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Clinical correlates of cerebral white matter abnormalities in patients with Parkinson's disease

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ABSTRACT

Objective: To determine if autonomic dysfunction, cognitive disorders or axial disability are associated with white matter lesions (WML) in Parkinson disease (PD).
Methods: We performed a retrospective cross-sectional review study on 204 consecutive PD patients who underwent cerebral MRI in our center between January 2012 and July 2016. For each patient, we scored the severity of WML and PV (periventricular) WML using the Fazekas score and using the ARWMC scale for WML and BG (basal ganglia) and clinical characteristics such as neurogenic orthostatic hypotension and cognitive function.
Results: 204 PD patients were included of whom n = 53 (26.0%) had neurogenic orthostatic hypotension (nOH). The presence of nOH was significantly associated with the severity of WML as defined by the Fazekas score and the ARWMC scale. An ordinal regression model confirmed this association with an OR of 0.41 (95% CI 0.18–0.92: p = .03) and an OR of 0.39 (95% CI 0.17–0.88: p = .02). There were no significant associations between WML and other co-variables, including hypertension, dopaminergic medication use, Hoehn and Yahr stage, gender and cognitive decline.
Conclusion: The presence of nOH is associated with WML severity in PD patients.

1. Introduction

Neurogenic orthostatic hypotension (nOH) is a common complication of neurodegenerative diseases. In patients with Parkinson's disease (PD), there is an overall prevalence of around 20% [1]. nOH may lead to transient loss of consciousness during rising or after prolonged standing, thus leading to falls and injuries [2]. But nOH may cause other damage as well. Specifically, it has been proposed that recurrent episodic hypotension following nOH may result in cerebral hypoperfusion, in turn causing anoxic damage to vulnerable areas of the brain, appearing as WML on cerebral imaging. Support for this hypothesis has come from prospective observational longitudinal cohort brain MRI studies showing an association between WML and a postural drop in blood pressure among PD patients. This is of clinical importance because these WML in PD patients are associated with gait disorders and cognitive impairment [3]. Alternatively, the association between nOH and cognitive decline [4] in PD may reflect shared underlying synuclein-related pathology, affecting both the autonomic nervous system (causing nOH) and (sub)cortex (causing cognitive decline). More knowledge on the consequences of nOH may lead to new therapeutic interventions.

The aim of the current retrospective study was to explore what factors are associated with WML in PD patients and if nOH in particular is associated with these WML.

2. Methods

2.1. Study design, settings and population

The study was conducted as a retrospective cross-sectional

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review study. The medical records of 204 consecutive PD patients during the period from January 2012 to July 2016 who had been evaluated at the outpatient Neurology department at the Radboud University.

Medical Center (Nijmegen, the Netherlands) and who underwent cerebral MRI were included. A diagnosis code (International Classification of Diseases) was used to identify these subjects (ICD-10 code 0501) from a list of all patients seen at the outpatient clinic during the aforementioned period. PD patients who were seen as secondary referrals but with brain MRI performed in another hospital were not included.

In two subsets of 28 and 50 PD patients, respectively, we were able to obtain additional prospectively collected data (described below), and these two groups are referred to as cohort 1 and cohort 2 further on. All patients from these two groups gave written informed consent for the additional data collection, as approved by the local ethics committee. For the 126 remaining patients, we used the clinical and imaging data collected as part of routine healthcare. This latter group with retrospective patients is referred to as cohort 3 further on.

2.2. Data collection

Our medical Epic Systems Corporation, Madison, Wisconsin USA (EPIC) was used to obtain the basic demographics and clinical data from each subject's visit closest to when the MRI was performed, with a maximum of six weeks between the visits and when MRI was performed. From the medical records, we obtained the following demographics and disease characteristics (all data are collected in a standardized manner): gender, age, duration of symptoms, Hoehn and Yahr (H&Y) stage and dopaminergic medication use and other medication. The following factors were scored as either present or absent based on history taking: hypertension (defined as a repeatedly elevated blood pressure exceeding a systolic pressure above 140 or a diastolic pressure above 90 mmHg), neurogenic orthostatic hypotension (defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg), anamnestic cognitive decline (patients and their next of kin were asked whether or not they felt that cognitive deficits, such as 'forgetfulness', were present), depression (defined by the occurrence of such an episode in the medical history of patients) and sleep disorders (patients and their next of kin were asked whether or not they felt such a disorder was present). In addition, we recorded the Mini Mental State Examination (MMSE) and frontal assessment battery (FAB) scores, as well as pull test and tandem gait results for the PD patients in the two prospective subgroups (cohort 1 and 2). Neurogenic orthostatic hypotension in the prospective cohorts were based on measurements of blood pressure between supine position and after 3 min of standing position, while in the retrospective subgroup the presence or absence of (symptoms of) nOH was based on anamnestic history taking (complaints of greying out or coat hanger pain after changes in posture, dizziness, light-headedness, weakness and fatigue, arising in relation to changes in posture or upon prolonged standing). Subjective complaints of OH in relation to the provoking conditions are specific and can offer clear guidance to the diagnosis of OH (Thijs et al., 2009).

For cerebral MRI, the amount of deep WML and PVL (periventricular) WML was scored using the Fazekas score (0 = absent, 1 = punctate foci, 2 = beginning confluence areas, 3 = large confluent areas). Furthermore, for the amount of deep WML and basal ganglia (BG) we used the age-related white matter changes scale (ARWMC scale). All the scoring was performed consistently by the same neuroradiologist (MB under supervision of FM). 10 patients with cerebral stroke, defined as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage [5], with an exception of lacunar infarcts, were excluded from our study to assure that none of the patients had vascular parkinsonism rather than PD. All imaging was performed using 3T MRI (Magnetom Trio, Siemens, Erlangen, Germany) using the following MRI sequences: 3D T1 MP RAGE (TRTE = 2300–4.71 ms, Flip angle 12°, voxel size 1 × 1x1 mm, FOV 256 mm); T2 TSE (TRTE = 5830-120 ms, Flip angle 120°, voxel size 0.6 × 0.6 × 3 mm, FOV 240 mm); T2 FLAIR (TR-TE = 9000-86 ms, Flip angle 150°, voxel size 0.7 × 0.6 × 5 mm, FOV 240 mm); proton density (TR-TE = 2000-20 ms, Flip angle 90°, voxel size 0.9 × 0.9 × 3 mm, FOV 240 mm); DWI (TR-TE = 3900-89 ms, b0 and 1000 s/mm2, Flip angle 90°, voxel size 1.3 × 1.3 × 5 mm, FOV 240 mm).

2.3. Outcome measurements and statistical analysis

The primary objective was to examine the distribution of WML severity between PD patients with nOH and without nOH. The secondary objective was to study if an association was present between nOH and the amount of WML, in an ordinal regression model, where additional factors were included into the model (age, gender, Hoehn and Yahr stage (H&Y), dopaminergic medication use, hypertension and cognitive decline).

Analysis of the primary outcome was evaluated by Mann Whitney U testing. For the secondary outcome measures, we performed an ordinal regression model with the individual white matters scores (Fazekas PVL, Fazekas deep WML, ARWMC WML, ARWMC BG) as dependent variables and with gender, dopaminergic medication use, hypertension, and cognitive decline as factors and age and H&Y as covariate. For the primary and secondary analysis, we applied a formal Bonn Ferroni with Holmes correction for multiple testing. For several secondary outcome measures in the cohort with prospectively collected data, we used Spearman correlation. All data are presented as absolute numbers or mean (with 95% confidence interval). Statistical analysis was performed using SPSS version 22 IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp). A p-value of <0.05 was considered statistically significant.

3. Results

Patient characteristics are summarized in Table 1. The entire group consisted of 204 patients, of whom 26.0% had neurogenic orthostatic hypotension. In the two groups where data was prospectively collected, 17.9% of patients had symptomatic OH and 31.0% asymptomatic. For the entire group, PD patients with OH showed a significantly different distribution of the severity of deep WML defined by the Fazekas score, as well as for the ARWMC scale compared to patients without nOH ($p = .003$; $p = .002$ respectively; Fig. 1). For the WML in the basal ganglia and for periventricular WML the distribution was identical for patients with nOH and those without nOH ($p = .24$ and .34, respectively; Fig. 1). For the cohorts 1, 2 and 3 we observed a similar distribution of results compared to the entire cohort (Fig. 1). In cohorts 2 and 3 the distribution in ARWMC WML between patients with and without nOH was significantly different ($p = .044$ and $p = .027$, respectively). For the Fazekas WML a trend was observed in cohorts 2 and 3 ($p = .031$ and $p = .052$, respectively). In cohort 1 the difference in Fazekas WML and ARWMC WML remained non-significant between patients with and without nOH ($p > .23$). For the other outcome measures in cohorts 1, 2 and 3 no differences were observed ($p > 0.6$). For the entire cohort of 204 patients we performed an ordinal regression model (Table 2). Fazekas PV WML (OR = 0.70

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