Hyperacute treatment of childhood stroke in Lyme neuroborreliosis: report of two cases and systematic review of the literature

Joerg Philipps(iD), **Bernhard Erdlenbruch, Michael Kuschnerow, Sunil Jagoda, Blerta Salihaj, Joerg Glahn and Peter Dieter Schellinger**

Abstract: The safety and efficacy of hyperacute reperfusion therapies in childhood stroke due to focal cerebral arteriopathy (FCA) with an infectious and inflammatory component is unknown. Lyme neuroborreliosis (LNB) is reported as a rare cause of childhood stroke. Intravenous thrombolysis (IVT) and endovascular therapy (EVT) have not been reported in LNB-associated stroke in children. We report two children with acute stroke associated with LNB who underwent hyperacute stroke treatment. A systematic review of the literature was performed to identify case reports of LNB-associated childhood stroke over the last 20 years. Patient 1 received IVT within 73 min after onset of acute hemiparesis and dysarthria; medulla oblongata infarctions were diagnosed on magnetic resonance imaging (MRI). Patient 2 received successful EVT 6.5 hr after onset of progressive tetraparesis, coma, and decerebrate posturing caused by basilar artery occlusion with bilateral pontomesencephalic infarctions. Both patients exhibited a lymphocytic cerebrospinal fluid (CSF) pleocytosis and elevated antibody index (AI) to *Borrelia burgdorferi*. Antibiotic treatment, steroids, and platelet inhibitors including tirofiban infusion in patient 2 were administered. No side effects were observed. On follow-up, patient 1 showed good recovery and patient 2 was asymptomatic. In the literature, 12 cases of LNB-associated childhood stroke were reported. LNB-associated infectious and inflammatory FCA is not a medical contraindication for reperfusion therapies in acute childhood stroke. Steroids are discussed controversially in inflammatory FCA due to LNB. Intensified antiplatelet regimes may be considered; secondary prophylaxis with acetyl-salicylic acid (ASA) is recommended because of a high risk of early stroke recurrence.

Keywords: acute treatment, childhood stroke, endovascular treatment, focal cerebral arteriopathy, intravenous thrombolysis, Lyme neuroborreliosis

Correspondence to:
Joerg Philipps
Department of Neurology and Neurogeriatrics, Johannes Wesling Klinikum Minden, Ruhr-University Bochum, Hans-Nolte-Str. 1, D-32429 Minden, Germany.
joerg.philipps@rub.de

Bernhard Erdlenbruch
Department of Pediatrics, Johannes Wesling Klinikum Minden, Ruhr-University Bochum, Minden, Germany

Michael Kuschnerow
Department of Diagnostic and Interventional Radiology, Johannes Wesling Klinikum Minden, Ruhr-University Bochum, Minden, Germany

Sunil Jagoda
Department of Anesthesiology and Intensive Care, Johannes Wesling Klinikum Minden, Ruhr-University Bochum, Minden, Germany

Blerta Salihaj
Joerg Glahn
Peter Dieter Schellinger
Department of Neurology and Neurogeriatrics, Johannes Wesling Klinikum Minden, Ruhr-University Bochum, Minden, Germany

Introduction

Childhood arterial ischemic stroke (AIS) is frequently associated with focal cerebral arteriopathy (FCA).[1] Lyme disease, the symptomatic arthropod-borne infection with *Borrelia burgdorferi* sensu lato, may present with various manifestations in the peripheral and central nervous system (CNS), including meningovascular involvement, that are denoted as Lyme neuroborreliosis (LNB). Although a rare event, cerebrovascular manifestations of LNB have been reported as potential cause of childhood AIS, especially in European regions with high prevalence of *Borrelia garinii*.[2] Management of childhood AIS due to LNB consists of early antibiotic treatment, usually a third-generation cephalosporine.[3,4] Platelet inhibition with acetyl-salicylic acid (ASA) as secondary prevention and steroids as treatment of inflammatory arteriopathy have been discussed in the literature.[2,5] The safety and efficacy of intravenous thrombolysis (IVT) and endovascular therapy (EVT) in the setting of childhood FCA, especially

with an infectious and inflammatory component, is unknown.[1] We present two cases of hyperacute stroke treatment of childhood AIS due to LNB-associated FCA. Feasibility, benefits, and potential risks of hyperacute treatment of LNB-associated childhood stroke are discussed, and a review of case reports with a focus on acute treatment is provided.

Methods

Patients

Two children treated at the Johannes-Wesling-Klinikum Minden, University Hospital of the Ruhr-University Bochum, Germany, in 2020 and 2021 are reported. Consensus-based clinical case report (CARE) guidelines were applied to present the two case reports.[6] The patients' legal representatives (parents) provided written informed consent to the publication. Further institutional approval was waived in accordance with German ethical regulations on case reports.

Literature review

A systematic review of the online database MEDLINE/PubMed using the search algorithm [(neuroborreliosis OR Lyme OR LNB) AND stroke AND treatment AND (children OR child) AND case AND report, year > 2001] was carried out. References in each identified article were reviewed to find additional published case reports. The identified articles were further processed according to the preferred reporting items for systematic reviews and meta-anlyses (PRISMA) checklist[7] in order to identify original case reports of childhood AIS as manifestations of LNB in the last 20 years.

Results

Case description 1

A 13-year-old boy presented 30 min after symptom onset with a sudden weakness of the right side and slurred speech. In the 3 weeks before, he had complained about headache, mild flu-like symptoms, fatigue, and myalgia. Neurological examination revealed a right directional nystagmus, dysarthria, brachiofacial hemiparesis, hemihypesthesia, and extensor plantar sign on the right side. The pediatric National Institute of Health stroke scale score (pedNIHSS) was 10. Emergency laboratory examinations were normal.

Cerebral magnetic resonance imaging [MRI; DWI/ADC (diffusion-weighted imaging/apparent diffusion coefficient), FLAIR (fluid-attenuated inversion recovery, SWI (susceptibility weighted imaging), and TOF (time-of-flight) angiography] showed a hyperintense area on DWI with ADC restriction in the medulla oblongata on the left side; FLAIR and SWI were normal. Imaging was affected by metal artifacts generated by the patient's orthodontic braces.

Systemic IVT was started 73 min after onset of symptoms in the MRI with a total dose of 45 mg alteplase in 1 h (0.9 mg/kg, 10% as initial bolus). Door-to-needle time was 43 min. Extracranial duplex sonography and transcranial color-coded duplex sonography (TCCS) revealed a slightly reduced flow velocity in the left vertebral artery (extracranial v2 segment and intracranial v4 segment) and a reduced diameter of the left vertebral artery compatible with congenital hypoplasia of the left vertebral artery. Flow in the extra- and intracerebral blood vessels was otherwise normal.

Follow-up MRI (DWI/ADC, T1, FLAIR, SWI, and gadolinium-enhanced MR-angiography) on day 1 (after removal of the braces) showed a hyperintense area on DWI with ADC restriction and very subtle hyperintensity in FLAIR in the medulla oblongata on the left side. Gadolinium-enhanced MR-angiography revealed a minimum irregularity in the diameter of the proximal basilar artery (BA) and a reduced diameter of the left vertebral artery (Figure 1). Axial T1 weighted images of the neck showed no signs of dissection. PedNIHSS 24 h after IVT was 10.

Lumbar puncture on day 2 yielded a lymphocytic cerebrospinal fluid (CSF) pleocytosis, elevated protein, and intrathecal *B. burgdorferi* IgG antibody synthesis (see Table 1). Other pathogens were excluded [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Tick-borne encephalitis (TBE), Varicella-Zoster Virus (VZV), herpes simplex virus (HSV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), *Treponema pallidum, Mycobacterium tuberculosis*, human immunodeficiency virus (HIV), Parainfluenza Virus, Parvovirus B19, Candida, Mycoplasma, *Listeria monocytogenes*]. Antibiotic treatment was started with cefotaxime (6 g/day for 14 days), acyclovir, and ampicillin being stopped after negative results for HSV/VZV and *L. monocytogenes*. A steroid pulse of 500 mg
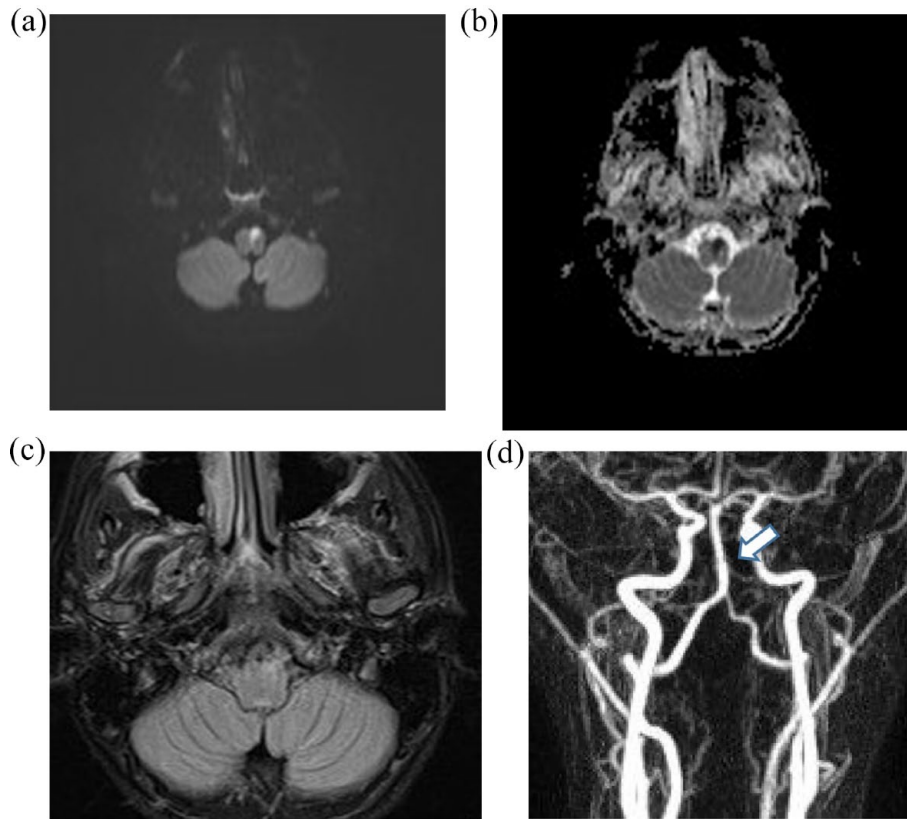
Figure 1. Patient 1, MRI on day 1: DWI (a), ADC (b), FLAIR-MRI (c), and gadolinium-enhanced MR-angiography (d): DWI-hyperintensity, ADC restriction in the left medulla oblongata, and minimum irregularity in the diameter of the proximal basilar artery (arrow).

methylprednisolone was administered for 5 days, then 50 mg of prednisolone were given per os and tapered over a period of 1 month. ASA 100 mg daily was administered continuously.

On day 3, dysarthria worsened and a marked dysphagia developed. Hiccup occurred constantly, hemiparesis and nystagmus were unchanged, and pedNIHSS was 12. He developed a febrile episode and an ampicillin rash.

A third MRI showed a new right side medulla oblongata infarct; the left side medulla oblongata DWI/FLAIR lesion was slightly larger than in the second MRI. In a control lumbar puncture on day 18, there was a mild lymphomonocytic pleocytosis and normal protein; *B. burgdorferi*-specific antibody index (AI) was again positive (Table 1). Further extensive laboratory examinations, including thrombophilia, were normal. Transesophageal echocardiography and electrocardiogram were normal. The patient and his family live in northern Germany, frequent hiking tours in the forest were reported, but no tick bites or erythema were recorded.

PedNIHSS on day 7 was 9; dysarthria and dysphagia slowly improved. On discharge to neurological rehabilitation, he was able to feed without a nasogastric tube but unable to walk. On follow-up 9 months later, he was able to walk unaided, pedNIHSS was 2, modified Rankin Scale (mRS) 2, and Barthel Index 95. Extracranial duplex sonography and TCCS were unchanged showing hypoplasia of the left vertebral artery and were otherwise normal. Platelet inhibition with ASA 100 mg/day was the only ongoing medication. He is able to live with his family and attend his former school.

Case description 2

A 6-year-old boy with a history of headache and fatigue for 4 weeks and vertigo on the day of admission presented to the emergency department with

Table 1. LNB-related CSF and serum laboratory results.

| Parameter	Normal value	Unit	Patient 1, day 2	Patient 1, day 18	Patient 2, day 0
CSF cell count	(<4)	[/µl]	155	36	45
CSF cytology		[% lymphomonocytes/ granulocytes/ plasma cells]	100/0/0	97/3/0	95/1/4
CSF protein	(<450)	[mg/l]	1070.7	325.8	413.5
CSF lactate	(<2.1)	[mmol/l]	2.67	2.17	1.68
IgG intrathecal fraction	(<5)	[%]	46	45	25
IgM intrathecal fraction	(<5)	[%]	63	65	90
Albumin quotient	(L/S $\times$ 10³, <4.9)		13.7	3.7	5.8
CSF CXCL13	(<30)	[pg/ml]	311.50	Not controlled	452.90
B.b.-specific AI IgG	(<1.5)		40.5	7.9	25.0
B.b.-specific AI IgM	(<1.5)		n.d.	n.d.	47.0
B.b. (VlsE) AI IgG	(<1.5)		40.2	8.0	17.3
Serum B.b. AB IgG	(<20)	[U/ml]	911	3632	61
Serum B.b. AB IgM	(<20)	[U/ml]	7	19	27
Serum VlsE AB IgG	(<10)	[U/ml]	399	1425	110
B.b.-specific bands detected in immunoblot[a]			IgG: p43, p14, Osp17, OspC, VlsE	Not controlled	IgM: p41, OspC; IgG: VlsE

AB, antibody; AI, antibody index; B.b., *Borrelia burgdorferi*; CSF, cerebrospinal fluid; LNB, Lyme neuroborreliosis; n.d., not detectable.
AI calculations (using the Q-Lim ratio) and B.b. serodiagnosis (standard two-tier testing, enzyme immunoassay followed by immunoblot) were performed by an accredited microbiology laboratory according to the current guidelines.[3]
[a]Microarray immunoblot (ViraChip®, Viramed Biotech, Germany).

a worsening impairment of consciousness, beginning 2h before. He was unable to speak and could not walk. Neurological examination revealed a progressive coma (worst Glasgow coma scale (GCS) 7, pedNIHSS 32), a rotating downbeat nystagmus, left ptosis, anisocoria, severe dysarthria, left hemiparesis, and then tetraplegia with bilateral extensor plantar sign. The patient exhibited intermittent decerebrate posturing. The accompanying father reported a family history of a heterozygous factor V Leiden mutation.

Cranial computed tomography (CCT) showed a hyperdense BA sign and was otherwise normal. Brain MRI including diffusion-weighted and ADC maps, three-dimensional TOF MR-angiography, SWI, and FLAIR images revealed acute bilateral pontomesencephalic DWI hyperintensities/ADC restrictions caused by extensive thrombotic occlusion (Figure 2(a)–(c)) of the BA. Thrombus formation was visualized in DWI and FLAIR sequences as a hyperintense signal in the BA (Figure 2(b) and (d)) and as a blooming artifact (susceptibility vessel sign) in SWI images (Figure 2(e)).

Three-dimensional rotational digital subtraction angiography (3D-R-DSA) confirmed total BA occlusion. EVT was successfully performed (Thrombolysis in cerebral infarction scale TICI 3)
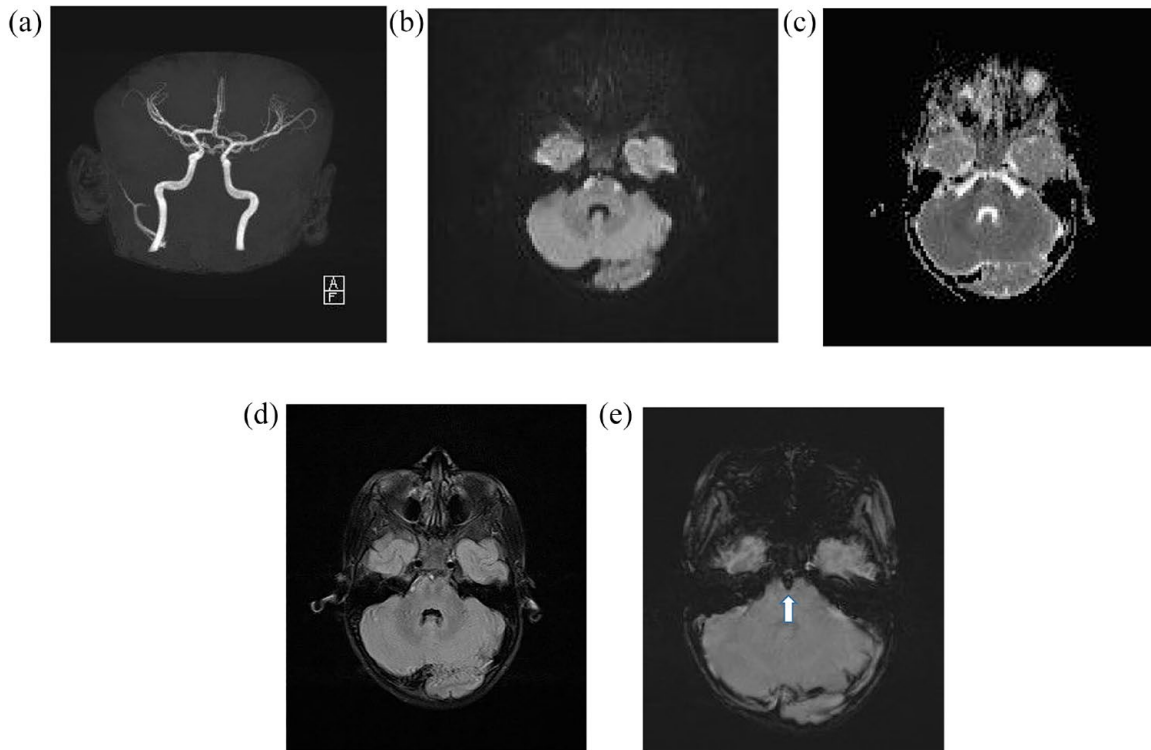
Figure 2. Patient 2, MRI on admission: time-of-flight MR-angiography (a), DWI (b), ADC (c), FLAIR (d), and SWI (e) images: basilar artery occlusion, acute bilateral pontomesencephalic infarctions in DWI/ADC but not in FLAIR images. Thrombus is visualized in FLAIR sequences as a hyperintense signal in the basilar artery and as a blooming artifact (arrow) in SWI images.

using a 5F femoral access, an aspiration catheter as first-line approach, and an Embotrap III® stent retriever. Small fragments of a thrombus were retrieved after three attempts within the stent retriever after injection of 5 mg alteplase into the proximal end of the thrombus. Door-to-groin time was 3.5 h; recanalization and reappearance of pontine branches were achieved 6.5 h after onset of symptoms (Figure 3). After EVT and a final rotational scan to exclude a periprocedural hematoma, ASA 100 mg IV (intravenous) was given.

Lumbar puncture had been performed directly before MRI and CSF showed a lymphomonocytic pleocytosis; protein was normal. IgG and IgM AI for *B. burgdorferi* were elevated (Table 1). Polymerase chain reaction (PCR) for HSV, VZV, and *L. monocytogenes* was negative. Further laboratory examinations including Factor V Leiden mutation were normal. Transthoracal echocardiography and electrocardiogram were normal. Living in northern Germany, frequent playing in the forest and multiple tick bites without erythema were reported.

Parallel to EVT, antibiotic treatment with cefotaxime, acyclovir, and ampicillin was started, and dexamethasone 4 mg IV was administered. Cefotaxime (3×1.3 g IV) continued for 16 days, dexamethasone was stopped on day 3, prednisolone 30 mg p.o. was given for 12 days, and then tapered over a period of 4 weeks.

A follow-up MRI 7 h after EVT showed regression of pontomesencephalic DWI/ADC lesions on the left but progression on the right side. Subtle bilateral pontomesencephalic hyperintensities in FLAIR maps were visible. Subtotal BA reocclusion and stenosis of the left posterior cerebral artery (PCA; P1 segment) were detected on TOF-MR-angiography (MRA) (Figure 4). TCCS revealed a highly reduced and turbulent, but orthograde flow in the BA; a high resistance index in both vertebral arteries (extra- and intracranial); and an elevated flow velocity in the PCA (P1 segment). After interdisciplinary discussion of treating neurologist, pediatrician, interventional neuroradiologist, and parents, the decision was made against a second attempt of EVT. Instead,
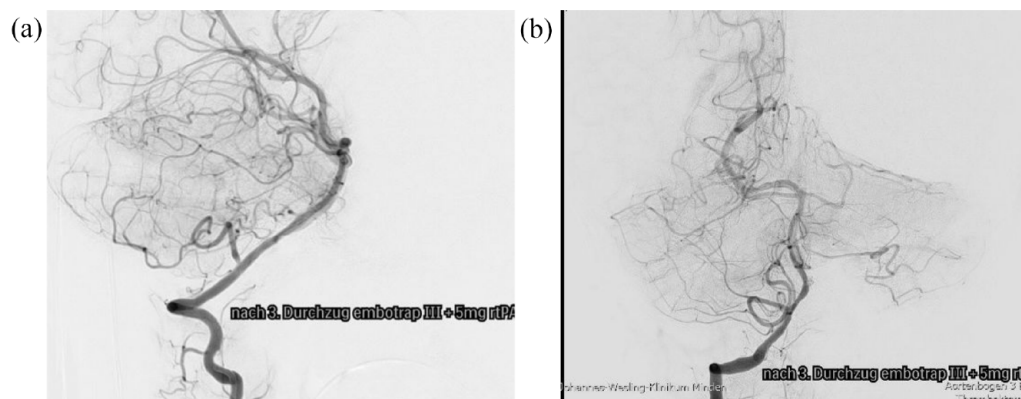
Figure 3. Patient 2: EVT with recanalization of the basilar artery (TICI 3) 6.5 h after onset of symptoms. Angiography in lateral (a) and posterior–anterior (b) view.

Figure 4. Patient 2: time-of-flight MR-angiography: subtotal basilar artery reocclusion. The vertebral arteries and the top of the basilary are still visible (in contrast to Figure 2(a)).

an off-label therapy with IV tirofiban (Aggrastat® 0.4 µg/kg/min for 30 min, then 0.1 µg/kg/min for 72 h) was started.

The patient was extubated 6 h after the second MRI and was able to communicate and move all extremities. He complained of double vision, and showed a left ptosis and a left side ataxia. After using a walking frame for children, he was able to walk unaided on day 5; on day 10, the pedNIHSS was 0. A third MRI on day 8 revealed stable bilateral pontomesencephalic hyperintensities, very subtle on FLAIR images, reduced flow in the proximal BA, and stenosis of the left P1 segment.

Extracranial duplex sonography and TCCS results gradually improved showing a normalized flow profile in both vertebral arteries and a reduced flow in the BA. Signs of stenosis in the PCA and flow abnormalities in the BA completely resolved on day 14; the patient was asymptomatic. He was discharged with a medication of ASA 50 mg/day and prednisolone 15 mg/day. Steroids had been tapered as scheduled in week 5, ASA 50 mg/day continued. On follow-up visits 6 weeks and 5 months after stroke, the patient was asymptomatic (pedNIHSS 0, mRS 0, Barthel 100); extracranial duplex sonography and TCCS were normal. The patient lives with his family and can carry out all normal activities.

Review of the literature

The systematic review of the online database MEDLINE/PubMed yielded 11 articles. Two articles not matching exactly the area of interest were excluded. The remaining articles contained 12 original case reports of LNB-associated childhood AIS.[2,8–15] Hyperacute reperfusion therapies are not reported. The main characteristics of the published cases are summarized in Table 2.

Discussion

We report two children with acute posterior circulation stroke associated with European LNB who underwent hyperacute stroke treatment. Both patients live in an endemic area (northern Germany) for *B. burgdorferi* sensu lato with a high prevalence of *B. garinii* in tick nymphs,[16] the latter being the predominant *B. burgdorferi* genotype in children with LNB.[17] They experienced

Table 2. Stroke characteristics and treatment of published case reports of LNB-associated childhood AIS in the last 20 years.

Author(s)	Sex Age	Stroke symptoms	Vascular pathology	Antibiotic treatment	Secondary prophylaxis	Steroid treatment	Outcome
Klingebiel et al.[8]	Female 6 years	Hemiparesis	ICA, ACA stenosis MCA branch occlusion	Ceftriaxone 100 mg/kg/day, 14 days pseudo-cholelithiasis, then cefotaxime 7 days	None	None	Hemiparesis concentration deficit after 6 months asymptomatic
Cox et al.[9]	Female 12 years	Hemiparesis Facial paresis	ACA, MCA stenosis	Ceftriaxone 2 g/day 30 days	ASA 38 mg/day	None	No follow-up reported
Rénard et al.[10]	Male 11 years	Hemiparesis Ataxia Aphasia	BA, MCA irregularity	Ceftriaxone for 21 days	None	None	No follow-up reported
Lebas et al.[11]	Male 8 years	Somnolence Hemiparesis	BA irregularity enhancement of vessel wall	Ceftriaxone for 28 days	Oral antiplatelet	Methylprednisolone 30 mg/kg pulses 3 days	Asymptomatic
Kohns et al.[12]	Female 5 years	Hemiparesis Vertigo	MCA stenosis	Ceftriaxone 35 mg/kg/day 14 days	ASA 3 mg/kg/day	Methylprednisolone 20 mg/kg pulses 3 days	Asymptomatic
Kurian et al.[13]	Male 12 years	Facial paresis Hemiparesis	BA, MCA, ACA stenosis, enhancement of vessel wall	Ceftriaxone for 4 weeks	ASA 3 mg/kg/day 1 year	Prednisone 2 mg/kg/day 4 weeks	Asymptomatic
Allen and Jungbluth[14]	Male 15 years	Leg weakness Ataxia Facial palsy	Stenosis posterior circulation	Ceftriaxone for 21 days	None	None	Mild hemiplegia, abducens, and facial nerve palsy
Wittwer et al.[15]	Female 5 years	Wallenberg syndrome	None observed	Ceftriaxone for 6 weeks	None	None	Improvement
Monteventi et al.[2]	Male 12 years	Confusion Hemiparesis	BA, PCA, MCA, ACA stenosis, enhancement of vessel wall	Ceftriaxone 2 g/day 28 days	ASA 100 mg/day 6 months	Prednisone 2 mg/kg/day 28 days	Asymptomatic
Monteventi et al.[2]	Male 8 years	Wallenberg syndrome	None observed	Ceftriaxone 2 g/day 21 days	ASA 100 mg/day 6 months	None	No follow-up reported
Monteventi et al.[2]	Male 9 years	Paresthesia Tremor	BA, VA stenosis	Ceftriaxone 2 g/day 14 days	ASA 150 mg/day 8 months	Prednisone 50 mg/day 5 days tapered	Asymptomatic
Monteventi et al.[2]	Male 13 years	Wallenberg syndrome	VA stenosis	Ceftriaxone 2 g/day 14 days	ASA 100 mg/day	None	Sensory hemisyndrome

ACA, anterior cerebral artery; AIS, arterial ischemic stroke; ASA, acetyl-salicylic acid; BA, basilar artery; ICA, internal carotid artery; LNB, Lyme neuroborreliosis; MCA, middle cerebral artery; PCA, posterior cerebral artery; VA, vertebral artery.

headache and fatigue; patient 1 reported myalgia in the weeks before admission. These otherwise unexplained symptoms, the lymphocytic CSF pleocytosis, and elevated AI for *B. burgdorferi* (Table 1) led to the diagnosis of definite LNB according to the current guidelines.[3,4] Although CNS manifestations can occur in early and late LNB, the presence of symptoms for less than 6 months and the elevated CSF CXCL 13 (Chemokine Ligand 13) confirm the diagnosis of an early stage of LNB. Extensive diagnostic workup excluded other reasons for AIS; thus, childhood AIS due to LNB-associated FCA was the final diagnosis.

Antibiotic treatment

Both children were treated with the third-generation cephalosporine cefotaxime as soon as the diagnosis of LNB was suspected. They presented as early LNB with LNB-associated stroke and received 14 (patient 1) and 16 (patient 2) days of IV antibiotic treatment. Duration of treatment ranged from 14 days to 6 weeks in the literature. Current guidelines[3,4] recommend an early antibiotic treatment with an IV third-generation cephalosporine or IV penicillin G for childhood LNB and a treatment duration between 14 days (early LNB) and 21 days (late LNB). Oral doxycycline is an alternative for children over the age of 8 years. All cases (12/12) found in the literature were treated with an IV third-generation cephalosporine, mostly ceftriaxone, none with doxycycline.

Acute thrombolytic and endovascular treatment

In both patients, the diagnosis of ischemic stroke was based on MRI in the hyperacute phase showing the specific combination of DWI hyperintensity/ADC restriction without signal abnormalities in FLAIR and SWI. As frequently observed in hyperacute stroke, the DWI/ADC restrictions do not completely represent the clinical picture. Patient 1 received IVT within the time window and dosage approved for adult stroke patients. The diagnosis of LNB was not suspected at the time of IVT; CSF examination (Table 1) was done on day 2. Side effects of IVT were not observed. A clinical deterioration of 2 points in pedNIHSS can be attributed to stroke progression confirmed on follow-up MRI, although a febrile episode may as well have contributed to the clinical deterioration. Follow-up showed an incomplete recovery with persisting hemiparesis with

significant impairment of hand function resulting in a pedNIHSS of 2, mRS 2, and Barthel Index 95. There are no randomized, controlled trials regarding IVT in acute childhood stroke; the TIPS Thrombolysis in pediatric stroke (TIPS) trial[18] had to be stopped because of low recruitment. In the absence of clinical trial data, expert opinion supports the use of the adult dosage of 0.9 mg/kg for IVT.[19] Developmental differences in plasminogen levels suggest that equivalent dosages might even be higher in children than in adults; thus, applying the regular dose of alteplase might err on the safe rather than the dangerous side with regard to hemorrhage risk.[18] Recent retrospective data illustrate a very low risk of symptomatic intracranial hemorrhage (sICH) sICH following IVT in childhood AIS.[20,21]

Patient 2 received acute EVT, intra-arterial thrombolysis, and an intensified antiplatelet therapy with IV tirofiban continued for 3 days after early and partial BA reocclusion. LNB was considered the most likely diagnosis at the time of EVT; antibiotic and anti-inflammatory treatments were started simultaneously. There were no side effects of EVT, alteplase injection into the thrombus, and tirofiban therapy. Follow-up examination showed a complete recovery in spite of imaging proof of subtle changes on FLAIR images corresponding to the initial pontine DWI lesions.

EVT was considered safe and effective in a childhood subgroup analysis of the Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands (MR CLEAN) study[22] and in a recent case-based review.[23] In the retrospective international multicenter Save ChildS Study,[24] the safety of EVT in children was comparable to EVT results in clinical trials for adults. No complications were reported, including six children with FCA. In a single-center cohort in the United States,[1] intracranial arteriopathy was found in 37% of cases; none of them received IVT or EVT. In a case series of children who underwent thrombolytic treatment including a review of the literature,[25] stroke etiology included cardiogenic and paradoxical embolism, spontaneous artery dissection, and stroke of unknown etiology. Children with infectious AIS are not reported. Correspondingly, hyperacute treatment (IVT or EVT) was not reported in the 12 cases with LNB-associated childhood AIS found in the literature. A major factor affecting eligibility for hyperacute stroke therapy in children is the presence of

medical contraindications, accounting for up to one-third of non-administered IVTs and EVTs.[1] Inflammatory FCA in theory may increase the risk of bleeding complications during EVT.[26] Secondary vasculitis is mentioned among the exclusion criteria for IVT in the TIPS study.[18] The previous AHA scientific statement[27] on treatment of childhood AIS classified LNB as an infectious (thus secondary) vasculitis. The current American Heart Association (AHA) scientific statement[19] introduces the more descriptive term of FCA-i (focal cerebral arteriopathy inflammation type), denoting an infectious or parainfectious process leading to localized vessel inflammation and secondary thrombus formation and stroke.[28] However, it does not mention LNB in this context. In addition to inflammation of the vessel wall, thrombosis of the affected vessels has been discussed in LNB.[2] This was observed in patient 2, as thrombotic BA occlusion led to a hyperdense BA sign in CCT and to a blooming artifact (susceptibility vessel sign)[29] on SWI images. The rapid clinical improvement after successful EVT with TICI 3 recanalization and reappearance of pontine branches would not have been observed had vessel inflammation been the only cause of BA occlusion.

In LNB, both in children and in adults, there is no clear semantic differentiation between infectious cerebral vasculitis and FCA-i.[13] In contrast to childhood stroke, in adults there is high-quality evidence (double-blind, placebo-controlled studies) for IVT, EVT, and the combination of both. Although acute reperfusion therapies have not been reported in LNB-associated stroke in adults,[5] both IVT and EVT can be administered following current guidelines providing clear recommendations that are mostly independent of the putative stroke etiology in the acute phase.

Platelet inhibition

Both patients reported in the present study received an early secondary stroke prophylaxis with ASA, ongoing until follow-up. Before administration of ASA, ICH as a potential complication of IVT and EVT with local alteplase injection was excluded. In the literature, ASA was given in 8/12 of reported cases with LNB-associated childhood stroke. Bleeding complications are not mentioned in the LNB cases reported in the literature. Platelet inhibition with ASA is recommended in childhood AIS, with a maintenance for 2 years to cover the period of most likely stroke recurrence.[19] This

recommendation should generally be followed in LNB-associated AIS, as childhood AIS due to intracranial FCA is reported to have a high risk of recurrence.[30] In addition, extracranial duplex sonography and TCCS should be performed at outpatient follow-up visits to detect recurrence of FCA or residual long-term vascular pathology that may warrant a longer duration of platelet inhibition.

In patient 2, partial BA reocclusion occurred in spite of prompt platelet inhibition with ASA, and antibiotic and anti-inflammatory treatments. Vessel patency was restored following platelet inhibitory therapy with the Glycoprotein IIb/IIIa antagonist tirofiban. This treatment attempt for progressive thrombotic stroke has been described in non-controlled case series in adults[31] and appeared to be safe in combination with EVT in a multicenter cohort study.[32] A recent meta-analysis suggests that tirofiban does not increase the risk of sICH in adult stroke patients treated with EVT.[33] Treatment of progressive thrombotic vessel occlusion with tirofiban in childhood AIS has not been reported in the literature and is not mentioned in current guidelines. Currently, there is no approved indication for tirofiban in stroke treatment. This treatment should be administered only after careful interdisciplinary consultation and discussion of potential complications such as bleeding and thrombocytopenia with the patient's legal representatives. In the present case, the rationale was to rapidly reverse and prevent further rethrombosis triggered by the inflamed vessel wall, as thrombectomy alone does not resolve the underlying cause of thrombus formation in inflammatory or infectious FCA.

Anti-inflammatory treatment

The two cases of childhood vertebrobasilar stroke due to early LNB described in the present report exhibit features of LNB-associated infectious and inflammatory FCA as described in the literature. Patient 1 showed a minimum irregularity in the diameter of the proximal BA. However, the localization of infarctions in the left and later right medulla oblongata is suggestive of local vascular pathology in medullary branches of the BA. Patient 2 showed total BA occlusion and later reocclusion and stenosis of the left PCA (P1 segment); FCA of the BA, and PCA is supported by MR-angiography and TCCS. 9/12 of reported cases showed involvement of the posterior circulation, a feature

discussed as a predominantly basal leptomeningeal obliterative inflammatory vasculopathy (endarteritis).[2] All case reports published in the last 20 years agree on the inflammatory, vasculitic, or arteritic origin[34] of FCA leading to stroke observed in LNB. A closer look reveals considerable uncertainty in the concept of LNB-associated vasculitis. Although perivascular inflammatory infiltrates without vessel wall necrosis have been described in histopathological specimens,[35] and focal MRI enhancement of the vessel wall as a controversial sign of vasculitis was observed in 3/12 of reported cases,[2,11,15] these observations do not fulfill strict criteria of vasculitis. In a larger review of 88 LNB-associated strokes in adults, only 4 patients are reported to have biopsy-proven cerebral vasculitis, without histopathological details.[5] As biopsy with demonstration of fibrinoid necrosis or inflammatory infiltrate of all layers of the vessel wall is the diagnostic gold standard of cerebral vasculitis,[36] a general classification of LNB-associated stroke as cerebral vasculitis is speculative. Further research on the pathophysiology of LNB-associated stroke is needed. The present cases show features of FCA but not the typically multifocal, beaded signs of vasculitic arteriopathy seen in most forms of cerebral vasculitis. The LNB-associated strokes in the presented cases can be attributed to a treatable FCA of infectious and inflammatory origin (FCA-i), and thrombotic vessel occlusion. This eventually thrombotic pathogenesis of stroke in LNB is in line with the original microscopical findings of Miklossy, who described 'complete obstruction of some leptomeningeal vessels by organized thrombus, leading to small medullary infarcts. Only in a few of (the examined posterior circulation vessels) was partial lymphocytic infiltration of the vessel wall also seen'.[35]

As a consequence of this uncertainty in the pathogenetic classification of LNB-associated stroke and since steroids could impair the immune response, the use of steroids is controversial. Suppression of the immune response in infectious diseases may both prevent tissue damage and facilitate spreading of the infectious agent, depending strongly on the specific mechanisms of disease. Thus, in the absence of clinical trial data, the use of steroids in LNB based on speculative mechanisms of disease cannot be generally recommended. If steroid treatment is initiated, it should be tapered rapidly and long-term steroid medication should be avoided. This is reflected in the literature, as steroids in addition to antibiotic therapy were given in 5/12 of reported cases only. The European Federation of Neurological Societies (EFNS) guidelines do not discuss anti-inflammatory treatment for LNB-associated stroke; for LNB, in general, it does not support the use of steroids because of the lack of sufficient data.[4] The current German guidelines on LNB discuss steroids for LNB-associated vasculitis as class IV evidence without a clear recommendation.[3]

Limitations

The present study has clear limitations as only two cases are presented. Comparison to the published literature is limited as most case reports were published in a period of changing awareness of acute childhood AIS and of hyperacute treatment possibilities.

Conclusion

On the level of case-based considerations, LNB-associated FCA should not be considered a medical contraindication for reperfusion therapies such as IVT and EVT in childhood AIS. As the etiology of AIS is usually unknown in the hyperacute phase, the decision should rather be in favor of IVT and EVT, even if LNB is suspected on admission. Early antibiotic treatment is indicated. An anti-inflammatory treatment attempt with steroids is discussed controversially in inflammatory FCA due to LNB. Given the high risk of rethrombosis after successful reperfusion therapy of inflammatory FCA, intensified antiplatelet regimes may be considered and early secondary prophylaxis with ASA is recommended.

Consent for publication

Written informed consent for publication was obtained from both patients' legal representatives. The need for further institutional approval was waived in accordance with German ethical regulations on case reports.

Author contributions

Joerg Philipps: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Bernhard Erdlenbruch: Investigation; Methodology; Supervision; Writing – review & editing.

Michael Kuschnerow: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Sunil Jagoda: Investigation; Methodology; Writing – original draft; Writing – review & editing.

Blerta Salihaj: Investigation; Writing – original draft; Writing – review & editing.

Jörg Glahn: Investigation; Supervision; Writing – review & editing.

Peter Dieter Schellinger: Conceptualization; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

ORCID iD

Joerg Philipps https://orcid.org/0000-0003-3327-3550

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Hutchinson ML, Beslow LA, Shih EK, *et al.* Endovascular and thrombolytic treatment eligibility in childhood arterial ischemic stroke. *Eur J Paediatr Neurol* 2021; 34: 99–104.

2. Monteventi O, Steinlin M, Regenyi M, *et al.* Pediatric stroke related to Lyme neuroborreliosis: data from the Swiss NeuroPaediatric Stroke Registry and literature review. *Eur J Paediatr Neurol* 2018; 22: 113–121.

3. Rauer S, Kastenbauer S, Hofmann H, *et al.* Guidelines for diagnosis and treatment in neurology – Lyme neuroborreliosis. *Ger Med Sci* 2020; 18: Doc03.

4. Mygland A, Ljostad U, Fingerle V, *et al.* EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol* 2010; 17: 8–16, e1–e4.

5. Garkowski A, Zajkowska J, Zajkowska A, *et al.* Cerebrovascular manifestations of Lyme neuroborreliosis – a systematic review of published cases. *Front Neurol* 2017; 8: 146.

6. Gagnier JJ, Kienle G, Altman DG, *et al.* The CARE guidelines: consensus-based clinical case reporting guideline development. *Glob Adv Health Med* 2013; 2: 38–43.

7. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.

8. Klingebiel R, Benndorf G, Schmitt M, *et al.* Large cerebral vessel occlusive disease in Lyme neuroborreliosis. *Neuropediatrics* 2002; 33: 37–40.

9. Cox MG, Wolfs TF, Lo TH, *et al.* Neuroborreliosis causing focal cerebral arteriopathy in a child. *Neuropediatrics* 2005; 36: 104–107.

10. Rénard C, Marignier S, Gillet Y, *et al.* [Acute hemiparesis revealing a neuroborreliosis in a child]. *Arch Pediatr* 2008; 15: 41–44.

11. Lebas A, Toulgoat F, Saliou G, *et al.* Stroke due to Lyme neuroborreliosis: changes in vessel wall contrast enhancement. *J Neuroimaging* 2012; 22: 210–212.

12. Kohns M, Karenfort M, Schaper J, *et al.* Transient ischaemic attack in a 5-year-old girl due to focal vasculitis in neuroborreliosis. *Cerebrovasc Dis* 2013; 35: 184–185.

13. Kurian M, Pereira VM, Vargas MI, *et al.* Stroke-like phenomena revealing multifocal cerebral vasculitis in pediatric Lyme neuroborreliosis. *J Child Neurol* 2015; 30: 1226–1229.

14. Allen NM and Jungbluth H. Lyme neuroborreliosis: a potentially preventable cause of stroke. *J Pediatr* 2016; 170: 334–334.e1.

15. Wittwer B, Pelletier S, Ducrocq X, *et al.* Cerebrovascular events in Lyme neuroborreliosis. *J Stroke Cerebrovasc Dis* 2015; 24: 1671–1678.

16. Estrada-Pena A, Cutler S, Potkonjak A, *et al.* An updated meta-analysis of the distribution and prevalence of Borrelia burgdorferi s.l. in ticks in Europe. *Int J Health Geogr* 2018; 17: 41.

17. Barstad B, Quarsten H, Tveitnes D, *et al.* Direct molecular detection and genotyping of Borrelia burgdorferi Sensu Lato in cerebrospinal fluid of children with Lyme neuroborreliosis. *J Clin Microbiol* 2018; 56: e01868-17.

18. Rivkin MJ, deVeber G, Ichord RN, *et al.* Thrombolysis in pediatric stroke study. *Stroke* 2015; 46: 880–885.

19. Ferriero DM, Fullerton HJ, Bernard TJ, *et al.* Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. *Stroke* 2019; 50: e51–e96.

20. Amlie-Lefond C, Shaw DWW, Cooper A, *et al.* Risk of intracranial hemorrhage following intravenous tPA (tissue-type plasminogen activator) for acute stroke is low in children. *Stroke* 2020; 51: 542–548.

21. Olivieri M, Sorg AL, Weinberger R, *et al.* Recanalization strategies in childhood stroke in Germany. *Sci Rep* 2021; 11: 13314.

22. van Es ACGM, Hunfeld MAW, van den Wijngaard I, *et al.* Endovascular treatment for acute ischemic stroke in children: experience from the MR CLEAN Registry. *Stroke* 2021; 52: 781–788.

23. Sun LR, Harrar D, Drocton G, *et al.* Mechanical thrombectomy for acute ischemic stroke: considerations in children. *Stroke* 2020; 51: 3174–3181.

24. Sporns PB, Kemmling A, Hanning U, *et al.* Thrombectomy in childhood stroke. *J Am Heart Assoc* 2019; 8: e011335.

25. Arnold M, Steinlin M, Baumann A, *et al.* Thrombolysis in childhood stroke: report of 2 cases and review of the literature. *Stroke* 2009; 40: 801–807.

26. Bigi S, Dulcey A, Gralla J, *et al.* Feasibility, safety, and outcome of recanalization treatment in childhood stroke. *Ann Neurol* 2018; 83: 1125–1132.

27. Roach ES, Golomb MR, Adams R, *et al.* Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke* 2008; 39: 2644–2691.

28. Gerstl L, Bonfert MV, Heinen F, *et al.* Childhood arterial ischaemic stroke: clinical presentation, risk factors and management. *Hamostaseologie* 2020; 40: 165–173.

29. Naggara O, Raymond J, Domingo Ayllon M, *et al.* T2★ 'susceptibility vessel sign' demonstrates clot location and length in acute ischemic stroke. *PLoS ONE* 2013; 8: e76727.

30. Bohmer M, Niederstadt T, Heindel W, *et al.* Impact of childhood arterial ischemic stroke standardized classification and diagnostic evaluation classification on further course of arteriopathy and recurrence of childhood stroke. *Stroke*. Epub ahead of print 7 December 2018. DOI: 10.1161/STROKEAHA.118.023060.

31. Mangiafico S, Cellerini M, Nencini P, *et al.* Intravenous tirofiban with intra-arterial urokinase and mechanical thrombolysis in stroke: preliminary experience in 11 cases. *Stroke* 2005; 36: 2154–2158.

32. Zhao L, Jian Y, Li T, *et al.* The safety and efficiency of tirofiban in acute ischemic stroke patients treated with mechanical thrombectomy: a multicenter retrospective cohort study. *Biochem Res Int* 2020; 2020: 5656173.

33. Fu Z, Xu C, Liu X, *et al.* Safety and efficacy of tirofiban in acute ischemic stroke patients receiving endovascular treatment: a meta-analysis. *Cerebrovasc Dis* 2020; 49: 442–450.

34. Parikh NS, Merkler AE and Iadecola C. Inflammation, autoimmunity, infection, and stroke: epidemiology and lessons from therapeutic intervention. *Stroke* 2020; 51: 711–718.

35. Miklossy J, Kuntzer T, Bogousslavsky J, *et al.* Meningovascular form of neuroborreliosis: similarities between neuropathological findings in a case of Lyme disease and those occurring in tertiary neurosyphilis. *Acta Neuropathol* 1990; 80: 568–572.

36. Berlit P. Diagnosis and treatment of cerebral vasculitis. *Ther Adv Neurol Disord* 2010; 3: 29–42.