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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Clinical Markers for Identifying Cholinergic Deficits in Parkinson's Disease

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ABSTRACT

Background: Cholinergic projection systems degeneration is associated with dopamine nonresponsive features of Parkinson's disease (PD). Cholinergic deficits are variable in nondemented PD. Identification of cholinergic deficits in PD may help with selection of suitable patients for targeted cholinergic drug treatment in PD. The objective of this retrospective multivariate predictor analysis study was to identify clinical markers indicative of cholinergic deficits in PD patients, as assessed by acetylcholinesterase ([11C]PMP) positron emission tomography.

Methods: One hundred thirty-seven PD patients (34 female) participated; median modified Hoehn and Yahr score was 2.5 (range, 1-4), average age 65.6 ± 7.4 years, and average duration of motor disease symptoms of 6.0 ± 4.2 years. Subjects were dichotomized as "normocholinergic" or "hypocholinergic" based on a 5th percentile cutoff from normal for the basal forebrain-cortical and pedunculopontine nucleus-thalamic cholinergic projection systems. Previously identified clinical indices of cholinergic denervation were used for statistical prediction of cholinergic deficits. Logistic regression determined which risk factors predicted cholinergic deficits. Sensitivity, specificity, and accuracy were determined for the (combinations of) significant predictor variables.

Results: Forty-nine (35.8%) hypocholinergic PD subjects were identified. The combination of rapid eye movement (REM) sleep behavior disorder (RBD) symptoms and fall history showed highest diagnostic accuracy (81.1%) for predicting combined thalamic and cortical cholinergic deficits. A combined assessment of 8.5 m walk time and lower score on the Montreal cognitive assessment scale provided diagnostic accuracy of 80.7% for predicting isolated cortical cholinergic denervation.

Conclusion: Assessment of clinical indices of cholinergic denervation may be useful for identifying suitable subjects for trials of targeted cholinergic drug treatments in PD. © 2014 International Parkinson and *Movement* Disorder Society

Key Words: Parkinson's disease; acetylcholine; acetylcholinesterase; PET; biomarkers

Parkinson's disease (PD) is a multisystem neurodegenerative syndrome with significant heterogeneity of motor and non-motor features.[1] Cholinergic projection systems degeneration is associated with specific motor and non-motor features of PD, independent of

TABLE 1. Average values and percentages for each of the clinical features associated with cholinergic deficits for the different groups

	Normocholinergic (n = 88)	Cortex and Thalamus Combined Cholinergic Deficits (n = 23)	Cortex-Only Cholinergic Deficits (n = 26)
Age (years)	63.9 ± 7.1	69.0 ± 7.4	68.4 ± 6.8
Sex (%female/male)	31.8/68.2	13.0/87.0	11.5/88.5
Motor disease symptom duration (y)	5.3 ± 3.8	8.2 ± 4.5	6.6 ± 5.0
UPSIT	17.4 ± 8.1	14.6 ± 8.0	13.8 ± 8.1
8.5 meter walk time (sec)	8.0 ± 1.8	10.0 ± 5.9	9.1 ± 2.8
MoCA	26.3 ± 2.4	25.1 ± 3.1	25.2 ± 2.9
Fall history (% no fall/% fall)	78.4/21.6	47.8/52.2	73.1/26.9
RBD (% no RBD/% RBD)	53.4/46.6	21.7/78.3	53.8/46.2

UPSIT, University of Pennsylvania smell identification test; MoCA, Montreal cognitive assessment; RBD, REM sleep behavior disorder.

nigrostriatal dopaminergic denervation; it is associated with impaired cognition,[2-7] falling,[8-10] slower gait speed,[11] rapid eye movement (REM) sleep behavior disorder (RBD),[12] and impaired olfaction.[6,13] In addition, older age, longer motor disease symptom duration, and male sex associate with cholinergic system degeneration in PD.[7,14]

Cholinergic system degeneration is heterogeneous in PD, and it may affect basal forebrain-neocortical or pedunculopontine nucleus-thalamic (PPN) projections differentially.[7] Heterogeneity of cholinergic system degeneration may explain clinical variation in PD. Optimal evaluation of cholinergic replacement therapy requires accurate identification of the subset of PD patients with cholinergic deficits. Clinical trials of cholinergic agents in PD would be facilitated greatly by inclusion of convenient clinical measures as markers of differential cholinergic system loss.

The purpose of this study was to identify convenient, cost-effective, and noninvasive clinical markers of cholinergic deficits in PD subjects. Our previous studies on markers of cholinergic denervation were mainly based on univariate analysis of a single clinical predictor variable. The objective of this retrospective study was to perform a multivariate predictor analysis to identify which combination(s) of clinical markers of cholinergic deficits best predict cholinergic denervation as assessed by acetylcholinesterase (AChE) positron emission tomography (PET).[6,7,10-14]

Methods
Subjects

This retrospective cross-sectional multivariate predictor study included 137 PD patients (34 female) who are part of an ongoing cohort study (ClinicalTrials.gov Identifier NCT01565473). The median modified Hoehn and Yahr score was 2.5 (range, 1-4),[15,16] average age of 65.6 ± 7.4 years, and average duration of motor disease symptoms of 6.0 ± 4.2 years. Patients met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[17] The diagnosis of PD was confirmed by the presence of a typical pattern of nigrostriatal dopaminergic denervation with vesicular monoaminergic transporter-type 2 PET.[18] Most subjects were on dopaminergic replacement therapy. None of the subjects were on anti-cholinergic or cholinesterase inhibitor drugs.

Written informed consent was obtained from all subjects before research procedures. The University of Michigan Medical School Institutional Review Board for human studies approved the study.

Clinical Risk Factors for Cholinergic Deficits

We dichotomized each cholinergic deficit–associated clinical feature into a "hypocholinergic risk factor" (risk is present = 1, risk is absent = 0). Cutoffs for continuous variables were based on 85% specificity cutoff as determined by receiver operating characteristic (ROC) analysis across all PD subjects. This approach yielded the following clinical indices for cholinergic deficits: age of 71 years or older, duration of motor disease symptoms of 9 years or longer, University of Pennsylvania Smell Identification Test (UPSIT)[19,20] score of 9 or lower, 8.5-meter walk time of 9.6 seconds or longer at self-selected gait speed, Montreal cognitive assessment (MoCA) test[21] score of 24 or lower, history of one or
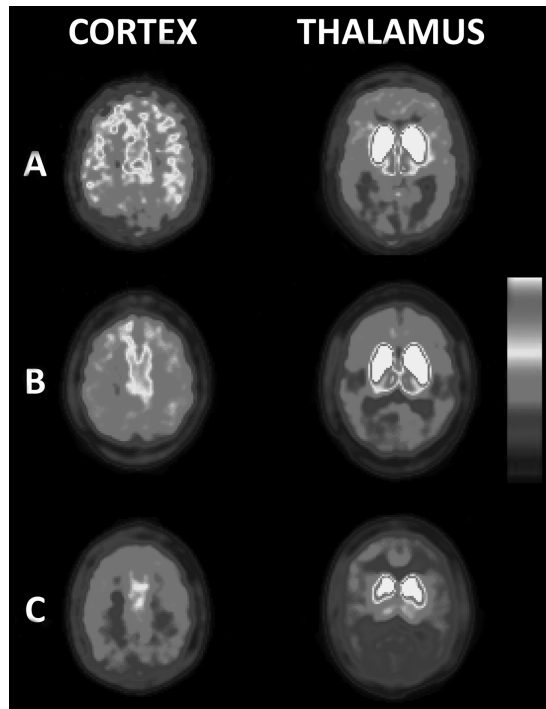
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FIG. 1. Averaged radioactivity from 40- to 70-min frames of dynamic [^{11}C]PMP PET for a subject with normal cortical and thalamic cholinergic innervation (row A), a subject with cortical-only cholinergic deficits (row B), and a subject with combined cortical and thalamic cholinergic deficits (row C). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

more falls in the previous year, presence of RBD as assessed by using the informant-based response to question 1 on the Mayo Sleep Questionnaire,[22] and male sex. Walk time was assessed in the morning, after overnight withdrawal of dopaminergic drugs (dopaminergic

"off" state). All subjects walked 8.5 meters in a hallway and were timed using a stopwatch.[11] The MoCA and University of Pennsylvania Smell Identification Test assessments were performed in the dopaminergic "on" state. Table 1 provides an overview of average values and percentages for each of the clinical features for the different groups.

Brain Imaging Procedures

All brain imaging procedures have been described in detail previously.[23] In short, all subjects underwent brain magnetic resonance imaging for anatomic co-registration with [^{11}C]PMP AChE PET[24] to enable a magnetic resonance imaging–based volume of interest analysis. Thalamic and neocortical [^{11}C]PMP AChE hydrolysis rates per minute (k_3), a measure of cholinergic terminal integrity, were estimated using reference tissue-based linear least squares analysis[25] with the striatum as the reference tissue.

Cholinergic Deficits

Subjects were characterized as either "normocholinergic" or "hypocholinergic" based on the 5th percentile cutoff from normal range neocortical or thalamic cholinergic innervation. There were 49 (35.8%) hypocholinergic PD subjects; 26 with cortical-only cholinergic denervation, 18 PD subjects with a combination of both cortical and thalamic cholinergic denervation, and five with thalamic-only cholinergic denervation. We grouped hypocholinergic subjects either as cortical-only hypocholinergic or as combined cortical and thalamic hypocholinergic (Fig. 1).

TABLE 2. χ^2 test results for the cholinergic deficits risk factor proportions of combined cortical and thalamic hypocholinergic PD subjects vs. normocholinergic PD subjects, and cortical-only PD subjects vs. normocholinergic PD subjects

		χ^2 (p-value)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Combined cortical-thalamic	*RBD*	7.3 (0.007)	78.3	53.4	58.6
	Fall history	8.5 (0.004)	52.2	78.4	73.0
	RBD & fall history	13.0 (<0.001)	34.8	93.2	81.1
Cortical-only	*Sex*	4.2 (0.041)	88.5	31.8	44.7
	Walking speed	4.4 (0.037)	34.6	84.1	72.8
	MoCA	7.3 (0.007)	42.3	83.0	73.7
	Walking speed & sex	3.8 (0.050)	26.9	88.6	74.6
	MoCA & sex	5.9 (0.015)	34.6	86.4	74.6
	Age	8.2 (0.004)	42.3	84.1	74.6
	Age & sex	5.7 (0.017)	30.8	88.6	75.4
	MoCA & age & sex	0.9 (0.349)	7.7	96.6	76.3
	MoCA & age	3.6 (0.057)	15.4	95.5	77.2
	Walking speed & age & sex	3.4 (0.067)	7.7	98.9	78.1
	Walking speed & MoCA & age & sex	3.4 (0.065)	3.8	100	78.1
	Walking speed & age	6.9 (0.009)	15.4	97.7	78.9
	Walking speed & MoCA & age	6.9 (0.009)	7.7	100	78.9
	Walking speed & MoCA	13.2 (<0.001)	19.2	98.9	80.7

Sensitivity, specificity, and accuracy for the different (combinations of) cholinergic deficits risk factors is included. Significant contingency table results are in italics. Table is sorted by increasing accuracy within each of the group comparisons.
PD, Parkinson's disease; RBD, REM sleep behavior disorder; MoCA, Montreal cognitive assessment test.

Statistical Analysis

Statistical procedures were performed using SPSS Statistics 20 (IBM, Chicago, IL, USA). Separate analyses were performed for the cortical-only hypocholinergic and the combined cortical and thalamic hypocholinergic groups. Stepwise (likelihood ratio) logistic regression was performed to determine which risk factors best predicted cholinergic group status (normocholinergic or hypocholinergic). For each of the significant predictors and for combinations of significant predictors (eg, all risk factors are present), the sensitivity (% true positive for risk factor across all hypocholinergic subjects), specificity (% true negative for risk factor across all normocholinergic subjects), and accuracy (proportion of true positives and true negatives across all subjects) were calculated. Area under the curve of ROC analysis was calculated for the combination of significant predictors with highest diagnostic accuracy. The proportion of negative and positive cases for each cholinergic deficits risk factor was compared between the normocholinergic and the hypocholinergic group, using the χ^2 test for contingency tables.

Results

For the combined cortical and thalamic cholinergic denervation group, results of stepwise logistic regression showed significant prediction of cholinergic deficits (2, $\chi^2 = 18.5$; $P < 0.001$) by presence of RBD (Wald = 8.7, $P = 0.003$) and fall history (Wald = 10.0, $P = 0.002$). The highest diagnostic test accuracy (81.1%; specificity 93.2%) was obtained with the combination of RBD presence and fall history (Table 2). Area under the curve of ROC analysis was 0.64.

For the cortical-only cholinergic denervation group, results of stepwise logistic regression showed significant prediction of cholinergic deficits (4, $\chi^2 = 21.8$, $P < 0.001$) by a longer walk time (Wald = 4.1, $P = 0.042$), lower MoCA score (Wald = 5.0, $P = 0.026$), higher age (Wald = 7.3, $P = 0.007$), and male sex (Wald = 4.2, $P = 0.040$). The highest diagnostic test accuracy (80.7%; specificity 98.9%) was obtained with the combination of walk time (9.6 seconds or longer) and lower MoCA score (24 or lower; Table 2). Area under the curve of ROC analysis was 0.59.

Discussion

The goal of this study was to identify combination(s) of convenient clinical markers that predict cholinergic deficits in PD patients. A history of falling, especially combined with RBD presence, may be indicative of combined cortical and thalamic cholinergic deficits. Longer 8.5-m walk time in combination with a MoCA score of 24 or lower may be indicative of cortical-only cholinergic deficits.

Ideally, studies should be conducted to identify markers that are specific to cholinergic system degeneration *exclusively*. However, this may be a challenging goal to achieve given the multisystem neurodegenerative nature of PD[26] and the effect of comorbidities on PD features.[27-30] Selection of effective cut-off criteria of the clinical features was based on high specificity but at the expense of lower sensitivity. The reason for this selection approach relates to the multisystem neurodegeneration process of PD in which clinical manifestations such as cognitive impairment or gait speed can have different contributing pathogenetic factors that are not limited to cholinergic denervation alone, such as noradrenergic denervation or amyloidopathy.[31,32] A more sensitive selection process would consequently include a greater number of PD subjects without cholinergic denervation. Therefore, we believe that in the presence of multisystem neurodegeneration recruitment for cholinergic augmentation therapy should prioritize specificity above sensitivity to maximize clinical response and minimize side effects.

A prerequisite of clinical trials of novel cholinergic augmentation therapies is the proper identification of the subset of PD subjects with cholinergic deficits. Cholinergic system PET imaging is a highly effective method for identifying cholinergic deficits but with restricted applicability because of relatively high expense and limited availability. We identified fall history in combination with presence of RBD as best predictors of combined cortical and thalamic cholinergic deficits; however, a history of RBD was based on clinical symptom endorsement of dream enactment behavior and not assessed by polysomnography.[12] Time to walk 8.5 m (9.6 seconds or longer) in combination with a MoCA score of 24 or lower were best predictors of isolated cortical cholinergic deficits. The development of patient stratification tools was recently recommended as the highest priority translational research recommendation in the final report of the "Parkinson's Disease 2014: Advancing Research, Saving Lives" meeting organized by the United States National Institute of Neurological Disorders and Stroke (http://www.ninds.nih.gov/research/parkinsons-web/PD2014). Although our findings will require validation in an independent cohort, the proposed method of patient selection based on clinical predictor variables may present a cost-effective and efficient method to enrich study populations for trials of cholinergic agents in PD. ■

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DNAJC13 Genetic Variants in Parkinsonism

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ABSTRACT

Background: A novel mutation (p.N855S) in *DNAJC13* has been linked to familial, late-onset Lewy body parkinsonism in a Dutch–German–Russian Mennonite multi-incident kindred.

Methods: *DNAJC13* was sequenced in 201 patients with parkinsonism and 194 controls from Canada. Rare (minor allele frequency < 0.01) missense variants identified in patients were genotyped in two Parkinson's disease case–controls cohorts.

Results: Eighteen rare missense mutations were identified; four were observed in controls, three were