ALEXITHYMIA IS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN PATIENTS WITH PARKINSON'S DISEASE

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Background – Cognitive dysfunction (CD) is a common non-motor symptom of Parkinson's disease (PD). Alexithymia is a still poorly understood neuropsychiatric feature of PD. Cognitive impairment (especially visuospatial dysfunction and executive dysfunction) and alexithymia share common pathology of neuroanatomical structures. We hypothesized that there must be a correlation between CD and alexithymia levels considering this relationship of neuroanatomy.
Objective – The aim of this study was to evaluate the association between alexithymia and neurocognitive function in patients with PD.
Methods – Thirty-five patients with PD were included in this study. The Toronto Alexithymia Scale–20 (TAS-20), Geriatric Depression Inventory (GDI) and a detailed neuropsychological evaluation were performed.
Results – Higher TAS-20 scores were negatively correlated with Wechsler Adult Intelligence Scale (WAIS) similarities test score (r =-0.71, p value 0.02), clock drawing test (CDT) scores (r=-0.72, p=0.02) and verbal fluency (VF) (r=-0.77, p<0.01). Difficulty identifying feelings subscale score was negatively correlated with CDT scores (r=-0.74, p=0.02), VF scores (r=-0.66, p=0.04), visual memory immediate recall (r=-0.74, p=0.01). VF scores were also correlated with difficulty describing feelings (DDF) scores (r=-0.66, p=0.04). There was a reverse relationship between WAIS similarities and DDF scores (r=-0.70, p=0.02), and externally oriented-thinking (r=-0.77,p<0.01). Executive function Z score was correlated with the mean TAS-20 score (r=-62, p=0.03) and DDF subscale score (r=-0.70, p=0.01)

PARKINSON-BETEGEK KÖRÉBEN AZ ALEXITHYMIA KOGNITÍV ZAVARRAL JÁR EGYÜTT

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Háttér – A kognitív zavar a Parkinson-kór gyakori nem motoros tünete. Az alexithymia a Parkinson-kór még ma is kevéssé megértett neuropszichiátriai jellegzetessége. A kognitív zavar (különösen a visuospatialis és a végrehajtó funkciók zavara) és az alexithymia hátterében ugyanazon neuroanatómiai struktúrák patológiája áll. Hipotézisünk szerint e neuroanatómiai kapcsolat következtében összefüggésnek kell lennie a kognitív zavar és az alexithymia mértéke között.
Cél – A vizsgálat célja az volt, hogy megvizsgáljuk, van-e összefüggés az alexithymia és a neurokognitív funkciók között Parkinson-betegek körében.
Módszerek – A vizsgálatba 35 Parkinson-kóros beteget vontunk be. A Torontói Alexithymia Skálát (TAS-20), a Geriátriai depresszió-kérdőívet (GDI), valamint részletes neuropszichológiai vizsgálatokat alkalmaztunk.
Eredmények – A magasabb TAS-20-pontszámok negatív összefüggésben álltak a Wechsler Intelligenciateszt felnőttváltozatának (WAIS) Similarities alskálájának pontszámaival (r = –0,71; p-érték: 0,02), az órarajzolási teszt (CDT) pontszámaival (r = –0,72; p=0,02) és a verbális fluencia (VF) mértékével (r = –0,77; p<0,01). Az érzelemazonosítási alskála pontszámai negatív összefüggésben álltak a CDT-pontszámokkal (r = –0,74; p=0,02), a VF-pontszámokkal (r = –0,66; p=0,04), valamint a vizuális emlékezet azonnali előhívását mérő alksála pontszámaival (r = –0,74; p=0,01). A VF-pontszámok az érzelemleírás nehézségét mérő alskála (DDF) pontszámaival is összefüggést mutattak (r = –0,66; p=0,04). Fordított irányú összefüggés volt kimutatható a WAIS

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Conclusion – Alexithymia was found to be associated with poorer performance on visuospatial and executive function test results. We also found that alexithymia was significantly correlated with depressive symptoms. Presence of alexithymia should therefore warn the clinicians for co-existing CD.

Keywords: *Parkinson's disease, alexithymia, cognitive impairment, visuospatial functions, executive functions*

Similarities és a DDT alskálák pontszámai (r = –0,70; p=0,02), valamint a külső orientáltságú gondolkodás alskála pontszámai (r = –0,77; p<0,01) között. Összefüggés volt kimutatható a végrehajtó funkció Z alskála és a TAS-20-pontszámok középértéke (r = –62; p=0,03), valamint a DDF alskála pontszámai között (r = –0,70; p=0,01).

Következtetés – Összefüggés volt kimutatható az alexithymia és a visuospatialis, valamint a végrehajtó funkciókat mérő tesztek eredménye között. Az alexithymia és a depresszív tünetek között szintén szignifikáns összefüggést találtunk. Az alexithymia megléte fel kell hívja a klinikus figyelmét a párhuzamosan fennálló kognitív zavarra.

Kulcsszavak: *Parkinson-kór, alexithymia, kognitív zavar, visuospatialis funkciók, végrehajtó funkciók*

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the nigrostriatal pathway, leading to decreased dopamine levels[1]. Median age of disease onset is around 60 years and incidence is shown to increase with age, up to 3% in those aged over 80 years[2].The etiology and underlying causes of PD are yet to be fully elucidated; however, various genetic and environmental factors have been strongly associated with the development and progression of disease. Motor symptoms manifest themselves such as bradykinesia, rigidity, rest tremor and postural changes/instability, which are often collectively referred to as 'parkinsonian symptoms'. Non-motor symptoms of PD include cognitive dysfunction (CD), mood and affect disturbances, behavioral changes, sensory deficits, urogenital dysfunction, constipation etc[3]. Although motor symptoms are usually observed first and thus considered the hallmarks of the disease, there is evidence that non-motor symptoms might precede motor symptoms, particularly disorders such as depression and hyposmia[4]. Among these non-motor symptoms, CD (or progressive cognitive decline) becomes a critical problem in the majority of patients and its results are often more severe than motor symptoms[3]. CD is present in around 25% of patients at diagnosis, and finally leads to Parkinson's disease dementia in up to 80% of patients within 10 years after diagnosis[5, 6].

Alexithymia is another non-motor symptom of PD. It is a personality trait which is defined as a cognitive-affective disorder characterized by problems in understanding emotional stimulus or describing them to other individuals, and also an inability to discriminate these from bodily sensations[7]. Few studies have shown that the pathogenesis of alexithymia and CD in PD frequently share common pathways (frontal areas, specifically the anterior cingulate cortex/ACC and prefrontal cortex)[8]. However, studies focused on elucidating the relationships between alexithymia and CD in patients with PD are lacking.

Purpose of the present study was to investigate the relationships and possible correlations between alexithymia, neuropsychiatric symptoms and CD in patients with PD.

Methods

Forty-five patients who were diagnosed as having idiopathic PD by a movement disorder neurologist according to United Kingdom Brain Bank Criteria[9] were consecutively enrolled in this study from the Neurology Department of the Bezmialem Foundation University Hospital outpatient clinic between August 2017 and July 2018. The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and was approved by the Ethical Committee of the Bezmialem Foundation University Hospital. Informed consent (written) was obtained from the participants after the nature of the procedures had been fully explained. Exclusion criteria were as follows: having vitamin B12 or folate deficiency, severe anemia, hypo- or hyperthyroidism, end-stage liver or kidney diseases, using psychiatric medications, having a history of stroke, dementia, any kind of brain surgery. Ten patients were excluded from the study according to our exclusion criteria.

Disease severity was determined via the Hoehn and Yahr Scale (HYS)[10] in all patients. Routine

Table 1. *Correlations* of cognitive tests and Toronto Alexithymia Scale-20 (TAS-20) and subscales scores*

Cognitive Domains	Neuropsychological Tests	TAS- 20 Total Score	TAS-20 Subscale Scores		
			Difficulty in identifiying feelings	Difficulty in describing feelings	External oriented thinking
Attention	*Digit Span:* Forward	r=0.04, p=0.91	r=0.35, p=0.32	r=-0.20, p=0.58	r=-0.83, p=0.82
	Backward	r=0.28,p=0.44	r=-0.93, p=0.80	r=0.39, p=0.26	r=0.46, p=0.19
Visuospatial Functions	Benton Judgement of Line Orientation Test	r=0.31, p=0.38	r=-0.09, p=0.80	r=0.58, *p=0.08*	r=0.27, p=0.45
	Benton Face Recognition	r=-0.14, p=0.71	r=-0.26, p=0.46	r=0.16, p=0.67	r=-0.31, p=0.39
	WMS** Visual Reproduction Subtest				
	Clock Drawing Test	r=-0.72, *p=0.02*	r=-0.74, *p=0.02*	r=-0.49, p=0.16	r=-0.52, p=0.12
Executive Functions	Stroop Test	r=0.02, p=0.96	r=0.23, p=0.52	r=-0.09, p=0.80	r=-0.14, p=0.69
	WAIS*** Similarities Phonemic	r=-0.71, *p=0.02*	r=-0.32, p=0.36	r=-0.70, *p=0.02*	r=-0.77, *p=0.009*
	Verbal Fluency: (KAS)	r=-0.51, p=0.13	r=-0.31, p=0.38	r=0.59, *p=0.07*	r=-0.29, p=0.41
	Semantic Verbal Fluency: (Animal)	r=0.72, *p<0.01*	r=-0.66, *p=0.04*	r=-0.66, *p=0.04*	r=-0.55, *p=0.09*
Verbal Memory	*Immediate Recall*				
	Verbal memory processing test total score	r=-.043, p=0.21	r=-0.18, p=0.61	r=-0.39, p=0.26	r=-0.43, p=0.22
	WMS Logical memory test (immediate recall)	r=-0.50, p=0.14	r=-0.32, p=0.37	r=-0.42, p=0.23	r=-0.53, p=0.12
	Delayed Recall				
	Verbal memory processing test (spontaneous recognition)	r=-0.23, p=0.53	r=-0.01, p=0.98	r=-0.40, p=0.26	r=-0.13, p=0.73
	WMS Logical memory test (delayed recall)	r=-0.49, p=0.16	r=-0.48, p=0.16	r=-0.28, p=0.44	r=-0.46, p=0.19
Visual Memory	*WMS Visual reproduction subtests:*				
	WMS I: immediate recal	r=-0.30, p=0.40	r=-0.09, p=0.81	r=-0.32, p=0.37	r=-0.37, p=0.30
	IWMS II: delayed recall	r=-0.39, p=0.27	r=-0.74, *p=0.01*	r=-0.06, p=0.87	r=-0.07, p=0.85
Language	Boston Naming Test	r=0.99, p=0.79	r=0.41, p=0.24	r=-0.03, p=0.93	r=-0.26, p=0.47

*Partial Correlations, *controlling for age, education level, GDI score.*
** WMS: *Wechsler Memory Scale*
***WAIS: Wechsler Adult Intelligence Scale

hemogram, biochemical and hormonal tests including thyroid functions were performed at enrollment. The duration of the disease and family history were noted. The Toronto Alexithymia Scale (TAS-20)[11] and Geriatric Depression Inventory (GDI)[12] were performed in all patients. Neuropsychological evaluation and tests were performed by trained occupational therapist and evaluated by a neuropsychologist experienced in general neurology and movement disorders.

Toronto Alexithymia Scale-20 (TAS-20): This scale is comprised of 20 items which measure alexithymia based on the evaluation of 3 subscales (recognition of feelings, expression of feelings and external-oriented thinking). Each item is rated on a 5-point Likert scale. Based on total score (ranging from 20 to 100), the presence and degree of alexithymia is determined as follows: 50 points is defined as no alexithymia, 51-60 points indicates high possibility for alexithymia, while those with a score in excess of 61 points are accepted to have definite alexithymia[13].

Geriatric Depression Scale (GDS): The 'long form' of the GDS (GDS-30) is a scale consisting of 30 questions answered with either 'yes' or 'no'. Each item represents 1 point; a score of 0-9 is accepted as normal, 10-19 is defined as mild depression, and >20 points is defined as severe depression. The Turkish language translation, validity and reliability of the GDS-30 have been performed[14, 15].

Neuropsychological evaluation consisted of Wechsler Memory Scale Revised (WMS-R) Number Range, WMS-R Visual Production Test, Verbal Memory Process Test, WMS Logical

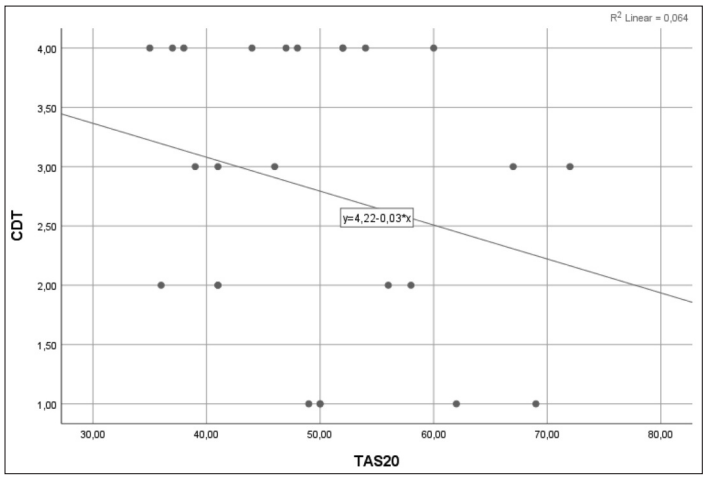

Figure 1. *Correlations between Clock drawing test (CDT) and Toronto Alexithymia Scale-20 (TAS-20)*

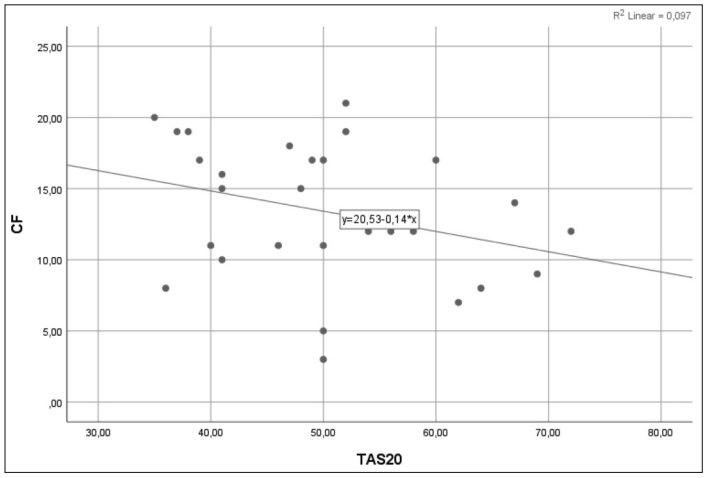

Figure 2. *Correlations between Category Fluency (CF) and Toronto Alexithymia Scale-20 (TAS-20)*

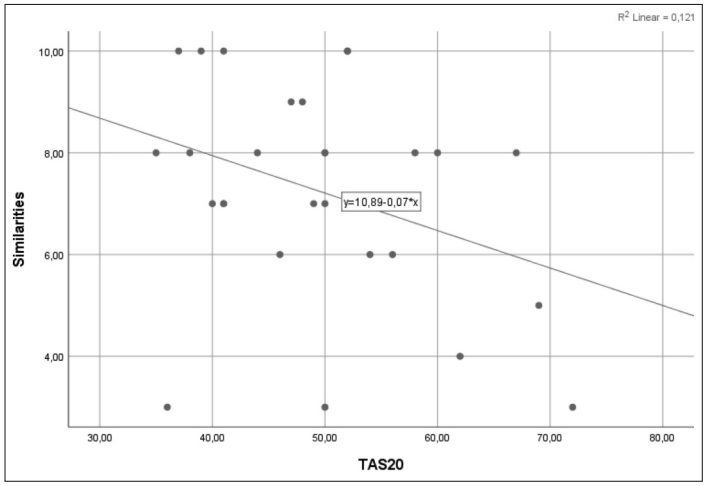

Figure 3. *Correlations between similarities and Toronto Alexithymia Scale- 20 (TAS-20)*

Memory, Benton Line orientation Test, Benton Face Recognition Test, Stroop Test, WMS Mental Control, Boston Naming Test, Verbal Fluency Tests (Animal Counting, KAS- verbal fluency test, Fruit-Name Fluency), Clock drawing test. Turkish version of a neuropsychological test battery was prepared to evaluate different domains of cognitive function including attention, executive function (EF), visuospatial functions (VSF), verbal memory (VeM) (immediate recall-IR and delayed recall-DR), visual memory (ViM) (IR and DR) and language. Turkish version of mentioned tests were used[16–20]. Neuropsychological evaluation of the participants was carried out by an occupational therapist experienced in neuropsychological testing and interpreted by a neuropsychologist blinded to patient data. Distribution of tests by cognitive domains can be seen in **Table 1**.

STATISTICAL ANALYSIS

The SPSS version 21.0 computer software (IBM, Armonk, NY, USA) was used for all statistical analyses. Descriptive statistical methods were used to analyze the data and frequency, percentage, mean, and standard deviation were used to describe the demographic characteristics of patients. Spearman correlation analysis was used to evaluate the relationship between HYS and TAS-20 score. Z scores were calculated for each cognitive domain. The relationship between alexithymia and cognitive domains were analyzed using partial correlation analysis controlling for age, gender, education level and GDI scores. The partial correlation analysis let us to avoid the effect of age, gender, educational level, depressive symptoms on cognitive functions and alexithymia levels. P values less or equal to 0.05 were considered to show statistical significance.

Results

A total of thirty-five patients (mean age 71.2±10.5 years, 22 male/13 female) with PD were included in the study. The mean duration of the disease (years) was 6.5±3.8, and the mean HYS score was 1.5±0.5. Demographic characteristics of the study group are given in **Table 2.** The mean TAS-20 score was 49.9±10.2 and GDI score was 10.3±6.7.

CORRELATIONS OF ALEXITHYMIA LEVELS

There was no correlation between TAS- 20 and HYS scores (r=0.23, p=0.24). TAS-20 scores were found to demonstrate a significant and negative cor-

relation with WAIS similarities test scores (r=-0.71, p=0.02), clock drawing test scores (r=-0.72, p=0.02), and semantic verbal fluency (r=-0.77, p<0.01, **Table 1**) **(Figure 1, 2, 3)**. Correlation analysis revealed a significant correlation between TAS-20 score and GDI score (r=0.44, p=0.03).

Correlations between alexithymia and cognitive domains

Executive function Z score was correlated with the mean TAS-20 score (r=-62, p=0.03) and difficulty describing feelings subscale score(r=-0.70, p=0.01).

Correlations of alexithymia subscales

Difficulty identifying feelings subscale scores were negatively correlated with the clock drawing test score (r=-0.74, p=0.01), and semantic verbal fluency test score (r=-0.66, p=0.04), visual memory delayed recall (r=-0.74, p=0.01), visual memory immediate recall (r=-0.74, p=0.01).

Difficulty describing feelings subscale scores were negatively correlated with semantic verbal fluency test score (r=-0.66, p=0.04) and WAIS similarities score (r=-0.70, p=0.02).

Externally oriented-thinking subscale scores were negatively correlated with WAIS similarities score (r=-0.77, p=0.01).

Correlations between TAS-20 subscales and cognitive tests can be seen in **Table 1**.

Table 2. *Demographic features of the study group*

	n=35
Age, years	71.17 ± 10.51
Gender	
Male	22 (62.8%)
Female	13 (37.2%)
Education	
Illiterate, n	2 (5.7 %)
Literate, n	4 (11.4 %)
Primary school, n	27 (77.1%)
High School, n	2 (5.7%)
Toronto alexithymia scale-20 score (mean)	49.9 ± 10.2
Geriatric depression inventory score (mean)	10.3 ± 6.7

Data are presented as mean ± Standard deviation

Discussion

With regard to the main issue of the present study, our data suggest a specific association between alexithymia and CD including visual-spatial abilities and executive functions. Our findings demonstrated a reverse and significant relationship between alexithymia levels and clock drawing, similarities, verbal fluency. We also found that alexithymia score was significantly correlated with the presence of depressive symptoms in patients with PD.

In the last three decades, non-motor symptoms of PD have become well recognized. Impairments of several cognitive domains, including working memory and executive functions, visuospatial skills have been shown to develop in the early stages of PD. Recent data have shown a reduction in the connection pathways that lie within the frontostriatal tract, suggesting that these are related to cognitive and behavioral disorders in patients with PD[21, 22]. Alexithymia is a behavioral non-motor symptom of PD which has received little attention[23]. Previous researches showed that the prevalence of alexithymia was significantly higher in PD patients than in healthy subjects[23–25]. Studies involving neuroimaging have shown that alexithymia may be caused by problems in frontal areas, especially the prefrontal cortex, and some studies suggested that connections between basal ganglia and prefrontal pathways are important in the emotional dysregulation observed in PD[24]. With this shared neuroanatomical background of CD and alexithymia in mind, we hypothesized that alexithymia is related with CD, especially associated with these brain structures which include frontal functions such as executive function, and visuospatial processing. It has been shown that impairment of executive functions is related to frontostriatal disorders in PD[26]. Previous studies demonstrated a relationship between alexithymia and executive dysfunction which was explained by the 'frontal model' of alexithymia[7, 8, 27, 28]. Our study supports their findings: we found relationship between alexithymia levels and similarities, verbal fluency which evaluate executive functions. In addition, patients who experience difficulty describing their feelings have lower verbal fluency test scores.

Visuospatial dysfunction is another core symptom of CD in PD. *Bogdanova* et al. have revealed that the visuospatial cognitive component reflecting parietal dysfunction was affected in alexithymic PD patients[8]. High TAS-20 scores were found to be associated with low visual-spatial ability test scores, especially those involving emotional stimulus[7, 8]. This suggests an association in these patients between alexithymia and right hemisphere dysfunction, as the right hemisphere is particularly involved in processing visual-spatial information[7]. Our patients who have higher alexithymia levels have lower clock drawing test scores which reflect impaired visuospatial function.

Investigators focused their research on the relationship between neuropsychiatric symptoms and alexithymia in PD[29–33]. *Costa* et al. carried out the first study about alexithymia and its relationship with depression in PD[31]. *Poletti* et al. confirmed their results[32]. Considering their findings and our results, it is feasible to suggest that the presence of alexithymia may be associated with the development of affective disorders including depression.

The present study has some limitations to be mentioned. First, the number of patients involved in the study is relatively low. Nevertheless, despite the relatively low number of patients enrolled in the study, our findings point to the importance of alexithymia in patients with PD. Secondly there were not healthy controls, and pharmacotherapy of the patients was not mentioned. Future studies with cross sectional design are needed.

The strength of this study is that we performed a detailed neuropsychological evaluation.

Finally, the present study demonstrates that TAS-20 score, indicating the severity of alexithymia, is associated with CD and depressive symptoms in patients with PD. We believe that alexithymia, which is roughly defined as lack of the ability to express emotions, is associated with poor cognitive functions (especially executive function and visuospatial function) and presence of depression in patients with PD. Therefore, alexithymia should be a focus of interest for neurologists who are confront with PD patients, and the presence of alexithymia should alert physicians to the possibility of CD and possible depression.

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DISCLOSURE OF INTEREST
The authors report no conflict of interest.

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