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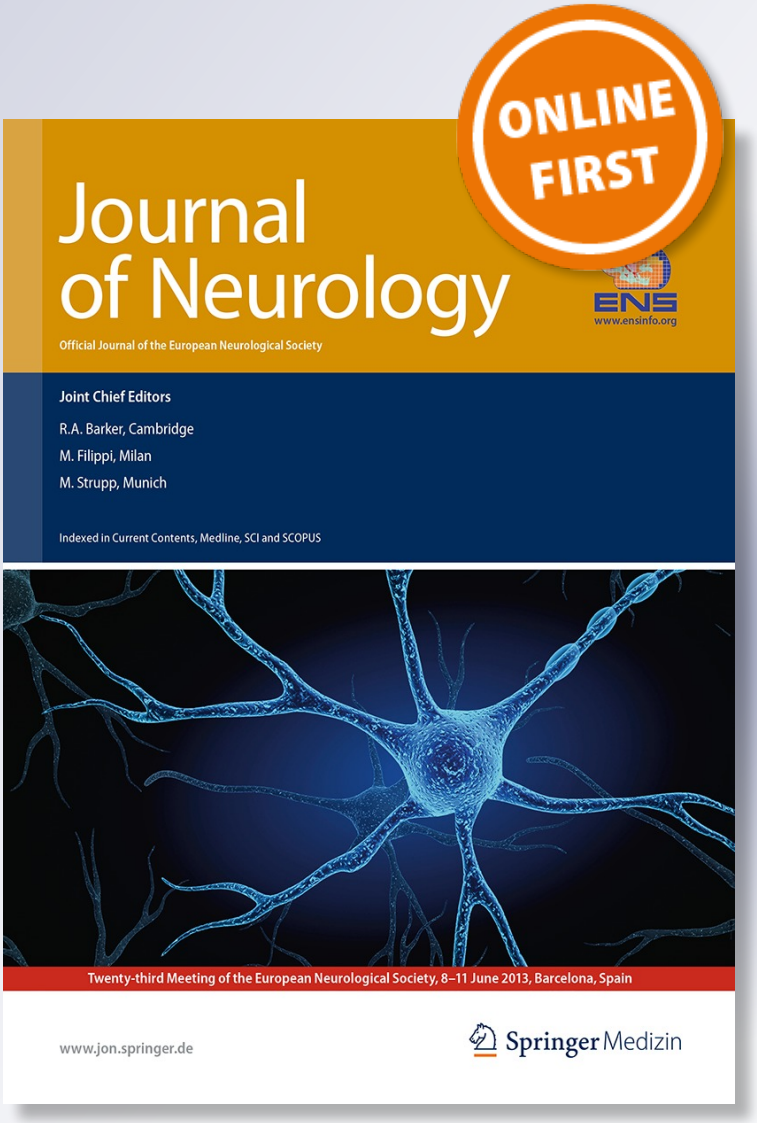

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ORIGINAL COMMUNICATION

Neuroborreliosis-associated cerebral vasculitis: long-term outcome and health-related quality of life

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Abstract Neuroborreliosis affects the nervous system after systemic infection with the spirochete *Borrelia burgdorferi*. Previously, cerebral vasculitis has been regarded as an extremely rare complication of neuroborreliosis. The data on the long-term outcome in patients with cerebral vasculitis due to neuroborreliosis are limited. The objective of this study was to perform a longitudinal analysis of cases of neuroborreliosis-associated cerebral vasculitis. We recruited all patients ($n = 11$) diagnosed with neuroborreliosis-associated in three neurological departments in an East German region. Inclusion criteria were sudden neurological deficits, magnetic resonance (MR) imaging findings that conform to cerebral ischemia or brain infarction, intrathecal synthesis of borrelia-specific antibodies, and non-atherosclerotic pathology of brain supplying arteries. Vasculitic changes were detected by digital subtraction angiography, MR angiography and/or transcranial Doppler ultrasound. Outcomes were measured by the modified Rankin scale (mRS) and EuroQoL Index. Cerebral vasculitis is a rare complication of Lyme disease (0.3 % of all cases in the endemic area). Ten out of 11 patients diagnosed with neuroborreliosis-associated vasculitis cerebral vasculitis using clinical, radiological and immunological criteria developed ischemic stroke or transient ischemic attacks (TIA), 7 patients had recurrent stroke. Vasculitic alterations could be demonstrated in 8 patients that all except one developed ischemic lesions. The median mRS was 3 (range 0–4) at admission and 2 (range 0–6) at discharge. The posterior circulation was affected in 8 of 11 patients; thrombosis of the basilar artery was detected in 2 patients, one died in the acute stage. Neuroborreliosis can cause recurrent stroke or TIA on the basis of cerebral vasculitis. Lumbar puncture is needed for detection of this potentially life-threatening condition. Early recognition and adequate therapy would possibly improve outcome.

Keywords Stroke · Neuroborreliosis · Vasculitis · Lyme disease · Quality of life

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Introduction

Neuroborreliosis is the involvement of the central and/or peripheral nervous system secondary to systemic infection by the spirochete *Borrelia burgdorferi* (*Bb*) sensu stricto in the United States and by *Borrelia garinii* or *B. afzelii* species in Europe. In a German study, *Bb* sensu lato infections in humans presented in 89 % as erythema migrans and in 3 % as neuroborreliosis [8]. A painful

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polyradiculoneuritis is the second frequent manifestation of acute Lyme disease in adults. Lyme neuroborreliosis may also present as progressive meningoencephalitis or as multifocal cerebral vasculitis that is characterized by thickening of the arterial intima and adventitia, perivascular lymphocytic infiltration and vessel obliteration [13, 17]. The latter is thought to occur very rarely; there are only very few case reports that demonstrate cerebral infarction on the basis of lyme disease-associated vasculitis [12, 21, 22, 24].

Similarly to many regions in Germany and Europe, ticks in the region of Eastern Saxony, Germany, are known to carry *Bb* sensu lato. A recent study in southern Lower Saxony showed 25 % of ticks to be affected by *Borrelia* species [20]. In the East German federal lands, the incidence of Lyme disease has been steadily increasing from 2002 to 2006 with a rate of 37.5 affected persons per 100,000 inhabitants in 2006 [20]. One-third of all reported cases were registered in Saxony, 15 % of which presented with a neuroborreliosis. These patients are at risk of cerebral vasculitis. Unfortunately, data on the long-term outcome in neuroborreliosis and associated vasculitis are limited.

We performed a longitudinal study aimed to investigate the long-term outcome in patients diagnosed with neuroborreliosis-associated cerebral vasculitis using clinical, radiological and immunological criteria in Eastern Germany.

Methods

We conducted a longitudinal multicenter study of in the region of Eastern Saxony, Germany. All cases diagnosed with neuroborreliosis-associated cerebral vasculitis using clinical, radiological and immunological criteria in the neurological departments of the Technical University Dresden, the Municipal Hospital Görlitz, and the Saxon Hospital Arnsdorf between 1997 and 2011 were recruited in this study. The adherence area of study sites is 622,100 inhabitants. Inclusion criteria were based on the national and international guidelines for cerebral vasculitis [2, 15] and on the national and international guidelines for neuroborreliosis [16, 19]: (1) Diagnosis of neuroborreliosis proven by pathological findings in the cerebrospinal fluid (CSF). Findings were: pleocytosis, increased total protein, break-down of blood–brain-barrier, positive oligoclonal bands, positive anti-Bb IgG and/or IgM antibodies (enzyme immunoassay, verified by immunoblot) and pathological CSF/serum antibody index of IgG and IgM antibodies (normal below 1.5). (2) Clinical signs and magnetic resonance imaging (MRI) changes that conform to cerebral ischemia. Conventional MRI sequences including diffusion-weighted sequences depicted acute cerebral ischemic tissue changes. (3) Vasculitic pathology of brain supplying arteries was visualized by conventional digital subtraction angiography (DSA), TOF MR angiography (MRA) and/or transcranial Doppler ultrasound. The study was approved by the local Ethic committee. Informed consent was obtained from all patients.

A comprehensive microbiological and immunological assessment was performed in each patient in order to exclude other infectious and non-infectious causes of the inflammatory CSF changes. All patients received a thorough diagnostic work-up according to the national guidelines for diagnostics of cerebrovascular diseases to exclude other causes of stroke [7].

Neurological deficits were assessed by the NIH Stroke Scale (NIH-SS) [3]; disability was estimated by using the modified Rankin Scale (mRS) [18]. Health-related quality of life (HrQoL) was assessed by the EuroQol 5D instrument (EQ-5D index and visual analogue scale [VAS]) [23]. The EQ-5D index ranges between 0 (worst HrQoL) and 1.0 (best possible HrQoL); the EQ VAS ranges between 0 (worst score) and 100 (best possible score). The follow-up evaluations were performed 5.2 ± 3.6 years following disease onset.

Results

Epidemiology, clinical characteristics and treatment

We diagnosed Lyme borreliosis-associated cerebral vasculitis in 11 patients (5 females and 6 males) with a mean age of 62 ± 12 years. The incidence of Lyme borreliosis in the study region is approximately 37.5 per 100,000 [20]. Considering the duration of the study (15 years) and the adherence area (622,100 inhabitants) the estimated proportion of cerebral vasculitis in patients with Lyme borreliosis amounted to 0.3 % ($11/37.5 \times 622.1 \times 15 = 0.003$) in this endemic area.

Nine patients developed ischemic stroke (7 of 9 recurrent ones), one patient developed recurrent transient ischemic attacks. In one asymptomatic patient, MR-angiography (MRA) detected a high-grade stenosis of the top of the basilar artery. Demographics, CSF findings and outcome are summarized in Table 1. In all but one patient, increased white cell count (159 ± 176 cells/μL) was seen in the CSF that consisted of lymphocytes ($n = 8$) or granulocytes ($n = 2$). Total protein was severely elevated (2,167 ± 1,260 mg/L) and pathological in all patients. Neuroborreliosis was confirmed by intrathecal anti-Bb antibody production that showed a positive serum-CSF antibody index (ratio) of IgG and/or IgM anti-Bb antibodies ($n = 11$). All patients had positive IgG antibodies in CSF as well as pathological IgG antibody index. In 5 patients CSF IgM was negative. Oligoclonal bands were pathological in 10 patients and not available in 1 patient.

All patients reported a history of tick bite. No reliable reports on erythema migrans or arthritis were available. One patient reported history of Bannwarth's syndrome preceding the cerebral infarction. No history of facial palsy or encephalomyelitis was reported by study patients.

Ten patients had ischemic lesions documented by diffusion-weighted images (DWI). Table 2 shows the type and time pattern of cerebral ischemia, imaging results and findings of vessel pathology. Corresponding to the majority of recurrent ischemic events (whether stroke or TIA), ischemic brain lesions were multiple in 7 of 11 patients with a clear predominance of the posterior circulation (Fig. 1). Typical vessel abnormalities were affections of the basilar artery ($n = 3$) and stenoses or irregular calibre of the posterior cerebral artery or vertebral artery ($n = 4$). Middle cerebral artery stenosis was seen in one patient, sagittal (venous) sinus thrombosis in another patient. A thorough diagnostic assessment did not reveal any other causes of sinus thrombosis.

All patients were treated with platelet inhibitors and received iv ceftriaxone (2–4 g daily for 2–3 weeks). In addition, four patients received corticosteroids (100–1,000 mg prednisolone daily) when intracranial vessel pathology related to vasculitis was detected. Prednisolone was administered orally. The initial dose was tapered over weeks.

Clinical outcome and health-related quality of life

The initiation of antibiotic treatment (2–3 weeks iv ceftriaxone) lead to rapid clinical improvement in most of patients, as reported in a treatment trial of late Lyme disease [4]. The initiation of add-on prednisolone therapy in four patients prevented further ischemic complications except the reocclusion of the basilar artery after local thrombolytic intervention in one patient.

Clinical outcome of patients was variable: one patient died in the subacute stage due to extensive basilar artery thrombosis, another patient survived the same complication with poor outcome (mRS = 5, Fig. 2). Another patient died 7 years after stroke onset at the age of 77 years. Median scores of NIH-SS and mRS were 4 and 3 in the acute phase, respectively, and 0 and 2 in the post-acute phase, respectively. Long-term outcome scores were available in 8 out of 9 survivors. Median mRS score was rated 3.

The HrQoL in patients with Neuroborreliosis-associated vasculitis measured by EQ VAS was reduced by 34 % compared to general German population (51.0 ± 24.8 vs. 77.4 ± 19) [9]. The EQ-5D was also considerably decreased and amounted to 0.55 ± 0.19.

Discussion

Lyme borreliosis has been very rarely identified as the cause of ischemic or hemorrhagic stroke [21, 22, 24]. The present study of neuroborreliosis associated with cerebral vasculitis and subsequent ischemic stroke or TIA is the largest data set currently available. It shows a distinct pattern that should give rise to the suspicion of vasculitic stroke associated with neuroborreliosis: relatively young patients (mean age of 62 years in our patients vs. 73 years

Table 1 Patient characteristics, CSF findings and neurological scores

Patient	Sex	Age at onset	CSF cell count (per μL)	CSF total protein (mg/L)	IgG Bb antibody index[a]	NIH-SS acute	NIH-SS post-acute	mRS acute	mRS post-acute	mRS long-term
1	F	47	18	2,181	2.2	8	7	4	4	3
2	F	49	76	4,443	15.7	4	17	3	5	5
3	M	69	71	962	13.9	6	33	4	6	na
4	M	73	49	876	16.9	0	0	0	0	3
5	F	66	307	1,419	31.4	4	0	3	1	1
6	M	55	2	2,377	34.1	2	0	2	1	3
7	F	77	42	1,690	14.8	2	0	4	2	3
8	F	74	530	2,138	6.1	5	3	4	2	na
9	M	70	31	982	4.9	3	3	2	2	6
10	M	52	295	4,479	17.3	0	0	0	0	2
11	M	46	331	2,294	19.1	4	0	2	0	1
Mean ± SD (median)		62 ± 12 (66)	159 ± 176 (71)	2,167 ± 1,261 (2,138)	16.0 ± 10.0 (15.7)	3.5 ± 2.4 (4)	5.7 ± 10.4 (0)	2.6 ± 1.5 (3)	2.1 ± 2.1 (2)	3.3 ± 1.7 (3)

CSF cerebrospinal fluid, *IgG antibody index* anti-borrelia IgG antibody serum-CSF ratio, *M* male, *F* female, *NIH-SS* NIH Stroke Scale, *mRS* modified Rankin scale, *na* not available

[a] IgG serum-CSF antibody index is normal below 1.5

Table 2 Type and location of ischemia, imaging results and vessel pathology

Patient	Ischemic infarct/ TIA	Anterior/posterior circulation	Single/ recurrent event	Lesion location	DSA/MRA/transcranial Doppler (TCD) findings	Clinical course/ remarks
1	Infarct	Anterior	Recurrent	Multiple: L precentral, R parietal, R centrum semiovale	DSA: generalized intracranial vasospasm	Incomplete recovery
2	Infarct	Posterior	Recurrent	Multiple: bilateral pontine, R cerebellar	MRA: basilar artery stenosis, later occlusion	Recurrent basilar artery thrombosis, local thrombolysis
3	Infarct	Posterior	Recurrent	Multiple: bilateral cerebellar, pontine, bilat. thalamic, later also midbrain and both PCA territories	MRA: basilar artery thrombosis	Basilar artery thrombosis, systemic thrombolysis
4	TIA	Anterior	Recurrent	L hemispheric lesion	MRA: normal, extracranial Duplex: R ICA stenosis	Complete recovery
5	Infarct	Posterior	Recurrent	Multiple: L MCA and PCA territories	MRA: irregular vertebral arteries, TCD: L PCA stenosis	Accompanying meningoencephalitis
6	Infarct	Anterior	Recurrent	Multiple: R MCA territory	MRA: multiple stenoses of R MCA and ACA	CSF pleocytosis missing
7	Infarct	Anterior	Recurrent	L subcortical	MRA normal, MR venography: sagittal sinus thrombosis	Sinus thrombosis, meningoencephalitis
8	Infarct	Anterior + posterior	Recurrent	Multiple: R striatum, L cerebellar, R pontine	MRA: irregular VA and R PCA; MRI: contrast enhancement of brainstem	Meningoencephalitis
9	Infarct	Anterior + posterior	Single	Multiple: R caudate, R subcortical, L thalamus	MRA: na, DSA: R ICA stenosis	ICA stenosis probably atherosclerotic
10	No infarct	Posterior	No event	No lesions	MRA: high grade stenosis of top of the basilar artery	No signs of atherosclerosis (normal IMT)
11	Infarct	Posterior	Single	R thalamus, peduncle	MRA: normal, TCD: normal, DSA: na	Complete recovery

TIA transient ischemic attack, *DSA* digital subtraction angiography, *MRA* magnetic resonance angiography, *R* right, *L* left, *ICA* internal carotid artery, *VA* vertebral artery, *PCA* posterior cerebral artery, *CSF* cerebrospinal fluid. *na* not available, *IMT* intima media thickness of carotid artery

in the community-based German study of first-ever stroke [10]), preceding complaints of headache, recurrent episodes of neurological deficits, brain imaging findings with multiple ischemic lesions, predominance of the posterior circulation and intracranial vessel pathology (in the absence of generalized atherosclerosis). Lumbar puncture disclosed CSF alterations including pleocytosis, increased total protein and detection of specific antibodies directed against *Bb*.

Our study revealed a highly variable short- and long-term outcome in terms of neurological deficit, handicap and HrQoL. During rehabilitation treatment, the NIH-SS normalized in 6 of 11 patients. Unfortunately, two patients with basilar artery thrombosis developed progressive severe deficits leading to death in one and to severe long-term handicap and low HrQoL in the other. HrQoL as measured by the EQ VAS, is grossly diminished in our cohort (51.0 ± 24.8) when compared with the age-matched normal German population (73.0) [9]. But also the comparison with a German cohort of stroke patients [6, 25, 26] as well as patients with subarachnoid hemorrhage (SAH) [5, 14] demonstrates a distinctly lower HrQoL in both measures, EQ-5D index and EQ VAS. Only with exclusion of the patient surviving basilar artery thrombosis, the long-term EQ VAS in our cohort (56.9) was comparable to the same score measured at discharge after SAH (57.8) [14]. Therefore, the long-term outcome of vasculitic stroke seems to be distinctly worse than in common stroke patients.

The association observed between neuroborreliosis and cerebral ischemia is based on the evolution of cerebral vasculitis as a known rare complication of Lyme disease. One patient in our sample has also developed a sinus thrombosis. The association of sinus thrombosis with neuroborreliosis has been described in the literature [1]. Proof of a causal relationship between cerebral vasculitis and neuroborreliosis by histological means, however, is difficult

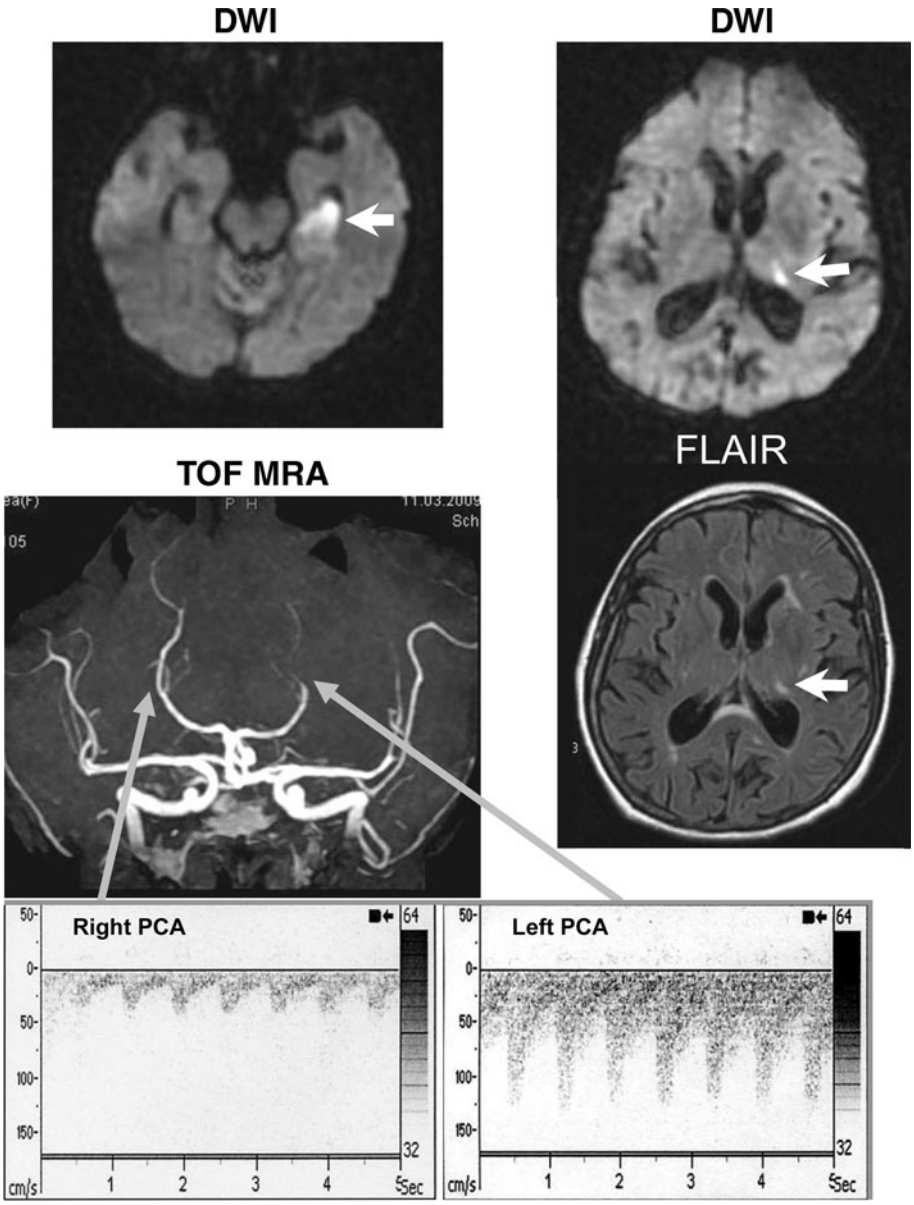

Fig. 1 66-year-old patient (Nr. 5 in sample) with borrelia-induced meningoencephalitis. Multiple ischemic lesions are visible in diffusion-weighted images (DWI) in the temporal lobe (*upper left*, *arrow*) and the thalamus (*upper right*, *arrow*) confirmed in FLAIR images (*lower right*, *arrow*). TOF magnetic resonance angiography (MRA) shows tight stenosis of the left posterior cerebral artery (PCA, *middle left*, *arrow*) with increased flow velocity as measured by transcranial ultrasound (*lower row*, *right*)

due to ethical and technical reasons; scarce autopsy results have been published detecting spirochetes in tissue sections [13]. In the clinical arena, we have to search for more indirect evidence. Wide-spread cerebral vasculitis affecting major cerebral arteries could be demonstrated by DSA only in one patient. It is conceivable, however, that also vessels without frank constriction, or occlusion, may nevertheless be affected because multiple lesions in various arterial territories are a regular imaging finding. The pathophysiology of cerebral vasculitis in neuroborreliosis is not fully understood. There are patients, which can develop local lesions without widespread signs of vasculitis. May and Jabbari [12] suggested that CSF pleocytosis and cerebral infarction would be suitable criteria to diagnose neuroborreliosis-associated vasculitis in these patients. In older patients with a vascular risk profile, the search for embolic sources (e.g., cardiac thrombus, atrial fibrillation, etc.) may eventually lead to alternative explanations. The best possible and most probable explanation of all clinical and ancillary findings should be favoured. In the future, improved imaging techniques, e.g., high-resolution MRI and arterial wall imaging [11], will possibly visualize vasculitic wall changes to support the diagnosis of cerebral vasculitis. The diagnosis did not change in our patients at follow-up investigations.

Limitations of our study are due to the limited number of patients, a variable diagnostic work-up, and non-conform treatment guidelines that included only by part iv or oral prednisolone therapy. The diagnosis of neuroborreliosis-associated cerebral vasculitis was made based on

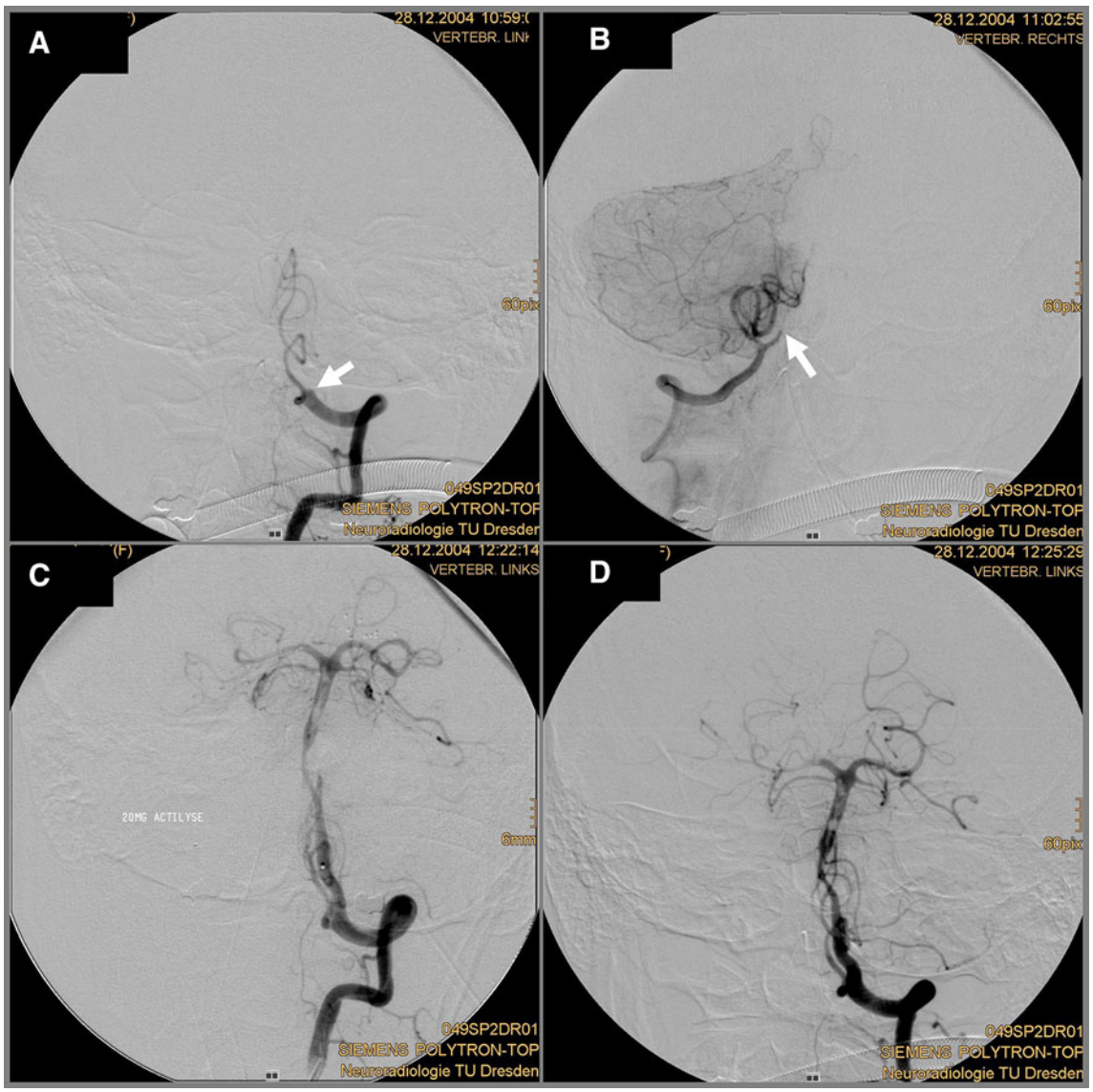

Fig. 2 49-year-old patient (Nr. 2 in sample) with progressive signs of basilar artery (BA) thrombosis and successful intervention. Digital subtraction angiography with selective injection into the left vertebral artery (VA) showing proximal BA occlusion (**a** *arrow*); injection into right VA that confirms BA occlusion (**b** *arrow*) and filling of the right posterior inferior cerebellar artery; local thrombolysis with alteplase (**c**, **d**) and partial recanalization of BA with a free-floating thrombus still visible in the distal part and remaining occlusion of the right PCA

clinical, radiological and immunological findings. No cerebral biopsies were performed due to ethical reasons (the clinical work-up was sufficient to provide the necessary treatment). Selection bias cannot be excluded due to the type of our study (referral- and hospital based).

Future directions are to search more consequently for Lyme vasculitis-associated strokes by examining CSF in younger stroke patients with recurrent ischemic events and imaging patterns of multiple lesions that affect the posterior circulation.

In summary, neuroborreliosis can cause recurrent stroke or TIA on the basis of cerebral vasculitis. Lumbar puncture is needed for detection of this potentially life-threatening condition that requires immediate antibiotic treatment along with optimal stroke care. Long-term outcome and HrQoL seem to be worse than in common stroke patients.

Conflicts of interest Nothing to declare.

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