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Excessive daytime sleepiness may be associated with caudate denervation in Parkinson disease

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ABSTRACT

Excessive daytime sleepiness (EDS) is one of the earliest and most common non-motor symptoms of PD, substantially impacting on patient's quality of life. Using the Parkinson's Progression Markers Initiative database, we performed a case-control study to investigate whether dopaminergic deficit is associated with the development of EDS using dopaminergic specific single photon emission computed tomography (SPECT) molecular imaging of dopamine transporters (DAT). We enrolled 84 early *de novo* PD patients with EDS and 84 without EDS, who were matched for age, gender, age of diagnosis, years of education and disease duration. We assessed and compared semi-quantified [^{123}I]FP-CIT SPECT, and motor and non-motor features among these two groups, alongside exploring the clinical and imaging correlates of EDS and the predictive significance of these markers in the development of EDS. PD patients with EDS had worse non-motor (MDS-UPDRS Part-I, $P < 0.001$) and motor (MDS-UPRDS Part-II, $P = 0.005$) experiences of daily living, as well as worse autonomic (SCOPA-AUT, $P < 0.0001$) and cognitive (MoCA $P = 0.05$) function, depression (GDS, $P = 0.002$), and reduced caudate DAT ([^{123}I]FP-CIT, $P = 0.024$) compared to PD patients without EDS. Lower caudate [^{123}I]FP-CIT values correlated with higher EDS scores ($r = -0.192$, $P = 0.013$). Among patients without EDS, 47 PD patients (56%) developed EDS over a median follow-up of 36 months. Cox multivariate analysis, including all clinical and imaging data available, revealed that abnormal caudate [^{123}I]FP-CIT uptake ($P = 0.030$) and disease duration ($P = 0.018$) were predictors for the development of EDS. Although our findings indicate that dopaminergic deficits in the caudate may be associated to EDS in patients with PD, the pathophysiological causality is debateable, given that dopamine caudate denervation may covary with dopaminergic involvement at other targets and with non-dopaminergic involvement.

1. Introduction

Excessive daytime sleepiness (EDS) is one of the most common and troublesome non-motor symptoms (NMS) in both early and advanced Parkinson's disease (PD) [1]. Although a range of NMS are primarily reported to be associated with non-dopaminergic deficits, such as depression [2], BMI changes [3] and fatigue [4], the dopaminergic system has also been identified as a pivotal contributor to non-motor symptoms in PD [5], reflecting the multisystem nature of the disorder. Politis and colleagues reported *in vivo* evidence of dopamine dysfunction in the hypothalamus of PD patients, suggesting a dopaminergic contribution to several non-motor symptoms, including sleep disorders, neuro-endocrinal problems and autonomic dysfunction [6]. NMS are often poorly identified and inadequately treated, highlighting the challenge attached with NMS management. Therefore, gaining an insight into the neurobiological mechanisms underlying these symptoms could improve management and the development of novel treatments.

The clinical heterogeneity of PD has led to the discovery of phenotypic subtypes of motor and non-motor symptoms [7]. Patients with daytime sleepiness, along with cognitive impairment, autonomic dysfunction and depression were recognised as a specific subtype of PD [7], instigating an interest in the clinical associations of EDS, alongside phenotypic and neurobiological risk factors of EDS development.

An amalgamation of dopaminergic denervation, nocturnal sleep disruption and dopaminergic medication is likely to be causative [8,9], though several studies have suggested that EDS may be a primary feature of PD, unrelated to dopaminergic therapies or nocturnal sleep disturbances [10]. A magnetic resonance imaging (MRI) brain morphometry study revealed that EDS in PD patients was related to atrophy of the medial cerebellar peduncle, suggesting that degeneration of the

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pontomedullary respiratory centres may underlie EDS development in PD [11]. Further, patients experiencing daytime sleepiness demonstrated a prominent impairment in circadian melatonin secretion, suggesting that circadian dysfunction may underlie excessive sleepiness [12]. A genetic component contributing to the pathogenesis of EDS has also been reported [13]. Furthermore, Saper and colleagues proposed that a "flip-flop switch" is responsible for the sleep-wake cycle in primates, whereby the suprachiasmatic nucleus regulates the internal rhythm between two switches, with hypocretin potentially playing a regulatory role [14]. The quantity of hypocretin-producing neurons and the CSF level of hypocretin-1 have been shown to be reduced in PD [15–17], with consistent loss of hypocretin-producing neurons demonstrated by a reduction in the number of post-mortem hypothalamic hypocretin neurons, acknowledged as the "gold standard" [16,17].

Disease variables found to be associated with EDS include longer disease duration, older age, severity of motor manifestations, depression, cognitive impairment and, non-tremor dominant motor phenotype [8,18], though not all epidemiological studies of PD have discovered the same picture or disease variables to be associated with EDS [19].

Studies investigating EDS and dopaminergic pathways discovered that subjective daytime sleepiness is associated with striatonigral degeneration [20], though others have proposed that it may be associated with extrastriatal dopaminergic loss in specific brain structures involved in alertness [21]. Thus, the role of the striatum in the development of EDS remains unclear.

We aimed to explore the relationship between EDS and striatal dopamine terminals, using [^{123}I]FP-CIT single photon emission computed tomography (SPECT), alongside determining the clinical correlates and risk factors in the development of EDS, in *de novo* (drug-naïve) PD patients. We hypothesised that EDS would be associated with striatal dopaminergic denervation.

2. Methods

The Parkinson's Progression Markers Initiative (PPMI) is a five-year observational, international, multi-centre study designed to provide insight into disease aetiology by identifying PD progression biomarkers. The present study was written according to the STROBE guidelines. This study is registered with ClinicalTrials.gov, number NCT01141023.

2.1. Cohort selection

We included PD patients aged $>$ 30 years old, who had a disease duration $\leq$ 2 years and were not on dopamine replacement therapy. Institutional review boards approved the study and written informed consent was obtained from all participants. From a total of 412 patients with PD, 84 had EDS according to the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) Part-I, item 1.8 "daytime sleepiness". This self-reported, self-completed instrument consists of 5 statements, rating from 0: normal to 4: severe, with a higher rating corresponding to a higher degree of EDS. The presence of EDS was defined as daytime sleepiness interfering with daily activities and social interactions (cut-off $>$ 1). All clinical and imaging assessments were performed in subjects who were not receiving any dopaminergic medication, at baseline. The cut-off values considered abnormal for all clinical and imaging variables were calculated as 2 S.D. from the mean of HCs, as previously stated [22].

Using propensity scores, PD patients with EDS were matched 1:1 for age, gender, age at disease diagnosis, duration of disease and years of education with 84 PD patients without EDS. Characteristics of patients included are summarised in Table 1.

2.2. Dopaminergic imaging

SPECT images were obtained 4 $\pm$ 0.5 h after administrating an injection of approximately 185 MBq [^{123}I]FP-CIT. [^{123}I]FP-CIT SPECT scans were analysed following the imaging technical operations manual (http://ppmi-info.org/). In brief, SPECT image volumes were spatially normalised to an Ioflupane template. The eight most prominent axial slices containing the striatum were summed and a standardised volume of interest (VOI) template was then applied to this image. VOI analyses were performed on the right and left caudate and putamen, employing the occipital region as the reference tissue. Specific binding ratios (SBR) were calculated as the ratio of the putamen or caudate VOI count density divided by the occipital cortex count density, minus one. This measure approximates the binding potential, BPnd, where the radioligand is in equilibrium at the target site and has previously been reported with Ioflupane SPECT [23].

2.3. Structural imaging

T1-weighted Magnetic Resonance Imaging (MRI) scans were acquired in the sagittal plane on 3T Siemens (TIM Trio and Verio) scanners (Erlangen, Germany), employing a magnetisation-prepared rapid-acquisition gradient echo sequence. The parameters of the MRI sequence were as follows: repetition time: 2300/1900 milliseconds; echo time: 2.98/2.96/2.27/2.48/2.52 milliseconds; inversion time: 900 milliseconds; flip angle: 9°; matrix: 256 $\times$ 256; and 1 mm^3 isotropic voxel.

Surface-based analysis was carried out using the freely available software package FreeSurfer (version 5.3, http://surfer.nmr.mgh.harvard.edu). In brief, the FreeSurfer preprocessing pipeline includes (1) removal of non-brain tissue; (2) automated Talairach transformation; (3) segmentation of subcortical white matter and deep gray matter structures (4) intensity normalisation (5) tessellation of the gray matter/white matter boundary; (6) automated topology correction; (7) surface deformation; and (8) registration of the subjects' brains to the common spherical atlas. The results implemented in FreeSurfer were visually inspected and manually edited, if required.

Regions-of-interest (ROIs) included subcortical structures such as caudate, putamen, accumbens, pallidum, thalamus, hippocampus and amygdala, as well as cortical structures such as precentral and postcentral gyrus, anterior and posterior cingulate, entorhinal cortex, fusiform gyrus, inferior and superior parietal cortex, inferior, middle and superior frontal cortex, insula cortex, parahippocampal cortex, inferior, middle and superior temporal cortex, lateral occipital and lateral orbitofrontal cortex.

2.4. Assessment of outcomes and follow-up

PD patients attended a follow-up visit once every year, where the physician reviewed the patient's condition. This included reassessing the patient for EDS development. Follow-up period was terminated either at the patient's last visit or if the patient developed EDS.

2.5. Dopaminergic therapy

Study participants could start dopamine replacement therapy (DRT) at any point after baseline as part of routine clinical care. A participant was considered to have received DRT (dopamine agonists, levodopa, monoamine oxidase type B (MAO-B) inhibitors) from the first time it was recorded at an annual study visit. Information about medication dosages was not readily ascertained in the database and is not included.

2.6. Statistical methods

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 22 and graphical illustration in GraphPad Prism 6. For all variables, Gaussianity was tested with Kolmogorov-Smirnov test. Multivariate analysis of variance (MANOVA) was used to assess the main effects of all clinical and imaging variables between the group of PD patients with EDS and PD patients without