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Cognitive and motor function in long duration *PARKIN* PD

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Abstract

Importance—The long term cognitive outcome in *PARKIN*-PD patients is unknown. This data may be meaningful when counseling *PARKIN*-PD patients.

Objective—Among early-onset PD (EOPD) patients with long disease durations, we assessed cognitive and motor performances, comparing compound heterozygote/homozygote *PARKIN* carriers to non-carriers

Design—Cross sectional study

Setting—Seventeen movement disorders centers

Participants—Forty-four participants in the Consortium on Risk for Early-Onset PD (CORE-PD) with PD duration greater than median (>14 years), including *PARKIN* compound heterozygotes/homozygotes combined (n=21), and non-carriers (n=23).

Main outcome measures—Unified Parkinson's Disease Rating Scale Part III (UPDRS), Clinical Dementia Rating (CDR) and neuropsychological performance. Linear regression models were applied to assess the association between *PARKIN* mutation status and cognitive domain scores and UPDRS. Models were adjusted for age, education, disease duration, language, and levodopa equivalent daily dose.

Results—Compound heterozygote/homozygote *PARKIN* mutation carriers had earlier AAO of PD ($p<0.001$) and were younger ($p=0.004$) at time of examination than non-carriers. They performed better on the MMSE ($p=0.010$) and were more likely to receive lower scores on the CDR ($p=0.003$). In multivariate analyses, *PARKIN* compound heterozygotes/homozygotes performed better on the UPDRS Part III ($p=0.017$), and on tests of attention ($p=0.022$), memory ($p=0.025$) and visuospatial ($p=0.024$) domains.

Conclusions and Relevance—Cross-sectional analyses demonstrate better cognitive and motor performance in compound heterozygote/homozygote *PARKIN* EOPD carriers than non-carriers with long disease duration, suggesting slower disease progression. Longitudinal follow up is required to confirm these findings.

Introduction

PARKIN mutations are the most common genetic mutations associated with early-onset Parkinson's disease (EOPD), defined by age at onset (AAO) of 50 or younger.[1] Two cross-sectional studies that examined cognitive performance in EOPD found similar neuropsychological performance between compound heterozygote/homozygote (CH/H) carriers and non-carriers of *PARKIN* mutations.[2, 3] However, it has been hypothesized that *PARKIN* CH/H carriers are less likely to develop dementia, and that longer follow-up is required to differentiate between the cognitive performance of CH/H carriers and non-carriers.[4] In order to explore this hypothesis, we repeated our analyses of the Consortium on Risk for Early-Onset PD (CORE-PD) study after recruiting additional participants and restricting the analyses to those with higher than median (>14 years) disease duration. Using cross-sectional data, we approximated long-term follow-up by examining the cognitive profiles of individuals with long PD duration, using a larger sample of EOPD than we previously reported.[2]

Methods

Participants

Participants with EOPD defined by AAO of PD ≤50 years were recruited from 13 centers participating in the CORE-PD study as previously described.[5, 6] Four sites, including San Juan (Puerto Rico), Albany, Atlanta, and Portland were later added to increase the number of *PARKIN* CH/H carriers and non-carriers with EOPD. Institutional review boards at all participating sites approved the protocols and consent procedures. We performed detailed examinations including a neuropsychological battery on 178 EOPD probands who had mutations in *PARKIN* and glucocerebrosidase (*GBA*) and on a subset of participants without known mutations.[6] To approximate long-term follow-up, we examined the distribution of PD duration, and selected individuals with disease duration greater than the median (14 years). We excluded carriers of *GBA* and *LRRK2* mutations. Because of the controversial role of heterozygous *PARKIN* mutations,[6–8] heterozygote carriers were also excluded. The analyses were performed on 21 *PARKIN* carriers of two mutations (4 homozygotes, and 17 compound heterozygotes) and 23 non-carriers of mutations in *PARKIN*, *PINK-1*, *DJ-1*, *LRRK2* or *GBA*.[5] Thirty eight of the 44 participants included in the final analysis were previously reported (Caccappolo et al, 2011).[2] Two of the new participants were CH/H *PARKIN* carriers and four were non-carriers.

Molecular genetic analyses

Participants were genotyped for *PARKIN*, *GBA*, *LRRK2*, *PINK-1* and *DJ-1* as previously described.[5, 9, 10] Beginning in 2010 we used multiplex ligation dependent probe amplification (MLPA)[7] in newly recruited probands and all probands recruited prior to 2010 with point mutations or dosage changes. All deletions and duplications identified via MLPA

were verified using real-time PCR. All probands with *PARKIN* mutations detected via the resequencing chip or with dosage detected via MLPA have had full sequencing of *PARKIN* exons and MLPA if not previously performed.

Clinical and Neuropsychological Evaluation

The clinical evaluation of CORE-PD participants has been previously described. [6, 11] In brief, it included The Unified Parkinson Disease Rating Scale (UPDRS)[12] which was performed in the "on" state, the Mini Mental State Examination (MMSE), the Clinical Dementia Rating (CDR) scale[13] and a neuropsychological battery. The neuropsychological battery used in this study was composed of measures corresponding to five cognitive domains: psychomotor speed, attention, memory, visuospatial function, and executive function (Supplementary Table 1). [2, 11, 14, 15] The battery included measures that could be administered in English or Spanish. A consensus panel, as previously described, (GBA neuropsych paper), assigned a clinical consensus diagnosis to each participant based on medical history, neurological examination and neuropsychological performance and functional impairment. Each participant was assigned a clinical consensus diagnosis based on medical history, neurological examination and neuropsychological performance and functional impairment, without knowledge of genetic status.[11] Participants were rated as cognitively normal, mild cognitive impairment[16] or demented.[11]

Statistical Analysis

Individual neuropsychological test scores were transformed to create Z-scores using means and standard deviations of the entire sample of PD cases. Composite scores for each domain were computed by averaging the mean Z-scores from the individual tests comprising each domain.[11] Demographic data, disease characteristics, MMSE, CDR score and neuropsychological test performance were compared between CH/H *PARKIN* carriers and non-carriers using Fisher exact, chi-square tests, and Student T tests as appropriate. Linear regression models were constructed to test the association between the genetic status (predictor) and UPDRS Part III and cognitive domain scores (outcomes), adjusting for age, duration of PD, education (truncated at 20 years), levodopa equivalent daily dose and language that the tests were administered in (Spanish or English).

Results

Demographic and clinical characteristics of the participants stratified by *PARKIN* genetic status are shown in Table 1. CH/H had earlier AAO of PD and younger age at time of examination than non-carriers. They performed better on the MMSE and were more likely to receive lower scores on the CDR, indicating better functional status, than non-carriers. Mean raw scores on individual neuropsychological tests are reported in eTable 2.

In models adjusted for age, gender, duration, education, levodopa equivalent daily dose and language (Table 2), CH/H *PARKIN* mutation status was associated with better performance on the UPDRS-III ($p=0.017$), attention ($p=0.029$), memory ($p=0.025$) and visuospatial ($p=0.024$) cognitive domains. Better cognitive performance in each of the cognitive domains was highly correlated with lower UPDRS-III scores (psychomotor speed $r= -0.503$, $p=0.001$; attention $r=-0.541$, $p<0.001$; memory $r=-0.597$, $p<0.001$; visuospatial $r= -0.635$, $p<0.001$ and executive function $r= -0.468$, $p=0.002$). Therefore, when each of the cognitive domains was included in the adjusted models with UPDRS-III as the outcome, the association between CH/H *PARKIN* mutation status and UPDRS-III was not significant. Similarly, when the UPDRS-III was included in the adjusted models with each cognitive performance domain as the outcome, the association between CH/H *PARKIN* mutation status and performance in each cognitive domain was not significant.

Discussion

Among EOPD patients, we have demonstrated that CH/H *PARKIN* carriers with long disease duration have better performance than non-carriers in attention, memory and visuospatial cognitive domains and on motor examination during the "on" state. Motor and cognitive performances were very strongly correlated as expected. These findings are consistent with the milder motor PD previously reported in CH/H *PARKIN* carriers compared to non-carriers in cross sectional analyses,[17] and with previously reported clinical observations that dementia is rare among CH/H *PARKIN* carriers.[1, 18–21] However, the differences in cognitive performance identified in the current study contrast with previous findings (including those from our own cohort), showing no significant differences in neuropsychological performance between CH/H *PARKIN* cases and EOPD non-carriers.[2, 3] A possible explanation for the discrepancy is that CH/H *PARKIN* carriers are less likely to develop the cognitive impairment and dementia that often occurs as PD advances, and that the pathology in *PARKIN*-PD remains circumscribed to the substantia nigra, even as the disease progresses. Autopsy data also support this hypothesis. Brain autopsies from CH/H mutation carriers demonstrate nigral atrophy, but without neurodegenerative pathology in cortex; neither Lewy nor Alzheimer's neuropathology is present in these brains, with rare exceptions.[22, 23] In contrast, Lewy bodies and Alzheimer's-like changes are the most common findings in autopsies of patients with PD-dementia.[24] We have also previously reported that CH/H *PARKIN* carriers are less likely to manifest hyposmia when compared to other EOPD.[25] These clinical findings, as well as autopsy data, suggest a more 'pure dopaminergic deficit' in *PARKIN*-related PD.

Our findings may have important implications for genetic testing and counseling for CH/H *PARKIN* carriers. Recent studies have demonstrated that PD patients are interested in genetic testing results, but they may not fully understand the implications of genetic results or the benefits of genetic counseling.[26–28] Considering that CH/H *PARKIN* carriers develop PD at a younger age than non-carriers, they may be concerned about their risk for dementia and their long-term ability to work. CH/H *PARKIN* carriers may benefit from the assurance that they have a lower risk for dementia compared to idiopathic PD patients.

The major strengths of our study include the size of our cohort given that it represents the largest sample size of mutation carriers with long disease duration reported to date, and the comprehensive neuropsychological battery employed. Our non-carrier EOPD group is likely an appropriate comparison group having been screened for mutations in *PARKIN, GBA, LRRK2, SNCA, PINK-1 and DJ-1*.[5] We previously showed, using the same battery and a non-carrier control group that EOPD non-carriers perform better than *GBA* mutation carriers.[11] A significant limitation of this study is its cross-sectional design of our study. In spite of our efforts to match the genetic groups by including only EOPD patients with a long disease duration, non-carriers were older and CH/H had a longer duration, though we did adjust for this in the analyses.

Future studies that investigate the effects of disease duration on cognitive and motor function, including those with longitudinal follow up, will help confirm our observation that *PARKIN*-PD may progress more slowly than idiopathic PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Dr. Caccappolo, Ms. Mejia-Santana, Dr. Tang, Dr. Rosado, Ms. Ruiz, Dr. Orbe Reilly, Dr. Mickel, Dr. Cote, Dr. Ford, Dr. Novak, Dr. Hiner, and Mr. Paucilo have nothing to disclose.

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Authors' contribution:

Alcalay RN analysis and interpretation, statistical analysis, acquisition of data and drafting original manuscript; Caccappolo E analysis and interpretation, acquisition of data and drafting original manuscript; Mejia-Santana H acquisition of data and critical revision of the manuscript for important intellectual content; Tang M –X acquisition of data, statistical analyses and critical revision of the manuscript for important intellectual content; Rosado L acquisition of data and critical revision of the manuscript for important intellectual content; Orbe Reilly M acquisition of data and critical revision of the manuscript for important

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Table 1

Clinical and demographic characteristics of EOPD probands with and without *PARKIN* compound heterozygote/homozygote mutations

	Non-Carriers N=23	Two mutations (compound heterozygotes/ homozygotes) N=21[1]	P value
Mean Age, years (SD)	61.5 (6.4)	53.1 (11.5)	0.004
Mean Age at onset, years (SD)	40.2 (4.0)	26.6 (10.0)	<0.001
Mean Disease duration, years (SD)	21.3 (4.2)	26.5 (9.7)	0.023
Mean Education, years (SD)	15.7 (4.2)	13.5 (2.8)	0.052
Neuropsychological testing in	13.0% (3)	23.8% (5)	0.448
Spanish (Number of subjects)			
Mean UPDRS-III (SD)	27.8 (10.1)	21.0 (7.0)	0.015
Mean Levodopa equivalent daily dose, mg (SD)	811 (366)	650 (530)	0.252
Ethnicity (Caucasian/Hispanic/Other %)	73.9%/21.7%/4.3%	61.9%/38.1%/0.0%	0.343
Gender (% Female)	9 (39.1%)	12 (57.1%)	0.365
Mean MMSE	27.9 (2.0)	29.2 (0.9)	0.010
CDR [#]			
0	40.9% (9)	76.2% (16)	0.003
0.5	9.1% (2)	23.8% (5)	
1	40.9% (9)	0.0%	
2	9.1% (2)	0.0%	
Clinical diagnosis			
Normal	21.7% (5)	28.6% (6)	0.018
Mild cognitive impairment	30.4% (7)	61.9% (13)	
Dementia	47.8% (11)	9.5% (2)	
Mean Psychomotor speed, Z-score (SD)	−0.58 (1.1)	−0.11 (0.74)	0.114
Mean Attention, Z-score (SD)	−0.64 (0.95)	0.00 (0.83)	0.027
Mean Memory, Z-score (SD)	−0.51 (0.91)	−0.14 (0.79)	0.162
Mean Visuospatial function, Z- score (SD)	−0.44 (1.3)	0.10 (0.59)	0.080
Mean Executive function, Z-score (SD)	−0.53 (0.90)	−0.07 (0.63)	0.057

[1] Four non-carrier participants completed only portions of the neuropsychological examination.

[#] one non-carrier did not receive a CDR score

Table 2

Linear regression models testing the association between *PARKIN* mutation status and cognitive domain performance among early-onset PD participants with disease duration >14 years

	Non-carriers compared to *PARKIN* compound heterozygotes and homozygotes[1]		
	Beta	**95% CI**	**P value**
UPDRS	4.7	0.89 – 8.50	0.017
Psychomotor speed	−0.32	−0.75 – 0.12	0.147
Attention	−0.42	−0.79 – −0.05	0.029
Memory	−0.36	−0.67 – −0.05	0.025
Visuospatial function	−0.48	−0.90 – −0.07	0.024
Executive function	−0.28	−0.58 – 0.01	0.061

[1] models are adjusted for age, gender, duration, education, levodopa equivalent daily dose and language in which the tests were performed (English or Spanish)