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Relationship of circulatory BDNF with cognitive deficits in people with Parkinson's disease

Hanan Khalil [a,*], Mahmoud A. Alomari [b], Omar F. Khabour [c], Aya Al-Hieshan [d], Jawad A. Bajwa [e,f]

[a] Jordan University of Science and Technology, Faculty of Applied Medical Sciences, Department of Rehabilitation Sciences, Irbid, Jordan
[b] Jordan University of Science and Technology, Division of Physical Therapy, Department of Rehabilitation Sciences, Irbid, Jordan
[c] Jordan University of Science and Technology, Faculty of Applied Medical Sciences, Department of Medical Laboratory Sciences, Irbid, Jordan
[d] Jordan University of Science and Technology, Faculty of Art and Sciences, Department of Applied Biology, Irbid, Jordan
[e] King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[f] Department of Neurology, National Neuroscience Institute, King Fahad Medical City, Riyadh, Saudi Arabia

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ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) and cognitive function are diminished in people with Parkinson's disease (PD). The relationship of cognitive function and serum level of BDNF, however is yet to be examined. The aim of this study was to examine serum BDNF levels in PD. Subsequently, the relationship of cognitive function to the serum levels of BDNF was evaluated.
Methods: Serum BDNF levels were measured in 29 idiopathic PD subjects and 30 healthy-matched controls using ELISA technique. Cognitive function was assessed using the Montreal Cognitive Assessment (MOCA) scale.
Results: Serum BDNF levels and MOCA total score were significantly lower ($P < 0.001$) in PD patients versus healthy controls. MOCA total score correlated with serum BDNF ($r = 0.44$; $P = 0.012$) but not with age, years of education, duration of disease and severity of symptoms. The regression analysis showed that serum BDNF accounted ($P = 0.019$) for 19% of MOCA total score variance.
Conclusions: The data confirm lowered serum BDNF in PD. Additionally; it suggests that BDNF may play a role in the cognitive deficit of PD. Further studies are required to identify association of BDNF in cognitive decline with PD.

1. Introduction

Parkinson's disease (PD) is associated with deficits in multiple domains of cognitive function, including executive function, information processing, learning, and recall [1]. These cognitive deficits may develop to dementia, thus increasing caregiver burden, social impairment and subsequent risk of nursing home placement [2]. Although a number of mechanisms have been implicated, still cognitive deficits in PD are not fully understood.

Brain derived neurotrophic factor (BDNF) is a member of the neurotrophin family which is expressed and functions in different brain compartments, particularly the hippocampus. It is pivotal for neuronal cell differentiation, survival, and maintenance [3]. BDNF is implicated in long term-potentiation (LTP), which is considered to be the neurophysiological basis for learning and memory [4]. Several studies, from animals [5] and human [6,7], have confirmed the importance of BDNF for learning and memory.

Although BDNF is found mainly in the brain, it is clear that it exists outside the central nervous system (CNS) and circulates systematically. As yet, evidence suggests that circulating BDNF levels (i.e. BDNF in plasma or serum) may reflect BDNF levels in the brain [8]. Within this realm, observations consistently show reduced levels of serum or plasma BDNF are associated with cognitive decline in health [9] and disease [10].

Reduced brain BDNF levels and expression in PD are well documented in post-mortem examinations [11,12]. However, only 3 studies with conflicting results examined circulatory BDNF levels in PD [13–15]. While 2 studies reported reduced BDNF [13,15], another showed increased BDNF levels compared to other neurological disorders and healthy control [14]. Thus, more investigations are needed to verify circulatory BDNF levels in PD. Additionally, very little is known about the relationship of circulatory BDNF with cognitive function in this population; to date there is only one study with a very small sample size that have examined this relationship in people with PD [16]. Therefore, the aims of the current study are to examine circulatory BDNF level, and the relationship of circulatory BDNF with cognitive function in people with PD. The results may identify the possible contribution of circulatory BDNF to cognitive function in this cohort, thus exploring treatment strategies to treat or slow down cognitive deficits in PD.

* Corresponding author at: Faculty of Applied Medical Sciences, Department of Rehabilitation Sciences, Jordan University of Science and Technology, Irbid 22110, Jordan.
E-mail address: hwkhalil8@just.edu.jo (H. Khalil).

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2. Materials and methods

2.1. Study design and subjects

This is a cross sectional observational study designed to examine the differences in circulatory BDNF between people with PD and healthy controls, and additionally to investigate the contribution of circulatory BDNF level to cognitive function in the PD population. Sequential PD patients attending routine neurology clinic appointment at King Abdulla University Hospital (KAUH), Irbid, Jordan were screened for eligibility by a neurology consultant between January 2014 and November 2014. Eligible subjects were invited to participate in the study. Healthy-age and gender matched individuals were recruited from the local community and served as the controls for this study.

Inclusion criteria of the PD patients included 1) diagnosis of idiopathic Parkinson's disease, confirmed by neurologist examination; 2) capacity to give informed consent; 3) Hoehn and Yahr (HY) stage 1 to 4 [17] during the "ON" clinical status; and 4) maintaining a stable medical regime for 4 weeks prior to initiation of the study. The exclusion criteria were the comorbid of neurological or inflammatory disease or the history of neurosurgical procedure. The study was approved by the Institutional Review Board of Jordan University of Science and Technology, King Abdulla University Hospital (KAUH).

2.2. Measurements

The Montreal Cognitive Assessment (MOCA) test was used to evaluate cognitive function [18]. The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-motor score [19] as well as the Hoehn and Yahr Staging Scale (HY) were also obtained [17]. Additionally, demographic data of each participant including age, gender, weight and education were recorded.

The MOCA is designed to assess 8 domains of cognitive function including attention and concentration, executive functions, memory, language, visual-constructional skills, conceptual thinking, calculations, and time and place orientation. It is an easy, yet comprehensive evaluation of cognitive function in different populations, including PD [20,21]. The total score of the test is out of 30 with a higher score indicating a better cognitive function. The test has been validated including the Arabic version which was used in this study [18].

The HY scale, which defines five stages of PD progression (1–5), was used to provide a global indication of PD severity [17]. The MDS-UPDRS is the most commonly used scale to assess disease severity for research and clinical purposes [19]. The MDS-UPDRS-motor score ranges from 0 to 132, with a higher score correspond to more severe motor disability. The total motor score of the MDS-UPDRS was used in analysis in this study. Additionally, summary measures corresponding to the four motor domains of PD were derived from the MDS-UPDRS motor [22]. These motor domains included: bradykinesia, postural reflex impairment-gait disturbance, rigidity, and tremor. These domains were calculated considering the heterogeneity of PD and the suggestion that the UPDRS is multidimensional and that individual domains may report different outcomes [22,23].

Bradykinesia was calculated based on 11 items: right and left finger taps, right and left hand movement, right and left arm supination–pronation, right and left toe taps, right and left leg agility, and global bradykinesia. Postural reflex impairment-gait disturbances domain was based on 5 items: arising from chair, gait, freeze of gait, posture, and postural instability. Rigidity score was derived from 5 items: rigidity on neck and all 4 extremities. Tremor was based on 10 items: resting tremor on chin-jaw and all 4 extremities, consistency of resting tremor and action and postural tremor of both upper extremities. Domain scores were calculated by summing the points allocated to each item within each domain.

2.3. Blood sampling and serum BDNF measurements

To determine levels of serum BDNF, non-fasting venous blood (5 mL) was collected from each participant into tubes without anticoagulant. Samples were allowed to clot at room temperature for 30 min. Serum samples were prepared by centrifugation at 1500 *g* for 10 min. Serum samples were then divided into several aliquots and immediately stored at −80 °C until assay. Serum BDNF levels were determined using the enzyme-linked immunosorbent assay (ELISA) method, using commercially available kits and as per the manufacturer's instructions (Human BDNF DuoSet ELISA Kit; R&D Systems, Minneapolis, MN, USA) [14]. This assay was fully described in our previous report [24].

All samples and standards were measured in duplicate. Samples of PD subjects and healthy controls were analyzed together in the ELISA templates, and possible variability between different assays was controlled using 4 samples of known BDNF concentration.

2.4. Statistical analysis

All statistical calculations were performed with SPSS (version 19; Chicago, IL). Group values were expressed in mean ± SD. For all statistical tests, α was set at prior at $P < 0.05$. Differences in serum BDNF and MOCA test between PD patients and healthy controls were examined using the independent sample t-test. The relationship between cognitive function and other variables including the serum BDNF concentration was examined using Pearson correlation coefficient (i.e. bivariate analysis). To additionally determine the significant predictors for reduced cognitive function, variables that were significantly correlated to cognitive function in bivariate analysis were selected for regression analysis. Index of goodness of fit of each estimated parameter was calculated after the construction of the regression model.

3. Results

Demographic and clinical characteristics of the participants are presented in Table 1. Data were collected from 29 PD patients (17 males, 12 females) and 30 healthy controls (17 males, 13 females). No significant differences were noted between groups in age, weight and years of education. Additionally, as in Table 1, serum BDNF levels and MOCA score were 48% and 25%, respectively, less ($P < 0.05$) in the PD patients versus healthy controls.

Table 2 shows that serum BDNF level correlated positively ($r = 0.44$; $P = 0.012$) with MOCA total score. No significant correlations were observed between MOCA total score and, age, years of education, weight, HY, and MDS-UPDRS (total motor score). Additionally, no significant correlations were observed between MOCA total score and any of the domain scores of the MDS-UPDRS.

As the serum BDNF was the only variable that correlated significantly with MOCA total score, single linear regression analysis was

Table 1
Clinical and socio-demographic characteristics in the PD patients and healthy controls.

	PD patients (n = 29)	Healthy controls (n = 30)	P value
Age (years)	59.4 ± 13.1	56.9 ± 12.8	0.46
Weight (kg)	69.9 ± 11.1	66.3 ± 9.6	0.19
Years of education	10.7 ± 4.8	11.3 ± 5.4	0.24
Duration of disease (years)	4.4 ± 2.7	–	–
HY	2.4 ± 0.7	–	–
MDS-UPDRS (motor score)	49.2 ± 16.5	–	–
MOCA total score*	18 ± 5	24 ± 4.9	0.0001
Serum BDNF (pg/mL)*	12.5 ± 5.5	24.2 ± 3.00	0.0001

Data are presented in mean ± SD. MDS-UPDRS: The Movement Disorders Society Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr Staging Scale; MOCA: Montreal Cognitive Assessment; BDNF; brain-derived neurotrophic factor.
* Significantly different between PD patients and healthy controls ($p < 0.05$.)