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Educational Attainment and Motor Burden in Parkinson disease

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Abstract

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OBJECTIVE—Greater educational attainment is a protective factor for neurodegenerative dementias. If education earlier in life leads to greater cerebral reserve, it may play a similar protective role in Parkinson disease (PD).

METHODS—We conducted a cross-sectional clinical-imaging study of 142 subjects with PD. All subjects underwent [¹¹C]dihydrotetrabenazine PET to confirm nigrostriatal dopaminergic denervation and brain MRI to estimate adjusted cortical grey matter volume.

RESULTS—After adjusting for possible confounders including cognitive and dopaminergic covariates, as well as non-specific neurodegeneration covariates (age, disease duration, and total adjusted cortical gray matter volume), lower years of education remained a significant predictor of higher total MDS-UPDRS motor score ($t=-3.28$, $p=0.001$). Education level associated inversely with white matter hyperintensities in a post-hoc analysis ($n=83$).

CONCLUSIONS—Higher educational attainment is associated with lower severity of motor impairment in PD. This association may reflect an extranigral protective effect upon white matter integrity.

Keywords

Parkinson disease; Education; Gray Matter; Dopamine; Neuroprotection

Introduction

Higher educational attainment is a protective factor for the development of dementias. A recent review of common risk factors for dementia suggested that modifiable risk factors explain approximately 30% of the worldwide prevalence of Alzheimer's dementia, with low educational status accounting for a greater fraction of this attributable risk than any other single risk factor.¹ Higher education may increase cerebral reserve capacity and/or augment compensatory mechanisms in healthy elderly, delaying the onset of cognitive decline later in life.²

Parkinson disease (PD) is a common neurodegenerative condition whose presenting features typically involves motor disability rather than cognitive impairment. The development and sustenance of compensatory mechanisms of neuronal function are described in inverse association with some motor features in PD,³ though risk factors for pathological changes in compensatory function are not well understood. We conducted a clinical-neuroimaging correlation study to explore potential associations between educational attainment and motor burden in PD.

Methods

Subjects

This retrospective cross-sectional study involved 142 subjects with idiopathic PD. All subjects met UK Brain Bank clinical diagnostic criteria for PD.⁴ All subjects displayed typical patterns of nigrostriatal dopaminergic denervation with monoaminergic [¹¹C]dihydrotetrabenazine (DTBZ) PET imaging. Subjects were recruited from Movement Disorders clinics at the University of Michigan Medical Center and the Veterans Affairs

Ann Arbor Health System. Demographic information for all subjects is presented in Table 1. All subjects underwent the Movement Disorders Society-revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor exam in the practically defined overnight "off" state. All subjects provided a detailed clinical history pertaining to their parkinsonian motor symptoms. Years of education were treated as an ordinal variable corresponding to the number of grades completed. For example, a high school graduate without additional schooling was classified as having 12 years of education and an individual whose highest level of education was a 4-year bachelor's degree was classified as having 16 years. All subjects underwent cognitive testing with the Montreal Cognitive Assessment (MoCA) after resuming their scheduled dopaminergic 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

DTBZ PET Imaging and Analysis—^{[11]C}-DTBZ vesicular monoamine transporter type 2 (VMAT2) PET imaging was performed in 3D imaging mode using an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN) in the dopaminergic "off" state. DTBZ distribution volume ratio (DVR) in the striatum was estimated as reported previously.⁵

MRI Imaging, Cortical Grey Matter Volume, and White Matter Hyperintensity Assessments—All subjects underwent brain magnetic resonance imaging on a 3T Philips Achieva system (Philips, Best, The Netherlands) utilizing an 8-channel headcoil. This protocol has been described previously by our group.⁶ Cortical grey matter volume was estimated using the Freesurfer toolkit (<http://www.surfer.nmr.mgh.harvard.edu/>).⁷ In each subject, the total cortical grey matter volume was divided by total intracranial volume to normalize for inter-subject variation in skull size. White Matter Hyperintensities (WMHs) were estimated using an automated method that uses cerebellar white matter, a region relatively unaffected by age-related leukoaraiosis, as a reference marker. The details of this method are reported elsewhere.⁸

Statistical Analysis

Descriptive statistics including means and standard deviations are presented for various demographic factors in Table 1. Multivariable linear regression analysis was used to explore the effect of education on MDS-UPDRS motor exam score using the following variables as covariates: age, disease duration, years of education, MoCA score, striatal DTBZ DVR, and cortical grey matter volume adjusted for intracranial volume.

Adjusted grey matter volume was chosen as a covariate since it has been shown to associate both with motor burden in PD⁹ and with higher education status.¹⁰ Age and disease duration were selected as covariates given their expected associations with overall motor burden severity. Striatal DTBZ was selected to control for the severity of nigrostriatal dopaminergic neurodegeneration. MoCA scores were selected as a covariate to account for the possibility

that subjects with more education may have higher cognitive reserve that influences elements of motor testing.

In the process of model building, we explored the effects of a number of variables that might modify the association between education and MDS-UPDRS motor score. These markers, which were tested using Pearson's correlation coefficient and independent t-tests, included a) height, which may be a proxy marker of perinatal exposures,¹¹ b) a categorical term for birth cohort date-of-birth prior to 1946—which may be a marker for early life nutritional status and psychological stress,¹² and c) Body Mass Index (BMI)—which may be a marker for sedentary behavior and metabolic syndrome. Because of its significant bivariate correlation with UPDRS motor score (see *Results*), BMI was included in the final multivariable model. Since it is possible that the long duration effects of dopaminergic medications may associate with favorable motor performance, even during standardized testing in the off-state, we also ran a secondary multivariable regression model testing the associations when Levodopa equivalent dose (LED) was substituted for Striatal DTBZ with all other variables remaining the same.

Other studies on normal aging^{13, 14} have suggested that WMH burden may be a downstream consequence of cardiovascular risk factor burden and limited physical activity during life—two factors that could plausibly associate with the level of educational attainments and might explain the influence of education on motor outcomes. We conducted a post-hoc analysis in a sub-cohort (n =83) with MRI data suitable or available for WMH analysis. This model included all of the covariates in the primary model and a continuous variable for supratentorial WMH severity. The outcome variable remained MDS-UPDRS motor score. All analyses were performed using SAS version 9.4 (SAS institute, Cary, NC).

Results

Demographic information for the cohort is presented in Table 1. We found a significant bivariate correlation between years of education and BMI ($\rho=-0.251$, $p=0.003$) but not with height ($\rho=0.04$, $p=0.60$). Subjects born before 1946 (n=79) showed no difference in level of education compared to those subjects born in 1946 or later (14.9 $\pm$ 2.9 vs. 15.6 $\pm$ 2.7; $t=1.48$, $p=0.14$) though there was a trend towards higher UPDRS motor scores in the older group of subjects (34.6 $\pm$ 13.4 vs. 30.30.5 $\pm$ 14.6; $t=1.76$, $p=0.081$). Our cohort was made up predominantly of individuals who self-identified as white. There were 7 total individuals who identified as other races (Asian =1, Native American =1, African-American=2, Multiple races =3). Non-white subjects showed no differences in UPDRS motor score compared to those who self-identify as white (32.8 $\pm$ 14.0 vs. 33.1 $\pm$ 15.4; $t=0.04$, $p=0.97$).

In our multivariable linear regression model, years of education, striatal DTBZ DVR, and duration of disease showed significant associations with MDS-UPDRS motor score after adjusting for all covariates (Table 2). In our secondary model ($F=8.51$, $p<0.0001$, $R^2=0.308$) using LED as a covariate rather than striatal DTBZ, age ($t=2.27$, $p=0.025$), disease duration ($t=3.37$, $p=0.001$), LED ($t=2.69$, $p=0.008$) and years of education ($t=-3.52$, $p=0.0006$) all showed significant associations with MDS-UPDRS motor score. MoCA score

($t = -0.72$, $p = 0.473$), BMI ($t = -0.21$, $p = 0.833$) and adjusted cortical grey matter volume ($t = -0.49$, $p = 0.623$) showed no significant multivariable associations with MDS-UPDRS motor score in this model.

In a post-hoc analysis of a subset of subjects ($n = 83$), the inclusion of a term for WMH burden into the regression model showed an overall significant model effect ($F = 5.00$, $p < 0.0001$, $R^2 = 0.351$). Disease duration ($t = 3.50$, $p = 0.0008$), Striatal DTBZ DVR ($t = -2.03$, $p = 0.046$), and Cortical grey matter volume ($t = -2.10$, $p = 0.039$) showed significant associations with MDS-UPDRS motor score while age ($t = 1.95$, $p = 0.055$), BMI ($t = 0.54$, $p = 0.593$), MoCA score ($t = -0.37$, $p = 0.710$), education level ($t = -1.40$, $p = 0.164$), and WMH burden ($t = -0.97$, $p = 0.336$) did not. In this sub-cohort, education level showed a bivariate Pearson's correlation with WMH burden ($\rho = -0.303$, $p = 0.005$) but not with Striatal DTBZ DVR ($\rho = 0.018$, $p = 0.873$) or Cortical grey matter volume ($\rho = -0.108$, $p = 0.332$).

Discussion

Educational achievement before the onset of PD is associated with the severity of motor disease burden. This association is not explained by nigrostriatal markers for PD disease severity but may instead relate to a protective effect of education upon white matter integrity. These findings suggest that factors that associate with both lower educational attainments and greater microvascular brain changes may mediate a more aggressive clinical course of PD.

Although our study explores motor outcomes, the concept of an education-augmented cognitive reserve has been well investigated in studies focusing on dementia, normal aging, and in Parkinson disease.^{15, 16} Hypothesized mechanisms for this relationship include a) greater education-associated cerebral volumes that are more resilient to neurodegenerative changes, b) more efficient recruitment of alternative brain networks that may be used for neurologic function or c) enhanced brain repair/recovery mechanisms.¹⁵ Our results are also consistent with previous smaller studies that have shown inverse correlations between balance performance in PD and educational attainments.^{17, 18}

WMHs were linked to lower education and greater MDS-UPDRS motor score in our post-hoc analysis. Although advancing age is a strong risk factor for the formation of WMHs, we controlled for age in each of our multivariable models, further raising the likelihood that education attainments in our study are a proxy measure for other contributors to microvascular brain changes. These contributors could conceivably include cardiovascular risk factor burden and sedentary behavior both of which have been linked to WMH burden. They might also include an education-associated resiliency of cerebral white matter to the effects of WMHs.

Education level was associated with BMI in our cohort suggesting that it may be a marker for other exposures and health behaviors during life. Years of education may associate with unmeasured genetic factors, postnatal nutritional factors, with an increased likelihood for receiving early childhood education, a tendency to pursue more cognitively stimulating

activities during life, and/or higher socioeconomic status that may confer a lower risk of cardiovascular comorbidities known to play a role in neurodegenerative conditions including PD.¹⁹ It may also associate with hobbies, employment history, and other cognitively tasking behaviors all of which may have protective effects on clinical features of neurodegeneration. These possibilities are not mutually exclusive. Our retrospective study design is limited in this regard since we did not prospectively collect data on health behaviors, leisure activities, or measures of overall physical health.

We have previously reported that frontal WMH burden associates with the rate of axial motor progression in PD independent of nigrostriatal dopaminergic denervation.¹⁹ It is possible that loss of subcortical white matter integrity in PD reflects either a) damage to axonal projection systems involved in various motor systems b) low-grade microvascular damage to downstream grey matter targets of relevant projection systems or c) is an independent trait marker for an unmeasured neuropathology relating to disease severity in PD. Such unmeasured pathology could conceivably include heterogeneities in cerebral perfusion, which is a known risk factor for WMH formation.²⁰ Cerebral blood flow (CBF) has been shown to decline more precipitously in healthy individuals over the age of 60 who decline to participate in regular physical activity.²¹ Physical activity and other health behaviors are in part thought to explain education-associated disparities seen in cardiovascular disease mortality.²² WMHs themselves may be a downstream consequence of limited physical activity and higher cardiovascular risk burden or may be a marker for health behaviors that give rise to greater brain microvascular impairments. Consistent with these possibilities, a previous normal aging cohort study demonstrated an inverse association between education and WMHs that was in part explained by an aggregate assessment of general health and variations in the degree of parental education.²³

When we substituted LED for Striatal DTBZ in a separate regression model, age also showed a significant association with MDS-UPDRS motor score. In the LED model, it is possible that advancing age may be serving more strongly as a marker for a variety of age-related neuropathologies—including an age-related loss of striatal dopamine terminals—that may influence motor outcomes as well.

We did not collect information regarding the nature or quality of education received earlier in life. Since our study is not longitudinal, we cannot test whether PD in individuals with different educational backgrounds progresses at different rates. The mean number of years of education in our cohort was high. Subsequently, these findings require verification in other cohorts with different educational backgrounds. We did not prospectively collect serologic data on vascular risk factors, limiting our ability to explore their influence on motor outcomes. It is also possible that socioeconomic status (SES) and race may influence the relationship between education attainment and motor outcomes. We did not collect detailed information on SES and our cohort features only a small fraction of individuals who identify as non-white limiting our ability to explore these variables. It is possible that higher education status corresponds, not to a difference in absolute motor severity, but rather to a difference in performance on formal motor testing. For example, individuals with higher education attainments might be more conditioned to engage cognitive attentional resources during the process of a formal motor testing, thereby improving elements of their motor

speed and overall graded performance on certain observed tasks that are part of the MDS-UPDRS motor exam. It is also possible that individuals with greater innate intelligence may pursue greater educational attainments over the course of life and that brain function related to innate intelligence, rather than education per se, is what associates with motor outcomes in PD.

In conclusion, greater educational attainments associate with lower scores on MDS-UPDRS motor testing for reasons that do not appear to relate to nigrostriatal dopaminergic denervation. Education may serve as a trait marker for factors that lead to impaired white matter integrity with aging. PD studies that focus on risk factors seen in normal and pathological aging may inform our understanding of how best to improve disease-specific outcomes.

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Table 1

Subject Demographics and clinical information

Clinical Characteristics of Overall Cohort (n =142)	Mean (Standard Deviation) or Frequency
Age (yr)	65.6 (7.8)
Gender	105 M / 37 W
Duration of motor symptoms (yr)	6.2 (4.3)
Years of Education (yr)	15.24 (2.82)
Hoehn and Yahr Scale	1.0, n = 4 1.5, n = 6 2.0, n = 35 2.5, n = 62 3.0, n = 28 4.0, n = 5 5.0, n = 1
MDS-UPDRS motor score	32.8 (14.0)
Body Mass Index	28.6 (5.1)
Levodopa Dose Equivalents (mg)	699.7 (542.8)
Percentage of Subjects taking Dopamine Agonist Medications	35.2%
Montreal Cognitive Assessment	25.9 (2.5)
Striatal DTBZ DVR	1.95 (0.32)
Total Cortical Gray Matter Volume/Intracranial Volume	0.300 (0.046)

Table 2

Multivariable Linear Regression Analysis

		t-test, p-value						
	Overall Model F-value, p-value,	Age	Disease Duration	Body Mass Index	Montreal Cognitive Assessment	Striatal DTBZ	Total Adjusted Cortical Grey Matter Volume	Years of Education
Total MDS-UPDRS Motor Exam Score	F = 8.47, p<0.0001, R ² = 0.307	t = 1.50, p =0.137	t = 4.44 , p< 0.0001	t = 0.68, p =0.497	t = -0.69, p =0.492	t = -2.65 , p= 0.009	t = -0.42, p = 0.674	t = -3.28 , p = 0.001