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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 up-and-go speed (TUG).

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.

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]

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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, $p = 0.047$).