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LETTER TO THE EDITORS

Subacute parkinsonism as a complication of Lyme disease

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Dear Sirs,

Lyme disease is a tickborne multisystemic bacterial infection due to *Borrelia Burgdorferi* (*BB*). Diagnostic criteria for neuroborreliosis are controversial but cerebrospinal fluid (CSF) analysis which demonstrates lymphocytic meningitis, positive ELISA *BB* serology, and positive anti-*BB* antibody index (AI) [defined by ratio of (ELISA titer in CSF/ELISA titer in serum) to (total IgG in CSF/total IgG in serum)] in a patient with no past history of neuroborreliosis allow, in most of the cases, the diagnosis [1], which will be supported by rapid improvement with doxycycline, ampicilline, or in neurological complications, ceftriaxone [2]. Parkinsonism has been reported in a few patients with a positive *BB* serology, but the relationship between *BB* infection and parkinsonism remains doubtful [3]. Herein, we report two patients who developed reversible subacute parkinsonism due to Lyme basal ganglia ischemic or inflammatory lesions.

A 63-year-old woman developed severe walking disorders deteriorating rapidly over 6 months. Clinical examination revealed lower limbs weakness, increased reflexes, bilateral extensor plantar, and dysuria, as well as a left akineto-hypertonic syndrome (UPDRSIII 27/108) and a bilateral peripheral facial palsy. Brain MRI identified several high signal intensities on T2-weighted (T2WI) and FLAIR images in the pons, and the periventricular and subcortical white matter, consistent with vascular demyelination. Similar lesions were observed in the right lenticular nucleus and the bilateral posterior limb of the internal capsules, rather consistent with chronic infarcts (Fig. 1a, b). Spinal cord MRI showed intramedullary high signal on T2WI at the T5/T6 level (Fig. 1c), without enhancement on post-gadolinium T1-weighted images. CSF study found 17 lymphocytes/mm^3, 1.33 g protein/l, a 0.35 g glucose/l, and an intrathecal anti-*BB* antibodies synthesis with an AI at 8 (normal <2). Lyme blood serology (IgG 1160 U/ml; IgM 20 U/ml) and Western Blot (22, 41, 60, 83 kDa bands) were positive. Complete blood count, C-reactive protein, vitamins B9-B12, angiotensin-converting enzyme, and ANCA levels were normal. Blood Syphilis serology and CSF BK cultures were negative. DaTscan showed a presynaptic dopaminergic denervation on the right striatum (striatum/occipital right ratio = 2.0 and striatum/occipital left ratio = 2.7; normal >2.5). Although the patient did not reported tick bite or erythema migrans, the diagnostic of neuroborreliosis was considered very likely and she received intravenously 2 g of ceftriaxone per day for 21 days. Nevertheless, clinical improvement was weak. Follow-up brain MRI 1 month later showed new high signal intensities on T2-weighted and FLAIR images on the head of the right caudate and the anterior part of the right lenticular nuclei. These lesions demonstrated high signal intensity on diffusion-weighted images (DWI) with low ADC values, and contrast enhancement on post-gadolinium T1-weighted images. These signal abnormalities were consistent with subacute infarction (Fig. 1d). Additional intramedullary high signal intensities were observed on T2-WI at C4, T3–T4, T5–T6, T7–T8, and T9, with enhancement on post-contrast T1-weighted imaging, consistent with subacute inflammatory lesions (Fig. 1e, f). Ceftriaxone treatment was extended by 21 days,

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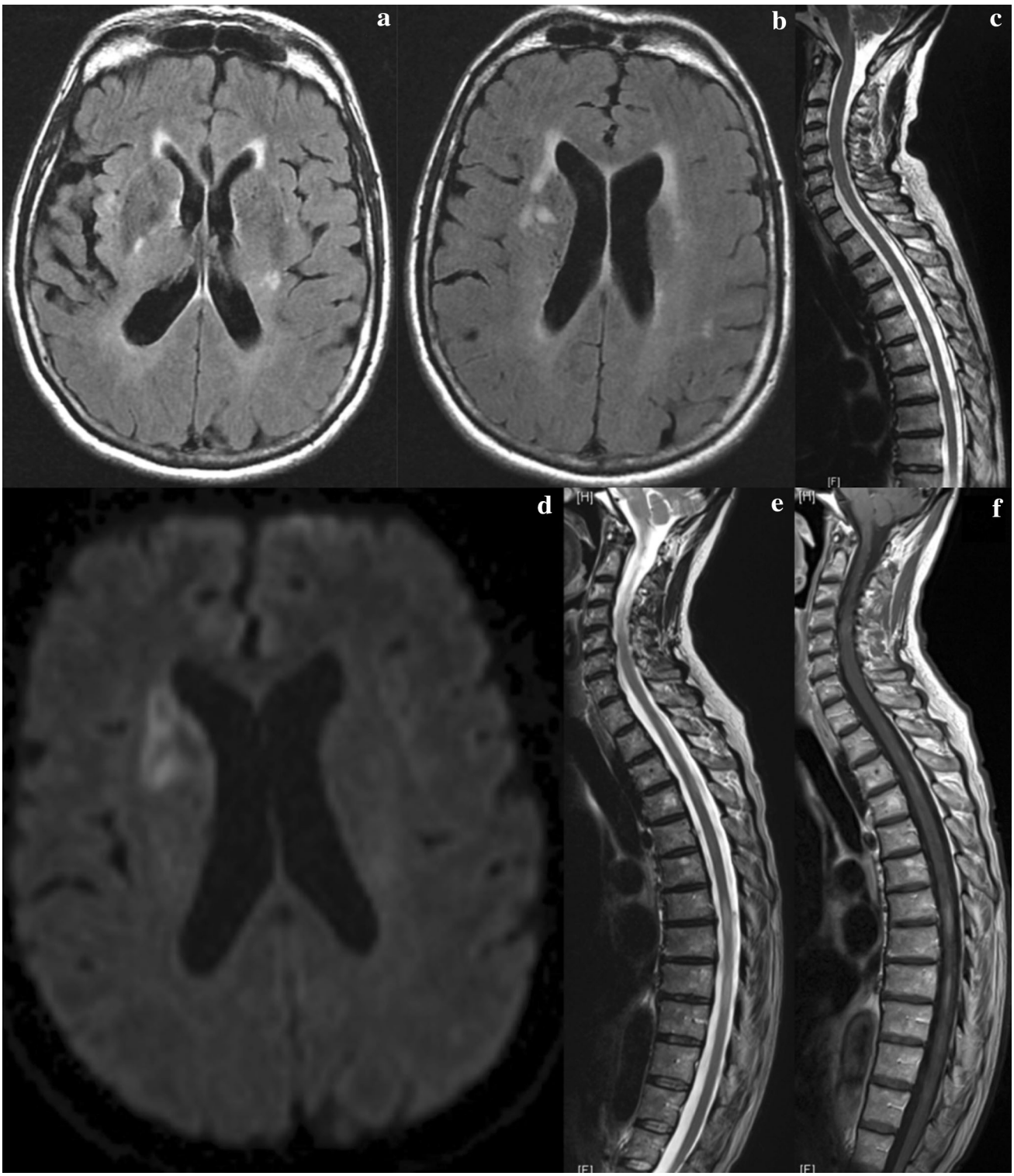

Fig. 1 Case 1 MRI at presenting symptoms (**a**, **b**, **c**). Brain MRI-Axial Flair images: high signal intensities in the bilateral posterior limb of the internal capsules (**a**) and in the right lenticular nucleus (**b**), consistent with chronic infarcts. **c** Spinal cord MRI- Sagittal T2-weighted image-Intramedullary high signal on T2WI at the T5/T6 level, without enhancement on post-gadolinium T1-weighted images (not shown). Follow-up MRI 1 month later (**d**, **e**, **f**). **d** Axial diffusion-weighted images (DWI): high signal intensities in the head of the right caudate and the anterior part of the right lenticular nuclei with low ADC values and contrast enhancement on post-gadolinium T1-weighted images (not shown), consistent with subacute infarctions. **e** Sagittal T2WI image: additional intramedullary high signal intensities at C4, T3–T4, T5–T6, T7–T8, and T9, with enhancement on post-contrast T1-weighted imaging (**f**), consistent with subacute inflammatory lesions

combined with 3 months of corticosteroid therapy (60 mg/day). Ldopa/carbidopa (300 mg/day) improved parkinsonism. Gait disturbance slowly improved, while facial palsies disappeared. Two months after the end of the treatment, UPDRSIII was 8/108, and brain and spinal cord follow-up MRI showed chronic brain infarcts on the right lenticular and caudate nuclei, unchanged focal supratentorial white matter and pontine lesions, and the complete resolution of the previously seen spinal cord signal intensity lesions.

A 55-year-old patient with a history of chronic neck pain developed over 2 months, a progressive marked asthenia. Due to a sudden dysarthria, he was hospitalized in the stroke unit. Clinical examination revealed a dysarthria which disappeared in less than 1 h, a left upper limb cerebellar ataxia and a bilateral asymmetric mild akineto-hypertonic parkinsonism (left predominant, UPDRSIII 9/108). Brain MRI showed a high signal intensity lesion on DWI with low ADC value in the right posterolateral thalamus, suggestive of an acute infarct (Fig. 2a). High signal intensity lesions were observed on T2WI and FLAIR in the centrum semi-ovale, the frontal and parietal white matter, the thalami, the bilateral posterior limb of the internal capsules, the cerebral peduncles (in particular in the left substantia nigra), the pons, and the left upper and middle cerebellar peduncles, consistent with chronic vascular lesions (Fig. 2b, c). MR angiography demonstrated a mild narrowing of the distal M1 segment of the right middle cerebral artery (Fig. 2d). CSF study found 100 lymphocytes/mm^3, protein level at 1.72 g/l, glucose level at 0.44 g/l, and an intrathecal anti-*BB* antibodies synthesis with an AI at 17 (normal <2). Lyme blood Western Blot (22, 41, 60, 66, 75, and 83 kDa bands) was positive. DaTscan demonstrated bilateral presynaptic dopamine denervation (striatum/occipital right ratio = 2.8 and striatum/occipital left ratio = 2.8; normal >3.0). Cardiovascular assessment (cardiac echography, carotid ultrasound imaging, and cardiac Holter monitoring) was normal and no risk factor was detected. The diagnosis of neuroborreliosis was suggested, and a 21 day treatment with 2 g per days of ceftriaxone was executed. Improvement occurred in a few days, and no dopaminergic treatment was required. Eight months later, neurological examination was normal with UPDRSIII 4/108. Follow-up brain MRI 4 months later showed the complete disappearance of the previously described signal abnormalities in the pons, the mesencephalon, the posterior limb of the internal capsule, and the thalami, with only remaining small T2WI-FLAIR hyperintensities in the supratentorial white matter and in the right posterior thalamus, consistent with chronic infarcts (Fig. 2e, f, g).

The two patients reported here, who developed subacute parkinsonism, fulfilled the diagnostic criteria for neuroborreliosis: no past history of neuroborreliosis, positive anti-*BB* antibody index, favorable outcome of neurological signs after specific antibiotic treatment, and absence of other diagnosis. In both cases, DaTscan demonstrated a presynaptic dopaminergic denervation which has been associated with striatal ischemic lesions due to Lyme probable vasculitis.

Acute or subacute cases of vascular parkinsonism due to focal ischemic lesion in basal ganglia are reported [4–7], and stroke is a rare complication of Lyme disease [1, 2]. Especially, in endemic region for *BB*, it should be searched in case of successive strokes with short intervals in several cerebral arterial territories, and/or in case of associated headache, recent cognitive impairment, or like in our cases, peripheral nerves or medullar involvement, typically in patients without any vascular risk factors [8]. Brain MRI may demonstrate ischemic or hemorrhagic non specific stroke injuries, while the involvement of various arterial territories, the presence of arterial caliber abnormalities, and of contrast enhancement of the arterial wall suggest vasculitis. Cerebral vasculitis can be isolated or associated with parenchymal lesions, and MRI can show, as in our cases, non-ischemic T2WI hyperintensities in the cerebral white matter and the spinal cord, with, in some cases, enhancement on post-contrast T1-weighted imaging. Similar MRI lesions can be found in other inflammatory, infectious, drug induced, or paraneoplastic vasculitis [9], and CSF analysis which demonstrates that a lymphocytic meningitis with a positive anti-*BB* antibodies index is essential to assess neuroborreliosis. As in our two cases, tick borne and/or erythema migrans can have been unnoticed.

Specific antibiotic treatment with ceftriaxone (2 g a day for 21 days) usually allows partial or complete regression of all symptoms. However, in some cases, as in case 1, where clinical or MRI signs were still worsening a few days after ceftriaxone treatment onset, corticosteroid have been associated to decrease the inflammatory mechanism [10, 11]. Due to the good clinical evolution and although MRI brain basal ganglia abnormalities remained, DaTscan was not controlled in our cases.

These two cases demonstrate that an acute or subacute parkinsonism may be a complication of Lyme disease. In front of an acute or subacute parkinsonism, especially in endemic region, neuroborreliosis should be discussed in case of associated headache, multisystemic neurological signs, or MRI basal ganglia vasculitis or inflammatory

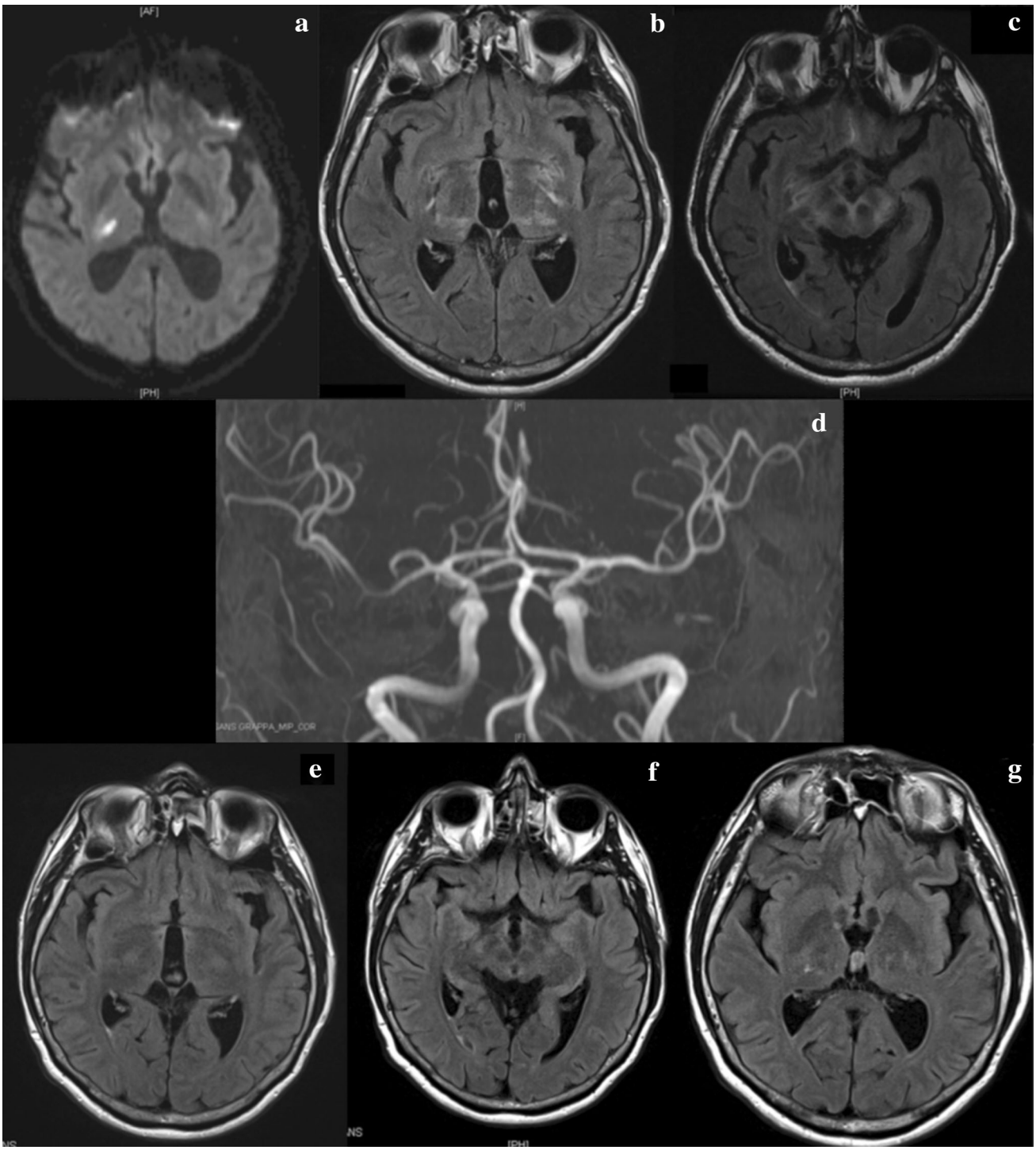

Fig. 2 Case 2 Initial brain MRI (**a**, **b**, **c**). **a** Axial diffusion-weighted image: high signal intensity lesion on DWI with low ADC value (not shown) in the right posterolateral thalamus, suggestive of an acute infarct. **b**, **c** Axial Flair images: high signal intensity lesions in the thalami, the bilateral posterior limb of the internal capsules (**b**), the cerebral peduncles (in particular in the left substantia nigra) (**c**), consistent with chronic vascular lesions. **d** MR angiography, coronal view: mild narrowing of the distal M1 segment of the right middle cerebral artery. Follow-up 4 month later-Brain MRI, axial FLAIR images (**e**, **f**, **g**). **e**, **f** Complete disappearance of the previous signal abnormalities in the mesencephalon (**a**), the posterior limb of the internal capsule and the thalami. **g** Remaining small hyperintensities in the right posterior thalamus, consistent with chronic infarcts. High signal intensities in the left thalamus represent cerebrospinal fluid flow artifacts

signs. Conversely, Lyme blood or CSF serology should not be asked for, even in endemic region, in case of progressive parkinsonism without any basal ganglia MRI lesions.

Compliance with ethical standards

Conflicts of interest M Koob declares honoraria from Guerbet. M. Anheim declares honoraria from Abbvie, Actelion Pharmaceuticals, and Teva. C. Tranchant declares honoraria from Abbvie, Teva, and Zambon.

Ethical standard This study has been performed in accordance with the ethical standarts laid down in the 1964 declaration of Helsinski and its later amendments.

Informed consent Both patients gave their informed consent for this study.

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