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The Relationship Between Ketamine and Memory Impairment: A Systematic Review

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Systematic Review

History

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ABSTRACT

Increasing evidence supports that ketamine affects cognitive function, but various studies have reported dissenting opinions. This study aimed to investigate the potential correlation between Ketamine usage and memory deterioration, which is crucial for informing clinical practice and public health interventions. A systematic review was conducted, and six databases were scanned according to the PRISMA guidelines. As a result, 50 studies were analyzed to investigate the relationship between Ketamine and memory deterioration. It was found that most studies provided evidence for the claim that there is a negative association between Ketamine and cognitive function, specifically in the realm of memory. Some studies emphasized gender differences; however, their results were inconclusive. Studies have also found that the impact of ketamine is not limited to cognitive functions; it extends to other aspects such as depression, suicidal ideation, and neurocognitive functions. In conclusion, it is evident that there is an association between Ketamine and memory deterioration however, this relationship is challenging to develop and further studies are required.

Keywords: Cognition, Ketamine, Memory, N-Methylaspartate

Ketamin ve Bellek Bozuklukları Arasındaki İlişki: Bir Sistematik Derleme

Sistematik Derleme

Süreç

Geliş: 16/03/2024
Kabul: 21/05/2024

ÖZET

Ketaminin bilişsel işlevleri etkilediğine dair bulgular giderek artsa da çeşitli çalışmalarda farklı görüşler ortaya koyulmuştur. Bu çalışma, klinik uygulamalar ve halk sağlığı müdahaleleri hakkında bilgi vermede çok önemli olan Ketamin kullanımı ile bellek bozuklukları arasındaki potansiyel ilişkiyi araştırmayı amaçlamaktadır. Çalışmada sistematik derleme yöntemi benimsenerek PRISMA kılavuzuna göre altı veri tabanı taranmış, Ketamin ve bellek bozuklukları arasındaki ilişkiyi araştıran 50 çalışma analize dahil edilmiştir. Çoğu çalışma, Ketaminin bilişsel işlevler, özellikle de bellek üzerinde olumsuz bir etkisi olduğunu göstermektedir. Bazı çalışmalar cinsiyet farklılıklarını vurgulamış; ancak bunların sonuçları yetersiz kalmıştır. Çalışmalar ayrıca Ketaminin etkisinin bilişsel işlevlerle sınırlı olmadığını; depresyon, intihar düşüncesi ve nörobilişsel işlevler gibi diğer yönler üzerinde de etkili olduğunu ortaya koymuştur. Sonuç olarak Ketamin ve bellek bozuklukları arasında bir ilişki olduğu açıktır, ancak bu ilişkinin tam anlamıyla açıklanabilmesi için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Biliş, Ketamin, Bellek, N-Metilaspartat

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Introduction

Ketamine hydrochloride, commonly referred to as Ketamine is a widely used dissociative anesthetic that is used medically for the induction and maintenance of anesthesia. It is considered one of the safest anesthetics, in contrast to opiates, ether, and propofol.[1,2] Nowadays Ketamine usage had varied to include depression treatment, suicidality, chronic pain, migraines, obsessive compulsive disorder, and even some post-traumatic stress disorder (PTSD) symptoms.[3-5] Introduced in 1962 for use as an anesthetic and an analgesic (pain reliever) and also for use in minor surgery, Ketamine is an old medicine. In 1970, the U.S. Food and Drug Administration (FDA) approved the drug, and it quickly became the most widely used battlefield anesthetic during the Vietnam War.[6] Since then, more researchers have been interested in its impact on mental health and have been involved in further investigating it and how it can be used to enhance or manage mental health crises.[7]

Ketamine and its usages

Ketamine is one of the most well-known forms of psychoplastogen. Ketamine impacts multiple receptors and pathways in the brain and body. Ketamine has a predominant action on two very important neurotransmitters: glutamate and gamma-aminobutyric acid (GABA). In fact, as the Brain & Behavior Research Institute points out, these two chemical messengers have opposite effects: “glutamate is the most common of the brain’s ‘excitatory’ neurotransmitters, while GABA has an opposite, inhibitory, role.” This combination has been shown to be an important outcome not only in enhancing mood but also in decreasing suicidal ideation.[8,9]

Ketamine was and is still being used for different purposes; it can provide pain relief and short-term memory loss, such as amnesia, during medical procedures. Another important use for Ketamine is sedation in general anesthesia because it is an induction and maintenance agent. Ketamine is also used to control symptoms of depression, respiratory depression, and acute suicidal ideation by blocking the N-methyl-D-aspartate (NMDA) site.[10-15]

Side effects of ketamine

Just like any other drug, Ketamine also has side effects, including both mental and physical. The most common mental side effects include sedation, dream-like state, decreased focus, agitation, anxiety, hallucinations, difficulty thinking, and many more. Physical side effects of ketamine include involuntary eye movements, seizures, nausea, vomiting, and elevated blood pressure. Although ketamine activates the sympathetic nervous system, which typically leads to tachycardia, there are documented cases where decreased heart rate occurs, influenced by factors such as individual physiological responses and dosage.[15,16] Frequent use of ketamine can lead to damage to various major organs, including the digestive tract, urinary tract, and brain. Ketamine impact on the brain leads to induction of long-term cognitive deficits, which was found among frequent users. Frequent ketamine users exhibit numerous cognitive impairments, but particularly a specific decline in spatial working memory.[17-18]

Ketamine and memory

Most other antidepressants act on one of the "monoamine" neurotransmitters, such as serotonin, norepinephrine, or dopamine. Ketamine, on the other hand, is believed to work in a way that targets glutamate, the most common excitatory brain chemical messenger. It supports and strengthens synaptic connections by coordinating the brain's ability to process cognitive thoughts, emotions, and neuroplasticity. Therefore, glutamate acts to direct one of the key agents in learning and remembering, which is forming responses to past experiences.

The role of the NMDA receptor as a key component in learning is supported since the levels of ketamine in the chronic and acute state associated with spatial memory deficits in human beings, and due to the fact that there is the existence of a high density of the NMDA, high-affinity non-competitive NMDA acid in the hippocampus. This study will establish the relationship between memory deficits and frequent ketamine use by finding the relevance from the literature.[16]

Method

This study used a systematic review method to collect, analyze, and interpret the data. In the systematic review, studies published on the relevant subject are scanned in detail. The studies are included in the review in line with the inclusion criteria, and the findings obtained are synthesized quantitatively and qualitatively.[19] This systematic review study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Attachment 1). PRISMA is a guide that provides transparency and accountability between papers in the presentation of results, specifying standards for reporting the results of systematic reviews.[20] In the current study, six databases were scanned in November 2023, and different combinations of the determined keywords were searched in the titles and abstracts of the studies using boolean operators (Table 1).

Table 1. Search Strategy

Databases	EBSCO, MEDLINE/PubMed, Science Direct, Scopus, Web of Science Core Collection, WILEY
Keywords	NMDA, Ketamine, Memory, Cognition
Inclusion/Exclusion	• Published in a peer-reviewed journal • In English • Research article • About Ketamine effects on memory during or after treatment • Available in full text

EndNote version 21.0, Clarivate Analytics, which is "a database application that is used to store, manage, and find bibliographic information", was used to extract the studies from the databases. Then, the titles and abstracts of the studies were examined individually and chosen according to the inclusion criteria. 50 studies that comply with the relevant criteria were determined as a result of the screening, and those studies were included in the scope of the review.

Ensuring validity and reliability in qualitative research can be explained by the concepts of credibility and confirmability. While credibility provides internal validity, confirmability provides external reliability.[21] The current study research's method, data, findings, and results were explained in a way that will provide the maximum benefits for the researchers. All included studies were analyzed in an unbiased and impartial manner with their sources. In this study, the studies included in the scope of the study were coded into a database using the Microsoft Office Excel program according to the pre-determined categories.

The research questions of this systematic review are as follows:

- What is the most used route for Ketamine?
- What is the most used dosage for Ketamine?
- If any, which other drugs were used in addition to Ketamine?
- Which scales were used the most to assess memory?
- What other scales were used the most in addition to memory assessment?
- Is Ketamine usage a contributive agent in memory deterioration?
- Does the effect of Ketamine differ among genders?
- What factors are mostly investigated with Ketamine use and its effect on memory?

Findings

All the studies that were included in this systematic review were based on the results of the inclusion and exclusion criteria, and they were examined in detail based on two aspects: characteristics of the studies and qualitative synthesis. In this section of the study, the findings will be analyzed in detail based on these two aspects.

Characteristics of the studies

A total of 50 studies were analyzed by the year of publication, and it was found that the publication years ranged from 1983 to 2022. Research on this topic was relatively limited during the late 1990s and early 2000s; however, there was a significant surge in research by the 2010s, followed by a subsequent decline as of 2022, as can be seen in Figure 1.

Studies were conducted using three different methods: clinical, experimental, and scale. The clinical method was the most used by 76%, followed by the experimental method by 18%, and the scale method came last with only 6% (Table 2). Most of the studies (80%) were interventional design and 20% were observational design. The universe sizes of the studies varied between nine and 1614 with an average of 104. 80% of the studies included both genders. Among these studies, eight were conducted only on male participants and six included only female participants (Table 2).

Detailed information about the studies, such as route and dose of Ketamine, memory, and other measurements, and the main findings are given in detail in Table 4. The studies were examined in detail for the application route of Ketamine, and it was found that most studies (72%) have used the intravenous method. Ketamine was not always applied alone; most of the time, it was combined with other drugs including Methadone and Morphine as opioids/analgesics, Propofol and Midazolam as anesthetics and sedatives/hypnotics, Haloperidol as Antipsychotics, and other drugs such as Saline and Methamphetamine (Table 2). It was found that increasing Ketamine doses leads to temporarily impaired cognitive functions (22-24). However, despite this variability, studies suggest that Ketamine, even at relatively low doses, can adversely affect cognitive functions (22, 23, 25-47).

It was also found that 59 different memory scales were used, and the most used was the MATRICS Consensus Cognitive Battery (n=8), followed by the Cogstate Brief Battery (n=6) (Attachment 2). 28% of the scales used were for working memory assessment and 20% were for general memory assessment. Other scales were also used to assist other parts of the memory, such as verbal, visual, and autobiographical memory (Table 3). In addition to scales for memory assessment, other scales were used in line with the specific purposes of the studies, such as the Montgomery–Asberg Depression Rating Scale (n=13), Brief Psychiatric Rating Scale (n=8), Clinician-Administered Dissociative States Scale (n=7) and Hamilton Depression Rating Scale (n=7) (Attachment 3). Most of the scales (66%) used were for mental health assessment followed by cognitive assessment (%13) and addiction assessment (5%) (Table 3).

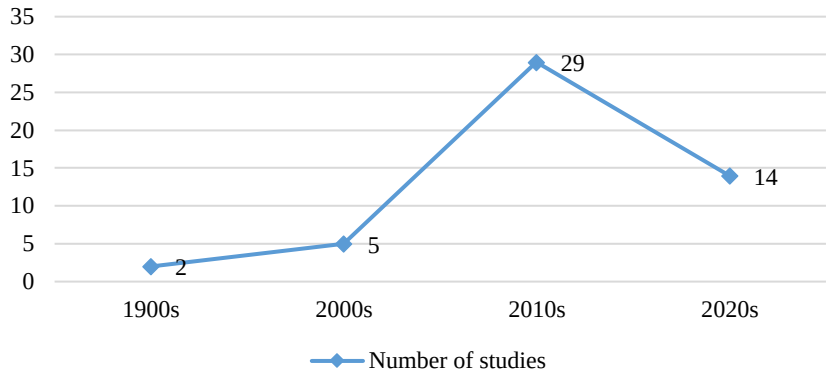

Figure 1. Distribution of studies by years

Table 2. Descriptive Findings of the Studies

Variable		Frequency (n)	Percentage (%)
Study Method	Clinical	38	76
	Experimental	9	18
	Scale	3	6
Study Design	Interventional	40	80
	Observational	10	20
Sample Gender	Only Female	3	6
	Only Male	4	8
	All	40	80
	N/A	3	6
Ketamine Route	Intravenous	36	72
	Nasal	2	20
	Oral	1	4
	Oral or nasal airway insertion	1	2
	N/A	10	2
Other Drugs	Anesthetics and Sedatives/Hypnotics	9	18
	Opioids/Analgesics	5	10
	Antipsychotics	1	2
	Other	15	30
	N/A	20	40

Table 3. The Type of Memory Scales Used in the Studies

	Frequency (n)	Percentage %
The Types of Memory Scales		
Working Memory Assessment	24	28
General Memory Assessment	17	20
Verbal Memory Assessment	12	14
Visual Memory Assessment	7	8
Autobiographical Memory Assessment	5	6
Other Memory Assessments	20	24
The Types of Other Scales		
Mental Health Assessment	84	66
Cognitive Assessment	17	13
Addiction Assessment	6	5
Personality Assessment	5	4
Psychomotor Assessment	5	4
Functioning Assessment	5	4
Diagnostic Assessment Tools	2	2
N/A	3	2

Table 4. Ketamine Findings Of The Included Studies

Study	Route and Dose	Other drugs (if any)	Memory Measurements	Other Measurements	Main Finding
(48)	Intravenous 0.5 mg/kg	Saline	Hopkins Verbal Learning Test-Revised (HVLT-R-DR) Controlled Oral Word Association Test (COWAT) Autobiographical Memory Interview – Short Form (AMI-SF) Medical College of Georgia Complex Figure Test (MCGCFT) Self-reported Global Self Evaluation of Memory (GSE-My)	Clinical Anxiety Scale (CAS) Clinical Global Impression (CGI) Brief Psychiatric Rating Scale (BPRS) Quick Inventory of Depressive Symptomatology— Self Report (QIDS-SR) EuroQol 3-level version (EQ-5D-3L)	The study found that ketamine treatment did not offer any cognitive or efficacy benefits compared with saline treatment. A minority of patients experienced psychological effects related to ketamine upon awakening from ECT, but overall, no serious safety or tolerability problems were observed.
(32)	Intravenous 20 and 40 mg/70 kg/h	N/A	Picture-encoding/recognition paradigm	Bond and Lader visual analog scale	At the 40 mg dose, a significant reduction in recognition picture recall performance characterized by an increase in the number of misses was observed.
(49)	N/A 0.5 mg/kg	N/A	Groton Maze Learning Test One-back test Two-back test International Shopping List Task Continuous Paired Associative Learning One Card Learning Test Groton Maze learning delayed International shopping list delayed	Clinician-administered PTSD Scale (CAPS-IV)	This study found that repeated ketamine infusions did not result in a significant decline in any measures of cognition. In contrast, there was a notable improvement in working memory after the completion of the infusion series.
(25)	N/A N/A	N/A	Authors' own questionnaire	Pelvic pain and urgency/frequency (PUF)	The study found that female ketamine offenders were more likely to develop severe cognitive impairment than males.
(50)	Intravenous 0.5 mg/kg	N/A	MATRICS Consensus Cognitive Battery (MCCB)	Beck Scale for Suicide Ideation (SSI)-part I Hamilton Depression Rating Scale adapted from the 17-item HAMD Global Assessment Scale (GAS)	The study found that ketamine as an NMDA receptor antagonist significantly improves working memory in patients with MDD.
(26)	Nasal 3.8 ± 2.7 g / day	N/A	Cogstate Brief Battery	Positive and Negative Syndrome Scale	The study found that ketamine-associated persistent psychosis patients had more severe symptoms than non-psychotic ketamine users. Both ketamine-associated persistent psychosis and schizophrenia patients had similar levels of cognitive impairment, worse than non-psychotic ketamine users, but not significantly different from each other after adjusting for demographic characteristics and antipsychotic dose.

(27)	Intravenous 0.23 mg/kg	N/A	IntegNeuro battery	Positive and Negative Syndrome Scale (PANSS) Clinician-administered Dissociative Symptoms Scale (CADSS) Visual Analog Scale (VAS)	The study found that ketamine can disrupt the ability to direct and sustain attention, response inhibition, working memory, verbal fluency, executive function, serial processing, immediate and delayed free verbal recall, speed of processing, reasoning, problem-solving, and emotion recognition.
(51)	Intravenous 0.5 mg/kg	N/A	Autobiographical Memory Interview – Short Form (AMI-SF) Autobiographical Fluency Task (AFT)	Hamilton Depression Rating Scale (HDRS) Beck Depression Inventory (BDI) Brief Psychiatric Rating Scale Visual analog scales (VAS) Structured Clinical Interview for DSM-IV Antidepressant treatment history form	The study found that subjects reported slight improvements or little change, suggesting that ketamine was not associated with memory impairment.
(29)	Intravenous 0.23 mg/kg–0.58mg/kg/h	Saline	The spatial WM task	Positive and Negative Syndrome Scale (PANSS)	The study found that even at higher doses, the effects of ketamine on perception, attention, working memory impairments, and declarative memory are relatively subtle.
(40)	Intravenous 3.4 g/d	N/A	Authors' own questionnaire	N/A	The study found that memory impairment was the most frequently reported long-term symptom by inpatients with ketamine dependence.
(30)	Intravenous up to 2 mg/kg	Propofol	Cambridge Automated Neuropsychological Test Battery Spatial Recognition Memory task (CANTAB SRM)	Hamilton Depression Rating Scale (HDRS) Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that memory impairment was the most frequently reported long-term symptom by individuals with ketamine dependence.
(31)	Oral or nasal airway insertion 0.5–0.74 mg/kg	Propofol	Authors' own questionnaire	Wisconsin Sedation Scale (WSS)	The study found that the incidence of memory loss after emergency department procedural sedation and analgesia (ED PSA) involving premixed ketamine-propofol (KP) administered sequentially is infrequent. This outcome is associated with moderate sedation levels and propofol doses less than 0.75 mg/kg.
(23)	Intravenous 0.3–0.15 mg/kg	Dexmedetomidine	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Cambridge Neuropsychological Test Automated Battery (CANTAB)	The study found a modest association between reduced psychomotor speed and accuracy and the concentrations of ketamine, norketamine, and Dexmedetomidine in the blood. In addition, a negative correlation was found between the blood concentrations of ketamine, norketamine, and Dexmedetomidine and

					performance on memory tasks. Notably, concurrent administration of ketamine with Dexmedetomidine but not with fentanyl results in synergistic effects on psychomotor performance and memory, while avoiding executive dysfunction.
(22)	Intravenous 8 mg/kg/h	Norketamine	Visuospatial working memory (SWM)	Visual Analogue Scale (VAS) Reaction/movement time (RTI) Stockings of Cambridge (SOC)	The study found that increasing doses of ketamine temporarily impaired higher-order cognitive functions, including visuospatial working memory and spatial planning.
(24)	Intravenous 250–300 ug/dl	N/A	Wechsler Memory Scale-Third Edition (WMS-III) Hopkins Verbal Learning Test (HVLT)	Beck Depression Inventory-II (BDI-II) State Trait Anxiety Inventory Minnesota Multiphasic Personality Inventory-2 (MMPI-2) McGill Pain Questionnaire Wechsler Adult Intelligence Scale-III) Connors' Continuous Performance Test (CPT)	This study found that deep ketamine infusion may not have a negative impact on cognitive function with prolonged treatment.
(34)	Intravenous 0.25 mg/kg	Nimodipine	Hopkins Verbal Learning Test (HVLT)	Brief Psychiatric Rating Scale (BPRS) Dissociative States Scale (CADSS) Biphasic Alcohol Effects Scale (BAES) Comparable Volume of the Ethanol Scale	The study found that both ketamine and nimodipine have additive effects on recall that were independent of the presence of cues intended to enhance memory retrieval, suggesting that each drug influenced memory encoding rather than memory retrieval.
(52)	Intravenous 0.5 mg/kg	N/A	Consensus Cognitive Battery (MCCB)	Montgomery–Asberg Depression Rating Scale (MADRS) Hamilton Anxiety Rating Scale (HAMA)	The study found that ketamine is harmful to neurocognition in chronic users and decreased performance on pattern recognition memory tasks and spatial working memory tasks. Furthermore, chronic ketamine users also suffer from deficits in verbal learning, visual learning, selective attention, and verbal fluency.
(38)	N/A 1 mg/kg	Etomidate	Folstein Mini-Mental State Examination	Montgomery– Asberg Depression Scale	The study found that the effect of ECT on memory is mediated by glutamate at N-methyl-D-aspartate receptors, suggesting that N-methyl-D-astarte antagonists may offer protection from memory dysfunction during ECT.
(39)	Intravenous 0.5 mg/kg	Lamotrigine	MATRICS Consensus Cognitive Battery (MCCB)	Montgomery–Asberg Depression Rating Scale (MADRS) Psychiatric Rating Scale (BPRS)	The study found that subjects who showed significant clinical response to ketamine within a 24-h period had more severe

				Clinician-Administered Dissociative States Scale (CADSS)	neurocognitive impairments, specifically on tasks that require information processing and working memory.
(41)	Intravenous 1.0 mg/kg	Equianalgesic	German Hamburg– Wechsler Intelligence Scale Immediate digital recall Anterograde Amnesia	Freiburg Personality Inventory Intelligence Quotient	The study found that ketamine isomers induce less tiredness and cognitive impairment and cause fewer declines in concentration capacity and primary memory.
(53)	Intravenous 0.5 mg/kg	Saline	California Verbal Learning Test short form (CVLT-II) Rey Complex Figure Test Columbia Autobiographical Memory Interview Short Form (AMI-SF)	Montgomery– Asberg Depression Rating Scale Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) Mini Mental State Examination Trail Making Test Parts A and B Stroop Color and Word Test	The study found that repeated ketamine treatment had no negative cognitive side effects, especially in the short term, adding to the growing body of evidence supporting the safety of ketamine and its impact on cognitive outcomes.
(42)	Intravenous 1–1.5 mg/kg	Thiopental	Wechsler Adult Intelligence Scale Rey auditory verbal learning test (RAVLT) Verbal fluency test	Hamilton Depression Rating Scale (HDRS) Benton visual retention test Trail making test Rey– Osterrieth complex figure test	The study found that subjects who used ketamine had worse results on some verbal memory measurements.
(54)	Intravenous 0.5 mg/kg	N/A	The N-back task	Montgomery– Asberg Depression Rating Scale (MADRS) Hamilton Anxiety Rating Scale (HAM-A) Brief Psychiatric Rating Scale (BPRS)	The study found that subjects showed great symptomatic improvement and increased working memory load within 4h of ketamine administration.
(55)	N/A 10 mg/kg	Psilocybin	EEG/ERP Recording	Altered State of Consciousness (ASC-R)	The group receiving ketamine showed significant improvements in verbal learning memory.
(56)	Intravenous 0.5 mg/kg	N/A	Cogstate Brief Battery	Hamilton Depression Rating Scale (HDRS) Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that after the last ketamine infusion, there was a significant improvement in the scores of visual memory, simple working memory, and complex working memory.
(57)	Intravenous 0.5 mg/kg	Midazolam	Cogstate Brief Battery	Brief Psychiatric Rating Scale (BPRS) Clinician-Administered Dissociative States Scale (CADSS) Young Mania Rating Scale (YMRS) Montgomery–Asberg Depression Rating Scale (MADRS)	Ketamine resulted in stable or improved neurocognitive functioning in most domains. These findings suggest the potential usefulness of complex working memory as a predictor of ketamine treatment response and its positive effects on neurocognition.
(43)	Intravenous 0.25 mg/kg	N/A	Berlin Affective Word List (BAWL)	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that ketamine affects MDD symptoms differently. It also found that the largest symptom reduction was in the cognitive domain.

(58)	Intravenous 0.12 mg/kg	Phosphodiesterase 10A inhibitor (TAK-063)	A-X Continuous Performance Test (AX-CPT) CNS Vital Signs Cognitive Battery	Psychotomimetic States Inventory (PSI) Columbia Suicide Severity Rating Scale (C-SSRS)	The study found that ketamine can induce changes in the BOLD signal in multiple regions of the brain during the resting state and working memory task.
(46)	N/A 2.06 mg/kg	Methadone	The two-back task	CAS (Chinese Affect Scale) CES-D (Catchment-Area Epidemiology Survey-Depression) Raven's Progressive Matrices Test Minnesota Multiphasic Personality Inventory-2 Barratt's Impulsivity Scale Version 11 The Iowa Gambling Task (IGT)	The study found that ketamine users did not show deficits in decision-making but exhibited strong impulsivity, antisocial personality, and poor response inhibition and working memory at levels similar to those of methadone users.
(47)	N/A N/A	N/A	Wechsler Memory Scale-Third Edition (WMS-III) Rey– Osterrieth Complex Figure (ROCF) Wisconsin card sorting test (WCST)	Beck Depression Inventory (BDI) Hospital Anxiety Depression (HADSA) Structured Clinical Interview for DSM-IV Severity of Dependence Scale (SDS)	The study found that ketamine users suffered from cognitive impairments, including verbal/visual memory and executive function.
(59)	Intravenous 0.5mg/kg	N/A	Consensus Cognitive Battery MATRICS	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that working memory and visual learning did not show significant improvement with ketamine treatment.
(60)	Intravenous 0.5mg/kg	N/A	Consensus Cognitive Battery MATRICS	Sheehan Disability Scale (SDS) Global Assessment of Functioning (GAF) Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that working memory and visual learning did not show significant improvement with ketamine treatment.
(61)	Intravenous 0.5 mg/kg	N/A	Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Letter–number sequencing Wechsler Memory Scale-Third Edition (WMS-III) Brief Visuospatial Memory Test-Revised Hopkins Verbal Learning Test-Revised (HVLT-R)	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found no significant improvement in working memory or visual learning after six infusions of ketamine.
(62)	Intravenous 0.5 mg/kg	Saline	Consensus Cognitive Battery (MCCB)	Hamilton Depression Rating Scale (HAMD-17)	The study found that neurocognitive function did not deteriorate after six ketamine infusions, whereas verbal learning and speed of processing improved over 13 and 26 days of observation, respectively.
(63)	Intravenous 0.3 mg/kg	Propofol	Mini-Mental State Examination (MMSE)	Hamilton Depression Rating Scale (HAMD-24)	The study found that ketamine anesthesia (KP) had a lower incidence of cognitive function impairment than the propofol anesthesia group (P).
(64)	N/A 0.5 mg/kg	Morphine Metoprofen	Mini-Mental State Examination (MMSE) Digital symbol substitution test	Visual Analogue Scale (VAS)	The study found that ketamine did not modify mood, cognitive, or memory functioning.
(65)	Intravenous	Saline	Working memory task and go/no-go task	Hamilton Depression Rating Scale (HDRS)	The study found that a 0.5 mg/kg dose of ketamine infusion can be slightly beneficial

	0.2 mg/kg or 0.5 mg/kg				for the cognitive function of patients with treatment resistance disorder (TRD).
(66)	N/A N/A	N/A	Brief Assessment of Cognition in Schizophrenia (BACS)	Conners' Continuous Performance Test (CPT) Wisconsin Card Sorting Test (WCST) Iowa Gambling Task (IGT) The Barratt Impulsiveness Scale (BIS)	The study found that the experience of ketamine use was not linked to verbal and working memory.
(28)	Intravenous 0.23 mg/kg bolus over 1 min followed by 0.58 mg/kg/h constant infusion for ~45 minutes	PF-04958242	fMRI Hopkins Verbal Learning Test (HVLT)	Positive and Negative Symptom Scale (PANSS) Clinician-Administered Dissociative States Scale (CADSS)	The study found that ketamine can significantly increase the reaction time during the spatial working memory task.
(67)	Intravenous 0.5 mg/kg	N/A	Cogstate Brief Battery	Hamilton Depression Rating Scale (HDRS) Beck Depression Inventory-II (BDI-II)	The study found that ketamine did not affect working memory performance.
(68)	Intravenous 0.5 mg/kg	Midazolam	Neurocognitive battery	Hamilton Depression Rating Scale (HDRS) Suicidal Idea (SSI) Beck Depression Inventory (BDI) Profile of mood states (POMS) Young Mania Rating Scale (YMRS) Systematic Assessment for Treatment of Emergent Events-General Inquiry (SAFTEE) Clinician-Administered Dissociative States Scale (CADSS) Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression	There was a correlation between memory improvement after ketamine administration.
(33)	N/A 100 ml/kg	Neuroleptan aesthesia	Patients' self-report	Authors' own questionnaire	The study found that patients in both the neurolept group (NLA group) and ketamine group had suffered from difficulties with memory and concentration after 3 months of surgery.
(35)	Intravenous 0.26 mg/kg	Haloperidol	Recall test Wisconsin Card Sorting Test (WCST)	Brief Psychiatric Rating Scale (BPRS) Clinician-Administered Dissociative States Scale (CADSS) Extrapyramidal Symptom Rating Scale Barnes Akathisia Scale	The study found that ketamine produced a delay-dependent impairment in word recall with no significant effect on immediate recall and more prominent impairments of post-distraction and delayed recall.
(36)	Intravenous 50 mg/kg	Saline	Clinician-Administered Dissociative States Scale (CADSS) Systematic Assessment for Treatment of Emergent Effects	Montgomery– Asberg Depression Rating Scale (MADRS)	The study found that after 4 h of ketamine infusion, patients felt strange or unreal, had

				Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) Hamilton Anxiety Rating Scale (HAM-A) Brief Psychiatric Rating Scale – Positive subscale (BPRS+) Young Mania Rating Scale (YMRS)	poor memory, and had weakness or fatigue.
(37)	Oral N/A	D-serine (DSR)	TesteIdentical Pairs (CPT-IP) Digit Memory Task Rey Auditory Verbal Learning Test (RAVLT) Category Fluency Test Benton Visual Retention Test (BVRT)	Visual Analogue Scale (VAS)	The study found that ketamine led to worse performance in verbal memory tasks.
(69)	Intravenous 0.5 mg/kg	Midazolam	MATRIC Consensus Cognitive Battery (MCCB)	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that ketamine had no specific effect on cognitive performance.
(70)	Nasal spray 28 mg, 56 mg, or 84 mg	N/A	Cogstate Brief Battery Hopkins Verbal Learning Test-Revised (HVLT-R)	Montgomery– Asberg Depression Rating Scale (MADRS) Clinical Global Impression–Severity (CGI-S) Patient Health Questionnaire 9-Item (PHQ-9) Sheehan Disability Scale (SDS) Columbia Suicide Severity Rating Scale (C-SSRS) Clinician-Administered Dissociative States Scale (CADSS) Brief Psychiatric Rating Scale (BPRS)	The study found that there was a slight improvement in function (visual, verbal, and working memory, executive function) in both treatment groups: esketamine/antidepressant; antidepressant/placebo
(44)	Intravenous 0.25 mg/kg	Propofol	Cogstate Brief Battery	N/A	The study found that mixing ketamine with propofol for sedation in colonoscopy led to fewer complications such as respiratory depression and hypotension, but it also led to more impairment in cognitive functions.
(45)	N/A N/A	Methamphetamine	Brief Assessment of Cognition in Schizophrenia (BACS)	N/A	The study found that the ketamine group performed worse than the METH group in the domains of verbal memory, working memory, attention and processing speed, and composite battery scores.
(71)	Intravenous 0.5 mg/kg	N/A	MATRICS Consensus Cognitive Battery (MCCB)	Montgomery– Asberg Depression Rating Scale (MADRS) Suicidal Idea (SSI)	The study found that six ketamine infusions led to an improvement in the speed of processing and verbal learning, which was partly accounted for by the improvement in the severity of depression symptoms over time.

Qualitative synthesis of studies

Qualitative synthesis of the 50 studies is reported on the basis of their content. The studies directly examining memory and ketamine use, which is the main focus of this research, were examined and found that 13 studies (26%) found ketamine enhanced memory functions,[49-51,54-57,62,63,65,68,70,71] 26 studies (52%) found it impairs the memory, concluding that ketamine can cause a deterioration in memory.[22,23,25-47,52] These studies have revealed the negative impact of ketamine on memory functions. More specifically, we discussed the observed decrease in recognition picture-recall performance at a specific dosage.[26,29,31-34] According to these studies, ketamine negatively impacted a broad spectrum of cognitive functions, including attention, response inhibition, working memory, verbal fluency, executive function, serial processing, and various aspects of memory recall. These findings emphasize the negative influence of ketamine on cognitive functions, warranting concern regarding its potential impact on both short-term and long-term memory function. Eleven studies (22%) found that ketamine had no impact on memory.[24,48,53,58-61,67,69,72,73]

Despite the majority of studies including both genders, only two of them have investigated gender differences, with one study finding that female ketamine users displayed a higher likelihood of developing severe cognitive impairment compared with their male counterparts,[25] and the other study displayed the opposite, with male ketamine users appearing to be more prone to suffer from memory-related problems compared with their female counterparts.[31] Some studies have focused their investigation on one gender; four of these studies included only male participants.[32,34,56,58] While one study reported a positive impact on memory,[56] two studies found that ketamine was a factor that deteriorated memory among male participants.[32,34] Three other studies investigated only female participants.[33,52,72] One study found no impact on memory,[72] and two studies found a negative impact.[33,52]

There were various factors mostly investigated with ketamine use and its effect on memory. Some studies investigated the effect of ketamine on memory among participants with *depression or suicidal ideation* (n=17). These studies found an association between ketamine, depression, suicidal ideation, and cognitive functions. 13 studies investigated the *neurocognitive effects and performance* of ketamine use and found a complex interplay between ketamine and neurocognitive functions.[36,49-53,56,57,59-62,65,67-70] While ketamine may initially have acute harmful effects on some cognitive domains in individuals with major depressive disorder or PTSD, repeated ketamine administration appears to reduce depressive symptoms and, in turn, leads to an improvement in various cognitive domains, including attention, working memory, verbal, and visuospatial memory. The findings also underline the potential benefits of ketamine in improving neurocognitive function in individuals who suffer from treatment-resistant depression, suggesting a mood-independent pro-cognitive effect, particularly in processing speed. The observed improvements in neurocognitive outcomes emphasize the intricate relationship between ketamine, cognitive function, and mental health outcomes.[22-24,26-28,35,49,56,57,62,69,73] Six studies applied *Electroconvulsive Therapy (ECT)* with Ketamine and their results varied. While administering Ketamine alongside ECT may lead to better antidepressant efficacy than certain anesthetics, it can also lead to a worsening in verbal memory. The impact of Ketamine on cognitive functions during ECT remains inconclusive, with some studies suggesting potential protective effects on memory, especially compared with other anesthetics. However, a randomized trial found no evidence of cognitive or efficacy benefits from low-dose Ketamine adjunctive to ECT for depression.[30,38,42,48,51,63]

Discussion and Conclusion

This study was designed to review studies examining the association between Ketamine and memory impairment. Among the included studies, certain themes were discovered from full-text readings, and those topics are written in italics in the qualitative synthesis of the study section. After analyzing the full texts of the included studies, it is important to highlight some of their limitations.

Limitations

One of the most notable limitations of these studies is the lack of long-term follow-up. Several studies have investigated the cognitive impact of Ketamine on short-term periods, neglecting to discuss its long-term outcomes. Therefore, it is recommended that future studies include extended follow-up periods to assess the persistence of cognitive effects and potential risks associated with prolonged ketamine use.

Another limitation of the study was the sample size and characteristics. Most of the studies had a small sample size, which may reduce the reliability and generalizability of the findings, emphasizing the need for larger cohorts in future studies. Studies also failed to compare genders and racial and ethnic groups. Future research should include participants with diverse characteristics and backgrounds.

There were also some limitations based on the design of the studies. Several studies did not have control groups, which may prevent the ability to compare outcomes between treatment and non-treatment conditions. In addition, studies conducted with an open-label design are susceptible to biases and placebo effects, potentially influencing the interpretation of treatment outcomes. Various other limitations such as specific population restrictions, incomplete data, study termination, and lack of examination of certain cognitive domains hinder the comprehensiveness and reliability of the research findings, indicating the need for improved study methodologies in future investigations.

This study also has some limitations. As mentioned in the Methods section, inclusion and exclusion criteria were determined for the search strategy. One of the exclusion

criteria was languages other than English; therefore, studies published in other languages were excluded from the review. In addition, only studies published in peer-reviewed journals were included; thus, chapters, conference papers, and dissertations were excluded. There were some studies meeting the search criteria, but the full text was inaccessible. While acknowledging these limitations, the findings of this study offer valuable insights poised to expand our current understanding of Ketamine, shedding light on both its potential benefits and associated side effects.

Conclusion

As a result of this study, it becomes evident that there is an association between Ketamine and memory deterioration; however, this relationship is challenging to develop. The complexities of the included studies necessitate a nuanced understanding of the correlation between Ketamine and memory deterioration. In light of these considerations, healthcare professionals and researchers should approach the issue comprehensively. Thus, it is recommended to include educational initiatives and awareness campaigns to inform individuals, particularly those at risk, about the potential consequences of Ketamine use on memory function. In addition, early detection and intervention strategies among vulnerable populations should be prioritized.

Based on the results of this systematic review, future studies should:

- Focus on longitudinal studies with qualitative components to provide insights into the multifaceted relationship between Ketamine and memory deterioration.
- Examine the effects of various doses of ketamine, particularly as an adjunctive anesthetic for ECT in elderly patients, while balancing efficacy and safety.
- Explore the neural mechanisms underlying the effects of ketamine on suicidal ideation using neuroimaging techniques and focus on functional outcomes, particularly long-term functioning, in addition to reductions in suicide.
- Include control groups, use techniques to assess brain changes, and investigate the potential pro-cognitive effects of Ketamine in larger studies, while ensuring comprehensive evaluation of cognitive function.
- Focus on psychological risk factors for Ketamine use and investigate cognitive problems specific to Ketamine users.

These studies might provide a deeper understanding of the factors influencing this association, which will help develop more effective prevention and intervention strategies.

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Genetic and Epigenetic Changes of CDKN2A in Gastric Cancer

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Review

History

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ABSTRACT

Gastric cancer is a multifactorial heterogeneous disease involving various subgroups with different molecular features and it is one of the leading causes of cancer deaths worldwide. Although dietary conditions (fried, fatty and salty foods), tobacco and alcohol consumption, and some gastrointestinal infections are important in gastric cancer, the development of the disease is complex. It is clear that tumor suppressor genes and proto-oncogenes have a significant impact on the formation of gastric cancer. CDKN2A is a tumor suppressor gene that encodes two different proteins, and methylation, deletion and other mutations of this gene are effective in both the development and prognosis of gastric cancer. CDKN2A hypermethylation is common in gastric cancer related with H. Pylori and EBV infections. A connection is often established between metastases of gastric cancer and losses of this tumor suppressor gene (deletions). In this context, possible changes in the CDKN2A gene should be taken into consideration as a biomarker in the treatment and follow-up of gastric cancer.

Keywords: Gastric cancer, tumor suppressor gene, CDKN2A, methylation, deletion

Gastrik Kanserde CDKN2A'nın Genetik ve Epigenetik Değişiklikleri

Derleme

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ÖZET

Mide kanseri, farklı moleküler özelliklere sahip çeşitli alt grupları içeren multifaktöriyel, heterojen bir hastalıktır ve dünya çapında kanser ölümlerinin önde gelen nedenlerinden biridir. Gastrik kanserde beslenme koşulları (kızarmış, yağlı ve tuzlu yiyecekler), tütün ve alkol tüketimi ve bazı gastrointestinal enfeksiyonlar önemli olmasına rağmen hastalığın gelişimi karmaşıktır. Tümör baskılayıcı genlerin ve proto-onkogenlerin mide kanserinin oluşumunda önemli bir etkiye sahip olduğu açıktır. CDKN2A, iki farklı proteini kodlayan tümör supresör bir gendir ve bu genin metilasyonu, delesyonu ve diğer mutasyonları mide kanserinin hem gelişiminde hem de prognozunda etkilidir. CDKN2A hipermetilasyonu, H. Pylori ve EBV enfeksiyonlarıyla ilişkili mide kanserinde yaygındır. Mide kanserinin metastazları ile bu tümör baskılayıcı genin kayıpları (delesyonlar) arasında sıklıkla bir bağlantı kurulmaktadır. Bu bağlamda, mide kanserinin tedavi ve takibinde biyobelirteç olarak CDKN2A genindeki olası değişiklikler göz önüne alınmalıdır.

Anahtar Kelimeler: Mide kanseri, tümör supresör gen, CDKN2A, metilasyon, delesyon

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Introduction

Gastric cancer (GC), a heterogeneous disease with sophisticated pathogenesis and regional variability, is one of the most common causes of cancer-related deaths worldwide.[1] GC patients are often diagnosed late and most of them are in an advanced stage at the time of diagnosis.[2] Some conditions such as high salt intake, smoking and alcohol consumption, Helicobacter pylori (H. pylori) infection are among the risk factors.[3] Pathologically, adenocarcinomas constitute more than 95% of the malignancies in the stomach, and the remaining rare neoplasms are lymphomas, sarcomas etc.[4] Gastric cancers can be classified as sporadic GC (majority of GC, usually over 45 years of age), early-onset GC (about 10%, predominance of genetic factors), gastric stump cancer (after gastrectomy), and hereditary diffuse GC (1–3% of all GCs).[5] These cancers are actually classified histologically as intestinal and diffuse (Lauren classification) or papillary, tubular, mucinous, and poorly cohesive (WHO classification).[6] Depending on the location of the tumor, it can also be grouped as cardial and distal.[7]

Etiology of Gastric Cancer

Environmental factors such as H. pylori infection, dietary conditions and lifestyle are often involved in the intestinal type of gastric cancer, however genetic abnormalities are more blamed in the diffuse type.[8] Intestinal type gastric cancer may occur with H. pylori infection accompanied by intestinal metaplasia and atrophy, but the diffuse type is usually caused by pangastritis, in which atrophy is not observed.[9] Smoking and excessive alcohol consumption have a significant importance in the development of gastric cancer. The presence of bacteria or viruses is clear in the etiology of gastric adenocarcinomas. While a significant portion of GC cases are associated with H. pylori, about 10% may result from Epstein Barr Virus infection.[10] Although most gastric cancers occur sporadically, approximately 5-10% of cases may be familial, such as hereditary diffuse gastric cancer, familial intestinal gastric cancer, etc.[11] Autoimmunity is also somehow related to gastric carcinogenesis, and diseases with an autoimmune basis, such as systemic lupus erythematosus, pernicious anemia, and type 1 diabetes, may be associated with the risk of GC.[12]

Genetics of Gastric Cancer

Cancer is a genetic disorder that involves alterations in tumor suppressor genes and protooncogenes and these genes significantly contribute to the development of malignancy through loss or gain of function.[13] Genetic changes that lead to cancer may arise from errors in DNA replication and cell division, epigenetic disorders, poor dietary conditions and DNA damage caused by harmful elements including cigarette and ultraviolet, or the problem may emerge through germline mutations from parents. Although gastric cancer is a common malignancy in the world, its molecular characteristics are not yet fully understood.[14] In fact, genetic, epigenetic and environmental elements act collectively and are effective in the formation and progression of the disease in gastric cancer.[15] GC, which is closely related to some genetic alterations, usually develops on the basis of activation in proto-oncogenes and/or inactivation in tumor suppressor genes.[16] Genes such as KRAS, PIK3CA, EGFR, ERBB3-4 with oncogenic activity and p53, CDKN2A, CDH1 with tumor suppressor activity are often mutated in various cancers, including gastric cancer.[17] Mahmud et al. emphasized that some HLA gene polymorphisms may be positively or negatively associated with the progression and mortality of H. pylori-related GC in certain populations.[18]

Tumor Suppressor Genes and CDKN2A Gene

Tumor suppressor genes (TSGs) regulate cell division by inhibiting cell proliferation. These genes also may promote apoptosis or may contribute to DNA repair. Some of the relevant genes can perform all of these functions. Therefore, TSGs have a significant effect in preventing cancer development. Tumor suppressor genes are in balance with proto-oncogenes in the organism in terms of the cell cycle and various signaling pathways. Proto-oncogenes have a dominant nature and mutation of a single allele may be sufficient for the development of cancer. However, TSGs have a recessive nature and both alleles must mutate for loss of function (two hit hypothesis). Loss-of-function mutations in TSGs may lead to cancer formation or progression of existing cancer.[19] Various tumor suppressor genes with different functions are found in humans, such as Rb1, p53, CDKN2A, PTEN, VHL, APC, NF1, NF2, BRCA1 and BRCA2. These genes undergo mutation, methylation or deletion in many cancers.

There are two major TSGs called CDKN2A and CDKN2B located on the short arm of chromosome 9 (9p21.3). CDKN2A is one of the most frequently inactivated TSGs, and its inactivation plays an important role in various common malignancies.[20] On this basis, it is also possible to encounter CDKN2A gene mutations, deletions and methylations in gastric cancer. Methylation is an epigenetic condition that leads to gene silencing. In a study by Xu et al., it has been noted that the hypermethylation of CDKN2A gene was significantly higher in GC than in non-tumor tissues.[21] On the other hand, somatic mutations of CDKN2A have been found to occur frequently in HPV-negative vulvar squamous cell carcinomas.[22] The CDKN2A gene encodes two distinct tumor suppressor proteins called $p16^{INK4a}$ and $p14^{ARF}$. Although these two proteins carry a different first exon in their structure (exon 1α & exon 1β), exons 2 and 3 are identical.[23] p16 blocks cell cycle progression by inhibiting two cyclin-dependent kinases (CDK4, CDK6) during the G1 to S transition in the cell cycle.[24] While MDM2 inhibits p53 by inducing its degradation via the proteasome, $p14^{ARF}$ prevents MDM2-mediated disruption of p53 by sequestering MDM2 and thus blocking MDM2-p53 interaction.[25] In the context of p53 protection, it is necessary to acknowledge that $p14^{ARF}$ is a tumor suppressor protein. Indeed, promoter methylation of $p14^{ARF}$ has been identified in a wide variety of human cancers, including gastric, colorectal, and prostate carcinomas.[26] The gene named CDKN2B encodes $p15^{INK4b}$ and Tu et al. state that inactivation of this tumor suppressor has a critical importance in pancreatic tumorigenesis.[27] Since CDKN2A and CDKN2B are located adjacently on the same region, co-deletions of CDKN2A and B may occur in various cancers.[28]

Epstein–Barr virus-associated gastric cancer (EBVaGC), a common malignancy related to EBV infection, display promoter hypermethylation of the CDKN2A gene.[29] Once viral DNA reaches a cell, it can be deactivated by methylation that also disrupts surrounding host DNA. This effect can be emerge even at the genomic level and lead to inactivation of tumor suppressor genes.[30] CDKN2A gene promoter methylation and p16 protein loss are much higher in gastric cancers with EBV than in tumors without EBV.[31] As a result, it has been shown that there is a close relationship between EBV and hypermethylation of the CDKN2A gene, and it has been reported that some of the gastric cancers contain EBV in the cancer cells.[32] In a study by Alves et al., inactivation of CDKN2A by promoter methylation in the DNA obtained from H. pylori positive gastric cancer samples was an important finding, especially in the diffuse subtype.[15] Intestinal metaplasia is accepted as a premalignant lesion of the gastric mucosa and most of the methylation sites in this condition, including CDKN2A, have also been shown to be hypermethylated in intestinal type GC.[33]

Deletions of CDKN2A

The loss of tumor suppressor genes plays an important role in the etiopathogenesis of cancers. In this context, CDKN2A gene deletions are frequently encountered in various malignancies. Homozygous deletion of CDKN2A can be seen in a significant proportion of diffuse pleural mesotheliomas via fluorescence in situ hybridization[34] and patients with this deletion have a worse survival compared to cases without this abnormality.[35] Similarly, a high frequency of homozygous deletions in the CDKN2A gene has been reported for anaplastic meningiomas.[36] Some studies suggest that homozygous deletion of CDKN2A in glioblastoma indicates a worse prognosis and these cases may profit from high doses of radiation.[37] In a study of Boşoteanu et al., homozygous deletion or monosomy of CDKN2A was detected in most cases of multiple primary melanoma and/or familial cutaneous melanoma.[38] Since CDKN2A is disabled in a remarkable proportion of melanomas (40-70%), treatments targeting CDKN2A loss provide a significant advantage for the intervention in melanoma.[39] CDKN2A deletions occur in human cancers, including gastric cancer, with inactivation of $P16^{INK4A}$ and $P14^{ARF}$, and these deletions are frequently encountered in the metastasis of GC.[40] Homozygous deletions of CDKN2A also increase angiogenesis.[41] Somatic copy number deletion (SCND) of CDKN2A has been reported to be highly associated with hematogenous metastasis of GCs and it has also been described that CDKN2A deletion can inhibit the expression of P53 and promote the phosphorylation of RB1.[42]

Although CDKN2A is a tumor suppressor gene, there are also studies that express its position differently in various cancers. For example, in a study by Zhu et al., the expression of CDKN2A was upregulated in hepatocellular carcinoma (HCC) tissues compared to non-tumor tissues, and HCC patients with high CDKN2A expression were shown to have poor survival.[43] Additionally, in a study by Hosny et al., it was determined that p16 tumor suppressor was overexpressed in almost all malignant ovarian germ cell tumors.[44] On the other hand, since p16 and Rb (Retinoblastoma) genes are two major components of the Rb pathway, it has been suggested that physiological deactivation of pRB in G1 phase will result in increase of p16 expression, thus pRb-negative tumors may exhibit high p16 expression.[45] However, the mechanism and genetic background of the upregulation or overexpression mentioned in these studies, and even the association of high CDKN2A expression with poor survival are not clear. Indeed, Wang et al declare that $p16^{INK4a}$ mRNA expression is significantly downregulated in GC tissues compared with normal tissues[46] and Oue et al suggest that silencing of CDKN2A by CpG hypermethylation is frequently seen in intestinal type GC.[33] Furthermore, cancers that develop on a viral basis contain a methylation pattern associated with downregulation of CDKN2A (p16), and EBV-positive gastric tumors may develop with hypermethylation of the CDKN2A promoter.[47] Additionally, loss of CDKN2A has been declared as one of the most common somatic copy number alterations in Chinese GC samples.[48] Although there is a decrease in overall survival in patients with CDKN2A methylation, and therefore low CDKN2A expression, larger studies and bioinformatic analyzes are needed to determine the clinical and molecular significance of CDKN2A hypermethylation clearly in GC.[21]

In conclusion, it is possible to state that CDKN2A mutations, deletions and methylation have a great importance in gastric cancer cases, both in terms of diagnosis and treatment and the course of the disease. CDKN2A deletions are associated with poor prognosis in gastric cancer and may even be responsible for gastric cancer metastases. It can be declared that the methylation profile of the CDKN2A gene is also effective as well as CDKN2A losses in gastric cancers. In this context, gastroenterologists, oncologists and medical geneticists should be in cooperation in the diagnosis and follow-up of gastric cancer cases.

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Comparison of Dosimetry Results Before 90Y Microembolization Treatment with 99mTc MAA and After 90Y PET/CT Treatment

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ABSTRACT

Radioembolization with Yttrium-90 (90Y) microspheres stands as an effective treatment option for liver tumors. The suitability of a patient for this treatment is routinely determined through dosimetry based on Technetium-99m Macro Aggregated Albumin (99mTc MAA) SPECT/CT images. This study aims to compare pre-treatment (pre) dosimetry results with 99mTc MAA and post-treatment (post) dosimetry results after 90Y microsphere therapy in patients seeking liver tumor treatment. Eleven patients undergoing liver tumor treatment were randomly included in the study. In 99mTc-MAA dosimetry, the calculated treatment activity was 1.3-6.2 GBq (mean 3.2±1.4), tumor dose was 125.1-527.5 Gy (mean 264.7±139.4), and liver dose was 19.4-38.8 Gy (mean 31.9±5.8). Post-dosimetry using PET/CT images after 90Y microsphere therapy revealed a tumor dose of 156.2-480.4 Gy (mean 266.5±102.9) and a liver dose of 20.6-37.4 Gy (mean 29.1±5.2). The doses exhibited good conformity for both tumor and normal liver tissue (p=0.85716 and p=0.53526, respectively). In conclusion, PET/CT-based post-dosimetry with 90Y microspheres proved to be an effective method in determining liver parenchymal tissue and tumor doses.

Keywords: 90Y microsphere therapy, dosimetry, 99mTc MAA, radionuclide therapy, 90Y microembolization

^{90}Y Mikroembolizasyon Tedavisinde ^{99m}Tc MAA ile Tedavi Öncesi ve ^{90}Y PET/BT Tedavi sonrası Dozimetri Sonuçlarının Karşılaştırılması

Araştırma Makalesi

Süreç

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ÖZ

Karaciğer tümörleri tedavisinde Yitriyum 90 (^{90}Y) mikroküreler ile yapılan radyoembolizasyon etkili bir tedavi seçeneğidir. Hastanın tedaviye uygunluğu rutinde ^{99m}Tc Makro Albümin Agregat (MAA) SPECT/BT görüntüleri üzerinden yapılan dozimetri ile belirlenir. Bu çalışmada, karaciğer tümör tedavisi için başvuran hastalarda ^{99m}Tc MAA tedavi öncesi (pre) dozimetri sonuçları ile ^{90}Y mikroküre tedavi sonrası (post) dozimetri yapılarak sonuçlarının karşılaştırılması amaçlandı. Çalışmamıza karaciğer tümör tedavisi için başvuran ve rastgele seçilmiş 11 hasta dahil edildi. ^{99m}Tc-MAA dozimetrisinde,^{99m}Tc-MAA dozimetri ile hesaplanan tedavi aktivitesi 1.3-6.2 GBq (ortalama 3.2±1.4), tümör dozu 125.1-527.5 Gy (ortalama 264.7±139.4) ve karaciğer dozu 19.4-38.8 Gy (ortalama 31.9±5.8) bulundu. ^{90}Y mikroküre tedavisinden sonra çekilen PET/BT görüntülerinden yapılan dozimetride tümör dozu 156.2-480.4 Gy (ortalama 266.5±102.9), karaciğer dozu 20.6-37.4 Gy (ortalama 29.1±5.2) bulundu. Dozlar, tümör ve normal karaciğer dokusu için iyi bir uyum gösterdi (p=0.85716 ve p=0.53526, sırasıyla). Sonuçta ^{90}Y mikroküreler ile PET/BT'ye dayanan post dozimetrinin karaciğer parankim doku dozunu ve tümör dozunu belirlemede etkili bir yöntem olduğu belirlendi.

Anahtar Kelimeler: ^{90}Y mikroküre tedavisi, dozimetri, ^{99m}Tc MAA, radyonüklid tedavi, ^{90}Y mikroembolizasyon

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Introduction

The majority of patients diagnosed with hepatocellular carcinoma (HCC) and secondary liver cancer are not eligible for curative surgical resection, and systemic chemotherapy alone rarely results in prolonged survival. Additionally, the excessive sensitivity of liver parenchymal tissue to radiation limits the achievement of desired doses in external radiotherapy. Hence, liver tumors are often characterized as having a poor prognosis in terms of radiotherapy. However, in contemporary medicine, radioembolization techniques have been developed and introduced into clinical practice as a novel treatment option.[1]

Radioembolization, also known as Yttrium-90 (90Y) microsphere therapy, involves delivering microspheres labeled with 90Y, emitting pure beta radiation, to the tumor microcirculation via intra-arterial administration.[2] 90Y microsphere therapy is a form of brachytherapy, also referred to as radioembolization, transarterial radioembolization (TARE), or selective internal radiation therapy (SIRT). It constitutes a targeted treatment for both primary and secondary liver tumors.[3]

Yttrium-90 labeled microspheres, emitting pure β-radiation, are delivered to liver tumors through microcirculation in the hepatic arteries. Particles emitted by the 90Y isotope, with a physical half-life of 2.67 days, have a maximum energy of 2.27 MeV and an average energy of 0.93 MeV. Beta particles with 0.93 MeV energy penetrate up to 11 mm within the tissue. The physical half-life of 90Y is 64.1 hours, with 94% of the radiation dose delivered within the first 11 days. Trapped within the tumor, 90Y-labeled microspheres allow for radiation of the tumor while preserving healthy liver tissue. Furthermore, the short distance covered minimizes the need for post-treatment radiation protection measures. There are two types of 90Y microspheres: resin microspheres with a diameter of 20 to 60 mm and glass microspheres with a diameter of 20-30 mm.[4,5]

In patients with normal liver and kidney functions, pre-dosimetry, known as hepatopulmonary angiography, is performed with Technetium-99m Macro Aggregated Albumin (99mTc-MAA) SPECT/CT before 90Y treatment to assess vascular anatomy. This allows determination of the hepatopulmonary shunt ratio and identification of any extrahepatic leakage into the intestinal system. While maximizing the radiation dose to the tumor, efforts are made to ensure that the dose to the liver parenchyma outside the tumor does not exceed 50-70 Gy. Additionally, by adjusting the tumor dose if necessary, based on the identified lung shunt ratio, efforts are made to keep the average lung dose below 35 Gy. Thus, pre-dosimetry allows for the estimation of the dose delivered to the tumor and normal liver, enabling the assessment of the optimal therapeutic 90Y activity.[6,7,8] Through 99mTc-MAA dosimetry, the distribution of 90Y microspheres in the liver and tumor can be predicted in advance. In contrast, post-dosimetry reveals the actual biodistribution of 90Y microspheres, aiding in the optimization of treatment planning. For instance, post-treatment dosimetry can be used to detect tumors that are being exposed to less radiation than is ideal, hence highlighting the necessity of additional adjuvant therapies or re-super-selective radioembolization. Alternatively, if it is thought that the previous treatment resulted in excessive radiation exposure, post-treatment dosimetry can select high-risk individuals for re-radioembolization. Lastly, in order to ascertain dose-response and dose-toxicity connections, quantitative post-treatment dosimetry data are essential.[5]

The aim of this study is to compare pre-dosimetry results with 99mTc-Macro Aggregated Albumin (MAA) and post-dosimetry results after Yttrium-90 (90Y) microsphere therapy in patients seeking liver tumor treatment.

Materials and Methods

This retrospective study examined a total of 11 patients (5 males, 6 females) with metastatic or primary liver cancer who underwent treatment with 90Y microspheres at the Department of Nuclear Medicine, Istanbul University-Cerrahpasa, Faculty of Medicine. Patients who had undergone pre-treatment 99mTc-MAA scintigraphy and post-treatment 90Y PET/CT imaging were included in this study. This study has been approved by the local Ethics Committee of Cerrahpaşa Faculty of Medicine, Istanbul University-Cerrahpaşa, in accordance with the Helsinki Declaration (No: 83045809-604.01.02-). Informed consent has been obtained from all participating patients.

As a pre-treatment exclusion criterion, patients with a hepatopulmonary shunt ratio greater than 20% after the administration of 99mTc-MAA were not included in this study. The inclusion criterion involved patients with a hepatopulmonary shunt ratio below 20% who were deemed to benefit from 90Y microembolization therapy by the clinician.

99mTc MAA Imaging

Following the administration of 99mTc-MAA, three-dimensional (3D) SPECT/CT and two-dimensional (2D) whole-body planar scintigraphy were performed using the Siemens Simbia T16 model SPECT/CT imaging device. Images were acquired using the triple energy window technique with a 140 keV and 20% window for the photopic energy of 99mTc radionuclide to correct for scatter.

For pre-dosimetry, 185 MBq (5 mCi) of 99mTc-MAA was administered in the interventional radiology department. Whole-body (WB) scintigraphy was performed with clinical protocol-compliant parameters of 256x1024 pixels, 15 cm/s speed, 128x128 pixels, 32 frames, and 30 s/frame. Calculations of dosimetry were carried out using the Simplicit90Y™ software program. The Simplicit90Y™ software (Mirada Medical LTD., Oxford, UK) determined the lung shunt ratio and regions of interest (ROIs) for the liver, lungs, and any area of interest in the body using 2D whole-body images.

For the 99mTc-MAA dosimetry, volumes of interest (VOIs) were drawn for the entire liver, perfused tissue, tumor, and any necrotic areas using SPECT/CT images. The prescribed tumor dose was determined while keeping the entire liver tolerance dose at a limit of 35 Gy. An average of 3.2±1.4 GBq of 90Y was administered to patients based on the pre-dosimetry obtained with 99mTc-MAA.

90Y PET/CT Imaging

90Y microsphere activities were administered to patients in interventional radiology for radioembolization treatment. After radioembolization, patients were admitted to the lead-shielded nuclear medicine treatment room. The next day, 90Y

PET/CT imaging was performed using the GE Discovery model 710 device.

Each bed position took 15 minutes to acquire (for a total of 30 minutes). To adjust for attenuation, a low-dose CT scan (120 kVp, 40 mAs) was acquired. With a 5 mm full-width at half-maximum Gaussian filter, PET images were reconstructed using standard Poisson ordered subset expectation maximization, which included resolution recovery, time-of-flight data, and adjustments for attenuation, randoms, and scatter.

Dosimetry Calculations

Calculations of dosimetry were carried out using personalized software, Simplicit90Y™ (Mirada Medical LTD., Oxford, UK), utilizing three-dimensional volumetric data. The dosimetry calculation process involved registering the images obtained from patients (whole-body, SPECT/CT, or PET/CT), segmenting SPECT or PET images, and determining the dosimetry calculations of the defined areas of interest (VOIs).[9] Since the Simplicit90Y™ program could not perform the reconstruction of SPECT or PET images, digital imaging and communication in medicine (DICOM) formatted reconstructed image data were utilized.[10] In the 11 included patients, VOIs were drawn for the entire liver, perfused area, and tumor based on segmentation with SPECT/CT and PET/CT images.

Statistical Analysis: SPSS program was used for statistical analysis, $p<0.05$ was considered significant. The Mann-Whitney U test was employed to determine if there was a statistically significant difference between the pre- and post-treatment dosimetric results in this study.

Results

Patient data and dosimetric calculations following the administration of 99mTc-MAA were evaluated using the Simplicit90Y™ software based on scintigraphic images (Figure 1). From the 99mTc-MAA images, the liver volume ranged from 928.3 to 3394.9 cm^3 (mean 1623±732), tumor volume ranged from 70.9 to 592.8 cm^3 (mean 339.4±227.4), the calculated amount of 90Y activity ranged from 1.3 to 6.2 GBq (mean 3.2±1.4), tumor dose ranged from 125.1 to 527.5 Gy (mean 264.2±139.4), and liver parenchyma dose ranged from 19.4 to 38.8 Gy (mean 31.9±5.8) (Table 1).

Patient data post 90Y microsphere treatment was evaluated through PET/CT images, and dosimetric calculations were performed using the Simplicit90Y™ software (Figure 2). The tumor volumes ranged from 168.8 to 793.1 cm^3 (mean 405.6±232.8), 90Y tumor doses ranged from 156.2 to 480.4 Gy (mean 266.5±102.9), and 90Y liver doses ranged from 20.6 to 37.4 Gy (mean 29.1±5.2) (Table 2).

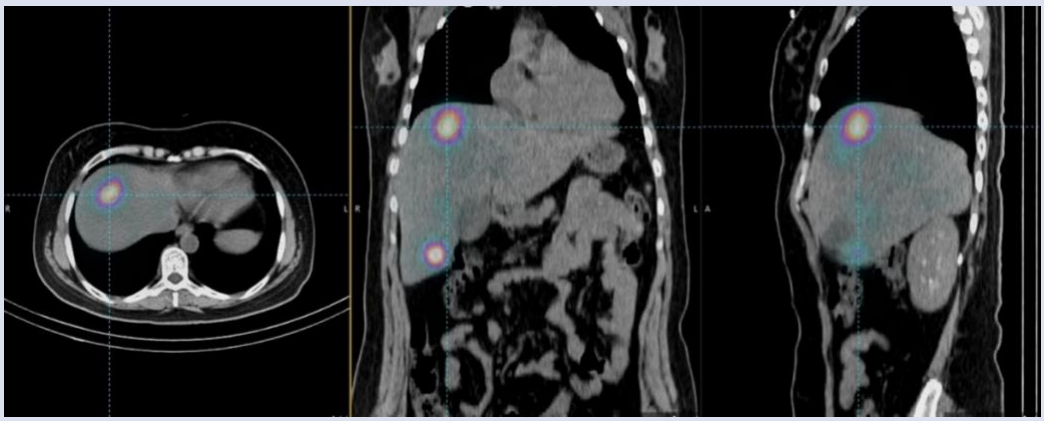

Figure 1: Short-axis, coronal, and sagittal cross-sectional views of the tumor in the liver from left to right in a SPECT/CT image taken after the administration of 99mTc-MAA in a patient. Yellow, blue, and red colors respectively indicate liver, lung, and tumor.

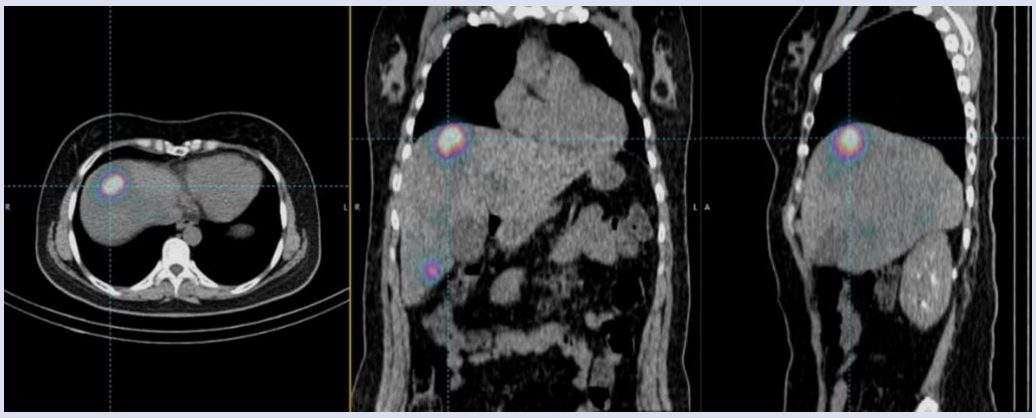

Figure 2: Short-axis, coronal, and sagittal cross-sectional views from left to right of PET/CT images taken after 90Y microsphere treatment, showing tumors in the patient's liver. Yellow, blue, and red colors respectively indicate liver, lung, and tumor.

Table 1: Liver and Tumor Volumes, and Doses Calculated from 99mTc-MAA Images

PatientNo	Liver volume(cm^3)	Tumor volume(cm^3)	90Y activity(GBq)	Tumor dose (Gy)	Liver parenchyma dose (Gy)
1	1824.3	165.2	3.7	129.7	36.3
2	2165.2	755.3	3.52	125.1	38.8
3	928.3	70.9	2.6	225.3	36.4
4	2221.4	592.8	3.4	186.2	29.6
5	1326.9	262.3	6.2	527.5	23.1
6	1340.1	466.4	3.2	143.6	32.1
7	1284.5	126.2	2.5	169.8	34.4
8	1196.3	300.1	1.3	321.3	33.6
9	1050.9	557.4	3.2	235.1	19.4
10	1119.8	151.2	1.3	380.2	32.4
11	3394.9	175.3	4.3	462.1	34.9
Mean±SD	1623±732	339.4±227.4	3.2±1.4	264.2±139.4	31.9±5.8

Table 2: Dosimetric results calculated from PET/CT Images in patients treated with 90Y microspheres

Patient no	Tumor volume (cm^3)	^{90}Y tumor dose (Gy)	^{90}Y liver dose (Gy)
1	202.4	222.6	37.4
2	793.1	196.2	28.2
3	196.2	201.5	29.4
4	659.3	190.8	22.5
5	202.2	480.4	24.2
6	639.4	213.8	34.7
7	335.4	156.2	29.8
8	442.1	334.6	28.5
9	616.4	213.3	20.6
10	168.7	322.1	33
11	206.7	400.1	32.6
Mean±SD	405.6±232.8	266.5±102.9	29.1±5.2

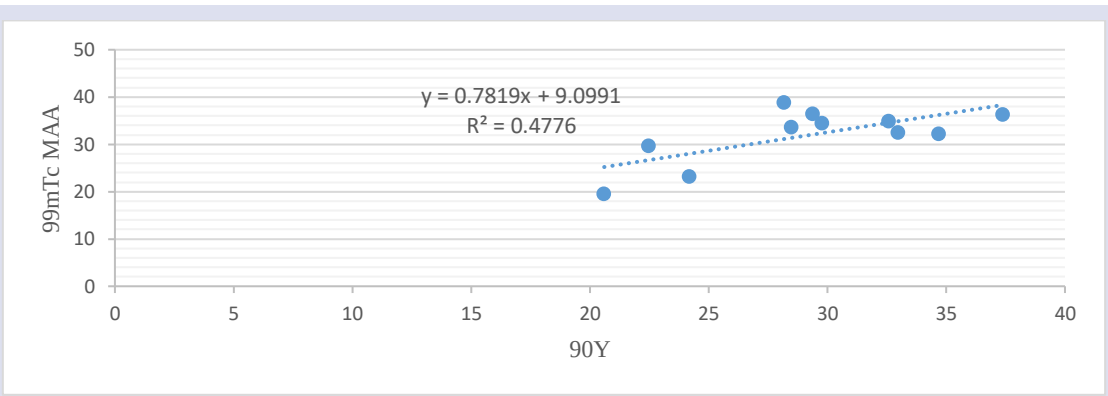

Figure 3: Correlation between pre-and post dosimetry results for the liver

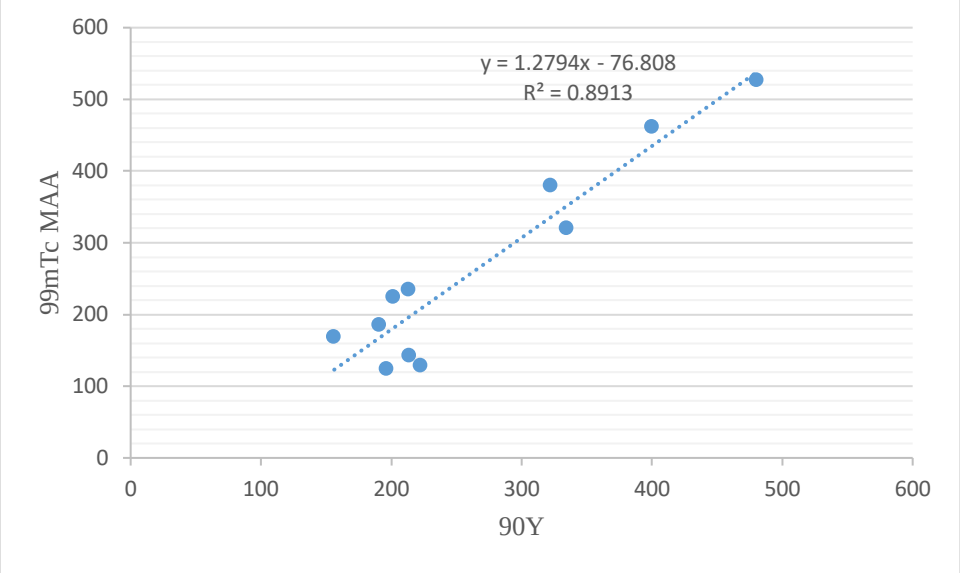

Figure 4: Correlation between pre-and post dosimetry results for tumor doses

The correlation of pre and post dosimetry results for the liver is shown in Figure 3, and the correlation graph of pre and post dosimetry results for tumor doses is shown in Figure 4.

The evaluation of liver and tumor doses in pre and post dosimetry was subjected to the Mann Whitney-U test. No significant difference was found between 99mTc-MAA and 90Y tumor doses (p=0.85716) for tumor doses. Similarly, no significant difference was observed between 99mTc-MAA and 90Y liver doses (p=0.53526).

The limitations of this study

In this study, it is recommended to increase the number of patients for the comparison of pre- and post-dosimetry and to evaluate the comparison using parametric tests. Additionally, due to the relatively small number of patients and the patient-specific nature of dosimetric calculations, heterogeneous distributions were observed in liver and tumor doses.

Discussion

The significance of personalized dosimetry in nuclear medicine for liver tumor radioisotope treatment is increasing day by day. Currently, investigating the differences or similarities between pre- and post-dosimetry remains a subject of research. However, there can be some variations between the calculated absorbed doses through dosimetry. The main reasons for these differences can be attributed to catheter differences, microsphere structure, and the number and structure of injected radioactive particles. Liver tumors can be successfully treated with 90Y radioembolization. In this study, pre-dosimetry with 99mTc-MAA SPECT/CT and post-dosimetry with 90Y PET/CT were performed on 11 patients to determine tumor and liver doses.

When reviewing studies on tumor doses, Martin et al., in a study on 79 patient data, reported not only a compatibility in terms of absorbed average doses but also in dose distribution between 99mTc-MAA dosimetry and 90Y microsphere PET/CT dosimetry. However, it was found that the doses absorbed by the tumor were 26% higher in pre-dosimetry than in post-dosimetry. The researchers found that the average absorbed doses of healthy liver were 49.47 ± 22.18 Gy and 54.53 ± 19.78 Gy for pre- and post-dosimetry, respectively. Overall, non-tumor liver doses showed a stronger correlation with tumor-free liver compared to the tumor, which was explained by increased heterogeneity of the microsphere within the target structure and a greater dose gradient in the tissue of the tumor.[11] Knesaurek et al. determined that the tumor doses of 16 patients were 234.72±172.54 Gy and 314.07±197.02 Gy for 99m Tc-MAA SPECT/BT and 90 Y PET/BT, respectively. An average difference of 25% was found for tumor dose, with a reported linear correlation between tumor doses at the level of r=0.71. Additionally, they demonstrated that the mean values of post-dosimetry 90 Y PET/CT dose results were slightly higher compared to pre-dosimetry values of 99m Tc-MAA SPECT/BT. They suggested that these differences might stem from variations in regions of interest (ROI), especially when the catheter tips in 99m Tc-MAA and 90 Y studies are positioned very similarly and away from major bifurcation points. They noted the importance of this situation, particularly for tumors smaller than 10 cm^3. The researchers also found that the normal liver doses were 42.02±22.36 Gy and 49.85±24.88 Gy for 99m Tc-MAA SPECT/BT and 90 Y PET/BT, respectively, with a linear correlation between the respective doses at r=0.86.[12] In our study, no significant difference was found in tumor doses between pre and post microsphere dosimetry (p=0.85716). Additionally, consistent with the literature, a strong correlation of R^2=0.8913 was found among tumor doses.

Yoo Sung Song et al. found a close correlation between doses absorbed by the tumor in 99mTc-MAA SPECT/CT and

90Y PET/CT dosimetry (r=0.64). However, the average tumor doses in pre-dosimetry 99mTc-MAA SPECT/CT were significantly lower than those in post-dosimetry 90Y PET/CT (135.4±64.2 Gy vs. 185±87.8 Gy). According to these researchers, the absorbed doses by the tumor and liver were 62.6±38.2 Gy and 45.2±32 Gy for 90Y PET/CT and 99mTc-MAA SPECT/CT, respectively (p=0.02).[13] Kao et al. compared tumor doses obtained from 99m Tc-MAA SPECT/CT pre-dosimetry with those from 90 Y PET/CT post-dosimetry in 23 patients. They found an excellent association between the outcomes of 99m Tc-MAA and 90 Y PET/CT for average tumor doses (+3.8% low median relative error with a 95% confidence interval ranging from -1.2% to +13.2%).[14] Our study yielded similar results to previous studies, with no significant difference found in tumor doses between pre and post microsphere dosimetry (p=0.85716). In our 90Y PET/CT post-dosimetry results, the tumor dose was found to be 156.2-480.4 Gy (mean 266.5±102.9 Gy). When examining the correlation of liver parenchymal tissue doses, a relationship with R^2=0.4776 at a low level was found, despite very small differences between pre- and post-dosimetry values (p=0.53526).

Conclusion

In radioembolization treatment, pre-treatment dosimetry with 99mTc-MAA SPECT/CT can be effectively used as a conservative method for planning activity to calculate the dose that was given to both the tumor and the healthy liver tissue. It was concluded that the dosimetry performed with 99mTc-MAA SPECT/CT before treatment is compatible with the dosimetry performed with PET/CT imaging after treatment.

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Scientific Productivity of Pain Physicians in Turkey: A Bibliometric Analysis Using Citation and H-Index Statistic

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ABSTRACT

Objective: Bibliometric studies prepared by evaluating publication numbers, citation numbers and h-indexes are studies that show the production in the field of science. By conducting a study on pain medicine specialists in Türkiye, the study aimed to determine the Hirsch Index (h-index) ratings, number of citations, and number of publications ratings using the Scopus database and to assess the impact of the gender, institution, and title on these parameters.
Methods: Pain physicians were identified via the Health Care Provider App Physician search tool, Council of higher education academic search tool, and websites of the institutions. This was followed by the determination of the h-index ratings, number of citations, and number of publications using the Scopus database.
Results: Of the 274 pain physicians evaluated in the present study, 139 (50.7%) were female and 135 (49.3%) were male. The mean number of publications was 38.76 ± 32.53, the mean number of citations was 543.48 ± 987.16, and the mean h-index value was 9.51 ± 6.85. 173 (63.1%) of the algologists were working as professors, 16 (5.8%) as associate professors, 12 (4.4%) as assistant professors and 73 (26.6%) as specialist doctors. Of the total physicians, 173 (63.1%) were professors, 16 (5.8%) were associate professors. The mean of the number of publications and citations, and the mean h-index value of the professors were found to be significantly higher than those of other physicians ($p<0.05$). No significant difference was found between the male and female pain physicians with respect to these parameters ($p>0.05$).
Conclusion: Our study is the first in our country to evaluate the number of publications, number of citations and h-indexes, which are important bibliometric parameters that show the scientific production of algologists. It was determined that the number of female pain physicians was higher, whereas the publishing activities and mean h-index values of male academicians were higher. Nevertheless, there were no significant differences between the genders.

Keywords: Bibliometrics, Gender, H-index, Medical faculty, Pain

Türkiye'de Algoloji Doktorlarının Bilimsel Üretimlerinin Atıf ve H-İndeks Biyometrikleri ile Analizi

Araştırma Makalesi

Süreç

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ÖZET

Amaç: Yayın sayıları, atıf sayıları ve h-index'ler değerlendirilerek hazırlanan bibliometrik çalışmalar bilim alanındaki üretimi gösteren çalışmalardır. Çalışmamızda Türkiye'de "Algoloji" alanındaki doktorların, Scopus veri tabanı kullanılarak belirlenen yayın, atıf sayıları, h-indeksleri ile cinsiyet, çalıştıkları kurum ve ünvanın bunlara etkilerinin değerlendirilmesi amaçlanmıştır.
Yöntem: Etik kurul onamının alınması ardından, Sağlık Hizmet Sunucu Uygulaması Doktor arama ekranı, Yükseköğretim akademik arama websitesi ve kurumların websiteleri aracılığı ile belirlenen "algologların" yayın sayıları, atıf sayıları ve h-indeksleri, Scopus veri tabanı kullanılarak belirlendi. Veriler SPSS paket programı kullanılarak analiz edildi.
Bulgular: Çalışmamızda değerlendirilen 274 algoloğun 139(50,7%)'unun kadın, 135(49,3%)'inin erkek olduğu belirlendi. Algologların scopus veri tabanındaki yayın sayısı ortalaması 38,76±32,53, atıf sayısı ortalaması 543,48±987,16 ve h-indeks ortalaması 9,51±6,85 olarak belirlendi. Algologların 173(63,1%)'i profesör, 16(5,8%)'ü doçent, 12(4,4%)'si doktor öğretim üyesi ve 73(26,6%)'i uzman doktor olarak görev yapmaktaydı. Profesörlerin yayın sayıları, atıf sayıları ve h-indeksleri ortalamaları, diğer ünvanlara sahip doktorlardan anlamlı olarak yüksek bulundu($p<0,05$). Erkek ve kadın doktorların yayın sayıları, atıf sayıları ve h-indeks ortalamaları arasında cinsiyete göre anlamlı farklılık tespit edilmedi($p>0,05$).
Sonuç: Çalışmamız ülkemizde algologların bilimsel üretimlerini gösteren önemli bibliyometrik parametreler olan yayın sayısı, atıf sayısı ve h-indekslerinin değerlendirildiği ilk çalışmadır. Çalışmamızda kadın doktorların daha fazla sayıda olduğu, erkek akademisyenlerin yayın aktiviteleri ve h-index ortalamalarının daha yüksek olduğu ancak cinsiyetler arasında anlamlı farklılık bulunmadığı tespit edilmiştir.

Anahtar Kelimeler: Ağrı, Bibliyometri, Cinsiyet, H-indeks, Tıp Fakültesi

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Introduction

Pain Medicine (Algology) is a rapidly advancing field, which attracts the attention of clinicians, and the patients' need for specialists in this field is constantly increasing. There are several pain medicine training programs accredited by the American Board of Medical Specialties (ABMS) and Accreditation Council for Graduate Medical (ACGME) that provide fellowship in Pain Management (Algology). In the field of pain medicine that requires a multidisciplinary environment, 92 of the 103 pain medicine fellowship programs in the United States (US) consist of 92 core Anesthesia programs, nine core Physical Medicine and Rehabilitation (PM&R) programs, and two core Neurology programs according to the 2018 data.[1] In addition to these three fields, physicians of Family Medicine and Emergency are entitled to enroll in pain medicine fellowship programs in the US.[1] The first pain unit was introduced in Türkiye during the mid-1980s, followed by the introduction of fellowship programs in the early 2010s; thus, pain medicine is strongly represented in our country.[2] According to the 2022 data, it was determined that there are currently 33 pain medicine training fellowship programs in Türkiye.[3]

Hippocrates said in the 5th century B.C. that "Divinum est opus sedare dolorem," which translates to "Divine is the work to subdue pain".[4] Currently, physicians have an increasing interest in this divine act. Belgrade et al.[1] stated that female physicians mostly preferred the field of pain medicine for research purposes, whereas male physicians preferred it to gain experience in monitoring patients who suffer from pain and due to their interest in multidisciplinary care. The gender-neutral evaluation showed that the interest in procedural skills and the desire to improve the patient's quality of life were the most prominent reasons for them to choose pain medicine as their preferred branch.

Gender inequality in the field of academic medicine is a deep-rooted problem since the past and continues to exist in the present. Despite the increase in the number of women in medical faculties, inequalities are observed in promotion and leadership positions.[5] According to the 2020 data, in the US, 25.3% (n = 176) of 696 academic pain physicians were female and 74.7% (n = 520) were male.[6] Further, this report revealed that among full-time professors, 84 (82.4%) were male and only 18 (17.7%) were female. Doshi et al.[7] stated that pain medicine ranks in the lower quartile range among the medical specialties that are preferred by women in the US, which is immediately above the male-dominant orthopedic surgery and neurosurgery fields. They reported that one of every 10 physicians specialized in anesthesiology and that 25% of anesthetists and 18% of pain physicians were female. According to the ACGME data, women representation was the least in the pain medicine (22%) field among the Anesthesia fellowship programs. In "hospice and palliative medicine" and pediatric anesthesiology, which are among the other fellowship programs of anesthesia, the rates were 63% and 57%, respectively.[7] The fact that it is a less preferred field chosen by women may be due to reasons similar to the branches underrepresented by women, such as interventional cardiology and interventional radiology, which have radiation exposure and subsequent infertility risks. Further, women may hesitate in choosing the male-dominant medical specialties. [7] The situation may be different in Türkiye since a fellowship program is preferred after a central clinical fellowship exam, and different cultural and strategic factors play a role in each country in the selection of branches of medicine.

The h-index, defined as the number of publications of a researcher cited at least h time, is a key bibliometric criterion to characterize the scientific output of a researcher in terms of both quality and quantity.[6] The bibliometric parameters used in the bibliometric analysis are indicators of academic productivity and efficiency. These bibliometric parameters include impact factor, h-, m-, e-, indices, Eigenfactor score, number of publications, and number of citations.[7]

In the previous studies of few countries, it has been reported that gender and academic title have an effect on bibliometric parameters and h-index and that there is gender inequality in academia.[9,10] Our literature analysis showed that the studies investigating the h-index ratings of Pain Medicine physicians who work as academicians in different countries using the Scopus database and examining the bibliometric data are very limited, and no such study has been conducted in Türkiye.[5]

This study on "Pain medicine" physicians in Türkiye aimed to evaluate the relationship among the institutions, titles, and genders as well as h-index ratings, number of citations, and number of publications obtained from the Scopus database.

Materials and Methods

After obtaining the approval from the university ethics committee (Decision no:2021/31-12, 6756-GOA,03.11.2021), physicians with a Ministry of Health-approved certificate in the field of pain medicine were searched using the Republic of Türkiye Social Security Institution Health Care Provider App Physician Search Tool (https://gss.sgk.gov.tr/SaglikHizmetSunuculari/pages/doktorArama.faces), Council of higher education academic search tool (https://akademik.yok.gov.tr/AkademikArama/), and websites of public and private universities on January 10, 2022.[11] Academic titles, including professor, associate professor, assistant professor and attending physician; gender; whether they were the head of the department or not; and their main medicine branches (Anesthesiology, PM&R, Neurology) at the time of the search were recorded based on the other studies in the literature.[6,12,13] Missing gender data were identified via Google and LinkedIn.[14] Faculty members, retired faculty members, research assistants, and fellows whose

academic title could not be completely determined were excluded from study. The number of publications, h-index, and total citations of each faculty member were recorded using the Scopus database, which was referenced in similar studies (http://www.scopus.com) .[5,14] The Scopus database was used due to the MEDLINE coverage and authorship differentiation tools.[6] These tools ensure that publications are attributed to the correct authors. Compared to other databases, Scopus showed the least inconsistency in content validation and quality.[15] If there are two or more entries for authors in the Scopus database, h-index values were calculated by analyzing both entries in common.[16]

Clinics where academics work were classified as clinics located in the west and east of the capital Ankara, according to the provinces.[6] The types of institutions where physicians are employed were classified as "University of Health Sciences (UHS)", "other public universities," and "private institutions and clinics."

To limit the fluctuations in time-varying data (i.e., number of publications, h-index), data collection was completed within a 5-day period from January 10, 2022 to January 14, 2022. Two authors (EO and VH) performed simultaneous data collection, and another author (YE) evaluated the inconsistencies.[16] This study was conducted in accordance with the principles of the Declaration of Helsinki, 2008.

Statistical analysis

The SPSS 24.0 statistical package was used. Continuous variables expressed as mean ± SD, median (minimum–maximum). Frequency data expressed as number and percentage (n, %). The Chi-square test was used in the analysis of frequency data. The Kolmogorov–Smirnov test was used to determine in the analysis of continuous data, whether the data were normally distributed. The test showed that the data were not normally distributed. For data analysis the Kruskal–Wallis, Chi square test and the Mann–Whitney U test were used. $P < 0.05$ was accepted as a significant difference.

Results

A total of 10041 publications belonging to 274 pain doctors were identified. The mean number of publications in the Scopus database of 274 pain medicine specialists who were included in the analysis was 38.76 ± 32.53, whereas the median value was 34 (1–155); the mean number of citations was 543.48 ± 987.16, whereas the median value was 303 (0–10085); and the mean h-index was 9.51 ± 6.85, whereas the median value was 9 (0–45).

Of the Pain physicians included in our study, 173 (63.1%) were professors, 16 (5.8%) were associate professors, 12 (4.4%) were asisstant professors, and 73 (26.6%) were attending physicians (Figure 1).

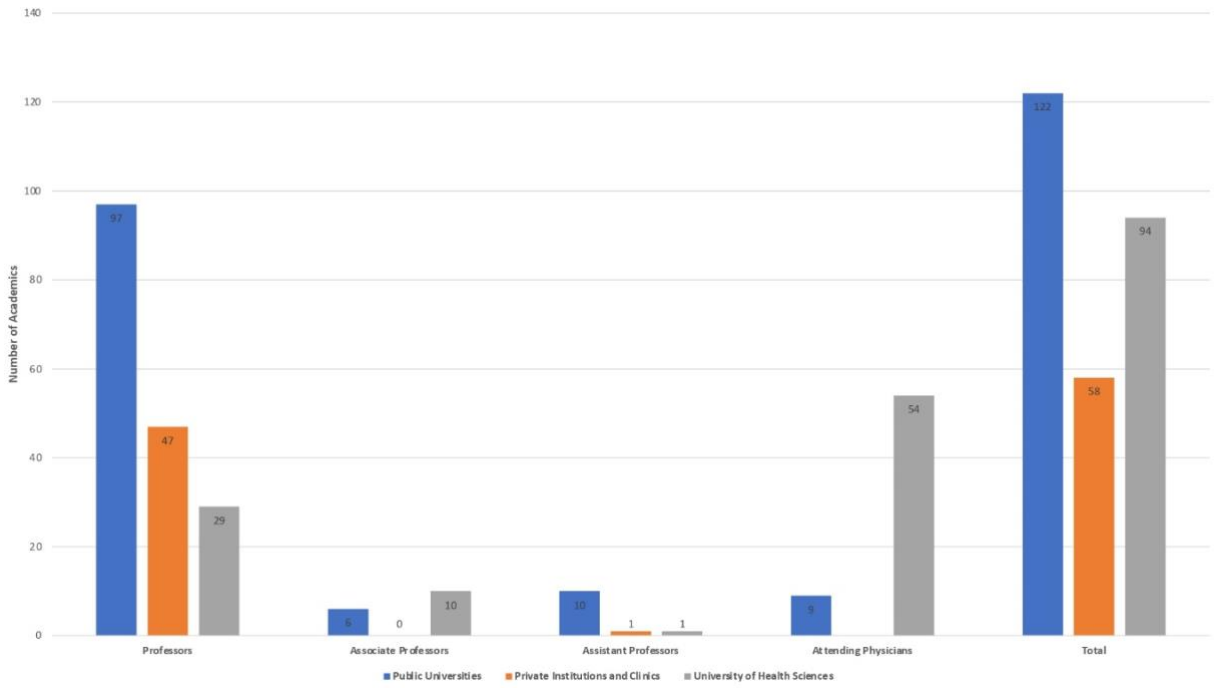

Figure 1: Institutions where doctors work by academic titles

Among those who met the inclusion criteria for this study, 139 (50.7%) were female and 135 (49.3%) were male. On the one hand, when the titles of female physicians were studied, it was observed that 88 (63.3%) were professors, 9 (6.5%) associate professors, 7 (5%) assistant professors, and 35 (25.2%) attending physicians. On the other hand, when the titles of male physicians were considered, 85 (63%) were professors, 7 (5.2%) associate professors, 5 (3.7%) assistant professors, and 38 (28.1%) attending physicians.

Although the number of female professors, associate professors, assistant professors, and attending physicians was higher than that of males, no statistically significant difference was found ($p = 0.873$) (Table 1). It was determined that 18 (12.9%) of the female physicians and 18 (13.3%) of the male physicians were the heads of the department ($p = 0.925$). When the relationship between being the head of the department and their title was evaluated, it was determined that there were statistically and significantly greater number of professors in this position ($p < 0.001$). However, no statistically significant difference was observed in the number of publications, number of citations, and h-index ratings between physicians with the title of the head of the department and other physicians without the title ($p > 0.05$).

When physicians were evaluated based on their main specialties, anesthetists constituted the largest majority (141 anesthetists; 51.5%) (Table 1). In our study, no statistically significant differences were found when the main specialties were evaluated according to the academic title. The superiority of anesthesiologists in the number in all academic titles is notable ($p > 0.05$).

No significant difference was found between those working in the west and east of the capital Ankara, geographically in terms of gender and title ($p > 0.05$). A significant difference was found in the evaluation according to the employing institutions, and it was noteworthy that all institution types were mostly localized in the west ($p = 0.024$) (Table 2).

A statistically significant difference was found when the institutions were evaluated by title ($p < 0.001$). This statistical difference can be explained by the fact that associate professors and specialists are mostly employed in UHSs, whereas professors are mostly employed in other public universities, private institutions, and clinics (Table 2).

A comparison between the publication activities of physicians by institutions showed that the number of publications, number of citations, and h-index parameters of the physicians in the state universities were significantly higher ($p < 0.001$). No significant difference was found between male and female pain medicine specialists in terms of the mean number of publications, mean number of citations, and mean h-index values ($p > 0.05$) (Table 3).

The mean values of number of publications ($p = 0.227$, Mann–Whitney U test), number of citations ($p = 0.962$, Mann–Whitney U test), and h-index ($p = 0.231$, Mann–Whitney U test) based on Scopus database did not significantly differ between the female professors and male professors in the field of pain medicine (Table 3).

There was no significant difference between male and female associate professors and assistant professors of pain medicine when the mean values of number of publications, number of citations, and h-index ($p > 0.05$) (Table 3) were calculated from the Scopus database.

When the number of publications, citiations and h-index data were evaluated according to the main specialties, statistically significant differences ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively) were found between PM&R and Anesthesia. Significant difference was found between "Neurology and PM&R" when the publication numbers were evaluated based on the main specialties ($p = 0.012$). (Table 4).

Discussion

Since a long time, gender inequality is a major issue in academic medicine. Although the number of female academicians has increased compared to the previous years, it was determined that their articles have a lower publication rate and that their academic career progresses slower than their male colleagues.[17] The gap between the ratio of males and females during admission to medical schools in Japan is known worldwide.[18]

Recently, a study showed that 50% of medical faculty graduates are female and that they comprise one-third of the US physician work-force on average.[6] The female physicians are underrepresented in the Pain Medicine department, and according to the 2017 Association of American Medical Colleges data, it was the sixth branch with the highest rate of male physicians in the non-surgical field.[19] Further, differences in the number of publications, citation rates, and h-index parameters between male and female authors have been addressed in the previous studies.[6,16] In this study, gender, institutions, publication activity, and leadership positions among pain physicians in Türkiye were investigated.

The bibliographic data of the physicians in the field of Pain Medicine in Türkiye and the analysis of the affecting factors revealed that there were 274 Pain medicine physicians and that the number of female professors, associate professors, and asisstant professors is higher than that of male academicians. There is no significant difference in terms of the distribution of academic titles of Pain Medicine physicians based on gender. No significant difference was observed between male and female Pain Medicine physicians in terms of the mean values of number of publications, number of citations, and h-index ratings.

Research productivity in academic medicine still plays a key role in the professional success. The parameters frequently used for academic advancement are the number of publications, number of citations, and h-index ratings. In the US, Orhurhu et al.[6] who conducted their study with faculty members in the pain medicine field stated that full-time professors are more likely to have higher h-index values with a statistically significant relationship between these two

parameters. It is stated that the increase in the number of publications, the h-index values and total citations was correlated with an increase in the academic title.[10] Our statistical analysis demonstrated that as the academic title increased, the number of publications, number of citations, and h-index values increased significantly.

In our study, the publication activities of male and female pain physicians were analyzed and although it was determined that the mean values of number of publications, number of citations, and h-index was lower among women than men, no statistically significant difference was found. Similarly, women showed lower productivity metrics, but no significant differences in h-index values were found between the males and females in a study, which evaluated 696 pain medicine faculties in the US.[6] Bastian et al.[20] and Chauvain et al.[21] found that there was no significant difference between the h-index values of males and females in the field of orthopedics and psychiatry. Our findings are consistent with the literature. Considering the shorter career length of female physicians due to increased work-life imbalances and domestic roles, it can be concluded that they can achieve this equality by spending more time on academic activities than male academics during their working period.

Table 1: Distribution of Academic Titles and Major Specialties by Gender, n (%)

	Female	Male	Total
Academic Title			
Professor	88 (63.3%)	85 (63%)	173 (63.1%)
Associate professors	9 (6.5%)	7 (5.2%)	16 (5.8%)
Assistant professors	7 (5%)	5 (3.7%)	12 (4.4%)
Attending Physician	35(25.2%)	38(28.1%)	73 (26.6%)
Major specialties			
Anesthesiology and Reanimation	66(47.5%)	75(55.6%)	141(51.5%)
Physical Medicine and Rehabilitation (PM&R)	41(29.5%)	40(29.6%)	81(29.6%)
Neurology	32(23%)	20(14.8%)	52(19%)
Total	139(50.7%)	135(49.3%)	274 (100%)

n: number

Table 2: Types and Locations of Institutions Where Physicians are Working n(%)

	Locations of the Institutes		p
	Clinics located in the west of Ankara	Clinics located in the east of Ankara	
Professors	138(65.7%)	35(54.7%)	0.146
Assoc. Professors	14(6.7%)	2(3.1%)	
Asst. Professors	8(3.8%)	4(6.3%)	
Attending Physicians	50(23.8%)	23(35.9%)	
Total	210(76.6%)	64(23.4%)	

	Institution Type			p
	Public Universities	Private Institutions and Clinics	University of Health Sciences	
Professors	97(56.1%)	47(27.2%)	29(16.8%)	<0.001
Assoc. Professors	6(37.5%)	0(0%)	10(62.5%)	
Asst. Professors	10(83.3%)	1(8.3%)	1(8.3%)	
Attending Physicians	9(12.3%)	10(13.7%)	54(74%)	
Total	122(44.5%)	58(21.2%)	94(34.3%)	

P<0,05, n:number, chi-squared test. Assoc. Professors: Associate Professors, Asst. Professors: Assistant Professors

Table 3: The Number of Publications, Citations and H-Index Averages (Mean ± Standard Deviation) and Median (Minimum-Maximum) Values Determined from the Scopus Database According to Academic Title and Gender in the Field of Pain Medicine in Türkiye

	Gender						Total		
	Female			Male					
	Number of Publication	Number of Citations	h-index	Number of Publication	Number of Citations	h-index	Number of Publication	Number of Citations	h-index
Professor n:173 (f:88, m:85)	50.56±27.72 47 (1-133)	775.66±1297.15 476 (0-10085)	12.22±5.30 12 (0-30)	56.02±30.81 52 (4-155)	783.92±955.28 634 (9-7485)	13.32±6.47 13 (1-45)	53.22±29.31 49,50 (1-155)	779.70±1139.75 547 (0-10085)	12.76±5.91 12 (0-45)
Assoc. Prof. n:16 (f:9, m:7)	25.55±11.22 25 (9-40)	349.33±366.40 195 (71-989)	7.77±2.58 7 (4-12)	43.42±40.06 22 (14-124)	288±311.78 119 (49-768)	8.42±4.64 7 (4-16)	33.37±28.16 23,50 (9-124)	322.50±333.87 152,50 (49-989)	8.06±3.51 7 (4-16)
Asst. Prof. n:12 (f:7, m:5)	12.37±10.86 7 (4-22)	118.50±152.40 39 (2-449)	4.75±3.45 3 (1-10)	6.37±2.26 7 (4-8)	19.75±16.03 9 (1-44)	2.25±1.28 2 (1-4)	8±5.47 7 (4-22)	70.16±128.27 30 (1-449)	3.33±2.70 2.50 (1-10)
Attending Physicians n:73 (f:35, m:38)	4.73±5.80 3 (1-14)	20.36±35.29 10.5 (0-63)	1.70±1.56 2 (0-3)	8.39±8.34 6 (1-31)	42.53±67.84 14 (0-301)	2.71±2.73 2 (0-11)	5.93±6.35 4 (1-31)	27.80±49.42 12 (0-301)	2.04±2.04 2 (0-11)
Total n:274 (f:139, m:135)	35.44±30.56 32 (1-133)	532.27±1096.89 292 (0-10085)	8.91±6.39 9 (0-30)	42.43±34.32 39 (1-155)	555.78±855 314 (0-7485)	10.17±7.29 9 (0-45)	38.76±32.53 34 (1-155)	543.48±987.16 303 (0-10085)	9.51±6.85 9 (0-45)

n:number, f:female gender, m:male gender, Mann–Whitney U test. Assoc. Professors: Associate Professors, Asst. Professors: Assistant Professors

Table 4: The Number of Publications, Citations and h-index Averages (Mean ± Standard Deviation) and Median (Minimum-Maximum) Values Determined from the Scopus Database according to the Major Departments of Physicians in the Field of Pain Medicine in Türkiye

	Anesthesiology and Reanimation	PM&R	Neurology	p Values		
				Difference Between Anesthesiology and PM&R	Difference Between Anesthesiology and Neurology	Difference Between Neurology and PM&R
Number of Publication	31.54±27.34 26 (1-124)	50.27±31.29 49 (1-148)	39.53±41.35 26 (2-155)	**< 0.001**	0.696	**0.012**
Number of Citations	302.30±350.43 196,50 (0-1664)	673.75±562.42 656 (0-2877)	973.32±1999.87 195 (0-10085)	**< 0.001**	0.188	0.058
h-index	7.45±5.09 8 (0-22)	12.21±6.17 13 (0-29)	10.67±9.76 9 (0-45)	**< 0.001**	0.145	0.084

Mann–Whitney U test, PM&R: Physical Medicine and Rehabilitation

It has been reported that women are promoted at a slower rate in academia and also have a lower publication rate than men.[22] Patel et al.[23] listed the career barriers of female doctors in the field of medicine as ineffective mentoring, implicit biases and a preference for working part-time. D'Souza et al.[16] evaluated 111 chronic pain programs and 35 acute pain programs in the USA and reported that female program directors were employed in 35 (31.5%) of all the programs, and the male representation rate was higher than women. In addition, they stated that female pain program directors have lower peer-reviewed publications than their male counterparts. They also reported that pain fellowship programs with female directors have higher number of female fellow trainees than those with male directors. In our study, however, no significant relationship was found between gender and clinical leadership (head of the department). Physicians who serve as the department heads are mostly professors with a statistically significant difference. In our country, the participation of physicians in the pain medicine fellowship programs with a central exam and the interest of both the genders in a popular branch ensured a more homogeneous distribution of the genders in pain medicine, resulting in an equal representation of males and females in leadership positions. It is necessary for the clinics to create an environment where women and men have equal opportunities in leadership positions for the equal representation to be sustainable.

When the publication activities based on institutions were examined in our study, it was determined that the number of publications and h-index ratings of physicians working at private institutions and other public universities were significantly higher than those employed in the UHSs. Similarly, the number of citations of physicians employed in other public universities was higher than those employed in UHSs. This may be due to the fact that after the Ministry of Health started to issue the pain medicine fellowship certificate to physicians who were working in this field in 2011, the physicians who have advanced academic titles, they continued to work at private institutions or other public universities, whereas new pain physicians are preferred to work at UHSs. We believe that this gap between the institutions will be narrowed as new pain physicians contribute to the literature with robust publications over time.

Evaluation of publication activity by the main specialties showed remarkable consequences. It was observed that the pain physicians from PM&R had greater number of publications than those from anesthesia. Pain physicians from PM&R also have significantly higher citation numbers and h-index values than pain physicians from anesthesia. The fact that anesthesiologists who work in a surgical branch cannot demonstrate sufficient publication activities unless they enroll in a fellowship program, which could be due to their busy schedules and shifts in our country, may lead to this significant difference. A study has been reported in the literature that examines the publication activities of anesthesiologists in Türkiye.[11] We anticipate that such bibliometric studies in other branches can enlighten the significant differences among the branches in terms of the publication activities.

Limitations

The websites from which we obtained the data may contain inaccurate or incomplete information. Although the information in the Scopus database is more accurate than in other databases, there is still a possibility that an author's publication was mistakenly attributed to someone else with the same name. In addition, the surnames of female physicians may have changed after their marriage. Therefore, physician information was checked from the public websites of the institutions in addition to the Scopus database to determine

the number of publications, h-index, or academic parameters before and after the surname change.

Secondly, h-index may not be a dynamic measure of increased scientific productivity over time. Physicians who had received many citations at the beginning of their careers and who had written articles will continue to collect citations and increase their h-index ratings, even if there is no more scientific activity. Therefore, m-index, which indicates the ratio of career length to the h-index, can be used in future studies.

Conclusion

Our study is the first to evaluate the number, gender distribution, academic title distribution, leadership positions, and Scopus database-based number of publications, number of citations, and h-index ratings of academicians working in pain medicine departments in various medical faculties. In our study, it was determined that there are 274 pain medicine physicians in our country and that the number of female professors, associate professors, asisstant professors, and attending physicians were higher than those of male physicians, but there was no significant difference between the genders. It was determined that the number of publications, number of citations, and h-index values of male academicians were higher than that of females, but there was no significant difference between the genders. It was shown that the publishing activity of physicians employed in private institutions and clinics and other public universities was higher than those in UHSs. It was concluded that pain physicians with PM&R and Neurology specialty had higher publication activity than pain physicians with anesthesia specialty.

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Prostat Cancer and Obesity

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ABSTRACT

Objective: Obesity and aggressive prostate cancer are two important clinical conditions because of the prevalence and obesity increases the aggressiveness of prostate cancer. In this study, our aim was to investigate obesity rates at the time of diagnosis in patients who underwent Ga-68 PSMA PET/CT.

Methods: 104 patients with newly diagnosed prostate cancer who underwent Ga-68 PSMA PET/CT between 2021 and 2022 for staging were included in this study. The patients' height and weight, pathology results and PSA values, which were recorded routinely before PET/CT, were obtained from Nuclear Medicine patient files. The formula [mass (kg) / height2 (m)] was used to calculate the body mass index (BMI). According to the PSA values and Gleason score of the patients, intermediate and high-risk patients were included in the study.

Results: The median age of the patients was 70.5 (range:40-87 yrs) at the time of diagnosis and 67 (64.4 %) patients had metastases at the time of diagnosis. Of the patients, 15 (14.4%) were in the intermediate risk group and 89 (85.6%) were in the high risk group. Of the patients, 33 (31.7%) were normal weight, 45 (43.3%) were overweight, and 26 (25%) were obese. There was no significant difference between prostate cancer risk groups and BMI (p=0.126)

Conclusion: As a result, the weight of the majority of the patients in our study was above normal. However, there was no significant difference between overweight and obese and prostate cancer risk groups. However, considering all the literature information, being overweight increases the risk of cancer, and attention should be paid to dietary habits.

Keywords: Prostate cancer, obesity, PET/CT, Ga-68 PSMA

Prostat Kanseri ve Obezite

Araştırma Makalesi

Süreç

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ÖZET

Amaç: Obezite ve agresif prostat kanseri, yaygın olması ve obezitenin prostat kanserinin agresifliğini artırması nedeniyle iki önemli klinik durumdur. Bu çalışmada amacımız, Ga-68 PSMA PET/BT yapılan hastalarda tanı anında obezite oranlarını araştırmaktı.

Yöntem: Bu çalışmaya yeni tanı almış prostat kanseri olan ve evreleme amacıyla 2021-2022 yılları arasında Ga-68 PSMA PET/BT yapılan 104 hasta dahil edildi. Hastaların PET/BT çekimi öncesi rutin olarak kaydedilen boy ve kiloları ile patoloji sonuçları ve PSA değerleri Nükleer Tıp hasta dosyalarından elde edildi. [mass (kg) / height2 (m)] formülü Vücut kitle indeksi (VKİ) hesaplamada kullanıldı. Hastaların PSA değerleri ve Gleason skoruna göre intermediate ve yüksek riskli hastalar çalışmaya dahil edildi.

Bulgular: Tanı anında hastaların median yaşı 70.5 (range:40-87 yaş) idi ve tanı anında 67 hasta (%64.4) metastatikti. Hastalardan 15'i (%14.4) orta risk grubunda ve 89'u (%85.6) yüksek risk grubunda idi. Hastalardan 33'ü (%31.7) normal kilolu, 45'i (%43.3) fazla kilolu ve 26'sı (%25) obezdi. Prostat kanser risk grupları ile VKI arasında anlamlı fark bulunmadı (p=0.126)

Sonuç: Sonuç olarak, çalışmamızdaki hastalardan büyük çoğunluğunun kilosu normalin üzerindeydi. Bununla birlikte kilolu ve obez olmakla prostat kanser risk grupları arasında anlamlı farklılık bulunmadı. Ancak tüm literatür bilgileri de dikkate alındığında, fazla kilolu olmanın kanser riskini artırdığı göz önünde bulundurularak beslenme alışkanlıklarına dikkat edilmelidir.

Anahtar Kelimeler: Prostat Kanseri, Obezite, PET/BT, Ga-68 PSMA

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Introduction

Prostate cancer is the 2nd commonly diagnosed cancer in men, after lung cancer, according to Globocan statistics.[1] In an epidemiological study conducted in Turkey, the incidence rate of prostate cancer was found to be 35 per 100000.[2] In the aforementioned study, the median age at diagnosis was 68 years and the median PSA level was 10.0 ng/ml. PSMA (Prostate Specific Membrane Antigen) expression is increased in all prostate cancers. Aggressiveness of the disease is associated with metastatic disease and recurrence.[3] Positron Emission Tomography / Computed Tomography (PET/CT) is a high-level diagnostic hybrid imaging method that provides imaging at the molecular level. Since it is a hybrid imaging system, it also provides morphological information. PSMA (prostate-specific membrane antigen) is a transmembrane protein primarily present in all prostatic tissues. PSMA expression increases at high levels in prostate cancer patients (approximately 100-1000-fold).[4] Since PSMA is used in both diagnosis and treatment, it has taken its place among the theranostic agents in nuclear medicine applications. PET/CT with Ga-68 PSMA (Gallium-68 Prostate Specific Membrane Antigen) is now recommended as an alternative to standard bone and soft tissue imaging with NCCN updated guidelines.[5] Ga-68 PSMA PET/CT has high sensitivity and specificity in detecting metastatic lesions, even at very low PSA levels.[6] Cerci et al.[7] reported that in multicenter study the reliability and worldwide applicability of Ga-68 PSMA PET/CT in the examination of patients with biochemical recurrence.

There are many studies in the literature linking cancer and obesity. Obesity, develops as a result of hypertrophy and hyperplasia in the adipose tissue. The increased mortality and morbidity associated with obesity is thought to be due to the increase in hormones, adipokines and cytokines produced by fat tissue.[8] Obesity and aggressive prostate cancer are two important clinical conditions because of the prevalence and obesity increases the aggressiveness of prostate cancer. In this study, our aim was to investigate obesity rates at the time of diagnosis in patients who underwent Ga-68 PSMA PET/CT.

Materials and Methods

This study comprised 104 people with new diagnoses of prostate cancer who underwent staging with Ga-68 PSMA PET/CT between 2021 and 2022. The patients' height and weight, pathology results and PSA values, which were recorded routinely before PET/CT, were obtained from Nuclear Medicine patient files. On the basis of their PSA values and Gleason score, the patients were categorized as low risk, intermediate risk, and high risk. Patients with a Gleason score ≤ 6 and PSA ≤ 10 were considered low-risk, patients with a Gleason score of 7 and/or PSA <10- ≤20 were considered intermediate risk, and patients with a Gleason score of 8-10 or PSA >20 were considered high-risk. According to risk classification, patients in the low-risk class were not allowed to participate in the study. Furthermore, study participation was restricted to individuals who had previously undergone any form of treatment (chemotherapy, irradiation, etc.).

^{68}Ga-PSMA PET/CT Imaging Protocol

Patients received an intravenous injection of 2 MBq/kg 68Ga-PSMA 45-60 min before the start of the acquisition. 68Ga-PSMA PET / CT imaging of all patients was performed with General Electric Discovery PET / CT 600 (GE Medical Systems, LLC, 3000 N. GRANDVIEW BLVD., WAUKESHA, WI., U.S.A.) device. First, using a 16-section scanner, CT imaging was done at 120 kV, 172 mAs, and 2.5 mm axial slice thickness for attenuation correction and anatomical correlation. PET imaging was carried out for around three minutes in each bed position in three dimensions, encompassing the cranium and feet. Using the iterative reconstruction method, CT and PET images were matched and fused into transaxial, coronal, and sagittal images. The Digital Imaging and Communications in Medicine (DICOM) protocol was used to transport the data to a processing workstation (AW Volume Share5, GE Medical Systems S.C.S, France). Subsequently, semi-quantitative and visual analysis was conducted. The SUVmax computed by standard methods from the activity in the most intense voxel in the 3-D tumor region from the transaxial whole-body images.

The formula [mass (kg) / height2 (m)] was used to calculate the body mass index (BMI). In the BMI classification, less than 18.5 was considered underweight, 18.5-24.5 normal, 25-29.9 overweight, 30 and over obese. However, our main limitation in this evaluation is that the majority of the height-weight data of the patients were recorded according to their statements rather than measurement.

Our study is retrospective. For this reason, ethics committee approval was not received. The Helsinki Declaration of the World Medical Association was followed in the conduct of this research.

Statistical Analysis

The statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS) for Windows 22.0 (SPSS, Inc., Chicago, IL, USA). The mean, standard deviation, frequency, and median were employed in descriptive statistics. Fisher's exact test or chi-square were used to statistically compare categorical data. A P value of less than 0.05 was considered statistically significant.

Results

At the time of diagnosis, 67 (64.4%) of the patients had metastases, and the median age of the patients was 70.5 (range: 40-87 years). Every patient is diagnosed with adenocarcinoma. 89 (85.6%) of the patients were in the high-risk group, and 15 (14.4%) were in the intermediate-risk group. Of the patients, 45 (43.3%) were overweight, 26 (25%) were obese, and 33 (31.7%) were of normal weight.

According to Table 1, there was no significant difference (p=0.126) among the BMI and prostate cancer risk categories. When comparing the BMI groups to the patients' metastatic status at diagnosis, there was not a

significant difference (p= 0.745). Age and risk categorization did not significantly vary (p=0.107), despite the fact that BMI increased with age (p=0.004). Table 2 indicates that there was no statistically significant correlation found between the BMI of our patients and the presence or absence of metastases.

Discussion

Studies conducted so far have shown that weight gain and obesity are considered risks for the development and survival of many cancers. There are proven data between esophagus, thyroid, colon, kidney, gallbladder, liver, rectum, melanoma, multiple myeloma, leukemia, lymphoma, prostate cancer in men, and postmenopausal breast and endometrial cancers in women, and obesity.[9] Freedland et al.[10] according to the review study, although obesity is not directly related to prostate cancer, they reported that obesity increases tumor aggressiveness in patients with prostate cancer, while weight loss can reduce the risk of non-metastatic aggressive disease. Similarly, another review reported that obesity increases the incidence of aggressive prostate cancer.[11] According to the data of our study, 43.3% of our patients were overweight and 25% were obese. However, no significant difference was found between overweight and obese and prostate cancer risk groups in our study. Furthermore, there was no relationship discovered between BMI and metastatic presence.

One of the major limitations of our study was the inhomogeneity of the patient population and the small number of patients. Also, our other limitation in this evaluation is that the majority of the height-weight data of the patients were recorded according to their statements rather than measurement.

Conclusion

As a result, the majority of the patients in our study were above normal weight. However, there was no significant difference between overweight and obese and prostate cancer risk groups. However, considering all the literature information, being overweight increases the risk of cancer, and attention should be paid to dietary habits.

Conflict of interest

There is not a conflict of interest.

Table 1. The relationship between prostate cancer risk groups and BMI classification of patients

BMI	Prostat Cancer Risk Classification		*p value*
	Intermediate Risk n (%)	High Risk n (%)	
Normal weight (18.5-24.9)	6 (18.2)	27 (81.8)	*0.126*
Overweight (25-29.9)	3 (6.7)	42 (93.3)	
Obese (≥30)	6 (23.1)	20 (76.9)	

Abbreviation: BMI: Body mass index

Table 2. The relationship between presence/absence of metastasis and BMI classification of patients

BMI	Metastases		*p value*
	Present, n (%)	Absent, n (%)	
Normal weight (18.5-24.9)	23 (69.7)	10 (30.3)	*0.745*
Overweight (25-29.9)	28 (62.2)	17 (37.8)	
Obese (≥30)	16 (61.5)	10 (38.5)	

Abbreviation: BMI: Body mass index

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Role of Uric Acid Levels as a Prognostic Indicator in Allogeneic Hematopoietic Stem Cell Transplantation: Insights from a Single-Center Study

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ABSTRACT

Uric acid (UA) acts as a richly available water-soluble antioxidant, contributing to approximately two-thirds of the overall free-radical-scavenging activity in human serum. It is discharged from damaged cells during the preparation for allogeneic hematopoietic stem cell transplantation (allo-HSCT). This study assessed how pretransplantation uric acid levels influence survival and mortality in allo-HSCT patients. In a retrospective analysis of 267 patients with hematologic diseases who underwent allo-HSCT, uric acid levels were documented on the day of allo-HSCT (day 0). Patients were divided into two cohorts based on their pretransplant uric acid levels: those at or below 4.4 mg/dL and those above 4.4 mg/dL. Among them, 153 (57.3%) were male, and 114 (42.7%) were female, with a median age of 31 years (ranging from 13 to 66). Those with serum uric acid levels of 4.4 mg/dL or lower exhibited notably poorer overall survival (OS) and disease-free survival (DFS) compared to those surpassing 4.4 mg/dL (p=0.032 and p=0.045, respectively). Our findings indicate an interrelation between low pretransplant serum uric acid levels and reduced survival rates in allo-HSCT patients. Further exploration into potential mechanisms, such as compromised antioxidative capacity in hypouricemia, may establish uric acid as a promising prognostic marker in allo-HSCT.

Keywords: Uric acid, Allogeneic Hematopoietic Stem Cell Transplantation, Survival, Prognosis

Allojenik Hematopoetik Kök Hücre Nakli' nde Ürik Asit Seviyesinin Prognostik Bir Belirteç Olarak Rolü: Tek Merkez Deneyimi

Araştırma Makalesi

Süreç

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ÖZET

Ürik asit (UA) suda çözünebilen zengin bir antioksidan olarak görevi görür ve insan serumundaki toplam serbest radikal süpürücü aktivitenin yaklaşık üçte ikisine katkıda bulunur. Allojeneik hematopoetik kök hücre nakli (allo-HKHN) için hazırlık sırasında hasarlı hücrelerden atılır. Bu çalışmada, allo-HKHN hastalarında nakil öncesi ürik asit düzeylerinin sağkalım ve mortaliteyi nasıl etkilediği değerlendirilmiştir. Hematolojik hastalığı olan ve allo-HKHN yapılan 267 hastanın retrospektif analizinde, ürik asit düzeyleri allo-HKHN gününde (0. gün) belgelenmiştir. Hastalar nakil öncesi ürik asit düzeylerine göre iki gruba ayrılmıştır: 4,4 mg/dL veya altında olanlar ve 4,4 mg/dL'nin üzerinde olanlar. Bunların 153 'ü (%57,3) erkek, 114' ü (%42,7) kadındı ve ortanca yaşları 31'di (13 ile 66 arasında değişiyordu). Serum ürik asit düzeyleri 4,4 mg/dL veya altında olanlar, 4,4 mg/dL'yi aşanlara kıyasla belirgin şekilde daha kötü genel sağkalım (OS) ve hastalıksız sağkalım (DFS) sergilemiştir (sırasıyla p=0,032 ve p=0,045). Bulgularımız, allo-HKHN hastalarında düşük pretransplant serum ürik asit düzeyleri ile azalmış sağkalım oranları arasında bir ilişki olduğunu göstermektedir. Hipoürisemide bozulmuş antioksidatif kapasite gibi potansiyel mekanizmaların daha fazla araştırılması, ürik asidin allo-HKHN' nde umut verici bir prognostik belirteç olmasını sağlayabilir.

Anahtar Kelimeler: Ürik asit, Allojenik Hematopoietik Kök Hücre Nakli, Sağkalım, Prognoz

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a well-established therapeutic approach for various hematological malignancies and non-neoplastic genetic disorders.[1,2] The treatment result of allo-HSCT depended on two primary variables: transplant-related morbidity or mortality (TRM) and disease recurrence.[3,4] Despite advancements in recent decades, infectious complications and graft-versus-host disease (GVHD) continue to be significant contributors to transplant-related morbidity or mortality (TRM).[5,6] Efforts have focused on identifying prognostic markers for allo-HSCT recipients, with UA emerging as a potential predictive marker for survival. However, the prognostic significance of UA in determining post-transplantation outcomes remains uncertain. UA is the end product of the purine metabolic pathway.[7] Humans do not possess urate oxidase or uricase, enzymes necessary to convert UA into the more soluble compound allantoin.[8]

Consequently, humans tend to have higher serum UA concentrations than most other mammals. However, the increased UA levels in humans have been considered beneficial, especially during increased oxidative stress.[9] UA can bind iron and inhibit iron-dependent ascorbate oxidation, protecting against oxidative stress-induced injuries. Consequently, a decrease in UA concentration may result in heightened oxidative stress.[10]

Oxidative stress, marked by heightened free radical activity, is considered a significant factor in conditions such as cancer, heart disease, and aging. UA is the principal natural antioxidant in peripheral blood, contributing to approximately 60% of the capacity for scavenging free radicals.[9] Moreover, the suggested antioxidant properties of heightened UA levels in humans are believed to provide neuroprotection against a range of neurodegenerative and neuroinflammatory disorders.[11-15]

The antioxidant impact of UA has not been sufficiently documented in patients undergoing allo-HSCT. Numerous studies present conflicting findings regarding the association between UA levels and overall survival among patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). While one previous retrospective study indicates no significant association between UA levels prior to transplantation and mortality following allo-HSCT,[16] another study suggests a negative association between UA levels and mortality. The antioxidant effect of UA has not yet been adequately reported in patients undergoing allo-HSCT.[17] Therefore, we aimed to evaluate the prognostic significance of pretransplant UA levels for survival outcomes in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods

Patient Cohort

Three hundred patients who underwent transplantation at Erciyes University Hematology Transplant Center between 2007 and 2016 were included for retrospective data analysis. After excluding individuals with missing UA levels on the day of hematopoietic stem cell transplantation (HSCT) (day 0) (n=33), the final dataset consisted of 267 patients. These patients were divided into two groups based on their pretransplant UA levels: those with serum UA levels of 4.4 mg/dL or lower (≤4.4 mg/dL) and those with levels exceeding 4.4 mg/dL (>4.4 mg/dL). The study was approved by the local ethics committee of Erciyes University (Approval number: 2021/338).

Transplantation Procedures and Prophylaxis Strategy

HSCT procedures followed standard protocols. Myeloablative conditioning (MAC) regimens included either cyclophosphamide/total body irradiation (TBI) or cyclophosphamide/busulfan. Non-myeloablative conditioning (NMA) was primarily administered to patients with aplastic anemia, with cyclophosphamide being the primary conditioning agent. Reduced-intensity conditioning (RIC) comprised fludarabine/busulfan, fludarabine/melphalan, or fludarabine/low-dose TBI. Prophylaxis against GVHD consisted of methotrexate plus cyclosporine A, with or without anti-thymocyte globulin (ATG).

Within the first four weeks following transplantation, patients were prescribed prophylactic antibacterial (moxifloxacin 1×400 mg/day) and antiviral (valacyclovir 1×500 mg/day) treatments. Antifungal prophylaxis consisted of fluconazole 2×200 mg/day until the 75th day post-transplantation. After engraftment, trimethoprim and sulfamethoxazole were administered twice daily, twice weekly, for pneumocystis jirovecii prophylaxis until day 180. Patients were scheduled for weekly visits during the initial month and biweekly visits for the subsequent three months.

Characterization of Transplant-Related Variables and Statistical Analysis

Patients diagnosed with acute leukemia in first or second complete remission (CR) or those with myelodysplastic syndrome (MDS) were categorized as standard risk for risk stratification associated with transplantation.[18]

Patients not falling into these categories were classified as high-risk. In instances of gender mismatch between donor and recipient, female donors matched with male recipients were considered high risk, while all other combinations were categorized as standard risk.[19] GVHD was evaluated according to established clinical criteria.[20,21]

The primary endpoints included overall survival (OS) and disease-free survival (DFS). OS was defined as the period from HSCT to death from any cause. DFS was delineated as the duration (in months) from the date of HSCT until disease recurrence was confirmed radiologically or histologically. Early transplant mortality referred to events occurring within the initial 30 days post-transplantation, while peritransplant mortality encompassed events within the first 100 days after transplantation.

We utilized the Mann-Whitney U test to compare continuous variables between the two groups. For

qualitative data comparison, we employed the Pearson Chi-Square and Fisher-Freeman Halton tests. Survival and mortality probabilities were estimated using the Kaplan-Meier method, with comparisons performed using the log-rank test. The optimal cut-off value for uric acid levels in predicting survival was determined through receiver operating characteristic (ROC) curve analyses. Furthermore, we conducted univariate and multivariate Cox regression analyses to identify the most significant risk factors affecting survival and mortality probabilities.

Variables that had a significance level of p<0.20 were included in the multiple models, and backward elimination was used to identify independent risk factors. Hazard ratios, along with 95% confidence intervals (CIs), were reported. A significance level of p<0.05 was considered statistically significant.

Results

Patients Attributes

A total of 267 patients participated in the study, with 153 (57.3%) being male and 114 (42.7%) female. Patient characteristics before transplantation are summarized in Table 1. The median age overall was 31 years (range 13-65). In terms of risk classification, 124 patients (46.4%) were categorized as high risk, while 143 (53.6%) were considered standard risk. Most patients underwent transplantation for acute leukemia (74.2%), while a smaller proportion received transplants for lymphoproliferative diseases (10.9%) or other conditions (15%). The median pretransplant uric acid (UA) level was 4.2 mg/dL (range 1.1-8.5 mg/dL). Among the patients, 198 (74.2%) underwent allo-HSCT within the first 12 months after diagnosis, while 69 patients (25.8%) underwent the procedure after completing the initial 12 months following diagnosis. In post-transplant evaluation, infections were identified as the primary complication, with 206 patients (77.2%) experiencing at least one episode of infectious events. GVHD emerged as the second most common complication during the post-transplant period.

Among the patients, 33 (12.4%) were diagnosed with acute GVHD, while chronic GVHD was observed in 98 (36.7%) cases. During the posttransplant follow-up, a total of 103 patients (38.6%) passed away. Within the initial 30 days after transplantation, 24 patients (9%) succumbed, while 12 patients (4.4%) passed away within the first 100 days post-transplantation. Fifty-five patients (20.6%) experienced relapse during the follow-up period. The OS and DFS were observed to be 90 months (range 52.3-105.7) and 98 months (range 78.2-115.4), respectively.

Establishing the Threshold for Low Serum UA Levels

The median serum UA value in the entire cohort was 4.2 mg/dl (range 1.1-8.5). Based on ROC analysis, the optimal cut-off value of UA to predict survival was determined to be 4.4 mg/dl. At this cut-off value, UA exhibited a sensitivity of 64.1%, a specificity of 51.2% (p=0.022), and an accuracy of 56.18% for predicting mortality. The area under the curve (AUC) was computed to be 0.583 (95% CI: 0.514-0.652; p<0.05).

Table 1. Patient characteristics

Variables	Results, n (%)
Age, years (<40/≥40)	183 (68.5)/84 (31.5)
Gender (male/female)	153 (57.3)/114 (42.7)
Diagnosis	
Acute leukemia	198 (74.2)
Lymphoproliferative diseases	29 (10.9)
Other diseases	40 (15)
Sex mismatch (standard risk/high risk)	166 (62.2)/101 (37.8)
Risk group (standard risk/ high risk)	143 (53.6)/124 (46.4)
Time to transplant (<12 months/*≥12months)*	198(74.2)/69(25.8)
Conditioning regimen	
MAC	208 (77.9)
NonMAC	26 (9.7)
RIC	16 (6.0)
MISSING	17 (6.4)
HLA match	
Full match	219 (82)
Mismatch	45 (16.9)
Unreleated	3 (1.1)
CD 34^{+}count, 10^{6}/kg, median (range)	7.01 (2.7-19.2)
Uric acid at HSCT Median in mg/dl (range)	4.2 (1.1-8.5)
Infection (yes)	206 (77.2)
Acute GVHD (yes)	33 (12.4)
Chronic GVHD (yes)	98 (36.7)
GVHD (yes)	123 (46.1)
DFS, m, median (range)	98 (78.2-115.4)
OS, m, median (range)	90 (52.3-105.7)
Peri-transplant mortality	12 (4.5)
Early-transplant mortality	24 (9)

DFS: disease-freesurvival; GVHD: graft-versus-hostdisease; HLA: human leukocyte antigen; OS:overall survival; m: month; MAC: myeloablative; NonMAC: nonmyeloablative; RIC: reduced intensity conditioning; HR: hazard ratio; CI: confidence interval

The association of OS with low serum UA levels

The median OS for patients with serum UA levels ≤4.4 mg/dL was 73.8 months (range, 31.35-116.2), whereas it was 101 months (range, 79.9-127.3) for those with serum UA levels >4.4 mg/dL. Our analysis revealed a significantly poorer OS among patients with low serum UA levels (p=0.029, Figure 1).

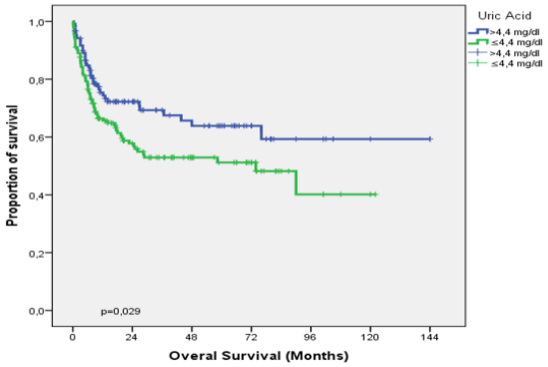

Figure 1. Patients with serum uric aci levels ≤4,4 mg/dl had significantly lower overall survival compared with those with serum uric acid levels >4,4 mg/dl (p=0,029)

Both univariate and multivariate analyses demonstrated that patients with serum UA levels ≤4.4 mg/dL exhibited significantly lower OS compared to those with levels >4.4 mg/dL (univariate hazard ratio [HR] for OS: 1.55, 95% CI: 1.04-2.33, p=0.031; multivariate HR: 1.57, 95% CI: 1.04-2.39, p=0.032), suggesting a heightened risk of mortality among patients with low serum UA levels ≤4.4 mg/dL. Detailed results of both multivariate and univariate analyses are presented in Table 2. In conclusion, low serum UA levels prior to allo-HSCT represent an independent risk factor for mortality.

Table 2. Univariate and multivariate analysis of parameters for overall survival (OS)

Variables	OS			
	Univariate		Multiple	
	HR (95% CI)	p	HR (95% CI)	p
Age, years				
<40	1.00			
≥40	1.022 (0.67-1.54)	0.918	-	-
Gender				
Male	1.00			
Female	1.444 (0.98-2.13)	0.062	-	-
Diagnosis				
Other diseases	1.00			
Acute leukemia	1.064 (0.59-1.91)	0.836	-	-
Lymphoproliferative diseases	1.357 (0.63-2.93)	0.437	-	-
Sex mismatch				
Standard risk	1.00			
High risk	1.053 (0.71-1.56)		-	-
Disease status				
Standard risk	1.00			
High risk	1.229 (0.82-1.83)	0.316	-	-
Conditioning regimen				
RIC	1.00			
NonMAC	1.842 (0.57-5.98	0.310	-	-
MAC	1.814 (0.67-4.95	0.245	-	-
Time to transplant				
<12months	1.00			
≥12 months	1.686 (1.12-2.54)	0.012*	1.552 (1.03-2.34)	0.037*
HLA Match				
Full Match	1.00		1.00	
MisMatch	2.270 (1.45-3.55)	0.001**	2.366 (1.48-3.79)	0.000**
Unrelated	3.502 (0.86-14.35)	0.081	3.759(0.91-15.46)	0.066
Uric asid				
>4.4	1.00			
≤4.4	1.558 (1.04-2.33)	0.031*	1.577 (1.04-2.39)	0.032*
$CD34^+$ Count	1.019 (0.94-1.11)	0.659	-	-
Infection (yes/no)	1.353 (0.83-2.20)	0.225	-	-
Acute GVHD (yes)	1.670 (1.03-2.78)	0.048*	1.539 (0.91-2.59)	0.107
Chronic GVHD (yes)	0.601 (0.39-0.91)	0.017*	0.593 (0.38-0.91)	0.016*
GVHD (no)	0.831 (0.56-1.23)	0,349	-	-

GVHD: graft-versus-host disease; HLA: human leukocyte antigen; RIC: reduced intensity conditioning; HR: hazard ratio; CI: confidence interval; * p<0.05, **p<0.01

In the multivariate analysis, risk factors associated with OS included HLA mismatched donor (HR 2.36, 95% CI: 1.48-3.79, p=0.001), time to transplant interval (HR 1.55, 95% CI: 1.03-2.34, p=0.037), and the presence of chronic GVHD (HR 0.59, 95% CI: 0.38-0.91, p=0.032). Parameters such as age, gender, diagnosis, gender mismatch, disease status, conditioning regimens, presence of infection, and the number of total infused CD34+ cells did not show a significant effect on OS (p>0.05).

The association of DFS with low serum UA levels

The median DFS for patients who had serum UA levels of ≤4.4 mg/dl was 83.2 (range, 72.9-93.4) months versus 115.9 (range, 104.2-127.3) months for patients with serum uric acid levels >4.4 mg/dl.

The disease-free survival rate was significantly lower in patients with UA levels were ≤4.4 mg/dl than those with UA levels >4.4 mg/dl (figure 2, DFS univariate HR 1.72, 95% CI: 1.09-3.01, p=0.044; multivariate HR 1.68, 95% CI: 1.03-3.06, p=0.045).

Table 3. Univariate and multivariate analysis of parameters for disease-free survival (DFS)

Variables	DFS			
	Univariate		Multiple	
	HR (95% CI)	p	HR (95% CI)	p
Age, years				
<40	1.00		1.00	
≥40	0.462 (0.23-0.92)	0.027*	0.431 (0.21-0.87)	0.018*
Gender				
Male	1.00		1.00	
Female	1.667(0.98-2.83	0.059	1.932 (1.09-3.44)	0.025*
Diagnosis				
Other diseases	‡	0.956	-	-
Acute leukemia	0.63(0.29-1.23)	0.166	-	-
Lymphoproliferative diseases	1.00			
Sex mismatch				
Standard risk	1.00			
High risk	0.778 (0.44-1.39)	0.384	-	-
Disease status				
Standard risk	1.00			
High risk	1.145 (1.25-3.69)	0,006**	2.456 (1.35-4.47)	0,003**
Conditioning regimen				
RIC	1.00			
NonMAC	‡	0.967	-	-
MAC	1.330 (0.41-4.27)	0.632	-	-
Time to transplant				
<12months	1.00		1.00	
≥12 months	1.928 (1.11-3.34)	0,019*	1.921 (1.07-3.44)	0.028*
HLA Match				
Full Match	1.00		1.00	
MisMatch	2.189 (1.16-4.09)	0.014*	1.311 (0.59-2.88)	0.501
Unrelated	‡	0.977		0.977
Uric asid				
>4.4	1.00		1.00	
≤4.4	1.726 (1.09-3.01)	0.044*	1.686 (1.03-3.06)	0.045*
$CD34^+$ Count	1.087 (0.97-1.22)	0.145	-	-
Infection (yes/no)	1.065 (0.57-1.98)	0.843	-	-
Acute GVHD (yes)	1.731 (0.87-3.44)	0.118	-	-
Chronic GVHD (yes)	1.058 (0.62-1.80)	0.836	-	-
GVHD (no)	1.204 (0.71-2.05)	0.493	-	-

GVHD: graft-versus-hostdisease; HLA: human leukocyte antigen; OS:overall survival; MAC: myeloablative; NonMAC: nonmyeloablative; RIC: reduced intensity conditioning; HR: hazard ratio; CI: confidence interval; *<0.05; **<0.01; ‡: HR could not be computed because all cases were censored in this group

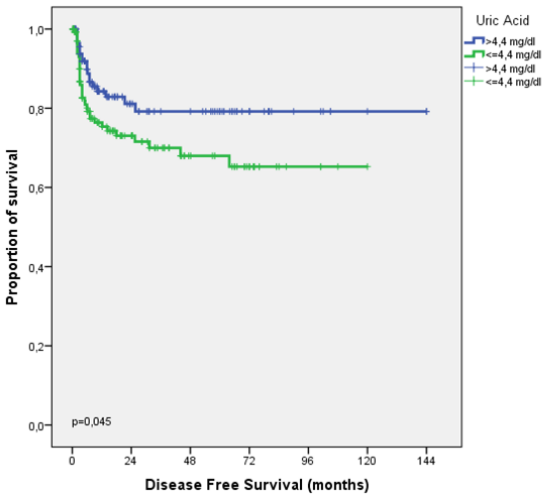

Figure 2. Patients with serum uric aci levels ≤4,4 mg/dl had significantly lower disease-free survival compared with those with serum uric acid levels >4,4 mg/dl (p=0,045)

Additional factors showing notable differences among groups were age, with patients older than 40 years having an increased risk compared to those younger than 40 years (HR 0.43, 95% CI 0.21-0.87; p=0.018); gender, where females faced a higher risk compared to males (HR 1.93, 95% CI 1.09-3.44; p=0.025); risk status, wherein patients with high transplantation-associated risk had significantly lower DFS compared to those with standard transplantation-associated risk (HR 2.45, 95% CI 1.35-4.47; p=0.003); and time to transplant interval, with patients undergoing allo-HSCT within 12 months from diagnosis (<12 months) having higher DFS compared to those undergoing allo-HSCT more than 12 months from diagnosis (≥12 months) (HR 1.92, 95% CI 1.09-3.44; p=0.028). The diagnostic parameters, gender mismatch, conditioning regimens, presence of infection, acute GVHD, chronic GVHD, and the total number of infused CD34+ cells did not exhibit a significant effect on OS (p>0.05). The multivariate and univariate analyses of variables for DFS are presented in Table 3.

Discussion

The attributes of both patients and donors before transplantation, along with factors occurring after transplantation, serve as crucial predictors of outcomes for allo-HSCT recipients. Many recipients remain in close proximity to the transplant center during the initial 90-100 days post-transplantation. Therefore, establishing prognostic factors is essential for identifying patients at high risk of poor outcomes. This study primarily focused on evaluating the predictive significance of pretransplantation low serum UA levels on the outcomes of patients who have undergone allo-HSCT during the post-transplant period. Recent research indicates that hypouricemia is associated with various inflammatory and degenerative diseases.[10,22-24] The link between hypouricemia and reduced antioxidative capacity has been noted. Toxicity induced by oxygen radicals initiates a chain reaction of lipid peroxidation, which in turn leads to damage to DNA, RNA, proteins, cellular membranes, and cellular organization.[9] In a study by Waring et al.[25], it was shown that elevated UA concentrations were linked to heightened serum antioxidant capacity and decreased oxidative stress during acute physical exercise in a group of twenty healthy subjects. UA is considered the predominant natural antioxidant in peripheral blood. Hence, our initial hypothesis primarily aimed to uncover any potential association between low serum UA levels and survival.

In our study, we conducted a retrospective analysis of data from 267 recipients of allo-HSCT to explore the relationship between serum UA levels and key transplant outcomes. We discovered that pretransplant low serum UA levels in allo-HSCT recipients were linked to inferior survival. This association could be explained by the reduced antioxidative capacity. Our findings align with those reported in the study by Ghasemi and colleagues.[17] The research findings indicated that serum UA levels falling below 3.4 mg/dl were linked to heightened mortality risk and diminished OS, with 3.4 mg/dl identified as the threshold value for serum UA level. Moreover, their findings revealed that patients exhibiting serum UA levels exceeding 3.4 mg/dl experienced a 37% reduced probability of developing GVHD, a significant factor contributing to transplant-related mortality (TRM).

Consistent with existing literature, our study also identified a higher mortality rate among patients who developed chronic GVHD following allo-HSCT (p=0.016).

In a separate study, Ostendorf et al.[16] demonstrated a notable correlation between low UA levels and the occurrence of acute GVHD. However, they did not find a significant association between low UA levels and OS or relapse. The lack of statistical significance regarding survival and serum UA levels in their study might be attributed to its single-center, retrospective design and inclusion of HLA-matched transplant recipients. The reduced antioxidative capacity attributed to hypouricemia may explain the inverse correlation observed between UA levels and GVHD in both studies (Ghasemi et al.[17] and Ostendorf et al.[16]), as well as the lower OS outcome reported in the former study.

Our results diverge from those reported in a prior prospective study by Penack et al.[26] Their research indicated that elevated UA levels prior to the commencement of conditioning correlated with increased mortality post-allo-HSCT. However, their study design varied as it was prospective and concentrated solely on allo-HSCT from HLA-identical sibling donors. Hence, they could not extrapolate conclusions from these results regarding the association between UA levels and outcomes in matched unrelated donor allo-HSCT or haploidentical allo-HSCT.

In our study, the time elapsed before transplantation emerged as a significant predictor for both OS and DFS. This could be attributed to some patients attaining remission earlier due to the efficacy of first or second-line chemotherapy regimens. It's important to note that patients resistant to chemotherapy underwent allo-HSCT at a later stage compared to those who achieved remission with first-line regimens. Particularly, patients transplanted within the early group (<12 months)

exhibited prolonged survival compared to those in the late group (≥12 months). This disparity was statistically significant for both OS and DFS (p=0.037 and p=0.028, respectively). Our study encountered several limitations: 1) It was conducted retrospectively at a single-center university hospital, making it challenging to ascertain the specific causes of death or infections. Therefore, additional multicenter studies may offer more comprehensive data concerning the relationship between serum UA levels and transplant outcomes. 2) Another limitation of our findings is that UA participates in complex reactions with various oxidants, potentially generating free radicals in diverse radical-forming systems. These radicals primarily target lipids (LDL and membranes) rather than other cellular components. Simultaneously, the hydrophobic environment created by lipids presents challenges to the antioxidant properties of UA. Furthermore, oxidized lipids may convert UA into an oxidant, contributing to cellular oxidative damage. The mechanisms underlying these reactions are intricate and not yet fully understood.[27] While a previous retrospective study demonstrated a positive correlation between UA levels before transplantation and mortality following allo-HSCT, our study revealed a negative association between UA levels and mortality. As a result, there remain unanswered questions regarding the potential involvement of UA in allo-HSCT, whether as an antioxidant or a regulator of allogeneic immune responses. Further research is warranted to elucidate and validate these observations. In conclusion, our study highlights that pretransplant serum low UA levels could potentially act as a predictive marker for outcomes among allo-HSCT recipients. Further investigation and verification of these results may warrant considering this parameter as a selection criterion for survival rate in future risk assessment tools for patients undergoing allo-HSCT.

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Two-year Experience with balloon-Expandable Transcatheter Aortic Valve Replacement in Severe Aortic Stenosis at a Tertiary Center

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ABSTRACT

Objective
Aortic stenosis (AS) is the most common valvular heart disease requiring intervention, particularly in developed countries. Transcatheter aortic valve replacement (TAVR) is indicated for patients with a high surgical risk and a post-procedural survival expectancy of more than 12 months. Over the years, the TAVR method has emerged as a significant treatment option for patients with symptomatic severe AS and has begun to be implemented in our country as well. The objective of this study was to evaluate the short and long-term outcomes of patients undergoing TAVR at our center, as well as to assess our institution's experience with the TAVR procedure.

Methods
This retrospective, single-center analysis included 16 consecutive patients with symptomatic AS who underwent TAVR between March 2022 and February 2024. All patients included in the study underwent implantation of a balloon-expandable TAVR valve. In the study, the demographic characteristics of patients preoperatively and during post-procedural follow-ups, their clinical status preoperatively and postoperatively, and echocardiographic findings were evaluated and compared.

Results
The mean age of the entire population was 78.3 ± 8.7 years, and 50% were women. Transfemoral access was used in 93.8% of patients. Implantation success was achieved in all cases. During the TAVI procedure, 12.5% of patients required permanent pacemaker implantation. The mean length of hospital stay for the entire cohort was 4.5±2.3 days. There wasn't show in-hospital deaths occurred before hospital discharge. During the follow-up, it was observed that 3 patients died from all-cause mortality. The mean follow-up duration of the study was 552 days, with the longest follow-up being 666 days. The significant improvement was noted in all echocardiographic parameters and functional capacity. No cases with moderate or severe aortic regurgitation, necessitating additional procedures.

Conclusion
Our center results with TAVR over a 2-year span consistent with broader studies. Despite some procedure-related complications, advancements in devices and techniques are expected to reduce these, enhancing outcomes with increased procedural experience. With medicine favoring less invasive approaches, TAVR is poised to become a more prevalent alternative to surgery across diverse patient cohorts.

Keywords: Aortic stenosis, complications, follow-up, transcathater aortic valve replacement

Şiddetli Aort Darlığında Tersiyer Bir Merkezde Yapılan Transkateter Aort Kapak Replasmanının İki Yıllık Sonuçları

Araştırma Makalesi

Süreç

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ÖZET

Amaç
Aort darlığı (AD), özellikle gelişmiş ülkelerde müdahale gerektiren en yaygın kapak hastalığıdır. Transkateter aort kapak replasmanı (TAVR), yüksek cerrahi risk taşıyan ve işlem sonrası 12 aydan fazla sağkalım beklentisi olan hastalarda endikedir. Yıllar içinde, TAVR yöntemi semptomatik ciddi AD'li hastalar için önemli bir tedavi seçeneği olarak ortaya çıkmış ve ülkemizde de uygulanmaya başlanmıştır. Bu çalışmanın amacı, merkezimizde TAVR geçiren hastaların kısa ve uzun vadeli sonuçlarını değerlendirmek ve TAVR prosedürü ile kurum deneyimimizi değerlendirmektir.

Yöntem
Bu retrospektif, tek merkezli analiz, Mart 2022 ile Şubat 2024 arasında TAVR geçiren 16 ardışık semptomatik AD'li hastayı içerdi. Çalışmaya dahil edilen tüm hastalar, balon genişletilebilir bir TAVR kapak implantasyonu geçirdi. Çalışmada, hastaların preoperatif ve postoperatif takiplerinde demografik özellikleri, klinik durumları ve ekokardiyografik bulguları değerlendirilip karşılaştırıldı.

Bulgular
Tüm popülasyonun ortalama yaşı 78.3 ± 8.7 yıl idi ve %50'si kadındı. Hastaların %93.8'inde transfemoral erişim kullanıldı. İmplantasyon başarısı tüm vakalarda sağlandı. TAVI işlemi sırasında hastaların %12.5'ine kalıcı kalp pili implantasyonu gerekti. Tüm kohort için hastanede kalış süresinin ortalama uzunluğu 4.5 ± 2.3 gün idi. Hastane taburculuğundan önce hiçbir hastanede ölüm olmadı. Takip sırasında, 3 hastanın tüm nedenlere bağlı olarak öldüğü görüldü. Çalışmanın ortalama takip süresi 552 gün olup, en uzun takip süresi 666 gündü. Tüm ekokardiyografik parametrelerde ve fonksiyonel kapasitede belirgin bir iyileşme gözlendi. Ek prosedür gerektiren orta veya şiddetli aort yetersizliği vakası bulunmadı.

Sonuç
Merkezimizdeki TAVR sonuçları, daha geniş çalışmalarla tutarlıdır. Bazı prosedürle ilgili komplikasyonlara rağmen, cihaz ve tekniklerdeki ilerlemelerin bunları azaltması ve prosedür deneyimi arttıkça sonuçların geliştirilmesi beklenmektedir. Tıbbın daha az invaziv yaklaşımları tercih etmesiyle, TAVR'in farklı hasta grupları arasında cerrahiye alternatif olarak daha yaygın bir seçenek haline gelmesi beklenmektedir.

Anahtar Kelimeler: Aort darlığı, komplikasyon, takip, transkatater aortik kapak replasmanı

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Introduction

Aortic stenosis (AS) is the most common valvular heart disease requiring intervention, particularly in developed countries.[1] Degeneration resulting from calcification is the most common cause of AS, and its prevalence is increasing with the ageing population.[2] In a community-based echocardiographic study, severe calcific AS was found in 2% of adults aged 65 and older, while aortic valve sclerosis associated with ageing but without significant stenosis was detected in 29%.[3] Approximately two-thirds of all cardiac valve surgical interventions are aortic valve replacements (AVR), with the aetiology mostly being aortic stenosis.[1]

In patients with valvular aortic stenosis, the decision for medical or interventional treatment is based on identifying the underlying cause and grading the severity of the valve stenosis.[4] In asymptomatic AS patients, once symptoms occur, regardless of the symptom level, survival worsens if the stenosis is not relieved. The time from the onset of symptoms to death in untreated patients can be as short as 2 years. In symptomatic severe AS patients, effective treatment that improves symptoms increases survival, and enhances exercise capacity is surgical or transcatheter aortic valve replacement (AVR).[5] The choice of intervention type in patients planned for aortic valve replacement depends on a comprehensive evaluation of patient characteristics, scoring systems, and comorbidities that pose surgical risk. Transcatheter aortic valve replacement (TAVR) is indicated for patients with a high surgical risk and a post-procedural survival expectancy of more than 12 months.[4] Randomized controlled trials have shown that in symptomatic severe AS patients who are inoperable surgically, TAVR reduces both mortality and hospitalizations compared to standard treatment.[6,7]

Over the years, the TAVR method has emerged as a significant treatment option for patients with symptomatic severe AS and has begun to be implemented in our country as well. Since 2022, the TAVR procedure has been initiated in our centre for all eligible patients. Considering that the success of the TAVR procedure increases with centre experience and comprehensive evaluation of the patient by the heart team, we aimed to evaluate the short and long-term follow-up results of patients undergoing TAVR in our centre and assess our centre's experience in this study.

Material and Methods

The study included patients who underwent TAVR with a diagnosis of severe AS at the Cardiology Clinic of Sivas Cumhuriyet Faculty of Medicine Hospital between March 2022 and February 2024. Our study was conducted in accordance with the Helsinki Declaration, and written consent was obtained from all patients with approval from the Sivas Cumhuriyet Ethics Committee with approval number 2024/03-19.

The interventional procedures for patients were performed by operators in our hospital's Cardiology Clinic. The diagnosis of severe aortic stenosis was established through echocardiographic evaluation (using GE Healthcare Vivid S70N GE Ultrasound, Norway) and clinical assessment by current guidelines. Patients diagnosed with symptomatic severe aortic stenosis were evaluated by the cardiology-cardiovascular surgery council to determine the intervention method. All patients were assessed by the Heart Team with the use of validated score systems including the Society of Thoracic Surgery (STS) risk score, and determined patient suitability for SAVR, TAVI or medical therapy. During the preoperative period, patients underwent coronary angiography performed by an invasive cardiologist. Significant coronary artery disease (CAD) was defined as ≥50% stenosis. Patients with ≥70% stenosis and deemed suitable for percutaneous coronary intervention underwent coronary revascularization. The aortic valve structure, degree of calcification, aortic anatomy, and peripheral arteries of the patients were evaluated by angiographic imaging using multidetector computed tomography (MDCT) by an expert radiologist. Planned valve measurements were calculated using the 3Mensio program guided by CT images. All patients were informed about the TAVR procedure before undergoing it, and consent was obtained from them or their relatives.

In the study, the demographic characteristics of patients preoperatively and during post-procedural follow-ups, their clinical status preoperatively and postoperatively, and echocardiographic findings (left ventricular end-systolic and end-diastolic diameters [LVESD, LVEDD], left ventricular ejection fraction [LVEF], left atrial diameter, systolic pulmonary artery pressure, aortic valve area [AVA], aortic valve gradients, and velocities) were evaluated and compared. Procedural characteristics and any complications that occurred were recorded. Patients were assessed at regular outpatient clinic visits using echocardiographic, clinical, and laboratory parameters. Parameters at the last follow-up were compared with preoperative parameters. Mortality data occurring within the hospital or during follow-ups were recorded.

Implantation Procedure

The TAVR procedure was performed in the catheterization laboratory with the presence of an anesthesiologist, a cardiovascular surgeon, and an invasive cardiologist, under full sedation. Sedaoanalgesia was initiated with midazolam (0.1 mg/kg/dose by slow intravenous infusion, maximum 10 mg) and continued with ketamine (1 mg/kg/dose by slow intravenous bolus, maximum 100 mg). The transfemoral route was prioritized for intervention in patients. In one patient deemed unsuitable for femoral access, the procedure was performed via the left subclavian artery approach. At the beginning of the procedure, sheaths were inserted into the femoral artery and femoral vein of the patients. Surgical cut-down incisions were not made during femoral artery interventions. All procedures were performed using vascular closure devices. A temporary pacemaker electrode was inserted into the right ventricle through the femoral vein. Following the crossing of the aortic valve, balloon-expandable MyVal TAVR valves of appropriate sizes were deployed in all patients under rapid pacing. Post-dilatation with a balloon was performed in patients showing non-central aortic regurgitation (AR) on aortography. Hemostasis was achieved in the femoral artery using vascular closure devices, and the procedures were concluded. Patients were closely monitored in the intensive care unit post-procedure to monitor for the development of temporary pacemaker requirements, pericardial effusion, or hemodynamic deterioration. Patients continued to receive aspirin and clopidogrel as antiplatelet therapy in the postoperative period.

Statistical Analysis

Statistical analyses were conducted using the SPSS program (version 29.0, Inc., Chicago, Illinois). Clinical and laboratory data of patients were expressed as mean ± standard deviation, median (interquartile range), and percentage (%). Wilcoxon test, a nonparametric test, was used for comparing pre- and post-procedural parameters, while the Student's t-test was utilized for comparing means of parametric variables.

Results

The study included 16 patients who underwent TAVR at our centre, with a mean age of 78.3 ± 8.7 years. Eight (50%) of the patients were female. The median follow-up duration was found to be 552 days. The demographic characteristics of patients, comorbidities, and medications used during the preoperative period are presented in Table 1. Hypertension (HT) and coronary artery disease (CAD) were present in 15 (93.8%) of the patients, heart failure (HF) in 7 (43.8%), and atrial fibrillation (AF) in 5 (31.3%). Among the patients, 9 (56.3%) were using beta-blockers, 8 (50%) were on loop diuretics, 7 (43.8%) were taking renin-angiotensin system inhibitors (RASi), and 4 (25%) were on oral anticoagulant therapy.

When evaluating the preprocedural echocardiographic characteristics of the patients, the mean LVEF was found to be 52% ± 8, the mean aortic jet velocity was 4.1 ± 0.6 m/s, the mean aortic valve gradient was 54.4 ± 15.0 mmHg, and the mean aortic valve area was 0.78 ± 0.14 cm^2 (Table 2). The mean QRS duration pre-procedure was 100 ± 30 ms, and the mean PR duration was 97 ± 52 ms (Table 2). Pre-procedural laboratory parameters of the patients are summarized in Table 2.

All patients included in the study underwent implantation of a balloon-expandable TAVR valve. Transfemoral access was used in 15 (93.8%) patients, while subclavian access was utilized in 1 patient. The most common valve size chosen was 26mm (56.3%). Post-dilatation was performed in 6 (37.5%) patients due to paravalvular AR observed after implantation. Positive inotropic agents were used in 3 (18.8%) patients due to hypotension or bradycardia during the procedure. No mortality, malign tachycardia, or need for resuscitation occurred in any patient during the procedure. Pericardial effusion not causing hemodynamic compromise was observed in 4 (25%) patients during follow-up. None of these patients underwent pericardiocentesis and were conservatively managed. Two patients required temporary hemodialysis during the in-hospital period post-procedure, but their hemodialysis needs ceased upon discharge. Atrioventricular block requiring pacemaker implantation was observed in 2 patients post-procedure. Permanent pacemaker implantation was performed without complications in these patients. Detailed procedural information and post-procedural complications are shown in Table 3. In our study, one patient required percutaneous coronary intervention due to coronary artery disease (non ST elevation myocardial infarction) during the follow-up period, 3 months after valve implantation, and successful left anterior descending artery revascularization was performed. The patient was discharged without any complications after the procedure.

The postoperative and follow-up echocardiographic findings of the patients are presented in Table 2. According to this, no patient had severe AR during follow-up after the procedure, while mild AR was observed in 2 patients. It was noted that NT-proBNP values decreased and QRS and PR intervals were slightly prolonged compared to pre-procedure values, but this did not have clinical significance and did not require additional intervention.

During the follow-up, it was observed that 3 patients died from all-cause mortality. The cause of death was sudden cardiac death in two patients, while one patient died due to septic shock and multiorgan failure that developed after pneumonia. The mean follow-up duration of the study was 552 days, with the longest follow-up being 666 days. Among the deceased patients in the study, the earliest mortality was observed on the 178th day.

Table 1. Clinical characteristics of patients

Baseline characteristics	
Age (years)	78.3 ± 8.7
Female, n (%)	8 (50.0)
Hypertension, n (%)	15 (93.8)
Heart failure, n (%)	7 (43.8)
Diabetes mellitus, n (%)	8 (50.0)
Coronary artery disease, n (%)	15 (93.8)
Dyslipidemia, n (%)	11 (68.8)
Atrial fibrillation, n (%)	5 (31.3)
Chronic obstructive pulmonary disease, n (%)	7 (43.8)
Cerebrovascular disease, n (%)	10 (62.5)
Chronic kidney disease, n (%)	2 (12.5)
Periferal artery disease, n (%)	3 (18.8)
Preprocedure medications	
Beta-blocker, n (%)	9 (56.3)
Renin-angiotensin system inhibitors, n (%)	7 (43.8)
Mineralocorticoid receptor antagonists, n (%)	1 (6.3)
Sodium-glucose cotransporter-2 inhibitors n (%)	4 (25.0)
Loop diuretics, n (%)	8 (50.0)
Oral anticoagulants, n (%)	4 (25.0)
Statins, n (%)	8 (50.0)

Table 2. Echocardiographic and laboratory findings before the procedure and at the last follow-up

	Preprocedure	Follow-up
Left ventricle ejection fraction (%)	52 ± 8	52 ± 9
LVDD (mm)	47.7 ± 4.3	47.2 ± 4.7
Left atrium diameter (mm)	45.5 ± 3.6	46.3 ± 4.4
IVS (mm)	12.9 ± 2.8	12.3 ± 1.4
Aortic velocity (m/s)	4.1 ± 0.6	2.0 ± 0.4
Maximum aortic gradient (mmHg)	86.6 ± 23.9	19.7 ± 5.1
Mean aortic gradient (mmHg)	54.4 ± 15.0	10.6 ± 2.6
Aortic valve area (cm^2)	0.78 ± 0.14	
Aortic annulus diameters (mm)*	24.3 ± 2.8	
sPAP (mmHg)	43.7 ± 15.2	33.5 ± 12.2
Moderate-Severe AR, n (%)	3 (18.8)	0 (0.0)
QRS duration (msn)	100 ± 30	122 ± 36
PR duration (msn)	97 ± 52	118 ± 54
Hemoglobine (g/dL)	12.2 ± 1.8	11.3 ± 1.7
Platelet	262 ± 95	200 ± 63
NT-proBNP (pg/ml)	4,252 (274-7,919)	2,329 (787-7,754)
LDL	95 ± 37	91.2 ± 35.3

AR: aortic regurgitation, IVS: interventricular septum, LDL: low density lipoprotein, LVDD: left ventricle diastolic diameter, NT-proBNP: N-terminal pro–b-type natriuretic peptide, sPAP: systolic pulmonary artery pressure.
*: calculated with computed tomography

Table 3. Procedural specifics and outcomes in individuals undergoing TAVR

Procedure details	
STS Score	4.4 ± 1.3
Acces site, n (%)	
- Right femoral	14 (87.5)
- Left femoral	1 (6.3)
- Subclavian	1 (6.3)
Valve diameter	
- 21.5 mm	1 (6.3)
- 23 mm	2 (12.5)
- 24.5 mm	3 (18.8)
- 26 mm	9 (56.3)
- 27.5 mm	1 (6.3)
Postdilatation, n (%)	6 (37.5)
Periprocedure inotropic support, n (%)	3 (18.8)
Procedure related complications and outcomes	
Pericardial effusion, n (%)	4 (25.0)
Hemodialysis, n (%)	2 (12.5)
Pacemaker implantation, n (%)	2 (12.5)
Blood transfusion, n (%)	2 (12.5)
Aortic regurgitation, n (%)	
- Mild	2 (12.5)
- Moderate	0 (0.0)
- Severe	0 (0.0)
Percutaneous coronary intervention, n (%)	1 (6.3)
Major bleeding, n (%)	0 (0.0)
Major vascular complication, n (%)	0 (0.0)
Coronary obstruction, n (%)	0 (0.0)
Annular rupture, n (%)	0 (0.0)
Device embolization, n (%)	0 (0.0)
Inhospital mortality, n (%)	0 (0.0)
Mean follow-up time (day)	552

Discussion

In our study, we evaluated the pre- and post-procedural clinical, laboratory, and echocardiographic characteristics of 16 patients who underwent TAVR procedures at our centre over approximately more than 2 years. Additionally, we investigated perioperative and postoperative complications as well as short and long-term mortality development. The mean age of the patients included in the study was 78.3 ± 8.7 years, and they had significant comorbid conditions accompanying them.

When compared to current TAVR studies, our study had similar characteristics in terms of mean age and comorbid conditions.[6,8,9] Current guidelines prioritize TAVR procedures, especially in the elderly population, but increasing age and comorbidities also increase procedural complications, thus increasing procedural risk factors.[4] In our study group, hypertension, coronary artery disease, and dyslipidemia were the most common comorbid conditions, with heart failure diagnosed in 7 patients. It is well-known that mortality and morbidity significantly worsen with the onset of symptoms related to heart failure, especially as symptoms of heart failure emerge in patients with severe aortic stenosis.[10] Therefore, it is crucial to assess the symptomatic status of the patient before deciding on valve interventions. Similarly, the development of heart failure is a parameter that predicts adverse outcomes both related to the disease and the TAVR procedure.

The mean LVEF was found to be 52 ± 8 in our patient's pre-procedure. When symptoms, findings, and LVEF were evaluated together in the patients included in the study, it was possible to classify the majority as having AS-HF. The relatively high LVEF in our study patients may have contributed to the low mortality and peri-procedural complication rates.

In our study, the pre-procedural and follow-up echocardiographic findings of patients were compared. The most important parameters determining the success of the TAVR procedure are the normalization of the aortic valve gradient and an increase in the effective aortic valve orifice area.[11,12] In this regard, a significant decrease in both maximum and mean aortic gradients was observed in our patients. The durability of the valve is currently one of the biggest concerns in TAVR procedures. In the current literature, there is no apparent degeneration reported in follow-ups extending up to 10 years.[13,14] In our 2-year follow-ups, there were no findings suggestive of degeneration associated with gradient increase.

The presence of paravalvular AR post-TAVR is a key determinant of procedural success and long-term outcomes. Reports exist in the literature indicating that moderate or severe paravalvular AR is observed in 1-10% of cases with balloon-expandable valves.[15] Factors such as proper valve sizing, the application of predilation or postdilatation in necessary cases, and the degree of aortic root calcification are fundamental predictors of post-procedural AR formation. In our patient group, there were no patients with moderate to severe AR observed post-procedure or during follow-up. This could be explained by relatively less calcification burden, optimal valve sizing, and the application of postdilatation in selected patients (37.5%).

Currently, there are two main types of valves available for TAVR procedures: balloon-expandable and self-expandable. Although there are some differences between valve types in terms of procedural complications and success, no significant differences have been observed in outcomes.[16,17] We performed all our procedures using balloon-expandable valve systems. It is known that in balloon-expandable valve procedures, complications requiring pacemaker placement due to conduction disturbances occur less frequently.[18] Consistent with current literature, in our study, conduction disturbances requiring permanent pacemaker placement were observed in 12.5% of cases post-procedure.

Current guidelines recommend transfemoral access as the preferred vascular access route for TAVR procedures. It is known that complication rates increase with the use of alternative vascular access routes. The most significant factor preventing the use of femoral access is the presence of peripheral artery disease. Although three (18.8%) of our patients had significant peripheral artery disease, only one procedure was performed using an alternative subclavian access route. In a study by Van Mieghem et al., the risk of major vascular access site complications was found to be above 10%, with arterial sheath size and female gender being significant determinants.[19] In our patients, no major bleeding or major vascular complications were observed either peri-procedurally or post-procedurally. The absence of bleeding complications, especially, is thought to be associated with the use of post-procedural vascular closure devices.

In large randomized controlled trials regarding transcatheter aortic valve implantation, the 30-day mortality rates have been found to range from 3.3% to 9.8%, while the 1-year mortality rates range from 14.2% to 30.7%.[20,21] In our study, with an average follow-up period of 550 days, the overall mortality rate was found to be 18.8%. This rate is consistent with current literature data. It is evident that careful preoperative preparation, proper management of comorbidities, and increased procedural experience will lead to a decrease in both postoperative complications and mortality. Therefore, TAVR procedures should be performed carefully in experienced centres. Although the results of our initial experiences with TAVR procedures, both procedure-related outcomes and follow-up results, are quite satisfactory, it is important to note that during the follow-up period, patients undergoing TAVR may require additional cardiac and non-cardiac interventions and treatments, given their age and other comorbid conditions. In our study, one patient required percutaneous coronary intervention due to coronary artery disease during the follow-up period, and successful revascularization was performed. There is a consensus that the use of balloon-expandable valves facilitates

coronary access. It should not be forgotten that TAVR patients may require additional cardiac and non-cardiac interventions and treatments during the follow-up period, considering both their age and other comorbid conditions.

With the development of new devices and increased experience, complications following TAVR have decreased compared to the beginning. The most lethal complications are associated with myocardial and major vascular injuries. Left ventricular perforation leading to cardiac tamponade occurs in approximately 2.5% of transfemoral TAVR procedures, requiring emergency pericardiocentesis and often emergency sternotomy. The frequency of wire perforations, mostly seen in early experiences, decreases as experience increases.[22] In our study, pericardial effusion developed in 4 patients (25%) after the procedure, but tamponade did not occur during follow-up. None of these patients underwent pericardiocentesis and were conservatively monitored.

In a study conducted by Uguz and colleagues involving patients who predominantly had two different valves implanted via the transfemoral route, it was reported that female gender, arterial calcification, and the sheath/iliofemoral artery ratio were independent risk factors for predicting vascular adverse events.[23] This study, conducted at an experienced center and including 211 patients, found a major vascular complication rate of 5.7%. The patients included in this study had a mean logistic EuroSCORE value of 21.04. In our study, which included a smaller patient group, no major vascular complications occurred. This can be explained by the selection of relatively lower-risk patients and the use of percutaneous closure devices in all patients. Therefore, in patients undergoing TAVI, the presence of conditions such as arterial calcification or peripheral arterial disease warrants greater caution regarding the risk of major vascular complications.

Following TAVR, a decrease in left ventricular end-diastolic pressure and gradients is expected to result in decreased myocardial strain and a consequent reduction in natriuretic peptide levels. It is known that natriuretic peptide (NP) levels decrease after TAVR in the absence of major complications.[24] In our study, a significant decrease in NP values was observed when comparing pre-and post-procedural values. This phenomenon can be associated with both the relaxation of the myocardium functionally and hemodynamically and with improvements in functional capacity and symptoms.

Our study has some limitations. Firstly, presenting a single-centre experience results in a limited number of patients. Additionally, the use of a single type of valve system for TAVR procedures is another limitation. Although there were no follow-up losses in our study, the lack of standardized follow-up periods for all patients may have affected the standardization of follow-up. Furthermore, the data regarding medical treatments used during follow-up are not clear.

Conclusion

According to current guidelines, patients with indications for AVR who are deemed inoperable or at high surgical risk, but with a life expectancy of more than 1 year, are recommended to undergo TAVR. The decision for transcatheter aortic valve implantation should be made by a heart team, taking into account factors such as surgical risk, individual risk, technical feasibility of TAVR, and patient preference. Our center adheres to these recommendations, and the results of TAVR procedures performed within a 2-year period are consistent with the findings of other studies in this field. Despite the development of some procedure-related complications, it is anticipated that with the use of new devices and procedural techniques, these complications will decrease, and better outcomes will be achieved as experience with the procedure increases. Considering the shift towards less invasive treatment modalities in medicine, we believe that TAVR will be used more frequently as an alternative to surgical treatment in different patient groups in the future.

Declaration of interests

The authors declare no conflicting interests.

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Analysing of The Effects of an Interleukin – 1 Receptor Antagonist and a RNA Polymerase Inhibitor on Neurodegeneration in the Hippocampal Cell Line

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ABSTRACT

Objective: The aim of the present study is to investigate the anti-neurodegenerative effects of favipiravir, a RNA polymerase inhibitor, and anakinra, an interleukin-1 receptor antagonist, on glutamate-induced cytotoxicity. Due to their heightened sensitivity to glutamate, the hippocampal HT22 cell line were used.

Methods: Five groups of cells were established to examine the effects of anakinra and favipiravir on glutamate-induced cytotoxicity. The control group received no treatment. The group induced with glutamate received 10 mM of glutamate for 24 hours. The anakinra group was exposed to different concentrations (1,10,25,50,100 µg) of anakinra for 24 hours. The favipiravir group was exposed to different concentrations (1,10,25,50,100 µg) of favipiravir for 24 hours. The anakinra+glutamate group was pre-treated with anakinra at various concentrations (1,10,25,50,100 µg) for 1 hour and then exposed to 10 mM of glutamate for 24 hours. The favipiravir+glutamate group was pre-treated with favipiravir at various concentrations (1,10,25,50,100 µg) for 1 hour and then exposed to 10 mM of glutamate for 24 hours. Effective doses were subsequently determined, and combinations of anakinra+favipiravir+glutamate were applied.

Results: Viability was not affected by the application of different doses of favipiravir alone ($p < 0.01$ compared to the control group). It was observed that the group treated with 100 µg anakinra showed higher viability compared to other groups ($p < 0.01$ compared to glutamate). Viability was not affected by the application of different doses of anakinra alone ($p< 0.01$ compared to the control group). However, anakinra was observed to prevent the cytotoxicity induced by glutamate when applied at 100 µg, exhibiting a protective effect against neurodegeneration at this dose. In the group where anakinra and favipiravir were combined and applied with glutamate, anakinra showed a protective effect against glutamate toxicity, but the combination of anakinra and favipiravir did not alter this effect.

Conclusion: More extensive animal and human studies are required to determine the clinical implications of these findings.

Keywords: Neurodegeneration, Hippocampal cell line, interleukin-1 receptor antagonist, RNA polymerase inhibitor.

İnterlökin - 1 Reseptör Antagonisti Ve RNA Polimeraz İnhibitörünün Hipokampal Hücre Hattında Nörodejenerasyon Üzerine Etkilerinin İncelenmesi

Araştırma Makalesi

Süreç

Geliş: 13/05/2024
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ÖZET

Amaç: Bu çalışmada bir RNA polimeraz inhibitörü; favipravirin ve İnterlökin-1 reseptörü antagonisti anakinranın, hipokampal hücrelerde glutamatla oluşturulacak sitotoksisite üzerine anti-nörodejeneratif etkilerinin araştırılması amaçlandı. Glutamata olan aşırı duyarlılığı nedeniyle HT22 hücre hattı kullanıldı.

Yöntem: Kontrol, glutamat (10 mM), anakinra (1,10,25,50,100 µg), favipravir (1,10,25,50,100 µg) ve anakinra+favipravir hücre grupları oluşturuldu Kontrol grubuna herhangi bir tedavi uygulanmadı. Glutamat ile indüklenen grubun hücrelerine 24 saat boyunca 10 mM glutamat verildi. Anakinra grubundaki hücrelere 24 saat boyunca çeşitli konsantrasyonlarda (1,10, 25, 50, 100 µg) anakinra verildi. Favipravir grubundaki hücrelere 24 saat boyunca çeşitli konsantrasyonlarda (1,10,25,50,100 µg) favipravir verildi. Anakinra+glutamat grubundaki hücreler, 1 saat boyunca farklı konsantrasyonlarda (1,10,25,50,100 µg) anakinra ile ön işleme tabi tutuldu ve ardından 24 saat boyunca 10 mM glutamat uygulandı. Favipiravir+glutamat grubundaki hücreler, 1 saat boyunca farklı konsantrasyonlarda (1, 10, 25, 50,100 µg) favipiravir ile ön işleme tabi tutuldu ve ardından 24 saat boyunca 10 mM glutamat uygulandı. Ardından etkili dozlar belirlenerek anakinra+favipiavir+glutamattan oluşan kombinasyonları uygulandı.

Bulgular: Yalnızca favipravirin farklı dozlarının uygulanmasınında viabilite üzerinde herhangi bir etkisi gözlenmedi ($p< 0.01$ kontrole göre). 100 µg anakinra uygulanan grupta hücre canlılığının diğer gruplara göre daha fazla olduğu gözlendi ($p<0.01$ glutamata göre). Anakinranın farklı dozlarının uygulanmasınında viabilite üzerinde herhangi bir etkisi gözlenmedi ($p< 0.01$ kontrole göre). Sitotoksisitenin anakinra 100 µg uygulamasıyla önlendiği gözlendi. Anakinranın bu dozda nörodejenerasyon üzerine koruyucu etkisi izlendi. Anakinra+favipravir+glutamat kombine uygulanan grupta ise anakinranın glutamat toksisitesine karşı koruyucu fakat anakinra+favipravir kombinasyonu bu etkiyi değiştirmediği gözlendi.

Sonuç: Ancak bu etkinin klinik açıdan önemi için daha detaylı hayvan ve insan çalışmalarına gereksinim vardır.

Anahtar Kelimeler: Nörödejenerasyon, Hipokampal hücre hattı, interlökin-1 reseptör antagonisti, RNA polimeraz inhibitörü.

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Introduction

It is important to investigate the pathogenesis of neurodegenerative diseases (NDD) and target cytokines and molecules to develop new treatment strategies. To achieve this aim, in vitro disease models, especially cell culture models can be utilized. Cell culture studies can be carried out in normal tissues or NDD models.

Glutamate is the primary excitatory neurotransmitter of the central nervous system involved in various neurophysiological functions. Disturbance of its homeostasis can have deleterious effects on neurons, which may result in cell death.[1] Called excitotoxicity, this pathological process can induce degeneration of neurons following excessive excitation of glutamate on specific ionotropic receptors. Activation of these receptors can lead to a neuronal Ca^2 influx that can mediate excitotoxicity through a series of events including activation of various enzymes in free radical production, mitochondrial dysfunction and normal cell development and functions and damage cell membranes, cytoskeleton and DNA.[2] Interestingly, excitotoxicity has been reported to be involved in several neurodegenerative diseases such as Alzheimer's disease (AD) and multiple sclerosis.[3] In vitro and in vivo studies have shown that excessive amounts of excitatory amino acids like glutamate and their analogues cause neurodegeneration.

It is known that glutamate produces acute and chronic neurodegenerative conditions and initiate cell death. Therefore, a healthy glutamate signal transmission is crucial for protection of neurons. The phenomenon of excitotoxicity, i.e. cell necrosis resulting from activation of excessive glutamate on the surface receptors, has been associated with various pathological conditions of the nervous system including seizures, ischemia, anoxia, hypoglycemia and inflammation.[4] Since the introduction of the concept of excitotoxicity, the fundamental dogma has been that glutamate-related cell damage or death results from activation of excitatory amino acid (EAA) receptors and these effects can be blocked by the use of competitive or noncompetitive l-glutamate receptor inhibitors.[4] Neurotoxicity secondary to exposure of neurons to high extracellular glutamate concentrations can occur via two different neuronal damage and death mechanisms. A short exposure to glutamate (5-15 minutes) leads to neuronal swelling, the breakdown of the cells and the release of lactate dehydrogenase depending on extracellular Na^+ and Cl^- concentrations.[4] This information about excitotoxic cell death is significant with respect to the role of glutamate in ischemic or hypoglycemic neuronal damage.

Glutamate reuptake is essential for the regulation of physiological extracellular glutamate concentrations and it is primarily mediated by high-affinity sodium-dependent transmitters. At least five different glutamate transmitters expressed on neuronal or glial cells (GLT-1, GLAST, EAAC1, EAAT4 and EAAT5) are well characterized [5] and up to 90% of the total glutamate reuptake is achieved in the adult central nervous system.[5] Disruption of GLT-1 expression in a few neurological diseases has been reported to be related to a change in glutamate uptake.[6]

Due to its oversensitivity to glutamate, the hippocampal HT22 cell line is used to model NDDs.[3,7,8,9] There have been several studies on glutamate-induced cytotoxicity in cell lines.[3,8,10,11]

Anakinra, an interleukin-1 receptor antagonist, is used for the prevention of inflammation in many autoinflammatory diseases. In the present study, possible effects of anakinra on inflammation and neurodegeneration in NDDs were examined. Besides, the HT22 cell line was utilized to examine the anti-inflammatory and/or anti-neurodegenerative effects of favipiravir, a RNA polymerase inhibitor. In addition to glutamate-induced cytotoxicity, cell viability was investigated.

Material and Methods

All steps of the study were completed in accordance with ethical principles. Ethical approval for the study was obtained from Sivas Cumhuriyet University Ethical Board of Non-Interventional Clinical Research (approval date: 20 Oct., 2021; approval number: 2021-10/39). The study was supported by Sivas Cumhuriyet University Scientific Research Projects Coordination Unit (the project number: T-984).

HT22 (SCC129) cell line was obtained from Merck ® cell collection and cultured in Dulbecco's modified eagle medium (DMEM) (Thermo Fisher Scientific, Altrincham, UK) containing 10% fetal bovine serum (FBS) (Sigma-Aldrich Co., St Louis, MO, USA), 1% penicillin/streptomycin (Sigma Aldrich Co., St Louis, MO, USA) and 1% L-glutamine. It was incubated under appropriate conditions (at 37 °C and atmosphere humidified with 5% CO2). The cells were passaged when they reached 80%-90% density. After passaging three times, the cells were seeded in a 96-well plate with a cell density of 1-104 in each well.

Anakinra, favipiravir and glutamate (Sigma-Aldrich Co., St Louis, MO, ABD) were dissolved in DMEM and stock solutions were formed before processing.

Cell groups were created to examine the effects of anakinra and favipiravir on glutamate-induced cytotoxicity. The control group did not receive any treatment. The cells of the glutamate-induced group were administered 10mM glutamate for 24 hours. The cells in the anakinra group were administered anakinra at various concentrations (1,10, 25, 50 and 100 µM) for 24 hours. The cells in the favipiravir group were administered favipiravir at various concentrations (1, 10, 25, 50 and 100 µM) for 24 hours. The cells in the anakinra + glutamate group were pretreated with anakinra at various concentrations (1, 10, 25, 50 and 100 µM) for one hour and then were administered 10mM glutamate for 24 hours. The cells in the favipiravir + glutamate group were pretreated with favipiravir at various concentrations for one hour and then administered 10 mM glutamate for 24 hours. After that, effective doses were determined and anakinra + favipiravir + glutamate combinations were administered.

Cell viability was evaluated by using the XTT test (Roche Diagnostic, MA, USA). Initially, HT22 cells were seeded in 96-well plates at the density of 1X104 cells in 100 µL DMEM per well and incubated for 24 hours. Glutamate-induced cytotoxicity was achieved as described before. Following 24-hours incubation, 96-well plate was removed and the wells were washed with phosphate-buffered saline. Then 100 µL DMEM without phenol red and 50 µL XTT were added to the wells and the plates were kept at 37 °C for 4 hours. Absorbance values were determined by using an ELISA microplate reader (Thermo Fisher Scientific, Altrincham, UK) at 450 nm. All the experiments were conducted three times and cell viability was expressed in percentages of live

cells and compared with that of the control group (untreated cells). Cell viability in the control group was considered as 100%.

All the measurements were performed three times. Statistical analyses of obtained data were made with Statistical Package Program for Social Sciences 23.0. Shapiro Wilk test was utilized to determine whether the data were evenly distributed. Mean and standard deviation were determined for descriptive statistics. One-way ANOVA was adopted to determine differences in the normally distributed data and Kruskal-Wallis and Mann-Whitney U test were utilized for the data without a normal distribution. Statistical significance was set at $p<0,05$.

Results

After glutamate-induced excitotoxicity in the hippocampal HT22 cell line, the effects of different concentrations of anakinra alone, favipiravir alone and the combinations of anakinra and favipiravir on cell viability were examined (Figure 1, Figure 2, Figure 3). Percentages of viable cells in the hippocampal HT22 cell line administered anakinra alone, favipiravir alone and the combination of anakinra and favipiravir were compared with those in the control cell line.

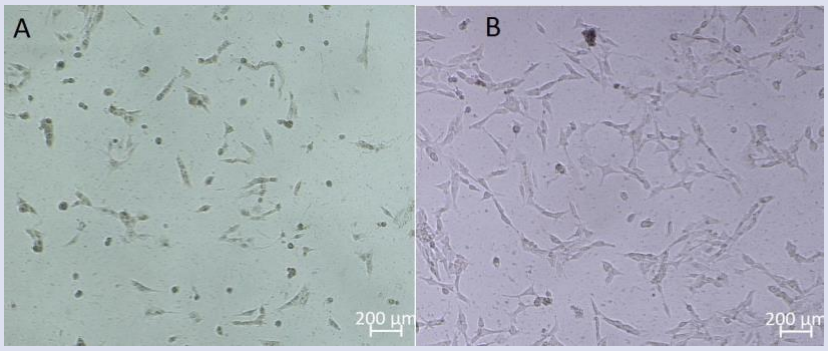

Figure 1. Microscopic Views of the Hippocampal HT22 Cell Line Morphology after Glutamate-Induced Excitotoxicity in Glutamate Group (A) and Control Group (B)

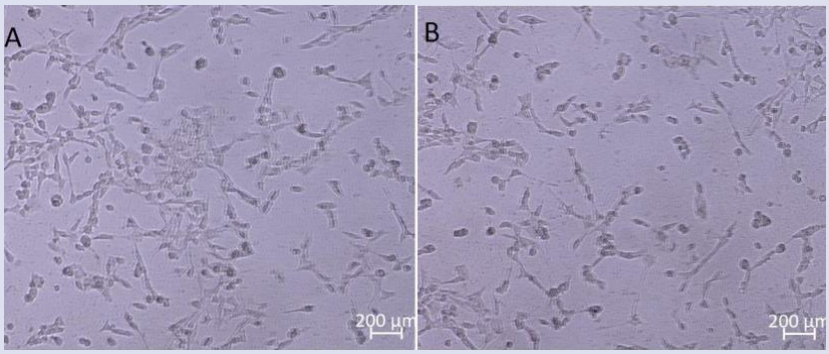

Figure 2. Microscopic Views of the Hippocampal HT22 Cell Line Morphology after Glutamate-Induced Excitotoxicity in Anakinra 100 µg-administered Group (A) and Favipiravir 100 µg-administered Group (B)

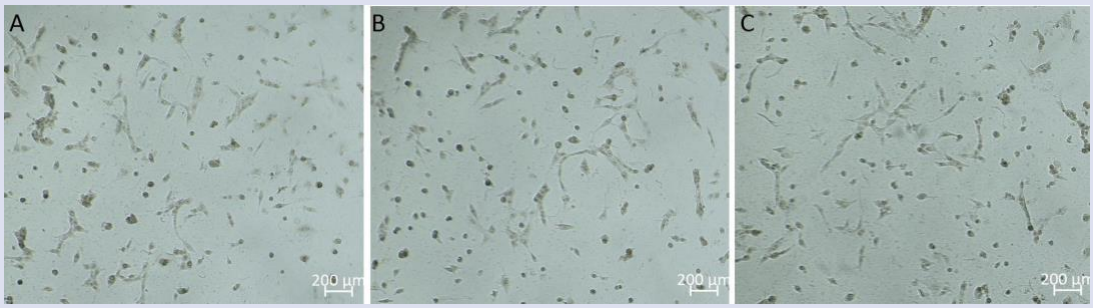

Figure 3. Microscopic Views of the Hippocampal HT22 Cell Line Morphology after Glutamate-Induced Excitotoxicity in Anakinra 100 µg and Glutamate-Administered Group (A), Favipiravir 100 µg and Glutamate-Administered Group (B) and Anakinra 100 µg, Glutamate and Favipiravir 100 µg-Administered Group (C)

When the effects of 100, 50, 25, 10 and 1 µM concentrations of anakinra on cell viability in the HT22 cell line after 10mM glutamate administration were evaluated, the cell viability was found to be significantly higher in the group administered anakinra 100 µM than in the other groups ($p < 0.01$ compared to glutamate). In other words, administration of different doses of anakinra alone did not have an effect on cell viability ($p< 0.01$ compared to the control group) (Figure 4).

Favipiravir at the doses of 100, 50, 25, 10 and 1 µM did not have an effect on cell viability after the administration of 10 mM glutamate to the HT22 cell line. In other words, different doses of favipiravir did not have an effect on cell viability ($p< 0.01$ compared to the control group) (Figure 5)

In the group administered a combination of anakinra, favipiravir and glutamate, anakinra 100 µM combined with favipiravir 100, 50, 25, 10 and 1 100 µM and glutamate 10 M was protective against glutamate toxicity, but the combination of anakinra and favipiravir did not change this effect (Figure 6).

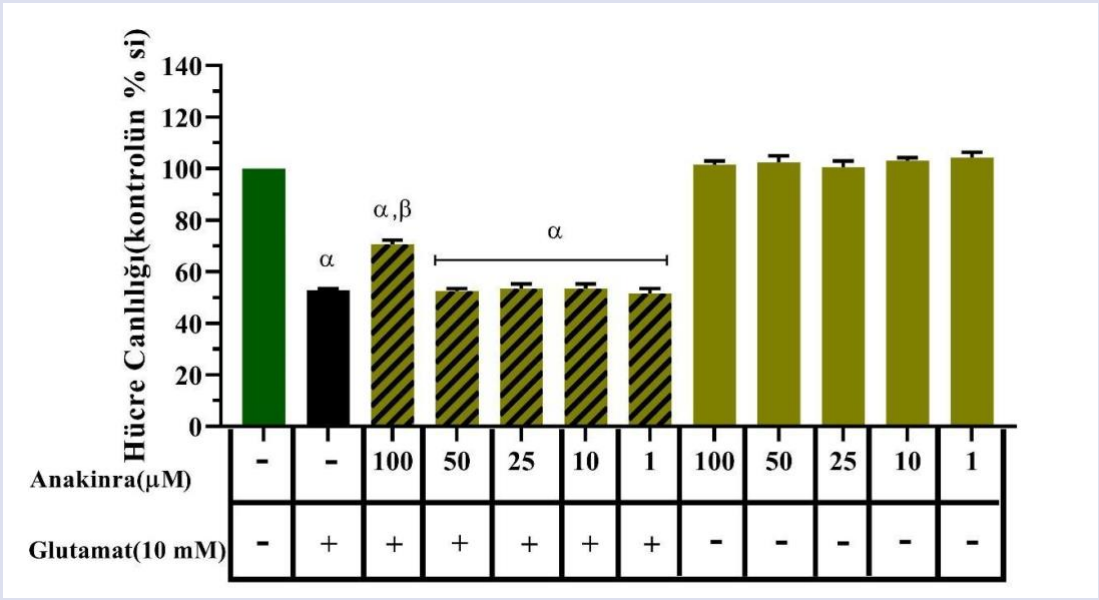

Figure 4. The Effect of Different Doses of Anakinra on Cell Viability in the HT22 Cell Line after Glutamate-Induced Excitotoxicity ($p < 0.01$ compared to glutamate) ($p< 0.01$ compared to the control group)

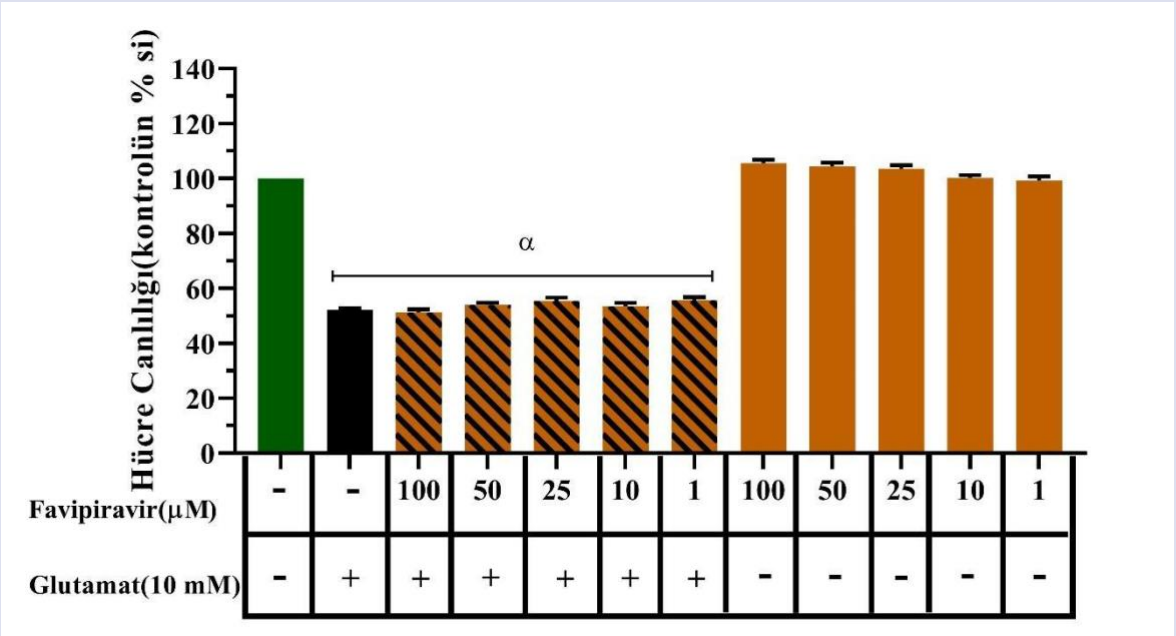

Figure 5. The Effect of Different Doses of Favipiravir on Cell Viability after Glutamate-Induced Excitotoxicity in the HT22 Cell Line ($p< 0.01$ compared to the control group)

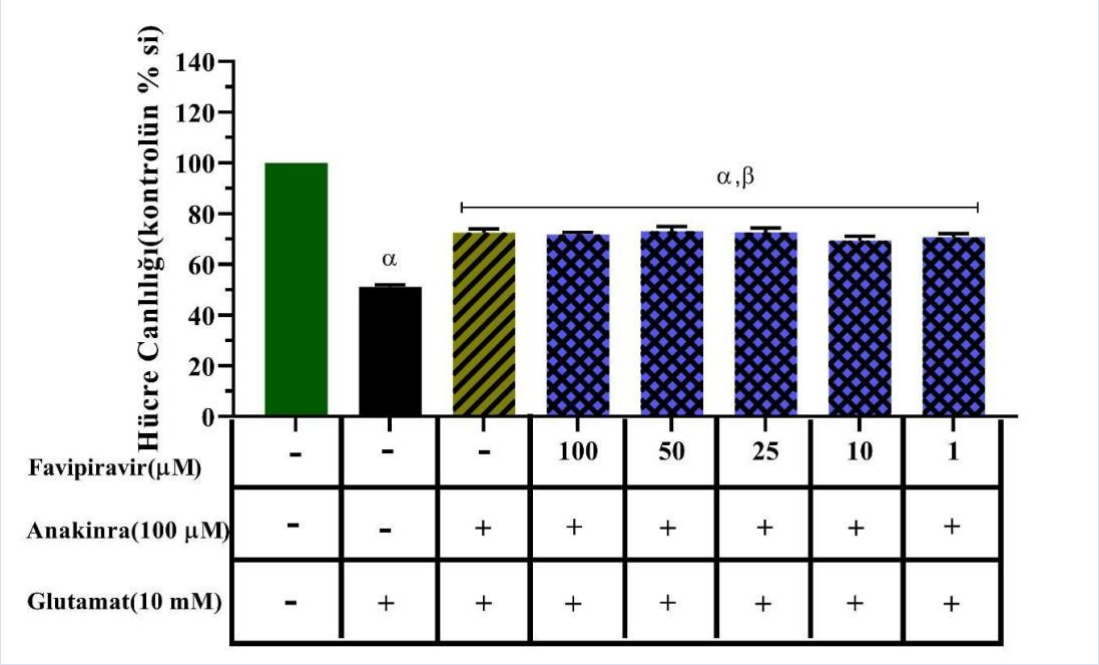

Figure 6. The Effect of the Combination of Anakinra and Favipiravir on Glutamate-Induced Excitotoxicity in the HT22 Cell Line

α; p< 0.01 compared to the control group
β; p< 0.01 compared to glutamate

Discussion

Hippocampal cells are sensitive to glutamate toxicity and suitable for in vitro neurodegeneration modelling. The present study aimed to examine the effects of anakinra and favipiravir individually and in combination at different concentrations on cell viability in glutamate-induced excitotoxicity in the hippocampal HT22 cell line.

High doses of favipiravir were used for the treatment of COVID-19 and anakinra, an anti-inflammatory drug approved by the Turkish Ministry of Health, is used to treat the patients developing respiratory failure when oxygen saturation decreases in cases of cytokine storms. Following COVID-19 infection, brain fog, which may also include many cognitive dysfunctions like forgetfulness, decreased attention and recalling and memory problems, appears. It is not known whether brain fog results from an inflammation involving glial cells, microglia and astrocytes affected by a cytokine storm and neurodegeneration accompanied by inflammation or neurodegeneration related to toxicity caused by high doses of drugs used individually or in combination. To our knowledge, none of the prior studies have focused on this issue.

NDDs include a group of diseases encountered and diagnosed at an increasing frequency today. Among the primary NDDs are AD, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease.[12,13] Frontotemporal dementia and spinocerebellar ataxias have also been considered as NDDs in some reports.[14] While some of these diseases can be characterized by memory and cognition disorders, others can present as difficulties in moving, speaking and breathing.[14] In vivo studies performed to understand cellular and molecular etiopathogenesis of these diseases can cause financial problems and waste of time and require trained workforce and sophisticated laboratory equipment. Therefore, in vitro studies on NDDs have become more important.

Experimental studies on NDDs have used rats, fruit flies, nematode worms and yeast cultures.[14] Besides, there have been studies using pluripotent stem cells recently.[14] Several studies have shown that protein aggregates are transmitted from neuron to neuron and have a role in the pathogenesis of NDDs. Moreover, recent studies have revealed that excessive activation of microglia and release of reactive oxygen radicals in addition to environmental toxins and endogenous proteins play a role in the development of NDDs.[15,16]

Several animal studies have attempted to showcase functional, neurochemical and anatomic differences between NDDs by employing positron emission tomography (PET) and magnetic resonance imaging.[17] Furthermore, various rat models have been utilized to perform preclinic imaging and examine neurovascular components by means of PET and single-photon emission computed tomography (SPECT).[18] However, these examinations are costly and impose additional temporal and environmental burdens such as laboratories. There are less costly and more molecular studies to replace them. For instance, a study by Woerman has shown transmission of florescent-labelled α-synuclein fibrils from one neuron to another in a primary rat cell culture.[19]

TREM2 variants, which play a role in the pathogenesis of NDDs, have also been studied. TREM2 receptors are expressed on various immune cells.[20] The effect of

interleukin-1 (IL-1), a proinflammatory cytokine, was investigated in a rat AD model.[21] It was suggested that increased hippocampal IL-1 levels can have a relation with memory problems in AD.[21]

In the current study, the effect of different doses of anakinra on cell viability in glutamate-induced excitotoxicity in the HT22 hippocampal cells was examined. The cell viability was higher in the group administered anakinra 100 µM than in the groups administered lower doses of anakinra ($p< 0.01$, compared to glutamate). Administration of anakinra at lower doses did not have an effect on cell viability.

Anakinra, an interleukin-1 antagonist, is used to treat many inflammatory diseases now.[22] It is important to suppress both apoptosis, natural part of aging and not recognized in daily life, and the inflammation developing in neuronal cells for various reasons.

Cliteur et al. utilized recombinant human IL-1ra (anakinra) to prevent microglial activation, inflammation and brain damage in patients with spontaneous intracerebral hemorrhage during the second phase of their randomized clinical study.[23] They divided the patients into three groups: the first group received a high dose of anakinra (500mg/day), the second group received a low dose of anakinra (100mg/day) and the third group received standard treatment. They found that the high dose of anakinra could cross the blood-brain barrier and could be useful in prevention of secondary neuroinflammation.[23] Consistent with their findings, the present study showed that high doses of anakinra protected HT22 hippocampal cell viability better. Anakinra was also employed for the treatment of cytokine storms that developed in COVID-19 infection.[24] It is known that anakinra is effective in inflammatory conditions presenting as intracellular caspase activation and the development of inflammasome complex.[25]

It was proposed that abnormal microRNA (miRNA) levels can be related to the pathogenesis of many NDDs (26). Especially miR-9-5p, miR-21-5p, miR-29, miR-132-3p, miR-124-3p, miR-146a-5p, miR-155-5p, and miR-223-3p were associated with the disease pathogenesis.[26] Also, genetic mutations in the progranulin gene played a role in the loss of functions in familial frontotemporal dementia.[27]

Proinflammatory mechanisms have been reported to be involved even in the early stages of AD.[28] Especially the role of cytokines like TNF-α and IL-1β has been underscored. Effects of these cytokines on synaptic plasticity have been shown in rat AD amyloidosis models.[28] Mcc950, anakinra -an IL-1 receptor antagonist- and etanercept -an anti-TNF-α agent- were utilized as an NLRP3 inflammasome inhibitor.[28] It has been reported that IL-1 blockage through anakinra could be effective in prevention of amyloidosis by inhibiting extracellular transthyretin accumulation and apoptosis in neurodegenerative diseases, especially AD.[25]

It is stated in the literature that accumulation of transthyretin and amyloid fibrils plays a role in the pathogenesis of familial amyloidotic polyneuropathy (FAP).[29] IL-1 blockage with anakinra has been shown to prevent transthyretin accumulation and toxicity in an experimental FAP model -V30M FAP rat model.[29] Several studies have also focused on the genetic regulation of macroautophagy in NDD models.[30,31] In some animal models of NDD, creatinine has been shown to be neuroprotective.[32] In vitro microfluidic models have been considered important to gain insight into the pathogenesis of NDDs.[33]

Favipiravir was used particularly for the antiviral treatment of SARS-CoV-2 infection.[34] Favipiravir, a nucleoside analogue originating from prasine carboxamide, inhibits viral polymerase.[34] However, further in vitro and in vivo studies are needed to elucidate the effects of anakinra and favipiravir on neuroinflammation and neurodegeneration.

Conclusion

None of the doses of favipiravir utilized in the present study had an effect on cell viability in the HT22 cell line following glutamate administration. Regarding the effect of all the doses of anakinra utilized in this study, anakinra 100 µM was more effective in cell viability in the HT22 cell line after glutamate administration than other doses of anakinra ($\beta < 0.01$ compared to glutamate). In other words, only administration of anakinra at different doses (1 µM, 10 µM, 25 µM and 50 µM) had no effect on cell viability. However, anakinra 100 µM was observed to prevent cytotoxicity produced by glutamate in the HT22 cell line. It was protective against neurodegeneration. In the group administered the combination of anakinra, favipiravir and glutamate, at the doses of anakinra 100 µM and favipiravir 100 µM, 50 µM, 25 µM, 10 µM and 1 µM and glutamate 10 mM, anakinra was protective against glutamate toxicity, but the combination of anakinra and favipiravir did not alter this effect. In conclusion, high doses of anakinra were observed to be protective against excitotoxicity induced by glutamate in the HT22 cell line.

Conflicts of interest

There are no conflicts of interest in this work.

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Authors' contributions

MS: concept, design, supervision, resources, materials, data collection, analyses, literature review, reporting. AKF: analyses, literature review, reporting, critical examination, other.

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Right Ventricular Myxoma Complicated by Stroke

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Case Report

History

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ABSTRACT

Cardiac myxoma is the most commonly diagnosed benign cardiac tumor. It is usually located in the left atrium and typically arises from the foramen ovale in approximately 75% of the cases, in the right atrium in 23%, and in the ventricles in only 2%. Symptoms depend on its size, mobility, and location. Neurological complications are seen in 20% to 25% of patients. Herein we present a case of right ventricular myxoma with patent foramen ovale which was complicated by stroke. The mass was surgically excised and patent foramen ovale was closed.

Keywords: Cardiac surgery, echocardiography, imaging, myxoma, stroke, valve disease

İnme ile Komplike Olan Sağ Ventrikül Miksoması

Olgu Sunumu

Süreç

Geliş: 02/05/2023
Kabul: 02/04/2024

ÖZET

Kardiyak miksoma kalbin en sık tanı alan iyi huylu tümörüdür. Genellikle sol atrium içinde saptanır ve olguların %75' inde tipik olarak fossa ovalisten, %23' ünde sağ atriumdan ve sadece %2' sinde ventriküllerden köken alır. Belirtiler miksomanın boyutu, hareketlilik derecesi ve yerleştiği yere bağlıdır. Nörolojik komplikasyonlar hastaların %20-25' inde gözlenir. Bu yazıda sağ ventrikül miksomaya eşlik eden patent foramen ovale saptanan ve inme ile komplike olan bir olgu sunuyoruz. Tedavide kardiyak kitle cerrahi olarak çıkarıldı ve patent foramen ovale kapatıldı.

Anahtar Kelimeler: Kalp cerrahisi, ekokardiyografi, görüntüleme, miksoma, inme, kapak hastalığı

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Introduction

Cardiac myxoma is the most commonly diagnosed benign cardiac tumor. Myxomas are usually located in the left atrium, and they typically arise from the foramen ovale in approximately 75% of the cases, in the right atrium in 23%, and in the ventricles in only 2%. Related symptoms depend on their size, mobility, and location. Neurological complications related with cardiac myxomas are seen in approximately 20% -25% of patients.[1] Herein we present a case of right ventricular myxoma with patent foramen ovale which was complicated by stroke.

Case Report

A sixty-year-old female patient presented to the outpatient clinic with exertional dyspnea and cough. Her previous medical history had no positive features. Upon physical examination, a systolic murmur was heard in the left upper parasternal border. Twelve-lead ECG revealed sinus rhythm with right axis deviation, tall R wave in V1, anterior ST segment depression and T wave negativity (Figure 1). Blood biochemistry and hemogram were normal. High-sensitivity C-reactive protein was 45.4 mg/L (N: 0-5 mg/L) and erythrocyte sedimentation rate was 25 mm/h (N: 0-30 mm/h). Transthoracic echocardiography revealed a 4.6 x 5.5 cm mass attached to the right ventricular outflow tract which protruded through the pulmonic valve during systole (Figure 2). The mass caused obstruction and CW-Doppler revealed approximately 36 mmHg systolic gradient in the right ventricular outflow tract and pulmonary artery (Figure 3). Left ventricular systolic functions were normal. There was moderate tricuspid regurgitation. In the subcostal view, a small patent foramen ovale (PFO) was detected with color Doppler (Figure 4). Transesophageal echocardiography and cardiac computerized tomography also revealed a large right ventricular mass, protruding into main pulmonary artery (Figure 5,6). There was no embolic material in pulmonary artery branches. The patient was discussed in the cardiology-cardiovascular surgery council and surgery was planned. However, the patient developed amnesia and slurred speech while waiting for the surgery day. Diffusion cranial magnetic resonance revealed a 1-1.5 cm acute ischemic lesion in the left frontotemporal area. 24-hour Holter monitoring showed no atrial fibrillation. Lower extremity venous Doppler and carotid and vertebral ultrasound were normal. Antiplatelet therapy was initiated. A preoperative coronary angiogram revealed coronary artery plaques. After the acute phase of the cerebral infarct, the cardiac mass was surgically resected and PFO was closed. The surgically excised mass was 4.5 x 5.8 cm in diameter. The macroscopic specimen of the mass demonstrated a jelly like mass including hemorrhagic areas. The microscopic examination revealed stellate cells which were spreaded in a loose myxoid stroma. There was no sign of pleomorphism, mitosis or other features suggestive of malignancy. The patient was diagnosed as right ventricular myxoma. The postoperative period was uneventful. A control echocardiogram was performed two months later, which was completely normal (Figure 7). She had no neurologic sequelae. We planned to follow the patient with annual echocardiograms as long as she has no complaints.

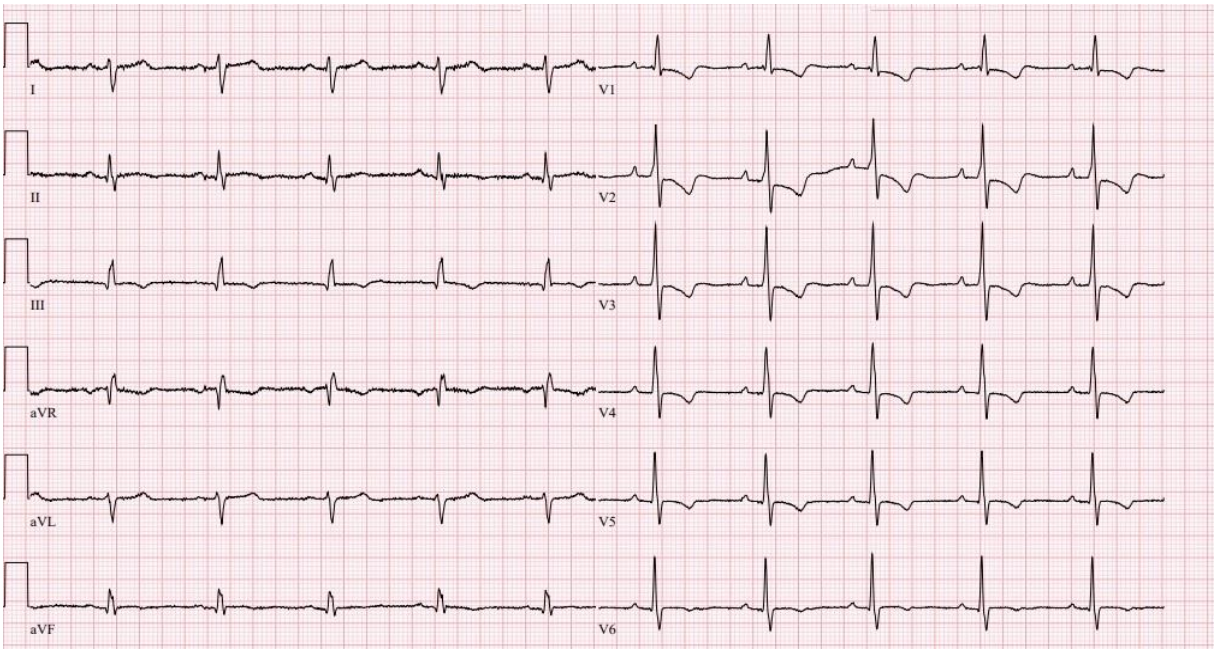

Figure 1: Twelve-lead electrocardiogram reveals sinus rhythm with right axis deviation, tall R wave in V1, anterior ST segment depression and T wave negativity.

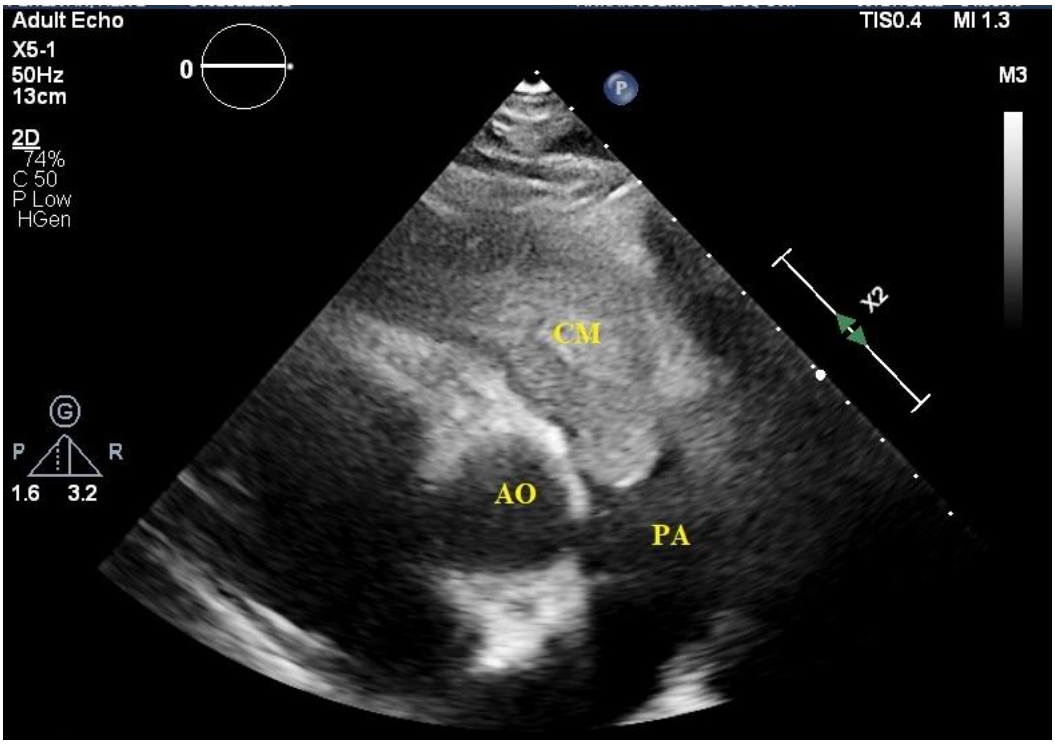

Figure 2: Transthoracic echocardiography revealing right ventricular mass protruding through the pulmonic valve during systole. Parasternal short axis view. CM: Cardiac myxoma, AO: Aortic valve, PA: Pulmonary artery.

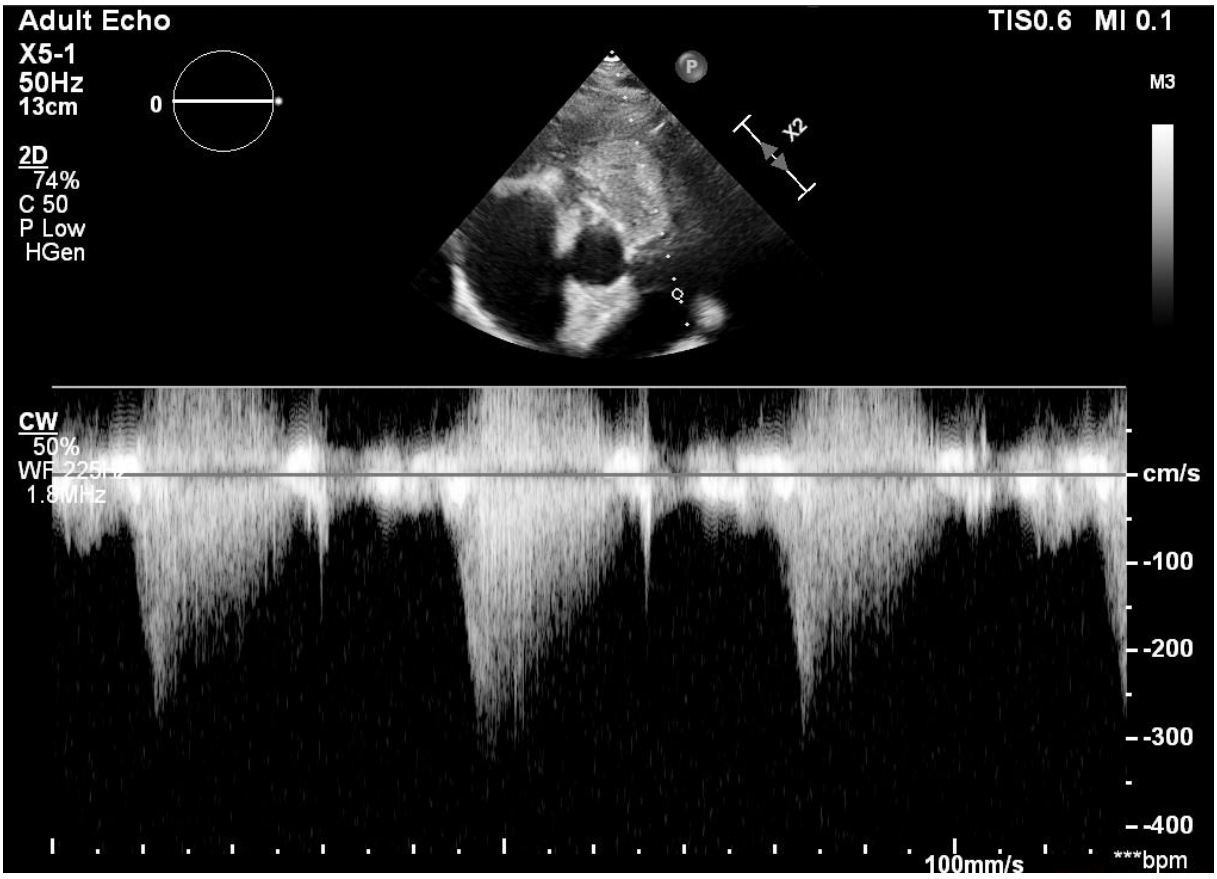

Figure 3: CW-Doppler revealing approximately 36 mmHg systolic gradient in right ventricular outflow tract and pulmonary artery. Parasternal short axis view.

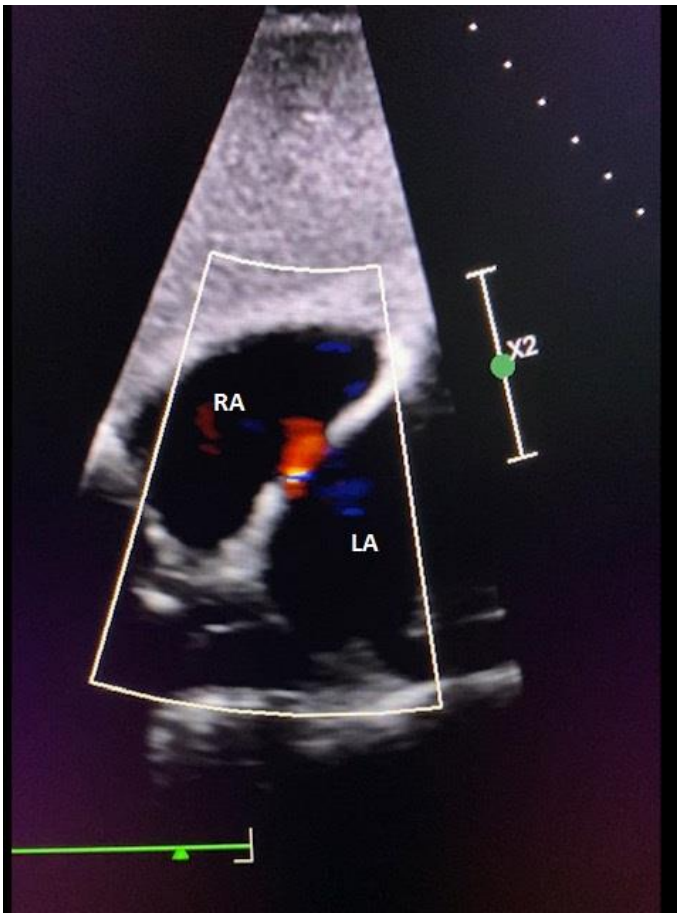

Figure 4: Transthoracic echocardiography revealing patent foramen ovale. Subcostal view. RA: Right atrium, LA: Left atrium.

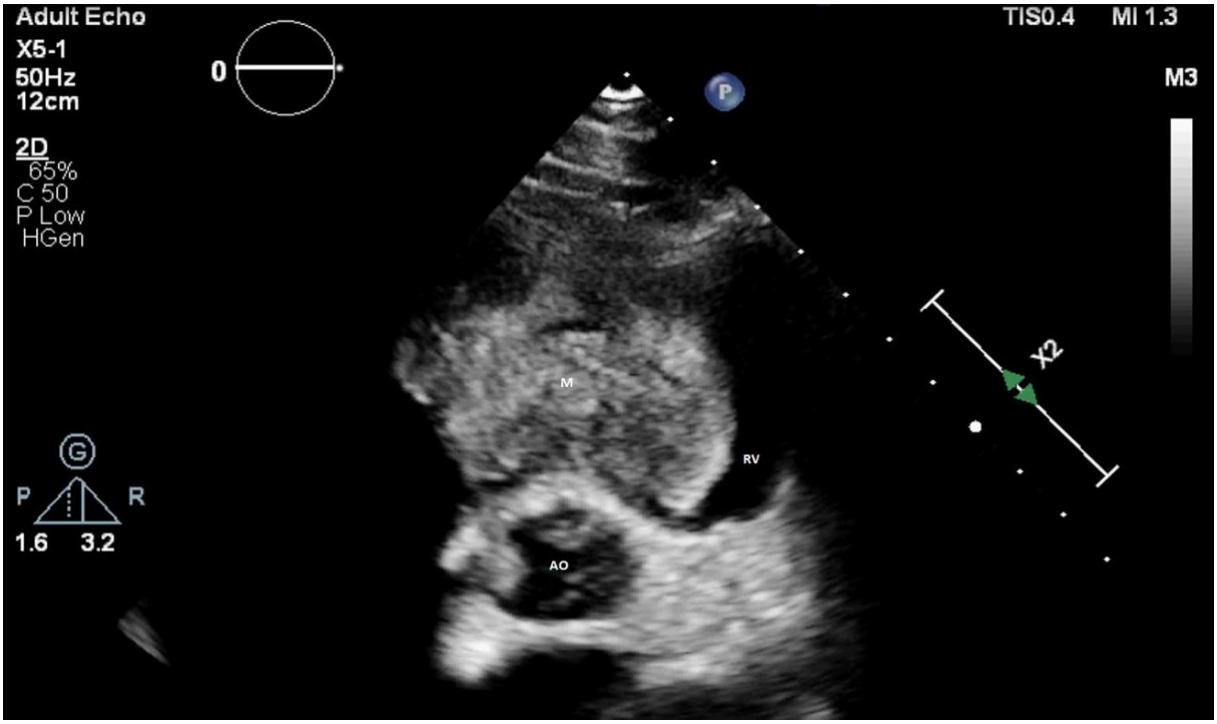

Figure 5: Transesophageal echocardiographic image of the mass. AO: Aortic valve, RV: Right ventricle, M: Myxoma

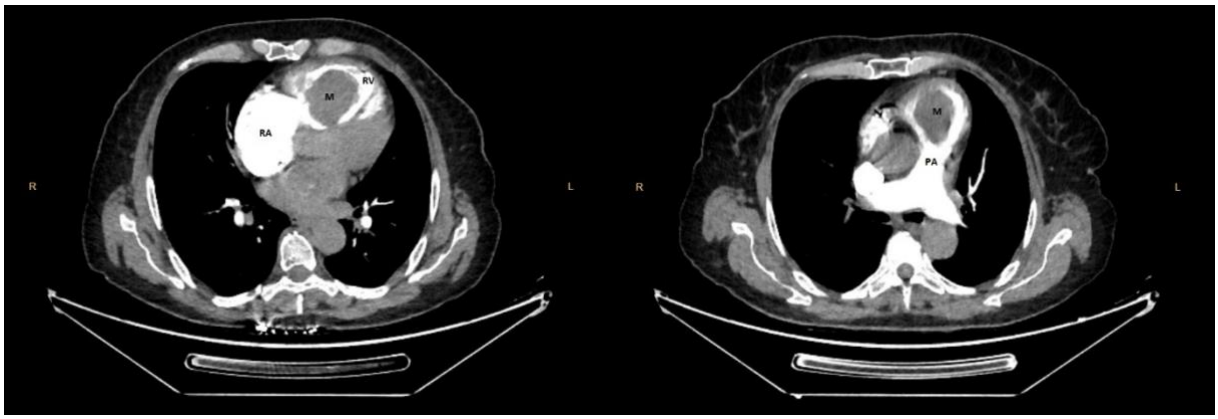

Figure 6: Cardiac computerized tomography also revealed the right ventricular mass, protruding into main pulmonary artery. PA: Pulmonary artery, RA: Right atrium, RV: Right ventricle, M: Myxoma.

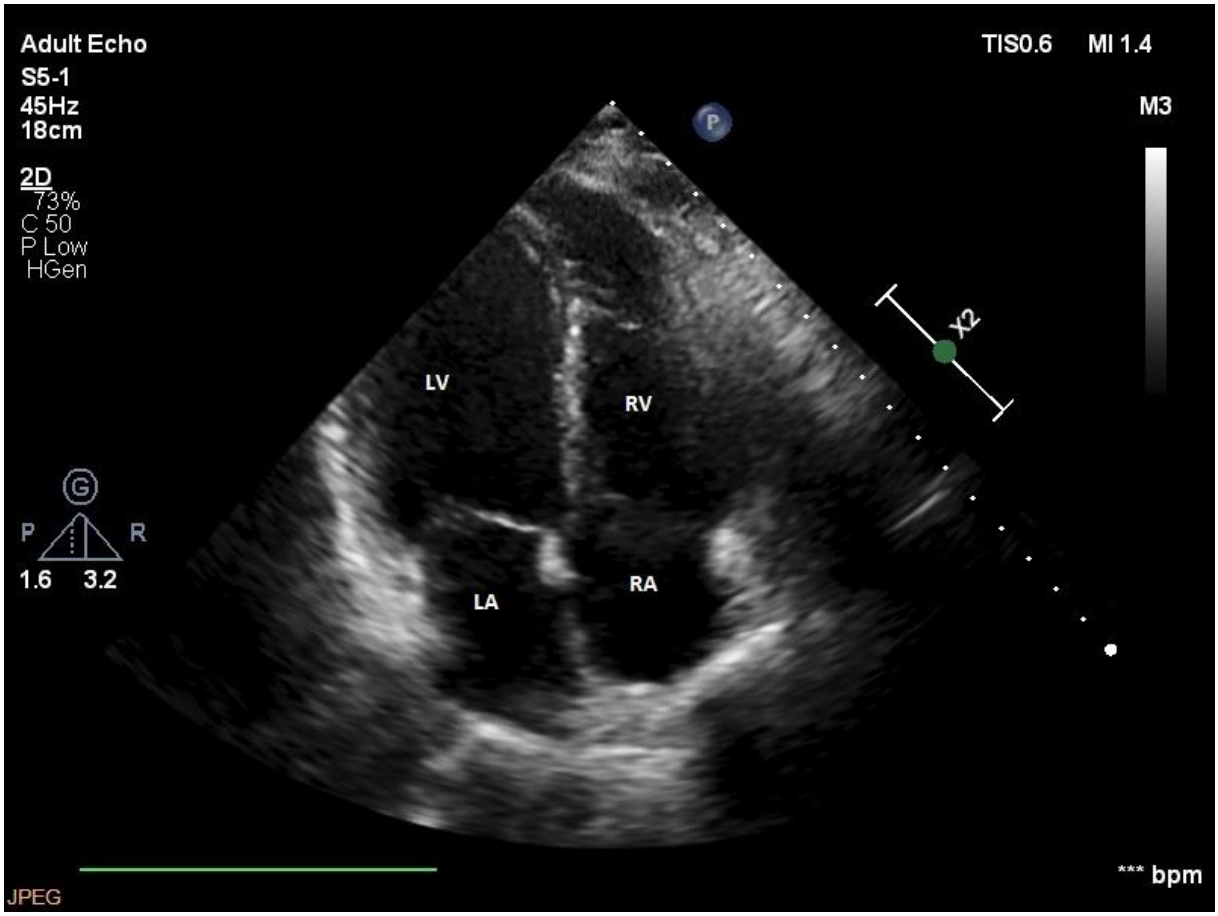

Figure 7: A control transthoracic echocardiogram was completely normal. Subcostal view. AV: Aortic valve, PA: Pulmonary artery, RA: Right atrium, RV: Right ventricle.

Discussion

We presented a case of right ventricular myxoma with patent foramen ovale complicated by stroke. The tumor was successfully resected. The clinical manifestations of ventricular myxomas can be classified as obstructive, embolic and constitutional. Clinic presentation of left-sided tumors are earlier than right-sided tumors with more severe shortness of breath.[2] Constitutional symptoms are fever, arthralgias, weight loss and Raynaud phenomenon, which may be attributed to overproduction of interleukin-6. The obstructive and embolic symptoms are different between left-sided and right-sided cardiac myxomas. For example, in patients with left-sided myxomas, obstruction may lead to pulmonary congestion, therefore dyspnea and syncope are the main complaints.

On the other hand, in patients with right-sided myxomas, peripheral edema, ascites, or superior vena cava syndrome are more common. Left-sided myxomas may cause peripheral embolism such as stroke, while right-sided myxomas can cause pulmonary embolism.[3] In a study Stefanou et al. screened 52 patients with left-sided cardiac myxoma and 13 had transient ischemic attack, ischemic stroke or retinal ischemia. Tumor friability, not the size, was associated with increased embolic risk. The embolic material can be detached tumor tissue, thrombotic material overlying the tumor, or a combination of both.[4] Our patient had elevated right heart pressures together with a PFO, and stroke probably developed due to paradoxical embolism. Patent foramen ovale, a tunnel-like structure between right and left atrium, is a common finding in general population. A right-to-left shunt and paradoxical embolism may occur when right atrial pressure increases, leading to the transit of embolic material into the systemic circulation. Our case is very rare that a right-sided myxoma caused systemic embolism through a PFO. A similar case report was written by Rao et al.[5] They presented a 62-year-old lady who experienced two episodes of acute stroke two weeks apart and she was found to have a large right ventricular myxoma and PFO. Molnar et al reported an ischemic stroke case with giant right atrial myxoma associated with PFO.[6] In another case report, a tricuspid myxoma caused paradoxical embolism through a PFO.[7] The first-line and gold standard noninvasive diagnostic modalities for cardiac myxoma are transthoracic echocardiogram and transesophageal echocardiogram. An echocardiogram enables us to evaluate preoperative localization, size, shape, mobility of the tumor as well as its hemodynamic consequences. Transesophageal echocardiography accurately detects atypical localization of myxomas. Cardiac-gated computed tomography and magnetic resonance scans provide supplementary data about the structure and function of cardiac tumors prior to surgical resection. Multimodality imaging is recommended in the diagnostic work-up.[8] The differential diagnosis for cardiac myxomas includes cardiac thrombi, fibromas, lipomas and nonmyxomatous neoplasms, the latter being malignant. About 20–25% of primary cardiac tumours are known to be malignant, the vast majority of them being sarcomas (95%), the remainder being lymphomas (5%). These malignant tumors are usually located intramyocardial and they are not pedunculated as most of the myxomas.[9]

The treatment of myxoma is surgical resection. The surgical mortality is reported as less than 5%, while the mortality rate of ventricular myxomas is slightly higher than that of atrial myxomas.[10] Once the diagnosis is made, the surgery should not be unnecessarily delayed. While awaiting to cardiac surgery, more than 8% of patients died of embolic, obstructive or other complications.[3] Our patient also had embolic stroke while awaiting to surgery, which further delayed the treatment. The need for antiaggregants and anticoagulants also complicate the perioperative period. There is no evidence for optimal time interval between cardiac myxoma related cerebrovascular event and cardiac surgery, but prolonged interval is associated with embolic recurrence.[4] Tumor recurrence may happen months or years after surgery, and its rate is approximately 5%. Recurrences usually occur in the first 4 years after surgical excision. The risk factors which are related to recurrence after surgery are; young age, family history of myxoma, inadequate surgical resection, intraoperative tumor implantation or multicentre growth.[10] There is also frequent recurrence of tumors associated with Carney complex.[11,12] Long-term follow-up with transthoracic echocardiography is recommended in all patients after tumor resection.[1]

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Unusual Clinical Presentation of Sarcoidosis with Thrombocytopenia, Bone Marrow Involvement, and Myocardial Infiltration: A Case Report

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Case Report

History

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ABSTRACT

This case study describes a 67-year-old female patient who presented with shortness of breath and quick exhaustion. In 2018, initial symptoms led to a diagnostic thoracic CT scan, which confirmed sarcoidosis using endobronchial ultrasound (EBUS). Despite the diagnosis, the patient did not receive treatment. A 2023 bone marrow biopsy revealed that the disease had progressed to include heart failure and thrombocytopenia. Transthoracic echocardiography (TTE) was used for cardiological examination, which revealed impaired left ventricular wall motion. Magnetic resonance imaging (MRI) revealed severe cardiac involvement by detecting full-thickness late gadolinium enhancement (LGE) in the left ventricle. This case report emphasizes the complexity and diversity of sarcoidosis symptoms, supporting a multidisciplinary approach for correct diagnosis and individual treatment approach.

Keywords: Sarcoidosis, Thrombocytopenia, Myocardial Infiltration, Bone Marrow Involvement

Sarkoidozun Trombositopeni, Kemik İliği Tutulumu ve Miyokard İnfiltrasyonuyla Birlikte Olağandışı Klinik Görünümü: Olgu Sunumu

Olgu Sunumu

Süreç

Geliş: 21/12/2023
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ÖZET

Bu vaka çalışmasında nefes darlığı ve çabuk yorulma şikayetleriyle başvuran 67 yaşında bir kadın hasta anlatılmaktadır. İlk semptomlar 2018 yılında, endobronşiyal ultrason (EBUS) kullanılarak sarkoidozu doğrulayan tanısal bir toraks BT taramasına yol açtı. Teşhise rağmen hasta tedavi görmemiştir. 2023 yılında yapılan kemik iliği biyopsisi, hastalığın kalp yetmezliği ve trombositopeniyi içerecek şekilde ilerlediğini ortaya koymuştur. Kardiyolojik inceleme için transtorasik ekokardiyografi (TTE) kullanıldı ve sol ventrikül duvar hareket bozukluğu tespit edildi. Manyetik rezonans görüntüleme (MRG), sol ventrikülde tam kat geç gadolinyum tutulumu (LGE) tespit ederek ciddi kardiyak etkilenmeyi ortaya koydu. Bu olgu sunumu sarkoidoz semptomlarının karmaşıklığını ve çeşitliliğini vurgulamakta, doğru tanı ve bireysel tedavi yaklaşımı için multidisipliner bir yaklaşımı desteklemektedir.

Anahtar Kelimeler: Sarkoidoz, Trombositopeni, Miyokardiyal İnfiltrasyon, Kemik İliği Tutulumu

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Introduction

Sarcoidosis is a systemic lung disease characterized by the formation of noncaseating granulomas, and its origin remains unknown. Despite the absence of a definitive cause, sarcoidosis is thought to arise from a genetically predisposed abnormal immune response to an unidentified antigen. While many studies suggest an equal female-to-male ratio, it is notable that more males than females receive a diagnosis between the ages of 20 and 45. However, the incidence of sarcoidosis tends to peak in females at a later age, typically between 50 and 65 years old.[1] The disease manifests as a multisystem inflammatory disorder, with the lungs and thoracic lymph nodes being the most commonly affected organs.[2] This disorder primarily impacts the lungs, but it can affect any organ.[3] Approximately 5% of individuals with sarcoidosis exhibit clinical indications of myocardial involvement.[4] Bernstein recorded the first case of cardiac involvement in sarcoidosis in 1929, concerning a 52-year-old tailor who died of heart failure.[5] Renal and bone marrow involvements are infrequent occurrences in individuals with sarcoidosis.[6]

The diagnosis is based on three criteria: a consistent clinical and radiological presentation, pathological confirmation of noncaseating granulomas, and the elimination of other disorders with comparable features, such as infections or malignancies.[7] Corticosteroids, such as prednisone, are commonly used in clinical practice to minimize inflammation.[8] When corticosteroids prove inadequate or are poorly tolerated, alternative immunosuppressive medications, including methotrexate, may be explored.[8] In cases resistant to conventional therapies or marked by intolerance, biological agents such as tumour necrosis factor (TNF) inhibitors, emerge as potential therapeutic options. TNF inhibitors have undergone evaluation; nonetheless, findings from controlled trials have shown marginal benefits, with studies reporting no discernible advantage.[9]

Case Report

A 67-year-old female patient with shortness of breath, rapid fatigue, and a history of gonarthrosis presented with atypical clinical characteristics of sarcoidosis. Shortness of breath and erythema nodosum were the first symptoms in 2018, prompting a thoracic CT scan, which revealed mediastinal lymphadenopathy and interstitial lung disease. Pathological findings validated the diagnosis of sarcoidosis based on endobronchial ultrasound (EBUS). Regardless of the diagnosis, the patient went untreated.

Since 2022, the patient experienced heart failure without a documented history of myocardial infarction. Concurrently, thrombocytopenia was first detected in December 2021 (platelet count: 40,000). Upon admission, the platelet count had dropped to 18,000, leading to hospitalization. An external centre conducted a bone marrow biopsy in 2023. The pathology results revealed normo/hypercellular bone marrow (25%-55% cellularity), erythroid hyperplasia with normoblastic maturation, myeloid hyperplasia with uninterrupted maturation, increased megakaryopoiesis, and two small non-necrotizing granulomas within the intramedullary and paracortical connective tissue, confirming sarcoidosis.

Despite the patient's thrombocytopenia, the cardiology department decided against angiography and instead performed a transthoracic echocardiography (TTE) to determine the cause of the patient's recurrent shortness of breath. The TTE results identified impaired left ventricular wall motion, with an ejection fraction (EF) of 40-45% and segmental wall motion abnormalities. Magnetic resonance imaging (MRI) revealed full-thickness late gadolinium enhancement (LGE) in the basal inferior-inferolateral wall of the left ventricle, along with a suspicious mid-wall LGE area in the basal inferoseptum. (Figure 1.) Although artefact-related considerations were acknowledged, these findings suggested significant cardiac involvement of sarcoidosis. The steroid treatment was initiated at a milligram per kilogram basis. Steroid therapy improved the platelet (PLT) count to over 100,000. The patient is currently being monitored under steroid therapy.

Dicusssion

Our case report emphasizes the complexities of sarcoidosis, as well as the difficulties involved with its identification and management. The unknown origin of sarcoidosis complicates its clinical course, emphasizing the importance of investigation of the various symptoms and the treatment approaches. In this case, the patient's presentation included shortness of breath and rapid exhaustion, which led to a diagnosis of sarcoidosis. Despite a clear diagnosis confirmed by EBUS and pathological findings, the patient went untreated, allowing the progression of the condition. The later development of heart failure and thrombocytopenia brought challenges, requiring a comprehensive approach to patient treatment. The decision not to perform angiography in favour of TTE and cardiac MRI emphasizes the significance of individual approach to different patient presentations. The Silesian voivodeship sarcoidosis epidemiology study found a growing incidence of the condition among younger men (25-50 years) and some older women (50-64 years). The study's observed tendency of increased occurrence in the age group of 50-64 years corresponds with the age range of our patient, implying that individuals who are older than the upper limit of the previously identified range may still be susceptible to sarcoidosis.[10] Based on the 1999 WASOG criteria and the 2014 WASOG organ assessment instrument, a study of 175 sarcoidosis patients at the Hospital Clinic of Barcelona, Spain, from 1990 to 2014, revealed useful insights into the disease's age-related clinical symptoms. Patients identified before the age of 40 had a higher prevalence of musculoskeletal symptoms and neurological involvement, but a lower prevalence of renal and splenic involvement. Those who developed the disease beyond the age of 65, on the other hand, had a decreased prevalence of cutaneous/musculoskeletal symptoms and little or no neurological involvement.[11] This study emphasises the

dynamic nature of sarcoidosis and accentuates the value of early detection and close monitoring, particularly in cases where there is a severe organ involvement. Corticosteroids have already been assessed and documented in the literature for the treatment of cardiac sarcoidosis. The purpose of the trial was to determine whether weekly methotrexate plus low-dose corticosteroids might effectively treat cardiac sarcoidosis. In a small cohort of seventeen individuals, they compared this combination to corticosteroids alone during three to five years. The combined medication was a potentially well-tolerated long-term treatment for cardiac sarcoidosis, as it dramatically stabilised ejection fraction, cardiothoracic ratio, and NT-proBNP levels without eliciting major adverse effects.[12]

Conclusion

Due to systemic involvement of sarcoidosis in patients, there is the potential for affecting every organ. We demonstrated the bone marrow involvement in a patient with thrombocytopenia, and we have found cardiac involvement in the same patient. Therefore, it is necessary to screen patients with sarcoidosis systematically.

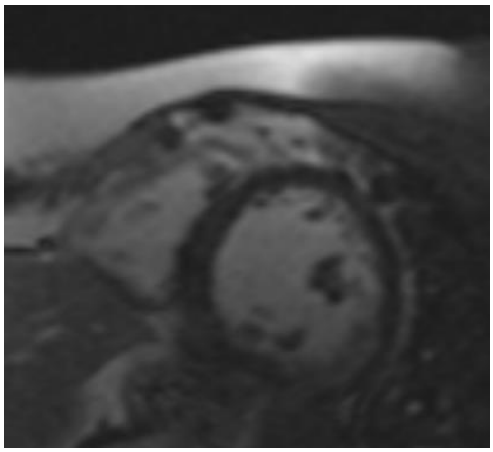

Figure 1. Full-Thickness Late Gadolinium Enhancement in Basal Inferior-Inferolateral Wall and Suspicious Mid-Wall LGE in Basal Inferoseptum of Left Ventricle

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Treatment Complexity in a Twin Adolescent Pair with Selective Mutism: A Case Report

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Case Report

History

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ABSTRACT

Selective Mutism (SM) is a disorder characterized by the individual's persistent inability to speak in specific social situations (e.g., school) where speech is expected, even though the individual is able to speak in other situations. It is a rare anxiety disorder and is often seen in children between the ages of 4-8. The presence of SM in family members is important in terms of both etiology and clinical course. While family burden is a factor that increases the incidence of SM, according to some research results, the clinical symptoms of twin cases diagnosed with SM are more severe than those of non-twins. A positive family history negatively affects the prognosis of SM and increases resistance to treatment. In this article, the diagnosis and treatment process of 14-year-old monozygotic twin adolescents who have been followed up with the diagnosis of SM for a long time will be discussed. The main treatment methods for SM are medication and psychotherapy. It is known that psychotherapeutic interventions in particular vary depending on individual differences. The most important purpose of this article is to draw attention to the differences in treatment interventions of twin SM cases and to evaluate the clinical features of the cases in the light of the literature.

Keywords: Selective mutism, monozygotic twin, adolescent

Selektif Mutizmli Ergen İkiz Çiftte Tedavi Karmaşıklığı: Bir Olgu Sunumu

Olgu Sunumu

Süreç

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ÖZET

Selektif mutizm (SM), bireyin başka durumlarda konuşuyor olmasına karşın, konuşmasının beklendiği özgül toplumsal durumlar (örn. okul), sürekli bir biçimde, konuşamıyor olması ile karakterize bir bozukluktur. Nadir görülen bir anksiyete bozukluğu olup sıklıkla çocuklarda 4-8 yaş aralığında görülmektedir. Aile bireylerinde SM varlığı hem etiyoloji hem de klinik gidişat açısından önemlidir. Aile yüklülüğü SM'nin görülme sıklığını artıran bir faktör iken bazı araştırma sonuçlarına göre, SM tanısı olan ikiz olguların klinik semptomları ikiz olmayanlara göre daha şiddetlidir. Aile öyküsünün pozitif olması SM'de klinik gidişatı olumsuz etkilemekte, tedaviye direnci artırmaktadır. Bu yazıda, 14 yaşlarında, uzun süredir SM tanısı ile takip edilen monozigot ikiz ergenlerin tanı ve tedavi süreci ele alınacaktır. SM'de başlıca tedavi yöntemi ilaç tedavisi ve psikoterapidir. Özellikle psikoterapötik müdahalelerin bireysel farklılıklar doğrultusunda çeşitlilik gösterdiği bilinmektedir. Bu yazının en önemli amacı, ikiz SM olgularının tedavi müdahalelerindeki farklılığa dikkat çekmek ve olguların klinik özelliklerini literatür eşliğinde değerlendirmektir.

Anahtar Kelimeler: Selektif mutizm, monozigotik ikiz, ergen

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Introduction

Selective Mutism (SM) is an anxiety disorder that is relatively rare compared to other anxiety disorders and it is characterized by the inability to speak in specific settings and situations where speech is anticipated, despite having the ability to speak[1]. Although precise percentages have not been established, research has reported that the frequency of selective mutism ranges from 0.11 to 2.2% and it is more common in girls than in boys[2,3]. Psychiatric comorbidities, particularly social phobia, specific phobia, and separation anxiety disorder, are extremely prevalent among SM patients[3,4].

Long-term follow-up research on the clinical trajectory of SM is scarce. In a study, the average disease duration for SM was found to be 9 years[5]. In general, it is suggested that in most untreated SM cases, mutistic symptoms gradually go away and that during adolescence and early adulthood, the majority of cases do not fulfill the diagnostic criteria for SM[6]. A poor prognosis is linked to advanced age, initial disease severity, and a family history of SM[7].

Although it has been reported that SM is more common in twins, it is unclear whether this is a referral bias[8]. Furthermore, it has been noted that the clinical symptoms of SM in twins are more severe than those in singletons[8,9]. This article aims to discuss the follow-up and treatment process of a pair of female monozygotic adolescent twins who have had SM for a long time. Written informed consent for the presentation and publication of the case was obtained from the patients and their parents on the condition that the patients' anonymity must be preserved.

Description and Presentation of Cases

Fraternal twin female patients, aged 14 years and 9 th-grade students, applied to our clinic accompanied by their mothers and at their mother's request, not speaking in social situations like school, friends, and foreign environments, and extreme shyness and timidity. In one-on-one interviews with different psychiatrists, nonverbal communication (making eye contact, using gestures and facial expressions, shaking the head) was achieved with both adolescents, but verbal communication was not established. Due to the patients' limited verbal communication, the mother provided the majority of the anamnesis information.

It was learned that the patients spoke on time and fluently, without any delay in speech and other developmental stages, and their "not talking to strangers" problems were initially noticed in the first grade of elementary school. The mother stated that until that date, as parents, they had observed that children did not talk to anyone when there were strangers at home, when they went out for a visit, or in other social environments, but they did not consider this as an abnormal situation because they spoke normally and fluently when there were no outsiders present at home (except for their grandmother, who they saw a lot). Without any preschool instruction, when the children entered elementary school together, in the same classroom, at the same desk, they did not experience separation anxiety. The mother were the children's primary caretakers, and they grew up in an isolated household setting with no friends. During the first half of first grade, the teacher observed that the sisters talked only to each other and did not talk to anyone including the teacher herself and their classmates; when they asked them questions or wanted to communicate with them, they acted as if they could not hear them at all; they did not even make eye contact; they did not participate in games with their classmates, and they were remarkably shy and introverted, and thus recommended that they receive a psychiatric evaluation from child and adolescent psychiatry. They had no triggers, stressful/traumatic life events, or stressors linked to their "not talking to strangers" problems. The children who were evaluated for the first time by a child psychiatrist in the second half of the first grade, it was reported that their mental development was normal, and considering the diagnosis of selective mutism, they were started on fluoxetine 5 mg/day medication. However, family members did not start drug treatment and did not go to child and adolescent psychiatry follow-ups because they thought that these problems would spontaneously resolve when they grew up, and they were worried about the side effects of drug treatment.

When the children started the second grade of elementary school, their classroom teacher changed and a male teacher whom the mother described as authoritarian, rude, rather harsh, and emotionally detached took over. The mother claimed that at that time, her children were more timid than ever at school and were reluctant to attend school. The classroom teacher again referred the children for a psychiatric evaluation due to their lack of verbal and nonverbal communication with him and their classmates. They next saw a different child and adolescent psychiatrist, who once more started them on 5 mg of fluoxetine per day. The dosage of fluoxetine was gradually increased to 20 mg/day during the follow-ups, and risperidone 0.25 mg/day was added to the treatment regimen. The mother mentioned that they received treatment with fluoxetine 20 mg/day and risperidone 0.25 mg/day for a year and that during this period, the children communicated only non-verbally with the classroom teacher and classmates with whom they were not close, and spoke with one or two classmates, albeit in whispers. Later, with the arrival of summer vacation, this treatment regimen was stopped by the parents, and the children were left without treatment for approximately 6 months. Throughout the subsequent processes, various medication therapies were selected for the children who were assessed by numerous child and adolescent psychiatrists before applying to our clinic (including selective serotonin reuptake inhibitors [fluoxetine, sertraline, escitalopram, fluvoxamine], imipramine from tricyclic antidepressants, mirtazapine from atypical antidepressants, antipsychotics [risperidone, aripiprazole, paliperidone, amisulpride] and hydroxyzine from antihistamines). Furthermore, even though many psychiatrists recommended that siblings attend separate classes, the children never attended separate classes because they refused to do so. In summary, as a result of the approximately 8-year

treatment process, which was not seriously interrupted, it was learned that the children could only communicate verbally and non-verbally at a limited level with very a few friends (one or two) with whom they were close, outside the home and family environment, and that they still did not talk to other people.

It was reported that children who were born as fraternal twins via planned and cesarean section had no health issues during or after birth and completed the neuromotor development stages on schedule. Except for selective mutism, the children's medical histories were free of significant mental or medical illnesses, and their neurological examinations revealed no pathology. According to family history, the mother was extremely quiet, timid, and introverted at a young age, and she became very excited when speaking in foreign environments, as well as having personality traits such as shyness and timidity. Apart from this, there was no feature in their family history, including speech-related disorders. Their 19-year-old brother and father were described as talkative, energetic, and outgoing.

When patients applied to our clinic, they had not received treatment in about 9 months. Follow-up and treatment of both cases continued with weekly meetings in the first month of treatment, and every two weeks thereafter. The therapy was implemented in the form of individual and child-focused parent interviews. Two different child psychiatrists conducted separate psychiatric interviews with the cases, and both noted that both cases were extremely anxious. During the psychiatric examination, only non-verbal communication was possible in both cases, and written communication was also provided in one case. Clinically, the intelligence of the cases was within normal limits and it was ascertained that their academic performance was good. The sentence completion test's contents were mostly about the "inability to speak"; there were no depressive items. Neither of them was persuaded to draw. The home video recordings yielded they were fluent in oral language and spoke freely. Autism spectrum disorders were excluded because the patients maintained normal communication and interaction within the family and did not have limited or repetitive thoughts and behaviors, and psychosis was excluded because they did not exhibit delusions, hallucinations, or other psychotic symptoms. Both cases were diagnosed with selective mutism and social phobia, and they were started on fluoxetine 20 mg/day and aripiprazole 5 mg/day, which had previously been shown to be the most effective for them. Two different child psychiatrists separately conducted behavioral treatment-oriented interviews with the cases, which included practice/exposure-based tasks, social skills acquisition, and new tasks. Furthermore, patients were now asked to attend separate classes at school, and 3 weeks of lorazepam treatment was added when their classes were separated. During the follow-ups, after the patients separated their classes at school, they established effective nonverbal communication with their teachers and classmates, as well as effective verbal and nonverbal communication with their close friends, began to hang out with their close friends during breaks, and were able to participate individually in group activities such as music and role-playing. Family members also commented positively on the cases' ability to form social relationships. During the outpatient clinic follow-up, verbal communication was possible in both cases, albeit in a low voice and whisper, but although the patients' social functionality improved, the expected symptomatic improvement had yet to be achieved. It appeared that the severity of selective mutism symptoms decreased as classes were separated at school. The cases were followed up and treated for about 8 months, but then the mother voluntarily ended the psychiatric interviews, stating that her children had recovered, albeit not completely.

Discussion

In this article, a pair of monozygotic female adolescents diagnosed with SM were presented, in whom psychotherapeutic and behavioral interventions were inadequately applied and the disease process was protracted, even though they received sufficient treatment support in the form of medication assistance. This case report underlines the importance of social isolation and a family history of SM and anxiety disorders, which contribute to treatment resistance and reinforcement and maintenance of mutism, despite strong drug support.

SM is an uncommon anxiety disorder that is strongly associated with other anxiety disorders, especially social anxiety disorder[3,4]. Most studies agree that girls are more likely than boys to develop SM, and some research has shown that SM is more common in twins and that their clinical characteristics are more severe[2,3,8,9].

The frequency and clinical presentation of SM in twins are poorly understood. However, studies indicate that in addition to strong genetic characteristics in twins, there are also environmental factors such as social isolation that strengthen the continuation of mutism and other clinical characteristics[8,9]. There are surprisingly very few studies or case reports in the literature regarding the occurrence of SM in twins[8-11], and according to some research, twins are disproportionately common in SM sufferers[11]. It is asserted that the twins struggle to grow apart and develop their own identities and that this is made worse by the fact that neither the parents nor the larger community can recognize the twins as two distinct people. In addition to the inability to develop an individual identity, it has been emphasized that twins exhibit mutual mirroring, which results in social isolation, the persistence of SM symptoms, and resistance to treatment[9]. We observed that our twin pair with SM had difficulty separating from each other, although they were encouraged to separate, that they could not demonstrate social skills because they could not gain an individual identity, and that they continued to see each other as the same unit. Thus, it was thought that their close interaction with each other and the use of the language they created among themselves hampered the individualization and socialization processes and disrupted ego development, so they were asked to have separate classes. Indeed, once our cases were separated into different classes and the twins' unity was broken, their verbal and nonverbal communication skills improved probably due to their social isolation

barriers decreased. Furthermore, the fact that the mother of the twin pair we present exhibits personality traits such as shyness, introversion, and timidity, although not severe enough to meet social phobia, may contribute to a lack of verbal communication in the family, social isolation, and behavioral inhibition. It is also clear that the mother's personality traits can cause a genetic predisposition for both SM and social phobia diagnoses in her twins. These factors can lead to the severity of SM symptoms remaining unabated and/or an inadequate response to treatment. In addition, negative prognostic factors such as the relatively older age of our cases and their high disease severity from the beginning may also explain the persistence of symptoms and poor response to treatment. Again, previous studies have shown that SM is strongly associated with other anxiety disorders, especially social anxiety disorder, and that almost all cases of selective mutism are diagnosed with social phobia[2-6,11]. Similarly, our cases were diagnosed with social phobia along with SM, and we think that this might contribute to the relatively poor prognosis.

Several approaches are used in the treatment of selective mutism, and it is generally recommended that pharmacological therapy and psychotherapeutic interventions be applied together. Psychotherapeutic interventions should involve the patient, his/her family, and his/her surroundings. It is advised that mental health professionals, school counselors, and speech therapists be part of the therapy team[3,4]. However, there is a dearth of evidence-based information regarding the care and treatment of twins with SM, and this data mostly originates from case reports[8-10]. There is an argument that suggests twins should be separated for treatment purposes to promote and enhance individuality, even if this is not supported by study findings[8-10]. It is highlighted that separating not only twins with SM but also twins with speech difficulties in environments such as schools will have extremely positive effects on speech and language skills[12]. We implemented behavioral therapy-based interventions to shatter the twins' unity, promote their socialization and individualization, assist their self-differentiation, and further their ego development. For each twin pair's assessment, treatment, and follow-up, we selected different therapists. We observed that various behavioral strategies we used had generally positive outcomes. In addition to behavioral interventions, pharmacological treatments, especially selective serotonin reuptake inhibitors, also have an important place in the treatment of SM. Because of this, we started our twin pair cases on fluoxetine and aripiprazole, two psychotropics that were most beneficial in the past and we continued drug treatments without significant side effects. In conclusion, observing rapid changes in their communication and interactions as a result of the "separating their classroom and social environments" technique applied for treatment purposes to increase the individuality of our cases, as well as drug therapy suggests that separating the environments of twins with SM during their treatment is an extremely important and necessary approach.

Conclusion

This study adds to the scant body of literature on twin pairs with SM therapy. The treatment method of the twin pair with SM that we present here demonstrates the complexity of SM treatment in twins, and points out the value of separating their social settings —like the school environment— to strengthen their individual unique identities and individuality. It was thought that our patients' interaction with each other and the use of the language they created among themselves led to the development of a symbiotic relationship over a long period, which contributed to the persistence of symptoms and the emergence of treatment resistance. Indeed, meaningful progress was made by arranging the twin pair's classroom and social surroundings to be separate and providing them with chances for separation and individualization.

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