Parkinsonism and Related Disorders xxx (2013) 1–4

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Risky driving and pedunculopontine nucleus-thalamic cholinergic denervation in Parkinson disease

Shiao-Pei S. Weathers [a], Vikas Kotagal [a], Nicolaas I. Bohnen [a, b, c], Kelvin L. Chou [a, d, *]

[a] Department of Neurology, University of Michigan, Ann Arbor, MI, USA
[b] Department of Radiology, Division of Nuclear Medicine, University of Michigan, Ann Arbor, MI, USA
[c] Neurology Service and GRECC, VA Ann Arbor Healthcare System, Ann Arbor, MI, USA
[d] Department of Neurosurgery, University of Michigan, Ann Arbor, MI, USA

ARTICLE INFO

Article history:
Received 25 February 2013
Received in revised form
26 August 2013
Accepted 31 August 2013

Keywords:
Parkinson disease
PET imaging
Driving

ABSTRACT

Background: It is unknown whether driving difficulty in Parkinson disease (PD) is attributable to nigrostriatal dopaminergic or extranigral non-dopaminergic neurodegeneration.
Objective: To investigate *in vivo* imaging differences in dopaminergic and cholinergic innervation between PD patients with and without a history of risky driving.
Methods: Thirty non-demented PD subjects (10 women/20 men) completed a driving survey. These subjects had previously undergone (+)-[^{11}C] dihydrotetrabenazine vesicular monoamine transporter 2 and [^{11}C] methyl-4-piperidinyl propionate acetylcholinesterase PET imaging. Acetylcholinesterase PET imaging assesses cholinergic terminal integrity with cortical uptake largely reflecting basal forebrain and thalamic uptake principally reflecting pedunculopontine nucleus integrity.
Results: Eight of thirty subjects reported a history of risky driving (been pulled over, had a traffic citation, or been in an accident since PD onset) while 22 had no such history (safe drivers). There was no difference in striatal dihydrotetrabenazine vesicular monoamine transporter uptake between risky and safe drivers. There was significantly less thalamic acetylcholinesterase activity in the risky drivers compared to safe drivers (0.0513 ± 0.006 vs. 0.0570 ± 0.006, $p = 0.022$) but no difference in neocortical acetylcholinesterase activity. Using multivariable logistic regression, decreased thalamic acetylcholinesterase activity remained an independent predictor of risky driving in PD even after controlling for age and disease duration.
Conclusions: Risky driving is related to pedunculopontine nucleus-thalamic but not neocortical cholinergic denervation or nigrostriatal dopaminergic denervation in PD. This suggests that degeneration of the pedunculopontine nucleus, a brainstem center responsible for postural and gait control, plays a role in the ability of PD patients to drive.

1. Introduction

Driving is a complex task that requires intact motor, perceptual, and cognitive function. Parkinson disease (PD) is a neurodegenerative disorder characterized by progressive motor, cognitive, and other non-motor (visual) manifestations, likely resulting from multiple neurotransmitter deficiencies. All of these manifestations may interfere with the ability to drive safely [1]. There is a growing body of literature regarding driving ability in PD. The greatest contributions to unsafe driving in patients with PD include declines in visual sensory ability, motion perception, and general cognition, all of which can be impaired in early PD [2,3]. PD patients commit more driving errors and have more collisions on driving simulation tasks compared to age-matched healthy controls [4]. PD patients also perform poorly on "on-road" driving evaluations compared to controls [5–8].

Physicians are often asked to assess a patient's driving ability, typically based on information that can be obtained in a routine office visit, such as a limited cognitive and motor examination. While motor and disease severity measures that may be performed in the office, such as the Unified Parkinson Disease Rating Scale (UPDRS) and the Hoehn and Yahr staging system, are not generally predictive of driving performance [1,9], there is some evidence that postural imbalance and gait problems may predict driving safety in

* Corresponding author. University of Michigan Medical School, 2301 Commonwealth Blvd., Ann Arbor, MI 48105-2945, USA. Tel.: +1 734 936 3087; fax: +1 734 232 1170.
E-mail address: klchou@med.umich.edu (K.L. Chou).

1353-8020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.parkreldis.2013.08.021

PD [10,11]. One study found that the postural imbalance and gait disorder (PIGD) subtype of PD was more likely to fail an on road driving assessment than the tremor dominant (TD) subtype [11]. Another measure shown to predict outcome on a road test in PD drivers was the Rapid Walk Test (RPW), an assessment of stride length, balance, and overall mobility [10].

Cognitive status may also predict driving safety in PD. Crizzle et al. [1], in an evidence based review, reported that several visual and cognitive tests, such as the Useful Field of View (UFOV) subtest 2, cumulative UFOV scores (based on 4 subsets), contrast sensitivity, Risk Index, Rey–Osterrieth Complex Figure Test (ROCF), Trails B, Trails B-A, and functional reach, were probably predictive of impaired driving performance in PD.

There is a need to explore mechanisms of neurodegeneration in PD that contribute to impaired driving ability. The association between driving in PD and neurobiological measures of dopaminergic and cholinergic denervation has not been explored. Nigrostriatal dopaminergic denervation is characteristically associated with PD motor severity. Cortical cholinergic denervation becomes more prominent with the emergence of PD dementia [12], while subcortical cholinergic denervation, specifically of the PPN-thalamic system, is associated with postural control and gait difficulty in PD [13]. Given that poor performance on cognitive tasks and postural instability appear to be more strongly associated with impaired driving performance than overall motor function, we hypothesized that risky driving would associate more strongly with cortical and PPN-thalamic cholinergic denervation than with nigrostriatal dopaminergic denervation in PD.

2. Methods

2.1. Subjects and driving survey

The subjects analyzed in this study were originally recruited for a research study on the PET imaging correlates of non-motor symptoms in PD (ClinicalTrials.gov Identifier: NCT01565473). As part of this larger study, participating subjects complete (+)-[^{11}C] dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) and [^{11}C] methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) PET imaging, Montreal Cognitive Assessment (MOCA), MDS-revised UPDRS and Hoehn-Yahr severity assessments. Thirty-eight participants who had completed these study assessments were sent a survey about their driving habits, behaviors, and general demographics. All subjects in our cross-sectional study met UK PD Society Brain Bank Research Center clinical diagnostic criteria for PD [14], and all subjects demonstrated evidence of striatal dopaminergic denervation on DTBZ PET imaging consistent with the clinical diagnosis of PD. Subjects with dementia, as defined by a Mini-Mental State Exam (MMSE) score <24, were excluded. No subjects were taking cholinesterase inhibitors or pure anticholinergic drugs.

Out of the total of 38 subjects who were mailed a driving survey, three subjects did not return the driving survey and five subjects reported on their driving survey that they were not current drivers. Thus, thirty total recruited PD subjects were analyzed.

The cohort was dichotomized into safe drivers ($n = 22$, 13M/9F) and risky drivers ($n = 8$, 7M/1F) based upon a positive response to one of three separate driving survey question items: have you been pulled over, received a traffic citation, or been involved in a motor vehicle accident since the onset of PD? In our cohort, 1 subject reported having been involved in an accident and given a ticket. Three subjects reported having been pulled over without being issued a ticket, and four subjects were pulled over and issued a ticket. These 3 questionnaire items have not been validated in PD but rather were chosen based on our estimation of their brevity and frequent use in routine clinical interactions with PD patients. Safe drivers had no self-reported history of any of these 3 items.

2.2. Standard protocol approvals, registrations, and patient consents

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

2.3. Imaging techniques

DTBZ and PMP PET imaging were 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 [15]. Before radioligand injections began, 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.

2.3.1. DTBZ PET imaging

No-carrier-added (+)-[^{11}C]DTBZ (250–1000 Ci/mmol at the time of injection) was prepared as reported previously [16]. 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 [17]. A series of 15 scan frames over 60 min was obtained as follows: four × 30 s; three × 1 min; two × 2.5 min; two × 5 min; and four × 10 min.

2.3.2. PMP PET imaging

[^{11}C]PMP was prepared in high radiochemical purity (>95%) by N-[^{11}C] methylation of piperidin-4-yl propionate using a previously described method [18].Dynamic PET scanning was performed for 70 min immediately following a bolus intravenous injection of 666 MBq (18 mCi) of [^{11}C]PMP. The dose contained less than 200 μg of cold PMP mass. Emission data were collected in 16 sequential emission scans (the DTBZ protocol plus an additional 10 min frame).

2.3.3. MRI imaging

All subjects underwent brain magnetic resonance imaging on a 3T Philips Achieva system (Philips, Best, The Netherlands) utilizing an 8-channel headcoil and the "ISOVOX" exam card protocol primarily designed to yield isotropic spatial resolution. 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, white matter, and CSF and provides high-resolution delineation of cortical and subcortical structures. These MRIs were used mainly for co-registration to PET images, but showed no evidence of large artery stroke, tumor, demyelination, or findings consistent with an atypical parkinsonian disorder.

2.4. Data analysis

Interactive Data Language image analysis software (Research systems, Inc., Boulder, CO) was used to manually trace volumes of interest (VOIs) on MRI images including the thalamus and striatum (caudate and putamen regions) of each hemisphere. Right and left hemisphere values were averaged together within subjects to create a composite score for each region. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal.

All image frames were spatially co-registered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session. These motion-corrected PET frames were spatially co-registered to the T1-weighted MR using standard co-registration procedures in SPM8b implemented in Matlab 2010b (The Mathworks, Natick, MA). Time activity curves for each VOI were generated from the spatially aligned PET frames. ^{11}C-DTBZ distribution volume ratio (DVR) was then estimated by using the Logan plot graphical analysis method [19] with the time activity curves as the input function and the neocortex as reference tissue for ^{11}C-DTBZ [17,19,20]. AChE hydrolysis rates (k_3) were estimated using a method using the striatum as the reference input tissue.

Demographic factors, clinical measurements, and PET outcomes were compared between safe and risky drivers using Fisher's exact test, two-sample pooled *t*-tests, or Satterthwaite's *t*-test as appropriate. In order to control for the effects of age and duration of disease on driving safety, multivariable logistic regression was used to model the likelihood of being a risky driver using age, duration of disease, and PET measure as predictor variables. Maximum likelihood estimates for each of these 3 predictor variables were calculated using the Wald Chi-square test. All analyses were performed using SAS version 9.3, SAS institute, Cary, NC.

3. Results

The mean time between survey completion and PET scan for all 30 patients was 125.1 days (SD 87.13 days, range 8–312 days). Table 1 compares safe and risky drivers. While risky drivers were slightly older (70.6 ± 12.9 vs. 65.1 ± 6.5 years) and had a longer disease duration (8.6 ± 6.5 vs. 4.4 ± 3.7), these differences were not statistically significant. There were no significant differences in gender, Hoehn and Yahr score, MDS-UPDRS motor score,

Please cite this article in press as: Weathers S-PS, et al., Risky driving and pedunculopontine nucleus-thalamic cholinergic denervation in Parkinson disease, Parkinsonism and Related Disorders (2013), http://dx.doi.org/10.1016/j.parkreldis.2013.08.021