LETTER TO THE EDITOR

To The Editor

Association Between Hypomimia and Mild Cognitive Impairment in *De Novo* Parkinson's Disease Patients

Keywords: Parkinson's disease, Hypomimia, Facial expression, Mild cognitive impairment

Hypomimia is one of the most distinctive clinical features in Parkinson's disease (PD). It is characterized by a reduction or loss of spontaneous facial movements and facial expression of emotions, and its severity differs among patients. The intriguing issue with hypomimia resides in the fact that it is still unclear whether the problem is purely motor or whether it may be related to other factors such as depression or cognitive problems.[1] Compared to tremor-dominant patients, akinetic-rigid/postural instability gait disorder PD subtype is more frequently associated with cognitive decline and greater motor severity that may also involve facial expression.[2] Since the perception and production of facial expressions are cognitive processes,[3] PD patients with more severe hypomimia therefore might well have higher rates of cognitive decline. Dementia contributes to lower patient autonomy and greater caregiver burden, and mild cognitive impairment in PD (PD-MCI) is considered a predementia stage.[4] Cognitive impairment can be present in early PD.[5] The association between the severity of hypomimia and cognitive impairment in PD has not been evaluated before.

Here, we performed a cross-sectional study to characterize the relationship between facial expression and cognitive impairment in a large sample of *de novo* PD patients. Newly diagnosed untreated PD patients from the Parkinson's Progression Markers Initiative (PPMI) were included in the study (http://www.ppmi-info.org/data). Patients with moderate or severe depression according to the Geriatric Depression Scale were excluded. All patients underwent clinical and cognitive evaluations. The clinical assessment included demographic data, motor evaluation including the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) and motor subtype, education, disease duration, depression score, and frequency of mild cognitive impairment (PD-MCI). Neuropsychological evaluation was undertaken and included the following tests: the Montreal Cognitive assessment for global cognition, letter number sequencing (LNS) for attention, Hopkins verbal learning test (HVLT) for immediate, delayed recall, and recognition for memory; phonemic fluency for executive function, semantic fluency for language, and judgment of line orientation for visuospatial function. Patients were classified according to severity of facial expression [MDS-UPDRS item question (Q) 3.2] ranging from 0 (normal facial expression) to 4 (masked facies with lips parted most of the time when the mouth is at rest). Only patients with a complete clinical and neuropsychological assessment were included. According to the level-I MDS task force MCI criteria, patients were diagnosed as cognitively normal (PD-CN) or PD-MCI.[4] Differences between clinical and neuropsychological characteristics among groups were analyzed. Variables with normal distribution were studied by Analysis of Variance (ANOVA), with application of Bonferroni's post hoc correction, whereas variables with non-parametric distribution were studied using the Kruskal–Wallis test. Chi-square test was applied to compare categorical variables. Correlations between facial expression and neuropsychological scores were examined using Pearson's correlation coefficient (r) adjusted for potential confounders (age, sex, education, disease duration, motor subtype, and UPDRS-III regardless of facial expression score to avoid collinearity). In order to assess the association between the degree of hypomimia (score from 0 to 4, MDS-UPDRS 3.2 item) and cognitive diagnosis (PD-CN or PD-MCI, as the dependent variable), a binary logistic regression was conducted, using age, sex, education, disease duration, motor subtype, and UPDRS-III as covariates. Odds ratios (OR) and confidence interval (CI) were obtained. Significance was set at $p < 0.05$.

Four hundred and fifteen PD patients were included: 65 (15.5%) were rated as having normal facial expression, 232 (55%) scored 1; 111 (26.4%) scored 2; 8 (1.9%) scored 3, and 1 PD patient rated as 4 (0.2%). Due to the low number of subjects that scored 3 or 4 on item 3.2, these were grouped together for further analysis. There were significant differences between the groups in age, gender, and MDS-UPDRS-III ($p < 0.05$). The frequency of PD-MCI was higher in the groups showing more hypomimia ($p < 0.005$, Table 1) and no significant differences existed among groups in the neuropsychological scores (Table 2). There was a weak negative correlation between immediate memory score (trial 3 from the HVLT) and a higher score on MDS-UPDRS item question 3.2 ($r = -0.111$, $p = 0.024$). No other significant correlations were found. Logistic regression analysis showed that more severe hypomimia was associated with the diagnosis of PD-MCI ($p = 0.024$, OR = 1.9, CI = 1.11–3.25).

In the present study, more severe hypomimia was associated with PD-MCI and weakly correlated with lower memory scores independently of motor severity and motor phenotype. This association has not been studied before and supports the notion that decreased facial expression may not be a purely motor, purely dopaminergic feature, and might be related to higher brain functions in PD, at least partially. Ricciardi et al. have demonstrated that PD face expressiveness could be associated with disrupted facial emotion recognition, one of the most critical components of emotional functioning and social behaviors.[6,7]

The neuropathological correlates of hypomimia remain unclear, but neuronal loss and Lewy body pathology in the amygdala have been suggested as contributing factors.[8] Furthermore, a body of evidence links the amygdala to facial emotion recognition.[9] These changes in the amygdala are also seen in PD dementia, and therefore cognitive impairment and hypomimia may share a common pathological substrate. Several limitations should be acknowledged, such as the use of level I MDS criteria for the diagnosis of PD-MCI, which provide less diagnostic certainty than level II criteria and do not allow the classification of PD-MCI into specific subtypes. In addition, evaluation of facial expression according to MDS-UPDRS III may not be sensitive enough. However, this is the most common

https://doi.org/10.1017/cjn.2020.93 Published online by Cambridge University Press

Table 1: Clinical features of the different groups

Facial expression score	0 ($n = 63$)	1 ($n = 232$)	2 ($n = 111$)	≥3 ($n = 9$)
Age (years)	62 (10.47)	64.5 (10.25)	67.2 (7.76)[a]	65.11 (10.31)
Gender (male/female, %)	29/34 (46.03/53.97)	82/150 (35.34/64.6)	28/83[b] (25.23/74.77)	1/8 (11.11/8.89)
Disease duration (years)	1.63 (1.73)	2.2 (2.35)	1.78 (1.31)	1.78 (1.2)
MDS-UPDRS III (w/o item 3.2)	14.48 (6.63)	18.96 (7.87)[a]	23.61 (8.74)[a,c]	26 (10.43)[a,d]
Motor phenotype PIGD/TD/ Indeterminate	12/21/30	30/129/73[a]	19/71/21[a,d]	1/7/1[b]
GDS	5.3 (1.59)	5.3 (1.54)	5.06 (1.33)	4.89 (0.93)
Education (years)	15.38(3.06)	15.45 (2.99)	15.70 (2.90)	15.67 (2.96)
PD-MCI (*n*, %)	4 (6.3%)	12 (5.2%)	16 (14.4%)[c]	3 (33.3%)[a,c]

GDS-15=15-item Geriatric depression score; MDS-UPDRS-III=Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III; PD-MCI=Parkinson's disease with mild cognitive impairment; PIGD: Postural instability and gait disturbance; TD=tremor dominant; w/o=without.
Group 3 includes patients with three or four in the MDS-UPDRS question 3.2.
Data are presented as mean (standard deviation) or number (frequency).
[a] $p < 0.005$ vs group 0.
[b] $p < 0.05$ vs group 0.
[c] $p < 0.005$ vs group 1.
[d] $p < 0.05$ vs group 1.

Table 2: Neuropsychological features of the different groups

Facial expression score	0 ($n = 63$)	1 ($n = 232$)	2 ($n = 111$)	≥3 ($n = 9$)
MoCA	27.52 (2.51)	27.20(2.34)	26.83 (2.82)	26.67(2.80)
LNS	10.67 (3.09)	10.63(2.64)	10.36 (2.41)	10.78(3.38)
SF animals	21.83(5.01)	20.83 (5.40)	20.95 (5.36)	19.33 (5.94)
SF vegetables	14.97 (4.78)	14.08 (4.25)	14.03 (4.89)	14.22 (4.38)
SF fruits	14.57 (4.11)	13.33 (3.96)	13.29 (4.29)	12.44 (4.21)
PF MoCA	13.08 (4.63)	12.72 (4.75)	13.51 (4.48)	12.44 (4.53)
HVLT trial 3	10.02 (1.73)	9.56 (1.79)	9.32 (1.78)	9.22 (2.11)
HVLT delayed recall	8.63 (2.40)	8.38 (2.56)	8.23 (2.53)	8.67 (2.18)
HVLT recognition	11.43 (0.84)	11.15 (1.27)	11.08 (1.11)	11.44 (0.73)
JLO	12.63 (1.90)	9.56 (2.08)	9.32 (2.25)	9.22 (3.24)

Group 3 includes patients with three or four in the MDS-UPDRS question 3.2.
Data are presented as mean (standard deviation) or number (frequency).
Montreal Cognitive assessment (MoCA) for global cognition, letter number sequencing (LNS) for attention, Hopkins verbal learning test (HVLT) for delayed recall, percentage of retention and recognition for memory; phonemic fluency for executive function, semantic fluency (SF) and Phonetic Fluency (PF) for language, and judgment of line orientation (JLO) for visuospatial function.

scale used in clinical practice. On the other hand, the main strength of the study is the large sample size of early untreated patients.

A higher degree of hypomimia at disease onset could indicate the need for early cognitive evaluation in PD patients, especially in those reporting cognitive complaints that are reflected in the PD-MCI criteria.[4] At the same time, more objective, automated measures[10] should be developed to determine which characteristics of hypomimia link it to cognitive decline in PD.

Acknowledgments

Data of this study were obtained from the Parkinson's Progression Markers Initiative (PPMI). PPMI industry partners: Abbvie, Allergan, Amathus Therapeutics, Avid Radiopharmaceuticals,

https://doi.org/10.1017/cjn.2020.93 Published online by Cambridge University Press

Biogen, Biolegend, Bristol-Meyers Squibb, Celgene, Denali, GE Healthcare, Genentech, GlaxoSmithKline, Janssen Neuroscience, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, Voyager Therapeutics.

Conflicts of Interest

The authors report no conflicts of interest regarding the study.

Statement of Authorship

CG: study concept and protocol design, statistical analysis, drafted, and revised the manuscript. DU: drafted and revised the manuscript. Both authors provided approval of final manuscript.

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https://doi.org/10.1017/cjn.2020.93 Published online by Cambridge University Press