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Forehead sympathetic skin responses in determining autonomic involvement in Parkinson's disease

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HIGHLIGHTS

- Forehead sympathetic skin response was examined in comparison to extremity SSR to test the hypothesis that forehead SSR might be impaired sooner than extremity SSR in PD.
- Forehead SSR was more sensitive than extremity SSR in determining autonomous nervous system dysfunction not only in the late but also in the early stage of PD patients.
- With further supportive research, forehead SSR might be used as a simple diagnostic electrophysiological test in the early diagnosis of ANS dysfunction.

ABSTRACT

Objective: The purpose of this study was to evaluate forehead sympathetic skin response (SSR) and demonstrate any differences with extremity SSR in determining autonomic nervous system (ANS) involvement in patients with Parkinson's disease (PD).
Methods: Twenty early stage, 20 advanced stage idiopathic PD patients and 20 healthy controls participated in this study. SSR of forehead, hands and feet, heart rate variability (HRV), orthostatic intolerance, QT intervals and dysautonomic symptoms were evaluated.
Results: Absent forehead SSR was determined unilaterally in 4, bilaterally in 7 early stage patients, and unilaterally in 4, bilaterally in 8 advanced stage PD patients; there was significant difference between early and advanced stage PD and control groups in terms of the lack of SSR ($p = 0.000$). Absent extremity SSR was determined in at least 1 extremity of 3 advanced stage PD patients, and none of the early stage PD patients. No difference was noted in HRV at rest between early and advanced stage PD and control groups ($p = 0.218$); but HRV at deep breathing was lower in both early and advanced PD patients compared to controls ($p = 0.014$, $p = 0.002$, respectively).
Conclusion: Forehead SSR is more sensitive in determining ANS dysfunction not only in late but also in early stage of PD.
Significance: With further supportive research, forehead SSR might be used as a simple diagnostic electrophysiological test in the early diagnosis of ANS dysfunction enabling proper treatment and increasing the quality of life of PD patients.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms including tremor, rigidity, bradykinesia and postural instability and non-motor symptoms including sleep dysfunction, neuropsychiatric symptoms, sensory disturbances and autonomic involvement (Olanow et al., 2009). The spectrum of autonomic nervous system (ANS) symptoms in PD consists of orthostatic intolerance, bladder and sexual dysfunction, hyperhidrosis and gastrointestinal problems (Magerkurth et al., 2005; Wüllner et al., 2007; Jankovic, 2008). Although autonomic involvement, as demonstrated by clinical and

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electrophysiological examinations, results partially from the neurodegenerative process itself, drugs used to treat PD also contribute in its development (Kikkawa et al., 2003; Zakrzewska-Pniewska and Jamrozik, 2003; Magerkurth et al., 2005; Muzerengi et al., 2007; Wüllner et al., 2007; Ziemssen and Reichmann, 2007; Shindo et al., 2008).

Sympathetic skin responses (SSR) defined as variation in electrical potential of the skin due to sympathetic sudomotor outflow, and heart rate variability (HRV), a marker of parasympathetic cardiovagal function, are simple and reliable electrophysiological markers of ANS involvement in PD. SSR of extremities has been shown to be impaired in PD in several studies (Wang et al., 1993; Choi et al., 1998; Zakrzewska-Pniewska and Jamrozik, 2003; Schestatsky et al., 2006). Additionally, pathologic truncal but not extremity alpha synuclein accumulation has been demonstrated in cutaneous peripheral nerves in skin biopsy samples of patients with PD (Ikemura et al., 2008; Miki et al., 2010), suggesting an earlier involvement of truncal post-ganglionic fibers due to better preservation and lesser denervation of the truncal autonomic skin nerves.

In this study, we hypothesized that forehead SSR might be impaired sooner than extremity SSR in PD due to preferential degeneration of autonomic nuclei projecting to the face. We examined forehead SSR in comparison to extremity SSR, and other parameters of ANS involvement including HRV, orthostatic intolerance, QT intervals and dysautonomic symptoms to demonstrate earlier involvement of ANS in PD.

2. Methods

2.1. Subjects

Forty patients with idiopathic PD (26 males, 14 females), including 20 early (Hoehn Yahr 1–2) and 20 late (Hoehn Yahr 3–5) stage patients, diagnosed by the U.K. Parkinson's Disease Society Brain Bank criteria (Hughes et al., 1992) at the Movement Disorders Outpatients Clinic of Bakirkoy Research and Training Hospital between June 2010 and December 2011, and 20 age-matched (by study group) healthy controls (11 males, 9 females) were included in this study, consecutively.

All subjects were examined and followed by movement disorders specialists. Clinical severity was determined according to Hoehn–Yahr (H–Y) scale and disability status was evaluated by unified Parkinson's disease rating scale (UPDRS) (Hoehn and Yahr, 1967; Fahn and Elton, 1987). Early PD was defined as having a Hoehn Yahr score of 1–2 and advanced PD was defined as having a Hoehn–Yahr score of 3–4–5. Subjects with vascular, drug-related or atypical parkinsonism such as Shy Drager syndrome, multisystem atrophy or progressive supranuclear palsy; concomitant potentially ANS involving diseases including diabetes mellitus, cerebrovascular diseases; polyneuropathy or carpal tunnel syndrome determined by nerve conduction studies; cardiac arrhythmia or implanted pacemaker; or subjects receiving any medications that might affect ANS including tricyclic antidepressants or beta blockers were excluded from the study. Control group consisted of volunteering healthy, age-matched hospital staff and their relatives with no disorders that might affect the ANS.

Dysautonomic symptoms were evaluated using the "Questionnaire on the Autonomic Nervous System Neurovegetative Laboratory Neurological University Hospital Freiburg" (Magerkurth et al., 2005). All examinations were performed in the morning, following 12 h of medication-free period, i.e. before the day's first medications, after the last doses of the previous day were received.

Blood pressures were measured at supine position after 10 min of rest, and upright position after 3 min of standing. The orthostatic hypotension (OH) definition of American Autonomic Society and American Academy of Neurology that required 'a decrease of $\geqslant$20 mmHg in systolic and a decrease of $\geqslant$10 mmHg in diastolic blood pressure when a person assumes a standing position' was used (The Consensus Committee of the American Autonomic Society and the AAN, 1996). ECG recordings were obtained after 10 min of resting and QT interval (QTc) was calculated by Bazett's formula ($QT/\sqrt{RR}$) (The Consensus Committee of the American Autonomic Society and the AAN, 1996).

The objective and content of the study was explained to all subjects in detail, and written informed consent was obtained from all subjects. The study was approved by institutional ethics committee and conducted in complete accordance with the Declaration of Helsinki.

2.2. Sympathetic skin response

All electrophysiological tests were performed with the Dantec Keypoint EMG/NCS/EP System device. SSR were recorded from forehead, hands and feet. Recordings were obtained at supine position in a quiet, air-conditioned room maintained at 22–24 °C. For extremity studies, active disc electrodes were placed in the middle of palms and soles, while reference electrodes were placed on the dorsum of hands and feet. Active electrodes were placed on the superolateral margin of the frontal eminence, and reference electrodes were placed approximately 3–4 cm laterally and 2 cm downwards in forehead studies (Fig. 1). Electrical stimulation (0.2 s duration and 30–100 mA intensity) was applied on the median nerve at wrist on the contralateral of the recording. Filter band pass was kept at 0.5–2 kHz, sensitivity was 0.5 mV and sweep speed was 5–10 s. Electrical stimulation was administered irregularly at a minimum of 30-s and 20-s intervals during extremity and forehead studies, respectively, to overcome habituation (Yildiz et al., 2008; Oh, 1993). The onset latency and peak-to-peak amplitude of SSR were evaluated. Ten consecutive stimuli were administered in each forehead and extremity zone. Stimulus intensity was increased if no response was obtained. If at least 5 consecutive 100 mA electrical stimuli could not elicit a consistent change larger than 50 μV from baseline, the result was recorded as absent SSR, and SSR was deemed pathological only if no response was recorded.

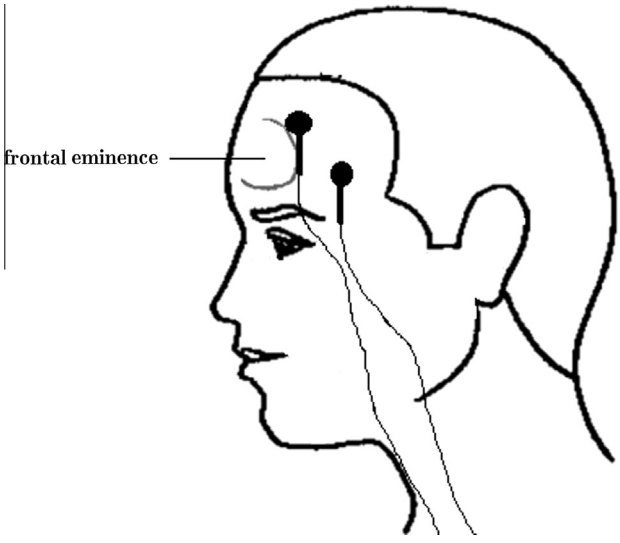

Fig. 1. Schematic demonstration of the placement of forehead electrodes.