Neuroscience Letters 653 (2017) 250–257

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Precuneus degeneration and isolated apathy in patients with Parkinson's disease

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HIGHLIGHTS

- PD patients with isolated apathy showed attentive and working memory dysfunctions.
- Hypometabolism and atrophy in the Precuneus is correlated with apathy severity.
- Precuneus degeneration can be one of neural substrates to isolated apathy in PD.

ARTICLE INFO

Article history:
Received 17 October 2016
Received in revised form 12 March 2017
Accepted 28 May 2017
Available online 1 June 2017

Keywords:
Apathy
Parkinson disease
Precuneus
Voxel-based morphometry
Fluorodeoxyglucose positron emission tomography

ABSTRACT

Introduction: To investigate isolated apathy in a set of consecutively enrolled Parkinson's disease (PD) patients without dementia, depression, and significant motor response fluctuations, by conducting neuropsychological and neuroimaging analyses.
Methods: One hundred twenty-four patients were eligible for inclusion in this study. Clinical information and data were collected from a predefined neuropsychological test battery, including the mini-mental status examination, apathy scale, geriatric depression scale, digit span test, Boston naming test, Seoul verbal learning test, controlled oral word association test, go-no-go test, and the Rey figure copy test. From matched groups of 10 non-apathetic and 12 apathetic patients in the initial cohort and 9 healthy controls, [^{18}F]fluorodeoxyglucose positron emission tomography and volumetric magnetic resonance images were acquired.
Results: Apathy was detected in 59.7% of the initial cohort. Apathetic patients had lower scores in the digit span forward, digit span backward, and immediate recall of verbal learning tests than did those without apathy ($p < 0.05$). The results were unaffected by parkinsonian motor severity and medication dose. Neuroimaging analyses revealed precuneus atrophy and hypometabolism in patients with isolated apathy. These precuneus changes were well-correlated with apathy severity ($p < 0.001$). Apathy severity was also positively correlated with gray matter volume in the superior frontal gyrus and cerebellar vermis, and with metabolism in the medial frontal and anterior cingulate regions ($p < 0.001$).
Conclusions: PD patients with isolated apathy showed attention and working memory dysfunction, and precuneus degeneration might be related to this distinctive nonmotor symptom in PD.

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http://dx.doi.org/10.1016/j.neulet.2017.05.061
0304-3940/

1. Text

Apathy is a nonmotor symptom defined by a lack of motivation and diminished goal-directed behavior [1]. It often coexists with depression or dementia [2], but can be an isolated symptom in Parkinson's disease (PD) [3]. The frequency of apathy in PD varies among the reported studies, however it is as high as 42% in PD population and 19% in drug-naïve PD patients [4,5]. Understanding the pathophysiological mechanism involved in apathy in PD and developing an appropriate management strategy is an important, but unresolved, clinical need of physicians because apathy can markedly affect patients' daily living activities and their health-related quality of life [2,6].

Interestingly, apathy has been observed in a variety of distinct clinical situations in PD. The most dramatic condition reported is apathy in patients with severe motor fluctuations. Apathy coexists with other "off"-related non-motor and motor symptoms [7], and it can be improved with dopaminergic drugs [8]. Mesolimbic dopaminergic denervation[9] has been reported in such cases and it is thought that this type of apathy is caused by a "hypodopaminergic state" in the limbic circuit [10]. However, apathy is also observed in patients not experiencing motor fluctuations, is often resistant to dopaminergic drugs, and is reported to herald dementia and cognitive decline in PD patients [6,11]. Attention, executive dysfunctions and memory impairment are cognitive features of PD patients with apathy [2,12]. Hypometabolism in the prefrontal cortex [13], cingulate cortex and insula [14], as well as reduced gray matter density in the frontal and parietal cortices[15] have been observed in apathetic PD patients. Therefore neurodegenerative process in cortical regions may be related with apathy in PD. However, an early event manifesting apathy in PD has not been fully described.

To identify a specific region responsible for isolated apathy that is independent of depression, dementia, and dopaminergic drugs, we undertook a two-stage analysis of non-demented and non-depressed PD patients without significant motor fluctuations: the first evaluation assessed neuropsychological test results collected from a retrospectively recruited cohort, and the second analysis was based on functional and volumetric neuroimaging data obtained from prospectively recruited apathetic and non-apathetic PD patients groups matched for demographic characteristics, PD-related clinical features, and dopaminergic medication doses.

2. Methods

2.1. Subjects

For the first evaluation, relevant information was collected by reviewing patient medical records at Seoul National University Boramae Hospital. The inclusion criteria included subjects who were diagnosed with PD by a movement disorders specialist according to the UK PD brain bank clinical diagnostic criteria [16], and who had been followed up for more than one year between March 2010 and August 2014 and were evaluated by apathy scale (AS) [5]. The presence of apathy was defined by an AS score > 14 in the absence of depression. The exclusion criteria included fluctuating apathy according to the patient's medication ON and OFF condition, the presence of dementia (defined according to the Movement Disorders Society Task Force guideline[17,18]), the presence of a clinical dementia rating score of 1 or more, the presence of clinically significant depression fulfilling the DSM-IV TR criteria or having a geriatric depression scale score >11, and taking anti-depressants (based on medical history). All patients were native Koreans. Clinical information obtained included age, gender, age at onset, ages at examinations, Hoehn & Yahr (HY) stage, unified PD rating scale (UPDRS) scores, and daily anti-parkinsonian medication dose.

Neuropsychological data were collected for eligible patients. The Seoul Neuropsychological Screening Battery(SNSB)[19] was performed, which is a standardized neuropsychological battery widely used in Korea. The battery was consisted of a mini-mental status examination(MMSE), geriatric depression scale (GDS) tests, a digit span test, a Boston naming test, a Seoul verbal learning test, a controlled oral word association test (COWAT), a Stroop test, a go-no-go test, and a Rey figure copy test. The neuropsychological tests were performed between Apr 2010 and Sep 2014.

For the second neuroimaging analysis, 12 apathetic and 10 non-apathetic patients were prospectively recruited from the patient group who completed the above neuropsychological test battery. These two groups were matched for age, HY stage, UPDRS score, and daily medication dose. These neuroimagings were done within a year from the above neuropsychological evaluations. Data from nine healthy subjects matched for patient groups' age were included for neuroimaging analysis as a control. These healthy subjects did not have a history of any neurological disease and were not on any medications.

The Institutional Review Board of Seoul National University Boramae Hospital approved this study. Within the prospective cohorts, all patients gave informed consent prior to participation in the study, in accordance with the Declaration of Helsinki.

2.2. Statistical analysis of the clinical data

Group comparisons were made using the *t*-test for continuous variables and the Chi-square test for categorical variables. Non-parametric tests were performed by Wilcoxon signed-rank test and Exact Fisher test. When comparing the neuropsychological profiles and UPDRS subscores between the apathetic and non-apathetic groups, a general linear model analysis was undertaken with age, education year, PD duration, and HY stage as covariates. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed by using SPSS software (version 21.0, SPSS Inc., Chicago, IL.) with two-sided significance set at 0.05.

2.3. Neuroimaging

2.3.1. T1-weighted magnetic resonance imaging

All subjects underwent magnetic resonance (MR) imaging in a 3.0 T MR scanner (Achieva, Philips Healthcare, Eindhoven, Netherlands). Three-dimensional T1-weighted data were acquired with a repetition time of 9.9 ms, an echo time of 4.6 ms, a slice thickness of 1 mm, and an image dimension of $179 \times 224 \times 224$.

2.3.2. [^{18}F]Fluorodeoxyglucose positron emission tomography

Considering possible effect of the medication, all subjects were undergone PET scan in overnight medication off state. Subjects underwent [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) scans in a GEMINI PET/Computed tomography (CT) scanner (Philips Healthcare, Andover, MA, USA) after fasting for at least 6 h. Image acquisition was done 40 min after intravenous injection of 4.8 MBq/kg of [^{18}F]FDG with scanning performed for 10 min using the following imaging parameters: slice thickness of 2 mm, matrix size of 128×128, and number of slices set to 90. After CT-based attenuation correction and scatter correction, the imaging data were reconstructed by applying the three-dimensional row-action maximum-likelihood algorithm (3D RAMLA).

2.3.3. Analysis of gray matter volume of the whole brain

The preprocessing steps for voxel-based morphometry (VBM) and the statistical tests were performed by using Statistical Parametric Mapping 8 (SPM 8; www.fil.ion.ac.uk/spm) implemented