

## Serum epidermal growth factor predicts cognitive functions in early, drug-naive Parkinson's disease patients

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**Abstract** Epidermal growth factor (EGF) has been proposed as a candidate biomarker for cognitive impairment in Parkinson's disease (PD). We aimed to assess the relationship between serum EGF and cognitive functions in early, drug-naive PD patients and evaluate the predictive value of EGF on cognitive functions in a 2-year follow-up study. Serum EGF was measured in 65 early, drug-naive PD patients, that underwent a comprehensive neuropsychological battery. Motor symptoms were assessed by means of the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III). Neuropsychological evaluation was repeated after 2 years. Spearman's rank correlation was

used to assess the relationship between serum EGF levels and neuropsychological variables. Linear regression analysis was used to evaluate the relationship between EGF and neuropsychological scores as well as other variables (age, gender, UPDRS-III, levodopa equivalent dose, and type of treatment at follow-up) potentially affecting cognitive performance. Variation over time in cognitive scores was analyzed using repeated-measures ANOVA. At baseline, EGF was the only significant variable associated with performance on semantic fluency ( $R^2 = 0.131$ ;  $p = 0.005$ ). EGF levels ( $p = 0.025$ ), together with UPDRS-III ( $p = 0.009$ ) and age ( $p = 0.011$ ), were associated with performance on frontal assessment battery ( $R^2 = 0.260$ ). At 2-year follow-up, EGF was the only significant variable to predict performance on semantic fluency ( $R^2 = 0.147$ ;  $p = 0.025$ ) and color naming task of Stroop color-word test ( $R^2 = 0.121$ ;  $p = 0.044$ ). Serum EGF levels are related to frontal and temporal cognitive functions in early, drug-naive PD patients and predict performance on frontal and posterior cognitive functions at 2-year follow-up. EGF is proposed as a potential serum biomarker for early cognitive impairment in PD.

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### Introduction

Cognitive impairment in Parkinson's disease (PD) patients without dementia can occur in the early stages of disease and may be associated with subtle changes in cognitive function that are not apparent to the patients, their families, or clinicians. Twenty-five percent of patients who have been newly diagnosed with PD may present some cognitive

dysfunction [1, 2]. Cognitive function may decline over time, with many patients eventually developing dementia [3]. However, some PD patients may exhibit early cognitive deficits that do not evolve into PD dementia or do so over an extended period [3, 4], but may be associated with subtle functional impairments [5]. The development of cognitive impairment is a significant transition for patients and families, yet its occurrence is unpredictable.

Epidermal growth factor (EGF) acts as a neurotrophic factor on dopaminergic nigrostriatal neurons in animal models of PD [6–8]. EGF mediates dopamine-induced proliferation of adult precursor cells in the mammalian subventricular zone [9], and increases hippocampal neurogenesis in slice cultures and damaged rodent brains [10, 11]. Expression of EGF/EGF receptor is widespread in the neocortex and limbic cortex, cerebellum, hippocampus and the midbrain. EGFR has been recently suggested to have a central role in neurometabolic aging and neurodegeneration [12]. Nevertheless, one of the best-known roles of EGFR in the brain is the maintenance of memory pattern formation in the hippocampus [13]. Moreover, a region-specific neurodegeneration involving the frontal cortex occurs in EGFR-null mice, supporting a role of EGF pathway in the maintenance of neuronal survival in this specific area [14, 15]. Recently, Chen-Plotkin et al. [16] screened more than 100 plasma proteins in a cohort of advanced PD patients and found that low plasma levels of EGF predicted cognitive decline assessed by means of the Mattis Dementia Rating Scale after a median follow-up of 21 months.

In the present study, we aimed to assess the relationship between serum EGF levels and cognitive functions in a cohort of drug-naïve PD patients and to evaluate the predictive value of EGF levels on neuropsychological functions, with particular regard to frontal and temporal functions, after a 2-year follow-up.

## Patients and methods

We enrolled *de novo*, drug-naïve patients with parkinsonism consecutively referred to the Department of Neurological Sciences of the University “Federico II” of Naples. Inclusion criteria were: (1) the presence of parkinsonian syndrome according to United Kingdom Parkinson’s Disease Society Brain Bank Diagnostic Criteria [17] (bradykinesia associated to tremor or rigidity or postural instability), (2) disease duration <2 years, and (3) no history of present or past therapy with pro-dopaminergic agents. Exclusion criteria were the presence of: (1) clinical signs satisfying the criteria of possible atypical parkinsonisms, (2) secondary or iatrogenic parkinsonism, (3) familial parkinsonism, (4) dementia according to recent

consensus criteria [18], and major depressive disorder according to DSM-IV criteria. Additional criteria for inclusion were lack of significant cerebral lesions at the MRI and/or CT or severe concomitant disease that might explain the presence of cognitive disturbances or focal brain metabolic alterations. None of the patients were treated with anticholinergic agents, choline esterase inhibitors, antidepressants, or other centrally acting drugs.

Patients underwent clinical re-evaluation 1 year later to assess the diagnosis of PD according to both exclusion and supportive criteria of the United Kingdom Parkinson’s Disease Society Brain Bank Diagnostic Criteria for Parkinson’s Disease [17]. All participants gave written informed consent, and the study was approved by the local ethics committee.

## Clinical and neuropsychological evaluation

Motor symptoms were assessed by means of the UPDRS (section III = UPDRS-III) scale, and global cognitive function by mini-mental state examination (MMSE). At baseline, all patients underwent a comprehensive neuropsychological battery that includes immediate and delayed recall of the Rey auditory verbal learning test, and delayed recall of the Rey-Osterrieth complex figure test to measure memory, Benton judgment of line orientation test, constructional apraxia test, and clock drawing test to assess visuospatial abilities. Attention/executive functions were evaluated by frontal assessment battery (FAB), phonological and semantic fluency task, copy task of Rey-Osterrieth complex figure test, Corsi’s block test, verbal span test, Trail making test: part B minus Part A (TMT:B–A), and interference task of Stroop color-word test. This latter test also includes two non-executive tasks (reading and colors naming task) that were entered in statistical analysis. This neuropsychological battery was also administered after a 2-year follow-up.

## EGF measurement

Venous blood samples were drawn at baseline visit in the morning after an overnight fast to evaluate IGF-I levels. Blood samples were centrifuged and frozen (–20 °C). To reduce analytical variance, the samples were batch-analyzed using the same assay lot. EGF concentrations were measured in serum by immunoassay (Quantikine<sup>®</sup> Human EGF Immunoassay, R&D Systems, Minneapolis, MN, USA). The WHO EGF International Reference Reagent 91/530 was evaluated in this assay. The mean intra-assay CV, determined by assaying the EGF concentration in three samples in replicates of 20, is reported by the manufacturer to be 2.0 %. The mean inter-assay CV, determined by assaying three samples replicates of 20, has been

determined to be 4.6 %. The minimal detectable (MDD) concentration of EGF is <0.7 pg/ml. Sera from 60 age-matched (36 M, 24 F; mean age  $58.8 \pm 7.2$  years) healthy controls recruited among spouses, relatives, or friends of patients or through local advertising were analyzed to obtain reference values for EGF. Neuropsychological examination was not performed on these healthy controls.

#### Statistical analysis

Spearman's rank correlation coefficient was used to evaluate the correlations between baseline EGF levels and clinical and neuropsychological variables at baseline and at follow-up. Neuropsychological variables that were found to be significantly related to EGF by means of Spearman's rank correlation test were used as dependent variables in linear regression analyses, and EGF, age, gender, and UPDRS were used as independent variables to assess whether these factors affected cognitive performance. A stepwise approach was employed. For linear regression analyses at follow-up, levodopa equivalent dose [19] and treatment with dopamine agonists (yes/no) or levodopa (yes/no) were also used as independent variables. All analyses were performed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA). Variation over time in cognitive scores was analyzed using repeated-measures ANOVA. In order to identify the effect of baseline EGF on cognitive functions, the PD population was stratified into two groups using the median EGF value ( $\leq 638$  and  $>638$  pg/ml).

#### Results

We enrolled 65 de novo, drug-naïve patients (39 M, 26 F; mean age  $59.7 \pm 8.3$  years). Mean ( $\pm$ SD) age at onset was  $58.5 \pm 8.3$  years and mean ( $\pm$ SD) UPDRS was  $14.5 \pm 6.7$ . At 2-year follow-up, none of the patients showed any clinical features suggestive of atypical or secondary parkinsonism and all had a positive response to dopaminergic treatment, confirming the diagnosis of idiopathic PD. Forty PD patients agreed to repeat neuropsychological evaluation at follow-up. Twenty-five patients did not undergo neuropsychological follow-up after 2 years due to missing their appointments or refusing to repeat the tests. However, their demographic and clinical features (sex, age, age at onset, UPDRS-III score) were not different from those of the patients completing the follow-up.

Mean ( $\pm$ SD) serum EGF levels were increased ( $646.5 \pm 196.3$  vs.  $336 \pm 153.4$  pg/ml;  $p < 0.001$ ) as compared to healthy controls. Mean ( $\pm$ SD) MMSE score was  $27.2 \pm 1.8$ . Table 1 shows mean ( $\pm$ SD) scores obtained by PD patients at baseline neuropsychological evaluation and number of patients with altered performance on specific neuropsychological tests according to Italian normative values. As shown in Table 1, PD patients at baseline presented major difficulties in frontal/executive tasks (FAB, Rey-Osterrieth complex figure test-copy and delayed recall, Stroop test) and visuospatial task (Benton judgment of line orientation test).

At baseline, Spearman's rank correlation analysis showed that EGF was related with immediate recall of Rey

**Table 1** Neuropsychological performance of early, drug-naïve PD patients at baseline

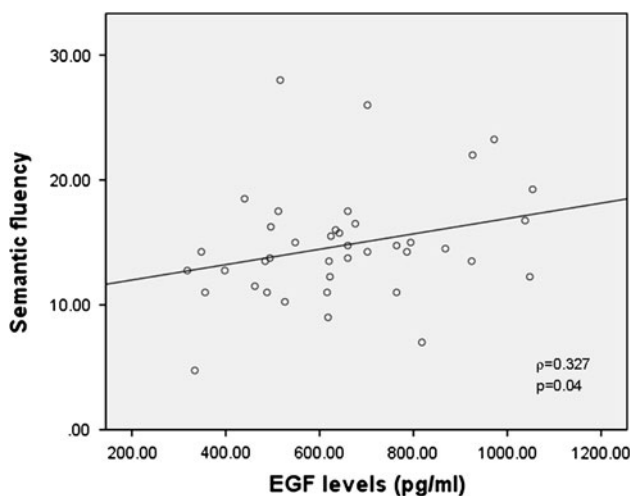
Neuropsychological task	Baseline (mean $\pm$ SD) ( $n = 65$ )	Altered $n$ (%)	Normal range
FAB	$13.9 \pm 2.5$	28 (43)	$\geq 13.4$ [29]
Phonological fluency	$29.2 \pm 10.7$	4 (6.1)	$>17.35$ [30]
ROCF-copy task	$29.3 \pm 6.3$	19 (29.2)	$>28.87$ [31]
Stroop test: interference	$14.1 \pm 8.5$	15 (23.1)	$>11$ [32]
Corsi's test	$4.8 \pm 0.8$	1 (1.5)	$>3.50$ [33]
Verbal span	$3.9 \pm 0.7$	10 (15.3)	$>2.75$ [33]
Semantic fluency	$18.9 \pm 6.8$	3 (4.6)	$>7$ [33]
TMT:B–A	$98.2 \pm 88.7$	3 (4.6)	$<186$ [34]
Stroop test: colors naming	$37.4 \pm 11.5$	14 (21.5)	$>28$ [32]
Rey auditory verbal learning test–immediate recall	$39.5 \pm 9.4$	5 (7.6)	$>28.53$ [30]
Rey auditory verbal learning test–delayed recall	$7.9 \pm 2.8$	5 (7.6)	$>4.69$ [30]
ROCF-delayed recall task	$12.4 \pm 5.9$	23 (35.3)	$\geq 9.46$ [31]
Clock drawing test	$7.4 \pm 3.3$	13 (20)	$>5$ [35]
BJLOT	$20.5 \pm 6.5$	17 (26.1)	$>18$ [36]
Constructional apraxia test	$11.3 \pm 2.1$	6 (9.2)	$>7.75$ [33]

FAB frontal assessment battery, ROCF Rey-Osterrieth complex figure test, BJLOT Benton judgment of line orientation test, TMT:B–A trail making test: B–A

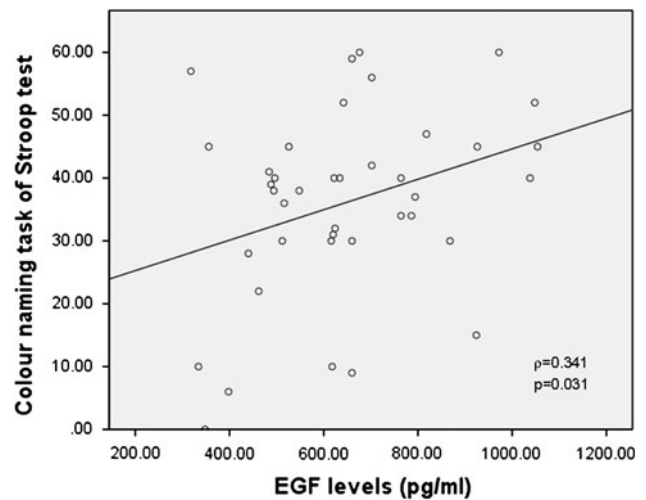
auditory verbal learning test ( $\rho = 0.274, p = 0.029$ ), semantic fluency ( $\rho = 0.261, p = 0.02$ ), constructional apraxia test ( $\rho = 0.282, p = 0.024$ ), FAB ( $\rho = 0.291, p = 0.02$ ), color naming task of Stroop color-word test ( $\rho = 0.270, p = 0.033$ ), and TMT:B–A ( $\rho = -0.292, p = 0.021$ ). Complete correlation results are shown in the Web table. EGF levels were not related to the MMSE score. By means of linear regression analysis we found that EGF was the only significant variable associated with semantic fluency ( $R^2 = 0.131; p = 0.005$ ). EGF levels ( $p = 0.025$ ), together with UPDRS-III ( $p = 0.009$ ) and age ( $p = 0.011$ ), were associated with performance on FAB ( $R^2 = 0.260$ ).

At 2-year follow-up, mean ( $\pm$ SD) levodopa equivalent dose was  $293 \pm 131$  mg/day; 67.6 % of patients were treated with dopamine agonists and 32.4 % with levodopa. Spearman’s rank correlation analysis showed that EGF was related with Corsi’s block span ( $\rho = 0.387, p = 0.014$ ), semantic fluency ( $\rho = 0.327, p = 0.04$ ) (Fig. 1), and color naming task of Stroop color-word test ( $\rho = 0.341, p = 0.031$ ) (Fig. 2). By means of linear regression analysis, we found that EGF was the only significant variable to predict semantic fluency ( $R^2 = 0.147; p = 0.025$ ) and color naming task of Stroop color-word test ( $R^2 = 0.121; p = 0.044$ ).

Repeated-measures ANOVA revealed that the time factor significantly affected cognitive functions ( $p < 0.001$ ); in particular, the following tests showed a significant worsening over time (Table 2): constructional apraxia test ( $p < 0.01$ ), copy task ( $p < 0.001$ ) and delayed recall ( $p = 0.012$ ) of Rey-Osterrieth complex figure test, and TMT:B–A ( $p < 0.001$ ). With regard to group effect, patients with baseline EGF  $\leq 638$  pg/ml showed significantly lower scores at semantic fluency ( $p = 0.022$ ), colors



**Fig. 1** Correlation between baseline EGF levels and semantic fluency at 2-year follow-up



**Fig. 2** Correlation between baseline EGF levels and color naming of Stroop test at 2-year follow-up

naming task of Stroop test ( $p = 0.005$ ), and interference task of Stroop test ( $p = 0.013$ ) as compared to patients with baseline EGF  $>638$  pg/ml at both evaluations (Table 2). There was no significant interaction between time and group on any neuropsychological measure.

**Discussion**

This study set out to assess whether EGF levels are related to cognitive functions in early drug-naïve patients and to evaluate if EGF may predict neuropsychological performance after a 2-year follow-up. We found that EGF levels are increased in de novo, drug-naïve PD patients as compared to healthy controls, suggesting a role for EGF as an early biomarker of PD. The pathophysiological changes underlying the relatively increased EGF levels in early PD are unknown. Interestingly, increased levels of EGF have also been found in Alzheimer’s disease (AD), although not allowing to distinguish AD from other dementias [20, 21]. Since EGF has recognized neuroprotective properties, we could speculate that elevated EGF levels in early PD may indicate a primarily activated system combating increased cell loss. According to this hypothesis, the failure of such a compensatory system indicated by relatively low levels of EGF in some patients could contribute to the pathogenesis of cognitive decline.

At baseline, we found an association between EGF levels and cognitive tasks evaluating verbal memory, visuospatial abilities, and attention/executive functions, indicating that higher EGF levels may predict a better performance on these tasks. Indeed, low EGF levels were found to be associated with poor performance on semantic fluency task by means of linear regression analysis. Several

**Table 2** Neuropsychological performances (mean  $\pm$  SD) at the two evaluations (baseline and 2-year follow-up) in PD patients stratified according to the median EGF value

Test	Time	EGF $\leq$ 638	EGF $>$ 638	Main effect: time		Main effect: group	
				<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Immediate recall of the RAVLT	T1	38.2 $\pm$ 10.2	43.9 $\pm$ 9.3	0.287	0.596	3.197	0.082
	T2	37.4 $\pm$ 12	43.5 $\pm$ 10.9				
Delayed recall of the RAVLT	T1	7.5 $\pm$ 3.3	8.8 $\pm$ 2.6	1.190	0.282	2.326	0.136
	T2	7.8 $\pm$ 4.1	9.5 $\pm$ 3.1				
Copy task of the ROCF	T1	29.5 $\pm$ 7.2	30.4 $\pm$ 5.5	23.639	<b>0.000</b>	0.213	0.647
	T2	24.6 $\pm$ 9.8	25.9 $\pm$ 8.7				
Delayed recall of ROCF	T1	12.9 $\pm$ 5.7	13 $\pm$ 6.3	7.009	<b>0.012</b>	1.218	0.277
	T2	8.4 $\pm$ 6.1	12.6 $\pm$ 8.7				
FAB	T1	12.9 $\pm$ 2.1	14.9 $\pm$ 2.3	0.116	0.735	3.275	0.079
	T2	13.8 $\pm$ 2.3	14.2 $\pm$ 2.4				
Phonological fluency	T1	26.3 $\pm$ 9.9	33 $\pm$ 12.7	0.072	0.790	4.104	0.052
	T2	25.6 $\pm$ 8.5	33 $\pm$ 14.6				
Semantic fluency	T1	16.1 $\pm$ 4.5	20.4 $\pm$ 5.3	2.063	0.160	5.739	<b>0.022</b>
	T2	15.6 $\pm$ 5.2	18.7 $\pm$ 6				
Stroop test: interference	T1	11.5 $\pm$ 6.1	17.6 $\pm$ 8.3	0.010	0.921	6.911	<b>0.013</b>
	T2	11.7 $\pm$ 6.4	17.6 $\pm$ 9.3				
Stroop test: colors naming	T1	30.9 $\pm$ 11.9	42.8 $\pm$ 11.7	0.067	0.797	9.162	<b>0.005</b>
	T2	31 $\pm$ 14.7	41.7 $\pm$ 12.4				
Corsi's test	T1	4.8 $\pm$ 0.7	4.8 $\pm$ 1	0.158	0.693	2.847	0.100
	T2	4.5 $\pm$ 0.6	5.2 $\pm$ 0.8				
Verbal span	T1	3.9 $\pm$ 0.7	4 $\pm$ 0.9	0.313	0.580	0.009	0.924
	T2	4.1 $\pm$ 1	4 $\pm$ 0.9				
TMT:B–A	T1	109.6 $\pm$ 55.4	74.5 $\pm$ 68.6	18.358	<b>0.000</b>	2.081	0.158
	T2	182.6 $\pm$ 122	151.7 $\pm$ 123.8				
BJLOT	T1	21 $\pm$ 4.7	19.8 $\pm$ 7.4	3.754	0.061	0.152	0.699
	T2	18.9 $\pm$ 5.6	18.8 $\pm$ 6.1				
Constructional apraxia test	T1	11.5 $\pm$ 1.7	12.2 $\pm$ 1.8	34.146	<b>0.000</b>	0.882	0.354
	T2	9.5 $\pm$ 2.9	10.1 $\pm$ 2.7				
Clock drawing test	T1	8.1 $\pm$ 2.6	8.4 $\pm$ 3.2	0.533	0.470	0.115	0.736
	T2	8.4 $\pm$ 2.2	8.7 $\pm$ 2.5				

Significant results are in *bold*

RAVLT Rey auditory verbal learning test, ROCF Rey-Osterrieth complex figure test, FAB frontal assessment battery, BJLOT Benton judgment of line orientation test, TMT:B–A trail making test: B–A

studies investigating verbal fluency task indicate that semantic word retrieval is mediated by inferior frontal and temporal brain areas, whereas the prefrontal cortex seems to play an additional important role during phonemic processing [22, 23]. Our results may suggest that low EGF levels are associated with altered cognitive functions mediated by frontal and temporal lobes.

At 2-year follow-up, we found that EGF levels were positively related to different cognitive tasks evaluating both attention/executive functions and color naming. After regression analysis, we found that EGF levels predict performance on semantic fluency task and color naming of Stroop test independently from other variables potentially

affecting cognitive functions. Impaired color perception may manifest as slowing of color naming [24], and central deficits of color processing have been generally associated with lesions affecting the occipital and posterior basal temporal lobes [25]. It is also known that semantic fluency is related to inferior frontal and temporal brain areas [22, 23]. Thus, our results suggest that baseline EGF levels may predict alterations of cognitive functions mediated by posterior (temporal and occipital) and frontal cerebral areas.

Results of repeated-measures ANOVA are consistent with regression analysis, since performance on both semantic fluency and color naming of Stroop test were

found to be significantly worse in patients with lower EGF values than in patients with higher EGF values at baseline, and this significant difference persisted at 2-year follow-up. Moreover, ANOVA showed that performance on interference task of Stroop test was also worse in patients with lower EGF values during 2 years of follow-up. This finding supports the hypothesis that alterations of executive functions mediated by frontal areas are related to low EGF levels.

A relation between cognitive performance and EGF in PD has recently been proposed by Chen-Plotkin et al. [16]. They screened more than 100 plasma proteins in a cohort of 70 PD patients with a median disease duration of 7 years and found that low EGF levels not only correlated with poor scores of the DRS at baseline but also predicted an eight-fold risk of cognitive decline to dementia-range of the DRS after a median follow-up of 21 months [16]. Our findings are in line with this previous study with regard to the positive relation between EGF levels and cognitive performance. However, unlike the previous study, we assessed patients in the early disease stages and explored the relationship between EGF and different cognitive domains by means of a comprehensive neuropsychological battery, thus suggesting a potential role for EGF as an early marker of cognitive dysfunction in PD. As in previous study, we correlated baseline serum EGF levels with cognitive functions at baseline and at follow-up, since our aim was to identify a possible biomarker predicting cognitive impairment. However, longitudinal measurement of EGF levels in future studies could also be useful in assessing the relationships with changes in cognitive functions.

EGF acts as a neurotrophic factor on dopaminergic nigrostriatal neurons and hippocampal neurons [6–8, 10, 11]. Moreover, in cell cultures, EGF stimulates the release of soluble non-amyloidogenic fragments of amyloid precursor protein [26]. EGF receptors are normally expressed by hippocampal, striatal, and cerebral cortical neurons in human brain [27, 28], and are reported to be reduced in the prefrontal cortex and the striatum of PD patients [6]. Although it is not known whether increased EGF expression in PD, such as in AD, contributes to the pathological process or represents an attempt at repair, our results, together with experimental evidence supporting a neurotrophic, neuroprotective role for EGF, are consistent with the second possibility.

The pathophysiology of cognitive impairment in PD is complex, involving multiple neurotransmitter systems and diffuse neurodegeneration, and there remain significant gaps in our knowledge of cognitively impaired, non-demented PD patients. A large prospective study has shown that cognitive deficits in tasks related to posterior cortical areas are associated with the development of dementia [4]. Interestingly, we found that low EGF levels

at baseline predicted poor performance on cognitive tasks related to temporal and occipital cortical areas at 2-year follow-up. Further follow-up study of our cohort of de novo patients is ongoing to assess the predictive value of EGF on the development of dementia.

Our results suggest that EGF is a potential serum biomarker for cognitive impairment in PD. If confirmed by further studies, the measurement of EGF might be useful both as a clinical diagnostic tool and in the design of trials aimed at preserving cognition in PD.

**Conflicts of interest** The authors declare that they have no conflicts of interest.

**Ethical standards** All human studies must state that they have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki

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