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JNBS emphasis on psychiatric and neurological disorders. However, studies on normal human behavior are also considered. Animal studies and technical notes must have a clear relevance and applicability to human diseases. Case Reports including current neurological therapies or diagnostic methods are generally covered by JNBS.

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• In vivo monitoring of electrical and biochemical activities of the brain
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All cover letters must contain the following: A statement that

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*Is the present study a new analysis of previously analyzed data? If yes, please describe differences in analytic approach.

*Are some of the data used in the present study being analyzed for the first time? If yes, please identify data (constructs) that were not included in previously published or submitted manuscripts.

*Are there published or submitted papers from this data set that address related questions? If yes, please provide the citations, and describe the degree of overlap and the unique contributions of your submitted manuscript.

*The full postal and email address of the corresponding author; *The complete telephone and fax numbers of the same;

*The proposed category under which the manuscript was submitted;

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Review Board(s).

*Whether or not the manuscript has been or is posted on a web site;

*That APA style (Publication Manual, 6th edition) has been followed;

*The disclosure of any conflicts of interest with regard to the submitted work;

*A request for masked review, if desired, along with a statement ensuring that the manuscript was prepared in accordance with the guidelines above.

*Authors should also specify the overall word length of the manuscript (including all aspects of the manuscript, except figures) and indicate the number of tables, figures, and supplemental materials that are included.

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Prepare manuscripts according to the Publication Manual of the American Psychological Association (6th edition).

Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the Manual.

Below are additional instructions regarding the preparation of display equations and tables.

Display Equations

We strongly encourage you to use MathType (third-party software) or Equation

Editor 3.0 (built into pre-2007 versions of word) to construct your equations, rather than the equation support that is built into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors.

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All manuscripts must include an English abstract containing a maximum of 250 words typed on a separate page. (It should contain headings such as Background, Aims and Objectives, Materials and Methods, Results, Conclusion etc.) After the abstract, please supply up to five keywords or brief phrases.

References:

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- Use Arabic numerals (1,2,3,4,5,6,7,8,9).
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According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1]
S variant is associated with the lower transcriptional activity of the promoter when compared to the L variant.[4,7-9,11]

The Reference Section:

• Journal Article:

Russell FD, Coppell AL, Davenport AP. In vitro enzymatic processing of radiolabelled big ET-1 in human kidney as a food ingredient. Biochem Pharmacol 1998;55(5):697-701. doi: 10.1016/s0006-2952(97)00515-7.

Gonen, M. Planning for subgroup analysis: a case study of treatmentmarker interaction in metastatic colorectal cancer. Controlled Clinical Trials 2003;24 : 355-363. doi: 10.1016/s0197-2456(03)00006-0.

• Authored Book:

Lodish H, Baltimore D, Berk A, Zipursky SL, Matsudaira P, Darnell J. Molecular cell biology. 3rd ed. New York: Scientific American; 1995.

Millares M, editor. Applied drug information: strategies for information management. Vancouver: Applied Therapeutics, Inc.; 1998.

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The publication of an article in the peer-reviewed journal JNBS is an essential building block in the development of a coherent and respected network of knowledge. It is a direct reflection of the quality of the work of the authors and the institutions that support them. Peer-reviewed articles support and embody the scientific method. It is therefore important to agree upon standards of expected ethical behaviour for all parties involved in the act of publishing: the author, the journal editor, the peer reviewer, the publisher and the society of society-owned or sponsored journals.

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Peer review assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper. Peer review is an essential component of formal scholarly communication, and lies at the heart of the scientific method. JNBS shares the view of many that all scholars who wish to contribute to publications have an obligation to do a fair share of reviewing.

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The Journal of Neurobehavioral Sciences

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Contents

Original Article

Evaluation of the Coexistence of Attention-Deficit Hyperactivity Disorder and Anxiety Disorder Symptoms

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Abstract

Aim: Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder, and its etiology of it has not been fully elucidated yet. We tried to evaluate the familial aspects of anxiety disorders and ADHD in this study. **Materials and Methods:** Our study group comprised 128 parents aged between 24 and 60 years (114 mothers and 14 fathers) of 128 children with diagnosis of ADHD (n = 47), anxiety disorders (n = 30), and ADHD + anxiety disorders (n = 51) who had been evaluated by the department of child and adolescent psychiatry. Findings of anxiety disorders and ADHD were evaluated in accordance with the Diagnostic and Statistical Manual-V Criteria. Beck Anxiety Inventory, Wender Utah Rating Scale (WURS), and Turgay's Adult Attention-Deficit Disorder (ADD)/ADHD Diagnosis and Evaluation Scale were applied to parents. **Results:** Anxiety levels, WURS, and Turgay's Adult ADD/ADHD Diagnosis and Evaluation Scale points did not be differentiated between groups. 16.7% (n = 5) of ADHD + anxiety, 6.4% of ADHD (n = 3), and 9.8% (n = 5) of anxiety group of parents were high-degree ADD/ADHD (+). **Conclusion:** Our study results show that there are some familial features of ADHD and anxiety disorders. Considering the relationship between these two disorders during the psychiatric care of children as well as their parents is deeply important for clinicians.

Keywords: *Anxiety, attention-deficit hyperactivity disorder, children, comorbidity, family*

Introduction

Attention-deficit hyperactivity disorder (ADHD) causes impairment in various areas of development. Its symptoms are also seen in adolescence and adulthood. Its incidence is high with various psychiatric disorders.[1] Conditions associated with various psychiatric disorders impress the clinical pattern and results of ADHD. Research results showed that 87% of adults with ADHD had a minimum of one and 56% had at least two accompanying psychiatric disorders.[2] ADHD has strong familial inheritance (55%–92%).[3] The incidence of ADHD was high in children whose parents were diagnosed with adulthood ADHD compared to healthy parents. It has been seen in family studies that the incidence of ADHD diagnosis in mothers, fathers, and kids with ADHD is 2–8 times higher.[4-7] Gene and environment interaction has a determinant role in occurrence of ADHD.[8]

Coexistence of anxiety disorders with ADHD is common. This togetherness has been extensively investigated in pediatric and adult ADHD studies. There are studies showing that about 15%–35% of kids and adolescents with ADHD have an anxiety disorder, which is significantly higher than the reported 2% rate in kids with the absence of ADHD.[9-11] Adulthood ADHD is often comorbid with anxiety disorders.[12-14]

There are various arguments about anxiety disorders and ADHD.[15-17] Some of them are: (a) although genetic risk factors are the same, different results occur as anxiety disorders and ADHD; (b) when anxiety disorders and ADHD co-occur, they form a separate ADHD subtype, or individuals with ADHD and anxiety disorders are phenotypically different from individuals with only one disorder; and (c) ADHD and anxiety symptoms have different transfer.[17,18]

In the past, studies have been conducted related to anxiety disorders and ADHD interaction.[19,20] There are reviews mentioning

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that anxiety is a widespread clinical aspect in ADHD and that it can significantly change the development and consequences of the disorder. However, defining the best criteria for grouping subspecies remains an unsolved problem.[10] Besides these, researchers have difficulty answering many questions about parents of kids diagnosed with ADHD. In respect of etiology of ADHD, yet to date, family studies have been paid less attention.[21]

Some results of studies show that ADHD and anxiety disorders interact continuously and consistently. These two disorders affect and also increase the prevalence of each other when compared to the frequency in society and display an independent transition.[15,16,22,23] Our study was planned to reveal the familial features of anxiety disorders and ADHD. Our first hypothesis is finding rate of anxiety disorders of parents of children with anxiety disorders score more meaningful than parents of children with ADHD on the Beck Anxiety Inventory (BAI) Scale. Second hypothesis is to find ADHD symptom scale points more meaningful in parents of kids with ADHD.

Materials and Methods

The ethics committee approval has been obtained from Haydarpasa Numune Training and Research Hospital Ethics Committee with a number of 21.02.2017 version 1. Protocol Code: 21.02.2017/V1.

The study was planned in a cross-sectional model, and we aimed to assess the frequency of anxiety disorders and ADHD levels in groups (parents of kids with ADHD, anxiety disorders, ADHD + anxiety disorders group).

Subjects

The sample consisted of 128 parents aged 24–60 years (114 mothers and 14 fathers) of 128 kids (n = 84 men, n = 44 women) with ADHD, anxiety disorders, and ADHD + anxiety disorders who had been applied to the child and adolescent psychiatry department between April 2017 and May 2017. All patient groups meeting the following criteria were counted in research.

Exclusion criteria for children were having a chronic disease, neurologic problems, and pervasive developmental disorder. Exclusion criteria for parents were mental retardation, minority, and having a psychiatric problem dependent on organic problems.

The research was approved by the Ethics Committee of Haydarpasa Numune Training and Research Hospital (Protocol Code: 21.02.2017/V1). We obtained written consent form from each parent. Children participating in the research were diagnosed with ADHD and anxiety disorder according to the Diagnostic and Statistical Manual (DSM)-V.

Anxiety disorders were evaluated in parents of children in three different groups (ADHD [n = 47], ADHD + anxiety disorders group [n = 30], and anxiety disorders group [n = 51]). Parents of a total of 128 children were evaluated in the adult ADHD unit of the adult psychiatry department. Only one of the parents for each child was included in the study. A structured clinical interview was applied with each parent to appraisal current and lifetime anxiety disorders and ADHD. Anxiety disorders and findings of ADHD were evaluated in accordance with the DSM-V.[24] Sociodemographic profiles and clinical features were collected in a sociodemographic form. BAI was administered to assess the severity of anxiety symptoms.

Assessment

Sociodemographic data form

This form is a specially developed questionnaire to determine the sociodemographic characteristics of the patients and to collect data.

Beck Anxiety Inventory

It is a Likert-type scale consisting of 21 items. The guidebook suggests 16 points as cutoff.[25] It has been revealed that BAI is more sensitive to principally detect panic symptoms than more general anxiety symptoms and its scores correlate with physiological measures of anxiety.[26-28]

Wender Utah Rating Scale

It evaluates ADHD signs throughout childhood in adults.[29] It has 61 items. The cutoff point was determined as 36.[30]

Turgay's Adult Attention-Deficit Disorder/Attention-Deficit Hyperactivity Disorder Diagnosis and Evaluation Scale

Turgay's Adult Attention-Deficit Disorder (ADD)/ADHD Diagnostic and Rating Scale was also administered.[31] Gunay *et al*. adapted it to Turkish.[32] It is composed of 58 items. The first part evaluates attention deficit, the second part evaluates excessive motor activity and impulsivity, and the third part evaluates characteristics of ADHD.

Statistical analysis

We used Number Cruncher Statistical System 2007 and Power Analysis and Sample Size. Descriptive statistical methods (mean, standard deviation, median, frequency, rate, and minimum and maximum) were used for evaluating our data. One-way ANOVA test is used for comparison of three and more groups. Tukey's test was used to examine the difference between groups. Kruskal–Wallis test was used for comparison of three and more groups with the absence of normal distribution. Pearson's Chi-square test and Fisher–Freeman–Halton test were used for qualitative data. Significance was evaluated as $P < 0.01$ and $P < 0.05$.

Results

Parents participated in our study were grouped into three groups: subjects with a kid diagnosed with

ADHD (n = 47), subjects with a kid diagnosed with anxiety disorder (n = 51), and subjects with a kid diagnosed with ADHD + anxiety disorder (n = 30). The mean age for parents of ADHD group was 33.91 ± 4.58 years, for parents of anxiety disorders group was 39.63 ± 6.60 years, and for parents of ADHD + anxiety disorders group was 38.27 ± 5.42 years. According to one-way ANOVA test, there was statistically difference between ages of the parents ($P < 0.01$). As a result of the pairwise comparisons, parents of anxiety disorder group ($P = 0.001$) and ADHD + anxiety disorder group ($P = 0.004$) were older than parents of ADHD group ($P < 0.01$). No difference was found between parents of anxiety disorder group and ADHD + anxiety disorder group in average age ($P = 0.549$, $P > 0.05$) [Table 1].

Statistical difference was determined among ADHD group and anxiety disorder group at repetition of grades at school (ADHD vs. anxiety disorders: $P = 0.0076$). We could not find any difference among other groups (ADHD vs. ADHD + anxiety disorders: $P = 0.2856$, anxiety disorders vs. ADHD + anxiety disorders: $P = 0.3379$).

We could not find any difference among groups in social properties, such as occupation changes, income level, receiving disciplinary punishment, having trouble with police, receiving traffic summons, and alcohol abuse by Fisher–Freeman–Halton test.

When we compare all three parental groups, we could not find any difference in presence of psychiatric disease in family, having a family member with a physical illness, presence of physical illness in the parents, and application to the psychiatry department ($P > 0.05$).

Beck anxiety scores of the total groups ranged from 0 to 52 points.

We could not find any difference among groups according to Beck anxiety scores ($P > 0.05$) [Table 2].

Table 1: Mean scores for demographic variables and child diagnoses by child group

	Diagnosis			*P*
	ADHD (*n*=47), *n* (%)	**Anxiety disorders (*n*=51), *n* (%)**	**ADHD + anxiety disorders (*n*=30), *n* (%)**	
Gender (parents)				
Male	7 (14.9)	4 (7.8)	3 (10.0)	0.549†
Female	40 (85.1)	47 (92.2)	27 (90.0)	
Gender (children)				
Male	34 (72.3)	30 (58.8)	20 (66.7)	0.368‡
Female	13 (27.7)	21 (41.2)	10 (33.3)	
Marital status (parents)				
Married	45 (95.7)	49 (96.1)	28 (93.3)	0.761†
Divorced	2 (4.3)	2 (3.9)	2 (6.7)	
Level of education				
Primary school	16 (34.0)	33 (64.7)	14 (46.7)	0.064†
Secondary school	9 (19.1)	6 (11.8)	4 (13.3)	
High school	16 (34.0)	6 (11.8)	9 (30.0)	
College	6 (12.8)	6 (11.8)	3 (10.0)	
Repetition of grades at school				
No	31 (66.0)	46 (90.2)	24 (80.0)	0.013*,‡
Yes	16 (34.0)	5 (9.8)	6 (20.0)	
Occupational status				
Employed	10 (21.3)	8 (15.7)	6 (20.0)	0.763‡
Unemployed	37 (78.7)	43 (84.3)	24 (80.0)	

*P<0.05, **P<0.01, †Fisher-Freeman-Halton test, ‡Pearson Ki-Kare test. ADHD: Attention-deficit hyperactivity disorder

Table 2: Comparison of the groups according to their anxiety levels

	ADHD (*n*=47), *n* (%)	**Anxiety disorders (*n*=51), *n* (%)**	**ADHD + anxiety disorder (*n*=30), *n* (%)**	*P*
Anxiety level according to beck anxiety				
Minimal anxiety (0-7 points)	24 (51.1)	18 (35.3)	13 (43.3)	0.30†
Mild anxiety (8-15 points)	15 (31.9)	16 (31.4)	8 (26.7)	
Moderate anxiety (16-25 points)	7 (14.9)	9 (17.6)	5 (16.7)	
Severe anxiety (26-63 points)	1 (2.1)	8 (15.7)	4 (13.3)	
Beck anxiety score	9.53±6.50	14.76±11.74	12.57±10.36	0.077‡

†Fisher-Freeman-Halton test, ‡Kruskal-Wallis test. ADHD: Attention-deficit hyperactivity disorder

There was a statistically significant relationship between the prevalence of generalized anxiety disorder (GAD) in groups [Table 3].

Twenty-five of 128 parents had childhood ADHD according to Wender-Utah Rating Scale (WURS). 13 of the total 125 parents were evaluated as high-degree ADD/ADHD (+) according to Turgay's cutoff scale. 16.7% (n = 5) of ADHD + anxiety disorder group, 6.4% of ADHD group (n = 3), and 9.8% (n = 5) of anxiety disorder group of parents were high-degree ADD/ADHD (+). No difference was observed between three groups at distribution of ADD/ADHD scale points.

There was also no difference between groups according to cutoff 36 points for WURS either using Pearson Ki-Kare test [Table 4].

Discussion

Anxiety disorders and ADHD are usually kept together.[33-36] We designed the study as cross-sectional type to measure the rate of anxiety disorders and ADHD symptoms in three groups. Our study was planned to reveal the familial features of anxiety disorders. We focused on parental anxiety and how anxiety interacts with ADHD.

The first point that needs to be discussed is the prevalence of anxiety disorders do not differentiate between groups, except GAD. The GAD prevalence was higher in subjects with a child diagnosed with ADHD + anxiety disorder (30% [n = 9]) than other groups. Comparing the rate of other anxiety disorders in three groups, the result was not in the statistically significant range. The majority of studies report that comorbid anxiety disorder, especially GAD, was very prevalent in adults.[37,38] The high rate of GAD in our study seems to be in agreement with other studies. The incidence of GAD in females is twice that of males.[1] Further, the overlap of anxiety disorders + ADHD in children may have influence in the issue. Something like the potential burden of care provided by a child with both disorders (anxiety disorders + ADHD) is higher than that of a child with only anxiety disorder or only ADHD. Because of the child's multiple psychiatric disorders, his/her behavior and effects on school, family, and social settings may cause more distress on parents. The other anxiety disorders of three groups were similar ($P > 0.05$), and the predicted group differences in anxiety levels were not observed. Although the rates of severe and moderate levels of anxiety were higher in the subjects with a child with anxiety disorder, no statistically significant difference (15.7% of participants had severe and 17.6% had moderate anxiety level) was noted. When we find that anxiety degree was high in parents of kids with only ADHD, we might have thought that anxiety occurred due to the burden proceed from an ADHD child.

Another interesting result of our study was that we did not observe any difference in childhood ADHD according to WURS scores among parents. We expect

Table 3: Distribution of anxiety disorders in all parents groups multiple diagnosis are included

	ADHD, *n* (%)	Anxiety disorders, *n* (%)	ADHD + anxiety disorder, *n* (%)	*P*
Panic disorder	3 (6.4)	8 (15.7)	6 (20)	0.187†
OCD	6 (12.8)	7 (13.7)	5 (16.7)	0.898†
PTSD	1 (2.1)	3 (5.9)	0	0.450†
Acute stress disorder	0	1 (2)	1 (3.3)	0.415†
Social phobia	6 (12.8)	5 (9.8)	6 (20)	0.429†
Agoraphobia	0	4 (7.8)	3 (10)	0.070†
Special phobia	14 (29.8)	18 (35.3)	18 (35.3)	0.813‡
Generalized anxiety disorder	4 (8.5)	10 (19.6)	9 (30)	0.048†

†Fisher's exact test, ‡Ki-Kare. ADHD: Attention-deficit hyperactivity disorder, OCD: Obsessive-compulsive disorder, PTSD: Posttraumatic stress disorder

Table 4: Comparison of the groups according to their Wender-Utah Rating Scale and Turgay's Adult Attention Deficit Disorder/Attention-Deficit Hyperactivity Disorder Evaluation Scale

	Mean±SD			*P*
	ADHD	Anxiety disorders	ADHD + anxiety disorders	
WURS	21.67±11.49	24.16±14.15	19.90±15.23	0.231†
Turgay's ADD/ADHD Evaluation Scale				
ADD score	5.87±4.61	6.88±4.80	7.36±5.58	0.387
ADHD score	5.19±4.38	5.03±4.51	5.06±4.58	0.985
Problem score	19.53±12.45	21.70±12.61	20.76±11.98	0.687
Total score	30.59±19.16	33.62±17.88	32.41±18.73	0.705

†Kruskal-Wallis test. ADHD (+):WURS >36. ADHD: Attention-deficit hyperactivity disorder, ADD: Attention deficit disorder, SD: Standard deviation, WURS: Wender-Utah Rating Scale

to find higher levels of WURS scores, so higher rates of childhood ADHD in subjects have a child with ADHD. There was no difference in Turgay's ADD/ADHD scale points either. When the studies from our country were examined, the adult-type ADHD rate was 6.8%–33.8% in parents of children with ADHD.[21,39] According to our study, the ADHD rate was 6.4% in hyperactivity group and 16.7% in ADHD + anxiety group of parents. The rate of ADHD symptoms in parents of kids with ADHD has been reported to be higher in many studies compared to control groups.[4,40,41]

In a similarly designed study, it has been shown that psychiatric symptoms and ADHD findings are less common in parents whose kids do not have ADHD or other disruptive behavior disorders, compared to parents of kids with ADHD. Parents of kids with ADHD got statistically higher scores than controls from subdivisions of Adult Attention Deficit Hyperactivity Scale.[4] Some properties usually seen in ADHD people did not show difference between three groups, except repetition of grades at school. The correlations of parents' psychiatric aspects with their children's psychiatric problems may change up to sex and a variety of symptoms.

It is a matter of curiosity how psychiatric problems of parents and children affect each other. Maternal clinical variables (ADHD, anxiety, and depression), compared to paternal variables, were more associated with children's variables. Segenreich *et al*. studied interactions of ADHD symptoms and anxiety symptoms in family members. The results showed that maternal attention deficit was associated with inattention and hyperactivity in kids. Anxiety disorder in mother was associated with attention deficit in children, and attention deficit in mother was associated with anxiety disorder in kids.[42] We did not assess the level of anxiety and hyperactivity of children in our study. Hence, we cannot compare the studies head to head. However, the frequency of anxiety disorders, which we could not find a difference between the groups, was mentioned.

Throughout the years, authors try to find the answers to questions if the two disorders are only two disorders that affect each other, do they each cause a different disorder or alter the course of the other? However, most of these studies are investigating the comorbidity of anxiety disorders in ADHD children or adults. In some studies, ADHD and anxiety disorder comorbidity is detected deeply. It has been reported that groups with ADHD and concomitant anxiety show higher problems in emotion regulation and problem-solving than groups with only ADHD or anxiety alone.[20] In addition, patients with ADHD + anxiety perform worse in working memory and express more physical anxiety symptoms compared to ADHD alone.[43] Previous studies have shown that both biological/genetic and extrinsic factors explain noticeable link in anxiety among family members.[44-46]

In addition, ADHD and anxiety disorders are correlated variables in households and should be considered together.[42] Our study design has limited probability of detecting causality and cannot resolve genetic and environmental factors; however, in the light of our results, assessing anxiety disorders in cases with having a kid with ADHD is substantial for care and course.

Kids diagnosed with ADHD + anxiety disorders are the ones who have difficulties in the management of their treatment. The data of our study are quite limited. In addition, not evaluating children's anxiety levels is another shortcoming of the study. However, examining both parents and children in the same study is a strong aspect of this study. The present study demonstrates that further family studies with larger sample sizes must be needed about the issue.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

The ethics committee approval has been obtained from Haydarpasa Numune Training and Research Hospital Ethics Committee with a number of 21.02.2017 version 1. Protocol Code: 21.02.2017/V1.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Melek Gözde Luş (%40) headed the subject enrollment, contributed with scale development process, data analysis, revision and theoretical background.
- Meliha Zengin Eroğlu (%60) contributed with scale development process, data analysis and wrote the whole manuscript.

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Original Article

Mental Health Status of Caregivers of Persons with Neurological Disability

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Abstract

Introduction: Neurological conditions have a long-term impact on the individual and their family and also affect one's general and mental health. **Materials and Methods:** This cross-sectional study aimed to assess the psychological morbidity among 50 primary caregivers of persons with a neurological disability and was conducted using a self-reporting questionnaire. **Results:** Most of them were female (64.0%), and predominantly, the caregiver was mother (50.0%). Most of the caregivers have reported felt nervous, tense, or worried during hospitalization (76.0%); felt unhappy during caregiving (86.0%); and faced difficulty to enjoy daily activities (74.0%). In addition to that, (98.0%) caregiver's have reported that their day to day work suffered, (70.0%) were unable to play a usual part in life. **Conclusion:** The study would highlight the need for screening the mental health of the caregivers of persons with neurological disabilities.

Keywords: *Mental health, neurological disability, psychological distress*

Introduction

Neurological disorders constitutes 6.3% of the total disability adjusted life years and this trend is projected to increase to 6.77 in 2030.[1] Which have become significant causes of disability and death worldwide.[2] In India, the average prevalence rate of common neurological disorders is 2394 and ranges from 967 to 4070/100,000 population.[3] Mental health issues are proportionately increasing worldwide and have become a global challenge; over 450 million people are suffering from some of the mental or behavioral disorders worldwide.[4] In India, as per the NIMHANS Mental Health Survey, the overall weighted prevalence of mental morbidity was 10.6% for current and 13.7% for lifetimes.[5]

Neurological conditions have a long-term impact on the individual and their family. Having a neurological condition affects one's general health and mental health, leads to stigmatization, causes impairments of functions, affects the quality of life, and contributes to financial security. Over time, the condition of the neurological disabilities will worsen as they produce various symptoms and functional impairments that often increase demands on informal caregivers. The patients are completely dependent on the caregiver for their activities of daily living such as bowel and bladder functions, transfers, locomotor, and self-care; caregiver issues are last to be attended both by the family members and the treating team.

Family members and friends are the major sources of informal caregivers to provide care to the person with a neurological disability living in the community.[1,6,7] The role of caregiving is an indispensable factor to support a person with a neurological disability to provide support to them. The caregiver burden and their psychological distress are the identified risk factors; this has been recommended to address the caregiver burden and distress involved in the care of persons with neurological disabilities. It is a well-known fact that the family members are affected by the patient's illness. Most of the studies have demonstrated that burden and distress are the two negative consequences due to the role of caregiving by the informal caregiver to the person with neurological disability.[8-10]

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The amount of time spent in providing care to the care recipient is directly proportional to caregiver distress.[11,12] Psychological distress was very high among family caregivers among persons with dementia.[13] Fatigue, stress, and depression in caregivers of MS patients are negatively correlated with their physical health status and mental health status.[14] It is imperative to study the psychological well-being of these caregivers. In the Indian setting, fewer studies have looked into identifying the impact of caregiving provided by informal caregivers to persons with neurological disabilities. The current study aims to identify the level of psychological distress among the informal caregivers of persons with neurological disorders emphasising the need for long-term clinical interventions.

Materials and Methods

The study was conducted as part of Caregivers support and education programme for Neuro rehabilitation from April 2017 to December 2017.

A total of 50 primary caregivers of persons with a neurological disability were included in the current study. It was a cross-sectional, hospital-based study with an explorative design. The data were collected from all admitted patients to the department of neurological rehabilitation. Patients with complete information were included in the study. Patients with incomplete information were excluded from the study. The data that were recorded consisted of the sociodemographic profile and clinical profile of the patients. Only those caregivers who are above 18 years, staying with the patient in the hospital and at the home, intensively involved in bringing the patient for treatment, follow-up, and medications were included in the study. Paid caregivers were excluded from the study; informed consent was obtained to participate in the study. A self-reporting questionnaire (SRQ) (World Health Organization [WHO] 1994) was used to assess depressive symptoms, anxiety, and psychosomatic complaints.

This was a 20-item questionnaire to obtain information on psychological distress, which was developed by the WHO-SRQ 20, 1994.[15] The complete SRQ consisted of 25 questions, which have to be answered by "yes" or "no." Of these 25 questions, 20 were related to neurotic symptoms, 4 to psychotic symptoms, and 1 to convulsions. The SRQ-20 consisted of the neurotic items; these revealed depressive symptoms, anxiety, and psychosomatic complaints and detected probable cases of common mental disorders with reasonable accuracy. After obtaining written informed consent from the participants, the interview schedule and SR20 were administered. After managing data properly, it was analyzed using SPSS (Statistical Package for the Social Sciences, International Business Machines, Armonk, New York, United States) 16 version and Microsoft Excel Software 2007 version and presented along with an intervention framework designed to reduce psychological distress.

Results

Persons with neurological illness (n = 50) were admitted to the neurorehabilitation ward for 6 months. The clinical profile of the person with neurological illness included Guillain–Barre syndrome (22%), myelopathy (6%), stroke (8%), transverse myelitis (4%), traumatic brain injury (8%), spinal cord injury (10%), postinfectious myelitis (2%), paraplegia (4%), and other neurological conditions (36%).

Table 1 shows that the total sample consisted of 50 caregivers, among these 32 (64.0%) were females, 18 (36.0%) were males, they were predominantly in the age group of 31–40 (26.0%), 30 (60.0%) were coming from the nuclear family, 36 (72.0%) were having BPL card status. Most of the time, it is mother 25 (50.0%) who was staying with the patient in the ward, she happened to be the main caregiver. These caregivers were taking care of the patients all through the illness at home and

Table 1: Sociodemographic profile

	Frequency (n=50), n (%)
Gender	
Male	18 (36.0)
Female	32 (64.0)
Age	
20-30	4 (8.0)
31-40	13 (26.0)
40 and above	33 (66.0)
Education	
Illiterate	2 (4.0)
Primary	11 (22.0)
Secondary	17 (34.0)
Degree	18 (36.0)
Postgraduate	2 (4.0)
Community	
Rural	31 (62.0)
Urban	19 (38.0)
SES	
BPL	36 (72.0)
APL	14 (28.0)
Type of family	
Nuclear	30 (60.0)
Joint	20 (40.0)
Caregiver relation	
Mother	25 (50.0)
Father	9 (18.0)
Relatives	7 (14.0)
Others	9 (18.0)
Duration of illness	
Up to 1 month	10 (20.0)
2-6 months	22 (44.0)
7 months-1 year	8 (16.0)
More than a year	10 (20.0)

BPL: Below poverty line, APL: Above poverty line, SES: Socioeconomic status

in the hospital; the highest duration of illness was 2–6 months (44.0%).

Table 2 shows the item-wise analysis of the psychological distress of caregivers. The table shows that (44.0%) of the respondents reported that they have frequent headaches, (54.0%) suffered from poor appetite, (50.0%) disturbed sleep or sleep disturbances, (44.0%) were easily frightened, (36.0%) had tremors, (76.0%) were felt nervous during hospitalization, (86.0%) experienced unhappy during caregiving, (46.0%) cried more than usual, and (74.0%) faced difficulty to enjoy of daily activities. (98.0%) caregiver's have reported that their day to day work suffered, (70.0%) were unable to play a usual part in life, (60.0%) lost in interest, (52.0%) felt tired in all the time, and (52.0%) felt easily tired.

Discussion

The impact of the neurological conditions on the affected individuals and their families is high and the person with a neurological disability living in the community requires high support and care by the informal caregivers. In India, the family is the first point of contact to provide care to the patient. All the 24 h of a day, and 7 days in a week, the family spends a large amount of time, energy, and resources in looking after the patient as part of caregiving; hence, it would negatively impact their mental health. The majority of the care comes from the informal caregivers to the person with neurological disabilities. In the current study, it was reported that almost all caregivers of persons with a neurological disability experienced a high level of distress during the hospitalization with a mean score of 25.55 ± 4.69. A cross-sectional study from Canada has reported that a significant proportion of informal caregivers of persons diagnosed with neurological conditions have experienced distress.[10] The community-based study conducted from Fiji also found that the role of caregiving was adversely affected on the psychological well-being of the caregivers of persons with spinal cord injury.[8] Another study entitled, "Quality of Life and Psychological Distress of Caregivers of Stroke People," also stated that domains of physical and mental health were highly negatively correlated with anxiety ($r = 0.56$) and depression ($r = 0.59$) among caregivers of persons diagnosed with stroke.[16] Other research studies from across the globe have found that caregiver's burden was positively correlated with depression ($r = 0.124$, $P \leq 0.01$, and anxiety ($r = 0.124$, $P \leq 0.05$), and caregivers of PwNC found to be at higher risk of mental health problems,[17] High levels of psychological distress,[18,19] and caregivers of persons with AD have reported higher caregiver burden[20] which is in line with our study.

Table 2: Psychological distress (Self-reporting Questionnaire) 20-item analysis

	Yes (%)
Headache	22 (44.0)
Poor appetite	27 (54.0)
Sleep badly	25 (50.0)
Frightened easily	22 (44.0)
Tremors/handshake	18 (36.0)
Nervous/tense/worried	38 (76.0)
Poor digestion	21 (42.0)
Trouble thinking clearly	22 (44.0)
Feel unhappy	43 (86.0)
Cry more than usual	23 (46.0)
Difficult to enjoy your daily activities	37 (74.0)
Difficult to make decisions	19 (38.0)
Daily work suffering	49 (98.0)
Unable to play usual part in life	35 (70.0)
Lost interest in things	30 (60.0)
Feeling as worthless person	6 (12.0)
Ending your life been on your mind	6 (12.0)
Feel tired all the time	26 (52.0)
Uncomfortable in stomach	16 (32.0)
Easily tired	26 (52.0)

A cross sectional study from Portugal has suggested that behavioural and psychological symptoms in dementia, neuroticism of the patients is associated with the distress levels of their caregivers.[21] Studies have confirmed that caregivers of people diagnosed with dementia will have the continuation of depression, anxiety, and sleep disturbances for as long as 10 years postcaregiving.[22,23] Patient's neuropsychiatric symptoms are associated with increased levels of burden and psychological distress in caregivers of people with dementia,[24] apathy and disinhibition,[25] sleep disturbances, and lack of initiative.[26] In line with the above findings, half of the study participants ($n = 25$) have reported issues related to their sleep. In the current study, most of the caregivers were female ($n = 32$) and above 40 years of age ($n = 33$); a recent study found that being female and age between 50 and 70 years were the determinants for higher psychological distress among caregivers of patients with dementia.[27]

In the present study, it was shown that most of the CGs of PwNC have reported that they feel tired all the time ($n = 26$) and difficult to enjoy their daily activities ($n = 37$). There is a directly proportional relationship between the amount of time spent providing care to the care recipients and caregiver distress, i.e., as the caregiving time increases, caregiver distress will also increase.[11,28] Almost all of the participants ($n = 49$) have stated that due to their caregiving role, they have found difficult to enjoy their daily work activities. Studies have demonstrated that the role of caregiving will affect their ability to make rational decisions;[29,30] $n = 19$ caregivers have reported the same in the present study.

Caregivers often need to take up new tasks that they are not trained to do. They neglect their own health by investing immense time, energy in taking care of the patient, spend

lot of money for the treatment, take up flexible jobs or sometimes even give up jobs for caregiving. They even limit their social participation, so that they are all the time with the patient. As they are at risk to develop mental health issues such as anxiety and depression, an Indian study has demonstrated that the majority of the caregivers of persons with chronic terminal illness had severe levels of anxiety and 96% of them have had some degree of depression.[31] Family caregivers may benefit from an educational plan that includes helping them to develop the skills they need to communicate their problems and concerns better. Often caregivers have to do decision making on several issues and they have expressed their concerns that they are not able to think clearly (n=22). A study from the USA has recommended that providing psychosocial support will help the caregivers to reduce their burden and distress levels.[32]

Family caregivers provide extraordinary uncompensated care involving significant amounts of time and energy for months or years and require the performance of tasks that were often physically, emotionally, socially, or financially demanding. They are constantly challenged to solve problems and make decisions as care needs change, yet they feel untrained and unprepared as they struggle to adjust to new roles and responsibilities.[32] As the caregivers prioritize patient's needs, their own needs often get marginalized. The caregiver information needs are ever-emerging; they are not always known at the time of a clinic visit. Physicians are frequently unable to address caregiver questions, a situation compounded by time constraints and cultural barriers. Pakenham has reported that emotion-focused coping and perceived uncertainty were associated with distress for caregivers.[33] Dementia caregiver's stress related psychological symptoms, and sleep disturbances that emerged during caregiving are long term in nature and difficult to be resolved.[22] Many caregivers (n = 38) in this study have conveyed that they were worried/nervous during the caregiving process. Psychological distress and sleep quality are long-term outcomes of the stress process.[34]

When it applies to the context of caregiving factors, studies have concluded that various factors such as personality traits[35] and coping[36] have an influence on the caregiver distress levels. Kristin and Mary have stated in their research the impact of caregiving on long-term psychological outcomes among dementia caregivers.[22] Identifying and understanding the risk factors of the informal caregivers, caregiving burden and psychological distress will assist in the development of interventions and appropriate support strategies, which will directly help the caregiver, care recipient, and health-care systems.[11] In summary, the current study findings demonstrated the mental health status of the caregivers of persons with neurological disabilities.

Conclusion

Neurological conditions have a long-term impact on the individuals and their family and require a long time of exhaustive caregiving. Most informal caregivers such as family members and friends have reported a high amount of burden and distress. It is obligatory to identify the risk factors of the burden and distress to develop the interventions and provide appropriate support strategies, which will directly help the caregiver, care recipient, and health-care systems. The study would highlight the need for screening the mental health of the caregivers of persons with a neurological disability.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

The study was conducted as part of Caregivers support and education programme for Neuro rehabilitation from April 2017 to December 2017.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Srikanth Pallerla (50%): Contributed to writing a manuscript draft, literature search.
- Berigai Parthasarathy Nirmala (50%): Contributed to writing a manuscript draft, review of the manuscript.

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Original Article

The Effects of Flavonoids in Curcumin on Neurobehavioral Deficits in Insulin-resistant Rats

Abstract

Background: Diabetes mellitus is a risk factor for dementia, particularly Alzheimer's disease (AD). In a Wistar rat model, we studied Alzheimer-like symptoms using a high-fat diet (HFD) and streptozotocin (STZ) to replicate insulin resistance and the resulting neurobehavioral abnormalities. Curcumin, a flavonoid in turmeric, was studied for its potential therapeutic effects. **Aim:** This study sought to look at the exploratory, discriminatory, and spatial cognitive indices in rats. **Materials and Methods:** Thirty-six male Wistar rats were randomized into six groups and given the following treatments: olive oil only for control; curcumin only for the curcumin group; HFD and three doses STZ for the diabetic rats; HFD, three doses STZ, and concurrent treatment with curcumin for the protective group; pretreatment with curcumin, then HFD and three doses STZ for a preventive group; and HFD, three doses STZ, and curcumin for a therapeutic group. Subsequently, line and center line crossing frequency assessed rats' exploratory activities; rearing frequency data assessed novel environment behavior. The novel object recognition test and Morris water maze test assessed discrimination and spatial memory. Data were analyzed using one-way analysis of variance and Tukey's *post hoc* test. $P < 0.05$ was considered statistically significant. **Results:** Our findings revealed that insulin resistance prolonged escape latency of untreated diabetic rats; contrariwise, curcumin significantly reduced escape latency, increased difference score in novel object recognition paradigm, and increased explorative activities. **Conclusion:** Oral curcumin improves exploratory activity, discriminating memory, and spatial memory in male Wistar rats with AD-like neurobehavioral impairments. Patients with neurobehavioral abnormalities and comorbid insulin resistance may benefit from the flavonoids in curcumin.

Keywords: *Alzheimer's disease, curcumin, insulin resistance, metabolic disorder, neurobehavioral deficits*

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Introduction

Diabetes mellitus is a serious problem of insulin control that is endemic. It is a huge public health concern.[1] According to estimates, there are around 171 million diabetics globally (3% of the population). The World Health Organization projected that 1.5 million fatalities were caused by type 2 diabetes mellitus (T2DM) in 2021 and that there will be 300 million diabetics globally by 2025.[2] Estimation of T2DM in Nigeria was reported[3] to be 5.77%, which translates to about 11.2 million Nigerians; they also found the highest regional frequency in the South–South region and the lowest regional prevalence in Nigeria's North-Western region. This epidemic is exacerbated by the fact that T2D is becoming more common in young people, defying the popular belief that it only affects persons over the age of 30 years.[4]

Poorly managed diabetes leads to complications and adverse damage in various organs in the body, notably in the heart, kidney, liver, eye, and blood vessels, where diabetic complications have been well documented and widely studied. In addition, are the less reported nervous complications with varying degrees of neurobehavioral deficits ranging from mild cognitive impairment to more adverse neurodegenerative diseases such as dementia.

Dementia is a brain disorder defined by a loss of intellectual ability severe enough

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to impede with either occupational functioning or normal social activities.[5] It is one of the several neurological consequences of poorly treated diabetes.[5] A report from several studies suggests that patients with diabetes have a 50%–75% increased risk of developing Alzheimer's disease (AD), and 80% of AD patients have either T2DM or impaired fasting blood glucose.[6] The Alzheimer's Association 2021 reported that one out of three seniors in America dies with AD or another dementia; AD kills more people than breast and prostate cancers combined; AD and dementias death in the US increased by 16% during the COVID-19 pandemic. The financial burden of AD and other dementias is about $355 billion and this figure is projected to rise to $1.1 trillion by 2050 if the solution is not proffered to this public health concern.[7]

Mitochondria dysfunction, oxidative stress, inflammation, dysregulated immunology, poor neuronal–glial communication, and an increase in neurotoxic chemicals are all factors that cause neuronal death in AD.[8] Amyloid-beta (Aβ) pathology characterized by the aggregation of insoluble (Aβ plaques) and tau pathology characterized by the formation of neurofibrillary tangles (NFTs) due to hyperphosphorylation of tau protein are the pathological hallmarks of AD.[8] According to mounting evidence, abnormal forms of tau protein damage neuronal structure and, as a result, neuronal function, resulting in neuronal cell death. According to growing evidence, aberrant forms of tau protein harm neuronal structure and function, leading to neuronal cell death. Tau proteins typically associate with tubulin to stabilize microtubules and aid vesicular transport. NFTs are hyperphosphorylated and aggregated forms of tau proteins. Tau becomes insoluble and loses its affinity for microtubules when it is hyperphosphorylated, resulting in neurodegeneration.[8]

Insulin resistance enhances age-related memory deficits and is a risk factor for AD, according to numerous studies. However, the biochemical and cellular connection between insulin resistance and AD is uncertain. In the same way that poor insulin function has been increasingly documented in T2D, decreased brain insulin levels/action may be a relationship between the two disorders.[1]

The role of metabolic abnormalities in the etiology of AD has been investigated. Glucose balancing is the most important of them, as it is involved in energy maintenance, energy utilization, neurogenesis, neuronal survival, and synaptic plasticity, all of which are essential for learning and memory. In the insulin-resistant condition, cellular sensitivity to insulin is diminished, resulting in hyperinsulinemia, which impairs insulin signaling and contributes to the etiology of AD. Neuroinflammation, oxidative stress, accumulation and aggregation of Aβ, and cell death are all signs of the steady but progressive neurodegenerative changes characterized in AD.[9] Treatments that control insulin resistance have been shown to reduce Aβ buildup in the brain of both human and animal models. As a result, therapeutic techniques that efficiently regulate insulin resistance will be of considerable assistance in AD, perhaps opening up a window of opportunity for the long-awaited permanent solution to the problem.[9]

The flavonoid; curcumin, which is found in the commonly consumed turmeric, has been shown to many positive effects.[10] It is thought to act as a neuroprotective agent by regulating neuronal insulin signaling and glucose metabolism.[10] Curcumin poses as a good candidate in our quest to identify a good, safe, readily available and affordable therapy to neurobehavioural defects in the insulin resistant state of T2DM, hence our study sought to evaluate the effects of curcumin on exploratory, discriminatory, and spatial cognitive indices in an insulin resistant rat model.

Materials and Methods

The postgraduate ethical review committee of the university granted ethical approval with the number (UERC/ASN/2016/654) for this study. A total of 36 adult male Wistar rats *(Rattus norvegicus)* weighing 170 g ± 30 and of about 15 weeks old were employed in this investigation. The rats were kept in cages with a 12-h light/dark cycle and normal room temperature/humidity, as well as free access to regular rat pellets, high-fat diet (HFD), and water. The rats were put into six groups, each having six rats.

Experimental design

After acclimatization, the animal models received the following treatments; control group rats received 1 ml olive oil; the curcumin group received 200 mg/kg BW curcumin; the diabetic/insulin-resistant model administered HFD for 60 days, then three doses of 40 mg/kg BW of streptozotocin (STZ); the protective group were administered HFD for 60 days, then exposed to three doses of 40 mg/kg BW of STZ as well as a concurrent treatment with 200 mg/kg BW curcumin all within 60 days; preventive group rats received pretreatment of 200 mg/kg BW of curcumin, followed by HFD for 60 days and three doses of 40 mg/kg BW of STZ; the therapeutic group rats were administered HFD and exposed to three doses of 40 mg/kg BW of STZ within 60 days followed by treatment with 200 mg/kg BW of curcumin for 21 days; All STZ treatments were done via the intraperitoneal route, whereas curcumin and HFD were administered orally.

After all treatments, the rats were fasted overnight, blood was taken from their tail veins, and the fasting blood glucose level was measured with a digital glucometer (Accu-Chek, Roche, Belgium). Diabetic rats were included in the study if their fasting blood glucose levels were <200 mg/mol.

Rats were subjected to memory tests 24 h after treatment completion in each group, exploratory behaviors were assessed using line crossing frequency and center line

crossing frequency, and novel environment behavior was assessed using rearing frequency, all of which are components of the open-field test conducted according to the methods of Gould *et al*.[11] The novel object recognition was evaluated according to the methods described by Lueptow,[12] and the Morris water maze test as described by Bromley-Brits *et al*.[13] was used to assess discriminating and spatial memory. Plasma glucose was measured with blood glucose meters using the glucose oxidase method and insulin concentrations in the blood were estimated using enzyme-linked immunosorbent kit (eBioscience, Inc., USA) according to the manufacturer's instructions.

Statistical analysis

The data were evaluated using a one-way analysis of variance; afterward, Tukey's *post hoc* test was conducted and the values were presented as mean ± SEM. $P < 0.05$ was considered statistically significant. Tables and bar charts with error bars were used to display the mean and standard error of the mean, respectively.

Results

The results from our study revealed [Table 1] a significant increase in the weight and weight difference of rats in the diabetic and protective group relative to the olive oil group; curcumin reduced the rate of body weight change in rats that received a pretreatment of it and after the model was created ($P \leq 0.05$).

Blood glucose levels

Figure 1 revealed a significant increase in blood glucose in diabetic rats, the protective group, and the preventive group (225.3 ± 45.59, 200.8 ± 31.76, and 223.3 ± 51.41), whereas a significant decrease compared to the diabetic rats was recorded in the therapeutic group with (154.0 ± 51.86) ($P \leq 0.05$).

Homeostatic model assessment–insulin resistance values across the groups

Figure 2 showed that olive oil and curcumin only group recorded (5.33±0.48 and 5.85±0.53 respectively), a significant increase was recorded in diabetic rats with (14.89±1.01), while a significant reduction relative to the diabetic group observed in the therapeutic group (7.20±1.48) ($P \leq 0.05$).

Line and center line crossing frequency

Figure 3 reveals that Control rats present with line crossing frequency 45.00±5.29. There was a significantly lower exploration in the diabetic rats; however, therapeutic group rats recorded increased explorative activities with line crossing 33.00±9.64. Similarly a significant increase in center line crossing was observed [Figure 4] in the Protective and Therapeutic group rats, while a significant decrease in center line crossing was observed in the untreated diabetic rats compared to the controls and therapeutic group rats ($P < 0.05$).

Rearing frequency

Figure 5 indicated that STZ+HFD reduced the rearing frequency in the rat model, olive oil treated control rats recorded a rearing frequency 14.00±1.00, curcumin treated control presents with 12.67±1.53, while a significant increase relative to diabetic group was recorded in therapeutic group rats 12.67±1.15 ($P < 0.05$).

Escape latency

In Figure 6, it was observed that the diabetic rats showed significantly increased escape latency (41.30 ± 9.04) compared to control rats (22.46 ± 9.80). Conversely,

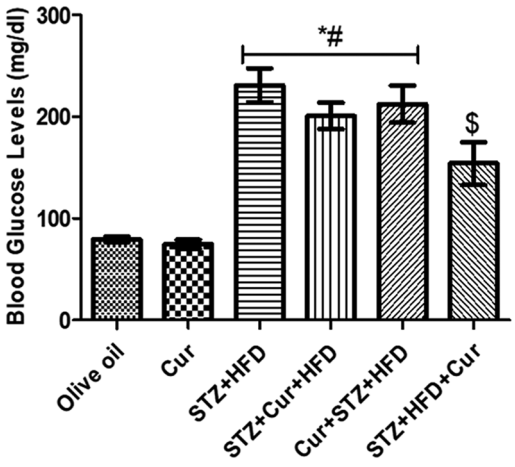

Figure 1: Effect of curcumin on the blood glucose levels in HFD + STZ-induced insulin resistance. Fasting blood glucose levels showed a remarkable reduction in the therapeutic group when compared to the untreated diabetic rats. "$" compared to the STZ + HFD group, "#" compared to the Cur group, and "*" compared to the olive oil group. STZ = Streptozotocin, HFD = High-fat diet, Cur = Curcumin data were mean ± SEM ($P < 0.05$) $n = 6$

Table 1: Comparison of weight change across the different groups, weight differences (g)

Groups	Initial weight (g)	Final weight (g)	Weight difference (g)
Negative control (olive oil)	147.40±8.58	177.57±6.19	29.83±1.22
Positive control (curcumin)	156.88±6.92	184.28±8.22	28.66±3.50
Diabetic group (STZ + HFD)	158.13±8.35	203.71±7.53*	45.16±1.98
Protective group (concurrent STZ + HFD + Curcumin)	147.65±4.92	185.40±3.47*	37.83±2.38
Preventive group (curcumin + STZ + HFD)	139.44±7.37	172.18±5.36	32.66±0.94
Therapeutic group (STZ + HFD + Curcumin)	156.28±2.41	188.41±3.68	31.33±2.18

Values are expressed as mean±SEM showing the level of significance in *$P<0.05$ compared to the negative control group. SEM: Standard error of mean, HFD: High-fat diet, STZ: Streptozotocin

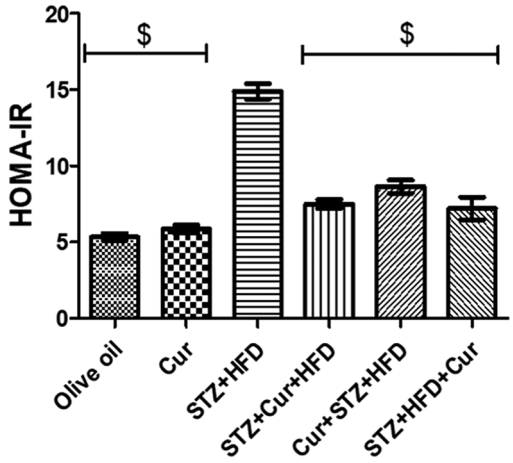

Figure 2: Effect of curcumin on homeostatic model assessment of insulin resistance (HOMA-IR) in HFD + STZ-induced Wistar rat model HOMA-IR index was highest in the untreated diabetic rats relative to the controls and the curcumin treated with significantly lower index values. "$" compared to the STZ + HFD group, STZ = Streptozotocin, HFD = High-fat diet, Cur = Curcumin, data were mean ± SEM ($P < 0.05$) $n = 6$

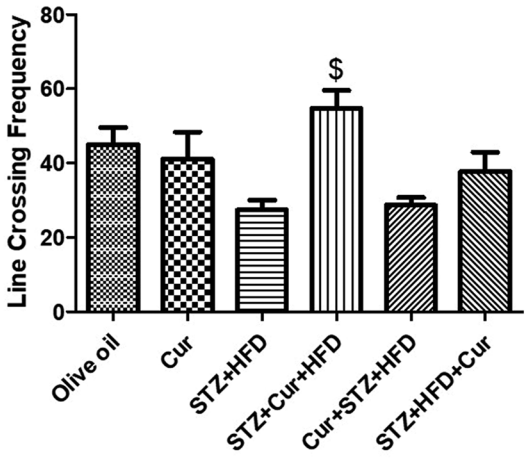

Figure 3: Line crossing frequency. The frequency of line crossing was reduced in the diabetic rats relative to control. Concurrent, pre-, and posttreatment with curcumin increased the line crossing frequency in curcumin-treated rats compared to the untreated diabetic rats. "$" compared to the STZ + HFD group. STZ = Streptozotocin, HFD = High-fat diet, Cur = Curcumin, data were mean ± SEM ($P < 0.05$) $n = 6$

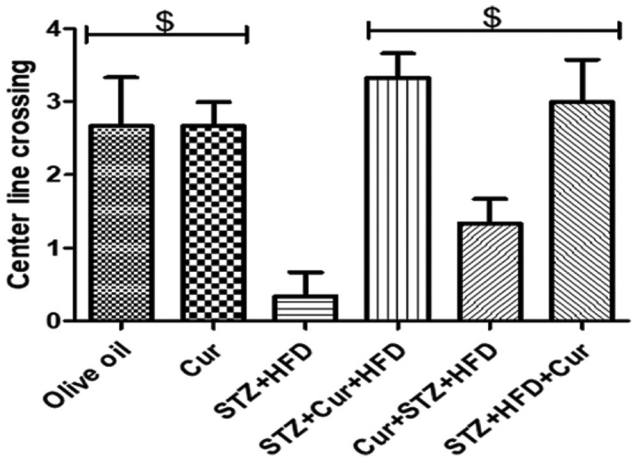

Figure 4: Center-line crossing. Center-line crossing frequency significantly increased in rats that took curcumin intervention relative to the untreated diabetic rats which recorded decreased explorative activities when compared to the control. "$" compared to the STZ + HFD group. STZ = Streptozotocin, HFD = High-fat diet, Cur = Curcumin, data were mean ± SEM ($P < 0.05$) $n = 6$

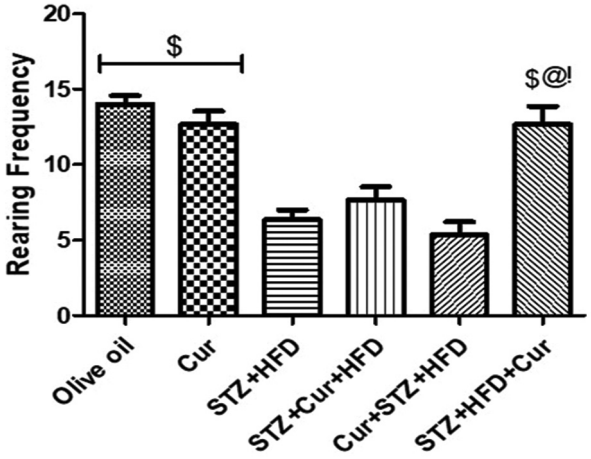

Figure 5: Rearing frequency. The frequency of rearing was observed to have decreased in the untreated diabetic/insulin-resistant rats relative to the control and therapeutic group rats. "$" compared to the STZ + HFD group, "!" compared to the Cur + STZ + HFD group and "@" compared to concurrent STZ + HFD + Cur group, STZ = Streptozotocin, HFD = High-fat diet, Cur = Curcumin, data were mean ± SEM ($P < 0.05$) $n = 6$

curcumin treatment significantly reduced the escape latency ($P < 0.05$).

Difference score in novel object recognition test across the groups

Figure 7 indicated that control rats recorded 11.33±3.57; a significant decrease in difference score relative to the controls was recorded in the untreated diabetic rats -4.32±1.528. Protective and Preventive group rats recorded 5.00±1.03 and 6.47±4.22 respectively, while a significant increase was recorded in the therapeutic group 11.32±4.51 ($P < 0.05$).

Discussion

Insulin resistance in diabetes mellitus is associated with a marked increase in blood glucose and a compensatory increase in insulin secretion but is devoid of insulin sensitivity and action. This increase in secretion leads to a cascade of events that prompt the promotion of metabolic imbalance and obesity. Obesity is consistent with the observed increase in body weight of our untreated diabetic/insulin resistant model; this finding is consistent with earlier reports from the work of Akbari and colleagues.[14]

Observable behavioral changes were investigated in this study employing various memory paradigms. STZ and

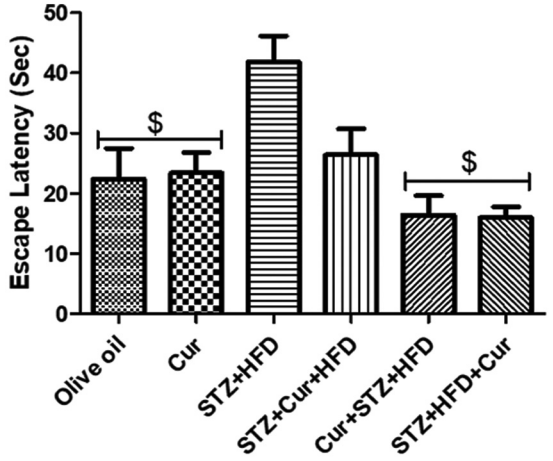

Figure 6: Escape latency. Effects of curcumin on spatial memory were evaluated, STZ + HFD treated rats showed weaker spatial memory performance relative to the control and the curcumin-treated rats. "$" compared to the STZ + HFD group. STZ = Streptozotocin, HFD = High-fat diet, Cur = Curcumin, data were mean ± SEM ($P < 0.05$) $n = 6$

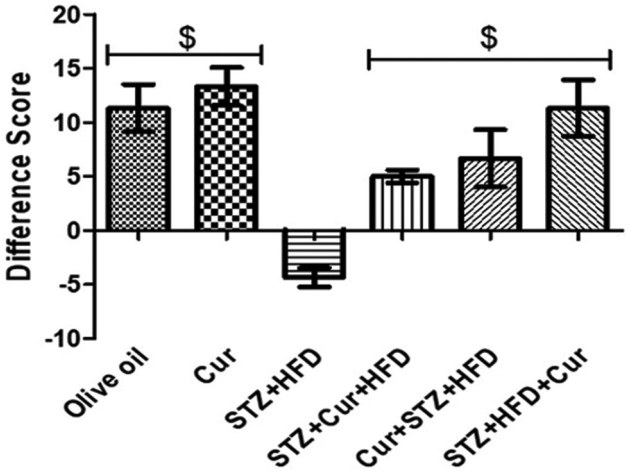

Figure 7: Difference score. The untreated diabetic rats recorded a negative figure difference score. "$" compared to the STZ + HFD group. STZ = Streptozotocin, HFD = High-fat diet, Cur = Curcumin, data were mean ± SEM ($P < 0.05$) $n = 6$

HFD reduced exploratory activities of rats in an open field test where line crossing frequency was measured without curcumin intervention. Compared to the control and curcumin-treated diabetic rats, there was a decrease in the frequency of line crossing in the untreated diabetic rats [Figure 3]. The data from this study on center line crossing [Figure 4] indicate a significant decrease in center line crossing in STZ and HFD exposed rats compared to the control and diabetic rats treated with curcumin.

While contrasting the rearing frequency of rats across the treatment groups, [Figure 5] showed that rats treated with olive oil only, curcumin only, and STZ, HFD start, followed by curcumin had a high frequency of rearing. This novel environment exploratory behavior in rodents depicts comfort and willingness to explore a new environment, while the untreated diabetic rats had reduced rearing frequency which suggests behavioral deficits caused by the deleterious effects of STZ and HFD.

Our evaluation revealed that spatial memory in untreated diabetic rats was impaired [Figure 6], contrary to the observed in the control and curcumin treated model where spatial memory was intact and no impairment; their shorter escape latencies compared to STZ and HFD exposed rats gives credence to this. These findings confirm the findings of Johansson and co-researchers,[8] who reported depression, and disturbances in drive and emotions in a translational study of mild behavioral impairment with a marked increase in tau deposition.[8]

Our study reported a link between recognition memory and insulin resistance, as indicated in [Figure 7] which shows rats from different groups had similar exploratory inclinations toward the same objects during the training phase. However, relative to the STZ and HFD exposed rats, the control and curcumin-treated rats identified the novel place and item from the familiar one in the testing phase.

Our findings suggested that curcumin administration improved spatial memory and cognitive function in diabetic rats with HFD and STZ-induced neuronal loss compared to untreated diabetic rats with HFD and STZ-induced neuronal loss, as earlier reported.[1]

In similarity to documented literature, our recent findings confirm that amyloid pathology and tau hyperphosphorylation in the AD model caused neuronal death and subsequent loss of synaptic plasticity, which could explain the reduction in recognition memory and poor cognition seen in untreated diabetic rats. The findings of our study show that curcumin is helpful in improving memory and correcting cognitive impairment and neurodegeneration in the insulin-resistant/hyperglycemic state as earlier reported by Ghorbani *et al*.[15]

Our findings showed that curcumin was able to enhance exploration and ameliorated the deficits initiated by STZ and HFD. These results build on evidence earlier reported by Yow and colleagues[15] which indicated that curcumin exerted ameliorating effects on anxiety and restored non-spatial recognition memory impairment induced by kainic acid. Hence, curcumin improved the reported deficits in a rat model of chemo-convulsant-induced epilepsy.[16]

Isik *et al*.[17] similarly conveyed the viewpoint that curcumin could halt oxidative injury and cognitive decline connected to aging by modulating the activities of various molecular targets, such as transcription factors, different enzymes, cell cycle proteins, receptors, and various adhesion particles.[15] This demonstrates that Alzheimer-like impairments and insulin resistance resulted in a significant decrease in exploratory and motor activities in rats, while curcumin treatment was able to mitigate the negative

effects and restore normal behavioral characteristics. These findings are similar to those reported by Yow *et al*.,[16] where curcumin was found to improve locomotor and exploratory activities in a rat model of epilepsy-induced with kainic acid.[16]

Curcumin was able to assist in keeping spatial and nonspatial memory intact in the animals that had curcumin intervention. This finding is similar to that of Yow *et al.* and Isik *et al.,*[16,17] where curcumin was able to exert the same memory retention effect in models of depression and epilepsy, respectively.

STZ-treated animals in the test phase traveled a substantially greater distance to the platform than controls, according to previous reports. The untreated diabetic model traveled a more confusing path to the escape platform[17] and spent much fewer seconds in the target quadrant with the escape platform than the model from the other groups. However, curcumin-treated models searched the escape platform for a significantly longer time in the target quadrant with the escape platform than STZ-treated animals.[17] Summarily, Choudhary and others reported that Intracerebroventricular administration of STZ caused a decline in spatial memory retention in their studied rat model, and similar to our findings they concluded that curcumin was able to alleviate the deficiencies.[18]

Conclusion

Curcumin played an ameliorative role against neurobehavioral deficits caused by streptozotocin and a HFD in the insulin-resistant animal models. Curcumin was able to promote memory retention and reduced escape latency, increased discriminative memory, and explorative deficits observed in the untreated diabetic/insulin-resistant rats.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

The authors confirm that this research work was done in compliance with approval from the University ethical review committee. The postgraduate ethical review committee of the University of Ilorin granted ethical approval for this study with the number (UERC/ASN/2016/654).

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Conflicts of interest

There are no conflicts of interest.

Author contribution subject and rate

- Abdullahi Abiodun Mohammed (50%): Design the research, data collection, analyses, and wrote the whole manuscript.
- Oluwole Busayo Akinola (50%): Supervised the research, Design the research, contributed with comments on research design and manuscript.

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Original Article

Uskudar Life Meaning and Goals Scale Validity and Reliability Studies

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Abstract

Aim: One of the important factors that cause stress today is aimlessness. Determining the meaning and purposes of life has an impact on both the mental and physical health of the individual. Two types of values are mentioned as tool values and purpose values. Measuring the life goals to include these values is seen as important for determining the life goal skills of individuals. Hence, it is aimed to measure meaning and purpose and to measure perceptions about it. **Materials and Methods:** This study aimed to carry out validity and reliability studies of the Uskudar Life Meaning and Goals Scale (USLIFE). The sample consisted of 1026 people from Turkey. Factor analysis revealed that the scale consists of seven factors. **Results:** The first factor "Abstract Meaning Skill" explains 14.59% of the variance, the second factor "Skill to Delay of Gratification" 10.31% of the variance, the third factor "Concrete Meaning Skill" 8.97% of the variance, the fourth factor "Internal Control Skill" 5.53% of the variance, the fifth factor "Medium- and Long-Term Planning Skill" 4.60% of the variance, the sixth factor "Belief in Death" 4.39% of the variance, and the seventh factor "Ego Ideal Perception" explains 3.87% of the variance. The seven-factor structure consisting of 28 items in total explained 52.28%. In addition, seven factors confirmed the USLIFE in the confirmatory factor analysis. Goodness-of-fit values were found to be acceptable. The Cronbach's alpha value of the scale was found to be 0.74. **Conclusion:** A valid and reliable scale, named "USLIFE," has emerged. This scale measures people's life goals skills and is graded in the five-point Likert type between "completely agree" and "never agree."

Keywords: *Life goals, life skills, scale, validity and reliability*

Introduction

One of the important factors that cause stress today is aimlessness. Determining the purposes of life has an impact on both the mental and physical health of the individual. It is important to create goals worth living for in psychology. Values that bind people to life, and values are the course of life goals.

Values guide our behavior and we try to understand others in line with values. Values are common concepts accepted by society as a whole.[1] It is also expressed as a cognitive representation of needs.[2,3] Although their behavior can be directed, it guides how people behave as high-level structures that do not depend on the situations that exist at the time.[4,5] In this context, if the person has adopted a value that contradicts himself, he does not conform to himself and may experience conflict. Thus, in order for the values to bring happiness, the person is expected to adopt values that are compatible with the person and the society in which he lives, which eliminates conflict or incompatibility within himself.[6]

Moral reasoning has an important place in one's decision-making. This type of reasoning includes three degrees. The most basic is that the person determines their decisions by considering the recent results. In this type of decision-making, the individual aims to save the existing day by considering his comfort at the moment. Average Moral reasoning includes social order, responsibility, and abstract thinking. The third species is based on more advanced thinking and aims to be altruistic, fair, and not to harm others.

Today, many researches are carried out on the value system of young individuals focusing on academic success.[7-11] In these researches, business life, perspectives on life, tolerance to differences, marriage, and

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family life perspectives are examined and it is discussed whether values are fully formed in young people.[12,13] However, studies have been found that emphasize that the value system has evolved into the online value system with the effects of social media.[14,15]

When the field article is examined, intelligence quotient (IQ) is considered important for scientific gain, emotional quotient (EQ) is considered important for life gain, and it is stated that EQ is learnable.[16] As a science aimed at gaining life, positive psychology operates based on people's own will, purposes, and values in the society in which they live and supports the EQ of people with a high IQ.[17] Thus, individuals with individual consciousness with EQ, which translates values into gains, can make sense of the society they live in from a spiritual point of view, regardless of the brain–mind spiral.

On the other hand, if anomie (normlessness) occurs in a society, social conflicts occur. This is due to the need for each individual to continue their life depending on the society. This demonstrates that values are vital and need to be supported with EQ.[18,19] Accordingly, EQ affects life goals and psychological well-being along with values.

Although the fact that individuals who are committed to the purpose they think that they can achieve their goal and they want it indicates a saturated life, it is not a guarantee of purely psychological well-being.[20-22] In one study, it was investigated which types of life goals lead to increased or decreased individual well-being, and the objectives are divided internally and externally. Accordingly, the purposes such as contribution to society, individual development, interpersonal communication, and physical well-being are "internal;" popularity, influence, and wealth are "external" purposes. In the research, it was found that internal objectives have a high level of self-esteem and self-realization from the parameters of individual well-being and positive, negative relationship with depression and anxiety. When the effect of external purposes on individual well-being was examined, a negative relationship emerged.[23] Subsequent research supported these results.

However, psychometric scales are also needed to measure the existing situation in determining values and life goals. When the measurement tools are examined, it is noted that the number of scales that can measure the life goals that take into account the cultural values of our country is descendent. When the field is examined, the Life Goals Scale (LGS) developed by Ilhan in 2009 is found. The scale of seven-point Likert consisting of 47 items consists of two upper factors and has nine sublevels; the internal coefficients of consistency of LGS are in the range of 0.74–0.90 for subdivisions and, when looking at the upper dimensions, are set at 0.85 for the inner and 0.77 for the external.[24]

On the other hand, there is a "LGS" in Scales of Psychological Well-Being, which was developed by Ryff in 1989 and adaptation to Turkish by Akin in 2008, consisting of a combination of six scales.[25,26] For the scale of six-point Likert, which has 14 expressions of each dimension and consists of 84 items, the reliability of the subscale of life purpose, i.e., the coefficient of internal consistency, was found to be 0.90. A study by scale found that as adolescents' self-esteem levels rise, their life purpose and positive relationships with others increase.[27]

Another scale, "Adolescent Form of Determining Life Goals in the Context of Positive Psychotherapy (PPYABÖ)," was developed by Eryilmaz in 2010 in the context of positive psychotherapy and on high school students.[28] The measuring tool is used to determine the life goals of adolescents in different departments and is rated as type of four-point Likert. The scale consists of three dimensions: success (career) objectives, relationship objectives and body (sensation) objectives, and Cronbach's alpha value of all sizes ranges from 0.68 to 0.85. In later years, the scale was also valid and reliable for university students by the researcher.[29]

In addition, the "LGS" developed by Aydiner in 2011, consisting of 31 items and 5 dimensions, is found in the literature.[30] Validity and reliability studies are shown to be "Personal Development," "Funds Gain," "Physical Appearance," "Social Responsibility," and "Individual Awareness." LGS five-point Likert (none, some, partly, much, and very much) types and contains plain expressions.

Tarhan (2015) refers to two types of values as tool values and purpose values, and therefore, the necessity of establishing measuring instruments to cover this context has arisen. Objective values indicate more abstract objectives in a person's life. Tool values are a way to achieve their goals in the life of the person. Although the objective values can be classified in themselves, they have virtues such as love, trust, being compassionate, enjoying doing goodness, having social boundaries, being honest and fair, being tolerant and peaceful, and sharing. Tool values are values that eliminate negative emotions such as being organized, congratulating success, saying nice words, showing relaxing, and relaxing qualities that are appropriate by others, trying to do the job, being canny, being soft and flexible in the face of situations, being polite to people, and making appropriate comments that are not considered wrong. On the other hand, considering that values are universally and culturally divided, it is clear that the values of this means and purpose will vary from culture to culture and even from nation to world. From this point on, measuring the life objectives to include these values is seen as important for determining the life goals skills of individuals.

When the field of young generations in our country and abroad is examined, research on generations and values

abroad does not reflect our country. Accordingly, it is stated that differences are arising from socioeconomic and cultural conditions in our country and even these differences are observed from school to school.[31] In fact, a study has found that people born in 1981 and beyond in our country have different expectations in terms of their career prospects than people in other countries.[32]

For this reason, it is seen that the scales of life objectives with limited dimensions are developed or adapted with scales aimed at measuring values in different fields such as work life, school life, and family life in our country to understand individuals at the micro-level.[33,34]

With this research, it is aimed to develop the multidimensional Uskudar Life Meaning and Goals Scale (USLIFE), which covers the objectives and tool values in question and is aimed at determining the life goals of the person.

Materials and Methods

The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee (61351342/April2021-27).

USLIFE was built up from people aged 15 and over for validity and reliability studies. In this context, the sample of the study was established from 1026 people over the age of 15 reached through the Internet throughout Turkey. Since scale development studies will be carried out, various opinions indicated in the field have been examined for the suitability of the data set for factor analysis. Accordingly, there is an opinion that the sample size can be between 100 and 250. Or it may be at least five to ten times the number of items in the scale.[35,36]

Considering that the scale consists of 28 items in the study, the number of 1026 samples is quite sufficient. In addition, 68.3% of the 1026 participants were women and 31.7% were men. When the age distributions are examined, the youngest of the participants is 15, the eldest is 71, and the average age is 33.

Measurement instruments

Uskudar Benevolance and Malevolance Scale

The Uskudar Benevolance and Malevolance Scale (USBEMA) consists of 35 items and 2 factors, developed by Tarhan and Tutgun-Ünal.[37] The first factor "Purpose Oriented" explains 35.2% of the variance and the second factor "Process Oriented" 7.9% of the variance and 35 items in Total scale explains 50.6% of the variance. In addition, two factors confirmed the USBEMA in the confirmatory factor analysis (CFA) (Chi-square/degrees of freedom: 3.38; RMSEA: 0.06; NFI:0.93; NNFI: 0.93; CFI: 0.96; GFI: 0.93; AGFI: 0.86). The internal consistency coefficient (α) of the scale was found to be 0.92. It has been developed to measure benevolence and malice toward purpose and process, and it is to measure honesty, keeping one's word, accountability, taking shelter in a transcendent power, empathy, being able to love and benevolently, patience and suffering, virtuousness, and concern for fair and equitable sharing. In the criteria validity study of USLIFE developed in this study, it was used considering that it may be associated with USLIFE.

Uskudar Life Meaning and Goals Scale

For the USLIFE validity and reliability studies, expert opinions were first obtained by generating a pool of items, and then, the content validity of the scale, structure validity with factor analysis, the discriminant validity analysis, and internal consistency reliability were made.

As a result of the examination of the article field of the material pool of the scale, it was built with the headings "Tangible Semantic Skills," "Belief in Death," "Skill to Delay of Gratification," "Abstract Semantic Skill," "Internal Control Skill," "Medium- and Long-Term Planning Skills," and "Perception of Ego Ideal" and items were produced within the scope of the objectives and tool values related to the subject under these headings. Thus, an expert opinion inventory of the scale consisting of 28 items was built and presented to the opinions of six experts. To evaluate the candidate items in the expert opinion inventory, the options "Item is appropriate to remain on the scale," "Item may remain on the scale but is unnecessary," and "Item is not appropriate to remain on the scale" are included. To include interdisciplinary opinion, the expert pool was composed of two academicians from each of the fields of psychology and psychiatry and two experts from communication sciences, and the inventories were sent to the experts via E-mail. Subsequently, with the help of the formula proposed by Miles and Huberman, the compliance rates of the items were calculated.[38]

Compliance rates are calculated using the ratings in the inventory for each item. Accordingly, it was noted that the relevant article did not descend below 0.80 by scoring between 0 and 1. In addition, in line with the opinions of the experts, the articles were reviewed and arranged in terms of spelling and grammar.

The 28-item candidate scale was rated from the lower level of "I do not agree at all" to the "I agree at all" level in the type of Likert without the article being eliminated after expert opinions and distributed to the participants via an online survey according to the principle of voluntariness in March 2021. After the data collection phase, the Explanatory Factor analysis (EFA) phase was started.

EFA is often applied as one of the statistical calculation techniques performed following a large number of variables within the scope of the structural validity of scale development. Bartlett test and Kaiser–Meyer–Olkin (KMO) test specified in the literature were applied to determine whether the data collected before EFA were

made met the conditions of factor analysis. KMO is rated as "excellent" to be 0.90 or above, "very good" to be in the range of 0.80–0.89, "good" to be in the range of 0.70–0.79, "medium" in the range of 0.60–0.69, "weak" in the range of 0.50–0.59, and less as "unacceptable."[39] In addition, the value of Bartlett sphericity is expected to make sense.

With EFA, which is made during the construction validity phase of the scales, the factor, in other words, the number of dimensions can be determined and self-worth statistics (eigenvalue) are used for this purpose. According to self-worth statistics, factors whose value is usually equal to or higher than 1 are taken into account.[40] If it is desired to create a distinction based on the subject, the researcher can determine the number of factors manually by empirical. It is ideal when the variance rate revealed by the factor analysis varies between 40% and 60% in social sciences. On the other hand, correlation values are looked at in the relationship of factors with each other and total in the building validity studies of the scale. When interpreting correlation values, while the range of 0.30–0.70 is "medium," it is stated that it indicates a "high" relationship above 0.70 and a "weak" relationship below 0.30.[41]

Differentiation validity studies are carried out to determine whether the items on the scales of the property to be measured are suitable and the item differentiation index is calculated. Accordingly, the answers given to each question are sorted as points and 27% of the upper group and subgroup are taken and the difference between the two groups is looked at by independent group *t*-test. The results reinforce the validity of studies by giving an idea of the internal consistency of the scale. Cronbach's alpha coefficients were calculated by analyzing the internal consistency of the item according to the item variances during the reliability studies phase. As a result of the studies, the validity and reliability of the USLIFE were revealed.

Implementation

Data collection was carried out from May 1 to 7, 2021, according to the principle of voluntariness through an online survey. The study group consisted of all individuals aged 15 and elder through randomly selected sampling. USBEMA and USLIFE were applied online to the participants. An average of 15 min to complete the applied survey was enough.

Data analysis

The USLIFE was divided into data sets for validity and reliability studies, and explanatory factor analysis (EFA), discrimination calculations, and reliability studies were carried out within the scope of structure validity on the 510-sample section. CFA was applied to the 516-sample section. In the discrimination validity studies, 27% of the upper group and subgroup were taken and the difference between the two groups was looked at by independent group *t*-test. The reliability coefficient of scales is determined by the value of Cronbach's alpha. SPSS 26.0 statistical program was used for all validity and reliability analyses. In addition, the AMOS program modeled for the interrelationship and compatibility of dimensions and calculated the value of goodness of fit (Chi-square/release value, RMSEA, NFI, NNFI, CFI, GFI, and AGFI).

Results

Validity and reliability studies of the Uskudar Life Meaning and Goals Scale

In this part of the study, evaluations were made for the USLIFE. Content validity of the scale, structure validity, discrimination validity, CFA, and reliability studies are contained within.

Content validity

USLIFE item pool was created from 28 items in the first stage and presented to expert opinions. Items were examined by six experts accompanied by an expert opinion inventory to include interdisciplinary opinions. After that inter rater reliability were calculated. Accordingly, the study looked at a compliance rate of 0.80 and found it appropriate that all 28 items remained on a draft scale. Thus, EFA was performed on 510 people of the data obtained by applying the 28-point draft scale to 1026 participants.

Structure validity-explanatory factor analysis

While AFA was made to determine the factor formation of the USLIFE, KMO coefficient and Bartlett sphericity test were examined whether the collected data complied with the factor analysis requirements. Accordingly, the KMO coefficient value was found to be 77.7. Bartlett sphericity test result found significant (X^2 = 3146,715, SD: 3.78, P = 0,000). Results showed the appropriateness of the data for factor analysis. In this direction, factor analysis was started with the 28-point draft scale obtained after expert opinions. After EFA was made, it was understood that it was in a seven-factor structure, since the self-worth (eigenvalue) was greater than 1 for the USLIFE. Accordingly, the highest 0.86 and lowest 0.45 for 28 items' factor loads were found. The explained variance rate was found as 52,288, which was to be understood to be acceptable. The eigenvalue of the factors in the structure that occurs as seven factors and the variance ratio explained are given in Table 1.

As shown in Table 1, the explanatory variance rate of the factor with equity of 4.08 is 14.59%. The variance rate of the second factor with an eigenvalue of 2.88 - 10.31%, the variance rate of the third factor with equity of 2.51 is 8.97%, the variance rate of the fourth factor with an eigenvalue of 1.55 - 5.53%, the variance rate announced by the fifth factor with equity of 1.28 - 4.60%, the variance rate of the sixth factor with equity of 1.23 - 4.39%, and the variance rate of the seventh factor with equity of 1.08 is 3.87%. The total variance rate was found 52.28%.

Another method is the screen pilot test for consider to determine the number of factors. The number of factors is determined by the changes in the points of slopes. The line chart of USLIFE, which appears to be seven-dimensional, is located in Figure 1.

After determining the number of factors, item factor loads were examined, the factor load value of the items was checked according to the conformity of the lower segment point to 0.44, and the factor structure was released. Accordingly, the item factor loads of the scale in the seven-dimensional structure are given in Table 2.

When the item factor load values were examined, the item load values of the seven-factor structure of the scale received appropriate values. Item factor load values were found to be highest 0.815 and lowest 0.447. In the next stage, the contents of the items are examined and the factors are given names.

Item sequences were taken into account when naming dimensions and the dimensions were reordered. Accordingly, the 11th, 19th, 20th, 22nd, 23rd, and 28th items have formed the first dimension and the items are evaluated in terms of content and the dimension is called "Abstract Meaning Skill." The 8th, 9th, 10th, and 17th items formed the second dimension. When the contents of the items are examined, it is understood that it is related to the "Skill to Delay of Gratification." The 1st, 2nd, 4th, and 26th items constitute the third dimension and are called "Tangible Semantic Skills." The 12th, 13th, 14th, and 15th items constituted the fourth dimension. By examining the contents, the dimension is called "Internal Control Skill." The 3th, 16th, 18th, and 27th items constituted the fifth dimension. Dimension is called "Medium- and Long-Term Planning Skills." The 5th, 6th, and 7th items constituted the sixth dimension, and when their contents were examined, it was found to be related to the "Belief in Death." Items 21, 24, and 25 constitute the seventh dimension. By examining the contents of the items, the dimension is called "Ego Ideal Perception."

On the other hand, in addition to building the items with positive expressions, some items should be recoded and evaluated in reverse code. Accordingly, it was found properly to evaluate the items of 1, 2, 5, 4, 5, 8, 9, 10, 12, 13, 14, 15, 17, 19, 20, 21, 23, 24, 25, 26, and 28 with reverse coding, and the items of 3, 6, 7, 11, 16, 18, 22, and 27 with direct coding on the scale. Respondents to the statements in the measurement tool will be scored by selecting the participation frequency statement rated from the "I do not agree at all" subfrequency level to the "agree at all" top frequency level (I do not agree at all: 1 point, totally agree: 5 points). In the next stage, the relationship of dimensions was examined and is shown in Table 3. When Table 3 is examined, it is seen that a correlation test is performed to understand the relationship

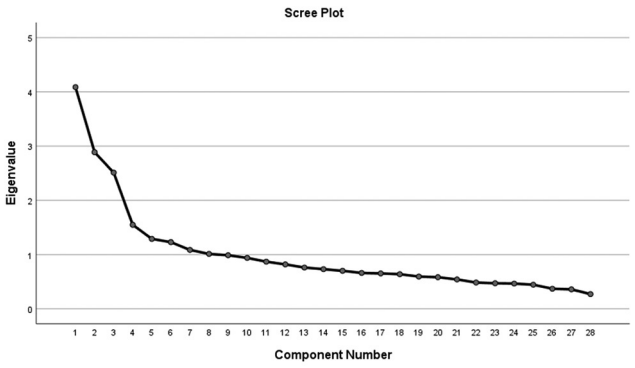

Figure 1: Screen pilot of USLIFE. USLIFE: Uskudar Life Meaning and Goals Scale

Table 1: Factor structure and explained variance rate

USLIFE	Eigenvalue	Variance	Cumulative variance
1st dimension	4.08	14.59	14.59
2nd dimension	2.88	10.31	24.90
3rd dimension	2.51	8.97	33.87
4th dimension	1.55	5.53	39.41
5th dimension	1.28	4.60	44.01
6th dimension	1.23	4.39	48.40
7th dimension	1.08	3.87	52.28

USLIFE: Uskudar Life Meaning and Goals Scale

Table 2: Factor load values of Uskudar Life Meaning and Goals Scale items

Item number	F1	F2	F3	F4	F5	F6	F7
M20	0.86						
M11	0.74						
M19	0.74						
M23	0.57						
M22	0.53						
M28	0.45						
M9		0.73					
M8		0.71					
M10		0.66					
M17		0.50					
M1			0.77				
M4			0.72				
M2			0.69				
M26			0.50				
M13				0.70			
M14				0.62			
M15				0.56			
M12				0.45			
M27					0.74		
M18					0.54		
M3					0.51		
M16					0.46		
M6						0.70	
M5						0.63	
M7						0.57	
M21							0.62
M24							0.59
M25							0.49

of dimensions with scale total. According to Pearson correlation coefficients, it was concluded that dimensions are moderately associated with the sum of scale ($r > 0.30$).

Discriminant validity

At this stage, item discriminant validity studies were carried out to determine whether the items on the scale measured the desired property. Data collected from 137 participants were sorted from large to small and difference tests were applied to data in the upper 27% and subgroups of 27%.

When Table 4 is examined, the results were found to be significant, and it was concluded that the USLIFE was a scale that measured the desired characteristics [Annexure 1]. Accordingly, the top score from the USLIFE is 140 and the minimum score is 28. The average score with 1026 participants was 104.

Convergent validity

At this stage, the relationship between the USBEMA and USLIFE, which is thought to be related to the validity of the criteria, has been tested. As shown in Table 5, a positively significant relationship was found.

Reliability studies

The Cronbach's alpha internal consistency coefficient of the scale was calculated in the scope of USLIFE's reliability studies and the Cronbach's alpha coefficient of the 28 items, which constitute USLIFE, was found to be 0.73. The resulting values showed an acceptable level of reliability of the scale. Thus, a valid and reliable "USLIFE" emerged. The internal consistency calculations of the USLIFE by dimensions and the scale total are in Table 6.

As shown in Table 6, the total Cronbach's alpha value was found 0.74 in the USLIFE which showed an acceptable degree of reliability. When the subscales were examined, the Cronbach's alpha value was found to be the lowest 0.54 and highest 0.75. Thus, the values taken by the dimensions also demonstrated acceptable reliability.

Confirmatory factor analysis

The goodness-of-fit values were tested by performing CFA with data set of 516 people following internal consistency coefficient calculations of factors and USLIFE total within the scope of structure validity of USLIFE, the relationship of factors with scale, and discriminant validity and reliability studies.

The model resulting from CFA performed in the AMOS program is given in Figure 2. Accordingly, the dimensions revealed by EFA are statistically verified and the results are in Table 7. Table 7 shows the goodness-of-fit index values of the USLIFE. Ki-square/release value according to the findings obtained in the validating factor analysis was found to be 3.38, RMSEA: 0.068, NFI: 0.93, NNFI: 0.93, CFI: 0.96, GFI: 0.93, and AGFI: 0.86. Thus, it is seen that these values meet the acceptable goodness-of-fit index values. It has been concluded that the USLIFE is verified by seven factors.

Table 3: Relationship of dimension to Uskudar Life Meaning and Goals Scale

Subscale/ scale	Tangible Semantic Skills	Belief in Death	Skill to Postpone Satisfaction	Intangible Semantic Skills	Internal Control Skills	Medium- and Long-Term Planning Skills	Ego Ideal Perception
USLIFE	0.45	0.43	0.46	0.72	0.57	0.30	0.55

USLIFE: Uskudar Life Meaning and Goals Scale

Table 4: Uskudar Life Meaning and Goals Scale's discrimination validity

Scale/dimensions	Group	*n*	X	SD	df	*t*	*P*
Tangible Semantic Skills	Upper group	137	17.98	1.59	272	41.88	0.00
	Lower group	137	9.68	1.68			
Belief in Death	Upper group	137	13.53	1.18	272	42.85	0.00
	Lower group	137	6.60	1.47			
Skill to Postpone Satisfaction	Upper group	137	18.26	1.10	272	38.43	0.00
	Lower group	137	10.67	2.02			
Intangible Semantic Skills	Upper group	137	28.53	1.17	272	47.03	0.00
	Lower group	137	15.51	3.01			
Internal Control Skills	Upper group	137	18.96	0.81	272	39.82	0.00
	Lower group	137	11.70	1.97			
Medium- and Long-Term Planning Skills	Upper group	137	18.08	1.10	272	35.28	0.00
	Lower group	137	11.20	2.00			
Ego Ideal Perception	Upper group	137	14.29	0.72	272	41.48	0.00
	Lower group	137	7.71	1.70			
USLIFE in Total	Upper group	137	117.31	5.39	272	42.41	0.00
	Lower group	137	87.83	6.10			

SD: Standard deviation, USLIFE: Uskudar Life Meaning and Goals Scale

Table 5: Convergent validity of Uskudar Life Meaning and Goals Scale

Scales	USBEMA
USLIFE	
r	0.72
P	0.00

USLIFE: Uskudar Life Meaning and Goals Scale,
USBEMA: Uskudar Benevolent and Malevolancy Scale

Table 6: Uskudar Life Meaning and Goals Scale and the reliability of dimensions

Scale/dimensions	Item number	Cronbach's alpha coefficient
Tangible Semantic Skills	4	0.70
Belief in Death	3	0.54
Skill to Postpone Satisfaction	4	0.63
Intangible semantic skills	6	0.75
Internal Control Skills	4	0.57
Medium- and Long-Term Planning Skills	4	0.58
Ego Ideal Perception	3	0.56
USLIFE	28	0.74

USLIFE: Uskudar Life Meaning and Goals Scale

Conclusion

The USLIFE is a measurement tool developed by researchers to measure individuals' life goals and meaning. Thus, in this study, it is aimed to measure whether there are goals that will add meaning to life and to measure perceptions about it. After validity and reliability studies, it was revealed that it consisted of 28 items and 7 factors, and the model built up from seven-factor structures was tested and verified with validating factor analysis.

The USLIFE is a five-point Likert scale, with the maximum score from the scale total being 140 and the minimum score being 28. Accordingly, the increase in the score taken from the USLIFE means that the individual's life-purpose skills increase.

To interpret the scores obtained from the USLIFE, the highest score and lowest score ranges that can be taken from the scale are determined and the range coefficients are calculated according to the five-point Likert scale. The total score taken from the scale is evaluated in terms of a person's life skills as "low level" in the range of 28–65 points, "intermediate level" in the 66–102-point range, and "high level" in the range of 103–140 points. The USLIFE has explained 52.28% of the total variance, which is considered acceptable for social sciences. Cronbach's alpha coefficient of internal consistency in reliability studies was found to be 0.74. Dimensions also provided internal consistency in themselves, and it turned out that USLIFE is a valid and reliable measuring tool. As a result of the CFA studies, the goodness-of-fit values of the scale were found to be at an acceptable level. Thus, it is thought that the USLIFE will provide detailed data with the seven-dimensional structure in which people involve in measuring life objectives. These dimensions are Tangible Semantic Skills, Belief in Death, Skill to Delay of Gratification, Intangible Semantic

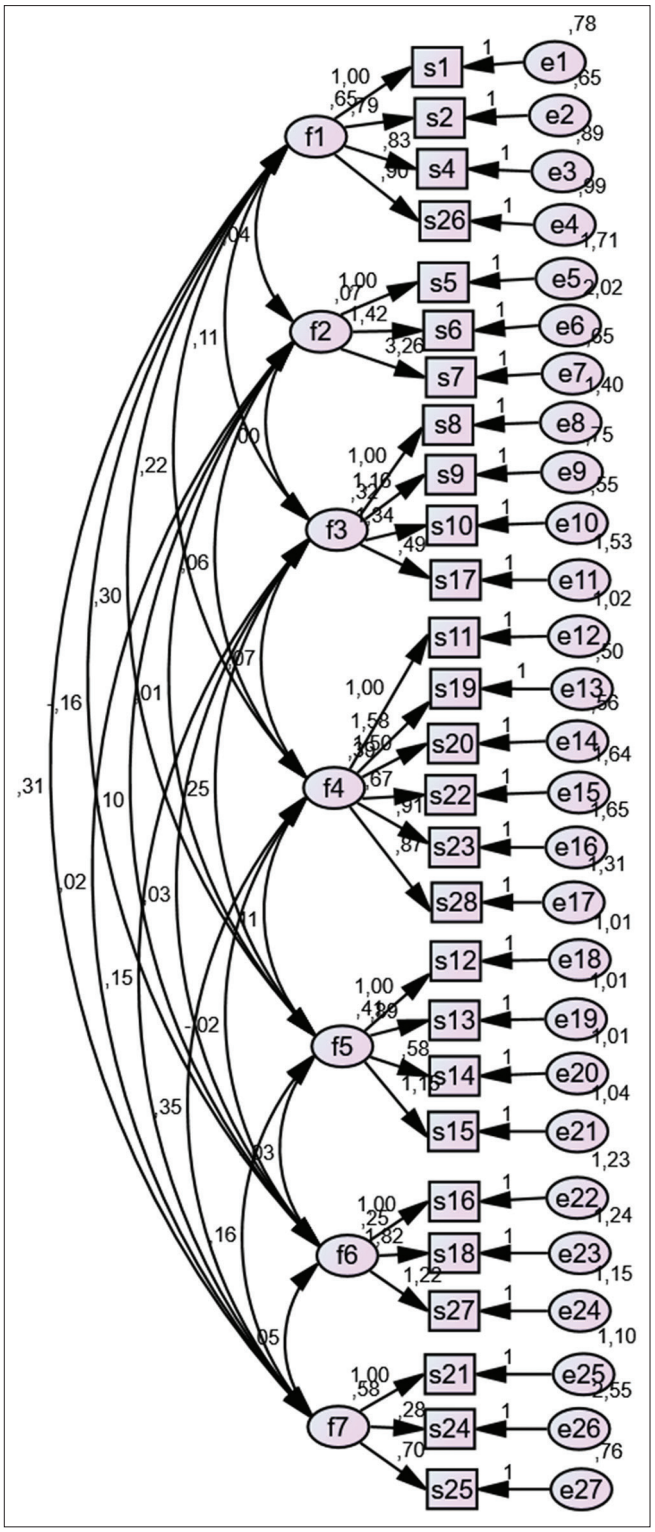

Figure 2: USLIFE's confirmatory factor analysis. USLIFE: Uskudar Life Meaning and Goals Scale

Table 7: Uskudar Life Meaning and Goals Scale of goodness-of-fit index

Goodness-of-fit index	Acceptable goodness-of-fit index values	USLIFE goodness-of-fit index values
χ^2/SD	<5	1024.821/303=3.38
RMSEA	<0.08	0.07
NFI	>0.90	0.93
NNFI	>0.95	0.93
CFI	>0.95	0.96
GFI	>0.90	0.93
AGFI	>0.85	0.86

SD: Standard deviation, USLIFE: Uskudar Life Meaning and Goals Scale, Chi-square/degrees of freedom: 3.38; RMSEA: 0.06; NFI:0.93; NNFI: 0.93; CFI: 0.96; GFI: 0.93; AGFI: 0.86

Skills, Internal Control Skills, Medium- and Long-Term Planning Skills, and Perception of Ego Ideal which are included in the scale and differ in this aspect from existing scales.

Although it is assumed that determining life goals shows a similar quality in the context of positive psychotherapy, the seven-dimensional structure of the USLIFE indicates that comprehensive results can be achieved when new dimensions are added. Thus, updating existing scales with new dimensions is seen as important for responding to new needs. It is thought that the USLIFE developed in the Turkish sample can be used in examinations with different variables in people aged 15 and over and will contribute to the literature with its multidimensional structure.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee (61351342/April2021-27).

Conflicts of interest

There are no conflicts of interest to declare.

Financial support and sponsorship

No funding was received.

Author contribution subject and rate

- Aylin Tutgun Ünal (%50): Design the research, data analysis and wrote the whole manuscript.
- Nevzat Tarhan (%50): Contributed with scale items, theoretical background and data collect.

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Annexure 1: Uskudar Life Meaning and Goals Scale

Item number	Items	Don't agree at all	Agree less	Moderately agree	Strongly agree	Agree at all
1	I dream of getting rich					
2	I dream of being famous					
3	My biggest wish is to be healthy first and foremost					
4	It is very important to have a position					
5	I don't care what kind of person I'm called after I die					
6	It's important to me what's written on my headstone after my life ends					
7	I pay attention to the steps I take to leave a good story behind					
8	I'd rather spend the day doing well than having trouble investing in the future					
9	When I face challenges, I don't push myself too hard, I change the subject					
10	I avoid targets that I will have difficulty with					
11	The concepts of "Flag," "Homeland," "God" are of great importance to me					
12	I like to wait for bigger gains, it is more important for me to get results immediately					
13	I can't control my passion for shopping					
14	I fall in love easily					
15	When I'm studying or getting bored doing a job, I quit right away					
16	When I'm doing things I don't like, I can keep thinking about what they're going to get me in the medium and long run					
17	I don't want to be in trouble to have more financially					
18	I dream of being an explorer, inventor, or Nobel laureate who benefits humanity					
19	For me, my own needs take precedence over national values					
20	For me, my own needs take precedence over religious matters					
21	It's more important to succeed in something I work for than human relations					
22	I believe in the saying, "The one who loves his country the most is the one who does his duty best"					
23	I'd rather not think about death and the afterlife					
24	I'd rather be admired and envied than useful to society					
25	If the goal is to be more successful and happy, it doesn't hurt to neglect my family					
26	I care a lot about other people praising me					
27	I like to take some risks and do new and different things					
28	My own happiness and desires are more important than many other things					

Items 1, 2, 4, and 26 are measuring dimensions of "Tangible Meaning Skills," 5, 6, and 7 dimensions of "Belief in Death," 8, 9, 10, and 17 dimensions of "Skill to Delay of Gratification," 11, 19, 20, 22, 23, and 28 dimensions of "Intangible Meaning Skills," 12, 13, 14, and 15 dimensions of "Internal Control Skill," 3, 16, 18, and 27 dimensions of Medium- and Long-Term Planning Skill," and 21, 24, and 25 dimensions of "Perception of Ego Ideal." The USLIFE is a self-assessment scale that measures a person's life meaning and goals skills and measures perceptions about it. The scale is suitable for applying to 15 years of age or older. Assessment: The total score taken from the scale is assessed as "low level" in the range of 28–65 points, "intermediate level" in the 66–102 points range, and "high level" in the range of 103–140 points. Notice: Items numbered 1, 2, 4, 5, 8, 9, 10, 12, 13, 14, 15, 17, 19, 20, 21, 23, 24, 25, 26, and 28 must be reverse-coded.
USLIFE: Uskudar Life Meaning and Goals Scale

Review Article

Evaluation of the Effects of Emotional and Violence-Related Genes in Athletes

Abstract

Investigation of the human genome involves the examination of many factors such as gene function, structural features of the genome, chromatin arrangement, recombination rate, and mutation to accurately understand its complex relationship with physiology and diseases. With the sequencing of the human genome, there is an increasing number of studies investigating the influence of genes during the development of behavior and personality traits. Studies show that complex behavior and traits are regulated by multiple genes. In this sense, genes that affect the dopamine pathway are studied in relation to the field of neuroscience. Studies on sports genetics include all of the studies in this field, such as the identification of genes that affect athletic performance, the elucidation of the mechanisms of action of these genes, and the determination of predispositions in terms of athletic performance. Considering the factors that determine success in sports, it is of great importance to create training and nutrition programs suitable for genetic structure not only in individual sports but also in team sports. This study will be presented as a review of the associations in the literature about catechol-O-methyltransferase, 5-hydroxytryptamine transporter, and monoamine oxidase, known in the literature as candidate genes that affect the personality and behavioral characteristics of athletes and are especially related to aggression.

Keywords: *Athletes, genetics, violence*

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Introduction

Violent behaviors in athletes can occur in different ways and the basis of these behaviors is frequently observed in competitions. When people who use violence in different societies are examined, it is seen that there are fundamental differences in terms of the causes of violence and the areas where violence takes place, but it is also possible to detect similarities and differences in genetic structures examined by genetic methods.[1] However, this situation should not be considered independent of the social conditions of the individual or society.[2]

Studies on sports genetics include all of the studies in this field, such as the identification of genes that affect athletic performance, the elucidation of the mechanisms of action of these genes, and the determination of predispositions in terms of athletic performance.[3] Considering the factors that determine success in sports, it is of great importance to create training and nutrition programs suitable for genetic structure not only in individual sports but also in team sports.[4]

In studies conducted to investigate aggressive behavior from neurological and genetic aspects, genetic structures and their relations with the environment are held responsible for the variability among people who exhibit aggressive behavior.

It has been seen in the studies that the genetic effect is more pronounced in individuals who deliberately display aggressive behavior than in individuals who display reactive aggressive behavior, and it has been emphasized that the most promising results for genetic studies on aggression are deliberately aggressive individuals.[5]

Aggression has been explained by Baron and Richardson as a form of behavior in which the target individual exhibits avoidance of exposure, with the aim of harming the person it is governed by. Aggressive behavior is defined as the

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behavior with the aim of harming the person to whom it is directed, and damage can be carried out in various ways such as the use of physical force.[6]

It is known that catecholamines (dopamine and norepinephrine), which are frequently mentioned in studies on behavioral genetics and produced in the human body, have vital importance as neurotransmitters in the central and peripheral nervous system. These chemicals are metabolized by monoamine oxidase (MAO). In this respect, it has been determined that this pathway has a significant effect on the determination of personality traits.[7]

In a study conducted with a total of 802 abused and neglected participants, the participants were followed up to adolescence and compared with the participants in the control group to evaluate how anger or aggression-like behaviors develop throughout life. In addition, MAO-A genotypes of these individuals were also examined. As a result of the research, it was found that individuals who were in such environments in childhood and had low gene expression exhibited more behavioral problems throughout their lives. However, statistically, it was also determined that those with high MAO-A expression levels in this group exhibited violent and antisocial behaviors at low intervals during adolescence. Low-level expression of the MAO-A genotype was not found to be a determinant of violence and antisocial behavior in individuals who were not abused in infancy or childhood.[8,9]

Aggressive behavior that is impulsive, particularly in serotonergic systems that are effective in the regulation of the dopaminergic system is known to be related to the deterioration of the balance between most neurotransmitters in the prefrontal cortex. In this respect as a result of studies, receptors 5-HT2 are known to suppress dopaminergic activity and control emotional and behavioral responses, in addition, receptors 5-HT2 reduce serotonergic activity are shown to be associated with impulsive aggressive behavior.[10]

In addition, serotonin, which has various effects on the central and peripheral nervous system, is one of the endogenous molecules. The presence of serotonin, known as a neurotransmitter chemical, in syndromes such as obsession, depression, addiction, and anxiety has been reported in the studies.[11]

Serotonin is thought to be part of an important mechanism that regulates anxiety. Serotonin (5-HT) is a type of hormone that gives the feeling of happiness, vitality, and wellness to individuals. The absence of serotonin causes a depressive, tired, bored mood, and while the chemical of serotonin is released in the brain, the blood vessels contract, and the blood vessels expand when serotonin level drops.[12]

Serotonin transporter protein (SERT or 5-hydroxytryptamine transporter [5-HTT]) is formed by the SLC6A4 gene, which ensures the recall of serotonin from the synaptic gap where it is secreted.[13]

It is known that there is an insertion/deletion polymorphism in the promoter region of the gene, and this allele containing the 44 bp region is called the long allele (L), and the allele without this region is called the short allele (S). Studies in the literature have shown that the S allele may be associated with anxiety and the SS genotype may be associated with aggression in children. In addition, individuals with the LL genotype were found to be more resistant to stress.[14]

The catechol-O-methyltransferase (COMT) gene is located on chromosome 22q11.2 and deletion syndrome may occur on this chromosome. Studies show that structural changes in the prefrontal cortex increase the risk of behavioral disorders and mental illness associated with this syndrome.[15]

In a study, the effect of COMT polymorphism on competitive performance was investigated on 57 male swimmers. According to COMT Val^{158}Met genotype, swimmers were separated as valine homozygous genotype and methionine carrier, and as a result, competitive performance was found to be higher in the methionine carrier group.[16]

In another study conducted with 16 judo athletes and 40 young people as a control group, the COMT gene, which was examined in relation to resistance to stress, personality traits, and aggression, was investigated. In genotypic distributions, it was determined that the Val/Val genotype of the COMT gene was higher in the athletes compared to the control group.[17]

Studies have shown that there is an inverse relationship between blood levels of 5-hydroxyindoleacetic acid, the main metabolite of serotonin, and aggressive behavior and tendency to violence. Genetic variants and polymorphisms mostly associated with serotonin, dopamine, and MAO have been described in individuals exhibiting aggressive behavior.[18] In most of the studies on behavioral traits, it has been shown that genes synthesizing MAO-A, COMT, and 5-HTT enzymes show polymorphism in pathways related to personal behavioral traits, and when the effects of different variants on behavioral tendencies of individuals are examined, violent behavior can be associated with these genes.[19]

Genetic research has included several of the genes related to anxiety, aggression, and depression that may be hereditary with personal differences. However, the 5-HT signal path is defined as (5-HTT), 5-HT1A receptor (HTR1A), and MAO-A.[20]

The 5-HTR1A is located inside the body in the entire gastrointestinal system and in the myenteric plexus. The serotonin receptor is located in the central nervous system in both the presynaptic and postsynaptic regions and the serotonin receptor is the most common.[21] By researchers with mice whose receptors were inactive 5-HT1A with

genetic methods in a study showed reduced aggression and increased fear.[22]

Another study determined that nonviolent suicides had more receptor density of 5-HT1A in their frontal cortex than suicide with violent.[23]

In another study, it was observed that men of a family known to be Dutch nationals demonstrated aggressive and antisocial behavior above normal. In this case, genetic studies on family members determined a mutation that causes the absence of most of the monoaminoxidase enzyme. However, it is known that the enzyme is responsible for the fragmentation of many important neurotransmitters in the brain. In addition, the variants of the MAO (MAOA-L) gene with more extreme activity are shown to cause more serotonin release than gene variants with higher activity (MAOA-H).[24]

Moreover, another study showed that MAO-A activity increased during long-term exercises in individuals and it is explained that it affects fatigue and athletic performance in response to serotonin production. Another study compared groups of individuals dealing with 468 South African triathlon sports with individual control groups who are not interested in this sport and 30 bp Variable Number Tandem Repeat (VNTR) polymorphism was detected on the MAO-A promotor site, and it was found to be directly related to its durability performance in this study.[25]

In another study, it has been observed that there has been an increase in behavioral disorders such as attention deficiency, hyperactivity, and depression, in people with MAOA-L genotypes who have experienced abuse during childhood. On the contrary, people with low MAOA genotype have been overly sensitive to emotional stimulus and increased activity in the amygdala and decreased activity in the frontal regions of their brain were detected.[26]

Conclusion and Recommendations

It is known that dopaminergic functions play a critical role in the behavior of the individual, and most studies show that the dopaminergic neurotransmission system is associated with complex processes such as attention, decision-making, and control.[27]

Individual performance competencies in sports are determined by the genetic structure and are explained as a process in which education and potential are combined. While athletic performance is a result of the interaction between genetics and training, it is known that both talent identification and management systems that provide training are very important in terms of success in sports.[28]

Parameters such as anxiety and aggression, which are known to affect performance in athletes, affect both the daily life of individuals and their success rates in competitions. Since anxiety deeply affects the performance of athletes, it has an important role for individuals to manage their anxiety and perform successfully. It shown that at Table 1; all these emotional states have an impact on the athletes' abilities and athletic performance, as well as their psychological state, due to the hereditary characteristics of genetic diversity. For this reason, it is important to determine the characteristics of stress, competition, and aggression, which have an effect on athletic performance and are known to be related to the processes of serotonergic, dopaminergic, and nonandrogenic systems. In addition, it is stated that the identification of genes that affect psychological states may contribute to the regulation of the athletic performance of athletes.[29]

Table 1: Monoamine oxidase and catechol-O-methyltransferase gene's effect

	Intracellular MAO-A gene	Extracellular COMT gene
Norepinephrine	MHPG, DHPG, VMA	NMN
Serotonın	5-HIAA	
Dopamine	DOPAC, HVA	MT-3

COMT: Catechol-O-methyltransferase, MAO-A: Monoamine oxidase-A, 5-HIAA: 5-hydroxyindoleacetic acid

As a result, it is not possible to associate the complex patterns of behavior that individuals exhibit with a single gene, or these behaviors are only affected by environmental factors. Gained identity and the interaction of the genetic structure and the environment are very important in the essence of behavior in individuals. In addition, epigenetic changes caused by environmental factors and lifestyles differentiate the gene expression but this creates patterns of individual behavior.[30]

In this case, environmental conditions strengthen biological differences, increasing the likelihood of aggressive behavior. Positive environmental conditions can contribute to some polymorphism concealment or the delivery of more positive responses.

Patient informed consent

There is no need for patient informed consent.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Emel Hülya Yükseloğlu (50%): Design the research, data collection, and analyze and wrote the whole manuscript. Contributed with comments on research design and slides interpretation.
- Buse Sabiha Bozaslan (50%): Organized the research and supervised the article write up. Contributed with comments on manuscript organization and write up.

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Case Report

Human Immunodeficiency Virus-Associated Dementia: Two Case Reports

Abstract

Human immunodeficiency virus (HIV) continues to be a serious public health problem in our country in the world and has serious effects on the central and peripheral nervous system. HIV-associated dementia (HAD), which may develop due to HIV infection, causes subcortical dementia that can progress with marked slowdown in reaction time and psychomotor speed, impaired cognitive flexibility, emotional lability, and apathy. Neurocognitive tests are the most appropriate tools for the neurocognitive assessment and staging of the disease. In this context, the Addenbrooke's Cognitive Examinations Revised (ACE-R) test may be preferred in the neurocognitive evaluation of patients considered to have HAD, in terms of its repeatability and easy applicability, as it allows us to evaluate many neurocognitive functions in detail.

Keywords: *Addenbrooke cognitive examination test, human immunodeficiency virus, human immunodeficiency virus-associated dementia*

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Introduction

Human immunodeficiency virus (HIV) causes primary failure of the immune system and makes the body vulnerable to infections and some types of cancer as a result.[1] Transmission routes are as follows: sexually transmitted from mother to baby, transmitted to medical personnel, transmitted by injector, and other tools. In our country, 45.6% of cases are observed sexually, and 0.97% are observed with the use of intravenous substances. HIV was first seen in the world in the United States in 1981 and in our country in 1985. According to the data of the Department of Infectious Diseases and Early Warning of the General Directorate of Public Health of the Ministry of Health of the Republic of Turkey, from 1985 to December 31, 2021, there were 30,293 HIV-seropositive individuals and 2083 acquired immunodeficiency syndrome cases. 81.2% of the cases were male, 18.8% were female, and 16% were made up of foreign nationals. The most common age ranges of the disease are 25–29 and 30–34, and the transmission route of 53.08% of the cases is unknown.[2] In addition to the direct effects of HIV infection on the immune system with the decrease of CD4 T-lymphocytes, it also has serious effects on the brain, spinal cord, and peripheral nerves in the nervous system. HIV-related neurological complications are seen in 40%–50% of patients and may be the first symptom in 10%.[2,3]

Although the incidence of neurological complications has decreased considerably in the postantiretroviral treatment (ART) period, neurocognitive deficits in HIV cannot be prevented.[4] Although ART treatment reduces cognitive decline and has positive effects on patients' daily life activities, there is still no complete cognitive improvement.[5] In previous studies, even in young people with HIV infection acquired in early childhood, moderate neurocognitive impairments may be observed. In another study, it was reported that 71% of patients with HIV infection are at risk for cognitive impairment.[6] Vascular and metabolic comorbidities such as diabetes mellitus, metabolic syndrome, and obesity, which are observed with increasing frequency in elderly people, also increase the prevalence of HIV-related neurocognitive impairment.[7,8] Slow response times, marked slowing of psychomotor speed, poor cognitive flexibility, and emotional lability or apathy can often be seen in HIV-associated neurocognitive disorder (HAND). HIV-associated

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dementia (HAD) is included in the subclassification of HAND.[9,10] Here, it is aimed to discuss two cases followed up with HAD, together with detailed examination, neurocognitive test results, and neuroimaging results in the light of literature. We consider that this case study, which examines neuroimaging and neurocognitive test results related to HIV-related dementia, will contribute to the literature.

Two Case Reports

Case 1

A 58-year-old female patient was admitted to the neurology outpatient clinic with the complaint of forgetfulness. When her anamnesis was questioned in more detail, it was learned that she was a homemaker, that she was being followed up and treated with a diagnosis of acquired immunodeficiency in our infectious diseases clinic, and that the complaint of forgetfulness had increased for 6 months. She stated that he forgot the place where she put the things, the words she would say in everyday life, and her routine chores. She had hypertension on her resume but was not taking medication. There was no feature in her family history. In her neurological examination, she was conscious, cooperative, and oriented. Cranial nerve examination was normal. She had moderate dysarthria. Neither motor lateralizing findings nor cerebellar pathological findings were detected. Deep tendon reflexes were normoactive. The Babinski's sign was found to be bilaterally positive. Romberg test was positive. When hemogram and biochemistry values are examined, erythrocyte sedimentation rate: 55 mm/h. HIV RNA (macro) value resulted in 598 IU/mL, CD4: 12.52/mm^3, and CD8: 18.13 mm^3. Cranial magnetic resonance (MR) examination revealed that lesions adjacent to the left lateral ventricular corpus, which may be compatible with the lacunae at the level of both the corona radiata, thalamus, basal ganglia and the lentiform nucleus. Diffuse nodular and patchy T2 fluid-attenuated inversion recovery (FLAIR) signal increases were observed in the frontoparietal, occipital, and subcortical deep white matter. T2 FLAIR signal enhancement areas in basal ganglia, external capsules and left thalamic localization; diffuse millimetric focal gradient ECHO hypointensities were reported in bilateral cerebellar hemispheres, brain stem and basal ganglia, and in both cerebral hemispheres [Figure 1]. Brain glucose metabolism was reported as normal in brain positron emission tomography (PET) examination. ACE-R test was used for the neurocognitive evaluation of the patient. In the ACE-R test, attention and orientation functions were partially preserved (13/18). While recording memory was preserved in memory processes, short-term memory, retrograde memory, recall, and recognition skills were impaired (9/26). While there was mild impairment in verbal fluency functions (6/14), language functions were preserved (20/26). While the perceptual skills, one of the visual-spatial functions, were preserved, the planning ability was impaired (9/16). In the clock-drawing test, planning and conceptualization were affected. As a result, it was interpreted that there is a deterioration in the temporolimbic type of memory processes and a deterioration in the ability to maintain attention and planning ability, which is one of the complex attention functions. The patient was considered to have HAD the current findings. Oral and written consent was obtained from the patient.

Case 2

A 47-year-old male patient was admitted to our neurology outpatient clinic with complaints of progressive forgetfulness for 4 months. When his anamnesis was questioned in more detail, he stated that he forgot and burned food on the stove twice, once lost his phone, and had disruptions in his daily life activities. While he was working in a medical waste unit in a hospital, he had an HIV-infected syringe stuck in his hand and his HIV serology was positive in his examinations. Thereupon, he was followed up in the infectious diseases clinic and his treatment was arranged. When the patient's history is questioned, it was learned that he had hypertension but did not use medication and had a history of head trauma due to a traffic accident 2 years ago. There were no features in his family history. In neurological examination, he was conscious, cooperative, and oriented. Cranial nerve examination was normal. Neither motor lateralizing findings nor cerebellar pathological findings were detected. Deep tendon reflexes were normoactive. The Babinski's sign was found to be bilaterally negative. The tandem walk was impaired. When the laboratory values were examined, no significant pathology was detected in the hemogram and biochemistry. HIV RNA (macro) resulted in 4353 IU/mL, CD4: 7.35/mm^3, and CD8: 3.17/mm^3. Cranial magnetic resonance imaging (MRI) examination revealed that the posterior fossa was consistent with a 70 mm × 86 mm × 35 mm retrocerebellar arachnoid cyst surrounding the left cerebellar hemisphere [Figure 2]. When the patient's past medical records were examined, it was seen that the existing arachnoid cyst was present in the cranial computed tomography (CT) taken after a head trauma 2 years ago and its sizes did not change [Figure 3]. In the brain PET examination, it was interpreted that there were 18-fluorodeoxyglucose PET/CT findings consistent with hypometabolism in a global patch pattern, except for both occipital and frontal cortices and basal ganglia, and these findings suggested inflammatory/vascular processes involving the cortical area. In the ACE-R test used for neurocognitive evaluation, attention and orientation functions were partially preserved (13/18); there was deterioration in memory processes such as anterograde memory, short-term memory, retrograde memory, recall, and recognition skills (8/26). There was severe deterioration in verbal fluency functions (5/14). He counted 11 words in semantic fluency test and only 3 words in lexical fluency test. There was a deterioration in the naming of the

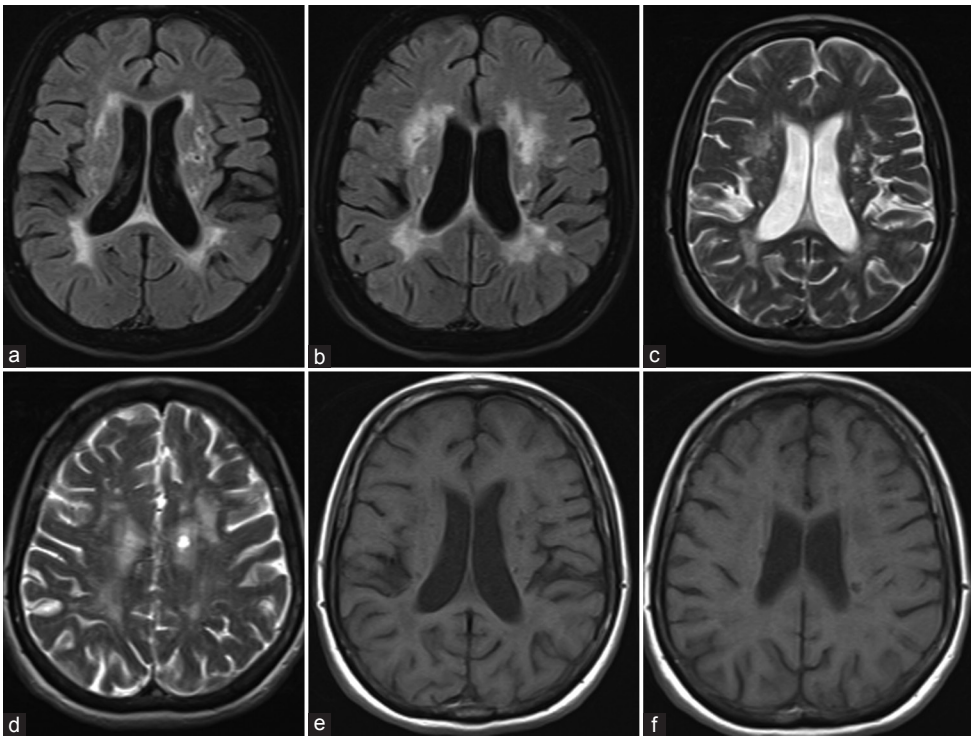

Figure 1: Cranial MRI FLAIR (a,b), T2 (c,d), and T1 (e,f) axial sequences of Case 1. MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery

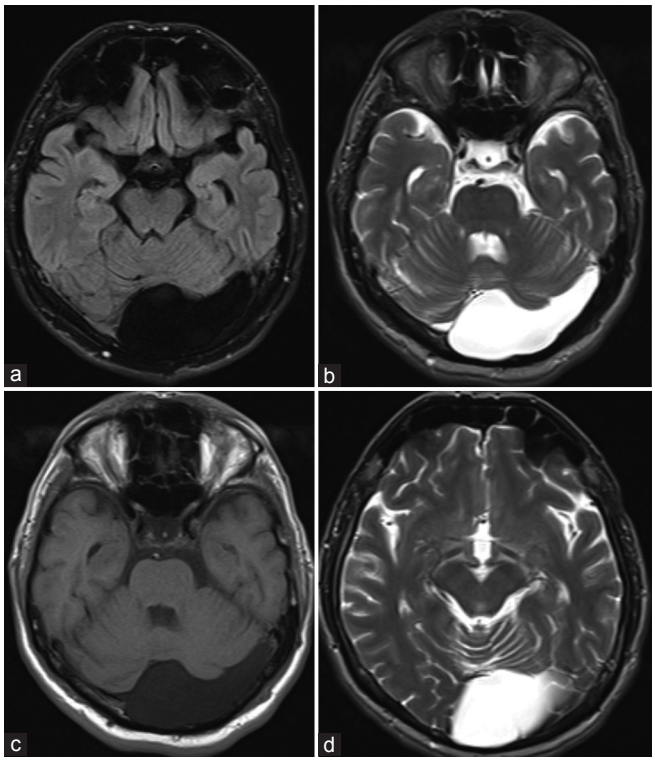

Figure 2: Cranial MRI FLAIR (a), T2 (b,d), and T1 (c) axial sequences of Case 2. MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery

confrontal associated with the left posterior areas (13/26). While the perceptual skills, one of the visual-spatial functions, were preserved, the planning ability was impaired (9/16). In the clock-drawing test, planning and conceptualization were affected. There were difficulties in learning verbal information. He could not retrieve any of the seven words in long-term memory, and he recognized three words in recognition, recognized one word by forced choice, and misrecognized one word. As a result, it was interpreted that there is a deterioration in the temporolimbic type of memory processes and a deterioration in the ability to maintain attention and planning ability, which is one of the complex attention functions. The patient was considered to have HAD the current findings. Oral and written consent was obtained from the patient.

Discussion

Cross-sectional studies show that about half of HIV-infected patients have cognitive impairment. Although a decrease in neurocognitive deterioration has been observed with ART treatments, providing the etiology, prognosis, and optimal treatment regimen in these patients still remains a great responsibility.[11] HIV-dementia complex is a subcortical dementia that progresses with progressive deterioration in attention and concentration, slowdown in psychomotor speed, and behavioral changes and results in death in less than a year.[9] In a consensus conducted in Italy in 2006, the subclinical classifications for HAND were determined as asymptomatic neurological impairment, mild neurocognitive impairment, and HIV-related dementia (HAD).[10] When its pathogenesis was examined, it was found that there were generalized atrophy in the brain, white matter changes causing leukoencephalopathy, microglial nodules typical of viral encephalitis, and multinuclear giant cells seen in staining

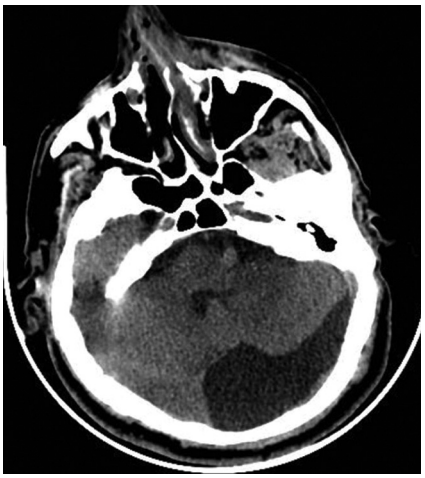

Figure 3: BT examination of Case 2

specific to HIV-infected cells.[10] Recent studies have shown that HAND is not associated with CD4 T-lymphocyte count and cerebrospinal fluid HIV RNA concentration. Although no HAND-specific neuroimaging findings are known, hyperintense white matter lesions with unclear boundaries can be seen symmetrically on cranial MRI examinations.[10] Currently, no treatment methods are known for HAND-treated HIV cases other than current ART methods.[12]

Neurocognitive tests were used for the neurocognitive evaluation and staging of the disease. In these tests, speech areas, attention skills, executive functions, abstraction skills, learning-remembering and memory processes, information processing speed, and motor functions are evaluated in detail.[12,13] In previous studies, the Mini-Mental Test (MMT), the Montreal Cognitive Assessment Scale, and the International HIV Dementia Scale were generally used.[3] We used the ACE-R test for neurocognitive evaluation in both cases. ACE was prepared at the University of Cambridge and Addenbrooke Hospital Neurology Clinic in 2000 and revised in 2005 and started to be used as ACE-R.[14] ACE-R is a test that can be applied in an average of 15–20 min and includes MMT, and is used for early diagnosis and differential diagnosis of dementia, to follow-up patients. There are a total of five subtests in the ACE-R test. The test is evaluated out of 100 points. These subtests are attention and orientation (18 points), memory (26 points), fluency (14 points), language functions (26 points), and visuospatial functions (16 points). In the ACE-R Turkish validity study, 73 limit values were determined to distinguish Alzheimer's disease from normal healthy people at the educational level of over 11 years, and 88 limit values were determined to distinguish patients with mild cognitive impairment from normal healthy people.[14] When the ACE-R test results of both the cases were evaluated, the ACE-R total score of the first case was 56/100, and the second case was 48/100.

A subcortical dementia is seen in HAD, especially as specific gray matter nuclei in the white matter tracts and subcortical areas are affected. As a result, slowed reaction time, significant slowdown in psychomotor speed, weakening of cognitive flexibility, emotional lability, and apathy can be observed clinically. It has been determined that HIV-seropositive individuals have lower neurocognitive performance than the control group, and neurocognitive test scores are found to be lower, especially in the areas of language functions, attention, orientation, concentration, memory, and praxis.[12,13,15] When the ACE-R tests were examined, temporolimbic type involvement, impaired attention maintenance, and planning skills were observed, and with the current findings, HIV-related dementia (HAD) was considered in both cases. The factors affecting the low detection of neurocognitive test scores have been investigated in previous studies. No direct relationship was found with age, gender, education level, body mass index, clinical stage, alcohol/substance use, concomitant cardiovascular/metabolic/psychiatric diseases, anemia, presence of opportunistic infections, and CD4 T-cell count.[15]

In conclusion, HAD should be kept in mind in clinical practice in patients followed up with HIV infection and in patients with rapidly progressive memory impairment and behavioral changes. In the neurocognitive evaluations of patients with suspected HAD, ACE-R test can be preferred in terms of being a test that evaluates memory, attention, orientation, fluency, language functions and visuospatial functions in detail, as well as reproducibility, including MMT, short duration, and easy applicability.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

There is no need for ethics committee approval.

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There are no conflicts of interest to declare.

Author contribution subject and rate

- Nefise Eda Arslanoğlu (40%): Contributed with literature research, writing of manuscript and treatment of patient.
- Nazlı Gamze Bülbül (30%): Contributed with comments on manuscript and treatment of patient.
- Mehmet Güney Şenol (15%): Organized the report and supervised the report write-up.
- Mehmet Fatih Özdağ (15%): Contributed with comments on manuscript organization and write-up.

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SARS-CoV-2 Infection-Related Acute Parkinsonism and Encephalitis: Is There a Clinicoradiological Correlation?

Abstract

COVID-19 infection can cause neurological manifestations as early and late complications (chronic COVID syndrome). These include headache, dizziness, confusion, acute cerebrovascular problems, ataxia, and seizures. COVID-19-related encephalopathy, encephalitis, and parkinsonism have been reported earlier; however, the possible links and pathophysiological mechanisms are unclear. In this report, we report a series of patients (n = 5) presenting with acute severe neurological syndromes such as parkinsonism, focal status epilepticus, or acute ataxia as a part of long-hauler COVID-19 infection. We categorized the clinico-radiological and electroencephalographic features in our cases to understand the clinical patterns in SARS-CoV-2 related brain cortex involvement. This might help in future for better clinical categorization for these COVID-19-related neurological manifestations.

Keywords: *COVID-19, encephalopathy, parkinsonism*

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Introduction

COVID-19 infection presents with various symptoms, including nonproductive cough, fever, myalgia, fatigue, dyspnea, diarrhea, and nausea/vomiting, while some patients are known to be asymptomatic.[1] COVID-19 infection can cause neurological manifestations as an early presentation such as confusion, anosmia, and ageusia.[2,3] A systemic review of COVID-19-related publications demonstrated a high likelihood of neurological manifestations in severe COVID-19 infection.[4] Mao *et al*. found central nervous system (CNS) manifestations in 25% of cases mainly presenting as headache (13%), dizziness (17%), impaired consciousness (8%), acute cerebrovascular problems (3%), ataxia (0.5%), and seizures (0.5%).

COVID-19-related encephalopathy and acute parkinsonism have been reported earlier.[5] However, the possible links and pathophysiological mechanisms are unclear. Proposed hypotheses include neurotropism of COVID-19 virus, basal ganglia lesions in a setting of COVID-19-induced thromboembolic encephalopathy, angiotensin-converting enzyme 2 (AEC2) receptor expression, SARS-CoV-2 proteins-related human protein dysfunction causing protein misfolding, and aggregation. COVID-19 pandemic could affect patients suffering from Parkinson's disease with worsening of both motor and nonmotor symptoms.[6] Long-hauler COVID-19 or chronic COVID syndrome can cause various CNS presentations which can be more disabling.[7]

In this report, we detailed a series of patients (n = 5) presenting with acute severe neurological syndromes such as parkinsonism, focal status epilepticus, or acute ataxia as a part of long-hauler COVID-19 infection.

Case Reports

All five patients presented as a cluster within few days of each other in June 2021 following COVID-19 infection as part of the second wave, which affected the city from where the patients belong. Two patients had acute-onset akinetic-bradykinesia syndrome with T2/FLAIR caudate hyperintensity on magnetic resonance imaging (MRI), two others presented with encephalopathy, focal status epilepticus, and periodic lateralized epileptic discharges (PLEDs)

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in electroencephalographic (EEG), and one patient had acute-onset cerebellar ataxia. Raised cerebrospinal fluid (CSF) protein with no or minimal cellular response was found in all the patients except one. The patients and their symptoms have been described here in group-wise categories.

Group 1

Acute-onset akinesia bradykinesia syndrome (Cases 1 and 2)

Case 1

A 71-year-old male, diabetic, systemic hypertensive, presented with dysarthria, left-sided slowing of movements, and confusional state. On examination, he had grade 3/4 rigidity in all four limbs and also neck rigidity of 3/4. The blink rate was reduced with hypomimia. He developed stimulus-sensitive myoclonus, which was more prominent over the right upper limb, especially on arousal. The myoclonus showed habituation on repeated stimulus. Computed tomography (CT) chest COVID severity score was 12/25. MRI brain showed asymmetrical FLAIR hyperintensity with mild diffusion-weighted images (DWIs) restriction in bilateral caudate and lentiform nucleus (right side more affected than left) along with left medial thalamus [Figure 1a and b]. CSF analysis showed proteins 111 mg% and 1 neutrophil without any fungal elements. He received a course of intravenous (IV) immunoglobulin 2 g/kg over 5 days. Over the next several weeks, the patient remained encephalopathic with persistent parkinsonism without any significant clinical improvement.

Case 2

A sixtynine year old male, who is a known case of ischemic heart disease, diabetes and hypertension developed sudden onset of headache and slowness of all activities of daily

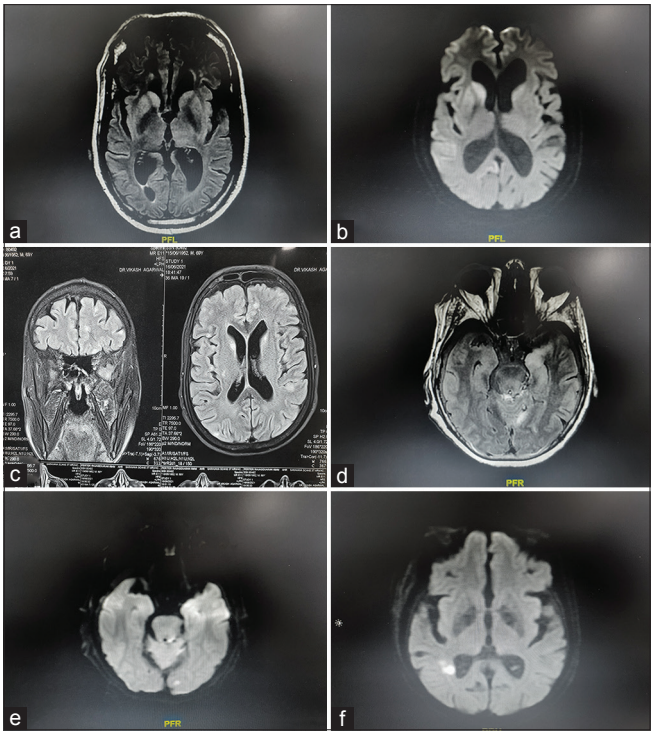

Figure 1: MRI Brain Changes showing specific areas of involvement

Table 1: Clinical, demographic and radiological data with outcomes

Case number	Age	Sex	Syndrome	MRI-DWI changes	CSF proteins (mg %)	CSF cell count	EEG	Comorbidities	Treatment	Outcome
1	71	Male	Parkinsonism with myoclonus	Bilateral caudate, lentiform neucleus	111	1	Diffuse theta-delta	Diabetes, hypertension	Immunoglobulins	No change bed bound
2	69	Male	Parkinsonism	Bilateral caudate, mesial frontal, posterior operculum	61	0	Not done	Diabetes, hypertension, coronary artery disease	Levodopa 400 mg per day	No further deterioration without improvment
3	86	Female	Encephalitis with status epilepticus	Bilateral insula, mesial frontal, hippocampus left >right	240	91	PLEDS left temporal region	Diabetes, coronary artery disease	IV methylprednisolone with antiseizure drugs	Died
4	65	Male	Right focal status epileptics with encephalopathy	Left paramedian frontal and left hippocampus	25	6	PLEDS left temporal region	Diabetes, hypertension, stroke	Antiseizure drugs	Died
5	52	Male	Acute ataxia	Normal	81	1	Not done	Diabetes	Symptomatic treatment	Improved clincally

DWI: Diffusion-weighted imaging, MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, EEG: Electroencephalogram, IV: Intravenous, PLEDS: Periodic lateralized epileptiform discharges

living with difficulty in walking. His examination showed bradykinesia on finger tapping, body bradykinesia along with finger–nose test impairment bilaterally [Video 1]. MRI brain showed T2/FLAIR hyperintensity in bilateral caudate and mesial frontal and opercular regions with mild DWI restriction [Figure 1c]. CSF analysis showed proteins 61 mg% with acellularity. He was treated with levodopa 400 mg per day with mild improvement in bradykinesia. However, his overall clinical status remained static. His positron emission tomography scan was done to rule out a paraneoplastic association and showed no evidence of metabolic active tissue in the viscera.

Group 2

Acute encephalitis with focal status epilepticus (Cases 3 and 4)

Case 3

An 86-year-old female, diabetic, hypertensive, and having ischemic heart disease, presented with a fall and comatose state 1 month post-COVID-19 infection. After 3 days of admission, she developed focal right hemiclonic status epilepticus, which needed intubation and IV anesthetic agents. MRI brain showed diffusion restriction in the left insular cortex and mild on the right insular cortex, mesial frontal lobe, and hippocampus along with perimesencephalic subarachnoid hemorrhage [Figure 1d and e]. CT angiography of the brain did not reveal any vascular malformation. CSF analysis showed proteins 240 mg%, 91 cells (mononuclear/PMN) with negative HSV DNA polymerase chain reaction (PCR). Both CSF and serum autoimmune encephalitis panels were negative. EEG showed PLEDs over the temporal region [Figure 2a and b]. She was treated with acyclovir and IV methylprednisolone pulse (1 g/day for 5 days). She continued to worsen clinically in the intensive care unit and expired due to secondary sepsis and cardiac arrest.

Case 4

A 65-year-old male, history of recurrent stroke (temporal lobe and right thalamic hemorrhage), hypertension, postdecompression, post-COVID-19 infection status, presented with right-sided hemiclonic seizures and status epilepticus. MRI brain showed diffusion restrictions in the left paramedian frontal and left mesial temporal (hippocampal head and body) [Figure 1f]. CSF analysis showed 25-mg proteins with six neutrophils, HSV DNA PCR test was negative. EEG showed PLEDs over the temporal region [Figure 2c and d]. His C-reactive protein was 204. He continued to be encephalopathic and 4 days after admission, he had sudden bradycardia and desaturation and could not be revived.

Group 3

Acute cerebellar ataxia with headache (Case 5)

Case 5

A fifity two year old diabetic presented with history of acute onset difficulty in walking since one month after a mild COVID-19 infection(which was treated at home based covid care). CT chest showed a CT severity score of 5/25. MRI brain was normal, Vitamin B_{12} >2000

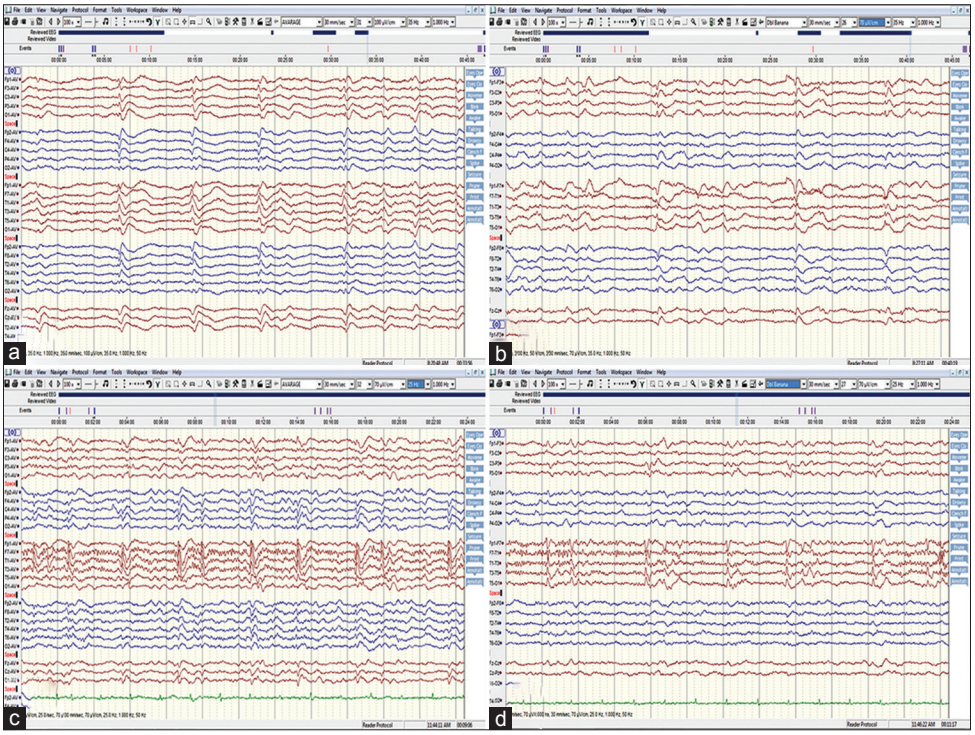

Figure 2: EEG epochs showing PLEDs

units. CSF analysis showed CSF protein was 81 mg% with 1 cell (lympho or PMN). CSF Gene XPERT MTB, culture, and fungal smear were negative. He was treated symptomatically and remains stable on follow-up.

Discussion

We described three groups of acute CNS manifestations of long-hauler COVID-19. All cases had a mild COVID infection 3–6 weeks before the neurological presentation along with multiple comorbidities, namely diabetes, hypertension or prior stroke, and showed MRI changes (except one case), with raised CSF proteins. We correlated the MRI changes with clinical presentation and associated findings.

The cases described in group 1 presented with post-COVID-19 infection acute parkinsonism and myoclonus with bilateral caudate hyperintensity and raised CSF protein. There was no history of prior parkinsonism in these cases or any suggestion of prodromal PD. A previous case described in the literature with akinetic-rigid syndrome, myoclonus, and DaT-single-photon emission computed tomography confirmed bilateral decrease in presynaptic dopamine uptake asymmetrically involving both putamina has drawn attention to post-COVID-19 parkinsonism with much skepticism.[8] Our first patient had similar myoclonus as reported in the previous case; however, the patient did not show any clinical improvement. It has been suggested by Lang *et al*. that the stress of SARS-CoV-2 infection could have unmasked a prodromal Parkinsons's disease and the acute parkinsonism could represent a preexisting nigrostriatal dysfunction.[9] We could not do the nuclear imaging studies in our cases which could have highlighted this viewpoint.

On analyzing the patterns in the MRI findings in correlation with the clinical syndrome, group 1 with acute parkinsonism showed bilateral caudate involvement on initial presentation and only later involvement of the extra basal ganglia regions (like mesial frontal in case number 2). However, group 2 showed a typical insulomesial frontal-hippocampal involvement in both cases. This finding may suggest a likelihood of limbic system involvement when the clinical presentation is encephalitis with focal status epilepticus. However, this observation needs more data with a larger sample size. A case of acute necrotizing encephalopathy has been described in relation to COVID-19 infection.[10] Similar case reports of acute disseminated encephalitis (acute disseminated encephalomyelitis) or ataxia have been reported.[11,12] The CNS injury is presumed to be due to a cytokine storm-mediated tissue damage; however, the degree of the severity of SARS-CoV-2 in our cases was mild. It can be postulated that the presence of comorbidities such as diabetes (which was present in all cases) or hypertension has made the CNS more vulnerable for an immune-mediated or a direct tissue injury subsequently with breach of the blood–brain barrier integrity. Immunotherapy has not altered the clinical course significantly in our cases. This may suggest that the pathophysiological mechanisms of SARS-CoV-2 brain injury are complex and needs further research. There is a need to develop standard treatment protocols in SARS-CoV-2-related CNS manifestations including the degree of intervention by immunotherapy.

Conclusion

Acute severe neurological syndromes such as parkinsonism, focal status epilepticus, or acute ataxia can be a part of long-hauler COVID-19 infection. These presentations have specific MRI findings in brain regions (such as the limbic system, mesial frontal, and basal ganglia) and show EEG changes with raised CSF proteins with variable clinical outcomes. There is a need for further studies in these specific subgroups which will help in better understanding of the role of future treatments including immunotherapy in long-hauler COVID-19 infection.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

There is no need for ethics committee approval.

Conflict of interest

There is no conflict of interest to declare.

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Author contribution subject and rate

- Vikash Agarwal (30%): Clinical concept and manuscript write up.
- Dolly Mushahary (10%): Technical support.
- Praveen Chander (10%): Clinical concept.
- Venkatraman.K (10%): Article review.
- Lakshminarayanan.K (10%): Article review.
- Sathish Kumar .V (10%): Article Review.
- S.Dinesh Nayak (20%): Clinical Concept.

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