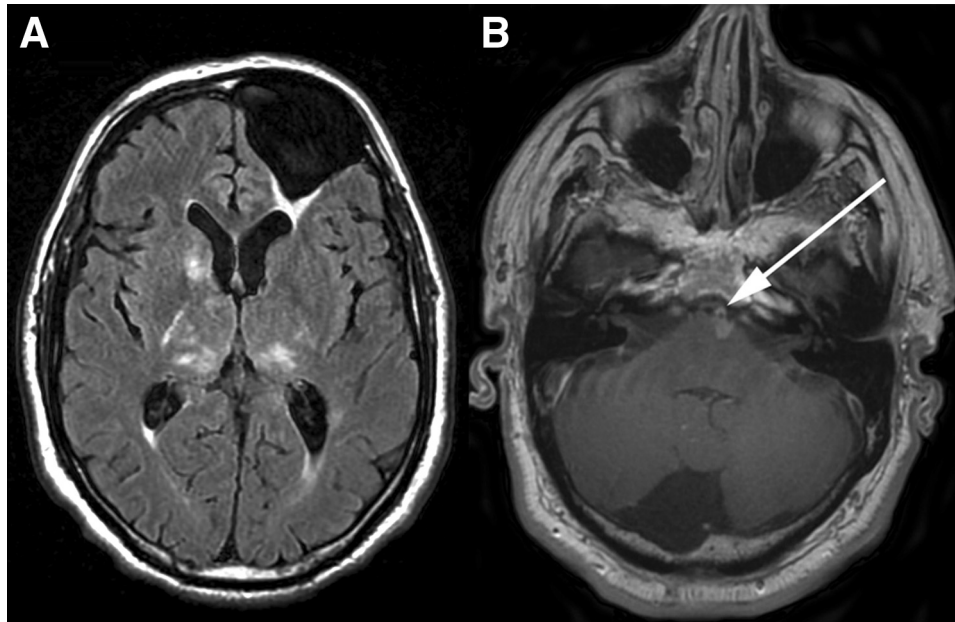
Figure 1. *Brain magnetic resonance imaging showing multiple ischemic lesions in both thalami, right lentiform nucleus, and right caudate nucleus on fluid-attenuated inversion recovery imaging (A), and T1 images 3-mm-thick axial with gadolinium (B) showing focal enhancement of the basilar artery wall in contact with the recent left pontine ischemic stroke (arrow).*

of 197 G/L, without coagulation disturbance, a CRP level under 5 mg/L, and negative human immunodeficiency virus and syphilis serology. CSF analysis revealed lymphocytic hypercellularity (28 cells/μL), high protein level (465 mg/dL), normal glucose level, and positive *B burgdorferi* serology (immunoassay, verified by immunoblot) and AI. The patient was treated with intravenous ceftriaxone for 21 days. The first follow-up cerebral MRI performed 6 months later showed new microbleeds but CSF normalization. Annual follow-up cerebral MRI has been stable for 5 years and the clinical outcome is good.

Case 4

A healthy 39-year-old male farmer was admitted because of repetitive episodes of paresis of the right arm for 2 weeks and a transitory aphasia. Arterial pressure at admission was 130/80 mm Hg. Cerebral MRI showed 2 recent ischemic lesions in the left middle cerebral artery territory (Fig 4, A,B), without anomaly of arteries on TOF-MRA. Blood tests showed a hemoglobin level of 14.6 g/dL, a platelet count of 150 G/L without JAK2 V617F mutation, CRP level under 5 mg/L, a normal
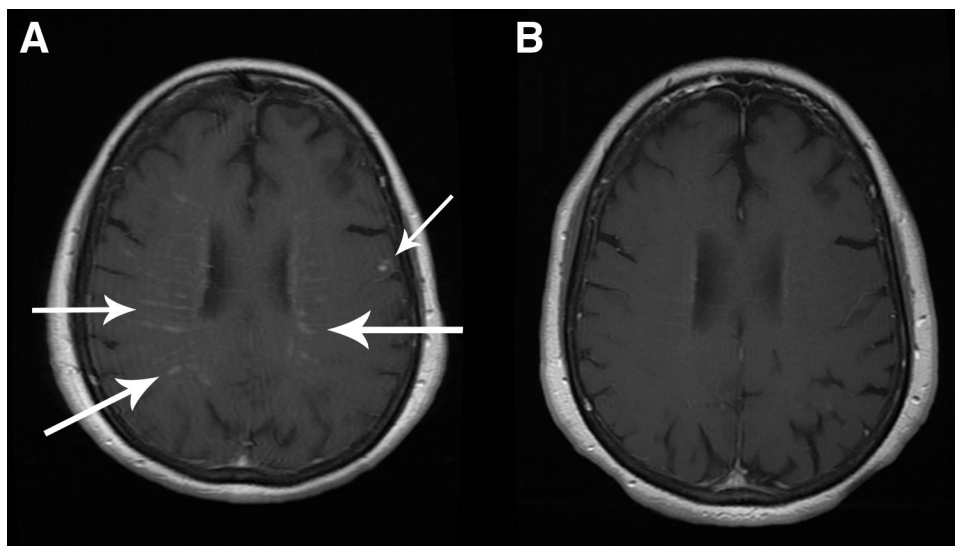

Figure 2. *Brain magnetic resonance imaging with axial T1 sequence with gadolinium showing diffuse meningeal and perivascular enhancement (arrows) (A) vanished 3 weeks after antibiotherapy with ceftriaxone (B).*
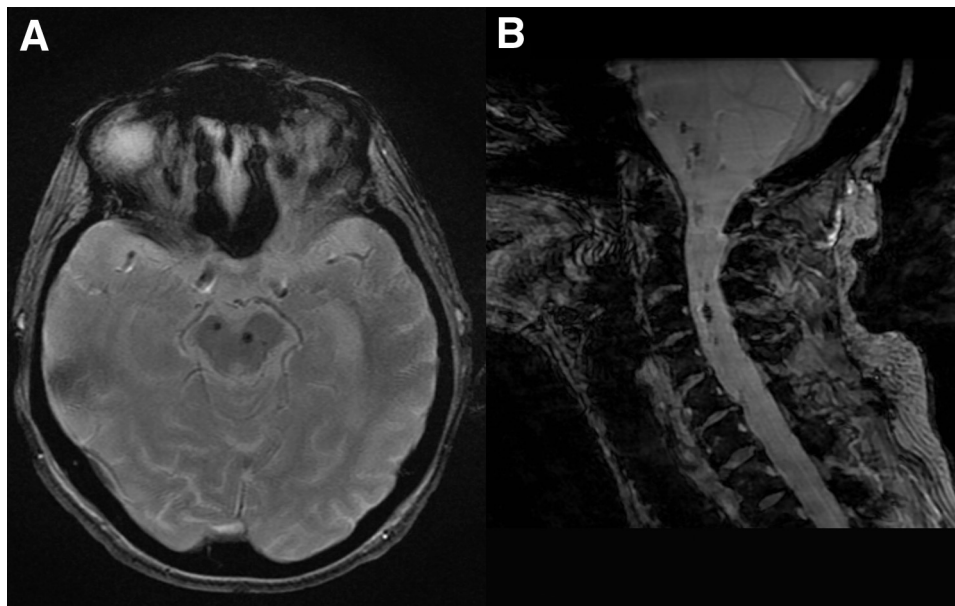
Figure 3. *T2*-weighted gradient-recalled echo resonance imaging showing multiple microbleeds in the midbrain (A), medulla oblongata, and anterior cervical spinal cord regarding C2-C3-C4 (B).*

homocysteine level, an LDL-cholesterol level of 1.06 g/L, and negative human immunodeficiency virus and syphilis serology. All the coagulation tests—prothrombin time, activated partial thromboplastin time, lupus anticoagulant, anticardiolipin antibody, and anti-β2-glycoprotein 1 antibodies—were normal. ECG, with 24-hour Holter monitoring, cervical ultrasonography, and echocardiography did not find any abnormality. It emerged later that the patient had contracted Lyme disease 3 years before and had been treated with oral antibiotics. CSF analysis showed no hypercellularity (<5 cells/μL) with normal protein (34 mg/dL) and glucose levels. However, *B burgdorferi* serology with IgG and IgM was positive in the

blood and CSF (immunoassay, verified by immunoblot), suggesting active recent infection although the AI was negative. The diagnosis of neuroborreliosis was considered as a possibility, and the patient was treated with intravenous ceftriaxone for 21 days. Outcome was favorable with no new episodes for 18 months on a daily dose of aspirin.

Case 5

A 5-year-old child was admitted because of vomiting, dysphagia, sensory loss, and nystagmus compatible with a left lateral medullary syndrome. She had been
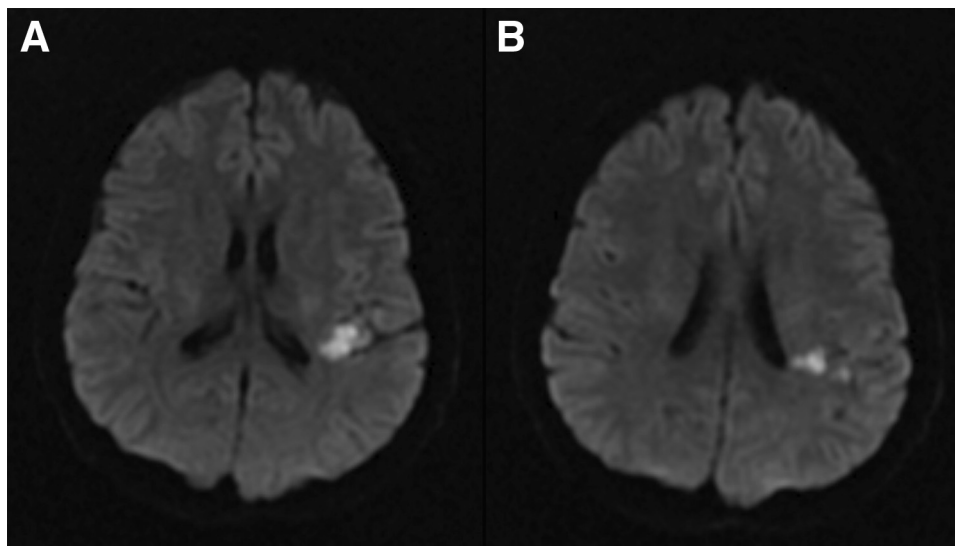

Figure 4. *Diffusion-weighted magnetic resonance imaging showing several acute ischemic lesions in the right superficial middle cerebral artery territory (A, B).*

Figure 5. *Brain magnetic resonance imaging showing acute ischemic stroke in left posterolateral medulla oblongata on diffusion-weighted imaging (A) and older right paravermian cerebellar infarct (arrow) on fluid-attenuated inversion recovery imaging (B).*

experiencing headaches and nausea for several weeks. Cerebral MRI revealed acute ischemic lesion of the left posterolateral medulla oblongata (Fig 5, A) and an older right cerebellar infarct (Fig 5, B), with no observed changes of arterial caliber on TOF-MRA. Laboratory workup showed a platelet count of 186 G/L, no coagulation disorders, and a CRP level under 5 mg/L. Cerebral angiography was normal. CSF analysis discovered lymphocytic meningitis (115 cells/μL) with high protein (115 mg/dL) and low glucose (39 mg/dL) levels. *Borrelia burgdorferi* serology (immunoassay, verified by immunoblot) and AI were positive. No history of contact with *B burgdorferi* was found. The patient was treated with intravenous ceftriaxone for 6 weeks. The outcome was favorable with neurologic improvement and absence of new episodes over a 5-year follow-up.

Discussion

Neuroborreliosis is estimated as being present in around 15% of affected patients and represents the most frequent manifestation of disseminated Lyme disease in Europe. Cranial neuritis and meningoradiculitis are by far the most frequent neurologic presentations.[41,42] In contrast, the incidence of cerebrovascular diseases in this infectious context seems to be low, even in endemic areas, but probably underestimated because of less specific features and difficulties in confirming diagnosis. The demographic characteristics of the patients studied here do not reveal any specific features. Most of the reported cases are described in endemic areas, such as Germany, Holland, Switzerland, Belgium, and the east of France. No gender predisposition is observed but the

mean age, 39 years, appears low in the context of cerebrovascular diseases. This could partly be explained by more extensive investigations to determine the cause of a stroke in a young patient. However, as for 3 of our cases, diagnosis can be suspected in elderly patients as well, even in the presence of other vascular risk factors. Diagnosis was suggested in the first case, despite age and atherothrombotic markers, because of ischemic cerebral recurrences at short intervals in several cerebral arterial territories without other obvious causes. In 3 of our cases, the presence of other neurologic symptoms, headache, certainly because of meningitis, cognitive impairment, and disturbance of gait, not explained by stroke, was also observed. At least one of these symptoms (headache, cognitive impairment, and disturbance of gait) is described in about 40% of cases, but probably not systematically checked for in other cases. Identifying these symptoms would be an indicator of meningitis or inflammatory lesions pointing towards neuroborreliosis. Although lymphocytic meningitis is usual, the first CSF assay was normal or with an isolated elevated protein concentration in about 10% of cases. The most specific laboratory result to confirm diagnosis seems to be AI.[43] However, diagnosis of 5 cases in the literature was based on clinical history and/or *B burgdorferi* serology with negative AI. Furthermore, *B burgdorferi* serology and AI were negative in our second case. Diagnosis of neuroborreliosis was considered and antibiotic therapy administered because of meningitis, cerebral vasculitis, and documented recent EM, with resolved CSF and radiological abnormalities. Negative serology and AI could be attributed to a too recent infection as contact with *B burgdorferi* had occurred no more than one

month previously. PCR and CSF cultures were not performed as the yield is low. Although we recognize that diagnosis of neuroborreliosis remains uncertain and debatable in this case, we decided to report it to suggest the possibility of a negative laboratory workup contrasting with strong clinical and radiological arguments. About 20% of early cases of neuroborreliosis do not present anti–*B burgdorferi* antibodies,[44] and diagnosis is considered as possible.[45] Our fourth case raises the issue of identifying Lyme disease as being the cause of the stroke. In this case, AI was negative and the serology positive, possibly a consequence of a former *B burgdorferi* infection, and the stroke classified as idiopathic. Nevertheless, *B burgdorferi* serology performed with immunoassay and confirmed by immunoblot suggested recent infection in this patient who was especially exposed to tick bites. The patient had been complaining of neurologic symptoms for only 2 weeks, which was probably a too short period for intrathecal production of antibodies to begin. This indicates a moderate sensitivity of serology and AI, between 55% and 80%, but with a strong specificity of the latter.[43] Negative AIs are usually reported in acute forms of neuroborreliosis, in the 6 weeks preceding contact or symptoms, as for cases 2 and 4.[46] This would suggest that a negative immunological investigation should not entirely rule out diagnosis when faced with characteristic clinical history. However, following the criteria proposed by Blanc et al,[43] diagnosis of neuroborreliosis in cases 2 and 4 cannot be completely affirmed but remains possible. Our study does not confirm that the most common location of stroke in the context of neuroborreliosis is in the posterior circulation. Involvement, with possible occlusion, of each type of cerebral artery has been observed from the perforant arteries to large caliber arteries such as the proximal middle cerebral, the basilar, and even the internal carotid artery. Thirty-five percent of patients presented recent ischemic strokes in multiple arterial territories on cerebral imaging. Hemorrhagic lesions, as in our third case, are less often encountered and are described as SAH or hemorrhagic stroke.[9,14,23,28,31] Signs of arachnoiditis, contrast enhancement in the blood vessel wall, and abnormalities of artery caliber observed on MRI support the hypothesis of vasculitis, sometimes confirmed by conventional angiography.[3,10,14,16,22,33,35] Possible radiological findings are both ischemic and hemorrhagic, and nonspecific. However, the multiterritorial aspect of strokes and signs of vasculitis may also be suggestive of a diagnosis of neuroborreliosis. All our patients received intravenous ceftriaxone as first-line treatment, but oral doxycycline has been reported as being effective to treat neuroborreliosis with central nervous involvement.[8,47] The prognosis of patients with neuroborreliosis-related strokes appears to be worse than for stroke of other origin, perhaps because it is the more serious cases that tend to be more diagnosed and reported. Nevertheless, short-term outcome in our 5 cases was favorable under treatment, and the patients' clinical states quickly improved. Long-term outcome also appears to be satisfactory after a median follow-up of about 3 years. CSF abnormalities often persist, as for our first case, without affecting recovery and are therefore attributed to autoimmune mechanisms rather than persistent infection.[5,13,33] Prognosis is mainly associated with the stroke localization as posterior circulation is associated with a poorer prognosis.[3]

Conclusion

This study raises several points about cerebrovascular diseases in Lyme neuroborreliosis. First, initial diagnosis is difficult to make because of a lack of specific clinical or radiological features, and complex to confirm because of moderate sensitivity of laboratory workup. However, in endemic areas, we suggest that physicians test for neuroborreliosis in patients without other obvious causes of stroke in the following situations: repeated strokes at short intervals, several recent strokes in different arterial territories, additional neurologic symptoms which cannot be explained by cerebral lesions (including headache, gait disturbance, or cognitive impairment), a history of infection with *B burgdorferi*, and radiological signs of vasculitis. Diagnosis requires confirmation by CSF assays although the incomplete sensitivity of *B burgdorferi* serology and AI should be kept in mind especially when the symptoms have been present for less than 1 month.

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