

Imaging of Lyme Neuroborreliosis: A Pictorial Review

Adam Garkowski,¹ Urszula Łebkowska,¹ Bożena Kubas,² Ewa Garkowska,¹ Katarzyna Rutka,¹ Elwira Gawarecka,¹ and Joanna Zajkowska³

¹Department of Radiology, Medical University of Białystok, Białystok, Poland, ²Independent Department, Laboratory of Molecular Imaging, Medical University of Białystok, Białystok, Poland,

³Department of Infectious Diseases and Neuroinfections, Medical University of Białystok, Białystok, Poland

Lyme neuroborreliosis is a common feature of *Borrelia burgdorferi* infection (as a neurological manifestation occurring in 10%–15% of all Lyme disease cases) and may involve any part of the nervous system, and its coverings, but usually manifests as lymphocytic meningitis, cranial neuritis, and/or radiculoneuritis. This review describes the imaging findings in Lyme neuroborreliosis: the focal point is on the manifestations of involvement visible on brain and spine imaging.

Keywords. *Borrelia burgdorferi*; imaging; Lyme neuroborreliosis; magnetic resonance imaging; magnetic resonance spectroscopy.

Lyme borreliosis ([LB] also known as Lyme disease) is a multisystem, multistage, zoonotic inflammatory disease transmitted by tick bite and caused by the *Borrelia burgdorferi sensu lato* (s.l.) spirochete complex. In the northern hemisphere, it is classified as the most common arthropod-borne disease. Transmission occurs after the bite of ticks infected with bacteria (the 3 common species: *Ixodes ricinus*, *Ixodes persulcatus*, and *Ixodes scapularis*). In Europe, approximately 65 500 patients are affected by this disease annually [1]. Reports from Poland pointed out that the number of patients with LB is increasing [2]. Lyme borreliosis can be characterized by 3 chronologically overlapping stages: early localized, early disseminated, and late disseminated stage. The clinical course of LB is variable, but the infection typically begins with erythema migrans at the tick bite site (Figure 1), ie, a skin lesion appearing several days or weeks after the bite. Disseminated disease associated with neurologic, cardiac, chronic skin, or articular involvement begins later (within a few months to years after disease onset). The late disseminated stage may manifest as arthritic and/or chronic neurologic symptoms occurring a few years later. Chronic neurologic symptoms usually include encephalopathy, presented primarily with cognitive disturbances or peripheral neuropathy, manifested primarily as spinal radicular pain or distal paresthesias or hypoesthesia [3]. Lyme borreliosis with neurological signs is called Lyme neuroborreliosis (LNB), and it

may develop at any time within the disseminated and late stage. Lyme neuroborreliosis is a common feature of *B burgdorferi* infection (as a neurological manifestation occurring in 10%–15% of all Lyme disease cases [3–5]) and may involve any part of the nervous system and its coverings, but it usually manifests as separate or simultaneous lymphocytic meningitis, radiculoneuritis, and/or cranial neuritis [1, 6]. Encephalitis, cerebral vasculitis, and/or myelitis are the most severe forms of LNB, but occur rarely [7]. This review describes the imaging findings in LNB. The focal point is on the manifestations of involvement visible on brain and spine imaging.

Case Definitions

The European Federation of Neurological Societies (EFNS), the American Academy of Neurology (AAN), and the Infectious Diseases Society of America (IDSA) have all recommended specific criteria for the diagnosis of LNB. The diagnosis of LNB relies on clinical and serological findings, as well as on the examination of cerebrospinal fluid (CSF). Current EFNS guidelines for establishing a definite diagnosis of LNB require fulfillment of 3 conditions: neurological signs suggestive of LNB without other obvious reasons, CSF pleocytosis, and intrathecal antibody synthesis specific to *B burgdorferi*. Lyme neuroborreliosis is also considered possible if solely 2 criteria are fulfilled [8]. According to guidelines of the IDSA and the AAN, the diagnosis depends on 3 different elements: the patient may have been exposed to *Ixodes* ticks in their endemic area, they present clinical symptoms that have been associated with LNB, and diagnostic testing (positive antibodies to *B burgdorferi* with or without positive *B burgdorferi* antibodies in the CSF) supports the diagnosis [9, 10]. Although US guidelines do not require intrathecal antibody synthesis in all patients, this is expected in central nervous system infection. The aforementioned intrathecal *B burgdorferii* antibody synthesis is often expressed as positive immunoglobulin G (IgG) B

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Correspondence: Adam Garkowski, MD, Department of Radiology, Medical University of Białystok, Poland, M. Skłodowskiej-Curie 24A, 15-276 Białystok (adam.garkowski@gmail.com).

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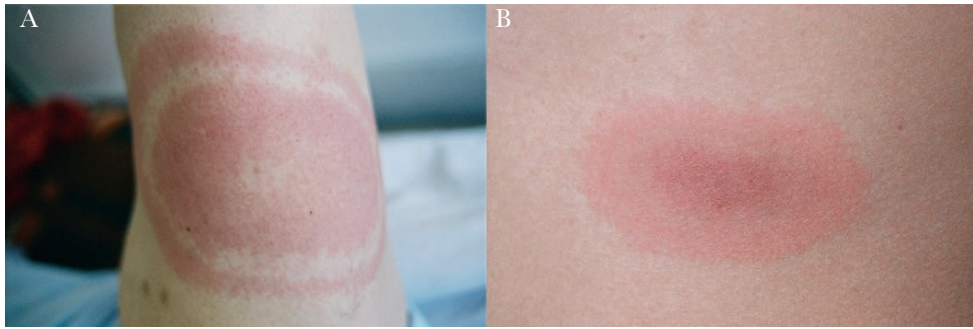


Figure 1. The typical erythema migrans rash in 2 different patients (A and B) as a localized reaction to the tick bite infected with *Borrelia burgdorferi*, which is virtually diagnostic of Lyme borreliosis.

burgdorferii antibody index, which differentiates intrathecal production of antibodies from extrathecal production with passive serum antibodies diffusion into CSF and confirms the diagnosis of LNB [11, 12].

IMAGING

Computed Tomography

Computed tomography (CT) scans of patients who developed nervous system involvement are usually normal. Reported CT abnormalities have included focal or multifocal areas of low density in the subcortical and/or periventricular white matter.

Magnetic Resonance Imaging

Due to its sensitivity and specificity, magnetic resonance imaging (MRI) may be perceived as preferable to CT regarding examination of lesions in the course of LNB. This modality offers higher anatomical resolution, better soft tissue contrast, and multiplanar imaging acquisition; it also utilizes nonionizing electromagnetic radiation.

Cranial Neuritis

The most common clinical presentation of early LNB in Europe and the United States is facial palsy [6]. Cranial nerve VII is most commonly involved, followed by cranial nerves VIII, V, IV, and III. Involvement of other cranial nerves rarely occurs. Unilateral cranial nerve palsy is more common than bilateral palsy, although multiple cranial nerves can be affected. The feature to emphasize in LNB is that the presence of multiple cranial neuropathies is otherwise unusual and should bring this diagnosis to mind. Enhancement after gadolinium chelate administration on T1-weighted images is the common finding (Figure 2C–F). Clinical symptoms of cranial neuritis usually corresponds with contrast enhancement of the affected nerve [13].

Lymphocytic Meningitis

Lymphocytic meningitis on MRI may manifest as meningeal enhancement, however it is rarely reported [13]. From our many years of experience we observed this radiological manifestation only in one patient with LNB in the spinal cord (Figure 3).

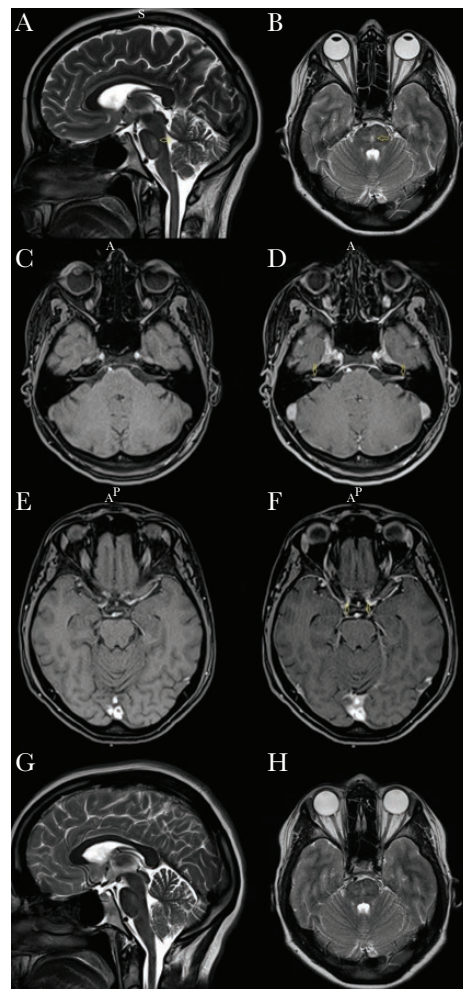


Figure 2. Magnetic resonance imaging (MRI) of a 28-year-old woman with meningitis, left peripheral facial nerve palsy and left abducens nerve. (A) Sagittal T2-weighted image, and (B) axial T2-weighted image revealed nonenhancing hyperintense lesion in the pons. (C) Axial precontrast T1-weighted image, and (D) axial postcontrast T1-weighted image showed bilateral facial nerve enhancement (arrows). (E) Axial precontrast T1-weighted image, and (F) axial postcontrast T1-weighted image revealed bilateral abducens nerve enhancement (arrows). The patient also had few small hyperintense nonenhancing punctate foci in the subcortical frontal white matter on T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequence (data not shown). Lumbar puncture showed lymphocytic pleocytosis in cerebrospinal fluid (CSF). Lyme serology was positive both in blood and CSF and intrathecal *Borrelia burgdorferi* antibody production was confirmed. Follow-up MRI 11 months after treatment showed visible reduction of the lesion (G and H).

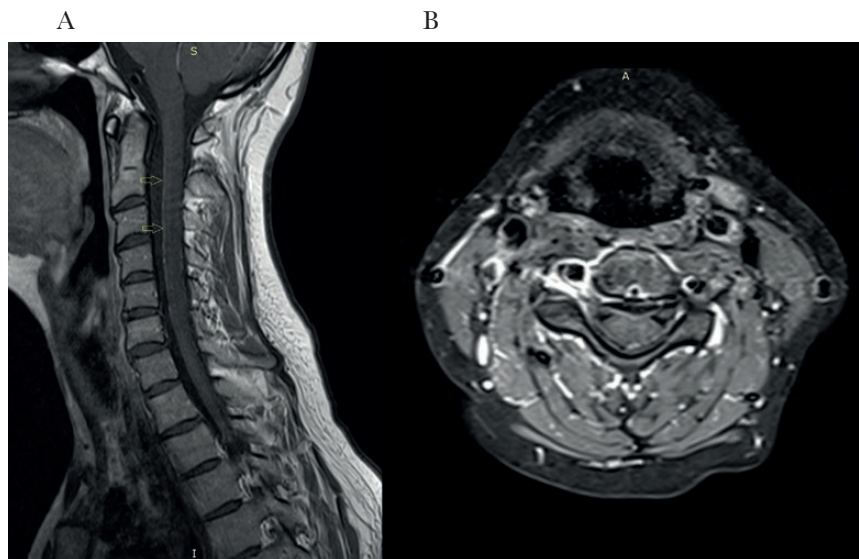


Figure 3. Magnetic resonance imaging of a 40-year-old woman with headache, neck, bilateral shoulder and arm pain. (A) Sagittal, and (B) axial postcontrast T1-weighted images demonstrated thin short-segment leptomeningeal enhancement of spinal cord (arrows). The cerebrospinal fluid (CSF) examination showed lymphocytic pleocytosis. A diagnosis of Lyme neuroborreliosis was confirmed by positive serologic findings of the serum and CSF. Intrathecal synthesis of *Borrelia burgdorferi* antibodies was confirmed by a positive immunoglobulin G antibody index.

Encephalitis

In a recent German study, 8 patients were classified as having encephalitis (12%) based on clinical features [7]. In reported cases, the most common MRI findings on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images include single or multiple small, usually nonenhancing subcortical and/or periventricular white matter hyperintensities that are most often present in the supratentorial region (cerebral hemispheres) (Figures 4 and 5). However, these lesions do not always correspond to clinical findings. In contrast to clinical features of encephalitis, these lesions are identified in approximately half of all patients with LNB, and it is virtually impossible to distinguish them from lesions observed in cerebral small vessel disease or multiple sclerosis [14, 15]. The statement that LNB causes nonspecific white matter lesions is based on

weak scientific evidence. In a study by Agarwal and Sze [13], the authors compared MRI findings of 66 patients suffering from LNB with 50 healthy control subjects. They found that white matter hyperintensities in patients with LNB are comparatively unusual. In rare instances, LNB can occur in association with white matter lesions similar to multiple sclerosis (and can mimicking this disease), whereas the usual clinical manifestation of LNB is with a lymphocytic meningitis, cranial neuritis, and/or radiculoneuritis, and an inflammatory CSF (Figure 6). Large “tumefactive” mass-like lesions similar to that of multiple sclerosis are very uncommon. In a study by Murray et al [16], 1 case of intracranial mass lesion was described. A 10-year-old patient was characterized by parenchymal low-density brainstem and hemispheric mass lesions with minimal ring enhancement seen on CT. On MRI, the lesion was diffusely hyperintense on

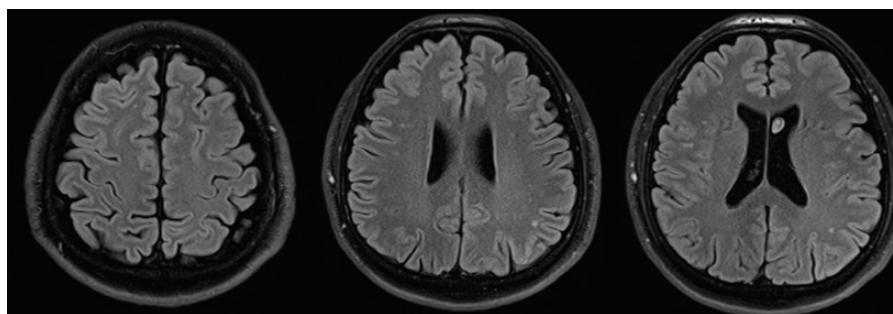


Figure 4. Magnetic resonance imaging of a 19-year-old woman with meningitis and right peripheral facial nerve palsy. The patient had multiple small hyperintense nonenhancing punctate foci in the subcortical white matter on fluid-attenuated inversion recovery (FLAIR) sequence (only in the in the supratentorial region). A diagnosis of Lyme neuroborreliosis was confirmed by positive serologic findings of the serum and cerebrospinal fluid. Intrathecal synthesis of *Borrelia burgdorferi* antibodies was confirmed by a positive immunoglobulin G antibody index.

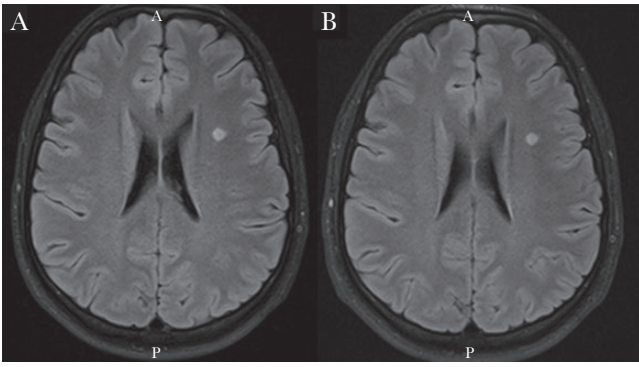


Figure 5. Axial magnetic resonance imaging (MRI) of a 19-year-old man with a right-sided facial nerve palsy and confirmed diagnosis of early Lyme neuroborreliosis (LNB). (A) Fluid-attenuated inversion recovery (FLAIR) image shows focal hyperintense lesion in the white matter of the left frontal lobe. The lesion did not enhance on contrast-enhanced T1-weighted images (data not shown), and there was no visible enhancement of cranial nerves (data not shown). (B) Follow-up MRI 12 months after treatment showed only a slight reduction in the size of the lesion. However, this lesion could also be incidental, and thus not related to LNB.

T2-weighted images, while T1-weighted images showed peripheral rim-like and nodular enhancement. In this case, LNB was confirmed by stereotactic biopsy and serological studies. A follow-up MRI scan showed the brainstem lesion to be smaller and without enhancement [16]. In rare cases, LNB may manifest as hemorrhagic encephalitis. In a report published in

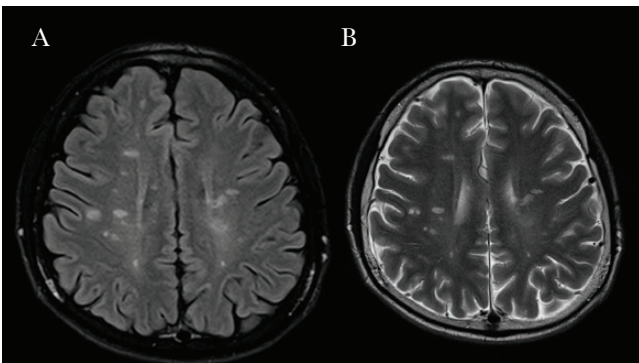


Figure 6. Axial magnetic resonance imaging of a 38-year-old man with early Lyme neuroborreliosis (LNB). The patient reported a several-week history of muscle weakness in the both limbs, and bilateral Babinski's sign was also present. (A) Fluid-attenuated inversion recovery (FLAIR) image, and (B) T2-weighted image shows numerous, mainly ovoid, hyperintense, periventricular white matter lesions perpendicular to the body of the lateral ventricle, initially assumed to be demyelination. These lesions did not enhance on contrast-enhanced T1-weighted images (data not shown) and were not present in the infratentorial region. At the beginning of treatment, intravenous methylprednisolone was given because of suspected multiple sclerosis. However, the therapy was discontinued because it was poorly tolerated by the patient. Later, further medical history revealed that the patient had a past history of tick bite (approximately 4 months earlier before noticeable symptoms). The cerebrospinal fluid examination revealed inflammatory features (lymphocytic pleocytosis), and intrathecal synthesis of *Borrelia burgdorferi* antibodies was confirmed by a positive immunoglobulin G antibody index. Then, the patient was treated with ceftriaxone for 21 days and showed gradual symptomatic improvement, which further confirmed the diagnosis of LNB, and finally the patient was discharged with substantial neurological improvement.

2020, Bonduelle et al [17] described the first case of patient with severe bilateral hemorrhagic temporal encephalitis due LNB successfully treated with ceftriaxone. The MRI showed hemorrhagic bitemporal lesions with a peripheral contrast enhancement (Figure 7) [17].

Myelitis

Spinal cord involvement clinically is believed to be fairly common in European LNB, yet it occurs less commonly in the United States. In a study (Schwenkenbecher et al [7]) of patients from Germany, myelitis was seen in approximately 7% of patients with LNB, and diagnoses offered on the basis of MRI spine imaging confirmed its occurrence in all of these patients (Figure 8).

Vasculitis

In rare reported cases, largely anecdotal, LNB is being considered as a cause of occasional strokes, manifested in intracerebral hemorrhages, subarachnoid hemorrhages, or—most commonly—cerebral vasculitis and subsequent ischemic strokes. These phenomena are observed in approximately 0.3% of patients with LB [18, 19]. This form of LNB has been demonstrated in several case reports that analyzed results of CT angiography (CTA), magnetic resonance angiography (MRA), or conventional angiography. Angiography may show different degrees and location of multifocal narrowing and poststenotic dilatation of the medium- and large-caliber cerebral vessels. In the reported cases, the middle cerebral, basilar, anterior cerebral, and posterior cerebral artery were most frequently affected. In some patients presented with LNB-associated stroke, angiographic showed no features of vasculitis [20]. If no abnormalities are revealed, it might mean delayed symptoms onset or involvement of small blood vessels not visible on conventional arteriographic images. Both MRA and CTA do not offer adequate sensitivity; thus, a normal angiogram does not exclude the diagnosis of vasculitis [21].

Proton Magnetic Resonance Spectroscopy

Numerous literature references concerning LNB do not discuss proton magnetic resonance spectroscopy (¹H-MRS) examinations of the brain in this disease. So far, only 2 published studies have described spectroscopic changes in the brains of patients with LNB. In their 2004 study of white matter of the frontal lobes of 12 patients at different stages of LNB, Ustymowicz et al [22] demonstrated a significant increase in choline (Cho)/creatine (Cr) and lipid (Lip)/Cr ratios when compared with the control group ($P < .001$). No statistically significant abnormality was observed regarding mean *N*-acetylaspartate (NAA)/Cr and lactate (Lac)/Cr ratios, although in 4 patients a decreased NAA/Cr ratio was found. The authors used short echo time (TE = 35 ms) and 1 voxel positioned within normal-appearing white matter of the frontal

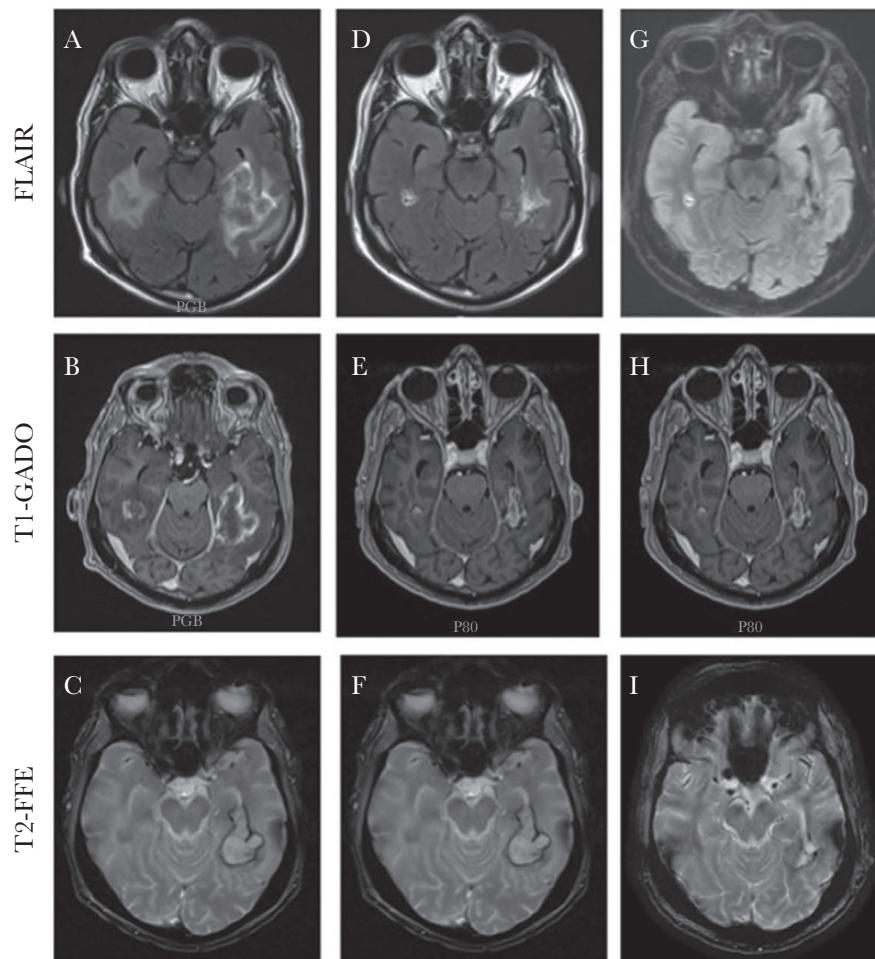


Figure 7. Magnetic resonance imaging (MRI) of the head of 55-year-old patient who was admitted for an acute confusional state with anterograde memory loss and falls. The cerebrospinal fluid analysis showed inflammatory features (lymphocytic pleocytosis), and intrathecal synthesis of *Borrelia burgdorferi* antibodies was confirmed by a positive antibody index. The MRI was performed on admission on day 0 (a–c), and follow-up was performed on day 30 (d–f) and at 1 year (g–i) (bottom). Onset MRI demonstrates bilateral edema of temporal lobes on fluid-attenuated inversion recovery (FLAIR) images (a) with peripheral enhancement after gadolinium injection (b) and hemorrhages (c). Control at month 3 (d–f) and 12 (g–i) revealed a subtotal resorption of edema (d and g) and hemorrhages (f and i) with subtle persistent gadolinium enhancement (h). Adapted from Bonduelle T, Tang HM, Marchal C, Thomas B. Severe Lyme neuroborreliosis with bilateral hemorrhagic temporal encephalitis. *J Neurol.* 2020;267:852–854.

lobe. They stated that ^1H -MRS changes in patients with LNB are not specific, but ^1H -MRS may be helpful in therapeutic choices and treatment monitoring by assessing tissue damage of the brain [22]. In our recent study, published in 2019, we performed ^1H -MRS examinations on 26 patients diagnosed with early LNB and 26 controls (healthy volunteers). In contrast to the previous ^1H -MRS study, the long TE (TE = 135 ms) was selected to evaluate the changes in the NAA/Cr ratio more precisely. In our study, we used 4 voxels, positioning first 2 symmetrically on the opposite sides of cerebral hemispheres, in the anterior region of frontal lobes (laterally with regard to the anterior horns of lateral ventricles). The other 2 voxels were also located symmetrically on the opposite sides of brain hemispheres, in the synovial center of the frontal lobes. For patients with LNB, a statistically significant decrease of the NAA/Cr ratio was observed within the anterior part of both

frontal lobes (respectively $P = \leq .001$ and $P = .001$ for the left and right lobe). The same may be stated regarding the posterior region of the lobes ($P = \leq .001$ and $P = .031$). However, no changes of statistical significance were observed for Cho/Cr ratio within any regions. No Lip and Lac peak was also observed in patients with LNB in this study. Although these findings are nonspecific, they suggest the presence of diffuse neuronal dysfunction or loss in patients at the early stage of LNB [23]. An example of ^1H -MRS spectra in patients with early LNB, together with a healthy control subject, is shown in Figures 9 and 10.

Nuclear Medicine Imaging

In very few case reports was the positron emission tomography (PET) used. Plotkin et al [24] reported a case of a 58-year-old woman who experienced progressive

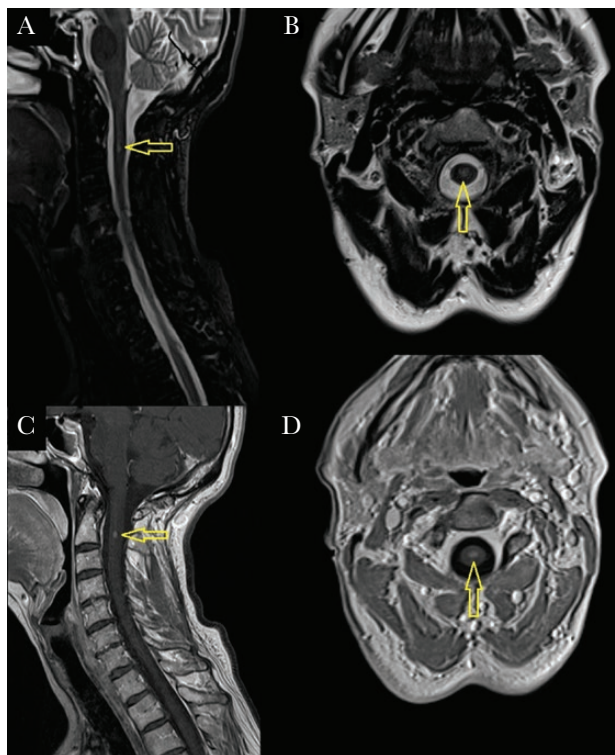


Figure 8. Magnetic resonance imaging (MRI) of a 56-year-old woman with Lyme neuroborreliosis-associated myelitis presented with peripheral left facial nerve palsy, meningitis, and decreased sensation in the upper extremities. The patient had a history of erythema migrans. Lumbar puncture showed lymphocytic pleocytosis in cerebrospinal fluid (CSF). Lyme serology was positive in both blood and CSF, and intrathecal *Borrelia burgdorferi* antibody production was confirmed. The patient was treated with ceftriaxone and was discharged with substantial neurological improvement. (A) Sagittal T2-weighted turbo inversion recovery magnitude (TIRM) sequence, (B) axial T2-weighted image, (C) sagittal postcontrast T1-weighted image, and (D) axial postcontrast T1-weighted image revealed hyperintense, homogeneously enhancing lesion in the cervical spinal cord (arrows).

dysesthesia, abasia, and ataxia together with nausea and vomiting. The MRI of her brain revealed a T2-hyperintense, nonenhancing lesion in the brainstem expanding towards to the cervical spinal cord and resulting in aqueductal stenosis of the median aperture. Then, the patient was also subjected to 2 consecutive [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) examinations. The first one showed increased glucose metabolism in the brainstem in line with signal abnormalities revealed on MRI. Subsequent serological tests confirmed the diagnosis of LNB. The second FDG-PET examination ordered after antimicrobial therapy demonstrated no abnormality in this area, reflecting clinical remission [24]. In a report of a pediatric case of a 15-year-old boy with confirmed LNB, an MRI showed acute ischemic lesions in the medulla, pons, and cerebellum corresponding with hypermetabolic areas on FDG-PET, suggesting inflammation/vasculitis (Figure 11) [25].

OTHER FORMS

It is possible that LNB may also mimic atypical dementia and normal pressure hydrocephalus. In one reported case of a patient with cognitive decline of 10 months duration and confirmed LNB, a cerebral MRI revealed periventricular lesions of white matter, mild dilatation of the lateral ventricles, and a borderline Evans' index. Remarkably, this patient responded dramatically to a 3-week-long administration of ceftriaxone [26]. However, this is based on anecdotal observations and not supported by systematic studies.

CONCLUSIONS

Lyme neuroborreliosis may affect any part of the nervous system, including its meninges. In all regions, the disease can attack the dura matter, leptomeninges, nerve roots, and cerebral and spinal parenchyma. In the vast majority of cases, the appearance of lesions is nonspecific, and for this reason LNB is included in a broad differential diagnosis. Although imaging features of LNB are nonspecific, cranial nerve or leptomeningeal enhancement can help in differentiation from multiple sclerosis.

Illustrative Case

The patient was a 28-year-old female, previously healthy but with a history of tick bite. She was admitted to the Department of Infectious Diseases and Neuroinfection of the Medical University of Białystok, presenting with a sudden onset of severe headache and vomiting. The physical examination showed peripheral left facial nerve palsy and left abducens nerve palsy. Inflammatory features revealed in the CSF examination were as follows: pleocytosis, 136 cells/mm^3 (91% lymphocytes); and protein, 0.801 g/L. The serum enzyme-linked immunosorbent assay revealed positive high titers of *B burgdorferi* antibodies (IgM, 50 Biomedica Borrelia units (BBU)/mL and IgG, 68 BBU/mL). Positive IgG antibody index confirmed the intrathecal synthesis of *B burgdorferi* antibodies. Antibodies to immunodominant antigens were identified owing to the immunoblot analysis (Virotech, Rüsselsheim, Germany). No abnormalities were revealed on the CT of the brain. The first MRI exam of the brain was performed, and it showed inflammatory lesion in the brainstem and pathological bilateral contrast enhancement of the facial and abducens nerves (Figure 2C-F). After the 21-day-long treatment with ceftriaxone, the patient was discharged with considerable neurological improvement. Two months later, a follow-up hospitalization and control CSF examination of the patient showed promising results: the CSF profile improved and pleocytosis was only residual (12 cells/mm^3). No further complaints were experienced or reported by the patient. The physical examination was normal; there were no detectable symptoms of cranial nerves palsy. A follow-up MRI scan was performed after 11 months since the first

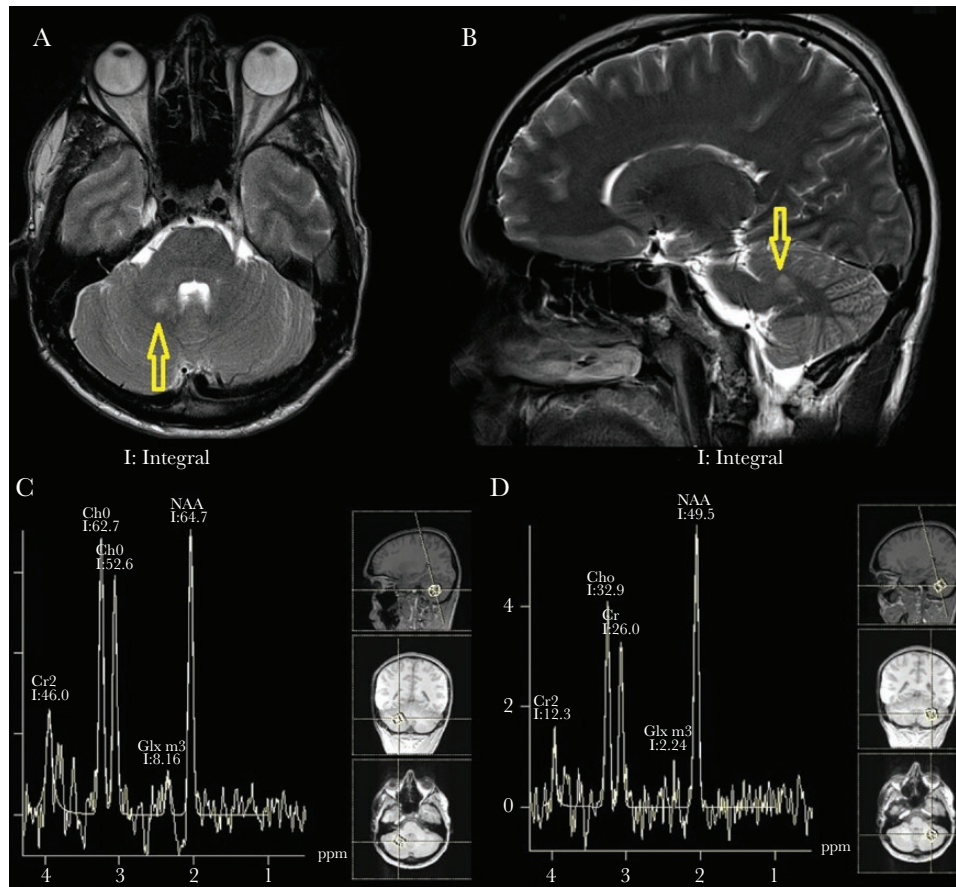


Figure 9. Magnetic resonance imaging (A and B) and proton magnetic resonance spectroscopy (^1H -MRS) (C and D) of a 32-year-old man with right facial nerve palsy and meningitis in the course of Lyme neuroborreliosis. The cerebrospinal fluid analysis showed inflammatory features (lymphocytic pleocytosis), and intrathecal synthesis of *Borrelia burgdorferi* antibodies was confirmed by a positive immunoglobulin G antibody index. (A) Axial, and (B) sagittal T2-weighted images demonstrated hyperintense lesion in the white matter of the right cerebellar hemisphere (arrows). (C) ^1H -MRS spectrum (single voxel spectroscopy) of the above-mentioned lesion shows marked elevation of choline indicating inflammation (arrow), (D) normal ^1H -MRS spectrum of contralateral control.

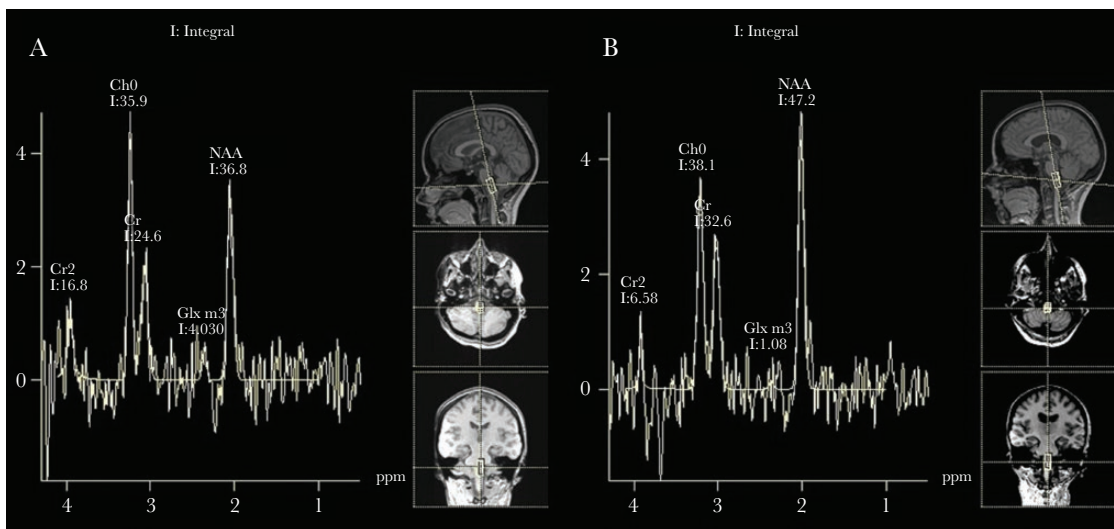


Figure 10. Single voxel ^1H -MRS spectrum of the normal-appearing medulla oblongata of the 2 persons (A and B). (A) A 22-year-old woman with left facial nerve palsy and meningitis in the course of Lyme neuroborreliosis. The cerebrospinal fluid analysis revealed lymphocytic pleocytosis, and intrathecal *Borrelia burgdorferi* antibody production was confirmed; ^1H -MRS spectrum shows marked elevation of choline and relative decrease of *N*-acetylaspartate indicating inflammation. (B) Normal ^1H -MRS spectrum obtained from a healthy woman of similar age in the same region.

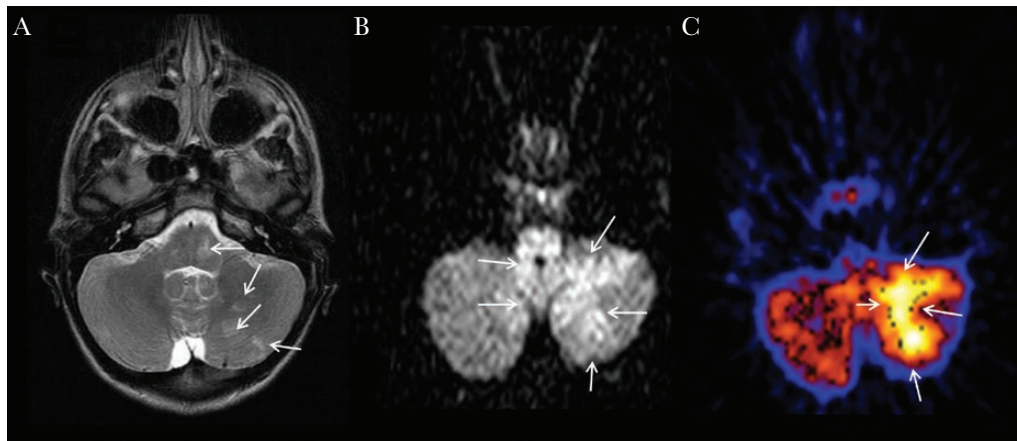


Figure 11. Magnetic resonance imaging showing (A) signal abnormality, suggesting inflammatory lesions in a vertebrobasilar distribution; medulla, pons, and cerebellum. (B) Corresponding restricted diffusion. (C) Corresponding hypermetabolic areas on fluorodeoxyglucose-positron emission tomography imaging suggesting inflammation/vasculitis. Magnetic resonance angiography (data not shown) demonstrated vessel irregularity or “beading” in the Circle of Willis (posterior circulation) consistent with vasculitis. Arrows indicate areas of abnormality. Adapted from Allen NM, Jungbluth H. Lyme neuroborreliosis: a potentially preventable cause of stroke. *J Pediatr* 2016;170:334-e1.

hospitalization, and it revealed significant reduction in the size of the lesion in the brainstem (Figure 2G and H), showing no pathological contrast enhancement within cranial nerves.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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