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2) Statistical analysis: A. Design, B. Execution, C. Review and Critique.

3) Manuscript: A. Writing of the first draft, B. Review and Critique.

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Gait function and locus coeruleus Lewy body pathology in 51 Parkinson's disease patients

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Abstract

Introduction—Gait impairment in Parkinson's Disease (PD) is often severely disabling, yet frequently remains refractory to treatment. The locus coeruleus (LC) has diffuse noradrenergic projections that are thought to play a role in gait function. Enhancement of norepinephrine transmission may improve gait in some PD patients. We hypothesized that the severity of PD pathology, and more specifically, Lewy bodies and neuronal loss in the LC, would correlate with the severity of gait dysfunction in PD.

Methods—Autopsy data from 51 patients, collected through the Morris K. Udall Parkinson's Disease Research Center, were correlated with clinical gait-related measures, including individual Unified Parkinson's Disease Rating Scale (UPDRS) Part II and III questions, total UPDRS Part III scores, and timed upand-go speed (TUG).

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Results—Neither the presence nor degree of Lewy body pathology in the LC on autopsy was associated with a higher UPDRS part III gait score. LC tau deposition and frontal Lewy body deposition were not correlated with any of the assessed gait measures. The degree of Lewy body pathology, independent of Braak stage, was positively associated with the severity of motor symptoms overall (UPDRS Part III total score).

Conclusion—Neither the degree of Lewy body nor tau pathology in the LC is associated with severity of gait disorders in PD. This finding may have implications for targeted noradrenergic therapies in patients with refractory gait disorders.

Keywords

Parkinson's disease; Gait; Locus coeruleus; Pathology; Autopsy

1. Introduction

Gait dysfunction in Parkinson's disease (PD), including freezing of gait, hypokinetic stride length, imbalance, postural instability, and increased risk for falls [1], contributes to reduced quality of life [2], and drives the majority of health care expenditures in PD patients [3]. Several aspects of gait dysfunction in PD are poorly understood, and many consider gait dysfunction to be the motor symptom least responsive to otherwise effective medical [4] or surgical [5] therapies. An improved understanding of the anatomy and neurochemical mechanisms of gait control is needed to develop targeted and effective therapies, beyond currently existing dopaminergic strategies, for PD-related gait disorders.

The current functional anatomy model of locomotor control includes a spinal mechanism for isolated rhythm generation [6,7]. Several brainstem areas are integral to supraspinal control, including a mesencephalic locomotor region (MLR), a subthalamic locomotor region and a cerebellar locomotor region [8]. Brainstem monoaminergic nuclei, including the locus coeruleus (LC) and the raphe nuclei (RN), are part of a “muscle tone excitatory system” [9] activated by the MLR, and allow for descending control of muscle tone. Feedback mechanisms [10] within the brainstem and feed-forward input ascending from the spinal cord allow for a balance of excitatory and inhibitory control over the noradrenergic output from the LC in normal locomotion. Of the parkinsonian gait symptoms, noradrenergic dysfunction in the LC is most closely linked to freezing of gait [11]. However, other mechanisms such as cholinergic output from brainstem centers [12], cortical atrophy [13], and subcortical white matter [14] changes have also been implicated in disordered gait.

Given the role of monoaminergic brainstem nuclei in the normal control of postural tone, the well-described α-synuclein deposition [15,16] and neuronal loss in the LC [17,18] of PD patients are likely to play an important role in PD-related disorders of posture and locomotion. In fact, evidence from both animal [19] and human [18] studies supports the role of the LC in PD-related gait disorders.

We hypothesized that the severity of PD pathology, including α-synuclein inclusions (Lewy bodies), neuronal loss, and other pathological evidence of neurodegeneration, would correlate with the severity of gait dysfunction measured by the Unified Parkinson's Disease

Rating Scale (UPDRS) and Timed Up and Go Speed (TUGS) in PD patients who had undergone autopsy. Establishing this relationship in humans would add to our understanding of the mechanism underlying dopamine-unresponsive motor symptoms in PD, and explore the utility of noradrenergic augmentation as a therapeutic mechanism.

2. Methods

2.1. Pathology

Autopsies were conducted by the Division of Neuropathology at Johns Hopkins. Brains were examined externally, fixed for two weeks in 10% buffered formaldehyde. Tissue blocks for microscopic examination were processed, embedded in paraffin, and cut at 10-μm thickness. All sections were stained with H&E; selected sections were silver-stained (Hirano method) and immunostained with antibodies against phosphorylated Anti-Tau (PHF-1) (a gift of Dr. Peter Davies) and α-synuclein (Transduction laboratories). The neuropathological assessment and diagnostic formulation followed the recommendations of the third report of the DLB Consortium [20]. The severity of Lewy body pathology (including Lewy bodies and neurites) was assessed semiquantitatively in the locus coeruleus, substantia nigra, cranial nerve nuclei IX & X, and middle frontal gyrus (range 0–4). In the locus coeruleus, we rated loss of neurons and astroglial proliferation as absent, mild/moderate, or severe. Pigment incontinence, neurofibrillary tangles, and Lewy bodies were reported as present or absent. If Lewy bodies were absent in the first slice on H&E staining, subsequent slices (up to 3) were analyzed for the presence of Lewy bodies and their density using anti-alpha synuclein stained slices. Braak stage was also determined [15].

2.2. Subjects

This analysis was part of a prospective clinico-pathological study with a longitudinal research cohort assessed for motor, cognitive, and psychiatric features of PD [21]. Subjects recruited from tertiary care and community practices included both older and younger individuals, with both shorter and longer disease duration (6–34 years), who provided pre-mortem consent for IRB-approved collection of clinical data and autopsy data from brain donation. Clinical assessments were performed every two years until autopsy or loss to follow-up. This study was approved by the Johns Hopkins University Institutional Review Board. In the current analysis, PD subjects with autopsy data and at least one documented TUGS and UPDRS were included. The following clinical variables were included in this analysis: sex, age at PD diagnosis, age at death, TUGS, and all UPDRS Part III individual item scores and the Part III total score from the most recent assessment.

2.3. Statistical methods

We reported clinical characteristics and pathological scores as means with standard deviations (Table 2). Spearman correlations were performed between baseline clinical variables and clinical gait ratings. For the exploratory analysis, we tested Spearman correlations between various ordinal pathological outcomes (independent variables) and clinical ratings (dependent variables). We also used Fisher's exact tests for association between categorical independent variables and clinical scores.

Independent variables included the pathological features listed in Table 1. Primary dependent variables included the gait- and posture-related UPDRS Part III items and TUGS. Secondary dependent variables included all UPDRS Part III items. Total UPDRS Part III scores and TUGS were tested for an association with pathological predictors using regression analyses after it was confirmed that there was a trend for linear association.

We explored significant correlations with ordinal logistic regression analyses, multinomial, or multiple regression analyses depending on whether the outcome variable was ordinal, categorical, or continuous. Regression techniques were used to evaluate the association between the presence of Lewy bodies in the LC and UPDRS Part III gait scores or the total Part III score, while adjusting for age at symptom onset, disease duration, Braak stage, and time from last clinical observation to autopsy as covariates in the model. To follow assumptions used by the ordinal logistic regression, UPDRS Part III gait scores of 0 & 1 and 3 & 4 were combined because of the small number of subjects with a gait score of 0 or 4, after we found that this did not affect the statistical significance of the model.

3. Results

The number of subjects with pathological data and mean results are reported in Table 1. A total of 51 autopsies contained pathological data from the LC. Demographic and clinical data are reported in Table 2. There was no difference in age at PD onset, sex, disease duration or age at death between those who did and did not have Lewy bodies in the LC at autopsy. Concurrent AD pathology was only found in 2 participants, so this was unlikely to confound trends in LC pathology. On review of pathological notes, no cases of infarct in the brainstem or basal ganglia were reported in the 51 subjects with LC pathology data. The difference in Braak stage between those with (2.86, 95%CI:2.47–3.25) and without (3.5, 95% CI:1.9–5.1) LC Lewy bodies was not statistically significant ($p = 0.34$). The average elapsed time between the most recent TUGS or UPDRS Part III and autopsy was 52.4 (SD = 31.4) or 37.4 (SD = 27.2) months, respectively.

3.1. LC Lewy bodies and gait function in PD

None of the UPDRS gait-related scores showed a significant association with the presence of Lewy bodies, density of Lewy bodies in the LC, degree of cell loss, or any other markers of LC pathology.

A multiple linear regression model adjusted for age at PD diagnosis, disease duration, Braak stage of PD pathology, and time from last UPDRS score to autopsy showed that for each 1-point increase in Lewy body score, the UPDRS Part III total score increased by an average of 7.6 points (95% CI: 0.12–15.1, $p = 0.047$).

The density of tau neurofibrillary tangles in the LC did not correlate with the UPDRS Part III gait item score, nor did it show a significant association with the other gait measures tested. The degree of Lewy body pathology in the frontal lobe (Brodmann's areas 8/9) also did not correlate with the severity of any of the clinical gait scores.

3.2. LC Lewy bodies and other motor scores

The degree of LC Lewy body pathology did not correlate with any of the other individual UPDRS Part III items with one exception: there was a significant association between the presence/absence of Locus coeruleus pigmentary incontinence (a marker of dopaminergic cell loss) and facial tremor ($p = 0.034$). Because an association between LC pathology and other motor sub-scores was not part of our original hypotheses, we corrected for multiple comparisons and this association did not meet significance with a corrected alpha.

3.3. Other brainstem Lewy pathology and gait

Neither substantia nigra Lewy body presence nor score was associated with any of the UPDRS gait items, while they did associate with rigidity ($p = 0.017$), hand grips ($p = 0.13$), speech ($p = 0.023$), and leg agility ($p = 0.013$). The presence of Lewy bodies in cranial nerve nuclei IX or X was also not associated with UPDRS gait score ($p = 0.809$) or any of the other gait-related items.

4. Discussion

Despite prior pathological and imaging evidence linking noradrenergic dysfunction and gait disorders in PD [11,18], we did not find a significant association between gait dysfunction (measured by gait-related UPDRS Part III subscores) and Lewy body deposition in the locus coeruleus. Loss of independent ambulation is one of the largest contributors to a decline in quality of life during the course of Parkinson's disease [2], and this study may suggest that structural demise of LC dopaminergic neurons alone does not simply explain postural instability and gait impairment in PD.

This finding is inconsistent with some recent findings that noradrenergic medications may improve gait function, and suggests that enhancement of noradrenergic function may not impact gait disorders as much as previously hoped. In support of this lack of association between noradrenergic tone and gait disorder, L-3,4-DOPS (droxidopa) is a noradrenergic medication shown to only minimally improve freezing of gait (FOG) in moderately severe Parkinson's disease (Hoehn and Yahr stage III), and had even less benefit in more advanced stages [22]. Similarly, methylphenidate did not show benefit in a composite motor score or gait measures in PD [23].

Furthermore, there was no association between the degree of neuronal loss or gliosis and the gait scores ($r = -0.08$; Fisher's exact $p = 0.214$). The latter finding may be due to a plateau in the degree of neuronal loss by autopsy, thereby potentially masking the association between neuronal loss in the LC and gait dysfunction.

Although previous work has shown a link between cortical function and gait dysfunction (especially freezing of gait) [24–26], we also did not find an association between the severity of cortical pathology and UPDRS gait-associated scores, including FOG (Fishers exact $p = 0.42$). The lack of an association between frontal pathology and measures of gait disorder in our study may be due to other gait-impairing processes that do not involve Lewy body deposition [27], the limitation of the specific region we sampled (Brodmann 8/9 =

dorsolateral prefrontal cortex and/or premotor area), or the type of pathological examination performed.

While specific UPDRS Part III gait measures were not associated with Lewy body density in the LC, a higher total UPDRS Part III (total motor score) was associated with the number of Lewy bodies in the LC. This association persisted even when controlling for the Braak stage of each brain, so that when comparing brains of the same overall Lewy body disease severity, higher Lewy body load in the LC still was associated with increased severity of PD motor signs. While the LC Lewy bodies may not be specifically involved in gait disorder, their presence must add to overall motoric disease severity. Future research targeting brain networks involved in parkinsonian motor symptom progression should include the LC along with other more established nodes, such as the substantia nigra.

4.1. Limitations

As with any study relying on autopsy data, pathological specimen collection and clinical rating collection were dissociated in time, leading to two main issues: 1) homogenization of pathological findings as patients reach an “end-stage” state, and 2) variability in time between the clinical ratings and autopsy. We addressed the second point by adding the amount of time between clinical scale and autopsy as a covariate in our regression models, realizing that pathological change may not be a simple linear correlate of elapsed time at various disease stages across all patients. Also, the semi-quantitative scale used for rating of pathology severity is suboptimal but follows standard neuropathology autopsy ratings.

One could also raise the question of whether the correlation between LC Lewy bodies and overall motor dysfunction is confounded by generalized Lewy body deposition, in concordance with the progressive spread of α-synuclein pathology [15], and that increasing LC Lewy bodies and more severe motor impairment are both results of more widespread Lewy pathology. In this case, we would expect that subjects with more severe frontal lobe Lewy body pathology would have more severe gait dysfunction, as the frontal lobe is typically affected with Lewy body deposition later in PD; however, we did not find a correlation between frontal lobe Lewy body presence and UPDRS Part III gait score ($r = -0.07$, $p = 0.78$). Neither SN nor CN IX-X Lewy body presence correlated with worsened UPDRS Part III gait score, suggesting that LC Lewy bodies are not simply a marker of more advanced brainstem pathology. Rather, our findings suggest that the presence of Lewy pathology in the LC is associated with dysfunction of that nucleus out of proportion to what would be expected from progressive accumulation of Lewy pathology throughout the brainstem.

4.2. Significance

In opposition to sparse clinical, imaging, and pathological data linking LC pathology with gait disorders in PD, our study on Lewy body pathology in 51 PD brains demonstrated no association between LC Lewy body pathology and PD gait dysfunction. On the other hand, there was an association between LC Lewy body score and global motor dysfunction in PD patients, indicating that noradrenergic dysfunctions may further complicate dopaminergic deficits underlying PD motor symptoms.

The LC and the noradrenergic system has been evaluated as a potential target for levodopa-unresponsive PD motor symptoms, including gait and postural abnormalities. While we found an association between overall motor function (total UPDRS Part III score) and LC Lewy body pathology, a specific association with gait disorder and postural instability did not exist. Our research supports the exploration of targeted therapies to augment norepinephrine function in hopes of improving motor function overall in PD, which have already been pursued with success where droxidopa has been available commercially [22,28]. However, it suggests that gait and postural instability may be caused by a more complex interaction between multiple neurotransmitter systems and motor control networks and that modifying the noradrenergic system alone may not improve gait or postural instability.

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Table 1

Neuropathological assessments in PD patients. Score reported as mean (ordinal variables) or % present (dichotomous variables).

Pathology variable (n)	N	Possible output	Mean score or % “present”	Range
LC Lewy Body Score	48	Score 0-4	1.8	0–4
Frontal (BA 8/9) Lewy Body Score	47	Score 0-4	1.6	0–4
LC neuronal loss and gliosis	47	Score 0-3	1.3	1–2
LC pigment incontinence/pigmented microphages	47	Present/absent	72%	Present/absent
LC Lewy body presence	51	Present/absent	92%	Present/absent
LC neurofibrillary tangle presence	42	Present/absent	31%	Present/absent
Pallor of LC	50	Present/absent	84%	Present/absent
SN Lewy body presence	47	Present/absent	96%	Present/absent
SN Lewy body score	47	Score 0-4	1.9	0–3
SN Neuronal loss gliosis	47	Score 0-3	1.4	1–2
CN IX – X Lewy body score	20	Score 0-4	2.4	0–3

LC = Locus coeruleus. BA = Brodman's area. SN = substantia nigra. CN IX-X = glossopharyngeal and vagal nerve nuclei.

Table 2

Baseline clinical characteristics and clinical data collected from most recent evaluation prior to brain donation in Parkinson's disease patients.

Clinical data	Lewy bodies absent LC	Lewy bodies present in LC	p-value	All subjects
Age at death (yr)	77.7 (9.7)	78.4 (8.6)	0.81[1]	78.2 (8.8)
Age at UPDRS (yr)	83.5 (2.1)	74.6 (1.2)	0.0326	75.3 (8.1)
Sex (% male)	61.5 (0.5)	65.6 (0.5)	0.80[1]	64.4 (0.5)
Age of onset (years)	66.0 (10.1)	60.6 (12.4)	0.17[1]	62.2 (11.9)
Disease Duration (years)	15.0 (5.2)	17.4 (6.5)	0.24[1]	16.7 (6.2)
UPDRS Part III: Gait	1.7 (1.0)	2.3 (1.2)	0.02[2]	2.1 (1.1)
UPDRS Part III: Postural Instability	1.6 (1.0)	2.1 (1.2)	0.38[2]	2.0 (1.2)
UPDRS Part II: Freezing	1.2 (1.3)	1.5 (1.4)	0.39[2]	1.4 (1.2)
UPDRS Part III: Generalized bradykinesia	1.8 (1.0)	2.1 (1.1)	0.88[2]	2.0 (1.1)
UPDRS Part III: Total	36.4 (14.7)	38.9 (10.8)	0.53[1]	38.2 (11.9)
TUG (seconds)	16.8 (6.2)	14.5 (7.4)	0.36[1]	15.2 (7.1)
Braak stage	3.5	2.9	0.341	2.9 (1.3)

P-values:

All data reported as mean (SD). UPDRS = Unified Parkinson's Disease Rating Scale. TUG = Timed Up-and-Go Score. LC = locus coeruleus.

[1] *t*-test of means

[2] Fisher's exact test.