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Short communication

Pilomotor function is impaired in patients with Parkinson's disease: A study of the adrenergic axon-reflex response and autonomic functions

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ABSTRACT

Introduction: Autonomic nervous system disturbances including sweating abnormalities and cardiovascular symptoms are frequent in Parkinson's disease (PD) and often precede motor involvement. Cholinergic vasomotor and sudomotor skin nerves are impaired in patients with PD even at early disease stages. We hypothesized that adrenergic pilomotor nerve function is similarly impaired in early PD and might constitute a novel diagnostic target.

Methods: We conducted a study in 12 PD patients (Hoehn&Yahr 1–2) and 12 healthy control subjects. Pilomotor function was evaluated after iontophoresis of phenylephrine on the dorsal forearm to elicit axon-reflex mediated pilomotor erection (goose bumps). Silicone impressions were obtained, scanned and quantified for pilomotor muscle impressions by number, area and axon-reflex spread. Vasomotor function was evaluated using laser Doppler flowmetry and sudomotor function via sympathetic skin response. Cardiac autonomic function was assessed via heart rate variability. Severity of autonomic symptoms was evaluated using the Scales for Outcomes in Parkinson's disease–Autonomic questionnaire.

Results: Pilomotor response was reduced in PD patients compared to control subjects (impression number: 12.2 ± 8.2 vs. 16.5 ± 5.9, $p < 0.05$; impression area: 10.8 ± 2.2 mm^2 vs. 24.8 ± 3.1 mm^2, $p < 0.01$; axon-reflex spread: 89.0 ± 10.6 mm^2 vs. 185.9 ± 10.8 mm^2, $p < 0.01$) and correlated negatively with severity of autonomic symptoms ($p < 0.01$). Similarly, sudomotor ($p < 0.01$) and vasomotor ($p < 0.05$) but not cardiac autonomic ($p =$ n.s.) function were reduced in PD patients versus control subjects.

Conclusion: Pilomotor function is impaired in early stages of PD. Pilomotor axon-reflex assessment might be useful in the investigation of disease related pathology and supplement other clinical markers of autonomic neuropathy in PD.

1. Introduction

In Parkinson's disease (PD) early diagnosis may allow timely symptomatic treatment and improvement of quality of life but only few techniques are available to assess prodromal and early symptoms [1]. Autonomic nervous system disturbances including impaired sweating and cardiovascular symptoms are frequent in

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patients with PD and often precede motor involvement and reduce quality of life [2]. The underlying pathophysiology may involve damage to autonomic postganglionic sudomotor and vasomotor nerve fibers [3]. However, the exact mechanisms are not fully understood. Peripheral autonomic sudomotor and vasomotor function can be assessed by quantification of axon-reflex mediated responses to pharmacological stimulation of cholinergic slightly myelinated and unmyelinated nerve fibers (small fibers) in the skin [4]. It was recently shown that iontophoretic stimulation of cutaneous adrenergic small fibers with phenylephrine elicits axon-reflex mediated pilomotor erection (goose bumps) in an indirect region surrounding the area of direct stimulation, which can be evaluated using the Quantitative Pilomotor Axon-Reflex Test (QPART) [5]. To date there are no studies on pilomotor function in PD.

We tested the hypothesis that pilomotor axon-reflex responsiveness is impaired in early PD and may constitute a useful tool to measure disease related pathology. We further sought to assess whether vasomotor, sudomotor and cardiac autonomic function show similar functional impairment.

2. Methods

2.1. Ethical standard

The study was approved by the Technische Universität Dresden Ethics Committee (Registration number: EK 12012013). Written informed consent was obtained from all subjects. The study was registered in the German Clinical Trials Register (registration number: DRKS00005033).

2.2. Subject selection

Patients with PD and healthy control subjects were recruited. Medical history was obtained and physical examination was performed in all subjects prior to the study. Exclusion criteria were treatment with beta-blockers or tricyclic antidepressants, any dermatological disorder affecting skin testing sites, known allergy to phenylephrine, consumption of more than 1 alcoholic beverage/day or nicotine, had evidence by history or exam of large fiber neuropathy. Additional exclusion criteria for control subjects were any acute or chronic disease and chronic intake of any medication. Subjects underwent single-day testing with self-reporting of adverse events.

2.3. Pilomotor function: quantitative pilomotor axon-reflex test (QPART)

Iontophoresis of phenylephrine was performed to evoke axon-reflex mediated pilomotor erection as previously described (Fig. 1A) [5]. A drug delivery capsule electrode (LI-611®, Perimed, Järfälla, Sweden) was attached to the testing region on the dorsal forearm and the inner chamber of this capsule (open to the skin surface) was infused with 0.4 ml of 1% phenylephrine solution. We randomly selected either the right or left arm for pilomotor assessment. Iontophoresis was performed with 0.5 mA over 5 min over a 1 cm diameter skin region using an iontophoresis stimulation device (Phoresor-PM850®, IOMED, Salt Lake City, UT, USA). Impressions of erect pilomotor muscles were obtained using a silicone based material (Honigum Light®, DMG, Hamburg, Germany) (Fig. 1B1). Cured silicone impressions were highlighted using toner and scanned using a high resolution scanner (CANON LiDE 700F®, Canon, Tokyo, Japan) (Fig. 1B2). Silicone scans were analysed by an investigator (BI) blinded to the study group using an image analyzing software package (Image Pro Plus 6.0®, Media Cybernetics, Bethesda, MD). Impressions of erect pilomotor muscles were quantified by number, area and spatial spread of axon-reflex mediated pilomotor erection (Fig. 1B3–5).

2.4. Vasomotor function: laser-Doppler flowmetry

The vasoconstrictory response of cutaneous blood vessels was assessed using a laser Doppler flowmeter (Periflux®, Perimed, Järfälla, Sweden) on the distal phalanx of the index finger as previously described [6]. Briefly, the lowest blood flow post–inspiration was subtracted from baseline flow. The result was divided by baseline flow to calculate the vasoconstrictory response. Time to 50% constriction ($\Delta t_{50\%}$down) and 50% redilation ($\Delta t_{50\%}$up) were also calculated.

2.5. Sudomotor function: sympathetic skin response

Sympathetic skin response was measured as previously described [7]. Briefly, the skin conductance level was measured in μSievert (μS) from two medial phalanges (third and fourth finger) with a data acquisition system (Powerlab®, AD Instruments, Dunedin, New Zealand). The maximum increase in amplitude following sudden deep respiration was calculated to quantify the sympathetic skin response as measure of functional reactivity of sweat glands.

2.6. Cardiac autonomic function: heart rate variability

Heart rate variability (HRV) was assessed using the data analysis software package (Chart 5®, AD Instruments, Dunedin, New Zealand) over 5 min under resting conditions followed by 5-min assessment under metronomic breathing at 6 cycles/minute with monitoring of chest movements as previously described [7]. Time domain analysis was performed by calculating the standard deviation of NN–intervals (SDNN). Frequency domain analysis was conducted via power spectrum assessment. Absolute power values were analysed for low frequency (LF; 0.04–0.15 Hz), high frequency (HF; 0.15–0.4 Hz) and total power (TP). The LF/HF ratio was calculated.

2.7. Evaluation of symptoms

Symptoms were assessed using Hoehn and Yahr staging, Scales for Outcomes in Parkinson's Disease–Autonomic (SCOPA–AUT), and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I–IV.

2.8. Statistical analysis

Statistical analysis was performed using STATA® version 11 (STATA Corp., TX, USA). Continuous data are presented as mean (±standard deviation), discrete data as percentages. Differences between groups and subgroups were analysed using Student's *t*-test or Wilcoxon rank–sum test, according to data type and distribution. Alpha level for statistical significance was set to 0.05. Pearson's correlation coefficient was determined to assess the association between pilomotor function and severity of symptoms.

3. Results

3.1. Subjects

Healthy control subjects ($n = 12$) were comparable to patients with PD ($n = 12$) in all baseline characteristics (age: 58.5 ± 11.5 years vs. 64.9 ± 8.1 years, $p = 0.1293$ gender: 67% females vs. 42% females, $p = 0.84$). In the PD group H&Y score was 1.7 ± 0.5 and 7 patients (58.3%) received anti-parkinsonian medication.

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