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LETTER TO THE EDITOR

Holmes tremor caused by a natalizumab-related progressive multifocal leukoencephalopathy: a case report and brief review of the literature

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Dear Editor;

Holmes tremor (HT) is a rest and intention tremor with an amplitude lower than 4.5 Hz. HT is usually caused by lesions involving the thalamus and occasionally the midbrain, most often due to cerebrovascular diseases or traumas [1]. Progressive multifocal leukoencephalopathy (PML) is a severe activation of JCV within the brain mostly involving the frontal and parietal lobes, and rarely the brainstem. PML has been reported as the main, although rare, complication of natalizumab treatment in multiple sclerosis (MS).

PML clinical features include progressive motor weakness, either focal or tetraparesis, and cognitive deficits that could evolve to consciousness disorders and coma. Parkinsonism as well as other movement disorders have been rarely described [2].

Here, we describe the case of a MS patient who developed a severe natalizumab-related PML and remained affected by a HT occurred during his recovery phase.

Case report

A 49-year-old man diagnosed with relapsing-remitting MS in his 30's was treated with beta interferon for 3 years and then shifted to natalizumab monthly infusions because of a lack of efficacy. He was treated for 7 years (a total of 86 infusions) with benefit. His Expanded Disability Status Scale (EDSS) was steadily maintained at 2.5 points. Consequently, he decided to continue on natalizumab despite being positive for JCV antibodies (index value 5.27) since his third year of treatment. An alternative treatment available at that time was fingolimod but it was not prescribed since a suspected Brugada syndrome. Other disease-modifying treatments (i.e., azathioprine, mitoxantrone, and glatiramer acetate) were not considered because of the high lesion load and the comorbidities.

On June 2015, he started complaining general weakness mostly involving the right limbs and blurred vision with diplopia. His motor and bulbar functions progressively deteriorated over 3 weeks reaching EDSS 6; a cerebral MRI showed new diffuse lesions at the pons, midbrain, and thalamus without contrast enhancement (Fig. 1). His cerebrospinal fluid revealed normal cell count (two mononuclear cells), normal proteins (25.3 mg/dL; normal values 15–45), type III oligoclonal bands with negative link index, and 300 copies/mL of JCV DNA in PCR. At this point, PML was diagnosed and natalizumab discontinued. He was then started on a combination of maraviroc (600 mg/day) and mirtazapine (30 mg/day). Nevertheless, his clinical conditions worsened quickly over days; in 1 week he became comatose and therefore, he was transferred to the intensive care unit where tracheotomy and PEG were positioned (EDSS 9). Consequently, plasma exchange was not performed.

A month later, he started to globally improve very slowly. In addition, 6 months after PML onset, he developed a 2–3 Hz rest and intention tremor that involved his head and left limbs, dramatically worsening during motor tasks. He also showed bradykinesia in the left hand during the hand grip (video). The following pharmacological approaches were tried and failed: levetiracetam up to 1500 mg/day, primidone up to 250 mg/day, propranolol up to 80 mg/day, clonazepam up to 0.5 mg/day, diazepam up to 1 mg/day, piracetam up to 1200 mg/day,

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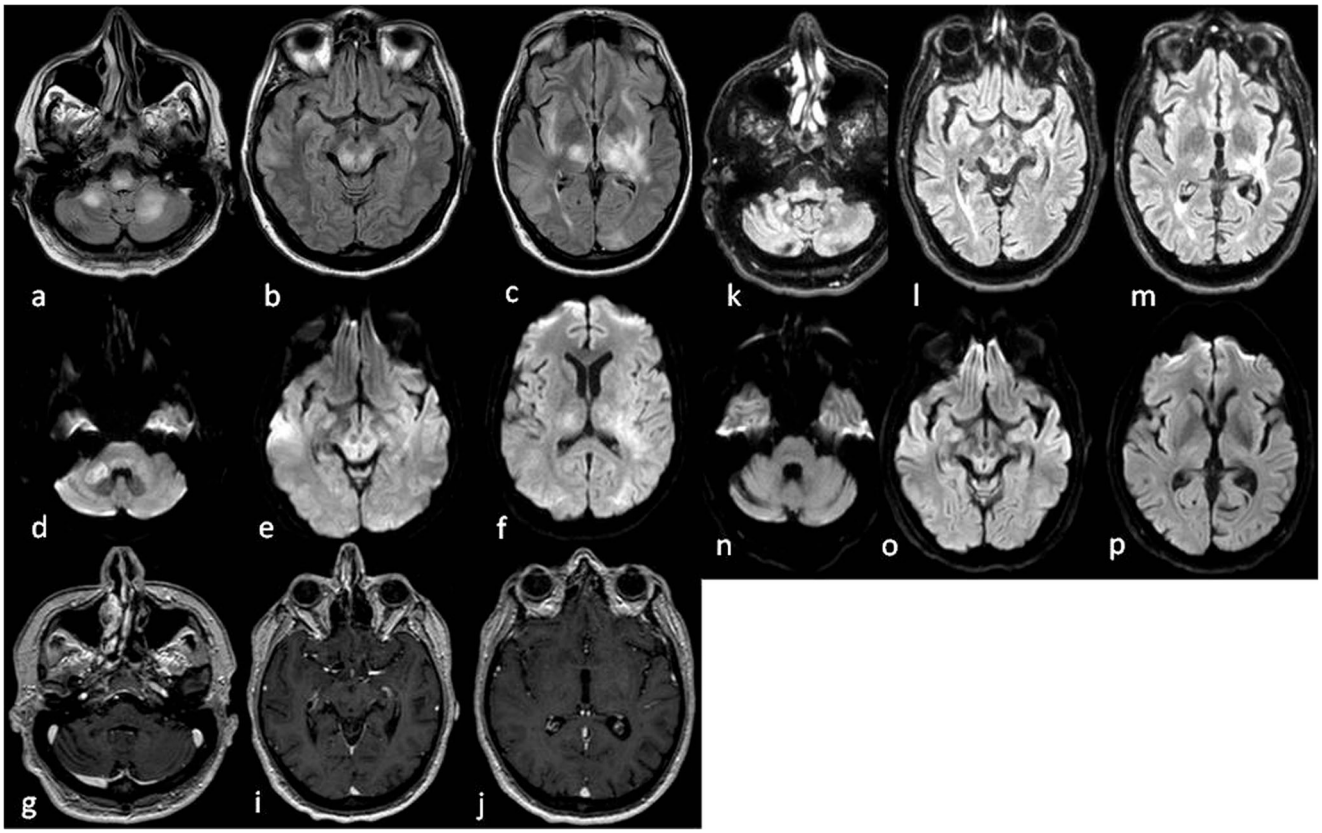

Fig. 1 1 **a**–**j** MRI of the patient in the acute and **k**–**p** in the recovery phase of PML. Particularly, **a**–**c** and **k**–**m** are FLAIR images, **d**–**f** and **n**–**p** are DWI; **g**–**j** are T1 after contrast agent (ca) injection. No T1 with ca in the recovery phase are available because of technical problems during the performance of the exam

topiramate up to 225 mg/day, delta-9-tetrahydrocannabidiol/cannabidiol (Sativex 3 puff/day), and levodopa up to 300 mg/day. While the first seven treatments did not provide any benefit, the last two were discontinued for side effects. During the next 24 months, the patient gradually recovered in his motor abilities. He was actually able to walk with assistance, but his tremor still persisted unchanged, representing the most invalidating neurological deficit. Therefore, treatment with deep brain stimulation (DBS) was considered but excluded due to the presence of multiple cerebral lesions.

Discussion

Our patient developed an HT in the recovery phase of a severe drug-induced PML that caused persistent disability and showed no response to several treatments over time. This is the first description of a typical HT caused by PML in MS. The location and time course of the JCV-related lesions are indeed consistent with the pathophysiology of HT, which generally develops 1 to 24 months after a midbrain lesion [1]. PML rarely causes movement disorders. HT has been reported mostly in immune-deficient patients (Table 1). Neither follow-up nor pharmacological strategies described such reports, mainly due to the short-survival of patients [3–8].

HT occurrence has also been described in few MS patients: three cases were reported by Raina et al. and were related to midbrain and thalamus lesions. They were treated without benefit with L-dopa, dopaminergic agonists, anticholinergic drugs, clonazepam, levetiracetam, and carbamazepine. As a matter of fact, HT in MS shows poor response to treatments, and even L-dopa, that was suggested to be effective in HT due to vascular lesions, was unable to provide benefit in both our and Raina's patients [1].

In conclusion, HT is an unusual movement disorder in patients with inflammatory diseases and shows poor response to treatments. To the best of our knowledge, no other cases of HT in drug-induced PML have been described so far. In the last years, cases of PML are increasing also in relation to the use of immunosuppressive therapies in autoimmune and hematological diseases [9, 10]. At the same time, long survival patients have been described and therefore clinicians should be aware of the possible association of movement disorders in these patients since they can represent challenging and invalidating conditions.

Table 1 Review of the published cases of HT and PML from 2000 and 2017

Reference	Gender/age at disease onset (year)	Onset symptoms	Immunodeficiency	Tremor features	Brain MRI lesion (T2 hyper-intensities)
[3]	F/57	Asymmetrical weakness at 4 limbs	No	- Right arm - Constant, spontaneous rapid, mostly arrhythmic -Both at rest and intentional	Postero-lateral left portion of mesencephalon
[4]	M/34	Weakness of right limbs	Yes (AIDS)	- Head and left arm with outstretched arms - Large-amplitude oscillatory, rhythmic (3–4 Hz) - Augmented on goal-directed movements	Left frontoparietal white matter, right superior cerebellar peduncle, and right posterior pons
[5]	F/33	Gait ataxia, speech disturbance, blurred vision	Yes (AIDS)	- Head tremor and episodes of irregular distal right arm tremor - High amplitude 4 Hz "no-no" type	Thalamus, mesencephalon red nuclei, pontine tegmentum, and cerebellum
	M/51	Generalized weakness, dysarthria, dysphagia, and visual difficulties	Yes (HIV)	"No-no" type head tremor at rest (increasing amplitude during maintenance of a fixed posture and intentional voluntary movements)	Cerebellum and middle cerebellar peduncle
[6]	M/47	Clumsiness and shaking of his right hand	Yes (HIV)	- Distal right upper limb - Rest and postural - Slow, irregular	Right middle cerebellar peduncle and adjacent cerebellar white matter
[7]	F/57	Diplopia	No	- Holmes type tremor on the right limbs	Multiple subcortical areas in both hemispheres
[8]	F/24	Involuntary jerk movement of fingers of left hand	No	- Rhythmic with goal directed movement	Ventrolateral right thalamus, posterior internal capsule, and putamen

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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