

Lyme disease presenting as multiple ischaemic strokes

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ABSTRACT

A 46-year-old man presented with recurrent left hemiparesis and headache. MRI of brain showed an acute right pontine and subacute right thalamic infarcts and MR angiogram showed multiple intracranial arterial stenoses, suggesting cerebral vasculopathy. There was a cerebrospinal fluid lymphocytic pleocytosis with *Borrelia burgdorferi* antibodies. Central nervous system Lyme disease occasionally presents with ischaemic strokes; this case is unusual in showing vasculopathy on brain imaging, supporting meningovascularitis as the likely mechanism.

INTRODUCTION

Lyme disease (from *Borrelia burgdorferi* infection (figure 1)) affecting the central nervous system (CNS Lyme) may cause meningitis, facial nerve palsy, headache, paraesthesias, fatigue, cognitive disturbance and polyradiculitis.¹ CNS Lyme is rare but occasionally causes ischaemic stroke, presumably due to intracranial vasculitis or vasculopathy.² This has been well reported in Europe^{3–12} but is surprisingly rare in North America, presumably because of genetic differences in the species of *Borrelia* between the two regions.^{13 14} We report a man from southern New England, USA, with multiple strokes in the setting of CNS Lyme and review the current literature.

CASE REPORT

A 46-year-old man from Rhode Island, USA, presented in December 2011 with acute onset left-sided weakness and numbness. He reported removing several ticks from his dogs over the summer and fall of that year in his rural residence, but did not recall any specific episode of tick exposure or skin rash on himself. He had a history of hypertension and hyperlipidaemia. MR scan of brain showed an acute right thalamic infarction and MR cerebral angiography showed decreased flow in

the right middle cerebral artery territory. A transoesophageal echocardiogram, carotid ultrasound scan and hypercoagulable panel were normal.

He presented again to the emergency department twice in the following 3 weeks. At the first visit he reported right-sided sharp throbbing headache; CT scan of head was normal and he was discharged home. On the second visit he had transient dysarthria, left-sided weakness and numbness, and left hand incoordination. Repeat MR scan of brain showed interval evolution of the right thalamic stroke and a new area of acute infarction in the right paracentral pons (figure 2). MR cerebral angiography showed attenuation of the distal right M1 segment of the middle cerebral artery with scattered stenoses of the Sylvian branches, and irregularities involving both A1 segments of the anterior cerebral arteries (figure 3), all confirmed on CT angiography (not shown).

Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis (100 leucocytes/mm³, 90% lymphocytes), zero red blood cells, elevated protein (180 mg/dL), normal glucose (41 mg/dL) and five

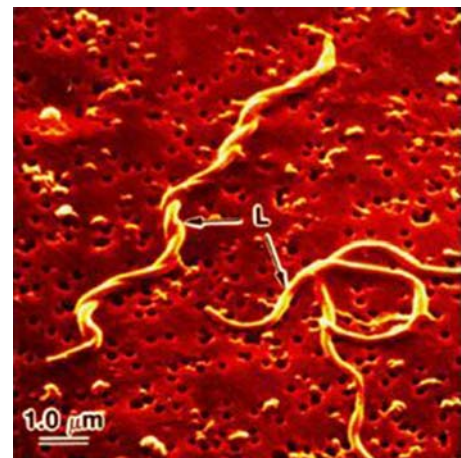


Figure 1 *Borrelia burgdorferi*.

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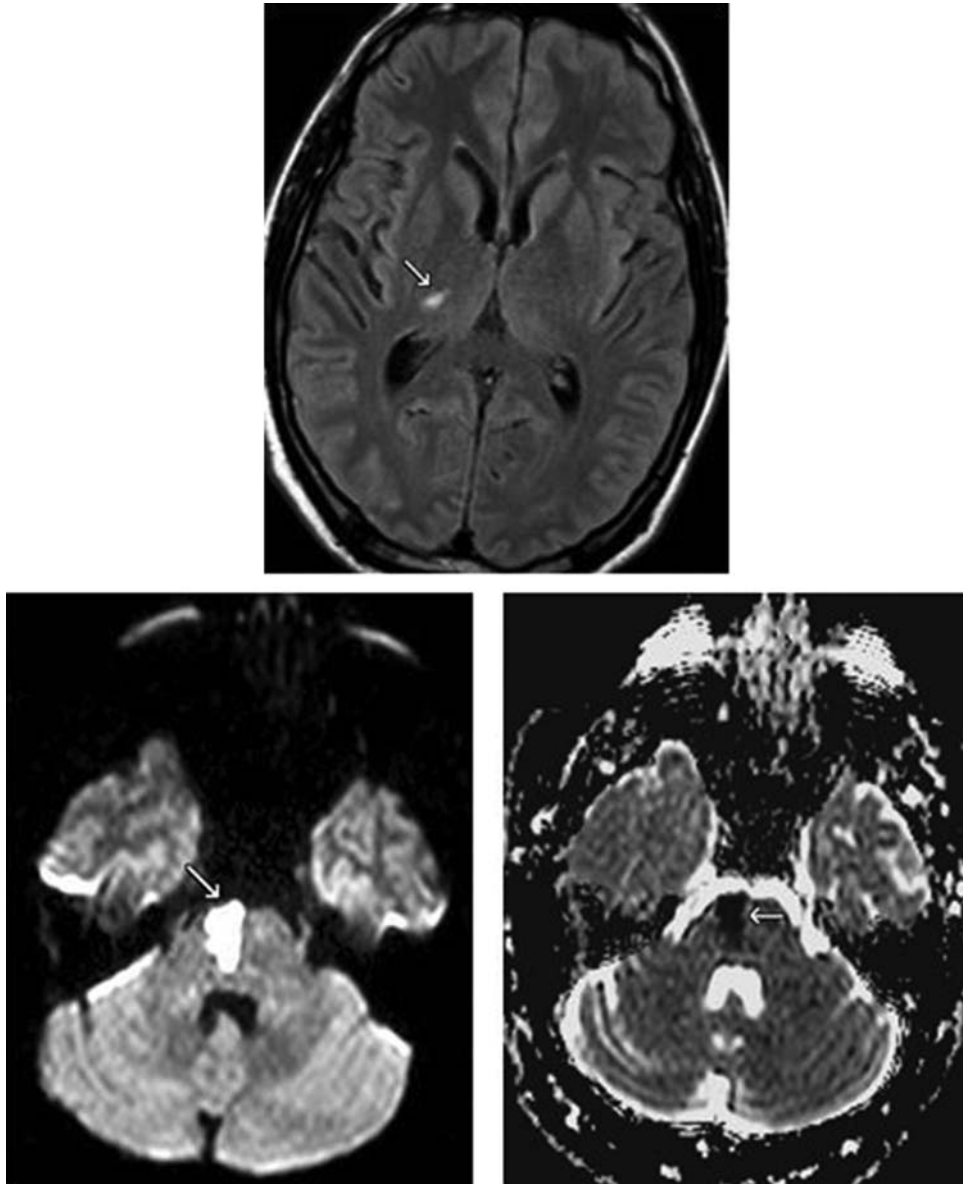


Figure 2 Acute pontine and subacute thalamic strokes. Above: MR scan of brain (fluid-attenuated inversion recovery sequence) showing hyperintensity of the right internal capsule posterior limb and thalamus consistent with previous stroke. Below: MR scan of brain (diffusion-weighted imaging and apparent diffusion coefficient maps) showing diffusion restriction in right paracentral pons consistent with acute stroke.

oligoclonal bands unique to the CSF. A CSF ELISA for total antibodies against *B. burgdorferi* was positive (5.71 LIV, normal <0.99). CSF western blot confirmed anti-*B. burgdorferi* antibodies (IgM band against 23 kd protein, IgG bands against 66 kd, 58 kd, 45 kd, 41 kd, 39 kd, 30 kd, 28 kd, 23 kd and 18 kd proteins). An extensive autoimmune and infectious laboratory workup was negative (box 1). He was treated with 4 weeks of intravenous ceftriaxone followed by 4 weeks of intravenous penicillin G. Subsequent CSF showed gradual resolution of the pleocytosis, falling protein levels, and clearance of IgM bands and decrease in IgG bands (table 1). Eight months after his diagnosis, repeat MR angiography showed significant interval improvement of persistent intracranial arterial

irregularities (figure 3). He still has mild residual left hand weakness. Repeat MR scan of brain showed no new silent ischaemic lesions. We did not test for tuberculosis, given the low clinical suspicion; his spontaneous improvement without proper treatment would have made CNS tuberculosis extremely unlikely.

DISCUSSION

Lyme disease is caused by infection with *B. burgdorferi*, a spirochaete that spreads via the bite of infected ticks. It is the most common tickborne infection in the USA and Europe. *Borrelia* is a heterogeneous group of spirochaetes. Most Lyme disease cases can be accounted for by three species: *B. burgdorferi sensu stricto* is responsible for infections in North America;

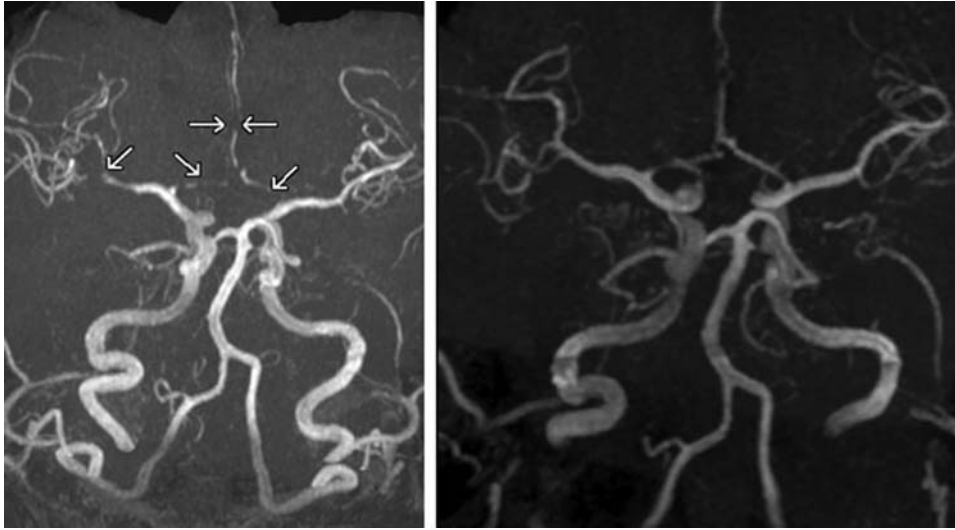


Figure 3 Multiple areas of intracranial stenoses before and after treatment. MR angiogram of brain shows multiple areas of attenuation and scattered stenoses involving bilateral anterior cerebral arteries and the right middle cerebral artery. Repeat MR angiogram 8 months after treatment shows significant interval improvement of focal stenoses.

by comparison, *B. burgdorferi sensu lato* strains, *Borrelia garinii* and *Borrelia afzelii* are more predominant in Europe and Asia.

There are differences between American and European Lyme infections. Pachner *et al* isolated *B. burgdorferi* from the CSF of American patients and *B. garinii* or *B. afzelii* from European patients. These spirochaetes injected into animals caused different disease manifestations, attributed to genetic variations between the strains.^{13 14} While the strains causing American Lyme disease induced a more robust inflammatory response in non-nervous tissues, those responsible for European Lyme better resisted the host's immune responses and more likely persisted in the nervous system.¹³ The pattern of neurological involvement also differed between the two groups of animals, confirming the clinical observation that CNS

Lyme manifests differently in Europe and in the USA. American CNS Lyme usually presents as aseptic meningitis, often with erythema migrans rashes, and shows higher rates of seropositivity; whereas European CNS Lyme typically presents as a painful polyradiculitis—Bannwarth's syndrome—rarely with a preceding erythema migrans rash and is more likely to induce intrathecal antibodies.

Stroke in the setting of CNS Lyme disease is rare. Hammers-Berggren *et al*¹⁰ found only 1 of 281 patients admitted to a hospital in Sweden with cryptogenic stroke had active CNS Lyme; they concluded there was little value in screening for Lyme serology in patients with acute stroke. Nonetheless, there have been multiple reports of CNS Lyme manifesting as stroke, particularly in European and in younger patients.^{3–12} Topakian *et al*⁴ reported two cases of cerebral vasculitis and stroke due to CNS Lyme and reviewed 15 previously published cases, 14 from Europe and 1 from the USA, noting that most patients had a prodromal stage lasting several weeks to months of non-specific complaints, such as headache, fatigue, difficulty concentrating, nausea and vomiting. Erythema migrans preceding stroke was rare, reported in only two cases, including the one American patient.

There have been only two reported cases of cerebral vasculitis and stroke in the setting of CNS Lyme acquired in the USA. In 1990, Brogan *et al*¹⁵ described a 37-year-old woman, 10 days postpartum, presenting with recurrent thunderclap headache; there was no CSF pleocytosis and in retrospect, reversible cerebral vasoconstriction syndrome seems the likely diagnosis. The second case, reported by Reik, was a 56-year-old woman with multiple strokes 18 months after antibiotic treatment for Lyme infection with facial

Box 1 Negative autoimmune and infective workup

Hepatitis B and C serology
 HIV 1 and 2 antibodies
Anaplasma Phagocytophilum antibody
Babesia microti antibody
Ehrlichia chaffeensis antibody
 C reactive protein
 Antineutrophil cytoplasmic antibody
 Sjögren's antibodies (anti-Ro, anti-La)
 Rheumatoid factor
 Anti-DNA antibody (native)
 CSF herpes simplex, cytomegalovirus and varicella zoster by PCR
 CSF cryptococcal antigen
 CSF syphilis serology

Table 1 Cerebrospinal fluid (CSF) studies

Date	Lyme antibody index	Lyme antibody IgG* (number of bands)	Lyme antibody IgM* (number of bands)	CSF leucocytes† (cells/mm ³)	CSF protein (mg/dL)
January 2012	5.71	9	1	100	180
February 2012	4.90	6	1	25	121
March 2012	4.56	6	0	21	100
June 2012	2.78	5	0	6	99
August 2012	Not done	6	0	2	80

*Confirmatory testing by western blot.

†Per cent of lymphocytes ranged 90–97 on all occasions.

neuritis,¹¹ there was lymphocytic pleocytosis with intrathecal production of Lyme antibodies. Although they did not report cerebral vascular imaging, Lyme meningovascularitis appeared to be the likely mechanism of stroke.

The pathophysiology of stroke in CNS Lyme is probably mediated by an inflammation of intracranial vasculature with subsequent narrowing and decreased blood flow. Whether this vasculopathy originates from direct infiltration of the vessel wall by spirochaetes, spread of inflammation from adjacent meninges or from deposition of immune complexes, remains unclear. In our patient, there were persistent arterial irregularities in the face of CSF normalisation 8 months after treatment, suggesting that the impact of inflammation on the arteries is permanent. Alternatively, one could speculate that the inflammatory mechanism preferentially involved arterial segments already affected by other processes, such as atherosclerosis.

Our patient presented very similarly to European cases of stroke in CNS Lyme. He had no preceding erythema migrans rash and produced intrathecal Lyme antibodies. Therefore, this clinical constellation is not unique to infection by *B. garinii* or *B. afzelii* but can be occasionally encountered in American infection caused by *B. burgdorferi sensu stricto*. The same is true for Bannwarth's syndrome; although thought to be a unique clinical hallmark of *B. garinii* infection, it also can occur in patients with infection acquired in the USA.¹⁶

Our patient's lymphocytic pleocytosis persisted 7 months following antibiotic treatment, not unlike other cases with reported follow-up CSF examination.^{4–6} Whether post-treatment pleocytosis represents an ongoing infection requiring another course of antibiotics, or possibly a secondary autoimmune phenomenon, is debateable. Several authors have advised against additional treatment if the clinical course is favourable.^{4–6} Despite the lack of evidence to support repeat treatment of patients with persistent symptoms of Lyme disease,¹⁷ we gave a second course of intravenous antibiotics because of persistent headache and pleocytosis of 25 white blood cells/mm³ on the first post-treatment CSF evaluation 1 month after the diagnosis.

CONCLUSION

In summary, clinicians should consider a diagnosis of CNS Lyme vasculitis in patients with cryptogenic strokes, particularly those who are younger, have prominent headache, have evidence of vasculopathy on cerebrovascular imaging and those who come from areas where Lyme disease is endemic. A CSF abnormality is a prerequisite for the diagnosis of Lyme CNS vasculitis.

Competing interests None.

Patient consent Obtained.

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