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Paired neurophysiological and clinical study of the brainstem at different stages of Parkinson's Disease

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HIGHLIGHTS

- In comparison with matched controls, VEMPs were consistently altered in patients with Parkinson's Disease (PD) and severity of abnormalities progressively increased with stage of disease.
- In PD significant correlation was found between VEMP alterations and both postural instability and REM sleep behavior disorder.
- Combined use of VEMPs may provide insights into pathophysiological dynamics of brainstem involvement at the earliest phases of PD.

ABSTRACT

Objective: To study brainstem function in Parkinson's Disease (PD) at different stages, through a battery of vestibular-evoked myogenic potentials (VEMPs) and compare the results with scores on clinical scales assessing the presence of symptoms linked to brainstem involvement.
Methods: Cervical, masseter and ocular VEMPs were recorded in patients with early PD ($n = 14$, disease duration 1.42 ± 0.7 years), advanced PD ($n = 19$, disease duration 7.26 ± 2.9 years) and in 27 age-matched controls. In PD, the following clinical scales were administered: Mini-BESTest, REM sleep Behavior Disorder Screening Questionnaire (RBD-SQ), PD Sleep Scale, Epworth Sleepiness Scale and Geriatric Depression Scale.
Results: Rate of VEMPs alterations was higher ($p < 0.001$) in PD than controls, but similar within PD groups. However, early and advanced PD showed a different pattern of abnormalities ($p = 0.02$), being latency delay prevalent in the former and absence in the latter. VEMP impairment correlated directly with RBD-SQ scores in both PD cohorts and inversely with Mini-BESTest scores in advanced PD.
Conclusions: VEMPs displayed progressive severity of alterations at different stages of PD, with remarkable correlations with presence of postural instability and RBD.
Significance: The combined use of VEMPs may provide interesting insights into the pathophysiological mechanisms of PD at the earliest and prodromal stage of the disease.

Abbreviations: AD, Alzheimer's Disease; BESTest, Balance Evaluation Screening Test; cVEMP, cervical vestibular-evoked myogenic potential; EDS, Excessive Daily Somnolence; ESS, Epworth Sleepiness Scale; GDS, Geriatric Depression Scale; H&Y, Hoehn & Yahr scale; IOM, Inferior Oblique Muscle; L-DOPA, Levodopa; mVEMP, masseter vestibular-evoked myogenic potential; oVEMP, ocular vestibular-evoked myogenic potential; PD, Parkinson's Disease; PDSS, Parkinson's Disease Sleep Scale; PPN, pedunculo pontine nucleus; RBD, REM Behavior Disorder; RBD-SQ, REM Behavior Disorder Screening Questionnaire; SCM, sternocleidomastoid muscle; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS III, part 3 (motor system) of the Unified Parkinson's Disease Rating Scale; VEMP, vestibular-evoked myogenic potential.

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1. Introduction

Neurophysiological investigation of the brainstem may provide useful information about the functional integrity of this region in physiological and pathological settings. Brainstem reflexes indirectly are able to assess segmental and suprasegmental mechanisms of control on this structure, which may be affected in a number of neurological diseases (Ongerboer de Visser and Cruccu, 1993). Moreover, they may assist clinicians by complementing clinical and neuroimaging data, providing additional information on the site of the lesion (Ongerboer de Visser, 1982).

In Parkinson's Disease (PD), besides direct brainstem lesions (Grinberg et al., 2010), a functional misconnection between the brainstem and higher structures, involving mainly non-dopaminergic pathways, seems to be present from the earliest phase of the disease (Grinberg et al., 2010). The general picture arising from neurophysiological studies of the brainstem in PD indicates a mismodulation of physiological afferent processing as well as of brainstem control over spinal motoneurons. As a consequence, an enhancement of interneuron excitability at the brainstem level (Kimura, 1973; Agostino et al., 1988; Cruccu et al., 1991; Basso and Evinger, 1996; Thevathasan et al., 2011) and a variation of the input–output gain of spinal motoneurons (Caliandro et al., 2011; Johnson and Heckman, 2014) may occur.

Among brainstem reflexes, the activity of central reflex volleys within the brainstem may also be effectively represented by the vestibular-evoked myogenic potential (VEMP), which is a transient change of the compound motor action potential in response to stimulation of vestibular receptors. The VEMPs that have been characterized in more detail and that have an established clinical role are the cervical VEMP (cVEMP) and the ocular VEMP (oVEMP). The cVEMP corresponds to the vestibulo-collic reflex (Colebatch et al., 1994) and is an expression of an ipsilateral pathway linking the VIII and XI cranial nuclei. The oVEMP corresponds to the vestibulo-ocular reflex (Rosengren et al., 2005) which is mediated by a crossed connection between the VIII and III cranial nuclei (Weber et al., 2012). Finally, the masseter VEMP (mVEMP), is a vestibular-evoked myogenic potential corresponding to the vestibulo-masseteric reflex, or VMR, which appears as a bilateral and symmetric biphasic positive/negative potential (p11/n15 wave) in the averaged unrectified EMG (Deriu et al., 2003). When the VMR is elicited by loud clicks, it partially overlaps with the acoustic-masseteric reflex (p16/n21 wave) so that, in normal hearing people, the n15 wave is not detectable and a p11/21 complex is visible (Deriu et al., 2005). Neurophysiologic criteria to discriminate the vestibular- and the cochlear-induced masseter responses have been defined and their inhibitory nature and origin clarified (Deriu et al., 2005, 2007, 2010). The neural pathway from vestibular receptors to the SCM is not characterised in humans, although the existence of monosynaptic projections from the vestibular complex to masseter motoneurons has been demonstrated in experimental animals (Giaconi et al., 2006; Cuccurazzu et al., 2007).

VEMPs have been largely used for the study of a number of neurological conditions affecting the brainstem for which they, singularly or in combination, have shown a potential for detection of otherwise clinically and radiologically silent lesions (Pollak et al., 2006; Boldingh et al., 2011; Habek, 2013; Magnano et al., 2014). In PD, the cVEMP has only been tested in patients with the full-blown disease, where a general pattern of absence and of amplitude reduction has been reported (Pollak et al., 2009; Potter-Nerger et al., 2012).

A complete battery of VEMPs, consisting of the cVEMP and, in addition, mVEMP and oVEMP, might be able to indirectly study the brainstem in its whole extension, possibly revealing abnormalities which can express the dysfunction of interneuronal loops operating at different levels. The use of such a battery seems worthwhile in PD, where brainstem involvement represents a key passage in the spreading of the pathological process from the earliest stages of the disease (Braak et al., 2003). Therefore this study is aimed at testing cVEMP, mVEMP and oVEMP in patients with PD at both early and advanced stages, to probe the function of the brainstem in different moments of the disease. Furthermore, a possible correlation between neurophysiological data and clinical evidence of the presence of non-motor symptoms was investigated, which may be linked to brainstem involvement.

2. Materials and methods

A total of 60 subjects (33 PD patients and 27 healthy subjects) participated in the study. The cohort was subdivided into three groups: early PD (n = 14, 46–75 years old) with newly diagnosed PD; late PD (n = 19, 52–77 years old) with advanced PD and healthy controls (n = 27, 41–85 years old). Patients were labelled as having "early" PD if onset of the very first putative symptoms of PD, based on clinical records or interview, was within 36 months from enrollment. Inclusion criteria were the presence of idiopathic PD according to diagnostic criteria (Gelb et al., 1999), with satisfying response to dopaminergic treatment and absence of dyskinesias, wearing off symptoms or ON/OFF fluctuations. Presence of mild or severe degrees of hearing loss, neurotologic and stomatognathic disorders, muscular and osteoarticular cervical disturbances, were excluded in both patients and controls by accurate neurological, ENT and odontostomatologic examinations. In addition, use of drugs modulating the central nervous system such as benzodiazepines, anti-epileptic or antidepressant drugs were used as exclusion criteria for all subjects. All participants were evaluated in a single morning session at the same hour of the day and by the same operator. Patients were assessed during the ON phase to minimize potential confounding effects of the lack of dopaminergic control and to reduce as much as possible any interference in VEMPs recording, possibly due to tremor or rigidity. The study protocol was approved by the local ethical committee (ID prot. N. 987, 19/09/2011) and all subjects gave their written informed consent prior to inclusion in the study.

2.1. Clinical evaluation

Patients underwent a thorough clinical examination with administration of the Unified Parkinson's Disease Rating Scale (UPDRS, with particular regard to the UPDRS III) and Hoehn & Yahr (H&Y) staging. Moreover, presence of symptoms that may be linked to a brainstem involvement (Grinberg et al., 2010; Iranzo, 2013) was assessed through a battery of self-administration tests. Presence of postural instability was evaluated through the Mini-Balance Evaluation Screening Test (Mini-BESTest), a 14-item scale derived from a wider one (BESTest, Horak et al., 2009; Franchignoni et al., 2010), which allows a quick and sensitive evaluation of static and dynamic balance in PD patients (King et al., 2012). Presence of symptoms suggesting REM Behavior Sleep Disorder (RBD) was assessed through the REM Sleep Behavior Disorder Screening Questionnaire (RBD-SQ), which has been proved to have high sensitivity as a screening tool for RBD in PD (Nomura et al., 2011). Excessive Daily Somnolence (EDS) was tested with the Epworth Sleepiness Scale (ESS) which evaluates the chance of getting asleep in some situations the patient may come across during daily life (Johns, 1991) and has found wide application as an easy and reliable tool for detection of EDS in PD (Kumar et al., 2003). The general quality of the nocturnal sleep was evaluated through the Parkinson's Disease Sleep Scale (PDSS), specifically val-