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Authors: Monteventi O, Steinlin M, Regényi M, Roulet-Perez E, Weber P, Fluss J

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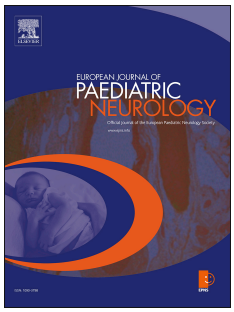

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Pediatric stroke related to Lyme Neuroborreliosis:

Data from the Swiss NeuroPaediatric Stroke Registry and literature review

O. Monteventi[a], M. Steinlin[b], M. Regenyi[b], E. Roulet-Perez[c], P. Weber[d],and J. Fluss[a]

[a]Pediatric Neurology Unit, Pediatrics Subspecialities Service, Geneva Children's Hospital, Switzerland

[b]Department of Neuropediatrics, Development and Rehabilitation, University Children's Hospital, Inselspital Bern, Switzerland

[c] Pediatric Neurology and Neurorehabilitation Unit, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

[d] University Children's Hospital Basel, Division of Neuropediatrics and Developmental Medicine, Basel, Switzerland

Corresponding author:

Dr. Joel Fluss, Pediatric Neurology Unit, Geneva Children's Hospital, 6 rue Willy-Donzé, 1211 Genève 4, Switzerland, email: joel.fluss@hcuge.ch

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INTRODUCTION

Recent data suggest that infection either directly or indirectly plays a major role in the pathogenesis of childhood AIS. Reports from the VIPS study (Vascular Effects of Infection in Pediatric Stroke) have emphasised in particular the role of minor clinical infection that could trigger endothelial injury leading to arterial wall damage and remodelling but the mechanisms remain largely unknown. [1,2] Along with these results, pediatric stroke literature in the past two decades has stressed the high prevalence of focal cerebral arteriopathy (FCA) in childhood ischemic stroke, whose infectious/inflammatory pathogenesis is strongly suspected. However, apart from the so-called post-varicella angiopathy, where varicella-zoster virus (VZV) infection can often be demonstrated in the CSF through PCR or intrathecal antibodies production, infectious agents are rarely identified. Some authors tend to hypothesize that infection, usually viral, in this context acts only as an inflammatory trigger in a susceptible child, possibly after mild trauma or in the presence of an underlying genetic susceptibility.[3,4] Circumstances where a direct infectious cerebral vasculitis is demonstrated are rare, but well known in the setting, for instance, of bacterial meningitis, where the associated cerebral vasculitis is thought to arise by contiguity with the inflamed cerebrospinal fluid (CSF) or via haematogenous spread.[5]

There has been a growing interest in the past decade on the role of tick-borne spirochetes belonging to the *Borrelia burgdorferi (B. burgdorferi) sensu lato group* in the aetiology of various neurological manifestations, especially in endemic regions, such as the major part of the northern hemisphere, including Switzerland. Lyme disease, the medical condition associated with symptomatic *B. burgdorferi* infection, has been clinically well characterised.[6,7] After being responsible in the initial stage of the disease for systemic and dermatological symptoms, various early and late neurological manifestations can occur, designated under the umbrella of Lyme neuroborreliosis (LNB).[8,9] It must be stressed that

the clinical expression of LNB varies between the European and American forms, in relation to different genospecies (mostly *B. burgdorferi sensu stricto* in the American LNB and *B. garinii* in Europe).[10,11] Cerebrovascular manifestations, reflecting meningovascular involvement in both early and late LNB, have been essentially documented in European adults and appear in recent reports to represent a potential cause of stroke in children and young adults. [12-14]

In this study, we sought as a primary objective to retrospectively identify all children who suffered from a stroke that can be attributed with confidence to Lyme disease, using the Swiss NeuroPaediatric Stroke Registry (SNPSR) as a database. The secondary objectives were to delineate clinical, biological and radiological characteristics that can help the clinician in early management. This was supplemented by a literature review of similar cases.

METHODS & PATIENTS

SNPSR case analysis

A retrospective review of the Swiss NeuroPaediatric Stroke Registry (SNPSR, a nationwide registry that was initiated in Switzerland in January 2000), was conducted. The SNPSR has been approved by the local ethics committee of the University Hospital of Berne, Switzerland, and by the Swiss authority responsible for public health.

This Registry comprises relevant clinical and radiological data on every single case of childhood ischemic stroke across Switzerland through regular recalls to hospital-based pediatric neurologists. The available data on 229 children diagnosed with arterial ischemic stroke or vasculitis and prospectively enrolled from 2000 to 2015, excluding neonatal arterial ischemic stroke and cerebral sinus venous thrombosis, were reviewed by two of the authors (O.M. and J.F.). Among these 229 children, 4 were suspected to have LNB-related stroke/vasculitis according to reported clinical information (past history of Lyme disease, tick

bites), indirect biological suggestive feature (predominant lymphocytic meningitis), and/or serological testing in favour of Lyme disease. Following this first step, the clinical and radiological files of these four cases were carefully examined. Cases were included in the study only if the diagnosis of LNB-related cerebrovascular events was supported by at least two among three conditions following modified guidelines of the European Federation of Neurological Societies (EFNS): i) stroke and/or vasculitis without other identified causes , ii) CSF pleocytosis, iii) *B. burgdorferi*-specific antibodies intrathecal production.[8] If necessary, complementary data were obtained by contacting the referring physician or by reviewing the patient's full hospital chart. Previous history of erythema migrans (EM) or tick bites was also recorded. The prevalence of LNB-related pediatric stroke in the studied period was calculated.

Literature review

A thorough literature review within the same time frame (2000-2015) was performed using the keywords "Lyme", "neuroborreliosis", "stroke", "vasculitis", "children", and "childhood" in various combinations on common search engines in medical sciences: PubMed, Ovid-Medline, Science-Direct, Google Scholar and through cross-referencing. We included relevant case reports, as long as the diagnosis of LNB-related stroke was supported by substantial clinical and biological evidence.

RESULTS

LNB-related stroke from the SNPSR

In the study period of 16 years (2000-2015), 229 children were registered in the SNPSR with acute ischemic stroke in Switzerland. Only 4 out of these 229 children could be attributed with confidence to LNB, giving a prevalence of 1.7% of LNB-related stroke. These four cases

are presented in detail in the section below. One child (case 1) had already been reported in a previous publication by one of the authors (JF).[15]

Case 1

A 12-year-old boy presented with an acute left hemiplegia, dysarthria, severe headache, nausea, vomiting, balance disturbance and irritability. A history of tick bites without cutaneous manifestations was reported the preceding summer, 6 months earlier. He has been complaining in the past 4 months of intermittent unexplained nausea and vomiting that have became daily in the past 10 days. Four days prior to admission, he started to report significant constant headache. On examination, the patient was disoriented anddrowsy, and showed a mild left hemiplegia. Imaging studies demonstrated multiple vascular stenoses and irregularities suggestive of multifocal vasculitis involving predominantly the basilar artery, where a concentric ring enhancement was noted (Figures 1a and 1b). Meningeal enhancement was not seen. Brain parenchymal infarction was not observed but scattered punctuate white matter lesions on both hemispheres were identified. Cerebrospinal fluid revealed a pleocytosis with mixed cellular distribution (1152 leucocytes/ml: 61% neutrophils, 39% lymphocytes), extremely high protein content (4.5 g/l), and low glucose (0.7 mmol/l). Extensive infectious and immunological work-up for infectious and non-infectious vasculitis was performed. Cerebral spinal fluid cultures were sterile. Ziehl-Nielsen stain was negative. Broad-range bacterial PCR for common causes of bacterial meningitis, as well as PCR for neurotropic viruses and for *B.burgdorferi* were all negative. Lyme infection was rapidly suspected and demonstrated by positive IgG titers on an initial enzyme-linked immunosorbent assay (ELISA): 3.57 (N 0.75-1), further confirmed by a Western blot (>10 visible bands). An additional search for anti-VLSE (Variable Like protein Sequence Expressed) IgG was also highly positive: 585 kAU/l (N<15). Evidence of intrathecal specific anti-*B. burgdoferi* IgG

production was found with an antibody index (AI) of 4.69 (N<2). The child was started on IV Ceftriaxone with 2 g/day for 4 weeks along with oral Aspirin 100 mg for 6 months. Oral Prednisone at a dose of 2 mg/kg/day was given for a total of 4 weeks based on the inflammatory aspect of the cerebral vessels. The patient exhibited a rapid recovery. Radiological follow-up at one year revealed complete normalisation of the cerebral vessels. Clinical follow-up showed no residual neurological deficit and the total disappearance of gastrointestinal complaints.

Case 2

A previously healthy 8-year-old boy was admitted to the emergency department for vertigo associated with acute vomiting and headache. Neurological status was suggestive of a Wallenberg syndrome. No history of tick bite or skin rash was recalled. MRI at day 1 revealed a recent laterobulbar infarct over the right posterior inferior cerebellar artery (PICA) territory, without any demonstrated vascular abnormality (Figure 2). Raising the possibility of a cerebral vasculitis, CSF analysis was performed and revealed a predominant lymphocytic pleocytosis (leucocytes 149/ml: lymphocytes 88.5%, plasmocytes 5.5%), elevated protein content (1.2 g/l) and normal glucose (2.5 mmol/l). The PCR in the CSF for *HSV-1*, *HSV-2*, *Listeria monocytogenes* and *B. burgdorferi* was negative. Lyme neuroborreliosis was suspected based on the detection by enzyme-linked fluorescent assay (ELFA) of *B. burgdorferi* IgG antibodies in the serum and in the CSF, respectively 3.96 (N: 0.75-1) and 5.35 (N<0.3), which was followed by a Western blot confirming the findings in both the serum and in the CSF (> 10 visible bands). The intrathecal synthesis AI was 5.8 (N<2). Both CSF and blood culture remained sterile. In addition, autoimmunity work-up was negative. The child was started on IV Ceftriaxone (2 g/day) for 21 days and Aspirin (100 mg/day). Clinical improvement was rapidly observed, and at 3-month follow-up, no recurrent stroke had

occurred, nor did the boy have any residual symptoms. Radiological follow-up data were not available for this patient (cf. *Table 2*). Further thrombophilia work-up revealed a heterozygous prothrombin mutation.

Case 3

A healthy 9-year-old boy was admitted to the emergency department for tiredness, pain, numbness, and low-grade fever for the last couple of days. No recent history of tick bite or skin rash was reported. He had however been treated with IV Amoxicillin two years earlier for a documented stage 1 Lyme borreliosis with EM.

Clinical, neurological and overall examinations were normal at first admission, and he was discharged on the same day after a biological work-up for Lyme disease. Symptoms spontaneously resolved within 3 days, but positive antibodies titers against *B. burgdorferi* (both IgG and IgM) in the serum on ELISA and immunoblot (IB) were observed. Due to normal neurological status, the assumption that the antibodies' persistence was related to the earlier infection, and spontaneous symptoms regression, a flu-like illness was presumed and no specific treatment was administered. Two months later, the child was re-admitted complaining of vomiting and vertigo. Clinical and neurological examinations were normal except for a subtle bilateral tremor. Following this finding, brain MRI was performed and showed two fresh right cerebellar micro-infarcts in the right PICA territory as well as narrowing of both vertebral arteries and the basilar artery (Figures 3a and 3b). Infectious or immune causes of vasculitis were considered in the differential diagnosis. Testing for systemic autoantibodies was negative. Serological studies showed elevated *B. burgdorferi* IgM and IgG titers, respectively >122 and >108 U/ml (N< 20) by ELISA, rapidly confirmed by a positive Western blot. Raising therefore the possibility of LNB, CSF analysis was promptly performed that revealed not only a lymphocytic pleocytosis (73 leucocytes/ml: 83%

lymphocytes, 4.5% monocytes) with mildly elevated protein content (0.7 g/l) and low glucose (2.8 mmol/l), but also intrathecal synthesis of both *B. burgdorferi* IgM (AI=4.1) and IgG (AI=2.1) Treatment was started with IV Ceftriaxone (2 g/day) for 2 weeks, oral corticosteroids (progressively tapered for a total duration of 7 weeks) and preventive Aspirin (100 mg/day) for 8 months. He rapidly recovered and clinical follow-up at one year revealed neither sequelae nor new stroke. Follow-up imaging up to 2 years revealed stable vessels irregularities.

Case 4

A 13-years-old boy was admitted to the ER complaining of facial asymmetry, left eye opening difficulty, gait instability and right-sided sensory disturbances. He had no relevant medical condition and denied any trauma. He recalled neither tick bite nor cutaneous lesion.

Clinical examination was remarkable for a left Horner syndrome, gait ataxia and sensory disturbances affecting the right body part. On imaging studies, a left laterobulbar stroke typical of Wallenberg syndrome was demonstrated. Magnetic resonance angiography (MRA) revealed irregular narrowing of the left vertebral artery. Intracranial vertebral dissection was initially suspected and the child started on low-dose Aspirin. As part of the stroke work-up, a Lyme borreliosis screening through ELISA was done but the results were considered doubtful and it was suggested to repeat it at distance. In addition, a heterozygous Factor V Leiden was identified.

The second ELISA done six weeks later revealed positive IgG and IgM titers (94 U/ml; N < 20) against *B. burgdorferi*, confirmed on Western blot and suggestive of a recent infection. A lumbar puncture was therefore performed; CSF analysis showed no pleocytosis, normal protein level and glucose values but revealed intrathecal synthesis of *B. burgdorferi* antibodies with an IgG AI of 12.66 and IgM AI of 6.68 (N < 0.3). Given this result, a

diagnosis of LNB was made, likely at the origin of the past stroke, and IV Ceftriaxone (2 g/day) was given for 2 weeks, along with Aspirin (100 mg/day) prophylaxis. Persistent stenosis on the left vertebral artery was seen on Doppler imaging 6 weeks after the initial event. At two years follow-up, the child had minor residual neurological signs in the form of sensory disturbance in the right arm, left eye ptosis, and minimal unsteadiness.

Summary of LNB-associated stroke from the SNPSR and the medical literature

Demographic data and previous medical history

A comprehensive literature review enabled us to find eight other cases of pediatric stroke attributed to Lyme neuroborreliosis.[13,16-22] Data from all 12 children (our own series and a literature review) are presented in Tables 1 and 2 respectively. All reported cases originated from European countries. Mean age was 9.9 years at diagnosis. The male/female ratio was 1.4/1. All children were immunocompetent. Two children out of the four of the SNPSR had an underlying inherited thrombophilia, but this was neither not searched for, nor documented in the eight cases from the literature. Previous history of tick bites was reported in two patients. Three children reported on history-taking an annular skin lesion consistent with EM. Only one was serologically proved in the acute stage and treated with Amoxicillin.

Acute manifestations

A range of clinical symptoms was reported: headache (n=8), vomiting (n=7), hemiplegia (n=7), facial palsy (n=5), vertigo (n=4), and cerebellar symptoms (n=4). Other less common symptoms included mental slowing, disorientation, somnolence, asthenia, limb pain, anorexia, neck pain, low fever, aphasia, and tinnitus.

Biological work-up

All children underwent a two-step serological work-up, first with ELISA or ELFA, which was supplemented for each patient by a Western Blot, which was able to confirm Lyme disease in all children. In order to confirm LNB, a lumbar puncture was likewise performed in all children, revealing in all but one CSF pleocytosis, usually with prominent lymphocytosis. In one child (Case 1, SNPSR), the cell distribution was atypical with predominant polynuclear cells. In another child (Case 4, SNPSR), CSF pleocytosis was absent but the lumbar puncture was performed with significant delay after the acute symptoms. Liquor protein and glucose content were not systematically reported. When available (n=10), pathological high protein level was identified in 9 cases. Cerebrospinal fluid glucose level was low in 3 cases, normal in 4 cases, high in one and unknown in the remaining patients. Intrathecal synthesis of *B. burgdorferi* antibodies was identified in all cases. *B. burgdorferi* detection by PCR in the CSF was reported in 6 cases and was negative.

Brain imaging

All patients underwent magnetic resonance imaging (MRI), supplemented by vessel imaging with MR angiography (MRA) in 6 cases, conventional arteriography in one case, and both techniques in 3 cases. For 2 cases, data regarding vessel imaging were not available.

Six out of the 12 cases had posterior circulation stroke, including three cases of Wallenberg syndrome due to laterobulbar ischemic stroke. Lenticulostriate stroke was found in 3 cases. One child only had an extensive cortical and subcortical infarct. One child had bilateral subcortical white matter stroke. Finally, one child with acute neurological deficits had no true parenchymal infarction and was labelled stroke-like.

Evidence of vessel wall narrowing or irregularities suggestive of vasculitis was found in 9 cases. In two cases, vascular imaging was reported to be normal. Data regarding vessels was

not available in one case. The vasculitis was purely focal in two children, both involving the posterior circulation. In 7 children, the vasculitis was multifocal, affecting large cerebral arterial branches and involving both the anterior and posterior circulation in 3 cases, the anterior only in 2, and the posterior circulation only in the remaining child. Contrast-enhanced vessel imaging was reported in 2 cases, with narrowing of basilar artery with a striking ring-enhancement. [15,17]

Treatment

Once the diagnosis was established, all children were treated with IV third-generation cephalosporins, usually Ceftriaxone at a dosage of 2 g daily. The duration of treatment was 2 weeks (n=3), 3 weeks (n=5), 4 weeks (n=1), and 6 weeks (n=1). One case received a course of 14 days of Penicillin G (225’000 UI /kg/day) prior to receiving third-generation cephalosporin treatment (35 mg/kg/day). Steroids were given in four cases. Low-dose Aspirin was started in 7 cases for 6 months in two children, and 8 months in one case; the duration of treatment was not reported in the other four cases.

Outcome and Follow-up

Clinical follow-up information was available in 10 cases, with a considerable range from 1 month to 5 years. Radiological follow-up imaging was obtained for 3 out of the 4 SNPSR cases and showed total regression of the vascular lesions in 1 and stable vascular lesions in the other 2.

Clinical outcome was excellent, with complete resolution of neurological deficits in 7 cases, and mild sequelae in 3 cases. Two cases had no available descriptive clinical information. None of the children had any stroke recurrence.

DISCUSSION

From our results, we can infer that European LNB can be incriminated in childhood arterial ischemic stroke, but in a very small subset of patients. Interestingly, even in an endemic country like Switzerland, it represents less than 2% of all childhood AIS aetiologies. While being extremely rare, clinical, radiological and biological features can however help the clinician to rapidly suspect the diagnosis and initiate the appropriate work-up and treatment.

The lack of a previous history of tick bite or an EM is common and should not cause one to disregard the possibility of Lyme-related stroke. Clinically, although the manifestations are variable, signs of brainstem/cerebellar dysfunction are particularly frequent and reflect a high prevalence of posterior circulation stroke, which should alert the clinicians to consider Lyme neuroborreliosis.

Imaging often reveals multifocal vessel irregularities affecting predominantly the posterior circulation suggestive of a multifocal vasculitis process. Combined anterior and posterior circulation involvement is also frequently observed. These imaging findings are similar to what has been reported in adults. [12,20,23] Marked contrast enhancement of the basilar artery has been suggested to be a potential marker but this finding needs to be replicated in further studies. [15,17] We wish to highlight the unusual occurrence of Wallenberg syndrome, in 3 out the 12 documented cases (including 2out of the SNPSR), which is only rarely reported in the pediatric literature.[24] This predilection for posterior circulation stroke differs significantly from the vast majority of cases of focal cerebral arteriopathy in childhood, including the post-varicella angiopathy, that exhibit a strong predilection to the anterior circulation, and more precisely to the M1 segment of the middle cerebral artery.[25] This posterior predilection is probably explained by a predominant basal leptomeningeal obliterative inflammatory vasculopathy (endarteritis), which has been reported in pathological studies and in experimental research.[26,27] There is interestingly a similarity with the pattern

of involvement seen in meningovascular syphilis, another spirochete, suggesting common pathogenesis. [28]

Whether an inherited thrombophilia, such as in two of our cases (2 and 4), can promote thrombi formation within the inflamed vessel is probable but its role is likely minor in comparison with the infectious process discussed above.[29]

Biological confirmation of LNB is mandatory and caution should be exercised before establishing the diagnosis, which has been blamed for a number of unexplained, badly systematized neurological symptoms.[30-32] As direct detection of the spirochete bv culture or by PCR has very low sensitivity, the diagnosis of LNB relies on a set of serological and biological arguments. Demonstration of *B. burgdorferi* specific antibodies in both the serum and in the CSF is essential and this was present in all reported cases. Following consensual guidelines, most laboratories use a two-step method: quantitative enzyme immunoassay (EIA), followed by immunoblot (IB) against specific surface antigens of *B. burgdorferi* genospecies) and the calculation of an antibody CSF/serum index to prove intrathecal synthesis, which in Europe is the gold-standard to establish the diagnosis of LNB. [8,33,34] Routine analysis of the CSF is also particularly relevant by typically showing predominant lymphocytic meningitis with high protein content, and possibly low glucose. Our case series tend to confirm the reliability of these biological markers in the setting of pediatric stroke related to LNB as the vast majority of affected children exhibited an inflammatory CSF with high protein content and all showed intrathecal synthesis. Only one child (case 4) had a normal CSF cell count which is occasionally seen and might be attributed in this specific situation to the diagnosis delay. Yet, in retrospect, the diagnosis of LNB-associated stroke is also likely in this situation. It must be acknowledged that specific antibodies against *B. burgdoferi* in the CSF can persist for years despite successful therapy, and are therefore not recommended to evaluate treatment efficacy. In case of persisting or recurrent symptoms, a

lumbar puncture can be indicated to search for persisting CSF pleocytosis and elevated protein, which appear to be more reliable markers of the course of the disease. [9,11] The adjunctive diagnostic role as a biomarker of the chemokine CXCL13, which has been shown to be highly elevated in the CSF in the very early course of pediatric and adult LNB, even before antibodies production, and also to decline rapidly after adequate therapy, appears promising. It might prove useful in atypical situations (high suspicion index but negative serology). [31,35]

The treatment of choice is IV Ceftriaxone (2 g/day or 50-75 mg/kg/day) for a duration of 14 to 21 days depending on the type of symptoms and their duration (early versus late neuroborreliosis). Oral Doxicyline might be a safe and efficient alternative but is reserved for children above eight years.[10] The role of adjunctive corticosteroids is uncertain but might eventually help in the acute phase of Lyme cerebral vasculitis in view of the important inflammatory component.[12,27] After adequate antibiotic treatment, rapid regression of symptoms usually occurs rapidly and recovery is usually excellent. Stroke recurrence has not been reported. Follow-up imaging studies demonstrate in most cases complete healing or stability of the vascular abnormalities within one year. Accordingly, low-dose Aspirin is empirically recommended for a duration that varies from 6 to 24 months independently of the causal pathogen in order to prevent recurrent stroke.[36,37]

In sum, LNB appear to be a very rare cause of childhood ischemic stroke, even in endemic countries. Being a treatable cause, clinicians must consider this diagnosis in children with unexplained cerebral vasculitis, involving in particular but not exclusively the posterior circulation, and CSF pleocytosis independently of a prior history of tick bite or EM, which is often lacking. Diagnosis still relies on appropriate serological testing in serum and CSF, which in combination have excellent sensitivity and specificity. Prompt treatment with third generation cephalosporin should ensure optimal recovery.

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Legends

Figure 1: a) MRA shows multifocal narrowing at the level of the circle of Willis, affecting predominantly the basilar artery (long arrow), the A1 segment of both cerebral arteries (short arrow), and the M1 segment of middle cerebral artery (dotted arrow) b) A ring-contrast enhancement of the basilar artery is showed (arrow).

Figure 2: On this axial T2-weighted image, a recent right laterobulbar infarct with high signal intensity is demonstrated.

Figure 3: a) Diffusion-Weight imaging shows a small cerebellar hemispheric stroke; b) on MRA, there is almost no visible flow in a large portion of the basilar artery (arrow).

Table 1. *Clinical, radiological and biological manifestations of Lyme neuroborreliosis associated stroke, SNPSR data*

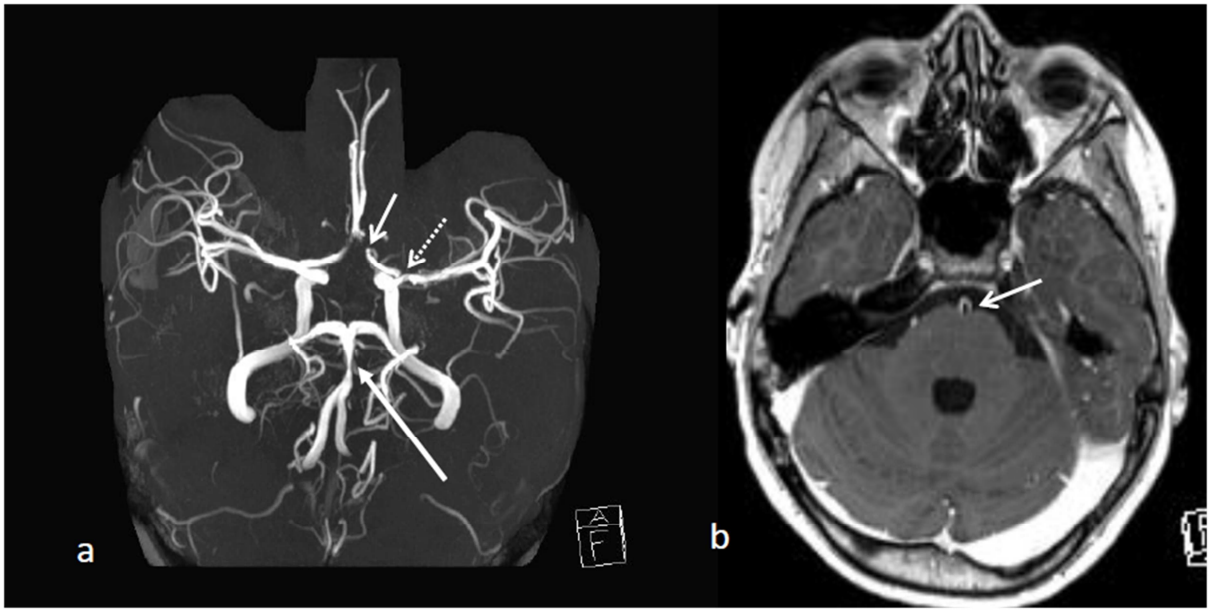
Cases	Gender /Age (years)	Acute main clinical symptoms	Neurological examination	Stroke localisation (CT, MRI)	Vascular imaging (CTA, MRA)	CSF pleocytosis	CSF Ig intra-thecal synthesis	Acute treatment/ Treatment's length	Clinical outcomes (sequelae)	Radiological outcomes
1	M/ 12y	Severe headache Nausea + vomiting Unsteadiness Dysarthria	Confusion L FP L hemiparesis	Stroke-like lesions	Multiple stenosis: BA ++, L PCA R + L MCA R + L ACA	+	+	IV 3GCs 2g/d for 28d Oral Prednisone 2mg/kg/d for 28d ASA 100 mg/d 6m	None (Total regression of clinical symptoms)	At 1 year: Total resolution of cerebral vessels lesions No new parenchymal lesions
2	M/ 8y	Vomiting Headache Rotatory vertigo	R Horner syndrome L FP Multidirectional nystagmus L sensory disturbances Ataxia (Wallenberg Syndrome)	R bulbar (R PICA territory)	None detected	+	+	IV 3GCs 2g/d for 21d ASA 100 mg/d for 6m	Diminution of initial symptoms at hospital discharge No available clinical follow-up	n/a
3	M/ 9y	Headache Vomiting Vertigo Right leg paresthesia	Subtle bilateral tremor	R cerebellum hemisphere (R PICA territory)	R + L VA stenosis Proximal BA stenosis	+	+	IV 3GCs 2g/d for 14d ASA 150 mg/d for 8m Oral Prednisone 50mg/d for 5 days then tapered	None (Normal neurological exam at hospital discharge)	At 1 year : Stable vascular lesions Diminished parenchymal lesions (less definable) No new parenchymal lesions
4	M/ 13y	Vertigo Unsteadiness Right-sided numbness	L FP Cranial nerves deficits (V, VII, IX, X, XI) L nystagmus L. Horner syndrome R sensory disturbances (Wallenberg Syndrom)	L bulbar (L PICA territory)	L VA stenosis near PICA emergence	n/a	+	IV 3GCs 2g/d for 14d ASA 100 mg/d	Mild (Minimal persistent right sensory hemisyndrom at hospital discharge, with intermittent left ptosis)	At 10 months : stable vascular lesions No new parenchymal lesions

ACA: Anterior cerebral artery, ASA: Acetylsalicylic acid, BA: basilary artery, B.b.: Borrelia burgdorferi, CTA: Computed tomography angiography, d: days, FP: Facial palsy, L: Left, VA: vertebral artery, M: male, m: months, MRA: magnetic resonance angiography, MCA: middle cerebral artery, n/a: not available, PCA: posterior cerebral artery, PICA: posterior inferior cerebellar artery, R: Right, VA: vertebral artery, 3GCs: third-generation Cephalosporins.

Table 2 : *Clinical, radiological and biological manifestations of pediatric stroke associated with Lyme neuroborreliosis; cases from the literature*

Reference (1st author and N°)	Gender/ Age(y)	Acute main clinical symptoms	Neurological examination	Stroke localisation (CT, MRI)	Vascular imaging (CTA, MRA)	CSF pleocytosis	CSF Ig intra-thecal synthesis	Acute treatment/ Treatment's length	Follow Up (months)	Clinical outcome (sequelae)	Radiological outcomes (months)
Wilke [18]	F/15y	Headache Vomiting Mental slowing R hempiparesis	R hemiparesis R hand ataxia Papillitis	L BG + L PLIC	n/a	+	+	Penicillin G 14 d *then* IV 3GCs 35mg/kg/d for 14d	5	None	Persistent lesions at 5m
Lebas [19]	M/8y	Vomiting, somnolence R hemiparesis	R hemiparesis Nuchal rigidity	L pons + L cerebellar hemisphere	Distal basilar artery irregularity + contrast enhancement	+	+	IV 3GCs for 28d IV Methylprednisolone 30mg/kg for 3d ASA (dose n/a)	9	None	Normal at 9m
Renard [20]	M/11y	Headache, fever Vomiting R hemiparesis Aphasia	R hemiparesis R dysmetria Expressive aphasia	Bilateral hypersignal in PLIC	Basilar artery + L MCA narrowing	+	+	IV 3GCs for 21d	n/a	n/a	n/a
Kohns [21]	F/5y	Transient R hemiparesis and Vertigo	Normal	L BG	Distal L MCA stenoses and 12 days later new L PCA stenosis	+	+	IV 3GCs 2g/d for 21d ASA 3mg/kg/d (length n/a) IV Methylprednisolone 20mg/kg/d for 3d	3	None	Persistence MCA lesions at 3m
Wittwer [22]	F/5y	Headache, dysphagia Nausea/Vomiting	Suggestive of Wallenberg syndrome	L postero-lateral medulla oblongata+ old R cerebellar infarct	normal	+	+	IV 3GCs for 6w	60	None	n/a
Klingebiel [23]	F/6y	Headache Nausea R hemiparesis	R hemiparesis	L fronto-parietal + L basal ganglia	Multiple narrowing involving the L ICA , LACA, LMCA and distal MCA branches occlusions	+	+	IV 3GCs 100mg/kg/d for 21d	12	Mild attention deficit (for 6mths) then None	L frontal Cortical & subcortical atrophy area No new lesion
Cox [24]	F/12	R hemiparesis speech difficulties	Isolated R hemiparesis + R FP	L subcortical infarct involving L BG, Caudate nucleus and corona radiate	L ACA subocclusion (A1) and stenosis L MCA (M1)	+	+	IV 3GCs 2g/d for 30d (for chronic Borreliosis) ASA 38mg/d	2	n/a	Unchanged stenosis proximal MCA/ACA (at 1m)
Allen [15]	M/15y	Headache	Bilateral FP R leg weakness Cerebellar signs	Diffuse infarcts in vertebrobasilar distribution (medulla, pons, cerebellum)	"Vessel irregularity in the circle of Willis"	+	+	IV 3GCs for 21 d	n/a	Mild residual neurological deficits	n/a

ACA : anterior cerebral artery, ASA: acetylsalicylic acid, BG: basal ganglia, d : day, EM : erythema migrans, F : female, FP: facial palsy, PLIC : posterior limb of the internal capsule, ICA: Internal carotid artery, L : left, M : male, MCA : middle cerebral artery, MRI : magnetic resonance imaging, MRA: magnetic resonance angiography, CTA: Computed tomography angiography, n/a: non available, PCA : posterior cerebral artery, R : right, w : weeks, 3GCs: third generation cephalosporins.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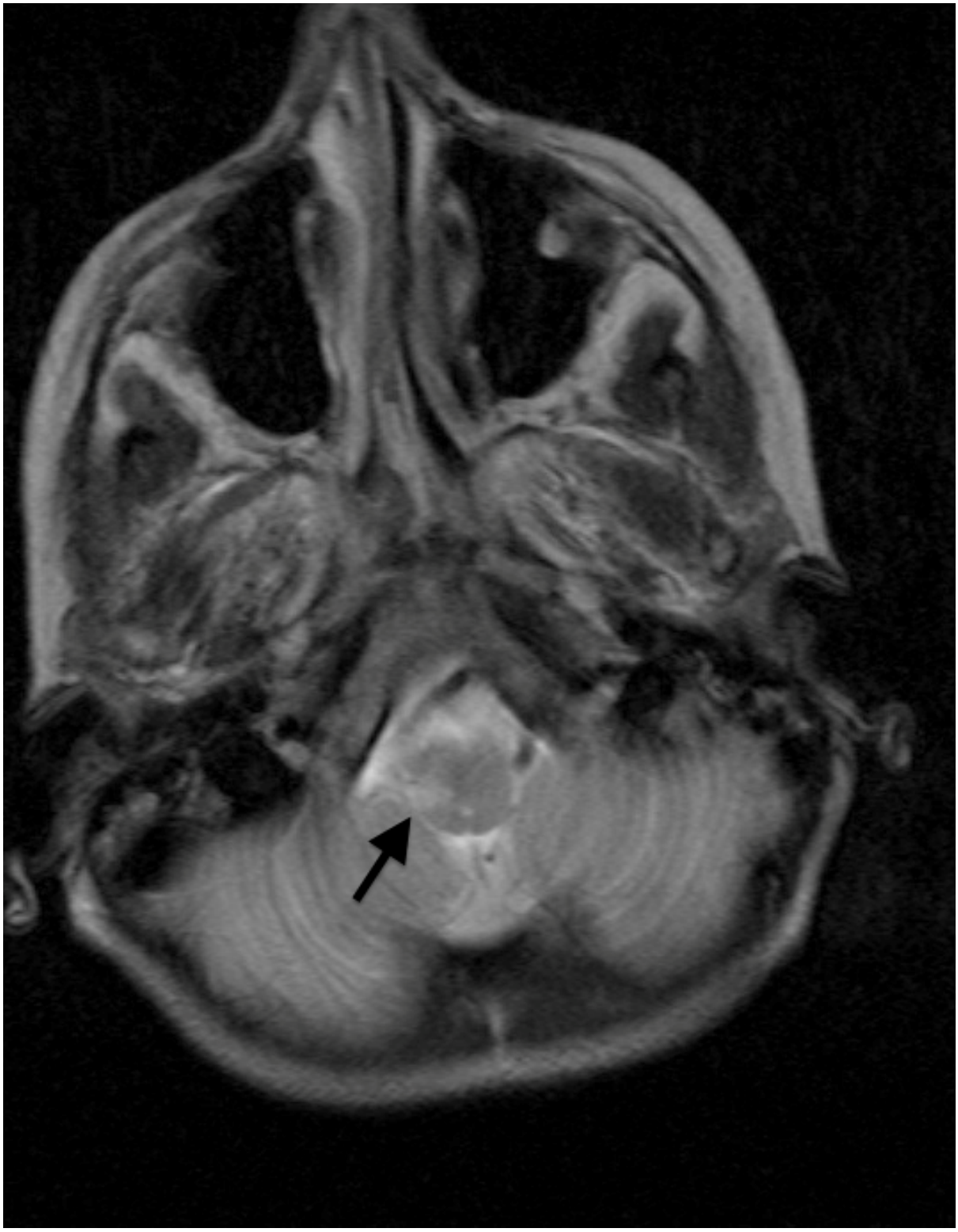

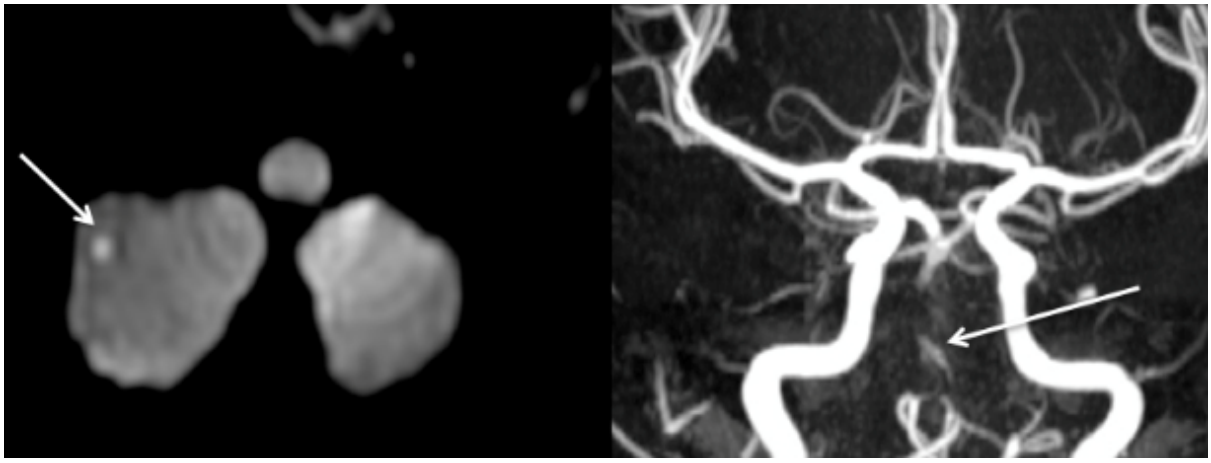

Highlights

- Lyme neuroborreliosis (LNB) is a rare cause of pediatric stroke, even in endemic regions
- Multifocal cerebral vasculitis, involving predominantly the posterior circulation, is a typical feature
- CSF pleocytosis is a distinctive feature of LNB-related pediatric stroke
- Diagnosis relies on intrathecal *B. Burgdorferi* antibodies production
- Prompt antibiotic treatment is associated with good outcome