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Original Article / Araştırma Makalesi

GALECTIN-3, AN INDICATOR OF INFLAMMATION AND OXIDATION, IS LINKED WITH THE SEVERITY OF ALZHEIMER'S DISEASE

ALZHEİMER HASTALIĞI'NDA İNFLAMASYON VE OKSİDATİF STRES GÖSTERGESİ OLARAK GALEKTİN-3'ÜN ROLÜ

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ABSTRACT

Introduction: Galectin-3 (Gal-3) is a multifunctional protein implicated in various biological processes, but the best-known role for galectin-3 is in acute and chronic inflammation. Inflammation plays an essential role in developing cognitive decline and dementia in old age. This study aims to investigate if galectin-3 can be an indicator of inflammation in Alzheimer's Disease (AD) pathogenesis and a feasible biomarker of the disease.

Methods: The study included 44 patients with Alzheimer's Disease and 44 patients with normal cognitive function. Patients with known acute or chronic infections, chronic inflammatory diseases, cancer patients, and patients with rheumatological diseases affecting galectin-3 levels were excluded. All patients underwent comprehensive geriatric assessment and cognitive assessment. Serum galectin-3 levels were measured.

Results: Analysis revealed that the galectin-3 level of the AD group was higher than the control group. However, it was not statistically significant. According to the Global Deterioration Scale (GDS), the galectin-3 levels of patients in the moderately severe AD group (GDS stage 6) were significantly higher than the patients in the mild-moderate AD group (GDS stage 4-5). There was a significant weak negative correlation between galectin-3 levels and the Digit Span Forward (r = - 0.216, P = 0.043) and Backward (r = - 0.233, P = 0.029) tests.

Conclusion: This study suggests that galectin-3 may play a role as an indicator of inflammation and oxidative stress in the pathogenesis of Alzheimer's Disease. It appears to be associated with the severity of AD. However, further and more extensive prospective studies are needed to clarify the association.

Keywords: Alzheimer Disease, Biomarker, Galectin-3, Inflammation, Oxidative stress

ÖZET

Giriş: Galektin-3 (Gal-3), birçok biyolojik süreçte rol alan multifonksiyonel bir protein olup en önemli rolü akut ve kronik inflamasyondadır. İnflamasyon, ileri yaşta kognitif gerilemenin ve demansın gelişmesinde önemli bir role sahiptir. Bu çalışmanın amacı galektin-3'ün Alzheimer Hastalığı (AH) patogenezindeki inflamasyonun bir göstergesi olup olmadığının ve bir biyobelirteç olarak kullanılabilirliğinin araştırılmasıdır.

Yöntemler: Çalışmaya, 44 Alzheimer hastası ve 44 normal kognitif fonksiyonlu olmak üzere toplam 88 hasta alınmıştır. Bilinen akut veya kronik infeksiyon tanısı olan, kronik inflamatuar hastalığı bulunan hastalar, kanser hastaları ve galektin-3 düzeyini etkileyen romatolojik hastalığı bulunan hastalar dışlanmıştır. Tüm hastalara kapsamlı geriatrik değerlendirme testleri ve nöropsikiyatrik testler uygulanmıştır. Serum galektin-3 düzeyleri ölçülmüştür.

Bulgular: Analizler sonucunda Alzheimer Hastalığı grubunun galektin-3 düzeyi, kontrol grubundan yüksek saptanmıştır. Ancak istatistiksel olarak anlamlı değildir. Global Detoriasyon Skalası (GDS) evrelemesine göre orta-şiddetli AH (GDS evre 6) grubundaki hastaların galektin-3 düzeyleri hafif-orta evredeki (GDS evre 4-5) hastalara göre istatistiksel olarak anlamlı şekilde yüksek saptanmıştır. Galektin-3 düzeyi ile sayı menzili ileri (r = -0,216 P = 0,043) ve geri (r = -0,233 P = 0,029) testi arasında ters yönde, düşük kuvvette, istatistiksel olarak anlamlı bir korelasyon saptanmıştır.

Sonuç: Bu çalışma, galektin-3'ün Alzheimer Hastalığı'nın patogenezinde inflamasyon ve oksidatif stres göstergesi olarak önemli bir rol oynadığını göstermektedir. Bu ilişki Alzheimer Hastalığı'nın şiddeti ile ilişkili görünmektedir. Ancak, bu ilişkiyi netleştirmek için daha fazla ve daha kapsamlı prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Alzheimer Hastalığı, Biyobelirteç, Galektin-3, İnflamasyon, Oksidatif stres

INTRODUCTION

Alzheimer's Disease (AD), a progressive neurodegenerative disorder, accounts for 50-80% of dementia cases (1). The pathology of Alzheimer's Disease is characterized by brain atrophy, formation of neuritic plaques containing beta-amyloid peptide, and neurofibrillary tangles containing hyperphosphorylated tau protein (2, 3). Inflammation and oxidative stress play an essential role in pathogenesis. Accumulation of reactive oxygen species damages the major cell components, primarily mitochondria, in specific brain regions (4, 5). Inflammation has an essential role in developing cognitive decline and dementia in advanced age (6). A state of chronic brain inflammation exists in AD, characterized by activation of microglia and astrocytes, recruitment of peripheral immune cells, and excessive proinflammatory mediators. Cytokines

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influence several different mechanisms that may induce or accelerate the development of neurodegeneration and the AD phenotype (6, 7). Persistent inflammation could play a role in the advancement of the disease and the decline of neurons (7).

Currently, the diagnosis of Alzheimer's Disease is made by clinical and cognitive assessment, neuropsychiatric tests, and excluding other causes of dementia. However, a definite diagnosis is possible by tracing characteristic pathological brain lesions, amyloid plaques, and neurofibrillary tangles in autopsy. Although the progression of the disease can be slowed down by early treatment, diagnosing the disease at an early stage is difficult. This clinical need has led to the search for biomarkers that can be used to diagnose Alzheimer's Disease in its early stages and to distinguish Alzheimer's Disease from other causes of dementia (8).

Galectins are a member of the animal lectin family with a beta-galactosidase affinity. Galectins interact with the cell surface and extracellular matrix glycoproteins through lectin-carbohydrate interaction. This interaction facilitates cell growth, increases cell survival, regulates cell adhesion, and induces cell migration (9-12). Galectin-3 (Gal-3) is a member of the Galectin family (13). Gal-3 is found in many cells and tissues. It is involved in many tasks, such as macrophage migration, fibroblast proliferation, and collagen synthesis (9, 12). However, the most crucial role of galectin-3 is in acute and chronic inflammation (14-17).

Galectin-3 has regulatory functions, especially in the hippocampus region of the brain. Due to its role in regulation and inflammation, we assume that gal-3 may have a role in cognitive functions and Alzheimer's Disease (10). This study evaluates the relationship between serum galectin-3 levels and Alzheimer's Disease.

MATERIALS AND METHODS

Study patients

This study was planned and conducted in a geriatric medicine outpatient clinic of a university hospital between December 2015 and May 2016. The study included 44 patients with Alzheimer's Disease and 44 patients with normal cognitive function. All patients underwent comprehensive geriatric assessment and cognitive assessment. The exclusion criteria were acute or chronic infections, chronic inflammatory diseases, cancer, and rheumatological diseases. Patients with coronary artery disease, diabetes mellitus, and hypertension were included in the study. But the patients who have these diseases were in a similar distribution both in Alzheimer's Disease and control group. There was no statistically significant difference in their distributions.

The required approval for conducting the study was obtained from the Ethics Committee of the Faculty of Medicine, Hacettepe University (Date 26.12.2014/ Number GO 14/649). The study protocol was in adherence with the principles in the Declaration of Helsinki. Informed consent was obtained from all participants.

Comprehensive geriatric assessment and cognitive assessment

The demographic characteristics, comorbidities, and medications of the patients included in the study were recorded in the form prepared. To assess patients' activities of daily living objectively, KATZ Activities of Daily Living (ADL) (18), Lawton-Brody Instrumental Activities of Daily Living (IADL) (19), and Disability Assessment for Dementia (DAD) (20) scales were performed. Among instruments used to assess basic activities of daily living (BADLs), Katz ADL is the most widely used one in clinical studies. The Katz ADL measures self-care tasks including; bathing, dressing, toileting, transferring to and from a chair, maintaining continence, and feeding.

The assessment is based on the patient's ability to perform tasks either independently or with assistance. The resulting score reflects the level of independence, with lower scores indicating a higher degree of dependence in basic ADLs (18). Lawton-Brody IADL scale assesses the more complex ADLs necessary for living in the community. The eight domains of function measured with the Lawton IADL scale are the ability to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for medications, and ability to handle finances. The acquired score reflects the level of independence, with increased scores indicating higher levels of individual capabilities (19). The DAD scale is a widely recognized assessment tool for evaluating the functional abilities of individuals with AD. This scale assesses the performance of BADL and IADL over the preceding two weeks. Comprising 10 domains and 40 items, the scale relies on caregiver interviews for information gathering. Six instrumental activities (meal preparation, telephoning, going on an outing, finance and correspondence, taking medications, leisure activities, and housework) and four basic self-care daily activities (hygiene, dressing, continence, and eating) were evaluated. The total score is between 0 and 100. Higher scores correspond to reduced functional disabilities, whereas lower scores are indicative of increased dysfunction (20).

Cognitive function assessment scales and objective diagnostic criteria were used for cognitive assessment. Mini-Mental State Examination (MMSE) (21), Clock Drawing Test (22), Montreal Cognitive Assessment Scale (MOCA) (23), Trail Making Test A and Trail Making Test B (24), Forward and Backward Digit Span Test (25), and Category Fluency Test (25) were performed. MMSE and clock drawing test were used as screening tests. MMSE is the most commonly used test to screen for dementia. It consists of 11 questions and is evaluated over 30 points. A score of <24 is the generally an accepted cutoff indicating the presence of cognitive impairment. It tests orientation, memory, attention,

calculation, recall, language, motor function, perception, and visuospatial abilities (21). The Clock drawing test is considered one of the first tests to fail in the early stages of dementia. The patient is asked to draw a clock, insert the numbers into it, and mark the said time. It is evaluated out of six points and <4 points is consistent with impaired cognitive function (22). MOCA is a rapid screening instrument developed specifically to evaluate the early stages of cognitive impairment. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The maximum achievable score is 30 points, and a score of 21 or higher is deemed within the normal range (23). The Trail Making Test is a neuropsychological assessment comprising parts A and B designed to accurately gauge executive functions such as intricate visual-motor conceptual screening, planning, organization, abstract thinking, and response inhibition. Each segment of the Trail Making Test involves 25 circles arranged on a sheet of paper. In Part A, the circles are sequentially numbered from 1 to 25, and the patient is required to connect the numbers with lines in ascending order. For Part B, the circles encompass both numbers (1 – 13) and letters (A – L). Similar to Part A, the patient connects the circles in ascending order, but in this case, there's an additional challenge of alternating between numbers and letters (e.g., 1-A-2-B-3-C, and so on) (24). Digit span test is particularly used to determine attention range, the ability to keep a certain amount of information in mind at a given time. It can be used in two formats, Forward Digit Span and Reverse Digit Span. Participants are presented with a random series of digits, and are asked to repeat them in either the order offered (forward span) or in reverse order (backward span) (25). The Category Fluency Test, a brief and easily administered assessment, has demonstrated its utility in AD diagnosis. The prevalent version often focuses on the semantic category of animals. The participant is asked to name as many animal names as possible in one minute. The number of animal names that a participant says in one minute is recorded as the categorical fluency score (25).

The diagnosis of AD is based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (26) and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) working group (27). All patients were evaluated with the Global Deterioration Scale (GDS) (28). GDS comprises seven stages, spanning from normal functioning to extremely advanced cognitive decline. These stages are stage 1 – No cognitive decline, stage 2 - Age-associated memory impairment, stage 3 – Mild cognitive decline, stage 4 – Mild Alzheimer's Disease, stage 5 – Moderate Alzheimer's Disease, stage 6 – Moderately severe Alzheimer's Disease, stage 7 – Severe Alzheimer's Disease. Patients diagnosed with Alzheimer's Disease have a GDS score of 4 or higher (28). When we divided the patients according to GDS staging, the number of patients per group was small. So we have to reunite the patients as normal (GDS 1-2), mild-moderate AD (GDS 4-5), and moderately severe AD (GDS 6) to perform the statistical analysis. For patients to be admitted to the normal cognitive functioning group, the conditions of not meeting the criteria of DSM-IV and NINCDS-ADRDA for dementia and not meeting the criteria of Petersen for mild cognitive impairment (MCI) (29) were sought after undergoing comprehensive geriatric assessment. The GDS score of the control group was 1 or 2. Mini Nutritional Assessment Short Form (MNA-SF) was used for malnutrition screening (30), and the Yesavage Geriatric Depression Scale short form was performed to screen for presence of depressive mood (31). The MNA-SF is extensively employed for evaluating the nutritional aspect in the comprehensive geriatric assessment. The instrument consists of six items that assess decline in food intake, weight loss, mobility, psychological stress, neuropsychological problems, and the body mass index (30). The Yesavage Geriatric Depression Scale short form is one of the most commonly used self-rated depression scales in the elderly. It is a very quick, easy-to-administer screening test. A score above five points may be compatible with depression, and should be evaluated with the patient's clinic (31). KATZ ADL test, Lawton-Brody IADL test, MNA-short form test, Clock drawing test, MMSE test, Three-word memory test, Attention and calculation test, Yesavage Geriatric Depression Scale-short form test, GDS, and DAD tests were administered by the same practitioner to all patients. On the other hand, the MOCA test, Trail test A and B, Digit span test, and Categoric fluency test were conducted by another practitioner for all patients.

Forty-four patients diagnosed with AD based on DSM-IV, NINCDS-ADRDA criteria, and neuroimaging methods, and who did not meet any of the exclusion criteria, were included in the patient group after cognitive evaluation. Forty-four individuals with normal cognitive function and no exclusion criteria were included in the control group. MRI was performed on all Alzheimer's Disease patients in our study. MRI has been used in the clinical diagnosis of AD and in distinguishing AD patients from other reasons of dementia, such as vascular dementia, and reversible cognitive dysfunction causes (subdural hematoma, normal pressure hydrocephalus, intracranial tumor, etc.). Dementia patients without any AD-specific findings in neuroimaging methods were excluded.

Laboratory measurements

Complete blood count, erythrocyte sedimentation rate, C reactive protein (CRP), renal function tests, fasting blood glucose, HbA1c, TSH, vitamin B12 level, vitamin D level, lipid profile, and galectin-3 level were requested as laboratory tests.

For galectin-3 measurement, blood samples were drawn

from the patients and centrifuged at 4000 × g for 10 minutes. All serum samples were kept at - 80°C until assayed. Serum galectin-3 levels were analyzed by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (R & D Systems, Minneapolis, USA). Measurements were carried out using an ELISA plate reader (BioTek Instruments Inc, Winooski, VT, USA), and results are presented as ng/mL.

Statistics

Statistical analysis was performed using the SPSS software version 22. First of all, the variables were analyzed by visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilks test) to determine whether or not they are normally distributed. Descriptive statistics are presented using mean and standard deviation (mean ± SD) for normally distributed variables, median (minimum-maximum, interquartile range) for skew distributed variables. Categorical variables are reported as numbers and frequencies. Comparisons between groups were performed by t-test, ANOVA, Mann Whitney U, or Kruskal Wallis tests according to normal distribution and number of groups for numerical variables, and chi-square test for categorical variables. The relationship between numerical variables was calculated by Pearson or Spearman correlation analysis. A value of $P < 0.05$ was considered to indicate a statistical significance.

RESULTS

The median (min-max) age of the participants was 78 (66 - 85), and 45 (51.1%) were female. Forty-four (50%) of the study participants were in the AD group, and 44 (50%) were in the control group with normal cognitive function. General characteristics are shown in Table 1. Accompanying diseases and laboratory results were similar between groups (Table 1). In the AD group, 20 (45.5%) patients were diagnosed with mild AD, 17 (38.6%) patients with moderate AD, and 7 (15.9%) patients with moderately severe AD, according to GDS. The cognitive and comprehensive geriatric assessment test scores are given in Table 2.

The median (min-max) galectin-3 level in the AD group was 7.52 (2.22-16.19) ng/ml, whereas the median (min-max) galectin-3 level in the control group was 7.02 (1.87-20) ng/ml. Although the median galectin-3 level was numerically higher in the AD group compared to the control group, the difference did not reach statistical significance ($P = 0.443$). The relationship between galectin-3 level and the stage of AD was evaluated (Figure 1). The median (min-max) galectin-3 level in moderately severe AD [GDS stage 6, 10.42 (6.29 - 13.59) ng/mL] was significantly higher compared to the mild-moderate stage [GDS stage 4-5, 7.09 (2.22 - 16.19) ng/mL] ($P = 0.007$), and the normal stage [GDS stage 1-2, 7.02 (1.87 – 20) ng/mL] ($P = 0.017$).

Correlations between cognitive assessment test scores and galectin-3 levels were performed, and Digit Span Test, which measures attention, was significantly correlated with galectin-3 levels. There was a statistically significant negative and weak correlation observed between galectin-3 levels and the scores on the Digit Span Forward ($r = -0.216$, $P = 0.043$) and Digit Span Backward ($r = -0.233$, $P = 0.029$) tests.

DISCUSSION

This study showed that galectin-3 levels were similar between AD and control groups. Although the galectin-3 levels in patients with Alzheimer's Disease were slightly higher than in control group, this difference was not statistically significant. In the AD group, the galectin-3 level was significantly higher in GDS stage 6 (moderately severe AD) patients than in other stages. Furthermore, a weak but significant correlation was found between the galectin-3 levels and the Digit Span Test scores, suggesting that the increase in galectin-3 may be associated with attention.

In the literature, Wang et al. demonstrated the association of AD with galectin-3. The relationship between galectin-3 levels and three different groups - Alzheimer's Disease, mild cognitive impairment, and normal cognitive status - was examined. The galectin-3 level in the AD group was significantly higher than in the normal group (13). They found no significant difference between AD-MCI or MCI-normal groups. The authors do not mention the stage of the disease in the AD group. In another study, Yazar et al. found that serum galectin-3 levels were higher in patients with AD compared with control group, in particular with increasing disease stage (32).

The results of our study revealed that severe stage had increased levels of galectin-3.

In our study group, patients in the severe stage were only 15.9%, and most of the patients were in mild and moderate stages. This may be the reason for the nonsignificant difference between AD and the control group. It may be possible that in an AD group with more severe stage patients, galectin-3 levels may be significantly higher than in normal group. Further studies with more significant numbers, including different stages, are required to clarify this aspect. To the best of our knowledge, in the previous studies, acute or chronic infections, chronic inflammatory diseases, cancer, and rheumatological diseases were not excluded, but these diseases can influence levels of galectin-3. One of the strengths of our study is excluding the possible factors that may be associated with galectin-3 levels. Acute or chronic infections, chronic inflammatory diseases, cancer, and rheumatological diseases were excluded. Therefore, we tried to examine the association between Alzheimer's Disease and galectin-3 independent of possible other factors. Another advantage of our study was the cognitive assessment tests performed. A comprehensive assessment was performed, including MMSE, GDS, MOCA, Trail Making Test, Digit Span Test, and Category Fluency Test.

Table 1. Demographic properties and general characteristics according to groups

	AD (n = 44)	Control (n = 44)	P value
Age (years); median (min-max)	78 (68-85)	78 (66-85)	0.33**
Gender Female; n (%)	26 (59.1)	19 (43.2)	0.135#
Educational level Illiterate; n (%) Primary and secondary school; n (%) High school and university; n (%)	 15 (34.1) 25 (56.8) 4 (9.1)	 9 (20.5) 17 (38.6) 18 (40.9)	0.003#
Smoker*; n (%)	2 (4.5)	1 (2.3)	
Family history of AD; n (%)	15 (34.1)	1 (2.3)	<0.001#
Hypertension; n (%)	25 (56.8)	32 (72.7)	0.12#
Coronary artery disease; n (%)	7 (15.9)	13 (29.5)	0.13#
Diabetes mellitus; n (%)	17 (38.6)	16 (36.4)	0.83#
Hypothyroidism; n (%)	6 (13.6)	6 (13.6)	1#
Hyperthyroidism; n (%)	1 (2.3)	2 (4.5)	1#
Dyslipidemia; n (%)	26 (59.1)	27 (61.4)	0.83#
Hb (g/dL); mean ± SD	13.4 ± 1.5	13.8 ± 1.5	0.17##
Leukocyte (x10^3/µL); median (min-max)	7200 (4400-16000)	7200 (4400-10400)	0.65**
ESR (mm/h); median (min-max)	12.5 (2-45)	10.5 (2-60)	0.37**
CRP (mg/dL); median (min-max)	0.38 (0.1-3.1)	0.4 (0.2-2.9)	0.71**
Creatinine (mg/dL); mean ± SD	0.91 ± 0.25	0.95 ± 0.24	0.51##
Albumin (g/dL); mean ± SD	4.2 ± 0.3	4.3 ± 0.3	0.23##
ALT (U/L); median (min-max)	13 (5-39)	15.5 (8-50)	0.001**
AST (U/L); mean ± SD	19.4 ± 4.9	23.1 ± 4.4	0.01##
FPG (mg/dL); median (min-max)	97 (97-214)	102 (77-212)	0.52**
HbA1c (%); median (min-max)	6.4 (5.5-10.3)	6.4 (5.3-8.6)	0.57**
TSH (µIU/mL); median (min-max)	1.3 (0.08-9.07)	1.75 (0.16-55)	0.19**
Vitamin B12 (pg/mL); median (min-max)	329 (67-1501)	282.5 (105-1160)	0.48**
Vitamin D (µg/L); median (min-max)	24.3 (5-92.5)	20.5 (5-65.8)	0.89**
LDL-C (mg/dL); median (min-max)	160 (80-358)	143 (80-239)	0.18**

Data are given as n (%), mean ± SD or median (min-max). AD: Alzheimer's Disease, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, FPG: Fasting plasma glucose, Hb: Hemoglobin, HbA1c: Hemoglobin A1c, LDL-C: Low density lipoprotein cholesterol, N: Number, SD: Standard deviation, TSH: Thyroid stimulating hormone

*: Statistical analysis was not performed because the number of patients in the groups was small. **Mann Whitney U test, #Chi-Square test, ##Student's t-test

Currently, there is no definitive biomarker for diagnosing Alzheimer's Disease. However, this is a hot topic, and ongoing studies demonstrate many promising biomarkers (33). Inferences can be made about the role of galectin-3 in the pathogenesis of AD when its known properties and functions are considered. Galectin-3 has been identified in the central nervous system and peripheral nervous system in macrophages/microglia, astrocytes, endothelial cells, and Schwann cells (34, 35). Activation of microglia and endothelial cells is associated with the pathogenesis of AD (13). Galectin-3 plays a role in the functioning of immune cells as well. Thus, upregulation of galectin-3 expression may be associated with immunological activation and regulation. However, the studies and information on this subject are scarce (13). It has been shown in mouse models that galectin-3 regulates functions in the brain, especially in the hippocampus region. In a study by Trompet et al., although observed differences were minor, they found that carriers of variant alleles within the lectin galactoside-binding soluble-3 gene (LGALS3) performed worse on the four neuropsychological performance tests compared with the carriers of the wild-type allele (10). In this study, it was discovered that the three LGALS3 polymorphisms were linked to elevated CRP levels, suggesting that a heightened proinflammatory profile might contribute to diminished cognitive performance in advanced age. However, even after accounting for CRP levels, the relationship between LGALS3 polymorphisms and cognitive function remained largely

Table 2. Results of comprehensive geriatric assessment and cognitive assessment test scores

	AD (n = 44)	Control (n = 44)	P value
KATZ ADL; median (IQR)	5 (4 - 6)	6 (6 - 6)	< 0.001**
Lawton-Brody IADL; median (IQR)	5 (1 - 11)	17 (15 - 17)	< 0.001**
MNA-short form; median (IQR)	11 (10 - 12)	14 (13 - 14)	< 0.001**
Clock drawing test; median (IQR)	0 (0 - 4)	6 (6 - 6)	< 0.001**
MMSE; median (IQR)	18 (12 - 22)	29 (27 - 30)	< 0.001**
Three-word memory test; median (IQR)	0 (0 - 1)	3 (3 - 3)	< 0.001**
Attention and calculation; median (IQR)	0 (0 - 1)	5 (5 - 5)	< 0.001**
Yesavage geriatric depression scale-short form; median (IQR)	2 (0 - 5)	0 (0 - 2)	< 0.001**
GDS 2 (Age-Associated Memory Impairment); n (%) 4 (Mild AD); n (%) 5 (Moderate AD); n (%) 6 (Moderately Severe AD); n (%)	 - 20 (45.5) 17 (38.6) 7 (15.9)	 44 (100) - - -	
DAD; median (IQR)	44 (23 - 70)	100 (100 -100)	< 0.001**
MOCA; median (IQR)	6 (3 - 11)	19 (16 - 21)	< 0.001**
Trail test A; n (%) Test score (sec); mean ± SD	4 (9.1) 71 ± 17.1	21 (47.7) 62.2 ± 13.95	< 0.001# 0.27##
Digit span test Forward; median (IQR) Backward; median (IQR)	 2 (1 - 4) 2 (0 - 2)	 4 (3 - 6) 3 (2 - 4)	 < 0.001** < 0.001**
Categoric fluency test; mean ± SD	8.3 ± 4.7	16.6 ± 4.5	< 0.001##

Data are given as n (%), mean ± SD or median (IQR). AD: Alzheimer's Disease, DAD: Disability assessment for dementia, GDS: Global deterioration scale, IQR: Interquartile range, KATZ ADL: KATZ activities of daily living, Lawton-Brody IADL: Lawton-Brody instrumental activities of daily living, MMSE: Mini-mental status examination, MNA: Mini nutritional assessment, MOCA: Montreal cognitive assessment, N: Number, SD: Standard deviation
**Mann Whitney U test, #Chi-Square test, ##Student's t-test

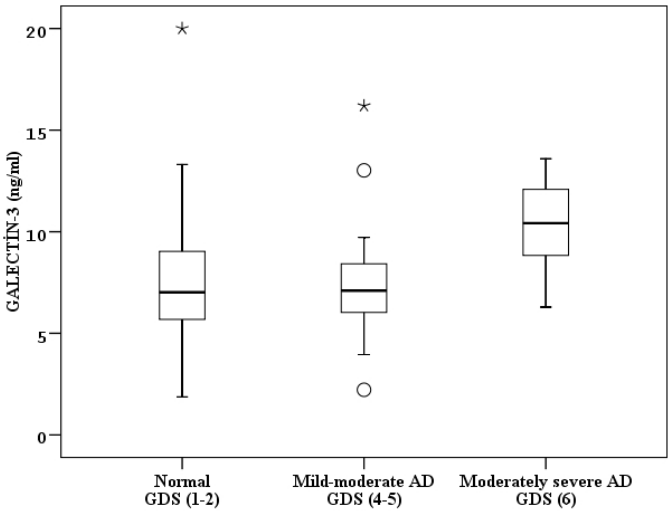

Figure 1. Galectin-3 levels according to GDS (Global Deterioration Scale) stage.
Galectin-3 levels were significantly higher in the moderately severe AD (GDS stage 6) group (GDS Stage 6: 10.42 [6.29-13.59] ng/mL, GDS Stage 4-5: 7.09 [2.22-16.19] ng/mL, GDS Stage 1-2: 7.02 [1.87-20] ng/mL; P = 0.032). The P values for the comparisons of moderately severe AD vs. normal GDS and moderately severe AD vs. mild-moderate AD were 0.017 and 0.007, respectively.

unchanged (10). Individuals exhibiting a proinflammatory profile face a heightened risk of cognitive decline compared to those with an anti-inflammatory profile (36, 37). In the geriatric age group, inflammation is a significant factor in the development of cognitive decline and dementia (6). Galectin-3, given its regulatory function in inflammation, may impact cognitive function in older individuals through its involvement in the inflammatory process (10). Therefore, the shared characteristics suggest the possibility that galectin-3 could serve as a potential biomarker for Alzheimer's Disease. Additionally, measuring galectin-3 is noninvasive, reproducible, inexpensive, and easy to implement. These all suggest that galectin-3 may be one of these promising biomarkers. The demonstration of elevated levels of galectin-3 at the severe stage of AD in our study supports that it may be a promising biomarker. Long-term follow-up studies with more patients will show this relationship more clearly.

There may be some possible limitations in this study. The first one is its cross-sectional design. While there is a notable increase in galectin-3 levels during the advanced stage, we can not say there is a cause-and-effect relationship. We can not tell whether the galectin-3 level increases due to the increase in inflammatory and oxidative stress load as the disease progresses or whether patients with high levels of galectin-3 at the early stages get to the advanced stage easily due to the excess of this burden. The second limitation concerns the patient number. Our patient number may not be enough for supporting galectin-3 as a biomarker for AD. Prospective studies with long-term follow-ups are needed to clarify this relationship.

CONCLUSION

Different hypotheses have been proposed to reveal the relationship between galectin-3 and AD. Our study found that serum levels of galectin-3 were higher in AD than in control subjects, though not significant. In addition, we found that galectin-3 levels in patients with moderately severe AD (GDS stage 6) group were significantly higher than in the earlier stages. These findings may support that galectin-3 is linked to AD, especially its severity. Galectin-3, a marker for inflammation and oxidation, may be a promising biomarker for AD, and prospective cohort studies should support this.

Additional information: Presented in at the 12th International Congress of the European Union Geriatric Medicine Society, 5-7 October 2016 Lisbon, Portugal. This study has been conducted as Dr. Gürkan Güner's specialization thesis.

Ethics Committee Approval: The required approval for conducting the study was obtained from the Ethics Committee of the Faculty of Medicine, Hacettepe University (Date 26.12.2014/ Number GO 14/649). The study protocol was in adherence with the principles in the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions: Idea/Concept: BBD, MH, MC, Design: BBD, MH, MC, Supervision: BBD, MH, MC, Data collection and/or processing: GG, MKK, MCK, HDV, AS, FA, Analysis and/or interpretation: GG, BBD, Literature search: GG, BBD, Writing: GG, BBD, Critical review: BBD, MH, MC, References and fundings: GG, Materials: -.

Conflicts of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1.Perkins P, Annegers JF, Doody RS, Cooke N, Aday L, Vernon SW. Incidence and prevalence of dementia in a multiethnic cohort of municipal retirees. Neurology 1997;49:44-50.
2.Mudher A, Lovestone S. Alzheimer's disease-do tauists and baptists finally shake hands? Trends Neurosci 2002;25:22-6.
3.Liu P-P, Xie Y, Meng X-Y, Kang J-S. History and progress of hypotheses and clinical trials for alzheimer's disease. Signal Transduction and Targeted Therapy 2019;4:29.
4.Cankurtaran M, Yesil Y, Kuyumcu ME, et al. Altered levels of homocysteine and serum natural antioxidants links oxidative damage to alzheimer's disease. J Alzheimers Dis 2013;33:1051-8.
5.Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med 2010;362:329-44.
6.Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. J Am Geriatr Soc 2002;50:2041-56.
7.Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in alzheimer's disease. Lancet Neurol 2015;14:388-405.
8.Khan TK, Alkon DL. Peripheral biomarkers of alzheimer's disease. J Alzheimers Dis 2015;44:729-44.
9.Dumic J, Dabelic S, Flogel M. Galectin-3: An open-ended story. Biochim Biophys Acta 2006;1760:616-35.
10.Trompet S, Jukema W, Mooijaart SP, et al. Genetic variation in galectin-3 gene associates with cognitive function at old age. Neurobiol Aging 2012;33:2232.e1-.e9.
11.Verkerke H, Dias-Baruffi M, Cummings RD, Arthur CM, Stowell SR. Galectins: An ancient family of carbohydrate binding proteinscarbohydrate binding proteins (cbps) with modern functions. In: Stowell SR, Arthur CM, Cummings RD, editors. Galectins: Methods and protocols. New York, NY: Springer US; 2022. p. 1-40.
12.Hara A, Niwa M, Noguchi K, et al. Galectin-3 as a next-generation biomarker for detecting early stage of various diseases. Biomolecules 2020;10:389.
13.Wang X, Zhang S, Lin F, Chu W, Yue S. Elevated galectin-3 levels in the serum of patients with alzheimer's disease. Am J Alzheimers Dis Other Demen 2013;30:729-32.
14.Henderson NC, Sethi T. The regulation of inflammation by galectin-3. Immunol Rev 2009;230:160-71.
15.Liu FT. Regulatory roles of galectins in the immune response. Int Arch Allergy Immunol 2005;136:385-400.
16.Liu FT, Hsu DK. The role of galectin-3 in promotion of the inflammatory response. Drug News Perspect 2007;20:455-60.
17.Boza-Serrano A, Ruiz R, Sanchez-Varo R, et al. Galectin-3, a novel endogenous trem2 ligand, detrimentally regulates inflammatory response in alzheimer's disease. Acta Neuropathologica 2019;138:251-73.
18.Arik G, Varan HD, Yavuz BB, et al. Validation of katz index of independence in activities of daily living in turkish older adults. Arch Gerontol Geriatr 2015;61:344-50.
19.Isik EI, Yilmaz S, Uysal I, Basar S. Adaptation of the lawton instrumental activities of daily living scale to turkish: Validity and reliability study. Ann Geriatr Med Res 2020;24:35-40.
20.Tozlu M, Cankurtaran M, Yavuz BB, et al. Functional disability in alzheimer disease: A validation study of the turkish version of the disability assessment for dementia scale. J Geriatr Psychiatry Neurol 2014;27:237-46.
21.Eker E, Yaşar R, Ertan T, Güngen C. Standardize mini mental test'in türk toplumunda hafif demans tanısında geçerlik ve güvenilirliği. Türk Psikiyatri Dergisi 2002;13:273-81.
22.Stähelin HB, Monsch AU, Spiegel R. Early diagnosis of

dementia via a two-step screening and diagnostic procedure. Int Psychogeriatr 1997;9 Suppl 1:123-30.
23.Selekler K, Cangoz B, Uluc S. Power of discrimination of montreal cognitive assessment (moca) scale in turkish patients with mild cognitive impairement and alzheimer's disease. Turkish Journal of Geriatrics 2010;13:166-71.
24.Cangoz B, Karakoc E, Selekler K. Trail making test: Normative data for turkish elderly population by age, sex and education. J Neurol Sci 2009;283:73-8.
25.Bosgelmez S, Yildiz M, Yazici E, et al. Reliability and validity of the turkish version of cognitive assessment interview (cai-tr). Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology 2015;25:365-80.
26.Association AP. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, USA: American Psychiatric Association; 1994.
27.McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of alzheimer's disease: Report of the nincds-adrda work group under the auspices of department of health and human services task force on alzheimer's disease. J Alzheimers Dis 1984;34:939-44.
28.Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136-9.
29.Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183-94.
30.Sarikaya D, Halil M, Kuyumcu ME, et al. Mini nutritional assessment test long and short form are valid screening tools in turkish older adults. Arch Gerontol Geriatr 2015;61:56-60.
31.Ertan T, Eker E. Reliability, validity, and factor structure of the geriatric depression scale in turkish elderly: Are there different factor structures for different cultures? Int Psychogeriatr 2000;12:163-72.
32.Yazar T, Olgun Yazar H, Cihan M. Evaluation of serum galectin-3 levels at alzheimer patients by stages: A preliminary report. Acta Neurologica Belgica 2021;121:949-54.
33.Xu M-m, Zhou M-t, Li S-w, Zhen X-c, Yang S. Glycoproteins as diagnostic and prognostic biomarkers for neurodegenerative diseases: A glycoproteomic approach. Journal of Neuroscience Research 2021;99:1308-24.
34.Nio-Kobayashi J. Tissue- and cell-specific localization of galectins, β-galactose-binding animal lectins, and their potential functions in health and disease. Anatomical Science International 2017;92:25-36.
35.Ramos-Martínez E, Ramos-Martínez I, Sánchez-Betancourt I, et al. Association between galectin levels and neurodegenerative diseases: Systematic review and meta-analysis. Biomolecules 2022;12:1062.
36.Campbell IL, Stalder AK, Chiang CS, et al. Transgenic models to assess the pathogenic actions of cytokines in the central nervous system. Mol Psychiatry 1997;2:125-9.
37.Ho GJ, Drego R, Hakimian E, Masliah E. Mechanisms of cell signaling and inflammation in alzheimer's disease. Curr Drug Targets Inflamm Allergy 2005;4:247-56.

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Original Article / Araştırma Makalesi

EVALUATION OF THE RELATIONSHIP BETWEEN SLEEP DISORDERS AND DEPRESSION IN PARKINSON'S DISEASE

PARKİNSON HASTALIĞI'NDA UYKU BOZUKLUĞU VE DEPRESYON ARASINDAKİ İLİŞKİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

Introduction: As the severity of the disease increases in Idiopathic Parkinson's Disease (IPD), additional problems such as sleep disorders and excessive daytime sleepiness confront us. In addition, the presence of depression negatively affects the quality of life of the patients with Parkinson's disease. In our study, we have aimed to show sleep disorders and daytime sleepiness in the advanced stages of IPD and their relationships with depression.

Methods: The aim of the study was to examine it with a cross-sectional research method between March 2012 and July 2013. 42 patients diagnosed with IPD and 48 healthy individuals who applied to the Movement Disorders Polyclinic of the Department of Neurology were included in the study. In the IPD group, the disease was graded with the Hoehn&Yahr (H&Y) evaluation scale. In the IPD, and control groups, depression was evaluated with the Hamilton Rating Scale for Depression (HAM-D). night sleep and daytime sleepiness with Parkinson's Disease Sleep Scale (PDSS), and daytime sleepiness with Epworth Sleepiness Scale (ESS). Data were evaluated for age, gender, marital status and compared with those of the control group.

Results: As the ESS scores of the IPD patients included in the study increased dramatically, PDSS scores of these patients decreased significantly (r = -0.615; p = 0.000). As ESS scores increased, the HAM-D scores also increased moderately but significantly (r = 0.388; p = 0.000). It has been also determined that as the PDDS scores increased, the HAM-D and Hoehn-Yahr (H&Y) scale scores decreased significantly with strong correlations between these rating scale scores (r=-0.569 p=0.000 for HAM-D; r=-0.63 p=0.000 for H&Y . As H&Y scale scores increased, a significant increase in HAM-D scores was observed (r = 0.422; p = 0.005).

Conclusion: Sleep disorder may be an important parameter in the general evaluation of and treatment approach to Parkinson's Disease (PD). In addition, depression in PD patients is a psychological problem that must be actively questioned, and treated by physicians when detected.

Key Words: Parkinson's disease; depression; sleeping disorders;

ÖZET

Giriş: İdyopatik Parkinson Hastalığı (İPH)'nda hastalığın şiddeti artıkça uyku bozuklukları, gündüz aşırı uyku hali gibi ek sorunlar karşımıza çıkmaktadır. Ayrıca depresyon varlığı parkinson hastalarının yaşam kalitesini kötü etkilemektedir. Çalışmamızda İPH' ın ileri evrelerinde uyku bozuklukları ile gündüz uykululuk hali ve bunun depresyonla ilişkisini göstermeyi amaçladık.

Yöntemler: Çalışma Mart 2012 ve Temmuz 2013 tarihleri arasında kesitsel araştırma yöntemiyle inceleme amaçlanarak, Nöroloji Ana Bilim Dalı Hareket Bozuklukları Polikliniği' ne başvuran, İPH tanısı alan 42 hasta ve 48 sağlıklı birey çalışmaya alındı. İPH grubunda Hoehn&Yahr (H&Y) Değerlendirme Skalaları ile hastalık derecelendirildi. Hamilton Depresyon Değerlendirme Ölçeği (HAM-D) ile depresyon değerlendirmesi yapıldı. İPH ve kontrol grubuna gece uykusu ve gündüz uyuklamalarının değerlendirildiği Parkinson Hastalığı Uyku Ölçeği (PHUÖ), gündüz uykululuğunun değerlendirildiği Epworth Uykululuk Ölçeği (EUÖ) uygulandı. Hastaların yaş, cinsiyet, medeni durumları değerlendirildi ve kontrol grubu ile karşılaştırıldı.

Bulgular: Çalışmaya alınan İPH' ın EUÖ skoru arttıkça PHUÖ skorunda anlamlı düzeyde azalma gerçekleşmektedir ve bu artışın derecesi güçlü bir düzeydedir (r=-0,615; p=0,000). EUÖ arttıkça HAM-D skorunda anlamlı düzeyde artış gerçekleşmektedir ve bu artışın derecesi orta düzeydedir (r=0,388; p=0,000). PHUÖ değeri arttıkça, Hamilton ve Hoehn-Yahr değerinde anlamlı düzeyde azalma gösterdiği belirlenmiştir ve bu ilişkinin dereceleri güçlüdür. (Hamilton için r=-0,569 p=0,000; Hoehn-Yahr için r=-0,63 p=0,000). H&Y değeri arttıkça HAM-D skorunda anlamlı artış gözlenmektedir (r=0,422; p=0,005).

Sonuç: Parkinson Hastalığının genel değerlendirmesi ve tedaviye yaklaşımında uyku bozukluğu önemli bir parametre olabilir. Ayrıca Parkinson hastalarında depresyon, hekimler tarafından aktif olarak sorgulanması ve saptandığında mutlaka tedavi edilmesi gereken bir ruhsal sorundur.

Anahtar Kelimeler: Parkinson hastalığı, depresyon, uyku bozuklukları

INTRODUCTION

Idiopathic Parkinson's Disease (IPD) is a progressive disorder clinically characterized with resting tremor, cogwheel rigidity, bradykinesia, and impairment of postural reflexes. In addition to these four major findings, autonomic, motor, sensory and cognitive complaints may also be observed. It was first described as "shaking palsy" by the British physician James Parkinson in 1817 (1). In Parkinson's disease, not only physical disorders affect lifestyle, but also non-motor symptoms such as sleep disorders and depression are common complaints that significantly affect the quality of daily life. Sleep disorders are extremely

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prevalent in PD patients, and up to 60% of PD patients have sleep disorders (2). Sleep disorders and daytime sleepiness negatively affect patient's daily life and energy (3). Sleep disorders described in IPD include insomnia, characterized by difficulty falling asleep or staying asleep; sleep movement disorders or rapid eye movement (REM) sleep behavior disorders (RDB) characterized by abnormal motor activity during sleep and hypersomnia characterized by respiratory disorders during sleep or daytime sleepiness and/or irresistible sleep attacks. Depression which is one of the common causes of insomnia, is very frequently seen in IPD (4). Complex, and poorly understood interrelationships exist between depression, sleep and fatigue. Insomnia can be a direct result of depression. Although the effects of sleep and depression in IPD patients have not been carefully studied, their impact on clinical condition of the patients has been confirmed in survey studies. In studies performed, sleep disorders have been observed more frequently in patients with IPD and depression (5).

In the light of all this information, our aim in this study is; to reveal the presence of sleep disorders, daytime sleepiness and their relationships with depression in the advanced stages of IPD.

METHOD

The aim of the study was to examine it with a cross-sectional research method between March 2012 and July 2013. 42 patients diagnosed with IPD and 48 healthy individuals who applied to the Movement Disorders Polyclinic of the Department of Neurology were included in the study. Before the research, ethical approval was obtained from the Local Ethics Committee (decision date 09.10. 13, decision number 2013/427. As a control group, age-matched individuals who had not health problems such as neurodegenerative disease, respiratory problems, diabetes mellitus, hypertension and heart failure were included in the study. The severity of depression was graded using the Hamilton depression assessment scale (HAM-D). Parkinson's Disease Sleep Scale (PDSS) was applied to the patient and control groups to evaluate night sleep and Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness. PDSS consists of 15 questions to be answered by the patient. PDSS may evaluate the quality of sleep as a whole throughout the night (question 1), difficulty in starting and continuing sleep (questions 2-3), presence of restless legs syndrome (RLS)-like symptoms at night (questions 4-5), nocturnal psychosis (questions 6-7), nocturia (questions 8-9), nocturnal motor symptoms (questions 10-13), restfulness of sleep (question 14) and daytime napping (question 15). The test is performed by giving a score ranging between 0 (very severe complaints) and 10 (no complaints) for each question. The total score is 150 (no sleep-related complaints). ESS consists of 8 questions, and each of which is evaluated by giving a score between 0 and 3. A total score of 10 or more indicates increased daytime sleepiness, and scores above 15 indicate pathological sleepiness. The same doctor and the same rating scores were used for the evaluations. The data were evaluated according to age, gender, marital status, caregiver and compared with the control group.

Statistical analysis

Chi-square analysis was used to test pairwise correlations between categorical variables. Relationships between age, time to diagnosis, PDSS, ESS, HAM-D scale scores were examined with Pearson correlation coefficient. The statistical significance level was taken as $p<0.05$ and SPSS (ver. 11.5) program was used in the calculations.

RESULTS

The IPD group consisted of 25 (59.5%) male, and 17 (40.5%) female patients, and the healthy control group comprised of 16 (33.3%) male, and 32 (66.7%) female participants. Thirty-two (76.2%), patients, and all (n: 48; 100%) of control subjects were married, while 10 (23.8%) patients were single. The mean (± SD) ages of the patients, and the control subjects were 69.38 (±10.331), and 66.46 (±11.570) years, respectively. Indicated percentages of patients diagnosed with IPD had a H&Y scale score of 1 (31%), and 4 (9.5%). The demographic characteristics of the patients are presented in Table-1.

Descriptive statistics for 9 variables of the patient and control groups and relevant variables between these groups were examined. The mean (± SD) PDSS, ESS and HAM-D scale scores of the patient group were found to be significantly higher than the corresponding scale scores of the control group (for all $p<0.001$). Information is presented in Table-2.

As is seen, the Epworth sleep scale scores increased significantly with age ($r=0.389$; $p<0.0001$), but PDSS scores decreased significantly with age ($r=-0.214$; $p=0.043$). Besides, as the time of diagnosis delayed, HAM-D and

Table 1. Distribution of gender and marital status in patient and control groups

	Gender		Marital Status		Total
	Male	Female	Married	Single	
Patients, n (%)	25 (59.5)	17(40.5)	32 (76.2)	10 (23.8)	42 (100.0)
Control subjects, n (%)	16 (33.3)	32 (66.7)	48 (100.0)	0 (0.0)	48 (100.0)
Total, n (%)	41(45.6)	49 (54.4)	80 (88.9)	10 (11.1)	90 (100.0)

Table 2. Descriptive statistics of patient and control groups in terms of relevant numerical variables

		n	Mean (± SD)	Minimum	Maximum	*p*
Age (years)	Patient	42	69.38(± 10.331)	47	85	0.212*
	Control	48	66.46 (±11.570)	40	89	
PDSS	Patient	42	111.69 (±22.733)	53	141	<0.001*
	Control	48	139.94(±6.019)	130	150	
ESS	Patient	42	6.17(±3.123)	2	15	<0.001*
	Control	48	2.69 (±2.135)	0	8	
HAM-D	Patient	42	10.43(±4.467)	4	24	<0.001*
	Control	48	6.48(±2.790)	2	14	
Time to diagnosis (years)	Patient	42	5.64(±4.355)	1	18	

* Chisquare. Note: This table displays descriptive statistics for each data. The statistics estimated are mean, minimum, maximum and standard deviation (SD). PDSS:P arkinson's Disease Sleep Scale, ESS: Epworth Sleepiness Scale, HAM-D: Hamilton Rating Scale for Depression

Table 3. Correlations between age, time of diagnosis, ESS and H&Y scale scores

		Time of diagnosis	ESS	HAM-D	H&Y	PDSS
Years	r	0.170	0.389	0.090	0.086	-0.214
	p	0.282	<0.0001	0.399	0.587	0.043
	n	42	90	90	42	90
Time of diagnosis	r		0.139	0.318	0.518	-0.476
	p		0.380	0.040	<0.0001	0.001
	n		42	42	42	42
ESS	r			0.388	0.250	-0.615
	p			<0.0001	0.111	<0.0001
	n			90	42	90
HAM-D	r				0,422	-0,569
	p				0,005	<0,0001
	n				42	90
H&Y	r					-,630
	p					<0,0001
	n					42

ESS: Epworth Sleepiness Scale, HAM-D: Hamilton Rating Scale for Depression, H&Y: Hoehn&Yahr, PDSS: Parkinson's Disease Sleep Scale.

Hoehn&Yahr scale scores also increased significantly (r=0.318 p=0.040 for HAM-D; r=0.518 p<0.0001 for Hoehn&Yahr). However, as the time to diagnosis was prolonged, the PDSS scores decreased significantly (r = -0.476; p = 0.001). As the Epworth Sleep scale scores increased, the HAM-D scale scores also increased significantly but moderately (r=0.388; p<0.0001). As the Epworth Sleep scale scores increased, the PDSS scores also decreased dramatically, and significantly (r=-0.615; p<0.0001). It was determined that as the PDSS scores increased, HAM-D and Hoehn&Yahr scale scores decreased significantly, with a strong interrelationship (r=-0.569 p<0.0001 for HAM-D; r=-0.630 p<0.0001 for H&Y). As the H&Y scale scores increased, the HAM-D scale scores increased significantly (r=0.422; p=0.005). The statistical analysis of these findings is summarized in Table-3.

Graphs for examining the relationships between age, diagnosis time, Epworth, Hamilton, H&Y numerical variables are shown in Figures 1,2,3.

DISCUSSION

Sleep disorder is extremely common in IPD and is seen in more than 75% of IPD patients (6). In our study, 84% of these patients had sleep disorders. Chaudhuri et al. (7) applied assessment tools of PDSS and ESS to demonstrate sleep problems in patients with Parkinson's disease and showed that there was a significant difference with this respect between especially the patients in the middle-advanced stage of the disease and the control group. In our study, PD patients had worse scores than the control group in all domains of PDSS. In our study, similar to the

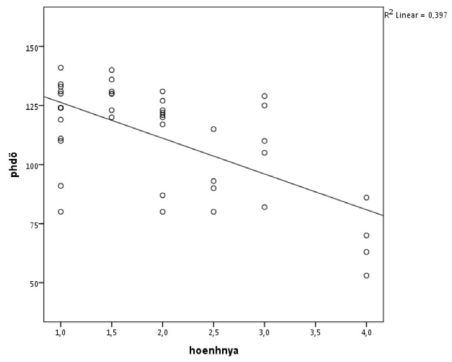

Figure 1. Graph demonstrating the correlation between H&Y and PDSS scores;

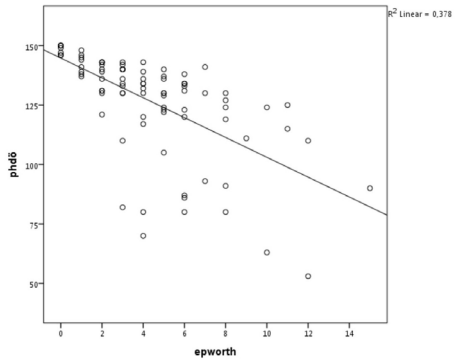

Figure 2. Graph demonstrating the correlation between ESS and PDSS scores;

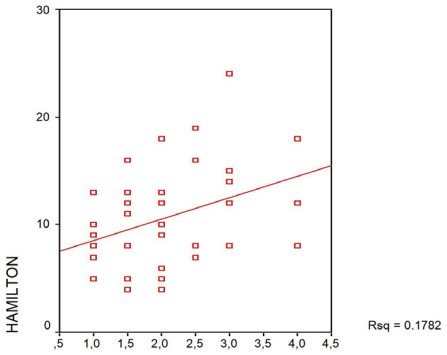

Figure 3. Scatter plot of the correlation between H&Y and HAM-D scale scores

literature, we have determined that as age, age at disease onset, degree of disability (higher Hoehn & Yahr scale scores), and the duration of the disease increased, sleep disorders worsened extremely with resultant increases in PDSS and ESS scores.

Excessive daytime sleepiness and sudden attacks of sleep during the day are also seen at a rate of 10-50% in IPD (8). In the meta-analysis of excessive daytime sleepiness in Parkinson's disease performed in 2021, Fei Feng et al. (9), observed excessive daytime sleepiness in approximately one third of PD patients. It has been found that patients have difficulty maintaining their alertness during a sedentary activity such as reading books or watching television, and if the clinical condition is more severe, sudden sleepiness may occur while eating or driving, which can be very dangerous (10). In our study, based on assessments made with ESS, we found that daytime sleepiness and sudden attacks of sleep were significantly more common in PD patients than in the control group.

A study on depression and major depressive disorder in PD patients suggested that Parkinson's disease may be a stressor for depression, but it does not necessarily trigger its onset. Beck Depression Inventory was used in a study and mild to moderate depressive symptoms had been detected in nearly 40% of the patients (11). Additionally, in another study, the age of onset, severity, duration, stage or subtype of IPD have been related to the time of onset or severity of depressive episodes (12). Similarly, in our study, as the severity of IPD increased and the patients got older, the severity of depression increased in PD patients as also confirmed by higher HAM-D scale scores obtained, consistent with the literature.

A strong and complex relationship exists between sleep and depressive disorders. Just as depression can lead to sleep problems, sleep problems can also cause or accompany depression. Sleep problems have been associated with increased disease severity in patients with depressive disorder (13). Another study has showed that depression is one of the common causes of insomnia and that depression is very common in IPD (14). In our study, the close relationship between insomnia and depression in IPD varied according to the stage of the disease, the age of the patient, and the time of diagnosis, supporting its relationship with sleep disturbance and depression in PD patients.

CONCLUSION

As a result, sleep disorders and frequent daytime naps are observed in IPD, which worsen significantly in parallel with the increase in the duration of the disease and the degree of disability. Sleep disorder may be an important parameter in the general evaluation of the disease and approach to its treatment.

The presence of depression creates diagnostic confusion and negatively affects the severity of Parkinson's disease, making treatment difficult. Therefore, depression in PD patients is a psychological problem that must be actively questioned and treated by physicians when detected. Thus, further negative effects of a psychological problem on the already impaired quality of life of these patients due to PD symptoms, can be prevented.

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Ethics Committee Approval: The study was approved by Düzce University Education and Research Hospital, Clinical Research Ethics Committee. (Approval date and number date 09.10. 13, 2013/427).

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

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REFERENCES

1. Palacios-Sánchez L, Torres Nupan M, Botero-Meneses JS. James Parkinson and his essay on “shaking palsy”, two hundred years later. Arq Neuropsiquiatr. 2017;75:671-2.
2. Liu H, Li J, Wang X, et al. Excessive Daytime Sleepiness in Parkinson’s Disease. Nat Sci Sleep. 2022;14:1589-609.
3. Sprajcer M, Owen PJ, Crowther ME, et al. Sleep disturbance in caregivers of individuals with Parkinsonism: a systematic review and meta-analysis. BMJ Open. 2022;12:062089.
4. Stefani A, Högl B. Sleep in Parkinson’s disease. Neuropsychopharmacology. 2020;45:121-8.
5. Suzuki K, Mivamoto M, Matsubara T. Detection and management of sleep disturbances in Parkinson’s disease. Nihon Rinsho. 2017;75:125-35.
6. Factor S.A., McAlarney T., Sanchez-Ramos J.R., Weiner W.J. Schlafstörungen und Schlafeffekte bei der Parkinson-Krankheit. Mov Disord 1990;5:280-5.
7. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson’s disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson’s disease. J Neurol Neurosurg Psychiatry. 2002;73:629-35.
8. Högl B, Seppi K, Brandauer E, et al. Increased daytime sleepiness in Parkinson’s disease: a questionnaire survey. Mov Disord. 2003;18:319-23.
9. Feng F, Cai Y, Hou Y, Ou R, Jiang Z, Shang H. Excessive daytime sleepiness in Parkinson’s disease: A systematic review and meta-analysis. Parkinsonism Relat Disord. 2021;85:133-40.
10. Baumann C, Ferini-Strambi L, Waldvogel D, Werth E, Bassetti CL. Parkinsonism with excessive daytime sleepiness--a narcolepsy-like disorder?. J Neurol. 2005;252:139-45.
11. Inoue T, Kitagawa M, Tanaka T, Nakagawa S, Koyama T. Depression and major depressive disorder in patients with Parkinson’s disease. Mov Disord. 2010;25:44-9.
12. Marsh L, McDonald WM, Cummings J, Ravina B. NINDS/NIMH Work Group on Depression and Parkinson’s Disease. Provisional diagnostic criteria for depression in Parkinson’s disease: report of an NINDS/NIMH Work Group. Mov Disord. 2006;21:148-58.
13. Aydın H. Uyku ve Bozuklukları. Ankara, Hekimler Yayın Birliği; 2007.
14. Lees, A.J.,Blackburn, N.A.Campbell, V.L. The nighttime problems of Parkinson’sdisaese Clin Neuropharmacol.1988;11:512-9.

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Original Article / Araştırma Makalesi

GASTRIC POLYPS: A RETROSPECTIVE ANALYSIS OF 5-YEAR SINGLE CENTER RESULTS

5 YILLIK TEK MERKEZ SONUÇLARININ RETROSPEKTİF ANALİZİ

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ABSTRACT

Introduction: Gastric polyps are mostly asymptomatic, seen incidentally on oesophagogastroduodenoscopy and are mostly benign lesions. They are less common than colon polyps and have a lower malignant potential. The main determinant of treatment planning is the histopathological features of the polyp. In this study, we aimed to retrospectively investigate the frequency, age, gender and localisation distribution, histopathological features, association with Helicobacter pylori (HP) and the presence of intestinal metaplasia (IM) in gastric polyps detected in our endoscopy unit.

Methods: Endoscopy reports of 4004 patients who underwent oesophagogastroduodenoscopy between January 2017 and January 2022 were retrospectively reviewed. The data of 67 patients with histopathological polyps were evaluated. Age, gender, endoscopic examination findings and histopathological data of the patients were obtained from hospital records and evaluated retrospectively.

Results: The lesions sampled in 67 (1.67%) of 4004 patients were histopathologically evaluated as polyps. Of the patients with polyps, 41 (61.19%) were female and 26 (38.81%) were male. The mean age of the patients was 60.28 years (38-87). The mean polyp diameter was 7.40 (3-60) mm. HP was positive in 18 of 58 patients (32.14%). IM was positive in 9 of 56 patients (16.07%). HP coexistence was present in 6 (66.67%) of these patients.

Conclusion: It is important to perform biopsy or polypectomy when polyps are detected in esophagogastroduodenoscopy and histopathological evaluation of the lesions found in the specimen in gastric resections. This evaluation is thought to contribute to the detection of possible malignancies. Investigation of the presence of HP and IM in patients with polyps due to the potential for malignancy development will contribute to early diagnosis and treatment.

Keywords: Gastric polyp, Helicobacter pylori, intestinal metaplasia, malignancy

ÖZET

Giriş: Gastrik polipler çoğunlukla asemptomatiktir, özofagogastroduodenoskopide rastlantısal olarak görülür ve çoğunlukla benign lezyonlardır. Kolon poliplerinden daha az görülürler ve daha düşük malign potansiyele sahiptirler. Tedavi planlamasının ana belirleyicisi polibin histopatolojik özellikleridir. Bu çalışmada, endoskopi ünitemizde saptanan gastrik poliplerin sıklığını, yaş, cinsiyet ve lokalizasyon dağılımını, histopatolojik özelliklerini, Helicobacter pylori (HP) ile ilişkisini ve intestinal metaplazi (İM) varlığını retrospektif olarak araştırmayı amaçladık.

Yöntemler: Ocak 2017 ile Ocak 2022 tarihleri arasında özofagogastroduodenoskopi yapılan 4004 hastanın endoskopi raporları retrospektif olarak incelendi. Histopatolojik polip saptanan 67 hastanın verileri değerlendirildi. Hastaların yaş, cinsiyet, endoskopik muayene bulguları ve histopatolojik verileri hastane kayıtlarından elde edildi ve retrospektif olarak değerlendirildi.

Bulgular: İncelenen 4004 hastadan, 67(%1,67) kişide örneklenen lezyonlar histopatolojik olarak polip olarak değerlendirildi. Polip saptanan hastaların 41'i (%61,19) kadın ve 26'sı (%38,81) erkekti. Hastaların ortalama yaşı 60,28 (38-87) idi. Ortalama polip çapı 7,40 (3-60) mm idi. HP 58 hastanın 18'inde (%32,14) pozitifti. IM 56 hastanın 9'unda (%16,07) pozitifti. Bu hastaların 6'sında (%66,67) HP birlikteliği mevcuttu.

Sonuç: Özofagogastroduodenoskopide polip saptandığında biyopsi veya polipektomi yapılması, mide rezeksiyonlarında ise spesmende saptanan lezyonların histopatolojik olarak değerlendirilmesi önemlidir. Bu değerlendirmenin olası malignitelerin tespitine katkı sağlayacağı düşünülmektedir. Malignite gelişme olasılığı nedeniyle polip saptanan hastaların HP ve IM varlığının araştırılmasının erken tanı ve tedaviye katkı sağlayacaktır.

Anahtar Kelimeler: Gastrik polipler, Helicobacter pylori, İntestinal metaplazi, malignite

INTRODUCTION

Gastric polyps are usually asymptomatic and are detected during endoscopic procedures due to complaints such as anemia and dyspepsia (1). In the literature, the incidence of gastric polyps is reported to be between 0.3-6%. The prevalence of different polyp subtypes is highly variable. With the increase in the frequency of endoscopy use and modern developments in endoscopy, there is an increase in the frequency of gastric polyp detection, Studies have shown that the prevalence of gastric polyps increased from 1.0% to 4.70% between 2004 and 2013 (2). Gastric polyps can be seen in different parts of the stomach. They originate from different cells and tissues. There are many subgroups of gastric polyps and there is no clear differentiation of these polyps endoscopically. Histopathological examination is considered essential for definitive diagnosis. Gastric

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polyps can be either neoplastic or non-neoplastic. The most common types of gastric polyps are hyperplastic polyps and fundic gland polyps. Those reported as adenocarcinoma, neuroendocrine tumor or ectopic pancreatic tissue are less frequent (3-5). Compared to colorectal polyps, the majority of gastric polyps are not neoplastic (6). In patients with Helicobacter pylori (HP) infection, hyperplastic and adenomatous polyps are more common than other polyps. Intestinal metaplasia (IM), on the other hand, is a precancerous lesion and requires close follow-up due to the risk of gastric cancer. It is thought that this evaluation will contribute to the detection of possible malignancies and investigating the presence of HP and IM in positive cases due to the possibility of malignancy development will contribute to increased awareness and early diagnosis.

METHODS

Patients who underwent esophagogastroduodenoscopy for various reasons in the General Surgery Endoscopy unit of our hospital between January 2017 and January 2022 and whose histopathological examination was found to be compatible with gastric polyp among the lesions described as gastric polyps in the procedure were included in the study. Endoscopy reports of patients who underwent retrospectively reviewed. The procedures were performed by General Surgery specialists using the Fujinon 4400 device. Among the lesions defined as gastric polyps in esophagogastroduodenoscopy, those whose histopathological examination was found to be compatible with gastric polyp were included in the study. Age, gender, patient's history, family history, endoscopy findings and histopathological data of the patients were obtained from hospital records.

Ethics committee approval was obtained from the ethics committee of Istanbul Medeniyet University with the number 2022/0326.

Statistical analysis was performed with use of standard descriptive statistical methods (mean, median, percentage, minimum, maximum).

RESULTS

Within the scope of the study, polypectomy was performed on 128 patients with endoscopic polyp image in 4004 esophagogastroduodenoscopy procedures performed in the defined period. The histopathological examination of the sampled lesions of 67 of these patients was reported to be compatible with gastric polyp, while the lesion result of 61 patients was not considered to be compatible with polyp. Of these 67 patients, 41 (61.19%) were female and 26 (38.81%) were male. The mean age of the patients was 60.28 years (38-87). A total of 80 gastric polyp samples were obtained from these 67 patients. Polyp diameter was larger than 1 cm in 10 patients, and lesions were less than 1 cm in 57 patients. The mean polyp diameter was found to be 7.40 (3-60) mm (Table 1).

Polypectomy was performed with the help of snare in 8 of these 67 patients, and polypectomy was performed with the help of forceps in 58 patients. Surgical polypectomy was performed in one patient because polypectomy could not be performed endoscopically. While 18 (27%) of the patients had more than one polyp, 49 (73%) patients had a single polyp. Multiple sessions of polypectomy were performed in five of the patients with gastric polyps. Two patients had a previous history of polypectomy. In both sexes, the most common polyp localization was the gastric corpuscle. In a total of 30 (37.5%) patients, gastric polyp corpus was localized (Table 2).

The most common type of polyp histopathologically was hyperplastic polyp. Hyperplastic polyps were observed in 39 (58.21%) patients. Polypoid lesions of 2 patients who were evaluated endoscopically as hamartomatous polyps were compatible with Peutz-Jeghers Syndrome in histopathological examination. Colonoscopy performed on these two patients revealed polyps in the colon. It was learned that the family members of one of these patients also had Peutz-Jeghers Syndrome. In the histopathological examination after polypectomy, malignancy was detected in a total of 4 patients. Polyp diameter was over 1 cm in 4 patients with malignancy. Adenocarcinoma was found in two of the patients and a Neuroendocrine tumor in one. In the histopathological examination of the polyp, which was detected in a patient with a previous history of subtotal gastrectomy for gastric carcinoma, the lesion was reported to be compatible with adenocarcinoma recurrence (Table 3).

Lesions of 67 patients in the study were also evaluated in terms of HP and IM. In 9 patients, it was observed that polypectomy material was not examined for HP and IM. HP was positive in 18 (32.14%) of the 58 patients examined, IM was positive in 9 (16.07%). This coexistance is stimulating

Table 1. Patient's characteristics.

Localization of polyps	Gender M/F	Number	%	Diameter of the polyp <1CM/ 1CM≤	The presence of malignity	HP+	IM+
Cardia	9/9	18	22,5	16/2	1	3	2
Fundus	6/5	11	13,75	11/0	0	2	1
Corpus	17/13	30	37,5	25/5	3	8	5
Antrum	12/7	19	23,75	17/2	0	7	3
Duodenum	0/2	2	2,5	1/1	0	1	0

M: Male, F: Female, HP: Helicobacter pylori, IM: Intestinal metaplasia

Table 2. Localization of polyps.

Localization of polyps	n	%
Cardia	18	22,5
Fundus	11	13,75
Corpus	30	37,5
Antrum	19	23,75
Duodenum	2	2,5

n: Number of polyps

in terms of its potential to increase the risk of developing malignancy HP association was present in 66.67% of the cases with IM (Table 4).

DISCUSSION

Upper gastrointestinal system polyps are usually asymptomatically detected incidentally during endoscopic examinations performed for other reasons. It is less common than colon polyps. There is no general consensus on the management of incidental gastric polyps, but the general trend is to perform or sample all polyps larger than 5 mm. The prevalence of gastric polyps shows regional variations. The prevalence of gastric polyps varies in a wide range between 0,34-29.8% in studies (7). In the study of Wang et al., the incidence of gastric polyps was reported as 29.8%, which is higher than the literature (2, 8, 9). In a study by Vatansever et al. conducted on 29940 patients in 2015, the prevalence of polyps was found to be 2.2%(10). In our study, 4004 patients underwent esophagogastroduodenoscopy and the prevalence was found to be 1.67%.

Gastric polyps can be seen in different anatomical parts of the stomach. In the study conducted by Fan et al. with 4043 gastric polyp patients in 10 years, polyps were detected in the corpus at a rate of 45% in 2004, while the frequency was reported as 64.25% in 2013 (11). Hailong et al., in a study conducted on 24121 patients in 2012, found an increase in the number of polyps located in the gastric corpus compared to years. In this study, the stomach corpus was seen as the anatomical region with the most polyps with 37.5% (12). In our study, 61.19% of patients were female. In other studies, it is stated that gastric polyps are detected more frequently in female patients (10,13).

Hyperplastic polyps are the most frequently detected polyps among gastric polyps and have been defined in different anatomical localizations in the literature. They are generally small in size and are mostly detected as a single (4). However, in recent studies, an increase in the incidence of fundic gland polyps has been reported. The widespread use of proton pump inhibitors (PPI) and the increase in HP eradication treatments can be shown as the reasons for the formation of this picture.

Carmak et al., in a study in which 121,564 esophagogastroduedonoscopy procedures were examined, reported the prevalence of gastric polyps as 6.35% and fundic gland polyps as 77% (7). In a 10-year study conducted by Fan et al. between 2004 and 2013, the frequency of fundic gland polyps was found to be 65%, and in this study, the frequency of fundic gland polyps was reported as 19% in 2004 and 77% in 2013 (6).

Table 3. Distribution of the histopathological types of the polyps.

Histopathological type	(n=67)	%
Hyperplastic polyp	39	58,21
Fundic gland polyp	13	19,4
Inflammatory polyp	6	8,96
Squamous papilloma	2	2,99
Adenomatous polyp	1	1,49
Hamartomatous polyp	2	2,99
Adenocarcinoma	2	2,29
Metastasis of adenocarcinoma	1	1,49
Neuroendocrine tumor	1	1,49

n: Number of polyps

Table 4. Coexistence of intestinal metaplasia and Helicobacter pylori

n=56	IM (+)	IM (-)
Helicobacter pylori (+)	6	11
Helicobacter pylori (-)	3	36
Total	9	47

n: Number of patients IM: Intestinal metaplasia

Yacoub et al., in a 10-year study involving 18496 patients, found the frequency of gastric polyps to be 0.46%, hyperplastic polyps to 55.9%, and fundic gland polyps to 18.1% (14). In another study, in 12,563 patients, hyperplastic polyp was found to be the most common type of polyp with 42.8% (12). In our study, hyperplastic polyp was found to be the most common polyp with a rate of 58.21% in 4004 procedures. However, since it was a retrospective study, patients' PPI use or HP eradication treatment history could not be evaluated.

Among gastric polyps, adenomatous polyps have a higher risk of malignancy, while hyperplastic polyps have a lower risk of malignancy. Hyperplastic polyps can be neoplastic or non-neoplastic. In the presence of hyperplastic polyps larger than 1 cm in diameter, with a stalk, a history of subtotal gastrectomy, and the presence of dysplasia, the malignancy potential increases, and polypectomy is required in these patients (15,16). The frequency of malignant transformation of hyperplastic polyps has been reported to be between 1.5% and 2.1% (17,18). It is also mentioned that fundic gland polyps associated with FAP also show malignant transformation. If multiple fundic gland polyps, dysplasia, or FAP are detected in esophagogastroduodenoscopy, other parts of the gastrointestinal tract should also be examined

to detect possible lesions (19, 20). When hamartomatous polyps are detected in esophagogastroduodenoscopy, detailed examination should be performed in terms of syndromes such as Peutz-Jeghers syndrome and juvenile polyposis syndrome. It should be kept in mind that genitourinary, breast and lung malignancies can be seen together in these patients, apart from the gastrointestinal system and gastrointestinal system, and family screening should be done (21, 22).

Although colon cancers are mostly defined as lesions that develop on the basis of polyps, gastric polyps pose a lesser risk in the development of gastric cancer. However, oxyntic atrophy caused by gastritis plays an important role in gastric carcinogenesis. Atrophic mucosa, on the other hand, forms the basis for the development of hyperplastic polyps and adenomas (5). Neuroendocrine tumors originating from enterochromaffin-like cells are detected in 0.6 to 2% of gastric polyps (23, 24).

Adenomatous polyps, the precursors of gastric adenocarcinomas, often occur as a consequence of atrophic gastritis. The risk of malignancy is highest with polyps >2 cm in size and those with villous features and associated with both size and histologic subtype. In gastric adenomatous polyps, intestinal type and fundic gland type adenomas are more likely to progress to carcinoma than foveolar and auxinic gland adenomas. Foveolar adenomas are typically single, small and rarely progress to malignancy (25).

Hyperplastic gastric polyps also have the potential for malignant transformation. Terada's study of 412 patients and 497 polypectomy materials showed that malignant transformation of hyperplastic gastric polyps can occur in 2.2% of cases and that malignant changes in hyperplastic gastric polyps develop in the order of hyperplasia-dysplasia-carcinoma (26).

The presence of HP infection leads to the development of chronic gastritis and is a serious risk factor for the development of noncardia gastric cancer (27). Intestinal metaplasia is also a precancerous lesion, increasing the risk of gastric malignancy by approximately 25%. Although it has prevented about half of gastric cancers with the diagnosis and treatment of HP, it has been reported that IM is effective in the development of gastric malignancy that cannot be prevented (28).

Endoscopic ultrasonography (EUS) is currently the most commonly used imaging modality for the diagnosis of submucosal gastric lesions. It can comment on the mucosal or submucosal depth of the gastric lesion and the echo level of the lesion (low level echo, equal echo, high level echo or hybrid echo) (29). Endoscopic mucosal resection (EMR) is a minimally invasive method that can be used for upper GI lesions smaller than 20 mm, provided that they can be easily removed and have a low risk of submucosal invasion (SMI). Endoscopic submucosal dissection (ESD) should be considered for bulky or superficial submucosal invasion risk gastric lesions (30).

The fact that our study was retrospective and the results of the cases with histopathological HP and IM could not be accessed during the process and the technical deficiencies in the evaluation of polyps are among the weaknesses of our study.

In future studies, reporting the follow-up results of patients with HP and IM will contribute to the literature.

CONCLUSION

With the widespread use of upper gastrointestinal endoscopy, it is critical to recognise, monitor and treat less common but clinically important lesions. The lesions may also be associated with polyposis syndromes. It is important to perform biopsy or polypectomy for polyps detected during oesophagogastroduodenoscopy and histopathological evaluation of lesions found in the specimen during gastrectomy. It is thought that this evaluation will help in the detection of possible malignancies and investigating the presence of HP and IM in positive cases due to the potential for malignancy development will contribute to early diagnosis and treatment.

Ethics Committee Approval: Ethics committee approval was obtained from the ethics committee of Istanbul Medeniyet University with the number 2022/0326.

Informed Consent: This study was done retrospectively.

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REFERENCES

1.Park DY, Lauwers GY. Gastric polyps: classification and management. Arch Pathol Lab Med. 2008; 132: 633-40.

2.Wang FW, Young SC, Chen RY, et al. The Prevalence and Risk Factors of Gastric Polyp in Asymptomatic Patients Receiving Health Examination. Gastroenterol Res Pract. 2018; 2018: 9451905.

3. Vos, S, van der Post, RS, Brosens, LAA. Gastric Epithelial Polyps: When to Ponder, When to Panic. Surg. Pathol. Clin.: 2020; 13: 431–52.

4.Goddard AF, Badreldin R, Pritchard DM., Walker MM, Warren B. The Management of Gastric Polyps. Gut 2010;

59: 1270–76.
5.Waldum H, Fossmark R. Gastritis, Gastric Polyps and Gastric Cancer. Int J Mol Sci. 2021;22: 6548.
6.Basnet, D. Makaju, R. Gurung, RB, Dhakal, R. Colorectal Polyps: A Histopathological Study in Tertiary Care Center. Nepalese Medical Journal. 2021; 4: 414-18
7.Olmez S, Sayar S, Saritas B, et al. Evaluation of patients with gastric polyps. North Clin Istanb 2018;5: 41-46
8.Carmack SW; The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients, Am J Gastroenterol. 2009; 104: 1524-32
9.Muehldorfer SM, Stolte M, Martus P, Hahn EG. Ell C. Diagnostic accuracy of forceps biopsy versus polypectomy for gastric polyps: a prospective multicentre study. Gut. 2002; 50: 465–70.
10.Vatansever S, Akpınar Z, Alper E, et al. Gastric polyps and polypoid lesions: Retrospective analysis of 36650 endoscopic procedures in 29940 patients. Turk J Gastroenterol. 2015; 26: 117-22
11.Fan NN, Yang J, Sun G, et al. Changes in the spectrum of gastric polyps in the Chinese population. World J Gastroenterol. 2015; 21: 9758-64.
12.Cao H, Wang B, Zhang Z, Zhang H, Qu R. Distribution trends of gastric polyps: an endoscopy database analysis of 24 121 northern Chinese patients. Journal of gastroenterology and hepatology.2012; 27: 1175-80.
13. Çiyiltepe H, Çetin DA, Gündeş E, et al. Endoscopic and histopathological features of the upper gastrointestinal system polyps: evaluation of 12.563 procedures. Turk J Surg. 2019;35: 98-104.
14.Yacoub H, Bibani N, Sabbah M, et al. Gastric polyps: a 10-year analysis of 18,496 upper endoscopies. BMC Gastroenterol. 2022; 22: 1: 1-7.
15.Han AR, Sung CO, Kim KM, et al. The Clinicopathological Features of Gastric Hyperplastic Polyps with Neoplastic Transformations: A Suggestion of Indication for Endoscopic Polypectomy. Gut and Liver 2009; 3: 271-75
16.Kang HM, Oh TH, Seo JY, et al. Clinical factors predicting for neoplastic transformation of gastric hyperplastic polyps Korean J Gastroenterol. 2011; 58: 184-89.
17.Hizawa K, Fuchigami T, Iida M, et al. Possible neoplastic transformation within gastric hyperplastic polyp. Application of endoscopic polypectomy. Surg Endosc. 1995;9: 714–18
18.Ahn, JY, Choi, KD, Roh, J, et al. Neoplasms arising in large gastric hyperplastic polyps: Endoscopic and pathologic features. Gastrointest Endosc 2014; 80: 1005-13.
19.Abraham, SC, Nobukawa, B, Giardiello, FM., Hamilton, SR., Wu, TT. Fundic gland polyps in familial adenomatous polyposis: neoplasms with frequent somatic adenomatous polyposis coli gene alterations. Am J Pathol 2000;157: 747-54.
20.Gullo I, Grillo F, Mastracci L, et al. Precancerous lesions of the stomach, gastric cancer and hereditary gastric cancer syndromes. Pathologica. 2020; 112: 166-85.
21.Gibson EG, Staub, J, Kanth P. Endoscopic Management of Hamartomatous Polyposis Syndromes. Curr Treat Options Gastro. 2021;19: 543–56.
22.Klimkowski S, Ibrahim M, Ibarra Rovira JJ, et al. Peutz–Jeghers Syndrome and the Role of Imaging: Pathophysiology, Diagnosis, and Associated Cancers. Cancers 2021; 13: 5121.
23.Modlin IM, Latich I, Zikusoka M, Kidd M, Eick G, Chan AK. Gastrointestinal carcinoids: the evolution of diagnostic strategies. J Clin Gastroenterol 2006; 40: 572– 82.
24.Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am 2011; 40: 1–18.
25.Waldum H, Fossmark R. Gastritis, Gastric Polyps and Gastric Cancer. Int J Mol Sci. 2021;22: 6548.
26.Terada T. Malignant transformation of foveolar hyperplastic polyp of the stomach: a histopathological study. Med Oncol. 2011; 28: 941-4.
27.Jonaitis P, Kupcinskas L, Kupcinskas J. Molecular Alterations in Gastric Intestinal Metaplasia. Int. J. Mol. Sci. 2021; 22: 5758.
28.Lam, SK, Lau, G. Novel treatment for gastric intestinal metaplasia, a precursor to cancer. JGH Open 2020; 4: 569-73.
29.Zhang Y, Huang Q, Zhu LH, Zhou XB, Ye LP, Mao XL. Endoscopic excavation for gastric heterotopic pancreas: an analysis of 42 cases from a tertiary center. Wien Klin Wochenschr. 2014; 126:509-14.
30.Ahmed Y, Othman M. EMR/ESD: Techniques, Complications, and Evidence. Curr Gastroenterol Rep. 2020:15;22-39.

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Araştırma Makalesi / Original Article

SİSTEMİK LUPUS ERİTEMATOZUS TANILI HASTALARDA HİPERMOBİLİTE SIKLIĞI VE BU HASTALARIN DEMOGRAFİK, KLİNİK ÖZELLİKLERİ

FREQUENCY OF HYPERMOBILITY IN PATIENTS DIAGNOSED WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND DEMOGRAPHIC, CLINICAL CHARACTERISTICS OF THESE PATIENTS

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ÖZET

Giriş: Eklem hipermobilitesi, sık görülen bir fiziksel özelliktir. Benign eklem hipermobilite sendromu (BEHS) tek başına olabileceği gibi, müsküloskeletal ağrı ile birlikte veya kompleks fenotiplerin bir parçası olarak görülebilmektedir. Romatizmal hastalıklarda eklem laksiteleri yıllar içerisinde bazı çalışmalarda araştırılmıştır. Lupus tanılı hastaların vücut yapılarında görülen değişiklikler konusunda literatürde çalışmalar bulunmaktadır. Beighton skoru, lupus sürecinde görülen manifestasyonlardan etkilenmez ancak bu skorlama lupus semptomlarını da içermektedir. Bu nedenle skorlama ve lupus arasındaki ilişki kafa karıştırıcı olabilmektedir. Bu çalışmadaki amaç romatoloji polikliniğimizde takipli lupus tanılı hastaların hipermobilite sıklığını ortaya koymaktır.

Yöntemler: Bu çalışmada, romatoloji polikliniğine 01.04.2023-01.10.2023 tarihleri arasında başvurmuş 40 sistemik lupus eritematozus (SLE) tanılı hastanın dosyaları retrospektif olarak incelenmiştir. Retrospektif olarak incelenen dosyalardan, hastaların hipermobilitelerini gösteren Beighton skorları kaydedilmiştir.

Bulgular: İncelememiz sonucunda hasta grubumuzun 20'sinin (%50) Beighton skorlarının dört ve üzeri olduğunu tespit ettik ve bu hastaları hipermobil olarak sınıflandırdık. Hastaları hipermobil olanlar ve olmayanlar olarak iki gruba ayırıp eklem ağrısı ve artrit yönünden baktığımızda, hipermobil olan yirmi kişinin dokuzunda (%45), hipermobil olmayan yirmi kişinin dördünde (%20) müsküloskeletal şikayet tespit ettik.

Sonuç: Sonuç olarak, hipermobilite spektrum bozuklukları, ciddi müsküloskeletal ağrıya neden olabilmektedir. Bu durum ise sistemik lupus eritematozus seyrinde hastalığın oluşturduğu artralji, müsküler ağrı veya artritle karışabilmektedir. Bu durum ise klinisyenlerce hastalığın remisyona girmemesi olarak algılanabilir ve immünsüpresif tedavi verilmesi veya tedavide basamak artırılmasıyla sonuçlanabilir. Bu nedenle lupus seyrinde eşlik edebilen hipermobilitenin ayrıntılı şekilde incelenmesi gerekmektedir.

Anahtar Kelimeler: Beighton skoru, hipermobilite, sistemik lupus eritematozus

ABSTRACT

Introduction: Joint hypermobility is a common physical feature. Benign Joint Hypermobility Syndrome (BJHS) can occur alone, with musculoskeletal pain, or as part of complex phenotypes. Detailed studies have been conducted over the years on additional laxities in rheumatic diseases. There are studies in the literature about the changes seen in body structures in patients diagnosed with lupus. The Beighton score is not affected by the manifestations seen during the lupus process, but this scoring also includes the maintenance of lupus. Therefore, the relationship between scoring and lupus can be confusing. The aim of this study is to reveal hypermobile patients diagnosed with lupus who were followed up in our rheumatology outpatient clinic.

Methods: The files of 40 patients diagnosed with systemic lupus erythematosus (SLE) who were registered at this intended rheumatology outpatient clinic between 01.04.2023 and 01.10.2023 are available retrospectively. The Beighton scores of patients were collected.

Results: As a result of our review, we found that 20 (50%) of our patient group had Beighton scores of four and above, and we classified these individuals as hypermobile. Musculoskeletal complaints were detected in nine of the twenty hypermobile patients (45%) and in four of the twenty non-hypermobile patients (20%).

Conclusion: As a result, hypermobility spectrum disorders can cause severe musculoskeletal pain. This condition may be confused with arthralgia, muscular pain, or arthritis that occurs in the course of systemic lupus erythematosus. This situation may be perceived by clinicians as not entering remission for the country and may result in immunosuppressive treatment or escalation in treatment. For this reason, hypermobility needs to be examined in detail to preserve its features in the course of lupus.

Keywords: Beighton score, hypermobility, systemic lupus erythematosus

GİRİŞ

Sistemik lupus eritematozus (SLE) etiyolojisi bilinmeyen, ancak birden çok genetik, epigenetik, hormonal ve çevresel risk faktörlerin katkıda bulunduğu otoimmün bir hastalıktır. Global insidansı 100.000'de 5.14 kişi olarak tanımlanmıştır ve her yıl yeni 0,4 milyon kişiye lupus tanısı konduğu tahmin edilmektedir (1). Ülkemizde ise lupus prevalansı 59/100.000'dir (2). SLE genç kadınlar, Afrika kökenli Amerikalılar ve Hispaniklerde daha sıktır. En sık 15 ile 45 yaş arası dönemde olmakla birlikte her yaşta görülebilir. Hastalığın belirtileri hafif dereceden hayatı tehdit eden ağır tutulumlara değin değişebilmektedir. Hastalık alevlenmeler

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ve remisyonlarla seyretmekte ve alevlenmeler tedavisiz bırakılırsa kalıcı organ hasarlarıyla sonuçlanabilmektedir (3). Hastalığın klinikteki manifestasyonları arasında, hastalar arasında tutulum çok heterojen olabilmesine karşın, ateş, eritematoz döküntü, poliartralji ve artrit, poliserozit (özellikle plörezi ve perikardit), anemi, trombositopeni, renal, nörolojik ve kardiyak patolojiler sayılabilmektedir. Lupus, Latincede kurt anlamına gelir. Bu hastalık yüz bölgesinde görülen bir döküntü sonrası, döküntünün eroziv doğası nedenli ''lupus'' olarak isimlendirilmiş ve bu döküntüler bir kurtun ısırık izlerine benzetilmiştir (4).

Eklem hipermobilitesi, sık görülen bir fiziksel özelliktir. Benign eklem hipermobilite sendromu (BEHS) tek başına olabileceği gibi, müsküloskeletal ağrı ile birlikte veya kompleks fenotiplerin bir parçası olarak görülebilmektedir. Genç kadınlarda %5-57 oranında görülürken erkeklerde görülme oranı %2-35 olarak tanımlanmıştır (5). Hipermobilite spektrum bozuklukları, eklem hipermobilitesi olan kişilerde görülen muskuloskeletal ağrıyı ifade eder ve ağrıya neden olabilecek diğer nedenlerin dışlanmasıyla tanı konulur. BEHS'li hastaların tanısında Beighton skoru kullanılır (Tablo 1). Bu skorlamada en düşük skor sıfır, en yüksek skor dokuz puanla ifade edilir, dört ve üzeri olan toplam skor BEHS olarak tanımlanır (6).

Romatizmal hastalıklarda eklem laksiteleri yıllar içerisinde bazı çalışmalarda araştırılmıştır. Lupus tanılı hastaların vücut yapılarında görülen değişiklikler konusunda literatürde çalışmalar bulunmaktadır. Beighton skoru, lupus sürecinde görülen manifestasyonlardan etkilenmez ancak bu skorlama lupus semptomlarını da içermektedir. Bu nedenle skorlama ve lupus arasındaki ilişki kafa karıştırıcı olabilmektedir. Bu çalışmadaki amaç romatoloji polikliniğimizde takipli 40 lupus tanılı hastanın hipermobilite skorları olan Beighton skorlarını ifade ederek sistemik lupus eritematozus seyrinde görülen hipermobilite sıklığını kendi örnek popülasyonumuzda ortaya koymaktır. Romatologları bazı durumlarda zorlayabilen lupus hastalığında hipermobilitenin oluşturabileceği etki konusunda klinisyenlere katkıda bulunmak amaçlanmıştır.

GEREÇ VE YÖNTEM

Romatoloji polikliniğine 01.04.2023-01.10.2023 tarihleri arasında başvurmuş sistemik lupus eritematozus (SLE) tanılı hastaların dosyaları retrospektif olarak incelenmiştir. Hastaların demografik özellikleri, tanı yakınmaları, hastalık seyrinde görülen tutulum organları, eklem tutulumları, izlemde kullanılan ilaçlar, muayene sırasında kaydedilen Beighton skorları hastane veri sistemi ve hasta dosyalarından incelenerek kaydedilmiştir. Çalışma protokolü, lokal etik kurula sunulmuş ve 28.11.2023 tarihli toplantı 2023.190.11.04 numaralı karar ile araştırma onayı alınmıştır.

Tablo 1. Beighton kriterleri

Beighton kriterleri (Toplam skor: 9)	SAĞ	SOL
5.metokarpal eklem dorsifleksiyonu >90˚	1	1
Başparmağın pasif olarak ön kol iç yüzüne değmesi	1	1
Dirseğin hiperekstansiyonu >10˚	1	1
Dizin hiperekstansiyonu >10˚	1	1
Ayakta ve diz ekstansiyonda iken el ayasının yere değmesi	½	½

BULGULAR

Belirlenen süreler arasında romatoloji polikliniğine başvurmuş 40 adet sistemik lupus eritematozus tanılı hasta çalışmaya dahil edilmiştir. Bu hastaların 34'i (%85) kadın, altısı (%15) erkekti. Çalışmamızdaki hastaların yaş ortalaması 38,75'ti. (maksimum 73, minimum 24) Çalışmamızdaki kadınların yaş ortalaması 37,9 ve erkeklerin yaş ortalaması 43,3'tü.

Hipermobiliteleri açısından hastalar incelendiğinde, hasta grubunun 20'sinin (%50) Beighton skorlarının dört ve üzeri olduğunu tespit ettik ve bu hastaları hipermobil olarak sınıflandırdık. Tanı yakınmalarına göre hastalarımızı incelediğimizde, on bir hastanın (%27,5) eklem ağrısı ile, iki hastanın bel ağrısı (%5), iki hastanın hipertansiyon (%5), 12 hastanın cilt döküntüsü (%30), iki hastanın aktif artrit ile (%5), dört hastanın malar raş ile (%10), iki hastanın dispne ve bir hastanın ise plevral effüzyon ile, dört hastanın ise yorgunluk ve eşlik eden anemi (%10) ile tanı aldığını saptadık (Tablo 2). Çalışmamızdaki hastaların tanı yıllarını da inceledik, en uzun süredir lupus tanılı hastamızın hastalık süresi on sekiz yıl idi. Dört hasta 2023 yılında yeni tanı almıştı.

Hastaları hipermobil olanlar ve olmayanlar olarak iki gruba ayırıp eklem ağrısı ve artrit yönünden baktığımızda, hipermobil olan yirmi kişinin dokuzunda (%45), hipermobil olmayan yirmi kişinin dördünde (%20) müsküloskeletal şikayet tespit ettik (Tablo 3).

Bu sürede romatoloji polikliniğine başvurmuş hastaların hepsi tanı süreleri içerisinde kortikosteroid ve hidroksiklorokin almıştı. Hastalarımızın 26'sının (%65) tanı süreçleri içerisinde immunsüpresif aldığını tespit ettik.

Tablo 2. SLE tanılı hastalarda tanı anındaki bulguların sıklığı (n=40)

Tanı anındaki bulgular	n	%
Cilt döküntüsü	12	30
Eklem ağrısı	11	27,5
Malar raş	4	10
Anemi	4	10
Bel ağrısı	2	5
Hipertansiyon	2	5
Artrit	2	5
Dispne	2	5
Plevral effüzyon	1	2,5

Tablo 3. Beighton skoruna göre hipermobil olan ve ol-mayanlarda müsküloskeletal şikayet sıklığı (n=40)

Hastaların hipermobilite durumu	Müsküloskeletal şikayet varlığı	
Hipermobil:(n=20) / Hipermobil olmayan:(n=20)	n	%
Hipermobil olanlar içerisinde	9	45
Hipermobil olmayanlar içerisinde	4	20

On iki hastada mikofenolatmofetil (%30), altı hastada siklofosfamid (%15), on yedi hastada azotiyopürin (%42,5), yedi hastada rituksimab (%17,5), iki hastada Ivlg (%5), iki hastada siklosporin (%5), üç hastada ise metotreksat (%7,5) kullanımı vardı. Tanımlanan süreler içerisinde romatoloji polikliniğimize başvurmuş lupus tanılı hastaların organ tutulumları incelendiğinde ise 13 hastada lupus nefriti (%32,5), 22 hastada lupus cilt tutulumu (%55), 20 hastada artrit (%50), on bir hastada hematolojik tutulum (%27,5) saptadık (Tablo 4).

TARTIŞMA

Sistemik lupus eritematoz (SLE), etyolojisi kesin bilinmeyen, heterojen, multisistemik tutulumu olan hastalıktır. Dünyanın her yerinde, her yaş ve cinsiyette lupus görülebilir ancak doğurganlık çağındaki kadınların hastalığı olarak bilinir. Başlangıç yaşı sıklıkla 20-30 yaş olarak tanımlanmıştır. Literatürde hastalık için kadın-erkek oranı 6-9 kat olarak görünmektedir (7). Bizim çalışmamızda kadın-erkek oranı yaklaşık altı kat olarak tespit edilmiş olup literatürle benzerdir.

Hastalığın seyri tutulan doku ve organa göre değişmekte olup hafif formdan hayatı tehdit eden multiorgan yetmezliğiyle sonuçlanabilen ağır formlara değin oldukça geniş bir aralıkta olabilmektedir. Literatürde en sık etkilenen organlar olarak deri, eklemler, böbrek ve hematolojik sistemler belirtilmiştir. Hastalık semptomları kişiden kişiye değişmekte olup bazı kişilerde akut bir enfeksiyona benzeyen ateş ve kırgınlık durumu, bazı kişilerde ise alevlenmeler şeklinde olan bir seyir ve yıllar içerisinde yavaş şekilde bozulma tanımlanmıştır (8). Çoğu hastada ise deri ve eklemler en sık tutulur ve hafif bir seyir görülür. Deri tutulumunda malar raş, cilt kabarıklıkları ve yamaları, yüz, boyun, göğüs ve dirseklerde kırmızı döküntüler tanımlanmıştır. Eklem tutulumları ise aralıklı gezici eklem ağrılarından pek çok eklemi ilgilendiren akut poliartrit tablosu arasında tanımlanmış olup hastalığın diğer semptomları ortaya çıkmadan yıllar öncesinde de görülebilmektedir. Uzun yıllar süren hastalıklarda ise ciddi eklem gevşeklikleri ve deformiteler tanımlanmıştır ve bu duruma Jaccoud artropatisi adı verilir (9). Bizim çalışmamızda da literatüre paralel olarak en sık görülen tutulumlar arasında cilt tutulumu ve eklem tutulumu görülmüştür.

Lupus hastalarında başvuru anında hiçbir hasta birbirinin aynısı değildir. Semptom ve bulgu aralığı oldukça geniş olmakla birlikte, en sık semptom ve bulgular yorgunluk, ateş, artralji ve artrit, malar raş, güneş ışığı ile artan deri döküntüleri, Raynaud fenomeni, dispne, göğüs ağrısı, baş ağrısı, konfüzyon ve hafıza kaybı olarak belirtilmektedir. 2019 yılında lupus hastalarında başvuru anındaki semptomlar için yapılan bir çalışmada, çalışma yapılan merkezdeki 2006 ve 2014 yılları arasındaki lupus hastalarının başvuru vizitleri incelenmiştir. Çalışılan lupuslu popülasyonda artraljinin %68, miyaljinin %56, artritin ise %48 oranında görüldüğü belirtilmiştir (10). Malar raşın da dahil olduğu deri döküntülerinin ise başvuru anında hastaların yaklaşık %38'inde görüldüğü belirtilmiştir, bizim çalışmamızda da ilk başvuru şikayetleri arasında deri döküntüleri görülme sıklığı benzer saptanmıştır.

Tablo 4. SLE tanılı hastalarda organ tutulumları (n=40)

Hastalarda organ tutulumları	n	%
Cilt tutulumu	22	55
Artrit	20	50
Böbrek	13	32,5
Hematolojik	11	27,5

Sistemik lupus eritematozus tedavisinin ise temel taşlarını hidroksiklorokin ve kortikosteroidler oluşturmaktadır (11). Hastalık alevlenmelerinde geleneksel immunsupresifler eklenmekte, dirençli hastalık, geleneksel immunsupresifler nedenli gelişen yan etkiler, moleküler SLE patogenezinin daha net anlaşılmasıyla birlikte ise küçük moleküller ve biyolojik ajanlar tedaviye eklenmektedir (12). Bizim çalışmamızda da hastalarımızın hepsi hidroksiklorokin ve kortikosteroid almıştı. %65'ine ise immunsupresif tedavi eklenmişti.

Hipermobilite ve lupus arasındaki ilişki tarihte bazı çalışmalarda incelenmiş ve lupuslu hastaların vücut yapılarının farklılığı bu çalışmalarda belirtilmiştir. On altı SLE tanılı hasta ve on dokuz sağlıklı kişinin olduğu bir çalışmada hipermobilitenin lupuslularda daha sık olduğu belirtilmiş ancak iki grup arası istatistiksel anlamlı bir ilişki bulunmamıştır (13). Seksen bir hasta ile yapılan başka bir çalışmada hipermobilite açısından lupuslular ve sağlıklı popülasyon arasında istatistiksel anlamlı fark saptanmıştır (14). 2018 yılında Iraklı lupus hastalarında yapılan başka bir çalışmada ise hipermobilite sıklığının hasta grubunda %52,8 olarak bulunduğu belirtilmiştir (15). Bizim çalışmamızda da hipermobilite sıklığı %50 bulunmuş olup bu çalışma ile benzer olarak saptanmıştır.

Öte yandan, dikkat edilmesi gereken bir diğer konu da lupusa eşlik edebilen bu hipermobilitenin hastalık seyrinde oluşturabileceği etkidir. Hipermobilite spektrum bozuklukları, ciddi müsküloskeletal ağrıya neden olabilmektedir. Bu durum ise sistemik lupus eritematozus seyrinde hastalığın oluşturduğu artralji, müsküler ağrı

veya artritle karışabilmektedir. Bu durum ise klinisyenlerce hastalığın remisyona girmemesi olarak algılanabilir ve immünsüpresif tedavi verilmesi veya tedavide basamak artırılmasıyla sonuçlanabilir. Bu nedenle lupus seyrinde eşlik edebilen hipermobilitenin ayrıntılı şekilde incelenmesi gerekmektedir. Hastanın klinik seyrinde gelişen ağrı veya müsküloskeletal diğer problemlerin hastalığın primer sonucu veya eşlik eden hipermobilite nedenli olup olmadığı klinisyenler tarafından değerlendirilmeli ve tedavi bu yönde şekillendirilmelidir.

Çalışmamızda kontrol grubunun bulunmaması önemli bir kısıtlılıktır. İlerleyen dönemde daha çok sayıda sistemik lupus eritematoz tanılı hasta içeren, çok merkezli, prospektif ve kontrol grubunun da bulunduğu, bu hastalarda görülen hipermobiliteve eklem laksiteleri üzerine yoğunlaşan çalışmalar, hipermobilite ve lupus arasındaki ilişkinin ve hipermobilitenin klinikte lupus hastalığı üzerine oluşturduğu etkinin daha iyi aydınlatılmasını sağlayacaktır.

SONUÇ

Lupus seyrinde eşlik edebilen hipermobilitenin ayrıntılı şekilde incelenmesi, ağrı veya müsküloskeletal problemlerin hastalığın primer sonucu veya eşlik eden hipermobilite nedenli olup olmadığının klinisyenler tarafından değerlendirilmesi ve tedavinin bu yönde şekillendirilmesi gerekmektedir.

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KAYNAKLAR

1.Qu Y, Li D, Liu W, Shi D. Molecular consideration relevant to the mechanism of the comorbidity between psoriasis and systemic lupus erythematosus (Review) Exp Ther Med 2023;26:482.
2.Pamuk ON, Balci MA, Donmez S, Tsokos GC. The incidence and prevalence of systemic lupus erythematosus in Thrace: A 12-year epidemiological study. Lupus 2016;25:102-9.
3.Spinelli FR, Berti R, Farina G, Ceccarelli F, Conti F, Crescioli C. Exercise-induced modulation of Interferon-signature: a therapeutic route toward management of Systemic Lupus Erythematosus. Autoimmun Rev 2023;22:103412.
4.Systemic lupus erythematosus. Jama. 1973;224:701-11.
5.Morlino S, Castori M. Placing joint hypermobility in context: traits, disorders and syndromes. Br Med Bull 2023;147:90-107.
6.Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol. 2000;27:1777-9.
7.Uramoto KM, Michet CJ, Jr., Thumboo J, Sunku J, O'Fallon WM, Gabriel SE. Trends in the incidence and mortality of systemic lupus erythematosus. Arthritis Rheum 1999;42:46-50.
8.Giffords ED. Understanding and managing systemic lupus erythematosus (SLE). Soc Work Health Care. 2003;37:57-72.
9.Chattopadhyay A, Ghosh A. Jaccoud's arthropathy. Rheumatology (Oxford) 2020;59:3117
10.Metry AM, Al Salmi I, Al Balushi F, et al. Systemic Lupus Erythematosus: Symptoms and Signs at Initial Presentations. Antiinflamm Antiallergy Agents Med Chem 2019;18:142-50.
11.Tanaka Y. State-of-the-art treatment of systemic lupus erythematosus. International Journal of Rheumatic Diseases 2020;23:465-71.
12.Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62:222-33.
13.Johnsson PM, Kohlin C, Rasmusson GR, Bengtsson AA, Sturfelt G, Nived O. Differences in body structure and function between patients with systemic lupus erythematosus and healthy individuals, with particular reference to joint hypermobility. Scand J Rheumatol 2017;46:40-3.
14.Gumà M, Olivé A, Roca J, et al. Association of systemic lupus erythematosus and hypermobility. Ann Rheum Dis 2002;61:1024-6.
15.Al-Osami MH, Mohammed S, Ali WI, Fawzi HA. The relationship between Hypermobility Syndrome and Systemic Lupus Erythematosus. Indian Journal of Public Health 2018;9:527.

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Original Article / Araştırma Makalesi

THE EFFECT OF CAFFEINE INTAKE LEVELS DURING PREGNANCY ON NEWBORN HEALTH

GEBELİKTE KAFEİN TÜKETİM DÜZEYİNİN YENİDOĞAN SAĞLIĞI ÜZERİNDEKİ ETKİSİ

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ABSTRACT

Introduction: Caffeine is a commonly used ingredient nowadays all over the world but the consumption of caffeine during pregnancy has been an uncertain topic about the impact on birth and childhood. So, we aim to examine the caffeine intake habits during the trimesters of pregnancy and to analyze the effects of caffeine levels on newborn health.

Methods: 42 women were included in the study. The Socio-demographic Characteristics Evaluation Questionnaire was completed in the first interview and, during this same interview; the Daily Caffeine Intake Levels Evaluation Form was given to be updated in assigned weeks and days. The Birth Information Form was completed after witnessing the birth and a review of the mother's files.

Results: The average daily caffeine intake levels were 509.8±353.2 mg and 193.7±116.5 mg pre-pregnancy and on average during the pregnancy period. There was no correlation between any type of socio-demographic findings and the average caffeine intake at any period of the pregnancy period, included the pre-conceptional period. It was also found that birth weight and height, and the 1 and 5 minute Apgar score decreased when caffeine intake was higher in the trimesters of the pregnancy.

Conclusion: More studies using standardized methods and a meta-analysis of these studies may help to discover the relationship between caffeine and pregnancy outcomes, neonatal and childhood health.

Keywords: Caffeine, intake, pregnancy, newborn, nursing

ÖZET

Giriş: Kafein günümüzde tüm dünyada yaygın olarak kullanılan bir bileşendir, ancak gebelik sırasında kafein tüketiminin doğum ve çocukluk üzerindeki etkisi belirsiz bir konu olmuştur. Bu nedenle, bu çalışmada gebeliğin trimesterleri boyunca kafein alım alışkanlıklarını incelemeyi ve kafein düzeylerinin yenidoğan sağlığı üzerindeki etkilerini analiz etmeyi amaçladık.

Yöntemler: Çalışmaya 42 kadın dahil edildi. Sosyo-demografik Özellikleri Değerlendirme Anketi ilk görüşmede dolduruldu ve aynı görüşme sırasında; Günlük Kafein Alım Düzeyleri Değerlendirme Formu belirlenen hafta ve günlerde güncellenmek üzere verildi. Doğum Bilgi Formu, doğum olduktan ve annelerin dosyaları incelendikten sonra doldurulmuştur.

Bulgular: Günlük kafein alım düzeyleri gebelik öncesi ortalama 509,8±353,2 mg ve gebelik süresince ortalama 193,7±116,5 mg idi. Herhangi bir sosyo-demografik bulgu ile gebelik öncesi dönem de dahil olmak üzere gebelik döneminin herhangi bir dönemindeki ortalama kafein alımı arasında bir korelasyon bulunmamıştır. Ayrıca, gebeliğin trimesterlerinde kafein alımı arttıkça doğum ağırlığı, boyu ile 1. ve 5. dakika Apgar skorunun azaldığı bulunmuştur.

Sonuç: Standart yöntemler kullanılarak yapılacak daha fazla çalışma ve bu çalışmaların meta-analizi, kafein ile gebelik sonuçları, yenidoğan ve çocuk sağlığı arasındaki ilişkinin keşfedilmesine yardımcı olabilir.

Anahtar Kelimeler: Kafein, tüketim, gebelik, yenidoğan, hemşirelik

INTRODUCTION

Caffeine is a commonly used ingredient nowadays all over the world. Despite widespread caffeine consumption, there is insufficient knowledge about its effects. Caffeine has a wide clinical spectrum and it may have different effects on different groups, such as adults, pregnant women, or babies. Although it is used to stay awake and cope with stress in significant amounts, and it has beneficial effects on some health issues, e.g., cardiovascular diseases, liver diseases, cancers (1), a person may need to seek treatment for substance use disorder if s/he cannot control the use of caffeine. Caffeine also affects fecundability, and it should be recommended that its consumption be reduced during pregnancy due to the impact on neonatal outcomes. In spite of such harmful effects on infants, caffeine has been used in neonatal intensive care units to prevent apnea (2).

The consumption of caffeine during pregnancy has been an uncertain topic in the literature concerning the impact on birth and childhood. In the literature the safe dosage of caffeine consumption remains unclear. While some authors concluded that there was no relationship between caffeine intake and miscarriage at any amount (3), another study

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showed that women who consumed more caffeine might have a greater increased risk of gestational problems (4), and a further study suggested a low birth weight, stillbirth, or small gestational age for women who consumed less caffeine (5). There has been no consensus about the safe dosage of caffeine intake during pregnancy between organizations related to maternal and neonatal health. A caffeine intake <200 mg /per day has been allowed for pregnant women by The American College of Obstetricians and Gynecologists (6), Dietary Guidelines for Americans (7), the European Food Safety Authority (8), and the UK National Health Service (9), despite the fact that up to 300 mg/day of caffeine intake in healthy pregnant women was not associated with any adverse effects (10). While it has been shown that a 100 mg/day caffeine intake could increase the risk of low birth weight, spontaneous abortion, or stillbirth (11,12). A 22nd-week pregnant woman who took 4000 mg caffeine in a single dose during a suicide attempt and was later treated with hemodiafiltration, reported that she gave birth in the 38th week to a healthy child (13). Reviews have also suggested that the evidence about the relationship between restricting caffeine intake and pregnancy, fetal, or neonatal outcomes was insufficient (11,14). The various results about the effects of caffeine on all relevant outcomes could be related to the CYP1A2 enzyme. The CYP1A2 enzyme's function is to metabolize caffeine in the human body. This enzyme's function during pregnancy can be affected by modulators associated with pregnancy and the fetal environment. It has been shown that the CYP1A2 enzymatic reaction could show 'inter-individual variation' (15), which causes different responses in pregnant women. Those who have higher CYPA12 enzyme activity have more pregnancy risks than those with lower CYPA12 activity (16).

To our knowledge, there are limited studies that have researched the impact of caffeine intake on the Apgar scores of newborns in the literature. As a result, in this study, we aim to examine the caffeine intake habits during the trimesters of pregnancy and to analyze the effects of caffeine levels on newborn health.

METHODS

The study was planned with a descriptive research design and data collected between February 2021 and July 2021. The measurements were performed during the pregnancy and the information was collected in the postconceptional period.

After obtaining approval from the ethics committee and after an institutional review, the research population was gathered which consisted of the women who had applied to Eskisehir Osmangazi University, Faculty of Medicine, Department of Obstetrics and Gynecology Polyclinic because of their pregnancy. The study sample included 49 women who were aged 18 and older, were non-smokers and were non-drinker. Furthermore, they did not have any chronic disease, had a healthy pregnancy so far, had not reached the ninth week of pregnancy, and agreed to participate in the study. All human subjects provided written informed consents with guarantees of confidentiality.

In this research, the data were gathered through face-to-face interviews by the researcher who designed the questionnaire and calculated the measurements. When a chronic disease was encountered in any period of the pregnancy, or when the pregnancy ended, these cases were excluded from the study. Three forms designed by the researcher were used in this research: The Sociodemographic Characteristics Evaluation Questionnaire, The Daily Caffeine Intake Levels Evaluation Form, and The Birth Information Form.

The Sociodemographic Characteristics Evaluation Questionnaire was completed during the first interview by the women who had come to the polyclinic to receive service and met the requirements of the study. This form included open-ended and close-ended questions regarding the woman and her partner's ages, educational backgrounds, occupations, duration of marriage, the type of family, monthly income, and any conditions special to the pregnancy.

The Daily Caffeine Intake Levels Evaluation Form was given during the first interview, and the women were asked to fill out the form on assigned weeks and days to record their daily caffeine consumption. The form also required the women to provide details regarding their consumption pre-pregnancy. They were asked to submit these forms when they came for a checkup after they had updated their form for the last time. In order to select a week in each trimester that would be chosen for analysis, a random draw was made which resulted in the 9th week of gestation in the first trimester, the 22nd week of gestation in the second trimester, and the 34th week of gestation in the third trimester being selected. A further draw was then made to select which day's caffeine intake would be used in the selected weeks and Friday was drawn. Their amount of consumed caffeine was calculated by the researcher after they had returned the form, and both the total amount and trimester average amount were computed according to the information recorded by the women.

The Birth Information Form was completed after the birth by examining the mother's files. This form included the infant's birth week, birth weight, height, and Apgar scores.

Continuous data are presented as Average ± Standard Deviation and categorical data in percentages (%). The Shapiro-Wilk test was used to analyze if the data follows normal distribution. To compare the groups which did not correspond with the normal distribution, the Kruskal-Wallis H test was used for the cases with groups numbered three and above, the Mann Whitney-U test was used for two. To compare the values in different measurements, the

Wilcoxon test was used when the group number was two, and the Friedman test was also conducted. Spearman's rank-order correlation was calculated to detect the direction and strength of the association between variables. Pearson's chi-squared test was used to analyze generated crosstabs. IBM SPSS Statistics 21.0 program was used for the analysis. The value $p<0.05$ was used to determine results as statistical significance.

RESULTS

From the original study sample of 49; 5 women, whose pregnancy resulted in a miscarriage, and two others, who had left the forms incomplete, were excluded from the study, which gave a total of 42 participants who were included in the study. It was found that the average age of women was 28.8±4.6 years, the average times pregnant was 2.0±1.3, the week of delivery for women was 37.7±0.7 on average, the average birth weight was 3409.0±343.6 g, the average birth height was 49.5±0.9 cm, and the average 1-minute and 5-minute Apgar scores were 9.3±0.6 and 9.6±0.5, respectively.

When the daily caffeine intake levels of the women participating in the study were examined, they were found to be 509.8±353.2 mg per day in the pre-pregnancy period, 173.5±159.9 mg per day in the first trimester, 206.4±114.3 mg per day in the second trimester, 195.7±139.7 mg per day in the third trimester, and an average of 193.7±116.5 mg per day during the pregnancy (Table 1). When the average caffeine intake levels were compared, it was observed that there was a statistically significant difference between groups and found that the highest caffeine intake was in the pre-pregnancy period (Table 1).

It was found that while the infant's birth weight and height increased as caffeine intake in the pre-pregnancy period and trimesters decreased; the 1-minute and 5-minute Apgar score decreased as caffeine intake increased in the trimesters of the pregnancy (Table 2).

Table 1. Daily Average Caffeine Intake Levels (mg) and Comparison of the Intake Levels Between the Gestational Periods

Caffeine intake	Mean±SD
Pre-pregnancy (1)	509.8±353.2
First Trimester (2)	173.5±159.9
Second Trimester (3)	206.4±114.3
Third Trimester (4)	195.7±139.7
Pregnancy average (5)	193.7±116.5
Between groups	(2-1) p = 0.000*; (3-1) p = 0.000* (4-1) p = 0.000*; (5-1) p = 0.000*

* Wilcoxon signed Rank test

DISCUSSION

Caffeine's metabolization rate begins to decrease in the first trimester and this downward trend continues until the birth (17). In addition, the blood-placental barrier cannot prevent caffeine's passage from the mother to the fetus because of the lipophilic nature of caffeine (18), the fetus itself does not have an enzyme to metabolize the caffeine (15). As a result, all caffeine taken by women crosses directly to the fetus without any metabolization process. Caffeine and its metabolites could be thought to cause vasoconstriction in the placenta as a historical attitude (19,20). However, an emergent study showed that acute coffee consumption only affected the amniotic fluid volume rather than fetal renal artery blood flow (21). Despite the possible harmful effect on both mother and her baby, 51.7-97 % of women continue to take in caffeine during their pregnancy (22,26) and maintained caffeine consumption at the same level as in their pre-pregnancy period (26). In a recent study, the consumption of caffeine was 59.2 ± 61.5 and 54.3 ± 55.4 mg/day in the first and third trimester, respectively, though the decline of the amount and daily use of caffeine were not statistically significant (24). In our study, the daily average caffeine intake levels were 509.8±353.2 mg and 193.7±116.5 mg in the pre-pregnancy and pregnancy period. In addition, the decrease of caffeine intake started in the first trimester and continued to the third trimester. Some studies have found that the intake levels were decreased once the pregnancy was learned, however, the level of caffeine intake in the third trimester was nearly the same as that in the pre-pregnancy period (27-29). Contrary to this, in our study, the caffeine consumption level in the pre-pregnancy and three trimester periods, without any health advice program being given, were found to be statistically significant and these significances were not related to any demographic findings.

There is no consistent evidence of an association between caffeine intake and newborn health. A Cochrane database about caffeine intake's effect on reproductive and newborn health concluded that the evidence is insufficient on the avoidance of caffeine to prevent low birth (14). Later, a review included 10 studies, and this showed that the risk of low birth increased with caffeine intake in 7 studies (30-35) A meta-analysis has recently demonstrated that caffeine consumption during pregnancy was associated with a 33% greater risk of lower birth (36). However, a recent study from Poland concluded that there was no relationship between caffeine intake levels and neonatal anthropometric parameters. In this research, 100 pregnant women completed a questionnaire to measure their daily caffeine intake (37). Another study examined the effects of caffeine intake on neonatal health with the blood level of caffeine and its metabolite paraxanthine to exclude the limitation of the self-reported caffeinated beverage consumption. It was found that decreased birth weight and length were statistically significant when associated with plasma caffeine and paraxanthine concentration while the

Table 2. The comparison of the daily average caffeine intake levels pre-pregnancy and in the trimesters with demographic findings

	Caffeine Intake Levels								
	Pre-pregnancy	The first trimester	The second trimester	The third trimester	During the pregnancy	Birth weight	Birth Height	1-minute Apgar	5-minute Apgar
Caffeine pre-pregnancy	1.000								
Caffeine in the first trimester	.328*	1.000							
Caffeine in the second trimester	.370*	.418**	1.000						
Caffeine in the third trimester	.221	.415**	.756**	1.000					
Avg. caffeine intake during the pregnancy	.320*	.739**	.829**	.846**	1.000				
Birth weight	-.399**	-.629**	-.746**	-.638**	-.823**	1.000			
Height	-.540**	-.489**	-.682**	-.576**	-.693**	.852**	1.000		
1-minute Apgar	-.197	-.386*	-.579**	-.635**	-.630**	.398**	.450**	1.000	
5-minute Apgar	-.011	-.241	-.510**	-.587**	-.533**	.353*	.361*	.605**	1.000

Spearmen correlation *p < .005; ** p < .001

low birth risk started from the level of 50 mg caffeine/day (38). In this study, we have shown that birth weight and height decrease with the increase of daily caffeine intake during pregnancy ($p < 0.05$). The association between the caffeine consumption level in the pre-pregnancy period and neonatal health has not been discussed before in the literature. We also found that the birth weight and length decreased with higher caffeine intake levels in the pre-pregnancy period and all the trimesters ($p < 0.05$).

The Apgar score is used to provide a standardized assessment for infants after delivery. The minimum and maximum scores are 1 and 10, respectively. The higher points show the wellness of the infant. In the literature, there are only two studies that have tried to show the association of caffeine intake level and the Apgar score (39,40). The two studies could not show any association. The reason for not being able to show the association between caffeine intake levels and Apgar score, as declared by the authors, was that the percentage of caffeine overconsumption was very low and the average intake level per day was also too low in the study population (40). In our study, for the first time in the literature, we found that there was a negative association between the 1st and 5th minute Apgar score and caffeine intake levels in the pre-pregnancy and all trimester periods on neonatal anthropometric parameters.

In our study, we did not examine the relation between caffeine intake and pregnancy outcomes and childhood problems. A limitation of the study was that the average caffeine intake levels were calculated by the questionnaire form designed by researchers as a result, data collection was self-reported, the individuals' caffeine metabolism was not examined, and the caffeine exposure of the fetus was not estimated. Another limitation was that the pregnant women were not separated into groups according to caffeine consumption levels, such as < or > 200 mg /day, thus we could not conclude any cut-off or safety dosage level for a daily caffeine intake that would help avoid its harmful effects. Strength of this cohort study was that non-smokers, non-drinker, and pregnant women who did not have any chronic illness were included in the study. Furthermore, all conditions that could affect neonatal health were excluded from the study.

This study was the first study from Turkey on the effects of caffeine intake level on neonatal health. We found that there was a negative association between the level of caffeine consumption during all three trimesters on the birth weight, length, and the Apgar scores. These negative effects were also detected when the caffeine intake level was higher in the pre-conception period for the first time in the literature. More studies using standardized methods and a meta-analysis of these studies may help to discover the relationship between caffeine and pregnancy outcomes, neonatal and childhood health.

CONCLUSION

The level of caffeine intake among pregnant women is still at a high level all over the world. The main goal of reducing caffeine consumption is to achieve healthy offspring. In clinical practice, the nurses should give education about the harmful effect of caffeine on fetal and neonatal health to pregnant and should encourage them to avoid decreasing the caffeine consumption.

Ethics Committee Approval: The study was conducted in accordance with the Helsinki Declaration and approved by Karabuk University Human Studies Ethical Comitee with protocol number 2018/9-21.

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

Authorship Contributions: Idea/Concept: YK, VYT, Design: YT, VYT, Supervision: YK, VYT, Data Collection or Processing: ED, Analysis or Interpretation: ED, Literature Search: YK, VYT, Writing: YK, ED, Critical Review: VYT, MT, References And Fundings: -, Materials: -.

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REFERENCES

1.Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 2017; 359:j5024.
2.Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnea in preterm infants. Cochrane Database Syst Rev. 2010;8:CD000140.
3.Hahn KA, Wise LA, Rothman KJ, Mikkelsen EM, Brogly SB, Sørensen HT, et al. Caffeine and caffeinated beverage consumption and risk of spontaneous abortion. Hum Reprod. 2015;30:1246-55.
4.Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Annu Rev Nutr. 2017;37:131-56.
5.Greenwood DC, Thatcher NJ, Ye J, Garrard L, Keogh G, King LG, et al. Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis. Eur J Epidemiol. 2014;29:725-34.
6.ACOG CommitteeOpinion No. 462: Moderate caffeine consumption during pregnancy. Obstet Gynecol. 2010;116:467-8.
7.Dietary Guidelines Advisory Committee. Scientific report of the 2015 Dietary Guidelines Advisory Committee: Advisory report to the Secretary of Health and Human Services and the Secretary of Agriculture. Washington DC: U.S. Department of Agriculture, Agricultural Research Service, 2015.
8.European Food Safety Authority. Panel on dietetic products, nutrition and allergies. Scientific opinion on the safety of caffeine. EFSA J. 2015;13:4102.
9.National Health Service. Should I limit caffeine during pregnancy? 2018. Available at: https://www. nhs. uk/ common- health- questions/ pregnancy/ should- i- limit-caffeine- during- pregnancy/ Accessed June 12,2018.
10.Wikoff D, Welsh BT, Henderson R, Brorby GP, Britt J, Myers E, et al. Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children. Food Chem Toxicol. 2017;109:585–648.
11.Rhee J, Kim R, Kim Y, Tam M, Lai Y, Keum N, et al. Maternal Caffeine Consumption during Pregnancy and Risk of Low Birth Weight: A Dose-Response Meta-Analysis of Observational Studies. PLoS One. 2015;10:e0132334.
12.Chen LW, Wu Y, Neelakantan N, Chong MF, Pan A, van Dam RM. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. Public Health Nutr. 2016;19:1233-44.
13.Nojima T, Naito H, Kosaki Y, Osako T, Tanaka K, Murata A, et al. Caffeine Intoxication in Pregnancy; a case Report. Archives of Academic Emergency Medicine. 2019; 7:e67.
14.Jahanfar S, Jaafar SH. Effects of restricted caffeine intake by mother on fetal, neonatal and pregnancy outcomes. Cochrane Database Syst Rev. 2015;9:CD006965.
15.Qian J, Chen Q, Ward SM, Duan E, Zhang Y. Impacts of Caffeine during Pregnancy. Trends Endocrinol Metab. 2020;31:218-27.
16.Sasaki S, Limpar M, Sata F, Kobayashi S, Kishi R. Interaction between maternal caffeine intake during pregnancy and CYP1A2 C164A polymorphism affects infant birth size in the Hokkaido study. Pediatr Res. 2017;82:19-28.
17.Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev. 1999;51:83-133.
18.Grosso LM, Bracken MB. Caffeine metabolism, genetics, and perinatal outcomes: a review of exposure assessment considerations during pregnancy. Ann Epidemiol. 2005;15:460-6.
19.Kirkinen P, Jouppila P, Koivula A, Vuori J, Puukka M. The effect of caffeine on placental and fetal blood flow in human pregnancy. Am J Obstet Gynecol. 1983;147:939-42.
20.Daly JW. Alkylxanthines as research tools. J Auton Nerv Syst. 2000;81:44-52.
21.Madendag IC, Sahin ME, Aydin E, Madendag Y. Effect of coffee consumption on fetal renal artery blood flow and amniotic fluid volume in third trimester of pregnancy. Pak J Med Sci. 2020;36:735-9.
22.Voerman E, Jaddoe VW, Hulst ME, Oei EH, Gaillard R. Associations of maternal caffeine intake during pregnancy with abdominal and liver fat deposition in childhood. Pediatr Obes. 2020;15:e12607.
23.Weng X, Odouli R, Li DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. Am J Obstet Gynecol. 2008;198:279.
24.Lamy S, Houivet E, Benichou J, Marret S, Thibaut F; Perinatal network of Upper-Normandy. Caffeine use during pregnancy: prevalence of use and newborn consequences in a cohort of French pregnant women. Eur Arch Psychiatry Clin Neurosci. 2021;271:941-50.
25.Aagaard SK, Larsen A, Andreasen MF, Lesnikova I,

Telving R, Vestergaard AL, et al. Prevalence of xenobiotic substances in first-trimester blood samples from Danish pregnant women: a cross-sectional study. BMJ Open. 2018;8:e018390.
26.Chen L, Bell EM, Browne ML, Druschel CM, Romitti PA; National Birth Defects Prevention Study. Exploring maternal patterns of dietary caffeine consumption before conception and during pregnancy. Matern Child Health J. 2014;18:2446-55.
27.Berglundh S, Vollrath M, Brantsæter AL, Brandlistuen R, Solé-Navais P, Jacobsson B, et al. Maternal caffeine intake during pregnancy and child neurodevelopment up to eight years of age-Results from the Norwegian Mother, Father and Child Cohort Study. Eur J Nutr. 2021;60:791-805.
28.Peacock A, Hutchinson D, Wilson J, McCormack C, Bruno R, Olsson CA, et al. Adherence to the Caffeine Intake Guideline during Pregnancy and Birth Outcomes: A Prospective Cohort Study. Nutrients. 2018;10:319.
29.Crozier SR, Robinson SM, Borland SE, Godfrey KM, Cooper C, Inskip HM; SWS Study Group. Do women change their health behaviours in pregnancy? Findings from the Southampton Women's Survey. Paediatr Perinat Epidemiol. 2009;23:446-53.
30.Hoyt AT, Browne M, Richardson S, Romitti P, Druschel C; National Birth Defects Prevention Study. Maternal caffeine consumption and small for gestational age births: results from a population-based case-control study. Matern Child Health J. 2014;18:1540-51.
31.Bracken MB, Triche EW, Belanger K, Hellenbrand K, Leaderer BP. Association of maternal caffeine consumption with decrements in fetal growth. Am J Epidemiol. 2003;157:456-66.
32.CARE Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. BMJ. 2008;337:a2332.
33.Chen LW, Fitzgerald R, Murrin CM, Mehegan J, Kelleher CC, Phillips CM; Lifeways Cross Generation Cohort Study. Associations of maternal caffeine intake with birth outcomes: results from the Lifeways Cross Generation Cohort Study. Am J Clin Nutr. 2018;108:1301-8.
34.Sengpiel V, Elind E, Bacelis J, Nilsson S, Grove J, Myhre R, et al. Maternal caffeine intake during pregnancy is associated with birth weight but not with gestational length: results from a large prospective observational cohort study. BMC Med. 2013;11:42.
35.Bech BH, Frydenberg M, Henriksen TB, Obel C,Olsen C. Coffee consumption during pregnancy and birth weight: does smoking modify the association? J Caffeine Res. 2015;5:65–72.
36.Jin F, Qiao C. Association of maternal caffeine intake during pregnancy with low birth weight, childhood overweight, and obesity: a meta-analysis of cohort studies. Int J Obes (Lond). 2021;45:279-87.
37.Wierzejska R, Jarosz M, Wojda B. Caffeine Intake During Pregnancy and Neonatal Anthropometric Parameters. Nutrients. 2019;11:806.
38.Gleason JL, Tekola-Ayele F, Sundaram R, Hinkle SN, Vafai Y, Buck Louis GM, et al. Association Between Maternal Caffeine Consumption and Metabolism and Neonatal Anthropometry: A Secondary Analysis of the NICHD Fetal Growth Studies-Singletons. JAMA Netw Open. 2021;4:e213238.
39.Modzelewska D, Bellocco R, Elfvin A, Brantsæter AL, Meltzer HM, Jacobsson B, et al. Caffeine exposure during pregnancy, small for gestational age birth and neonatal outcome - results from the Norwegian Mother and Child Cohort Study. BMC Pregnancy Childbirth. 2019;19:80.
40.Jarosz M, Wierzejska R, Siuba M. Maternal caffeine intake and its effect on pregnancy outcomes. Eur J Obstet Gynecol Reprod Biol. 2012;160:156-60.

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Olgu Sunumu / Case Report

BİR SAĞLIK ÇALIŞANI KABUSU: GEÇ TANI ALAN KIRIM KONGO KANAMALI ATEŞİ OLGUSU

A HEALTHCARE WORKER'S NIGHTMARE: DELAYED DIAGNOSIS OF CRIMEAN-CONGO HAEMORRHAGIC FEVER CASE

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ÖZET

Kırım Kongo Kanamalı Ateşi viral hemorojik ateş grubunda yer alan, akut seyirli, bulaşıcı ve mortal bir hastalıktır. Tanı konulması gecikmesi durumunda hasta ile yakın teması olan sağlık çalışanları için ciddi risk taşımaktadır. Bu olgu sunumuyla, atipik seyir nedeniyle geç tanı aldığından hasta ile yakın temas kuran sağlık personelinin ribavirin profilaksisi almak durumunda kaldığı bir Kırım Kongo Kanamalı Ateşi olgusunu sunarak bu konudaki farkındalığı arttırmak amaçlanmıştır.

Anahtar kelimeler: Geç tanı, KKKA, proflaksi

ABSTRACT

Crimean-Congo Hemorrhagic Fever is an acute, contagious, and fatal disease that belongs to the viral hemorrhagic fever group. A delay in diagnosis carries a severe risk to healthcare professionals who have close contact with the patient. This case report aims to raise awareness on this issue by presenting a case of delayed diagnosis of Crimean-Congo Hemorrhagic Fever due to its atypical clinical course so that healthcare personnel had close contact with the patient and had to receive ribavirin prophylaxis.

Keywords: CCHF, delayed diagnosis, prophylaxis

GİRİŞ

Kırım Kongo Kanamalı Ateşi (KKKA) Bunyaviridae ailesinde Nairovirus cinsi içerisinde yer alan zarflı bir RNA virüsü tarafından oluşturulan viral kanamalı ateş hastalığıdır. Dünyada en fazla Asya, Afrika ve Güney Doğu Avrupa'da görülen KKKA, ülkemizde de özellikle İç Anadolu Bölgesi ve Doğu Anadolu Bölgesi'nin kuzeyinde endemik olarak görülmektedir (1,2). Virüsü taşıyan Hyalomma cinsi kenelerin ısırığı ana bulaş yolu olmakla birlikte kan ve vücut salgılarının teması ile insandan insana bulaş da olabilmektedir. Bu sebeple yeterli koruyucu önlemin alınmadığı ve geç tanı alan vakalarda sağlık çalışanlarına ciddi bulaş riski bulunmaktadır (3).

Bu olgu sunumu ile amacımız, KKKA'nın atipik seyir gösterebileceğinin akılda tutulması, özellikle endemik bölgelerden gelen hastaların ayrıcı tanısında KKKA'nın atlanmaması ve klinik şüphe halinde tanı testleri ile aksi ispat edilene kadar koruyucu önlemlerin alınmasının önemini vurgulamaktır.

OLGU

Bilinen dahili hastalığı olmayan, Çankırı'da merkezde yaşayan ev hanımı 44 yaşında kadın hasta, 2019 mayıs ayının başında başlayan 3-4 gündür olan halsizlik ve kanlı, mukussuz, kahverengi ishal yakınması ile acil servise başvurdu. Yapılan tetkiklerinde trombositopeni tespit edilmesi üzerine hasta İdiyopatik Trombositopenik Purpura (ITP) ve gastrointestinal kanama ön tanısı ile hastanemize sevk edildi. Hastanemize başvurusunda alınan anamnezde herhangi bir kene teması olmadığını, çevresinde benzer şikayetleri olan başka birileri bulunmadığını ifade eden hastanın fizik muayenesinde; genel durumu iyi-orta, bilinci açık, koopere, oryante, ateş 36.5 0C, nabız 104/dakika, kan basıncı 110/70 mmHg, satürasyon oda havasında %95 ve bilateral alt ekstremitelerde birleşme eğilimi gösteren vaskülit benzeri peteşiyel tarzda döküntüleri mevcuttu (Şekil 1).

Yapılan tetkiklerinde lökosit sayısı 9140/mm^3, nötrofil 7590/mm^3, lenfosit 1090/mm^3, hemoglobin 16 gr/dl, trombosit 16.000/mm^3, Direk/İndirekt Coombs negatif, böbrek fonksiyon testleri normal, aspartat amino tansferaz (AST) 260 U/L, alanin aminotransferaz (ALT) 77 U/L, laktat dehidrogenaz (LDH) 760 U/L, kreatin kinaz (CK) 223 U/L, INR: 1.36, protrombin zamanı (PT) 54.9 sn, CRP 30 mg/L, d-dimer 80 mg/L, fibrinojen 0.90 g/L olarak bulundu. Periferik yaymada trombosit 20.000-30.000/mm^3 ile uyumlu idi ve atipik hücre saptanmadı.

Çekilen EKG'de göğüs derivasyonlarında yaygın T negatifliği, akciğer grafisinde sağ akciğerde minimal sıvı tespit edilen hasta kardiyolojiye konsülte edildi (Şekil 2). Hastaya ekokardiyografi (EKO) yapıldı. EKO'da restriktif tip diyastolik disfonksiyon tespit edildi. Yapılan abdominal ultrasonografi tetkikinde pelviste yaygın sıvı ve safra duvar kalınlığında artış gözlenen hasta akalkülöz kolesistit olarak değerlendirildi.

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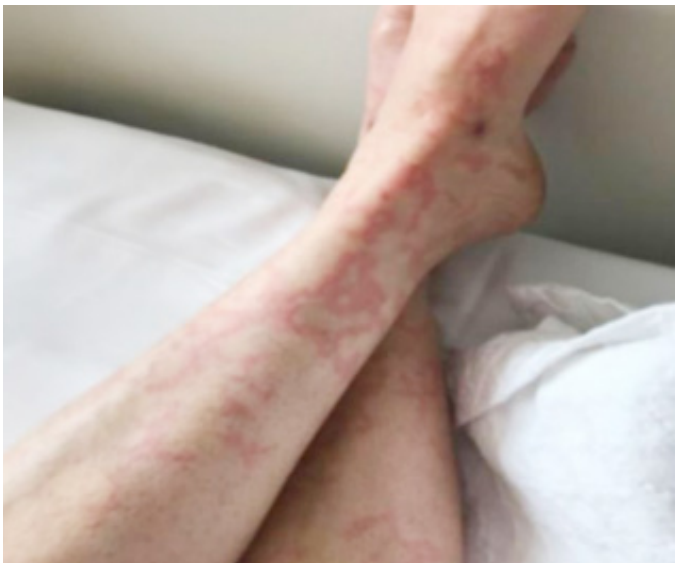
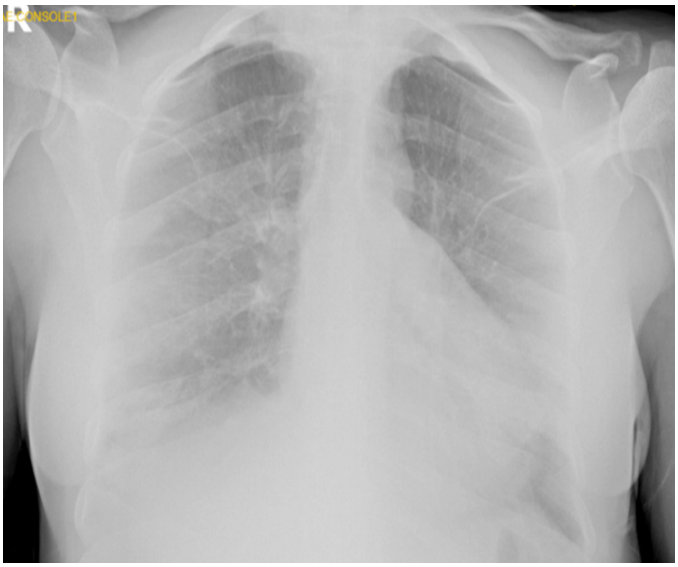


Şekil 1. Alt ekstremitelerde görülen vaskülit benzeri lezyonlar



Şekil 2. Sağ akciğerde minimal sıvı

Acil serviste yapılan tetkikleri sonrasında hasta ileri tetkik ve tedavi amaçlı acil iç hastalıkları servisine yatırıldı. Oral alımı kesilen hastaya uygun sıvı replasmanı, taze donmuş plazma, trombosit süspansiyonu ve ampirik seftriakson 2x1 gr IV tedavisi planlandı. Hastanın trombositopeni etiyolojisine yönelik olarak TORCH paneli, açık hepatit paneli (Anti HAV IgM, Anti HAV IgG, HBsAg, Anti HBs, Anti HBc IgG, Anti HCV), Anti Nükleer Antikor (ANA) paneli ve Lyme hastalığına (Anti-borelia IgG/IgA) yönelik tetkikleri planlandı. KKKA ekarte edilmek üzere Halk Sağlığı Kurumu Laboratuvarı'na KKKA PCR tetkiki gönderildi. Servis yatışından hemen sonraki saatlerde karın ağrısı şiddetlenen hastanın yapılan fizik muayenesinde batın bölgesinde yaygın hassasiyet haricinde bir değişiklik tespit edilmedi. Kontrol amaçlı laboratuvar ve görüntüleme tetkikleri planlanan hastanın ani olarak bilincinin kapandığı ve kardiyak arrest olduğu görüldü. Hastaya 15 dk kardiyopulmoner resüsitasyon (CPR) uygulandı. CPR sonrasında yanıt alınan hasta Anestezi Yoğun Bakım Ünitesi'ne nakil edildi. Hastanın yoğun bakım ünitesinde aynı gün exitus olduğu görüldü. Sonraki gün Türkiye Halk Sağlığı Kurumu Laboratuvarı'ndan hastanın KKKA PCR testinin pozitif olarak sonuçlandığı öğrenilmesi üzerine infeksiyon hastalıkları kliniği ile görüşüldü. Aynı gün içerisinde hastaya acil serviste abdominal ultrasonografi çekilirken, EKO tetkiki yapılırken ve servis yatışı sonrası arrest olduğunda CPR için müdahale edilirken hastanın vücut salgıları ile temas ettiği belirlenen veya şüphelenilen 7 hekim ve 2 hemşireye profilaktik amaçlı 10 gün boyunca günde 2 gr ribavirin tedavisi başlandı. Profilaksi başlanılan sağlık çalışanları KKKA bulguları konusunda bilgilendirildi. Toplam 8 sağlık personelinin tamamı profilaksi süresini tamamlarken bir sağlık personeli karın ağrısı ve karaciğer fonksiyon testlerinde hafif yükselme nedeniyle 5. günde ribavirin kullanımını sonlandırdı. Profilaksi sonrasında hiçbir personelde KKKA bulgularına rastlanmadı.

TARTIŞMA

KKKA ateş, bulantı, kusma, karın ağrısı, miyalji ve kanama bulguları ile seyretse de atipik prezentasyonlar ile karşımıza çıkabileceği akılda tutulmalıdır (4,5). Literatürde geç tanı alan KKKA vakaları sonrasında hasta ile yakın teması olan kişilere yönelik profilaksi yapılan çalışmalar bulunmakla birlikte, profilaksinin etkinliği konusunda net bir görüş bildirilmemiştir (6-8).

Güven ve ark yaptıkları bir çalışmada, farklı tanılar nedeniyle yapılan klinik seyri sonrasında hayatını kaybeden bir hastada KKKA tanısı konulması üzerine hasta ile teması olan sağlık çalışanlarını yüksek, orta ve düşük risk grubu şeklinde sınıflandırılmış, yüksek riskli ve orta riskli sağlık çalışanlarına profilaktik olarak ribavirin tedavisi uygulamıştır. Çalışmada profilaksi yapılan ve yapılmayan hiçbir sağlık çalışanında KKKA bulguları saptanmamış, yapılan KKKA PCR testi tüm temaslılar için negatif olarak sonuçlanmış ancak bazı sağlık çalışanlarında ribavirin kullanımı sonrası birtakım yan etkiler gözlenmiştir (7).

Güner ve ark'nın klinik deneyimlerini paylaştığı başka bir çalışmada, KKKA nedeniyle takipli hasalara yakın teması olan, infekte hasta kanları ile kontamine iğne batması olan ve/veya vücut salgılarına temas eden toplamda 7 sağlık çalışanına profilaktik olarak ribavirin tedavisi başlamıştır. Profilaksi başlanan 6 sağlık çalışanının hiçbirinde KKKA bulgular gözlenmemiş ve yapılan KKKA PCR testi negatif olarak sonuçlanırken; 1 sağlık çalışanında KKKA bulguları saptanmış, yapılan KKKA PCR testi pozitif olarak sonuçlanmış ancak ribavirin tedavisi sonrası hasta iyileşmiştir (8).

Olgu sunumumuzda hastanın endemik bölgeden ilkbahar aylarında başvurması KKKA hastalığı açısından anlamlı

olmakla birlikte öyküsünde kene teması olmaması, kırsal bölgede yaşamaması ve döküntülü lezyonlarının sadece alt ekstremitede olup vasküliti taklit etmesi nedeniyle ayrıcı tanılarda romatolojik ve hematolojik patolojiler de düşünülmüştür. Bu sebeple hasta ilk başvurduğu merkezde ön tanıda öncelikli olarak gastrointestinal kanama ve ITP düşünülerek hastanemize sevk edilmiştir. Hastanemizde yapılan değerlendirmede ön tanılar içerisinde KKKA düşünülmekle birlikte yapılan tetkiklerde akalküloz kolesistit, akciğerlerde bilateral minimal plevral mayi ve restriktif tip diyastolik disfonksiyon tespit edilmesi tipik KKKA kliniğinden uzaklaştıran bulgular olarak yorumlanmıştır. Bu süreç içerisinde acil servisten sevk edilirken ön tanıda KKKA düşünülmemesinin ve sevk sonrasında saptanan başka patolojiler için acil serviste pek çok ileri tetkik yapılmasının hastanın KKKA tanısı açısından vakit kaybetmesine neden olduğunu düşünmekteyiz. Hastadan ancak acil iç hastalıkları servisine yatışı sonrasında KKKA PCR testi gönderilmiş ve servis yatışını takiben saatler içerisinde kardiyojenik arrest sonrası hayatını kaybettikten sonra hastaya KKKA tanısı konulabilmiştir. Bu dönemde hastanın vücut salgıları ile temas eden toplamda 9 sağlık çalışanına ribavirin profilaksisi başlanmış, profilaksi boyunca ve sonrasında hiçbir sağlık çalışanında KKKA bulgularına rastlanmamış, bir sağlık çalışanı ribavirin yan etkileri nedeniyle profilaksi süresinin yarısını tamamlayabilmiştir.

Sonuç olarak, özellikle endemik bölgelerden bahar ve yaz aylarında başvuran, trombositopeni ve karaciğer fonksiyon testi yüksekliği bulunan hastalarda kene teması olup olmadığına bakılmaksızın KKKA ayrıcı tanıda mutlaka düşünülmeli ve şüphelenilen her hastaya müdahale esnasında uygun ekipman ile yaklaşılması gerektiği akılda tutulmalıdır. Bununla birlikte her ne kadar etkinliği, dozu ve süresi tam olarak belirtilmemiş olsa da, riskli yakın temas durumlarında infeksiyon hastalıkları ile görüşülerek ribavirin profilaksisi açısından temaslı kişiler değerlendirilmelidir.

Ek bilgi: Bu olgu sunumu 23. Ulusal İç Hastalıkları Kongresi'nde poster olarak sunulmuştur. (PS 040, 6-10 Ekim 2021, Elexus Otel, KKTC)

Bilgilendirilmiş Onam: Hastadan bilgilendirilmiş onam alınmıştır.

Yazarlık Katkısı: Fikir/Kavram: MVC, YEÖ, Tasarım/ Dizayn: MVC, MÖ, Denetleme/Danışmanlık: MVC, Veri Toplama ve/veya işleme: MÖ, YEÖ, Analiz ve/veya Yorum: MÖ, YEÖ, Literatür Taraması: MVC, Makalenin Yazımı: MVC, Eleştirel İnceleme: MÖ, Kaynaklar ve Fon Sağlama: -, Malzemeler: -.

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KAYNAKLAR

1.Fillâtre P, Revest M, Tattevin P. Crimean-Congo hemorrhagic fever: An update. Med Mal Infect. 2019;49:574-85.

2.Uyar Y, Çarhan A. Kırım Kongo Kanamalı ateşinin ülkemizdeki epidemiyolojisi. Türk Hij Den Biyol Derg. 2009; 66: 13-6.

3.Charrel RN, Attoui H, Butenko AM, et al. Tick-borne virus diseases of human interest in Europe. Clin Microbiol Infect. 2004;10: 1040-55.

4.Rehman K, Bettani MAK, Veletzky L, et al. Outbreak of Crimean-Congo haemorrhagic fever with atypical clinical presentation in the Karak District of Khyber Pakhtunkhwa, Pakistan. Infect Dis Poverty 2018; 7:116.

5.Krüger HJ, De Wet R, Blumberg LH, et al. Atypical presentation of Crimean-Congo haemorrhagic fever: Lessons learned. S Afr Med J. 2019;109:91-4.

6.Elaldi N, Bodur H, Ascioglu S, et al. Efficacy of oral ribavirin treatment in Crimean-Congo haemorrhagic fever: A quasi-experimental study from Turkey. J Infect 2009; 58: 238– 44.

7.Guven G, Talan L, Altintas ND, et al. An unexpected fatal CCHF case and management of exposed health care workers. Int J Infect Dis 2017;55: 118-21.

8.Guner R, Hasanoğlu I, Tasyaran MA, et al. Is ribavirin prophylaxis effective for nosocomial transmission of Crimean-Congo hemorrhagic fever? Vector-Borne and Zoonotic Diseases 2014;14: 601-5.

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Editöre Mektup / Letter to Editor

ALZHEİMER DEMANSIYLA İLİŞKİLİ AJİTASYONUN TEDAVİSİNDE FDA ONAYLI İLK ve TEK İLAÇ: BREXPİPRAZOL

THE FIRST AND ONLY FDA APPROVED DRUG FOR THE TREATMENT OF AGITATION ASSOCIATED WITH ALZHEIMER'S DEMENTIA: BREXPIPRAZOLE

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Sayın Editör;

Alzheimer Demansı (AD), yaşam beklentisinin kısalması ile ilişkilendirilen ve bilişsel gerileme ile karakterize edilen ilerleyici, nörodejeneratif bir hastalıktır. Son epidemiyolojik veriler, dünya çapında AD'lı insan sayısının 46,8 milyondan 2050 yılına kadar 131,5 milyona çıkacağını göstermektedir. AD'lı bireylerin yaklaşık yarısında ajitasyon gibi belirtiler ortaya çıkmaktadır. Ajitasyon, AD'de sıkça görülen nöropsikiyatrik semptomlardan biridir. Ajitasyonun, hastalığın ilerlemesinin hızlanması, hastaneye yatma riskinin artması, fonksiyonel düşüş ve yaşam kalitesinin azalmasıyla ilişkilendirildiği gözlemlenmiştir (1-3). Ajitasyon; anksiyete, sinirlilik, motor huzursuzluk ve anormal seslendirmenin yanı sıra hızlanma, gezinme, saldırganlık, bağırma ve gece rahatsızlıkları gibi gözlemlenebilir davranışları içeren geniş bir semptom yelpazesini kapsar (4). En sık karşılaşılan davranışsal belirtilerden biri ajitasyon, hastanın iç sıkıntısı nedeniyle aşırı hareket etmesini ifade eder ve bir kez başladığında hastalık süresince devam etme eğilimindedir. Ajitasyon, fiziksel olarak saldırgan olmayan davranışlar (huzursuzluk, adımlama, tekrarlayıcı davranışlar, eşyaları saklama, uygunsuz giyinme veya soyunma); fiziksel olarak saldırgan davranışlar (vurma, itme, çekme, ısırma, tekme atma, kavga etme); sözel olarak saldırgan olmayan davranışlar (negativizm, tekrar etme, konuşmalara karışma, sürekli ilgi isteme); ve sözel olarak saldırgan davranışlar (bağırma, garip sesler çıkarma, küfretme, öfke patlamaları) olarak kategorilere ayrılabilir. Hastalık ilerledikçe, ajitasyonun görülme sıklığı demansın ileri evrelerinde erken evreye göre yaklaşık 3.5 kat artar (5).

Kolinerjik sistemdeki eksiklik, ajitasyon veya saldırganlık sergileyen AD hastalarında daha şiddetli görünmektedir. AD ayrıca hipokampus ve frontal lobdaki serotonerjik sistemin yaygın eksiklikleriyle de ilişkilidir. Ajitasyonun ortaya çıkışı, frontal lob işlev bozuklukları ve özellikle de orbitofrontal korteks (OFC) ve anterior singulat korteksin (ACC) anormal aktivasyonuyla ilişkilidir. Serotonerjik sistemin bozulması, AD hastalarında ajitasyon ve irritabilitenin başlangıcını açıklamaya kısmen katkıda bulunabilir; dopaminerjik değişiklikler de rapor edilmiştir ve artan dopaminerjik serebellar dönüşüm, fiziksel olarak ajite edilmiş davranışlarla bağlantılıdır (4).

Demansın ilerleyen evrelerinde artan ajitasyon davranışının yönetimi, bakım verenler için giderek zorlaşan bir durum haline gelmektedir. Demanslı bir bireyin fiziksel ajitasyon davranışı sonucunda bakım verenlerde fiziksel yaralanmalar meydana gelebilir. Ayrıca, laf atma, küfretme, fiziksel uygunsuz yaklaşımlar gibi davranışlar, bakım verenin sosyal çevresinin ve desteğinin azalmasına neden olabilir. Hastanın evden habersiz çıkması veya kendisine zarar vermesi gibi durumlar, bakım verenin sürekli olarak hastayı gözlemlemesi gerektirebilir ve bu da işten ayrılma gibi sonuçlar doğurabilir, ekonomik kayıplara yol açabilir. Dolayısıyla, ajitasyonu olan demans hastasına bakım verenlerin üzerindeki yük artmaktadır. Bu yük ve bakımla ilgili sorunlar, bakım verenlerin duyarlı, kırılgan, fiziksel ve duygusal olarak tükenmiş hissetmelerine yol açabilir. Yükü fazla olan bakım verenler, daha sinirli ve sabırsız olabilir ki bu da hastalarda psikiyatrik ve davranışsal semptomların artmasına veya alevlenmesine neden olabilir. Bu durumların sonucunda, hastanın farmakolojik tedavi için hastaneye yatırılması gerekebilir ve tedavi maliyetleri artabilir. Benzer şekilde, bakım verenin fiziksel ve psikolojik sağlık sorunları, ekonomik zorluklar yaşaması tedavi maliyetlerini artırabilir. Bakım verenin ajitasyonu yönetme konusundaki zorlukları, hastanın bakımevine yerleştirilmesine yol açabilir.

AD' ye yönelik ajitasyon gibi belirtileri tedavi etmek için onaylanmış farmakolojik tedaviler bulunmamaktaydı. Bu durum, bu hasta popülasyonu için karşılanmamış önemli bir tıbbi ihtiyaç yaratmakta ve aynı zamanda bakıcılar için önemli bir sıkıntı kaynağı oluşturmaktaydı. Alzheimer hastalığına bağlı demansla ilişkili ajitasyonu tedavi etmek için onaylanan ilk ve tek tedavi olan Brekspiprazol (REXULTI) 2023 yılı mayıs ayında Amerika Birleşik Devletleri Gıda ve İlaç Dairesi (FDA) onayı almıştır.

Brekspiprazol, ajitasyon davranışlarına aracılık eden

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beyin devrelerindeki noradrenerjik, serotonerjik ve dopaminerjik sistem fonksiyon bozukluklarını hedefleyen atipik bir antipsikotiktir. Brekspiprazol, Amerika Birleşik Devletleri'nde (ABD) 2015 yılında ilk kez yetişkinlerde şizofreni tedavisi ve majör depresif bozukluğun (MDB) tedavisinde antidepresanlara yardımcı tedavi olarak onaylanmıştır. O zamandan beri, Brekspiprazol dünya genelinde 60'tan fazla ülkede onay almıştır (6). Brekspiprazol, dopamin D2 kısmi agonisti, serotonin 5-HT1A reseptöründe kısmi agonisti, serotonin 5-HT2A/5-HT2B ve noradrenalin α1B/α2C reseptörlerinde antagonist olarak görev yapan yeni bir üçüncü nesil antipsikotiktir (6). Brekspiprazol, bir reseptör kısmi agonisti (D2, D3, 5-HT1A) ve reseptör antagonistidir (5-HT2A/B, α1B/α2C). İlginçtir ki bu ilaç aynı zamanda aripiprazolden üç kat daha yüksek afiniteyle histamin H1 reseptöründe bir antagonist olarak da görev yapar (6). Böylece, Brekspiprazolbeyinde ajitasyon, saldırganlık, dürtüsellik, uyarılma ve psikoz ile ilgili birden fazla reseptör üzerinde etki gösterir. Bu farmakodinamik özellik muhtemelen AD' li hastalarda ajitasyona karşı klinik olarak anlamlı etkinliğini açıklamaya yardımcı olabilir.

Brekspiprazol' ün AD' ye bağlı demansla ilişkili ajitasyonun tedavisindeki etkinliği, 12 haftalık, randomize, çift kör, plasebo kontrollü, sabit dozlu iki çalışmayla belirlendi. İlk çalışmada hastalara 1 veya 2 miligram (mg) Brekspiprazol verildi (7); ikinci çalışmada hastalara 2 veya 3 mg Brekspiprazol verildi (8). Bu iki çalışmadaki birincil etkililik son noktası, 12. haftadaki Cohen-Mansfield Ajitasyon Envanteri (CMAI) toplam skorunda başlangıca göre değişiklikti. CMAI, demans hastalarındaki belirli ajitatif davranışların sıklığını derecelendirmek için bakım verenlerden gelen geri bildirimleri kullanan 1'den 7'ye kadar derecelendirilen likert tipi ölçektir. Her iki çalışmada da 2 mg veya 3 mg Brekspiprazol alan hastalar, 12. haftada plasebo grubundaki hastalarla karşılaştırıldığında toplam CMAI skorlarında istatistiksel olarak anlamlı ve klinik olarak anlamlı iyileşmeler gösterdi (7, 8). Alzheimer hastalığına bağlı demansla ilişkili ajitasyonun tedavisi için önerilen Brekspiprazol başlangıç dozu; 1 ila 7. günlerde günde bir kez 0.5 mg, 8 ila 14. günlerde günde bir kez 1 mg, 15. günden sonra ise 2 mg'dır. Önerilen hedef doz günde bir kez 2 mg'dır. Dozaj, klinik yanıt ve tolere edilebilirliğe bağlı olarak en az 14 gün sonra günde bir kez 3 mg'lık maksimum önerilen günlük doza yükseltilebilir (7, 8). Alzheimer hastalığına bağlı demansla ilişkili ajitasyonu olan hastalar arasında ilaca bağlı ciddi bir yan etki gözlenmemiştir. En sık görülen yan etkiler arasında baş ağrısı, baş dönmesi, idrar yolu enfeksiyonu, nazofarenjit ve uyku bozuklukları (hem uyku hali hem de uykusuzluk) yer alır (7, 8).

Sonuç olarak, Alzheimer demansıyla ilişkili ajitasyonun tedavisi konusunda daha fazla anlayış ve etkin tedavi seçenekleri geliştirmek amacıyla devam eden araştırmalara ihtiyaç bulunmaktadır. Alzheimer demansıyla ilişkili ajitasyonun tedavisi, sürekli olarak gelişen bir alan olup, yeni tedavi seçenekleri arayışını sürdürmek önemlidir. Brekspiprazol, bu alanda umut vadeden FDA onaylı ilk ve tek ilaç özelliğini korumaktadır. Bu alandaki ilerlemeler, bu semptomları yaşayan bireylerin yaşam kalitesini artırabilir ve aynı zamanda bakım verenlere destek sağlayabilir.

Yazarlık Katkısı: Fikir/Kavram: DS, Tasarım/Dizayn: DS, Denetleme/Danışmanlık: DS, Veri Toplama ve/veya işleme: DS, Analiz ve/veya Yorum: DS, Literatür Taraması: DS, Makalenin Yazımı: DS, Eleştirel İnceleme: DS, Kaynaklar ve Fon Sağlama: -, Malzemeler: -.

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KAYNAKLAR

1. Banerjee S, Smith SC, Lamping DL, et al. Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. J Neurol Neurosurg Psychiatry. 2006;77:146-8.
2. Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, et al. nstitutionalization risk and costs associated with agitation in Alzheimer's disease. Alzheimers Dement. 2019;5:851-61.
3. Rockwood K, Sanon Aigbogun M, Stanley J, et al. The Symptoms Targeted for Monitoring in a Web-Based Tracking Tool by Caregivers of People With Dementia and Agitation: Cross-Sectional Study. J Med Internet Res. 2019;21:e13360.
4. Liu KY, Stringer AE, Reeves SJ, et al. The neurochemistry of agitation in Alzheimer's disease: a systematic review. Ageing Res Rev. 2018;43:99-107.
5. Schein J, Houle CR, Urganus AL, et al. The Impact of Agitation in Dementia on Caregivers: A Real-World Survey. J Alzheimers Dis. 2022;88:663-77.
6. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350:589-604.
7. Grossberg G, Lee D, Slomkowski M, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials. Am J Geriatr Psychiatry. 2023;31:99-100.
8. Lee D, Slomkowski M, Hefting N, et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. JAMA Neurol. 2023;80:1307-16.

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Letter to Editor / Editöre Mektup

IS SERONEGATIVE SJÖGREN'S SYNDROME: AN OVERLOOKED ENTITY?

SERONEGATİF SJÖGREN SENDROMU: GÖZDEN KAÇAN BİR ANTİTE Mİ?

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Dear Editor,

Primary Sjögren's syndrome (PSS) is a systemic autoimmune disease. It causes chronic inflammation and dysfunction of the exocrine glands, especially the salivary glands, resulting in dryness of the eyes and mouth. An estimated 0.01% to 0.72% of the population is affected by Sjögren's syndrome (1). Patients may present with a range of clinical manifestations, from sicca symptoms to potentially severe extra glandular and/or systemic features. These may include inflammatory arthritis, parotitis, interstitial lung disease, neurological dysfunction, cryoglobulinaemia and lymphomas. SS diagnosis is based on the combination of clinical, serological, and functional tests with histological biomarkers. To diagnose PSS, internationally accepted classification criteria require objective measures of reduced tear or saliva production, as well as immunological abnormalities confirmed either by detecting anti-SSA/Ro autoantibodies or through histological findings of focal lymphocytic sialadenitis in labial salivary glands (2). Patients with SS commonly present with autoantibodies such as anti-Ro/SSA, anti-La/SSB, antinuclear antibodies (ANA), and rheumatoid factors (RF). Patients who meet the criteria for SS but do not have the typical serum antibodies are referred to as seronegative SS patients. The prevalence of seronegative SS in SS cohorts varies widely in the literature, ranging from 8% to 37% (3). Minor salivary gland biopsy (MSGB) represents the cornerstone for the diagnosis of seronegative pSS, allowing the study of the characteristic focal infiltration of B- and T lymphocytes. Here we present 3 cases of seronegative SS with different organ involvement (Table 1).

A 54-year-old woman was admitted to the pulmonology department 1 year ago with the complaint of increasing dyspnea, which had been present for about 2 years. In the Computed tomography (CT) taken; diffuse peribronchovascular thickening and ground glass changes with tiny cysts along the bronchovascular bundles in both lungs (lymphocytic interstitial pneumonia) have a pattern and in respiratory function tests (FEV1 63%, FVC 71%, and DLCO 70%), ıdiopathic interstitial lung disease was considered due to its restrictive character. She was treated with inhaled bronchodilators and systemic steroids when necessary. She has been referred to us for rheumatological diseases due to joint pain. On questioning, she stated that she had dry mouth for an average of 3-4 years, she did not know about dry eye. Schirmer test was <5 mm/5 minutes. ANA, RF, anti-Ro/SSA, and anti-La/SSB were negative. The erythrocyte sedimentation rate (ESR) was 25 mm/h, and C-reactive protein (CRP) was 1 mg/dl (0-5). On MSGB, the focus score was >1 and 4 lymphocytic aggregates and amyloid staining was negative. PSS was diagnosed and prednisolone and cyclophosphamide treatment was started. The patient whose dyspnea decreased with treatment, is in the 18th month of treatment and continues to be followed up with azathioprine 150 mg/day and prednisolone 5 mg/day.

A 48-year-old female patient was examined with fatigue and joint pain, in laboratory tests performed total bilirubin 2.57 mg/dL (0.3-1.2 mg/dL), gamma-glutamyl transpeptidase (GGT) 570 IU/L (normal < 55 IU/L) and Alkaline phosphatase 280 IU/L (normal 30-120 IU/L), aspartate transaminase (AST) 112 IU/L (normal 8-35 IU/L) and alanine transaminase (ALT) 125 IU/L (normal 10-45 IU/L) levels high. The immunological study confirmed the presence of positive anti-mitochondrial antibody (AMA) and negative ANA and anti-smooth muscle antibodies (ASMAs). A liver biopsy was performed after confidently ruled out viral, metabolic, and malignant causes. The liver biopsy revealed an expansion of port spaces due to an abundance of inflammatory infiltrate, primarily consisting of lymphocytes and plasma cells, with rare eosinophils. Additionally, there was evidence of interface hepatitis and peri-portal fibrosis. Primary biliary cholangitis(PBC) was considered in the patient. The patient was started on ursodeoxycholic acid and her cholestasis enzymes decreased during follow-up. She was referred to us due to rheumatological diseases due to pain in her fingers and wrist. It was learned that she had dry mouth for 4-5 years and dry eye for 2 years and that she used tears. On physical examination, she had arthralgia, and her tongue was dry. ANA, RF, anti-Ro/

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Table 1. Baseline characteristics of three patients with primary Sjögren's syndrome.

Feature/Clinical manifestation	Case 1	Case 2	Case 3
Age	54	48	44
Gender/female	+	+	+
Dry mouth	+	+	+
Dry eyes	+	+	+
Schirmer / mm/5 minute	<5	<5	<5
Focus score	>1	>1	>1
Anti-SSA/Ro and anti-La/SSB	negative	negative	negative
ANA and RF	negative	negative	negative
ESR (mm/h)(0-20)	25	32	40
CRP (mg/dl)(0-5)	1	3	25
Arthralgias	+	+	+
Arthritis	-	-	-
Parotitis	-	-	+
Interstitial lung disease	+	-	-
Primary biliary cholangitis	-	+	-
Treatments	Corticosteroids Hydroxychloroquine Cyclophosphamide	Corticosteroids Hydroxychloroquine	Corticosteroids Hydroxychloroquine Antibiotics

ANA: Antinuclear antibody, RF: Rheumatoid factor, ESR: Erythrocyte sedimentation rate, CRP:C-reactive protein

SSA, and anti-La/SSB were negative in serological tests and MSGB was performed. Focus score>1 and there were 3 aggregates. PBC overlap with PSS was considered. Hydroxychloroquine 200 mg/day and prednisolone 5 mg/day were added to treatment. She is in the 12th month of her treatment and her follow-up and treatment continue.

A 44-year-old woman was referred for evaluation of painful, bilateral parotitis. The patient had a history of recurrent parotitis episodes occurring every one or two months for the past four years. These episodes were associated with elevated levels of CRP and which usually required antibiotic therapy. On questioning, the patient had dry mouth, dysphagia and arthralgia. The dry eye was unknown. The patient's physical examination revealed mildly swollen parotid glands bilaterally. Laboratory tests showed ANA, RF, anti-Ro/SSA, and anti- La/SSB negative. Schirmer test <5 mm/5 minutes. A labial biopsy of MSGB showed six lymphoid aggregates, several focuses on periductal lymphoid cell infiltration with glandular and ductal atrophy. The patient has been diagnosed with PSS based on these findings. Hydroxychloroquine 200 mg/day and prednisolone 5 mg/day were initiated for PSS. She was started on a prophylactic course of amoxicillin–clavulanic acid 1000 mg twice a day (seven days), after a month this was reduced to 500 mg every evening. After six months of remission of parotitis attacks, prophylactic therapy was stopped. In the 9th month of her treatment, her follow-up continues without parotitis attacks.

Diagnosing PSS can indeed be challenging. Approximately 30% of cases involving dryness in mucous membranes are attributed to age-related glandular atrophy or medication use (4). Sicca symptoms are widely prevalent in the general population and can have a variety of causes, the large majority of which are not associated with autoimmune disease (5). As a result, pSS might be overlooked. Seronegative Sjögren's syndrome can be accurately diagnosed by identifying autoantibody biomarkers associated with SS through a MSGB. It is important to perform further investigations to avoid missing this diagnosis in clinical settings. Seronegative patients often face delayed diagnosis compared to their seropositive counterparts (6). In a study conducted in seronegative patients, it was observed that SSA/Ro-52 autoantibodies were detected in saliva before autoantibodies appeared in serum (7). It has been stated that this method may help in the early detection of autoimmunity and can replace serum anti-SSA/Ro Ab (7). Based on this, the concept of seronegativity may be expanded in the coming years to include not only plasma antibodies but also salivary glands antibody negativity. Moreover, we must persist in conducting further research to discover novel disease-specific autoantibodies, thereby making substantial advancements in the diagnosis of these patients. Serological classification of patients can aid in predicting clinical and patient outcomes in those with seronegative SS. Further research is necessary to determine the extent of its impact.

In summary, clinicians should be cautious of SS in patients who present with sicca symptoms or other clinical

features typical of SS, even if they do not have the typical SS autoantibodies. Therefore, it is important to objectively measure lacrimal function, for example, by conducting a Schirmer test, and to refer the patient for MSGB when necessary. The importance of early recognition, diagnosis, and management of SS is reflected by patients presenting with late and/ or serious complications, reduced quality of life, and increased health service utilization.

Informed Consent: Informed consent was taken from the patient.

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REFERENCES

1. Brito-Zerón P, Baldini C, Ramos-Casals M, et al. Sjögren syndrome. Nat Rev Dis Primers 2016;2:16047
2.Shiboski CH, Shiboski SC, Mariette X. et al. International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017;76:9-16.
3.Brito-Zerón P, Acar-Denizli N, Ng WF. et al. How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). Clin Exp Rheumatol 2018;112:102-12.
4.Villa, A, Wolff, A, Proctor, G. et al. World Workshop on Oral Medicine VI: a systematic review of medication induced salivary gland dysfunction. Oral diseases. 2016;22:365-82.
5.Mariette X. Sjögren Syndrome: A Forgotten or an Overdiagnosed Entity? J Rheumatol 2023;1:2023-0964.
6.Karahan S, Karabulut A. Is there a need for such a naming: seronegative primary Sjogren's syndrome? Turk J Immunol 2021;9:128-33.
7.Kamounah S, Tayob N, Wong DTW. et al. Immunoassay Detects Salivary Anti-SSA/Ro-52 Autoantibodies in Seronegative Patients with Primary Sjögren's Syndrome. Immunohorizons 2023;7:554-61.