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Epidermal Growth Factor (EGF) is Associated with Memory and Executive Functioning in Progressed Parkinson's Disease

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Abstract

Objectives: Epidermal Growth Factor (EGF) is a candidate biomarker for cognitive functioning in Parkinson's disease (PD). Relationships between EGF and cognition were explored in progressed PD. Methods: EGF levels were obtained from a heterogeneous sample of PD patients referred for clinical neuropsychological evaluation. Correlation and effect size analyses evaluated relationships between EGF and cognitive measures. Results: EGF was associated with measures of executive functioning and memory. Conclusion: EGF corresponds to cognition in progressed PD. Findings are consistent with previous studies, and support further investigation of EGF's utility as a biomarker for cognitive functioning in PD.

Keywords: Parkinson's disease; Biomarker; Cognitive impairment; Executive functioning; Memory; Epidermal growth factor

Background

In addition to motor symptoms, cognitive impairment is pervasive in Parkinson's disease (PD) [1,2]. Identifying biomarkers associated with cognitive dysfunction in PD will help researchers better understand the underlying neurobiological mechanisms. Moreover, such markers could serve as outcome measures in clinical trials of novel interventions. Application would be enhanced if markers were easily available through outpatient visits.

Epidermal Growth Factor (EGF) has received support from several recent studies as a blood serum biomarker for cognitive functioning in Parkinson's disease (PD). In a large heterogeneous sample of PD patients, Chen-Plotkins et al. [3] identified EGF as predictive of clinically significant cognitive decline over 18-24 months. This finding is particularly compelling given that cognition was tracked with a summary measure from the Mattis DRS-2, a dementia screening instrument. More recently, Pellechia et al. [4] found EGF levels in newly diagnosed, drug-naïve PD patients were related to memory and executive functioning obtained from an extended neuropsychological testing battery at baseline and two-year follow-up.

The correspondence between EGF levels and cognition in progressed PD patients who are already presenting cognitive impairment remains unclear. This is critical given EGF's potential utility in clinical trials of neurocognitive interventions. The purpose of the current evaluation was to explore relationships between EGF levels and cognitive functioning in a heterogeneous sample of PD patients referred for clinical neuropsychological evaluation of cognitive concerns.

Methods

Participants were PD patients followed in a university hospital movement disorders clinic. Diagnosis of idiopathic PD based on British Brain Bank criteria [5]. Referral for comprehensive clinical neuropsychological evaluation was made if concerns of cognitive decline were raised during the visit. Patients who agreed to be seen for neuropsychological evaluation were subsequently offered the opportunity to participate in the research protocol. All participants were informed that decision to participate would not affect treatment, and the neuropsychologist (THT) was blind to participation status. The study was approved by the Institutional Review Board of the Medical University of South Carolina and all participants provided written consent. The study coordinator (AD-D) performed informed consent and drew blood during the clinic visit. Following collection, serum samples were processed and run in duplicate for EGF levels (Quantikine Human EGF Immunoassay, R&D Systems, Minneapolis, MN). Neuropsychological examinations were scheduled between 30 and 90 days from date of blood draw.

Neuropsychological evaluation was performed by a fellowship-trained neuropsychologist, consistent with guidelines put forward by the MDS Task Force for Level-II diagnosis of Mild Cognitive Impairment and Dementia in Parkinson's Disease [6-8]. The evaluation was completed in a single visit for each patient. Visits typically lasted about 3 hours, including clinical interview and formal neuropsychological testing. All patients were evaluated while subjectively "on" medication, with breaks allowed as needed. Following standard clinic practices, test battery construction was based on referral question, limitations due to motor dysfunction, and psychometric properties. Test measures were included for analysis if at least 10data points from the study sample were available.

In keeping with methodology employed by Pellechia et al., log10 transformation was applied to normalize EGF levels [4]. Raw scores on cognitive tests were corrected for demographic characteristics

according to test manuals. Notable exceptions were for DRS-2 total score, which is often interpreted in its raw form, and Judgment of Line Orientation (JOLO), wherein conversion to percentile range requires a full scale IQ estimate [9]. Relationships between EGF levels and cognitive measures were explored using Pearson product-moment correlations. Given the limited sample size of this exploratory study, reporting of all observed correlation values with corresponding effect sizes, using Ezekiel correction for population correlation estimates based on small samples [10], was favoured over an arbitrary a priori threshold for statistical significance.

Results

A total of 20 PD patients were enrolled; complete data sets were available for 17 participants and are reported below. The final sample was composed predominantly of men, with mean age of 66.1 years (4.9), and mean education of 14.9 years (2.3). Average duration of illness was 8.5 years (4.8), with mean Hoehn and Yahr Stage of 2.38 (.70), and mean levodopa equivalent dose of 731.6 (433) [11]. Two patients were being treated with quetiapine. None had history of neurosurgery or carried diagnosis of a comorbid neurological disorder. Mean EGF was 765 pg/ml, CV=3.71. Using the MDS Task Force criteria described above, 10 participants (59%) met criteria for Mild Cognitive Impairment, and 1 patient met criteria for dementia (6%). Relationships between EGF and education, r=.035, was negligible, and relationship between EGF and age was minimal, r=.198. Though not statistically significant, stronger relationships were observed between EGF and levodopa equivalent dose, r=-.342, 95% CI: [-.71, .17], and duration of illness, r=-.384, 95% CI: [-.73, .12].

As illustrated in the (Table 1), the typical PD patient performed below the 50th percentile on most tests administered; however, significant variability, ranging from percentiles suggesting deficit (below 10th percentile) to superior functioning (above 90th percentile) was observed within the sample. Relationships between EGF and most cognitive measures were in the direction predicted by previous studies. EGF levels accounted for about 10% or more of the variance in two measures of executive functioning: verbal fluency (D-KEFS semantic fluency) and psychomotor sequencing (D-KEFS Trails); and two measures of memory: verbal learning (CVLT-2 Total), and visual recognition (CVMT Delay). The adjusted effect size for the relationship with psychomotor sequencing was within the moderate range, r=.75, adjusted Cohen's d=.53.

Domain	Measure	n	Mean (SD)	Mean %ile [-SD, +SD]	Pearson r	Effect Size
Global	DRS-2 (Raw Total Score)	16	138.13 (4.21)		0.24	0
Visuospatial	JOLO	17	22 (5.04)		0.26	0.01
Language	Boston Naming	15	46.87 (8.59)	38 [12, 71]	-0.01	0
Executive Functioning	D-KEFS Phonemic Fluency	16	10.13 (4.01)	52 [10, 92]	0.03	0
	D-KEFS Semantic Fluency	16	9.94 (4.06)	49 [8, 91]	0.33	0.05
	D-KEFS Verbal Fluency Switch	15	9.4 (3.18)	42 [10, 81]	-0.02	0
	D-KEFS Trails	13	7.81 (4.79)	23 [1, 81]	0.75	0.53
	D-KEFS Trails Switch	12	7 (5.05)	16 [<1, 75]	0.32	0.02
	D-KEFS Color Naming	14	10.29 (3.65)	54 [13, 91]	0.19	0
	D-KEFS Color-Word Inhibition	11	9.27 (4.1)	40 [5, 87]	0.09	0
Attention	WMS-3 Digit Span	17	9.82 (2.83)	48 [16, 81]	0.21	0
Verbal Memory	CVLT-2 Total Learning	17	42.47 (13.37)	23 [2, 72]	0.39	0.1
	CVLT-2 Long Delay Free Recall	17	-0.79 (1.16)	21 [12, 34]	0.19	0
	CVLT-2 Recognition d-prime	17	-0.53 (1.23)	30 [17, 45]	0.1	0
	WMS-3 Logical Memory I	17	9.35 (2.57)	41 [14, 74]	0.23	0
	WMS-3 Logical Memory II	17	10.41 (2.81)	55 [21, 86]	0.04	0
Visual Memory	CVMT Total Learning	14	69.57 (11.99)	24 [1, 87]	0.24	0
	CVMT Delay Recognition	14	2.57 (1.87)	25 [3, 73]	0.36	0.06

Table 1: Central tendencies of neuropsychological measures and correlations with EGF, DRS-2 = Mattis Dementia Rating Scale, 2nd Edition. JOLO=Judgment of Line Orientation D-KEFS = Delis- Kaplan Executive Function System. WMS-3 = Wechsler Memory Scale, third edition CVLT-2= California Verbal Learning Test, second edition CVMT = Continuous Visual Memory Test

A follow-up analysis examined whether EGF predicted psychomotor sequencing beyond variability accounted for by illness duration and levodopa treatment. Non-negligible bivariate correlations were observed between psychomotor sequencing and disease duration, r=.545, 95%CI: [-.85, .01], and levodopa treatment, r=-.421, 95%CI: [.79, .17]. Accordingly, two separate stepwise linear regression analyses were performed, with EGF and clinical variable entered in the first step, and the corresponding interaction term in the second. In neither model did the interaction term result in statistically or clinically meaningful changes in variance explained in psychomotor sequencing (Δ R2<.02). After controlling for both motor duration and levodopa equivalence in partial correlation analysis, the relationship between EGF and psychomotor sequencing remained statistically significant, r=.731, p=.011, with moderate effect size, adjusted Cohen's d=.50.

Conclusion

EGF levels in progressed PD were associated with measures of executive functioning and memory. EGF uniquely predicted a measure of executive functioning after controlling for factors related to disease progression. These results are consistent with previous investigations finding relationships between EGF and global cognitive functioning in PD [3], and executive functioning and memory in de novo PD patients [4].

Current results further support EGF as a candidate biomarker for cognitive functioning in PD. Positive findings in progressed PD patients presenting with cognitive concerns suggest that EGF measurement could prove valuable as an outcome measure or mediating/moderating factor in clinical trials. The primary limitation of this study is small sample size. We attempted to minimize the likelihood of spurious correlations through the use of log transformation of EFG (ergo, reducing leverage of outliers) and highly conservative correction for Type I error [10]. Critically, establishing consistency in findings between a small heterogeneous sample (n=17, disease duration=8.5 (4.8) years) with the larger, highly circumscribed sample (n=65, newly diagnosed) reported by Pellechia and colleagues, is also encouraging. A specific example is the relationship between EGF and semantic fluency. In our sample, this was estimated with a Pearson correlation of r=.33; Pellechia's group estimated the relationship at p=.36 using Spearman-rank correlation coefficients [4].With such close correspondence, EGF might therefore be considered for application in futility studies.

Enthusiasm for EGF as biomarker for cognitive functioning is tempered by lack of information regarding the meaning of EGF levels at various stages of illness. Additionally, there are no published studies demonstrating stability in the short-term, where disease process would be unlikely to affect values, but medication or transient physiological conditions could confound measurement. In our sample, EGF appeared related to disease progression (i.e., duration and treatment), but not age. However, the extent to which EGF levels might change over the course of PD progression in accordance with cognitive changes remains unknown. Taken together with previous studies, our findings warrant further longitudinal studies that will inform potential application in clinical trials.

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