Neurological Sciences (2019) 40:2415–2417
https://doi.org/10.1007/s10072-019-03924-1

LETTER TO THE EDITOR

Orthostatic tremor and behavioral frontotemporal dementia: a case report with 7 years of follow-up

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Received: 29 January 2019 / Accepted: 7 May 2019 / Published online: 25 May 2019

Dear Editor in Chief,
Orthostatic tremor (OT) is a rare hyperkinetic disorder characterized by postural unsteadiness due to a high-frequency tremor, between 13 and 18 Hz, involving predominantly the legs and trunk, when the patient stands upright. Primary OT appears without evidence of any structural brain disease; however, a close link with parkinsonism has been demonstrated [1]. Patients with OT often report non-motor symptoms, such as anxiety, depression, social avoidance and reduction of leisure activities. They may have neuropsychological deficits, particularly those relying on integrity of the prefrontal cortex [2].

We report here the case of a woman who was referred to our rehabilitation department at the age of 66 for unexplained postural unsteadiness. She had started to exhibit tremors in the upright position at the age of 64, firstly considered a functional tremor caused by anxiety. The patient had undergone the resection of esophageal cancer with a regular follow-up. Her shakiness progressively worsened, causing difficulty standing upright and limitations in daily activities involving a prolonged upright position. Our neurological evaluation found primary OT with pathognomonic bilateral high-frequency (17 Hz) leg tremor when upright that disappeared during walking. She had mild left hypo-diadochokinesis with asymmetrical deep tendon reflexes. Brain MRI was normal. During posturographic assessment, the patient's total sway path on firm ground increased mainly with eyes closed and she displayed abnormal postural strategies during the tests using a foam platform. Over time, her symptoms became more severe with a strong feeling of instability, fear of falling, and fatigue in less prolonged standing positions and disabling instability upon standing causing falls. She was no longer capable of completing posturographic tests. At the age of 68, she suffered a left diaphyseal humeral fracture caused by an accidental fall; despite very lengthy and repeated physical therapy, she developed elbow rigidity with flexor muscle hypertonia treated with botulinum toxin. No longer wanting to leave the house led to a consequent loss of interest in any activity, except for playing with an iPad using only the right hand. Her condition gradually developed into severe asymmetric extrapyramidal syndrome with neck and upper limb dystonia. At the age of 69, abnormal ocular motility occurred with impairment of vertical smooth pursuit and slowing down of saccadic movement. The dopaminergic presynaptic system of the basal ganglia displayed by cerebral single-photon emission computed tomography (SPECT) was compromised. She started clonazepam and levodopa therapy, with a poor response. At the age of 70, she showed head drop and camptocormia, impairment of postural reflexes, and bradykinesia with severe freezing causing repeated falls. During finger-to-nose test, she displayed right arm intention tremor.

Looking back at our patient's history, she already had cognitive deficits when she started to show the first signs of OT. Over time, she developed a more evident socially inappropriate behavior showing overfamiliarity with strangers, episodic impulsivity, apathy with social withdrawal, and insensitivity. She displayed ritualistic behaviors, for example repetitive trips to the bathroom and compulsive iPad playing. Her changes in behavior, personality, emotion, and executive control meet the diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD). Neuropsychological tests showed deficits in executive tasks and sparing of visual-spatial skills. The patient underwent a preliminary genetic examination that did not show any changes in progranulin and C90RF72. The blood tests, including a thyroid function test, were normal.

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Paraneoplastic syndrome was not considered as the patient had undergone the resection of esophageal cancer with a regular follow-up. She started therapy with levetiracetam and amitriptyline and consequently her insomnia lessened and she appeared more responsive. Electrophysiological measures of tremors were performed using electromyography (EMG) on the quadriceps muscle that confirmed high-frequency tremor in spite of pharmacological therapy. Brain TC showed asymmetrical cortical atrophy (Fig. 1). At present (age 73), she is completely apathetic towards every family suggestion and is unable to maintain the upright position without help.

As previously described by De Bie [3], our patient also developed an extrapyramidal syndrome with typical signs of progressive supranuclear palsy (PSP). During the course of the disease, there were overlapping features of corticobasal degeneration. One peculiar feature was the presence of

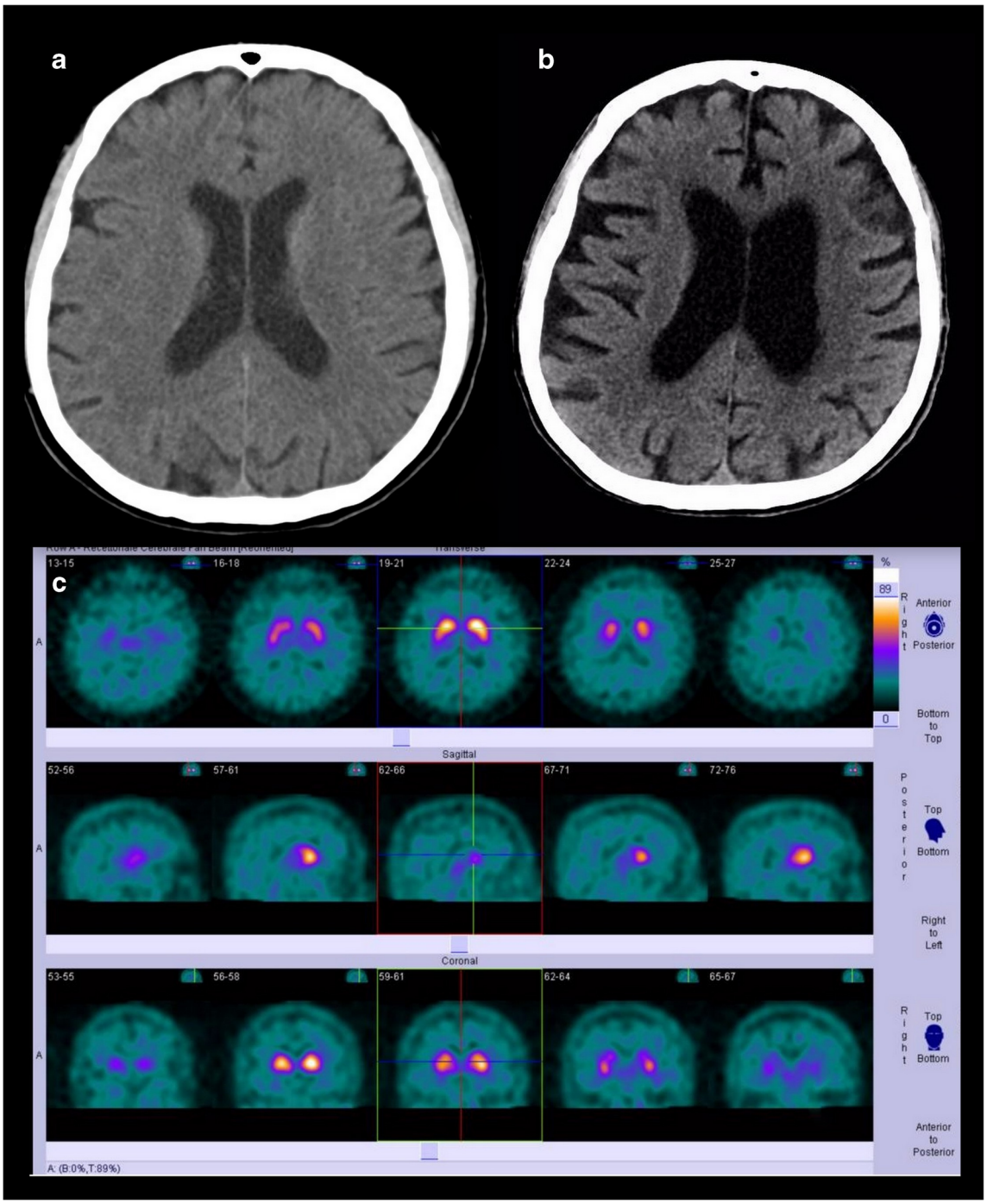

Fig. 1 Neuroimaging evolution of the patient's movement disorder. **a** Brain TC in 2011. **b** Brain TC in 2018 showing more severe atrophy of the right Sylvian fissure. **c** [123I]-FP-CIT-SPECT imaging confirmed the compromised dopaminergic presynaptic system of the basal ganglia

cognitive impairment corresponding to the behavioral variant of frontotemporal dementia (bvFTD) when she started to show the first signs of OT.

The pathophysiological mechanisms underlying primary orthostatic tremor are not fully clear. As shown by Shöberl [4], OT network may already exist during rest, triggered by sensory inputs during standing, and involving the cerebello-thalamo-cortical pathways already described for other common disorders. Gallea et al. [5] demonstrated the functional relevance of cerebello-thalamo-cortical connections using multimodal neuroimaging. He highlighted the contribution of the cerebellum and its output pathways to the premotor and motor cortices in the postural imbalance of patients with OT. The supplementary motor area plays an important role in postural balance control and contributes to the modulation of anticipatory postural adjustments leading to step initiation. Both the activation of the supplementary motor area and step initiation are impaired in extrapyramidal syndrome, with freezing of gait. Frontal areas are involved both in the control of lower limb movements during gait and in causing freezing of gait. Moreover, the cerebello-thalamo-cortical pathways involved in the pathophysiology of orthostatic tremor could be modulated by frontal areas. Our clinical case, with the overlap of different motor and non-motor signs, suggests that the co-occurrence of OT, freezing of gait, and behavioral frontotemporal signs may be linked to the selective involvement of the frontal areas.

Availability of data and material Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Research involving human participants and/or animals Not applicable.

Ethics approval and consent to participate Not applicable.

Consent for publication The patient gave written consent for publication.

All authors read and approved the final manuscript.

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