Published in final edited form as:

J Parkinsons Dis. 2017 ; 7(1): 143–147. doi:10.3233/JPD-160985.

Cerebral amyloid burden and Hoehn and Yahr stage 3 scoring in Parkinson disease

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Abstract

Background—Progression to Hoehn and Yahr (HY) stage 3 marks the transition to advanced disease staging and disability in Parkinson disease (PD).

Objective/Methods—We conducted a case-control study of 36 PD subjects at HY stage 2.5 or 3, with groups matched for gender, age, and disease duration. Positron Emission tomography (PET) imaging included dihydrotetrabenazine [¹¹C]DTBZ and Pittsburgh Compound B [¹¹C]PiB.

Results—Subjects with HY 2.5 differed from HY 3.0 in mean cortical PiB distribution volume ratio (1.14 vs. 1.23; Wilcoxon two-sample Z=2.36, p=0.024) but not striatal DTBZ PET.

Conclusion—Cortical amyloid burden differentiates subjects below and at HY stage 3. These results suggest that cortical amyloid accumulation influences the transition from HY2.5 to HY3 and that cortical amyloidopathy may be a therapeutic target in PD.

Keywords

Parkinson disease; Amyloid; Positron Emission Tomography; Cerebral Cortex

Introduction

The Hoehn and Yahr scale (HY) is the most widely used staging scale for Parkinson disease (PD) [1]. Transitions from scores of 2.5 to scores of 3 on the modified HY scale mark a worsening in quality of life [2] and an increase in the risk of medication-refractory disease

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Conflicts of interest:

V.K. none

N.I.B. none

M.L.M. none

K.A.F. none

R.L.A. none

features such as dementia and mortality [3, 4]. Although striatal dopaminergic neuropathology accounts for many of the early motor features of PD, *in vivo* imaging studies suggest floor effects to striatal dopaminergic denervation that occur both in early PD [5] and at HY stage 3 disease [6], at which point progressive disease burden is driven by other factors. Identifying and targeting pathological risk factors that mediate the transition to HY3 is an important priority in PD clinical science.

Extranigral pathologies of various forms associate with clinical features of disease progression in PD. Progressive β -amyloid (A β) plaque burden is a pathological feature of brain aging seen in parkinsonian conditions and can be estimated through cerebrospinal fluid analyses or through Positron Emission Tomography (PET) assessments using A β amyloid ligands [7]. The presence of cortical A β pathology within PD is associated with axial motor and cognitive features [8, 9].

Although A β pathology is not a current target of ongoing PD clinical trials, it is a chief focus of experimental therapeutic approaches in other neurodegenerative disorders including Alzheimer's disease (AD) where immunomodulatory agents have been shown to alter amyloid burden [10]. If A β plaque accumulation is linked to a clinically meaningful marker of disease progression in PD, it may also be a useful therapeutic target in future PD trials.

Methods

Subjects

We conducted a nested retrospective case-control study (n=36) with subjects drawn from a larger cross-sectional cohort study of amyloid PET imaging in PD. Details on the larger cohort study (n=62) are reported elsewhere [11]. Subjects were recruited from Movement Disorders Neurology clinics at the University of Michigan and the VA Ann Arbor Health System. The diagnosis of PD was established using the UK Brain Bank clinical diagnostic criteria [12]. In all subjects, nigrostriatal dopaminergic denervation was confirmed by typical patterns seen on DTBZ PET imaging. From this study, we restricted our sample to subjects who were classified either as having HY scores of 3 (cases) or 2.5 (controls) on a standardized Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor examination performed in the dopaminergic "off" state [13]. Subjects from both groups were matched in a 1:1 fashion for age, gender, and disease duration. Matching was conducted while blinded to the PET imaging results. Subjects at HY stage 3 were first identified and then were matched to available HY stage 2.5 subjects for first for gender, followed by age, then followed by disease duration. Any HY3 subjects in our cohort lacking a gender-matched HY 2.5 subject whose age was $\pm$ <10 years of their own, were not included in the matching for this case-control study in order to limit the influence of age as a relevant confounder on PiB comparisons between groups. A total of 36 subjects, 18 at HY stage 2.5 and 18 at HY stage 3, were included in the final analysis. Subjects completed the Montreal Cognitive Assessment (MoCA) after taking their regular PD medications.

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.

Imaging

All subjects underwent brain magnetic resonance imaging on a 3T Philips Achieva system (Philips, Best, The Netherlands) utilizing an 8-channel headcoil. Dihydrotetrabenazine [11]C-DTBZ vesicular monoamine transporter type 2 (VMAT2) and [11]C-Pittsburgh Compound B (PiB) PET imaging were performed in 3D imaging mode using an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN). DTBZ imaging was performed in the dopaminergic “off” state. Additional details of our imaging protocols are reported elsewhere [11]. Regions of interest were defined on SPGR T1 MRI sequences and coregistered to PET. The Logan plot graphical analysis method was used for calculating distribution volume ratios (DVRs) using a cerebellar reference region for a bihemispheric cortical PiB assessments and a supratentorial global cortex reference region for striatal DTBZ DVR.

Statistical Analyses

Demographic and clinical factors between the two groups of subjects were compared using two-sample t-tests. To reduce the influence of outliers in this sample and in keeping with the recommendations of the MDS HY task force regarding inter-group comparisons [14], nonparametric testing using the two sample Wilcoxon rank sum test was employed to compare regional PET imaging findings between the two groups. We conducted an exploratory analysis using Satterthwaite t-tests to compare MoCA scores in the original cohort of 62 PD subjects after grouping subjects into those with either a low HY score (< 2.5 ; $n=35$) or a high score (≥ 3 ; $n=27$). Within each of these 2 larger HY groups, we then tested bivariate associations (Spearman’s rho) between MoCA scoring and cortical PiB DVR to explore the clinical-pathological significance of the proposed HY < 2.5 vs. HY ≥ 3 threshold. All analyses were conducted using SAS 9.3 (Cary, NC).

Results

Clinical and imaging data for the two groups of subjects is presented in Table 1. Mean MDS-UPDRS motor exam scores were higher in HY3 subjects. The two groups did not differ in MoCA scores. There were no differences in striatal DTBZ DVR between the two groups. Cortical PiB DVR was lower in the HY 2.5 compared to HY3 subjects by about 9.2% (1.14 ± 0.19 vs. 1.23 ± 0.19 ; Wilcoxon two-sample $Z=2.36$, $p=0.024$). As mentioned above, subjects in this nested case control study were drawn from a larger cross-sectional study. In the larger 62 person cohort, subjects with low HY scores (< 2.5) showed no differences in MoCA scoring compared to subjects with high HY scores (≥ 3) (25.9 ± 5.7 vs. 25.9 ± 2.4 ; $t=0.02$, $p=0.98$). Subjects with HY scores of < 2.5 showed no correlation between cortical PiB DVR and MoCA score ($n=35$; $\rho=-0.11$, $p=0.53$). Subjects with HY scores of ≥ 3 , however, showed a significant inverse association, with higher PiB DVR values correlating with lower MoCA scoring ($n=27$; $\rho=-0.44$, $p=0.023$).

Discussion

PD subjects with HY stage 3 disease show a greater degree of cortical amyloid burden than age-matched HY stage 2.5 subjects. In our study, this difference does not appear to relate to differences in age, gender, disease duration, cognitive impairment, or the degree of nigrostriatal dopaminergic denervation. These findings have implications on how we conceptualize the role of A β pathology in PD and about the role of extra-striatal changes (e.g. the cerebral cortex) that characterize the progression of PD from HY stage 2.5 to 3.

The initial Hoehn and Yahr staging was reported in 1967 and created as a functional status scale for individuals with idiopathic PD and other similar disorders [15]. The scale itself was updated by a Movement Disorders Society Task Force in 2004 which also surveyed MDS members about the perceived clinical and research utility of the HY scale [14]. A large majority of respondents reported using the scale in clinical and research practice but also acknowledged that its non-linear properties limit its broader application [14]. Assessing the transition from stage 2.5 (mild bilateral disease with recovery on pull test) to 3.0 (mild to moderate bilateral disease; some postural instability; physically independent) depends heavily on the motor examination & pull test and the rater's definition of physical independence. The nature of this staging assessment highlights both its limitations (coarse granularity) and strengths as a proxy variable for overall motor disability.

Although the MDS-task force acknowledges that examiners' ratings of HY stage can be influenced by subject comorbidity burden [14], it is notable that, in addition to their role as scale confounders, the accrual and worsening of medical comorbidities may play a pathogenic role in PD progression. Other community based studies have shown an association between comorbidity burden and PD disability [16, 17]. Comorbidities, in particular vascular risk factors, are known to associate with the degree of cerebral amyloid burden in normal aging [18]. The same vascular risk factors may play a role in the progression of amyloid burden in PD.

Cortical PiB findings in PD were previously reported by our group to have clinical associations with PD non-motor and motor features, including cognitive impairment and postural instability and gait difficulty (PIGD) related features [8, 9, 11]. This study's exploratory analysis suggests the existence of a possible threshold effect for cortical amyloid burden, whereby at or above a certain stage, amyloid burden may be more closely associated with PD cognitive decline. Whether amyloid burden is a state or trait marker for clinical decline, however, is less clear. Although amyloid pathology associates with greater disease burden, so too do other forms of cortical pathology [19] [20]. Collectively, these findings support the idea that the accrual of cortical changes in PD marks a transition from low-disability disease to high-disability disease. This may reflect an important role for the maintenance of cortico-striatal connections in the compensatory network that prevents postural instability in PD. Directly intervening on cortical pathologies is not a current focus of disease-modifying efforts in PD, but deserves consideration in the design of future PD trials.

Limitations of our study include its small sample size and cross-sectional design, the latter of which limits our ability to measure amyloid changes within subjects from one HY stage to the next. Because our study presents data from a small sample of 36 subjects, it is possible that the estimated difference in cortical PiB burden between subjects at HY 2.5 or 3 is influenced by sampling bias, cohort-specific characteristics, or other unmeasured sources of imprecision. Our use of a matching strategy in this case-control study was chosen to reduce the influence of relevant confounding variables. Modest differences in comorbid cerebral amyloid burden may have clinical implications on the natural history of PD. Cortical A β amyloidopathy may be a useful target for novel treatments in PD. Longitudinal studies are needed to explore disease-specific risk factors for cerebral amyloid burden in PD.

Acknowledgments

The authors wish to thank the study subjects who contributed their time and effort toward this study.

Funding

This work was supported by the Department of Veterans Affairs; the Michael J. Fox Foundation; and the NIH (grant numbers P01 NS015655, P50 NS091856, and RO1 NS070856).

Financial Disclosures

Dr. Kotagal receives funding from the NIH (P30AG024824 KL2), VA Health Systems (IK2CX001186 and AAVA GRECC), and the Blue Cross & Blue Shield of Michigan Foundation.

Dr. Bohnen has research support from the NIH, the Michael J. Fox Foundation (MJFF) and the Department of Veteran Affairs.

Dr. Muller has research support from the NIH, the Michael J. Fox Foundation (MJFF) and the Department of Veteran Affairs.

Dr. Frey has research support from the National Institutes of Health (NIH), GE Healthcare, and AVID Radiopharmaceuticals (Eli Lilly subsidiary). Dr. Frey also serves as a consultant to AVID Radiopharmaceuticals, MIMVista, Inc, Bayer-Schering, and GE Healthcare. He also holds equity (common stock) in GE, Bristol-Myers, Merck, and Novo-Nordisk.

Dr. Albin serves on the editorial boards of *Neurology*, *Experimental Neurology*, and *Neurobiology of Disease*. He receives grant support from the NIH and MJFF. Dr. Albin serves on the data safety and monitoring boards of the LEGATO trial (ICON/Teva) and an early phase trial of anti-sense oligonucleotides in Huntington disease (IONIS).

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Table 1

Cohort Demographic, Clinical, and Imaging Factors

	HY stage 2.5 (SD)	HY stage 3.0 (SD)	
Age	67.5 (7.0)	68.1 (6.3)	T=-0.27, p=0.78
Disease duration	6.61 (3.0)	6.72 (3.9)	T=-0.10, p=0.92
Gender	4W/14M	4W/14M	$\chi^2=0.0$, p= 1.0
UPDRS motor exam	29.6 (9.3)	42.4 (13.1)	T = -3.35, p=0.002
MoCA	25.3 (2.3)	25.9 (2.7)	T= 0.73, p =0.47
Cortical PiB DVR	1.14 (0.19)	1.23 (0.19)	Z=2.36, p =0.024
Striatal DTBZ	1.95 (0.39)	1.81 (0.16)	Z=-0.71, p =0.48