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Short-latency afferent inhibition in patients with Parkinson's disease and freezing of gait

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Freezing of gait (FOG) is one of the most common gait disturbances in patients with Parkinson's disease (PD). Recently, a PET study has documented that PD patients with FOG display cholinergic deficits selec- tively driven by nucleus basalis of Meynert (nbM)-neo- cortical denervation and not by peduncolopontine nucleus (PPN)-thalamic degeneration. Short-latency afferent inhi- bition (SAI) is a neurophysiological technique that allows evaluating major cholinergic sources in the central nervous system in vivo. We sought to determine whether central cholinergic circuits, evaluated by means of SAI testing, are impaired in patients with PD with FOG (FOG?) as compared to those without (FOG-). SAI and neuropsychological data were collected in 14 FOG? and 10 FOG-. SAI was also performed in 11 healthy control subjects. Demographic, clinical, and cognitive data were compared by using non-parametric tests. Parametric tests were used to compare electrophysiological results among groups. FOG? and FOG- had similar SAI without significant differences with controls (p = 0.207). None of the PD patients had SAI values outside the normal range ([72 %). FOG? presented poorer executive and visuospatial performances as compared to FOG-. Despite the presence of cognitive deficits, SAI failed to detect any significant decrease of cholinergic activity in FOG?. However, nbM-related cholinergic dysfunction cannot be ruled out. In fact, integrity or even increased activation of PPN-related

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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

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cholinergic circuits may mask an eventual nbM dysfunction thus resulting in normal SAI findings. Indeed, selective PPN cholinergic neurons sparing maybe a distinctive features of FOG. Alternatively or complementary, FOG pathophysiology is underpinned by non-cholinergic neurotransmitters dysfunction.

Keywords Freezing Gait Cholinergic activity PPN SAI Cognition TMS Parkinson's disease

Abbreviations

FAB	Frontal assessment battery
FDI	First dorsal interosseous
FOG	Freezing of gait
FOG-Q	Freezing of gait questionnaire
H&Y	Hoehn and Yahr
ISI	Interstimulus intervals
LEDD	Levodopa equivalent daily dose
MCI	Mild cognitive impairment
MDS	Movement disorders society
MEPs	Motor-evoked potentials
MMSE	Mini-mental state examination
nbM	Nucleus basalis of Meynert
PD	Parkinson's disease
PPN	Peduncolopontine nucleus
15-RAWLT	Rey's auditory 15-word learning test
RBD	REM-sleep behavior disorders
SAI	Short-latency afferent inhibition
TMS	Transcranial magnetic stimulation
TPCT	Ten-point Clock test
UPDRS	Unified Parkinson's disease rating scale
VH	Visual hallucinations

Introduction

Freezing of gait (FOG) is a common and disabling symptom of Parkinson's disease (PD). It is characterized by the episodic feeling of feet ''glued'' to the floor preventing the generation of effective stepping despite the intention to walk (Giladi and Nieuwboer 2008). FOG is one of the most common gait disturbances in PD and is frequently associated to balance and speech dysfunction as to frontal cognitive impairment (Amboni et al. 2008, 2010; Naismith et al. 2010). Based on the dopaminergic responsiveness, it is possible to identify: (a) FOG which appears in the off state, and disappears in the on state (treatment responsive FOG); (b) FOG indistinctly present in off and on states (treatment non-responsive FOG); (c) FOG present during on state and absent in the off state (drug-induced FOG), the rarest form (Nieuwboer and Giladi 2013).

Despite different models have been proposed, the mechanisms underlying FOG and gait disturbances in PD are not fully understood (Nutt et al. 2011). It has been hypothesized that various degrees of alteration in the interplay between the peduncolopontine nucleus (PPN) and both fronto-striatal and basal ganglia circuits may generate a wide range of gait disturbances in PD, including FOG (Nieuwboer and Giladi 2013). Recently, it has become increasingly evident that a close interplay between gait and cognition exists (Amboni et al. 2013; Tessitore et al. 2012) and that multiple neurotransmitter deficits may contribute to determine both gait and cog- nitive dysfunction in PD, with a major role exerted by cholinergic networks (Yarnall et al. 2011). Indeed, beyond its direct role in cognition, recent studies provide compelling evidence that cholinergic system may cru- cially contribute to gait dysfunction (Rochester et al. 2012).

There are two major cholinergic projection systems in the brain: the subcortical system originating in the PPN in the brainstem and the cortical system ascending from the nucleus basalis of Meynert (nbM) in the substantia innominata of the basal forebrain. Overall, cholinergic activity in the brain can be estimated with short-latency afferent inhibition (SAI), a technique that non-invasively assesses an inhibitory circuit in the sensory-motor cortex. In fact, SAI is considered a surrogate measure of cholinergic activity allowing in vivo evaluation of central cholinergic circuits under the effect of ascending pro- jection from nbM (Di Lazzaro et al. 2002) and PPN (Oliviero et al. 2005). Accordingly, SAI has been increasingly used to identify those symptoms possibly underpinned by cholinergic dysfunction in a variety of neurodegenerative diseases. Indeed, in PD, SAI abnor- malities have been linked with slower gait disturbances (Rochester et al. 2012), with dementia (Celebi et al. 2012) and mild cognitive impairment (MCI) (Yarnall et al. 2013), further confirming the role of cholinergic dysfunction in the development of both gait and cogni- tive dysfunction in PD. Likewise, SAI has been found to be reduced in PD patients with visual hallucinations (VH) or REM-sleep behavior disorders (RBD) (Man- ganelli et al. 2009; Nardone et al. 2013), suggesting that cholinergic dysfunction may be the major anatomo- functional basis for VH- and RBD-associated cognitive deficits as well.

To our knowledge, studies evaluating SAI in PD patients with FOG as compared to those without are lacking. Thus, based on these premises, we sought to determine whether central cholinergic circuits, evaluated by means of SAI testing, are impaired in PD patients with FOG, namely with treatment non-responsive FOG. We also evaluated the cognitive profile of all the patients enrolled.

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To our knowledge, studies evaluating SAI in PD patients with FOG as compared to those without are lacking. Thus, based on these premises, we sought to determine whether central cholinergic circuits, evaluated by means of SAI testing, are impaired in PD patients with FOG, namely with treatment non-responsive FOG. We also evaluated the cognitive profile of all the patients enrolled.

Patients and methods

Subjects

Patients with a diagnosis of PD according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank (Hughes et al. 1992) were consecutively screened at the Movement Disorders Centre, University Federico II, Naples, Italy. Consecutive series screening methodology was used only for screen- ing purposes. Inclusion criteria were: (1) age of 40 years or older in order to exclude early onset parkinsonism; (2) a Hoehn & Yahr (H&Y) stage equal or less than 2.5 while in on state; (3) disease duration less than 10 years; (4) antiparkinsonian treatment at a stable and optimized daily dosage during the 4 weeks prior to study entry. Exclusion criteria were: (1) treatment with cholinesterase inhibitors, benzodiazepines, neuroleptics, anti-cholinergic or anti-depressant drugs; (2) major depression according to the Diagnostic and statistical manual of mental dis- orders fourth edition criteria; (3) dementia according to clinical diagnostic criteria proposed by the Movement Disorders Society (MDS) commissioned Task Force (Emre et al. 2007); (3) presence of VH or RBD; (4) clinically significant or unstable medical conditions including serious cardiovascular or cerebrovascular dis- ease or other conditions possibly affecting gait. The recruitment lasted for 2 years and involved all the clinics performed in our center (four clinics per week).

Among eligible subjects, we identified patients with treatment non-responsive FOG according to the follow- ing three steps assessment: (1) identification of off and on states based on brief semi-structured interview aimed at detecting the periodic reappearance of motor and non- motor symptoms, and their response to medication intake; (2) identification of FOG based on the following two conditions that had all to be fulfilled: (a) score [0 to item 3 of the FOG questionnaire (FOG-Q) (Giladi et al. 2000), (b) patients' recognition of the condition when it was demonstrated to them by an experienced clinician mimicking the phenomenon; (3) detection of FOG sub- types based on the following question ''*When do you experience FOG*?'' (a) *only during the best moments of the day* (*on state*); (b) *only during the worst moments of the day* (*off state*); (c) *in both* (*on and off state*)''. Treatment non-responsive FOG was defined as FOG present during both on and off state (point 3, response c). Absence of FOG was defined when neither condition of the point 2 was fulfilled. Patients presenting FOG either only during on state or off state were not included in this study.

Clinical evaluation

Clinical and motor functions were evaluated with the H&Y, parts I–IV of the Unified Parkinson's disease Rating Scale (UPDRS) and the FOG-Q. In order to compare the amount of the administered dopaminergic drugs, levodopa equivalent daily dose (LEDD) was computed for each patient.

Electrophysiological evaluation

Magnetic stimulation

Transcranial magnetic stimulation (TMS) of the motor cortex was performed with a high-power magnetic stimu- lator (MagPro X100, Medtronic, Denmark). A figure-of- eight coil (with external loop diameters of 9 cm) was positioned at the scalp over the right or left (according to the more affected side) hand motor area to evoke motor responses [motor-evoked potentials (MEPs)] in the con- tralateral first dorsal interosseous (FDI) muscle. MEPs were recorded through surface electrodes with the active electrode on the motor point of the muscle and the refer- ence electrode on the metacarpophalangeal joint of the index finger. MEPs were amplified and filtered (bandwidth 3 Hz to 3 kHz) using a Keypoint electromyograph (Medtronic).

Short-latency afferent inhibition (SAI)

SAI was investigated by applying the technique descri- bed by Tokimura and colleagues (Tokimura et al. 2000). Conditioning stimuli were single electrical pulses (200 ms) applied through bipolar electrodes to the median nerve at the wrist (cathode proximal). The intensity of the conditioning peripheral stimulus was set at just over the motor threshold to evoke a visible twitch of the thenar muscles. The N20 wave of cortical somatosensory response was recorded with active elec- trode attached 2 cm behind C4/C3 (10–20 International System) and reference electrode 2 cm behind C3/C4. A total of 500 responses were averaged twice and super- imposed to identify the latency of the N20 peak. The intensity of the test cortical magnetic shock was adjusted to evoke an MEP in relaxed FDI muscle with peak-to- peak amplitude of *1 mV. SAI was tested at different interstimulus intervals (ISIs) determined on the basis of the N20 wave latency. ISIs ranged from 2 to 8 ms after N20 latency and were investigated in steps of 2 ms. For each ISI, we calculated the amplitude of basal MEP (average of five consecutive responses obtained after

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