Parkinsonism and Related Disorders xxx (2013) 1–5

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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

Diabetes is associated with postural instability and gait difficulty in Parkinson disease

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ARTICLE INFO

Article history:
Received 18 September 2012
Received in revised form
11 December 2012
Accepted 22 January 2013

Keywords:
Diabetes
Parkinson disease
PET
Dopamine
Postural instability and gait difficulty (PIGD)

ABSTRACT

Background: Comorbid diabetes may be associated with more severe motor impairment in Parkinson disease. In normal elderly individuals, diabetes is associated with parkinsonian features, including gait difficulty and rigidity, though not tremor. Whether diabetes contributes to increased motor dysfunction in Parkinson disease by exacerbating nigrostriatal dopaminergic denervation or through intensification of extranigral pathology is unknown.

Methods: We performed a case–control study ($n = 39$) involving 13 Parkinson disease subjects (age 66.4yrs ± 5.5; duration of disease 6.9yrs ± 4.4) with diabetes and 26 age, gender, and duration-of-disease-matched Parkinson disease controls without diabetes. All subjects underwent [^{11}C]dihydrotetrabenazine vesicular monoamine transporter type-2 positron emission tomography imaging to assess striatal dihydrotetrabenazine distribution volume ratio and Unified Parkinson disease rating scale motor examination to determine rigidity, bradykinesia, tremor, and postural instability and gait difficulty subscores. Magnetic resonance imaging scans were analyzed to assess leukoaraiosis burden.

Results: After controlling for nigrostriatal dopaminergic denervation, Parkinson disease subjects with diabetes displayed greater postural instability and gait difficulty subscores ($t = 3.81$, $p = 0.0005$). There were no differences in bradykinesia, rigidity, or tremor subscores between cases and controls. The association between diabetes and postural instability and gait difficulty persisted after controlling for comorbid hypertension and body mass index. Leukoaraiosis, distal vibratory sense, and levodopa dose equivalents did not differ significantly between cases and controls.

Conclusions: Diabetes may contribute to postural instability and gait difficulty in Parkinson disease through mechanisms other than nigrostriatal dopaminergic denervation.

1. Introduction

Motor subtype heterogeneity in idiopathic Parkinson disease (PD) is a common disease feature but the pathophysiologic factors that underlie motor heterogeneity are not well understood. Postural instability and gait difficulty (PIGD) is a motor subtype seen more frequently later in the disease course [1] and is associated with worse quality of life [2]. Although PD is historically thought of as disorder of nigrostriatal dopaminergic denervation, PIGD symptoms show a limited response to dopaminergic treatments [3]. Relatively poor response to dopaminergic treatments likely reflects the multifactorial etiology of PIGD in PD. Increased PIGD burden is perhaps the most significant motor feature contributing to higher disability scores on the Hoehn and Yahr scale [4] though the causes and factors related to PIGD progression in PD are not well understood.

The presence of diabetes in otherwise normal elderly individuals is associated with parkinsonian motor features, including gait disturbance and rigidity, though not tremor or bradykinesia [5]. Comorbid diabetes may contribute to motor impairments in PD. Cereda et al. reported a case–control study of PD subjects with and without antecedent diabetes and found that PD subjects with diabetes exhibited higher motor scores and received higher doses of dopaminergic medications [6]. A greater proportion of recently diagnosed PD subjects with antecedent diabetes were assessed as Hoehn and Yahr stage III (20.2%) compared to non-diabetic PD subjects (4.5%). These finding suggests that diabetes may

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http://dx.doi.org/10.1016/j.parkreldis.2013.01.016

preferentially exacerbate axial motor impairments. The more intensive dopamine replacement therapy documented by Cereda et al. in their diabetic PD subjects suggests that diabetes may be associated with greater nigrostriatal dopaminergic denervation. Axial motor dysfunctions, however, are generally less responsive to dopamine replacement and considerable data suggests that extranigral pathologies underlie axial motor dysfunctions [7]. We performed a case–control study of subjects with PD with and without a history of diabetes to determine if comorbid diabetes is associated with greater impairment of specific motor features of Parkinson disease, independent of the degree of nigrostriatal dopaminergic denervation.

2. Subjects and methods

2.1. Subjects and clinical test battery

This case–control study involved 13 PD subjects with a history of diabetes (cases) and 26 PD subjects with no history of diabetes (controls). Diabetes status was determined through subject self-report in a standardized interview. All 13 cases had type-2 diabetes (DM2). Diabetic medications amongst cases included metformin ($n = 9$), sulfonylureas ($n = 5$), insulin ($n = 3$), and thiazolidinediones ($n = 3$). The two groups were matched with regards to age, gender, and duration of disease (Table 1). All subjects underwent a standardized assessment of height and weight to calculate body mass index as well as a clinical evaluation to determine whether they carried a known history of comorbid hypertension.

All subjects met the UK Parkinson Disease Society Brain Bank Research Center clinical diagnostic criteria for PD [8]. Striatal [^{11}C]dihydrotetrabenazine (DTBZ) PET findings were consistent with the diagnosis of PD in all subjects. No subjects had evidence of previous large artery strokes on Magnetic Resonance Imaging (MRI). The Unified Parkinson Disease Rating Scale (UPDRS) was performed in the "off" state after withholding dopaminergic medications overnight. To explore associations between diabetes and motor heterogeneity in PD, UPDRS Motor exam subscores were calculated for the following categories: Bradykinesia (facial expression, right and left finger tapping, right and left hand movements, right and left pronation and supination of the hands, right and left toe tapping), Tremor (right and left upper extremity postural tremor, right and left upper extremity kinetic tremor, right and left arm rest tremor, right and left leg rest tremor), Rigidity (right arm, right leg, left arm, and left leg), and Postural Instability and Gait difficulty (posture, postural stability, gait).

2.2. Standard protocol approvals, registrations, and patient consents

The study was approved by the Institutional Review Board of the University of Michigan. Written informed consent was obtained from all subjects.

3. Imaging techniques

3.1. DTBZ PET imaging

DTBZ PET Imaging was performed in 3D imaging mode using an ECAT HR + tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum (FWHM)) over a 15.2 cm axial field-of-view. A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field-of-view [9]. Before beginning radioligand injections, a 5-min transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and re-projection routines. All subjects were studied in the supine position, with eyes and ears unoccluded, resting quietly in a dimly lit room.

No-carrier-added (+)-[^{11}C]DTBZ (250–1000 Ci/mmol at the time of injection) was prepared as reported previously [10]. Dynamic PET scanning was performed for 60 min immediately following a bolus injection of 55% of 555 MBq (15 mCi) of (+)-[^{11}C]DTBZ dose (containing less than 50 μg of cold DTBZ mass) over the first 15–30 s of the study, while the remaining 45% of the dose was continuously infused over the next 60 min, resulting in stable arterial tracer levels and equilibrium with brain tracer levels after 30 min [11]. A series of 15 scan frames over 60 min were obtained as following: 4 × 30 s; 3 × 1 min; 2 × 2.5 min; 2 × 5 min; and 4 × 10 min.

3.2. MRI imaging

All subjects underwent brain magnetic resonance imaging on a 3T Philips Achieva system (Philips, Best, The Netherlands) utilizing either an 8-channel or 15-channel headcoil. A standard T1-weighted series of a 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI = 9.8/4.6/1041 ms; turbo factor = 200; single average; FOV = 240 × 200 × 160 mm; acquired Matrix = 240 × 200. One hundred and sixty slices were reconstructed to 1 mm isotropic resolution. This sequence maximizes contrast among gray matter, leukoaraiosis, and CSF and provides high-resolution delineation of cortical and subcortical structures.

3.3. Leukoaraiosis burden MR imaging analysis

Supratentorial leukoaraiosis burden was estimated in 36 of 39 total subjects using an automated routine involving the analysis of co-registered FLAIR and SPGR MRI sequences for each subject [12]. This method was previously validated [13] and uses cerebellar white matter, a region relatively unaffected by age-associated leukoaraiosis, as a reference region for comparison of supratentorial

Table 1
Demographic profiles of cases and controls.

	Mean ± SD		Group comparison [significance]
	PD subjects with diabetes ($n = 13$)	PD subjects without diabetes ($n = 26$)	
Gender (M/F)	11/2	22/4	$\chi^2 = 0.00$, $p = 1.00$
Mean age (yrs)	66.5 ± 6.4	66.3 ± 5.1	$t = 0.14$, $p = 0.89$
Mean duration of disease (yrs)	6.84 ± 4.7	6.98 ± 4.4	$t = 0.09$, $p = 0.93$
Mean Hoehn & Yahr scale	2.7 ± 0.72	2.3 ± 0.58	$t = 1.62$, $p = 0.11$
Mean striatal DTBZ DVR	2.10 ± 0.51	1.84 ± 0.26	$t^a = 1.77$, $p = 0.10$
Body mass index (BMI)	33.4 ± 6.0	27.6 ± 3.7	$t = 3.73$, $p = 0.0006$
History of statin use	46.2%	34.6%	$\chi^2 = 0.49$, $p = 0.49$
History of hypertension	69.2%	34.6%	$\chi^2 = 4.2$ $p = 0.04$
Levodopa dose equivalency	784.2 ± 745.0	886.8 ± 681.0	$t = 0.43$, $p = 0.67$
Supratentorial white matter hyperintensity burden ($n = 36$)	−5.37 ± 2.3	−5.24 ± 1.6	$t = 0.12$, $p = 0.91$
Brainstem white matter hyperintensity burden ($n = 35$)	−3.75 ± 4.4	−3.78 ± 4.3	$t = 0.08$, $p = 0.93$
Mean vibratory sense duration (seconds)	8.4 ± 4.5	8.8 ± 4.0	$t = 0.29$, $p = 0.77$
Mean global cognitive *Z*-score ($n = 37$)	−0.94 ± 0.85	−0.39 ± 0.95	$t = 1.70$, $p = 0.10$

PD = Parkinson disease, DTBZ DVR = [^{11}C]dihydrotetrabenazine distribution volume ratio.
[a] Satterthwaite *t*-test due to unequal variance.

Please cite this article in press as: Kotagal V, et al., Diabetes is associated with postural instability and gait difficulty in Parkinson disease, Parkinsonism and Related Disorders (2013), http://dx.doi.org/10.1016/j.parkreldis.2013.01.016