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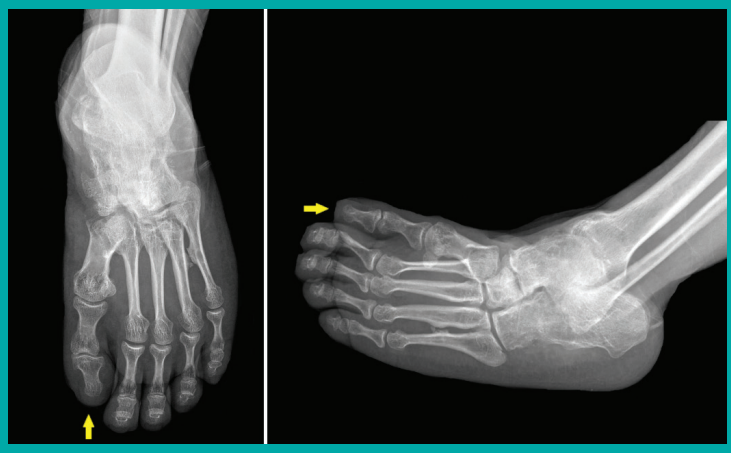

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ORIGINAL ARTICLE

Post-COVID Syndrome: From the Perspective of Physiatrists

ABSTRACT

Objectives: The presence of various symptoms with a duration that exceeds the acute phase of coronavirus disease 2019 (COVID-19) is called post-COVID syndrome (PCS). This study aimed to evaluate the patients with PCS who applied to outpatient clinics of Physical Medicine and Rehabilitation (PMR).

Methods: This study included 70 patients who developed PCS after COVID-19 infection and 45 patients who recovered completely from the infection without ongoing symptoms related to the disease as a control group. The patients' demographic and clinical features were recorded. The signs in the acute phase of COVID-19 infection, the treatment content, location, duration, and persistent symptoms were recorded. The patients' kinesiophobia, anxiety-depression levels, and quality of life were evaluated.

Results: The study population consisted of 78 (67.8%) women and 37 (32.2%) men, with an average age of 48.88±12.89. The frequency of females was significantly higher in the PCS group than in the control group (p=0.024). The most common complaints reported by PCS patients were fatigue (64.3%), weakness (44.3%), myalgia (35.7%), and back pain (31.4%). PCS was significantly higher in patients hospitalized during the acute infection, those with COVID-19 pneumonia, and those with chronic diseases, especially hypertension. The kinesiophobia scores of patients in the PCS group were considerably higher than those of patients in the control group (p<0.001).

Conclusion: PCS appears to be related to the female gender and the severity of the acute disease. In this study, the most frequently reported persistent symptom by patients with PCS was fatigue, and back pain was the most common reason for admission to the PMR outpatient clinics.

Keywords: Anxiety, depression, long COVID, kinesiophobia, physical medicine and rehabilitation, post-COVID-19 syndrome

In 2020, the world faced an extraordinary and devastating experience due to the pandemic coronavirus disease 2019 (COVID-19). Millions of people have been infected, and more will continue to be infected in the protracted pandemic. Although most COVID-19 patients recover completely, some experience persistent symptoms months after recovery, and some may even develop new symptoms. This clinical condition that occurs after acute infection is defined as post-COVID-19 syndrome (PCS) (1). Acute COVID-19 was described as the presence of signs and symptoms of COVID-19 lasting up to four weeks, while ongoing symptomatic COVID-19 was described as the persistence of signs and symptoms lasting between four and twelve weeks; the presence of persistent symptoms and signs during or following acute infection lasting more than twelve weeks and not explained by another diagnosis was called PCS by the United Kingdom (UK) National Institute for Health and Care Excellence guidelines (2). Various terminologies have been proposed throughout the pandemic, including post-COVID-19 condition, long COVID, and long-haul COVID. Although different descriptions have been proposed, PCS is accepted as symptoms that persist for three months from the onset of COVID-19 infection, or the beginning of new symptoms or fluctuations after the acute infection, and cannot be explained by another diagnosis (3). The estimated prevalence of PCS ranges from 9% to 63% (4). The most commonly reported PCS symptoms include fatigue, headache, dyspnea, musculoskeletal pain, sleep disturbances, and cognitive impairment (5). PCS mainly requires at least one of the symptoms listed above. Among the most frequently reported musculoskeletal symptoms and signs are fatigue, myalgia, arthralgia, back pain, energy loss, muscle weakness, sarcopenia, impaired exercise capacity, and low physical performance (6). Dyspnea, reduced exercise capacity, and lower limb strength lead to poor quality of life in post-COVID-19 individuals (7). The adverse effects of COVID-19 on

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health, including psychological and physical deterioration, continue to be reported during the prolonged COVID-19 pandemic. However, the available knowledge of PCS, especially musculoskeletal manifestations, is still insufficient. Therefore, this study aimed to describe the frequent clinical characteristics of PCS from the perspective of physiatrists regarding musculoskeletal system problems and evaluate measures of kinesiophobia, depression, anxiety, and quality of life in individuals after experiencing COVID-19.

METHODS

Study Design and Patients

This study was designed as a cross-sectional study and was carried out between November 2021 and May 2022 in the outpatient clinics of a state hospital's PMR Department. The study protocol followed the principles of the Declaration of Helsinki, and the local ethics committee approved the study (decision no: 2021.06.15, date: 16.09.2021). Inclusion criteria were patients admitted to the PMR outpatient clinics with PCS symptoms after recovering from COVID-19, whose diagnosis was confirmed by positive nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) test results, or who had a thorax computed tomography scan showing features of COVID-19 pneumonia although with negative PCR testing; they had to be older than 18 and volunteer to participate in the research. Exclusion criteria included being newly diagnosed with COVID-19 and therefore in quarantine at home or hospitalized for treatment; having suspected COVID-19; being pregnant. Inclusion criteria for non-PCS controls included having recovered completely from COVID-19 without any residual symptoms, being at least three months post-COVID-19 infection, being older than 18, and volunteering to participate in the research. Exclusion criteria for controls were physical or mental disability, acute or chronic infection, other health problems, or being in quarantine for acute COVID-19. Sociodemographic characteristics of the patients and clinical features, details of acute COVID-19 infection, content, location, and duration of the treatment, and persistent symptoms at follow-up were recorded.

Kinesiophobia

To evaluate the patients' fear of movement, known as kinesiophobia, the Tampa Scale of Kinesiophobia (TSK) was used. The scale includes 17 items concerning injury or re-injury in work-related activities, anxiety, and avoidance. Each item is scored on a 4-point Likert-type scale, from 1 (strongly disagree) to 4 (totally agree). The total score ranges from 17 to 68, with higher scores indicating an increased level of kinesiophobia. A cut-off score for a high degree of kinesiophobia is defined as >37 points by Vlaeyen et al. (8). The reliability and validity studies of the Turkish version of the scale were conducted by Tunca Yilmaz et al. (9).

Anxiety and Depression

To determine the patients' levels of anxiety and depression, the Hospital Anxiety and Depression Scale (HADS) was employed. The scale consists of 14 items with two subscales, seven for anxiety and seven for depression. Each item is scored from 0-3, and each subscale is scored from 0 to 21. A score of ⩾8 defines anxiety and depression. The validity and reliability studies of the Turkish version of the scale were carried out by Aydemir et al. (10).

Quality of Life

To assess the patients' quality of life, the Short Form-12 (SF-12) was utilized. This questionnaire contains 12 items across eight subdimensions: physical functioning (2 items), role-physical (2 items), bodily pain (1 item), general health status (1 item), vitality (1 item), social functioning (1 item), role-emotional (2 items), and mental health (2 items). Each item is scored on a 0-4 Likert-type scale. The total Physical Component Summary (PCS-12) score is calculated by summing the scores of general health, physical functioning, role-physical, and bodily pain subdimensions, and the total Mental Component Summary (MCS-12) score is calculated by summing the scores of social functioning, role-emotional, mental health, and vitality subdimensions. The PCS-12 and MCS-12 subscales are scored from 0 to 100, with higher scores indicating a better health status. The validity and reliability studies of the Turkish version of the questionnaire were performed by Kütük and Soylu (11).

Statistical Analysis

The sample size was calculated using the G * Power (v3.1.7) program, with at least 45 patients required for each group with $\alpha = 0.05$, 95% power, and an effect size (d) of 0.701. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 software (IBM Corporation, Chicago, IL). The Shapiro-Wilk test was used for data distribution analysis. The collected data were expressed as frequency (%) for nominal and categorical variables, median (min-max) for non-normally distributed variables, and mean ± standard deviation (SD) for normally distributed variables. The independent sample t-test and Mann-Whitney U test were used to compare continuous and discrete variables, respectively. The Pearson chi-square and Fisher's exact tests were used to compare categorical variables. The Spearman correlation coefficient (r) was used to determine the correlation between kinesiophobia scores and anxiety-depression and quality of life scores. Correlation coefficients were interpreted as follows: 0-0.25 indicated a weak correlation, 0.25 to 0.50 a weak-to-moderate correlation, 0.50-0.75 a strong correlation, and 0.75-1 a very strong correlation. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Overall, during the study period, 115 patients with a mean age of 46.88±12.89 were included in this study. Patients were divided into two groups according to the presence or absence of PCS. The PCS group comprised 53 (75.7%) women and 17 (24.3%) men. The control group included 25 (55.6%) women and 20 (44.4%) men. The female frequency was significantly higher in the PCS group than in the control group (p=0.024), as seen in Figure 1. The general characteristics of the patients are summarized in Table 1. The admis-

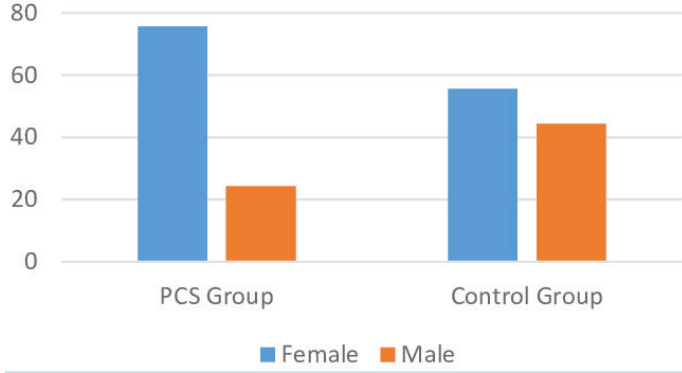

Figure 1. Gender distribution of the PCS and control group.

Table 1. General characteristics of patients

	Total (n=115)	PCS group (n=70)	Control group (n=45)	p
Age (years)	46.88±12.89	48.25±13.25	44.75±12.13	0.156
Gender				
Female	78 (67.8)	53 (67.9)	25 (32.1)	**0.024***
Male	37 (32.2)	17 (45.9)	20 (54.1)	
Education level				
Unschooled	4 (3.5)	4 (100)	0	0.306
Primary school	53 (46.1)	34 (64.2)	19 (35.8)	
High school	24 (20.9)	13 (54.2)	11 (45.8)	
University	34 (29.6)	19 (55.9)	15 (44.1)	
Occupation				
Student	2 (1.7)	1 (50)	1 (50)	0.432
White collar	26 (22.6)	15 (57.7)	11 (42.3)	
Blue collar	13 (11.3)	5 (38.5)	8 (61.5)	
Housewife	61 (53)	42 (68.9)	19 (31.1)	
Self-employment	2 (1.7)	1 (50)	1 (50)	
Retired	11 (9.6)	6 (54.5)	5 (45.5)	
Height (cm)	163 (145-181)	163 (145-181)	165 (149-176)	0.716
Weight (kg)	75 (49-120)	75 (49-120)	73 (50-114)	0.733
BMI (kg/m²)	26.9 (17-45.3)	27.65 (17.4-45.3)	26.3 (17.2-40)	0.068

Values are mean±SD (standard deviation), median (min-max), or percentage (n,%). *p values are statistically significant (p<0.05) and are shown in bold. PCS: Post-COVID-19 syndrome, BMI: Body mass index.

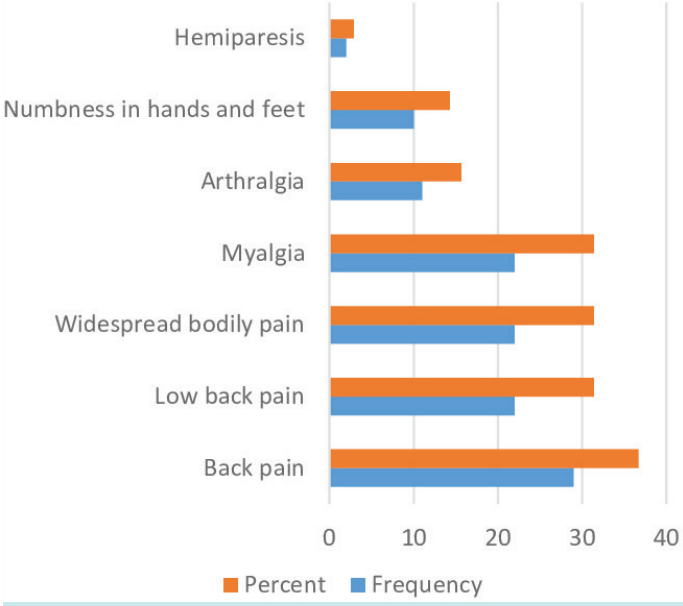

Figure 2. Admission reasons of the patients to the PMR outpatient clinics.

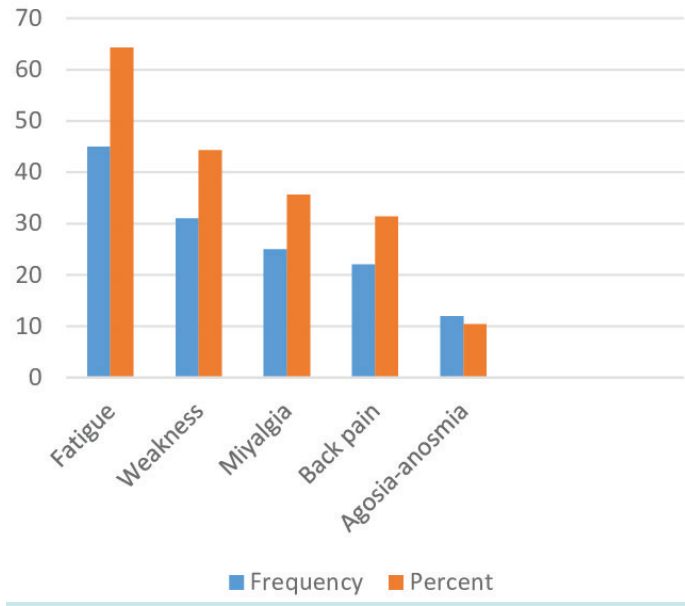

Figure 3. Frequency of most common persistent symptoms in patient with PCS.

sion reasons of patients with PCS to the PMR outpatient clinic were back pain (36.7%), widespread bodily pain (31.4%), low back pain (31.4%), myalgia (21.4%), arthralgia (15.7%), numbness in the hands and feet (14.3%), and hemiparesis (2.9%), as seen in Figure 2. The most common persistent symptoms in patients with PCS were fatigue (64.3%), weakness (44.3%), myalgia (35.7%), and back pain (31.4%), as seen in Figure 3. COVID-19-related features, including symptoms in the acute phase of SARS-CoV-2 infection (fever, cough, dyspnea, myalgia, anosmia, ageusia), the treatment content, location, duration, comorbidities, need for respiratory support, and mechanical ventilation are shown in Table 2. It was observed that the incidence of pneumonia and hospitalization was significantly higher in patients with PCS during the acute infection period than in the control group (p=0.002 and p=0.033, respectively). Among the symptoms seen during the acute COVID-19 infection period, shortness of breath and fatigue were observed significantly more frequently in the PCS group, while the duration of symptoms was longer in the PCS group (p=0.040, p=0.033, and p=0.020, respec-

Table 2. COVID-19-related features of the patients

n (%), Med (Min-Max)	Total (n=115)	PCS Group (n=70)	Control Group (n=45)	p
Symptomatology				
Throat ache	107 (93)	41 (59.4)	28 (40.6)	0.697
Headache	61 (53)	38 (62.3)	23 (37.7)	0.739
Rhinorrhea	57 (49.6)	35 (61.4)	22 (38.6)	0.907
Cough	90 (78.3)	56 (62.2)	34 (37.8)	0.573
Shortness of breath	27 (23.5)	21 (77.8)	6 (22.2)	**0.040***
Fever	55 (47.8)	34 (61.8)	21 (38.2)	0.842
Diarrhea	11 (9.6)	6 (54.5)	5 (45.5)	0.749
Anosmia-agnosia	43 (37.4)	29 (67.4)	14 (32.6)	0.264
Back pain	60 (52.2)	37 (61.7)	23 (38.3)	0.855
Myalgia	107 (93)	68 (63.6)	39 (36.4)	0.055
Arthralgia	39 (33.9)	26 (66.7)	13 (33.3)	0.362
Fatigue	109 (94.8)	69 (63.3)	40 (36.7)	**0.033***
Duration of symptoms (days)	10 (5-50)	10 (5-50)	10 (5-15)	**0.020***
Chronic disease				
Yes	52 (45.2)	41 (78.8)	11 (21.2)	**<0.001***
No	63 (54.8)	29 (46)	34 (54)	
Comorbidities				
Hypertension	17 (14.8)	15 (88.2)	2 (11.8)	**0.012***
Diabetes mellitus	19 (16.5)	14 (73.7)	5 (26.3)	0.210
Coronary heart disease	8 (7)	5 (62.5)	3 (37.5)	0.922
Hyperlipidemia	8 (7)	5 (62.5)	3 (37.5)	1.000
Thyroid dysfunction	8 (7)	7 (87.5)	1 (12.5)	0.146
COPD	1 (0.9)	1 (100)	0	1.000
CKD	1 (0.9)	1 (100)	0	1.000
Fibromyalgia	5 (4.3)	5 (100)	0	0.155
Smoking habits				
Smoker	16 (13.9)	11 (68.8)	5 (31.2)	0.586
Non-smoker	86 (74.8)	50 (58.1)	36 (41.9)	
Ex-smoker	13 (11.3)	9 (69.2)	4 (30.8)	
Time since COVID-19 (months)	5 (3-18)	5 (3-15)	6 (3-18)	0.684
SARS-CoV-2 RT-PCR test				
Positive	107 (93)	64 (59.8)	43 (40.2)	
Negative	8 (7)	6 (4.9)	2 (25)	0.479
Pneumonia				
Yes	37 (32.2)	30 (81.1)	7 (18.9)	**0.002***
No	78 (67.8)	40 (51.3)	38 (48.7)	
Treatment place				
Home	97 (84.3)	55 (56.7)	42 (43.3)	**0.033***
Hospital	18 (15.7)	15 (83.3)	3 (16.7)	
Treatment time (days)	5 (5-30)	5 (5-30)	5 (5-10)	0.279
Treatment agents				
Hydroxychloroquin	31 (27)	19 (61.3)	12 (38.7)	0.955
Favipiravir	71 (61.7)	45 (63.4)	26 (36.6)	0.483
Moxifloxacin	23 (20)	16 (69.6)	7 (30.4)	0.339
LMWH	20 (17.4)	17 (85)	3 (15)	**0.015***
Mechanical ventilation				
Yes	3 (2.6)	3 (100)	0 (0)	
No	112 (97.4)	67 (59.8)	45 (40.2)	0.279
Need of intensive care unit				
Yes	4 (3.5	4 (100)	0 (0)	
No	111 (96.5)	66 (59.5)	45 (40.5)	0.154

Values are mean±SD, median (minimum-maximum), or percentage (n, %) *p values are statistically significant (p<0.05) and are shown in bold. COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease.

Table 3. Kinesiophobia, anxiety-depression, and quality of life scores of patients

n (%), Med (Min-Max), Mean±SD	Total (n=115)	PCS Group (n=70)	Control Group (n=45)	p
HADS-Anxiety	7 (1-19)	8 (1-19)	6 (2-14)	0.119
HADS-Depression	6 (0-19)	6 (0-19)	5(1-10)	0.054
SF-12 PCS	38.44±9.16	38.50±9.29	38.33±9.08	0.921
SF-12 MCS	48.85 (20.47-63.27)	48.94 (20.47-63.27)	48.85 (22.75-63.27)	0.733
TKS	35.54±8.46	38.02±8.80	31.68±7.06	**<0.001***
TKS				
<37	64 (55.7)	30 (46.9)	34 (53.1)	**0.001***
>37	51 (44.3)	40 (78.4)	11 (21.6)	

Values are mean±SD, median (minimum-maximum), or percentage (n, %) *p values are statistically significant (p<0.05) and are shown in bold. HADS: Hospital anxiety and depression scale, SF-12: Short Form-12, PCS: Physical component score, MCS: Mental component score, TKS: Tampa kinesiophobia scale.

tively). In addition, the frequency of accompanying chronic diseases, especially hypertension (p=0.012), was significantly higher in the PCS group (p<0.001). The kinesiophobia scores of patients with PCS were significantly higher than those in the control group (p<0.001). There was no significant difference between the patients with and without PCS regarding anxiety and depression levels and quality of life scores, as shown in Table 3. Kinesiophobia levels showed a weak to moderate positive correlation with anxiety levels (r=0.258, p=0.005) and depression levels (r=0.397, p<0.001). Kinesiophobia levels also exhibited a weak but significant negative correlation with quality of life scores (for PCS r=-0.259, p=0.005; for MCS r=-0.231, p=0.013).

DISCUSSION

Findings from this study suggest that female gender, disease severity, hospitalization, pneumonia in acute infection, and comorbidities, especially hypertension, may be risk factors for PCS. The most frequent persistent symptom in patients with PCS was fatigue, and back pain was the most common admission reason to the PMR outpatient clinics. A high degree of kinesiophobia was observed in patients with PCS. However, quality of life and anxiety-depression levels were similar in patients with and without PCS.

COVID-19 infection has been reported to have equal prevalence in men and women, but male gender is a risk factor for higher disease severity and mortality (12). This study found a higher frequency of females in the PCS group than males. Peghin et al. (3) identified female gender as an independent risk factor for PCS six months after COVID-19 infection. Sudre et al. (13) reported that long-term COVID was associated with female gender, advanced age, and high body mass index. Poyraz et al. (14) found female sex and previous psychiatric disorders as related risk factors for PCS. Some studies have indicated that women have higher rates of long-term COVID-19 symptoms than men after hospital discharge (14-16).

Although a few studies reported that men are as likely to experience long COVID symptoms as women (17,18), female gender seems to have a higher risk for PCS manifestations. Immunological differences based on gender are thought to play a role in this disparity (19).

Fatigue was the most common persistent symptom in patients with PCS, and back pain was the most common admission reason to the PMR outpatient clinics. Fatigue is a common symptom during both the acute COVID-19 infection and the post-COVID period. Persistent fatigue has been reported in a significant minority of COVID-19 patients 16-20 weeks after symptom onset, ranging from 13% to 33% (20). Self-reported fatigue was the most typical complaint among a large group of long-COVID patients in a COVID symptom study (13). Cares-Marambio et al. (21) noted that fatigue and dyspnea were the most frequent symptoms of long-term COVID-19. Patients with back pain during the acute COVID-19 infection often had higher rates of pneumonia (22). The severity of acute COVID-19 infection, older age, smoking, and lower physical activity levels have been identified as risk factors for persistent musculoskeletal symptoms in patients recovered from COVID-19 (23).

PCS prevalence was significantly higher in patients hospitalized during the acute COVID-19 infection, in those with COVID-19 pneumonia, and in those with chronic diseases, particularly hypertension. Chen et al. (24) reported that around 34% of non-hospitalized and 54% of hospitalized patients experienced symptoms post-acute phase of COVID-19. Muñoz-Corona et al. (25) observed that at least one symptom persisted 12 weeks after hospital discharge in 75.9% of patients. Among these patients, 6.38% had one symptom, 19.22% had two symptoms, and 60.28% had three or more. Román-Montes, et al. (26) reported a 76% prevalence of PCS in hospitalized Mexican patients with severe or critical COVID-19. Nasserie T, et al. (27) found that 72.5% of hospitalized patients experienced at least one ongoing symptom post-acute infection. Previous studies identified female gender, high body mass index, older age, hospitalization, prolonged immobilization, need for mechanical ventilation, and comorbid disorders such as hypertension as risk factors for PCS (4,27-29). Smoking, severe COVID-19, lower oxygen saturation upon admission, and extensive lung involvement were also linked to an increased frequency of PCS (26).

The mechanisms underlying the development of PCS and PCS-related musculoskeletal signs are not yet fully understood. In the literature, one hypothesis is that changes in viral load and prolonged inflammatory responses of the human immune system may contribute (3,30). A positive outcome indicates the eradication of infection by the immune response while providing resistance to re-infection. Conversely, a weak immune response with the persistence of viral triggers may promote a chronic phase of

the disease (31). However, current data on the immune response to SARS-CoV-2 infection and its relationship with PCS need further clarification. Huang et al. (15) observed decreased seropositivity and median titers of neutralizing antibodies compared to the acute phase in patients six months after hospital discharge, but they could not establish a connection to PCS due to limited serological data. Additionally, some studies have suggested that SARS-CoV-2 variants may pose an additional risk for PCS after COVID-19. One such study by Antonelli et al. (32) found that individuals infected with the delta variant had a higher risk of PCS than those with the omicron variant.

This study found that kinesiophobia scores in patients with PCS were significantly higher than in the control group. Kinesiophobia levels had a weak but significant positive correlation with anxiety (r=0.258, p=0.005) and depression (r=0.397, p<0.001) levels. They also had a weak but significant negative correlation with quality of life scores (for PCS r=-0.259, p=0.005; for MCS r=-0.231, p=0.013). Kinesiophobia, the fear of movement, contributes to the chronicity, persistence, and exacerbation of pain (33). Herrero-Montes et al. (34) reported that nearly 57% of patients with post-COVID pain exhibited potential kinesiophobic behavior. Higher kinesiophobia levels are associated with decreased physical activity (35). Studies have also shown that older men with post-COVID-19 sarcopenia experienced kinesiophobia (36,37).

This study observed poor quality of life scores, especially in the physical component subdimensions in the SF-12, in all patients with and without PCS. However, there was no significant difference in quality of life scores between the patients with and without PCS. Muñoz-Corona et al. (25) studied patients 90 days after discharge and reported that 75.9% of PCS patients had poor scores, especially in the physical and general health subdimensions in SF-36. The authors also reported that patients with joint pain, fatigue, and dyspnea had lower scores than patients without those symptoms. A recent meta-analysis showed that 58% of the post-COVID-19 patients had reported poor quality of life. In the same analysis, the poor quality of life was considerably higher among post-COVID-19 patients with ICU admission and fatigue (30). In many patients, persistent symptoms may result in them reducing their work hours or quitting altogether, which can increase their financial distress (38).

Limitations

This study has several limitations. First, it was a single-center study with a small sample size, introducing potential selection bias; it relied on self-reported patient symptoms and cross-sectional surveys, which may introduce information bias. Secondly, the cross-sectional design does not allow for follow-up data at different times. Thirdly, kinesiophobia, anxiety, and depression levels may interact and possibly affect other body systems. Further research is required to understand the risk factors causing PCS.

CONCLUSION

In conclusion, PCS appears to be associated with the female gender, the severity of the acute illness, and comorbidities, especially hypertension. In this study, the most frequently reported persistent symptom in patients with PCS was fatigue, and back pain was the most common reason for admission to the PMR outpatient clinics. Kinesiophobia levels were higher in patients with PCS than in those without. Future research is necessary to clarify the risk factors that contribute to PCS and to develop the best treatment strategies.

Ethics Committee Approval: This study was conducted with the permission of the Kırıkkale University Faculty of Medicine Local Ethics Committee (decision no: 2021.06.15, date: 16.09.2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.T.B., C.U., E.Ü.A.; Design – F.B.U., Z.T.B., Z.K.Ü.; Supervision – E.Ü.A., Z.T.B.; Data Collection and/or Processing – Z.T.B., F.B.U., C.U., Z.K.Ü; Analysis and/or Interpretation – F.B.U., Z.T.B., E.Ü.A.; Literature Search – Z.T.B., C.U., F.B.U.; Writing – Z.T.B.; Critical Review – E.Ü.A.

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ACADEMIC JOURNAL OF HEALTH

ORIGINAL ARTICLE

The Relationship Between Revised Cardiac Risk Index and Postoperative Morbidity After Major Abdominal Oncologic Surgery

ABSTRACT

Objectives: Major abdominal surgery is associated with postoperative morbidity, including perioperative cardiac ischemic events. Preoperative risk stratification is important for optimal surgical care, which is only possible once the risk has been identified. We aimed to determine a relationship between the Revised Cardiac Risk Index (RCRI) and postoperative morbidity after major abdominal oncologic surgery.

Methods: Ethics committee approval was obtained by protocol number 2018-04151. A total of 350 patients, aged over 18 years, undergoing elective major abdominal oncologic surgery and were expected to continue for more than two hours participated in the study. ASA classification, RCRI score, duration of surgery, and postoperative morbidity survey (POMS) on postoperative days 1 and 5 were recorded. We followed the length of hospital stay, hospital admissions after discharge, and postoperative mortality within 30 and 90 days.

Results: There was no significant correlation between RCRI and postoperative first-day morbidity (p=0.233). A moderate positive correlation was found between the ASA classification and the RCRI (r=0.443; p<0.001). The patients with high ASA scores had high RCRI scores. The most common morbidities were renal (99,1%), pain (93,7%), and gastrointestinal morbidity (84.3%) on the postoperative first day. As the RCRI score increased, the length of hospital stay was longer; however, this difference was not statistically significant (p=0.180). There was a weak positive correlation between the RCRI score and mortality (r=0.127, p=0.017).

Conclusions: Our study showed an insufficient correlation between RCRI as a preliminary assessment tool and postoperative morbidity. We considered a need for different risk-scoring systems that are practical and useful in predicting patients with a high risk of morbidity after major abdominal oncologic surgery.

Keywords: Major abdominal oncologic surgery, postoperative morbidity survey, revised cardiac risk index

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Morbidity is a more common occurrence after major surgery in high-risk patients. The postoperative mortality rate in the subgroup of high-risk patients is over 80%. This group constitutes more than 15% of the patients undergoing surgery. Advanced age, comorbid disease, major surgery, and emergency surgery are significant factors increasing risk (1,2). Oncologic surgery is one of the high-risk subgroup surgeries. These high-risk patients usually have preoperative risk stratification before undergoing any oncologic intervention.

The techniques and strategies to reduce postoperative adverse outcomes are the basis of the concept of perioperative care. Preoperative exercise programs ("prehabilitation"), optimization of fluid and inotropic therapy, antibiotic therapy, and preoperative anemia treatment are essential components of perioperative care (3,4). The proper use of such resources depends primarily on recognizing "at-high-risk" patients.

Lee's revised cardiac risk index, developed by modifying the Goldman index, is an essential tool for classifying patients into risk categories for postoperative cardiac complications (5). The RCRI is widely used for preoperative risk assessment in non-cardiac surgery (6,7). Few studies investigate the relationship between RCRI and postoperative morbidity in non-cardiac surgery (8-10).

Postoperative morbidity and mortality are some of the most used study endpoints in the lit-

Table 1. Revised Cardiac Risk Index (RCRI)

Criteria	POINT
High-risk surgery Intraperitoneal; intrathoracic, suprainguinal vascular	1 Point
History of ischemic heart disease History of myocardial infarction (MI); history of positive exercise test, current chest pain considered due to myocardial ischemia; use of nitrate therapy or ECG with pathological Q waves	1 Point
History of congestive heart failure Pulmonary edema, bilateral ral or S3 gallop; paroxysmal nocturnal dyspnea; chest x-ray (CXR) showing pulmonary vascular redistribution	1 Point
History of cerebrovascular disease Prior transient ischemic attack (TIA) or stroke	1Point
Pre-operative treatment with insulin	1 Point
Pre-operative creatinine >2 mg/dL / 176.8 µmol/L	1 Point

erature, indicating the quality of surgery and postoperative care. The Postoperative Morbidity Survey (POMS) is the only published prospective method to define short-term morbidity after major surgery (11).

Applying RCRI to risk stratification prior to major cancer surgery has been described in limited literature (12,13). Perioperative risk-mitigation strategies, guided by tools like the RCRI, may improve patient outcomes through better resource allocation and individualized perioperative monitoring or rehabilitation. Therefore, we aim to investigate the association between the RCRI and postoperative morbidity following major abdominal oncologic surgery.

METHODS

The study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the University of Health Sciences Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee (reference number: 2018-04151). Patients were included in the study after they were informed about the study and their consent was obtained. The patients were followed up for 90 days after surgery.

Patient Populations

The study included 350 patients aged >18 years undergoing major abdominal oncologic surgery expected to last longer than two hours. Gastrointestinal (colorectal, pancreatic, gastric surgery), gynecologic cancer (endometrial, ovarian tumor, debulking), and urological surgery (cystectomy, prostatectomy, and nephrectomy) cases were defined as major abdominal oncologic surgery. The exclusion criteria were patients under 18 years of age and those undergoing emergency surgery.

Data Collection

We recorded patient characteristics, American Society of Anesthesiology (ASA) Physical Status Score, Revised Cardiac Risk Index score (RCRI, Table 1), and duration of surgery. Perioperative patient management was performed according to the anesthesiologist's preference. The Postoperative Morbidity Survey (POMS) was recorded by an independent researcher on the postoperative first and fifth day.

The RCRI risk score was calculated by a 1-point assignment for each of the following variables:

1) High-risk surgery (intra-thoracic, vascular, and intra-peritoneal);
2) History of ischemic heart disease;
3) Heart failure;
4) Stroke or transient ischemic attack;
5) Insulin-dependent diabetes mellitus;
6) serum creatinine levels ⩾2 mg/dL for a maximum score of 6 (Table 1).

All patients received at least 1 point on the RCRI as major abdominal surgery for cancer is considered a high-risk intervention.

The POMS, consisting of clinical observation and a questionnaire, is a published method of describing a reliable and valid survey of short-term postoperative morbidity following major surgery (11,14). It is a nine-domain tool, and for each of the nine domains, morbidity is recorded in the presence or absence of preset criteria. POMS are assessed by direct patient interrogation and examination, review of clinical notes and patient follow-up schedules, data from the hospital clinical information system, and consultation with patient caregivers (Table 2).

In-hospital mortality, 30-day and 90-day mortality, admission to the intensive care unit, the length of hospital stay, and re-hospitalization after discharge were recorded.

Statistical Analysis

Patients were categorized into 4 risk classes (1, 2, 3, and ⩾4) depending on the number of preoperative risk factors according to the RCRI (6). Clinical characteristics were summarized and compared between these cohorts. The main hypothesis was to find a correlation between RCRI and POMS. Thus, using the Fisher exact test with four degrees of freedom, we determined that a sample size of 350 patients had a power of 90% to detect an adequate degree of 0.05 (α) and an effect size of 0.2.

Statistical analysis data were evaluated by uploading to the computer via SPSS (Statistical Package for the Social Sciences for Windows v.27.0, SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test evaluated whether the groups conformed to normal distribution. Categorical variables are reported with percentages, while continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR). Pearson's χ^2 test and Fisher's exact test were used to determine the statistical significance of differences between categorical variables. Results with $p<0.05$ were considered statistically significant.

Table 2. Postoperative Morbidity Survey (POMS)-defined morbidity

Morbidity type	Criteria	Source of data
Pulmonary	Has the patient developed a new requirement for oxygen or respiratory support?	Treatment chart Patient observation
Infectious	Currently on antibiotics and/or has the patient had a temperature of ≥38°C in the last 24 h?	Observation chart Treatment chart
Renal	Does the patient have any of the following: Oliguria (<500 ml day^{-1})? Increased Serum Creatinine (>30% from preoperative level)? Urinary catheter *in situ*?	Fluid balance chart Biochemistry result Treatment chart
Gastrointestinal	Unable to tolerate enteral diet (oral or tube feed)? Is the patient experiencing nausea, vomiting, or abdominal distention? (Use of antiemetic)	Patient questioning Fluid balance chart Treatment chart
Cardiovascular	Has the patient undergone diagnostic tests or therapy within the last 24 h for any of the following: New MI? Ischaemia or hypotension (requiring drug therapy or fluid therapy >200 ml h^{-1})? Atrial or ventricular arrhythmias? Cardiogenic pulmonary oedema/new anticoagulation (warfarin/heparin/fragmin)?	Treatment chart Note review
Neurological	Does the patient have new confusion/delerium, focal deficit, or coma?	Note review Patient questioning
Wound complication	Has the patient experienced wound dehiscence requiring surgical exploration or drainage of pus from the op wound with/without isolation of organisms?	Note review Pathology result
Haematological	Has the patient required any of the following within the last 24 h: rBC/platelets/FFP/cryoprecipitate?	Treatment chart Fluid balance chart
Pain	Has the patient experienced surgical wound pain significant enough to require parenteral opioids or regional analgesia? New postoperative pain significant enough to require parenteral opioids or regional analgesia	Treatment chart Patient questioning

Table 3. Patients characteristics of stratified by the RCRI

Revised Cardiak Risk Index						
	Total (n=350)	**1 (n=222)**	**2 (n=99)**	**3 (n=27)**	**≥4 (n=2)**	**p**
Age (year)	59.9±12.3	56.4±12.1	65.2±9.8	67.5±9.7	79.5±9.1*	**0.001***
ASA classification (n)						**0.001***
I	11	11	0	0	0	
II	209	164	40	5	0	
III	124	46	56	20	2	
IV	6	1	3	2	0	
Duration of surgery (min)	180±70	184±73	174±66	169±57	180±84	0.535
Sex (n) (Female/Male)	172/178	105/117	51/48	15/12	1/1	0.735

RCRI Revised Cardiac Risk Index. n=number of patients. Continuous variables are presented as mean±SD, Categorical variables as count.

RESULTS

This study included 350 patients aged between 19 and 95 (59.9±12.3 years). Patients with a higher RCRI score tended to be older (RCRI≥4: 79.5±9.1 years vs RCRI 1: 56.4±12.1 years, p<0.001). The mean age was significantly lower in patients with an RCRI of 1 than those with RCRI≥2 (p<0.001, Table 3). Hypertension (33.4%), diabetes mellitus (24.3%), and coronary artery disease (11.4%) were the most common comorbidities in the study.

A history of ischemic heart disease was present in 32.2% (118) of the patients, congestive heart failure in 4.6% (16), and a history of cerebrovascular disease in 1.7% (6). Twenty-eight (8.0%) patients were receiving preoperative insulin therapy. Two patients (0.6%) had preoperative creatinine elevation. All patients were in the high-risk surgery group. Demographic distributions, RCRI scores, and ASA classifications of patients according to their operation types are given in Table 3. A moderately positive correlation was found between ASA and RCRI (r=0.443; p<0.001). Patients with high ASA scores also had higher RCRI scores (Table 3).

Postoperative Morbidity

While there was no significant correlation between RCRI and postoperative first-day morbidity (p=0.196, r=0.06), a weak positive cor-

Table 4. Postoperative Morbidity Incidence

Variables n (%)	First day morbidity	Fifth day morbidity
Pulmonary Morbidity	17 (%4.9)	23 (%6.6)
Infectious Morbidity	27 (%7.7)	64 (%18.3)
Renal Morbidity	347 (%99.1)	86 (%24.6)
Gastrointestinal Morbidity	295 (%84.3)	107 (%30.6)
Cardiovascular Morbidity	19 (%5.4)	17 (%4.9)
Neurological Morbidity	5 (%1.4)	2 (%0.6)
Wound Morbidity	5 (%1.4)	6 (%1.7)
Hematological Morbidity	44 (%12.6)	22 (%15.7)
Pain Morbidity	328 (%93.7)	55 (%15.7)

Variables were given as n (%).

relation was found between RCRI and morbidity on the fifth postoperative day (r=0.13; p=0.01). The most common morbidities were renal (99.1%), pain (93.7%), and gastrointestinal morbidity (84.3%) on the postoperative first day (Table 4). Gastrointestinal and renal morbidities were found to be the most common on the fifth postoperative day (Table 4). The frequency of cardiovascular morbidity on the fifth postoperative day was higher in patients with an RCRI≥3 compared to those with scores of 1 and 2 (p=0.012, Table 5).

Discharge Data

The mean length of hospital stay was 10.11±8.3 days (Table 6). The length of hospital stay was longer in patients with a higher RCRI, but the difference was not statistically significant (p=0.180). The number of patients requiring intensive care was 28 (8%). Thirty-three patients (9.4%) were readmitted within 30 days after dis-

Table 5. Postoperative Morbidity Survey by RCRI

Postoperative morbidity survey, Variables n (%)	RCRI 1 (n=222)	RCRI 2 (n=99)	RCRI 3 (n=27)	RCRI ≥4 (n=2)	p
Pulmonary morbidity					
- Postoperative first day	8 (3.6)	6 (6.1)	2 (7.4)	1 (50)	0.269
- Postoperative fifth day	11 (5.0)	7 (7.1)	4 (14.8)	0 (0)	0.106
Infectious morbidity					
- Postoperative first day	19 (8.6)	6 (6.1)	1 (3.7)	1 (3.7)	0.472
- Postoperative fifth day	39 (17.7)	18 (18.2)	7 (25.9)	0 (0)	0.531
Renal morbidity					
- Postoperative first day	219 (98.6)	99 (100)	27 (100)	2 (100)	0.655
- Postoperative fifth day	51 (23)	27 (27.3)	8 (29.6)	0 (0)	0.614
Gastrointestinal morbidity					
- Postoperative first day	185 (83.3)	84 (84.8)	24 (88.9)	2 (100)	0.824
- Postoperative fifth day	58 (26.4)	36 (36.3)	12 (44.4)	1 (50)	0.061
Cardiovascular morbidity					
- Postoperative first day	11 (5.0)	7 (7.1)	1 (3.7)	0 (0)	0.745
- Postoperative fifth day	8 (3.6)	4 (4.1)	5 (18.5)	0 (0)	**0.012***
Neurological morbidity					
- Postoperative first day	3 (1.4)	2 (2.0)	0 (0)	0 (0)	0.761
- Postoperative fifth day	1 (0.5)	1 (1.0)	0 (0)	0 (0)	0.592
Wound morbidity					
- Postoperative first day	4 (1.8)	1 (1.0)	0 (0)	0 (0)	0.858
- Postoperative fifth day	5 (2.2)	1 (1.0)	0 (0)	0 (0)	0.758
Hematological morbidity					
- Postoperative first day	18 (8.2)	21 (21.2)	5 (18.5)	0 (0)	**0.004***
- Postoperative fifth day	14 (6.4)	5 (5.1)	2 (7.4)	1 (50)	0.762
Pain morbidity					
- Postoperative first day	208 (93.7)	94 (95.9)	24 (88.9)	2 (100)	0.344
- Postoperative fifth day	29 (13.2)	17 (17.3)	8 (29.6)	1 (50)	0.076

Data are given as n (%). n: number of patients.

Table 6. Discharge Parameters

	Revised Cardiak Risk Index				
	Total (n=350)	**1 (n=222)**	**2 (n=99)**	**3 (n=27)**	**≥4 (n=2)**	**P**
Length of hospital stay (day)	10.1± 8.3	9.7±8.2	10.7±9.3	10.1±6.7	12±2.8	0.180
Patient readmitted within 30 days (n)	33	25	8	0	0	0.252
In-hospital mortality, n (%)	3 (0.8)	1 (0.4)	0 (0)	2 (7.4) *	0 (0)	**<001***
30-day mortality, n (%)	6 (1.7)	3 (0.8)	0 (0)	3 (11) *	0 (0)	**<001***
90-day mortality, n (%)	10 (2.9)	4 (1.8)	1 (1)	5 (18.5) *	0 (0)	**<001***

Continuous variables are presented as mean±SD ; categorical variables as count (percentage), number of patients n= (%). *RCRI 3 compared to RCRI 1 and 2.

charge. There was no statistically significant correlation between the RCRI and the length of hospital stay (Table 6, r=0.09, p=0.06).

Mortality Data

The hospital mortality rate was 0.8%, and the 90-day mortality was 2.9%. The mortality rate was significantly higher in patients with an RCRI≥3 (18.5%) compared to those with an RCRI≤2 (1.5%) (p<0.001, Table 6) for 90-day mortality. There was a weak positive correlation between mortality and both RCRI and ASA scores (respectively, r=0.127; p=0.017, and r=0.224; p<0.001).

DISCUSSION

The study demonstrated that the RCRI was insufficient for predicting postoperative morbidity following major abdominal surgery, with non-cardiac morbidity being more common than cardiac morbidity.

The RCRI is one of the best predictors of cardiac risk in non-cardiac surgery and has been utilized in various studies to predict non-cardiac postoperative morbidity (8-10). Ackland et al. (8) found an association between the RCRI and postoperative morbidity, as well as prolonged hospital stays in elective orthopedic surgery. However, our study could not demonstrate a relationship between RCRI and morbidity.

Previous studies have indicated an association between a high RCRI and extended hospital stays. (8,11,14) The mean hospitalization time for our patients was 10.11±8.3 days. Although hospital stay lengthened as ASA and RCRI scores increased, there was no significant relationship between the mean hospital stay and ASA and RCRI scores.

The in-hospital mortality rate was 0.8% in our study, lower than the 1.5% reported in the cohort study by Lee et al., (6) which evaluated 1422 patients. They considered cardiac events and examined patient groups with varying postoperative morbidities, including major vascular surgeries. Our study focused on a homogeneous patient group with similar operation times and expected postoperative morbidity levels.

The 90-day mortality rate was higher at 18.5% in patients with an RCRI of ≥3 in our study. Jakobson et al. (2) observed a 3-month mortality rate of 17.8% in patients with an RCRI of ≥3 in major gastrointestinal surgery. The adverse impact of a higher ASA physical status and revised cardiac risk index on short-term mortality is well-documented (15-17). The long-term survival of patients undergoing major abdominal surgery for malignancy is influenced by numerous factors, such as the presence or development of postoperative complications, whether the surgery was radical or palliative, and comorbidities. Both short- and long-term mortality rates were significantly higher in patients with postoperative complications. Our study indicated that high ASA and RCRI scores are associated with long-term mortality.

In the past, retrospective data analysis was frequently used to evaluate the type and frequency of complications. However, this approach may be inadequate for assessing the frequency and accuracy of complications due to many methodological limitations (18). The Postoperative Morbidity Survey (POMS) is the only published prospective method to identify short-term morbidity after major surgery and has been substantiated by reliable validity research (11,19). Nevertheless, POMS has its limitations, as it includes parameters such as postoperative oxygen and urinary catheterization, which are accepted as routine after major surgery. Consequently, in our study, the most common morbidity on the first postoperative day was renal morbidity, primarily due to routine urinary catheterization. Howes et al. (14) modified POMS by excluding the presence of urethral catheterization alone and pain as diagnostic criteria in their study. When oliguria and an increase in serum creatinine were used as criteria, renal morbidity was reported as 11.8%. If we had excluded data from routine urinary catheterization in our study, renal morbidity would have been 6% on the first postoperative day.

Postoperative gastrointestinal dysfunction is approximately doubled in patients undergoing laparotomy, with mechanical trauma playing a crucial role in this complication (20,21). Gastrointestinal system morbidity was the most common fifth-day morbidity at 30% in our study. Occult hypovolemia from fluid losses and bleeding is common after major surgery, disrupting global oxygen delivery. Compensatory splanchnic vasoconstriction maintains blood flow to vital organs, leaving the gastrointestinal tract vulnerable to ischemia (22,23). A limitation of our study was its observational nature; we could not standardize critical parameters that may cause gastrointestinal complications, such as intraoperative fluid management and the use of non-steroidal anti-inflammatory drugs. Intraoperative hemodynamic changes were not evaluated.

It has been reported that cardiac complications are the most common morbidity after non-cardiac surgery (24-26). However, in our study, cardiovascular morbidity was less frequent than other types of morbidity but was associated with poor outcomes. Similar to our findings, Ackland et al. (8) indicated that non-cardiac morbidity was more prevalent than cardiac morbidity. Notably, high rates of cardiovascular complications (18%) developed in patients with a high RCRI score, underscoring RCRI as a robust index for classifying patients into risk categories to predict cardiovascular complications, as recommended by guidelines.

CONCLUSION

The incidence of complications after major abdominal surgery is substantial, markedly increasing postoperative morbidity, mortality, and hospital stay duration. In practice, the assessment of risk assessment methods is challenging due to performance bias: the identification of high-risk individuals can lead to significant disparities in care, potentially equalizing the postoperative mortality and morbidity rates of these patients with those at lower risk. The RCRI does not adequately reflect the risk of postoperative morbidity, while the ASA and increased RCRI scores do reflect the risk of mortality. The number of patients with RCRI≥3,4 was low in our study, suggesting a need for further research involving more patients with high RCRI scores. Another limitation was our failure to evaluate preoperative anemia, intraoperative bleeding, and intraoperative events.

Our results did not detect an association between RCRI and postoperative mortality, contrary to existing literature. We advocate for practical and convenient risk-scoring systems to predict high-risk patients and enhance perioperative care quality. Risk-scoring tools may lead to better outcomes when considering intraoperative events at the operation's end.

Ethics Committee Approval: This study was conducted with the permission of the University of Health Sciences Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Local Ethics Committee (decision no: 2018-04/51, date: 18.04.2018).

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ACADEMIC JOURNAL OF HEALTH

ORIGINAL ARTICLE

Comparison of Intracardiac and Intrathecal KCL Application as an Alternative Method in the Reduction of Multiple Pregnancies in the First Trimester: Results of a Tertiary Centre

ABSTRACT

Objectives: This retrospective study compares the outcomes of intracranial (IC) and intrathoracic (IT) potassium chloride (KCl) applications for fetal reduction in multiple pregnancies.

Methods: Nineteen patients undergoing termination between December 2022 and November 2023 were analyzed. Transabdominal IC (n=8) and IT (n=11) KCl groups were compared for maternal age, gestational age, indication for reduction, and procedural details. P-values <0.05 were interpreted as statistically significant.

Results: While both groups exhibited similar maternal characteristics, the number of fetuses before reduction differed significantly (p=0.016). No significant distinctions were observed in operative time, reduction outcomes, or obstetric complications between the IC and IT groups (p>0.05). Premature rupture of membranes occurred in 13.3% (IT) and 23.1% (IC), with no significant intergroup differences.

Conclusion: The study suggests that IC KCl application may be a viable alternative, potentially simplifying the procedure without compromising safety or efficacy. The findings advocate for a nuanced approach to selecting the reduction method based on fetal position and number, highlighting the need for further research with larger sample sizes.

Keywords: Fetal reduction, intracardiac fetosid, intrathecal fetosid, multiple pregnancy

It is known that the frequency of multiple pregnancies is increasing today. The widespread use of assisted reproductive techniques and ovulation induction drugs are the main reasons for this (1). Above all, the difficulty of achieving pregnancy forces clinicians to transfer two or more embryos (2). However, increased perinatal morbidity and mortality are directly related to the number of fetuses. The risk of premature birth between 28-32 weeks increases fivefold for twin pregnancies and twentyfold for triple pregnancies (3).

Additionally, the presence of congenital anomalies in multiple pregnancies is another important factor that increases the risk of premature birth. The loss of the baby with the anomaly in the womb also leads to impaired neurological development and potentially to the fetal death of the other twin (4).

Reduction of multiple pregnancies (RMP) is a procedure preferred in the first trimester or early second trimester to reduce the number of fetuses. The aim is to decrease the number of fetuses to one or two and improve the poor outcome for the mother and newborn by selecting the fetus with the anomaly, if present, when performing the procedure (3). Reducing pregnancy to a singleton or twins by means of reduction has been shown in many studies to significantly improve outcomes compared to doing nothing (5).

RMP can be performed transvaginally or transabdominally under ultrasound guidance (6). Various methods are available, including the route of access, the timing of the procedure, and the fetotoxic agents used. KCl is generally used as a fetotoxic agent, but other agents such as digoxin have also been tested in some studies (7). Amniotic fluid, the fetal umbilical cord, intracardiac, intrathoracic (IT), and intracranial (IC) methods may be preferred for the application of the fetotoxic agent (8).

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Our study aimed to compare two procedures preferred in our clinic for fetal reduction: intracranial KCl administration and intracardiac KCl application. All these methods are applied transabdominally. The objective of our study was to assess and evaluate the procedural duration, maternal complication rate, and neonatal outcomes. As the number of fetuses increases, the process becomes progressively more challenging due to the increase in the number of placentas, amniotic membranes, and the varying positions of the fetuses. Hence, we aimed to demonstrate that the intracranial technique, as an alternative approach, can be employed with equivalent safety and duration.

METHODS

This research retrospectively analyzed a total of 19 patients who had pregnancy terminations at the Etlik City Hospital Perinatology Clinic, between December 2022 and November 2023. The study was conducted under the principles of the Declaration of Helsinki. The local ethics committee granted ethical permission (approval number: AEŞH-EK1-2023-745). Medical records and the hospital information management system were used to retrieve patient data.

Maternal age, parity, gestational weeks, type of pregnancy (spontaneous or assisted reproduction), number of pregnancies (triplets or higher order fetuses), indication for fetal reduction (fetal anomaly or multiple pregnancy), number of fetuses before fetal reduction, reduced number of fetuses, and finishing number of fetuses were recorded from the hospital database.

Indications for fetal reduction include multiple pregnancies, fetal malformation, cervical factors (post-cervical conization, cervical insufficiency), uterine malformation, and uterine fibroids. Indications for fetal termination include fetal structural anomalies, chromosomal anomalies, amniotic fluid abnormalities, fetal hydrops, infections, maternal drug or teratogen use, radiation exposure, and maternal reasons.

According to the specific puncture site, the patients were divided into a transabdominal intracranial KCl fetal reduction injection group (Transcranial KCl group) and a transabdominal KCl fetal reduction injection group (Transabdominal KCl group). An ultrasound examination is performed before the operation. The fetal position and placenta position are determined. A 22-gauge needle was used to puncture the fetal heart or cranium through the abdomen under ultrasound guidance. KCl was injected for fetal termination. A 22-gauge needle is placed into the thorax or cranium of the targeted fetus, 2 to 3 mL of potassium chloride is injected, and asystole is observed for at least 3 minutes. The procedure is then repeated for additional fetuses as required, with a different needle or occasionally with the same needle puncture.

Statistical Analysis

All statistical analyses were performed using the RStudio integrated development environment for statistical computing (Affero General Public License v3; published 2011. RStudio for Linux, version v2021.09.4+403.pro3 Ghost Orchid; September 19, 2022; developed by Posit, PBC) to analyze the data. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. The Levene test was used to assess the homogeneity of variances. Descriptive analyses were presented using means and standard deviations for normally distributed variables. An independent samples t-test was used to compare these parameters among the groups. For the non-normally distributed numerical data, descriptive analyses were presented using medians and interquartile ranges (Q1-Q3). The Mann-Whitney U test was conducted to compare these parameters among the groups. For categorical variables, descriptive analyses were presented using frequency and percentage. Relationships between categorical variables were analyzed with the Chi-square test or Fisher's exact test (when Chi-square test assumptions do not hold due to low expected cell counts). A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Table 1 shows the comparison between the two different treatment groups of pregnant women who underwent the feticide procedure.

Table 1. Maternal and gestational characteristics

	Transabdominal KCL n (11)	Transcranial KCL n (8)	p
Age	31.8±6.0	30.0±4.2	0.474
Parity (Median (min-max))	1 (0-3)	1 (1-2)	0.490
Mode of conception			
Assisted reproduction	6 (54.5%)	6 (75%)	0.633
Spontaneous	5 (45.5%)	2 (25%)	
Indications for fetal reduction			
Fetal anomaly	4 (36.4%)	1 (12.5%)	0.243
Triplet or higher order of fetuses	7 (63.6%)	7 (87.5%)	
Gestational age at reduction	13.6±1.9	12.3±1.0	0.081
Number of fetuses prior to fetal reduction			
2	5 (45.5%)	1 (12.5%)	0.016
3	3 (27.3%)	7 (87.5%)	
4	3 (27.3%)	0	

The study was conducted with a total of 19 pregnant women who underwent transabdominal KCl (n=11) and transcranial KCl (n=8) procedures. The mean ages of transabdominal KCl and transcranial KCl patients were 31.8±6.0 and 30.0±4.2 years, respectively (p=0.474). There was no significant difference between the two groups in terms of parity, mode of conception (assisted reproduction, spontaneous), indications for fetal reduction (fetal anomaly, triplet or higher order of fetuses), or gestational age at reduction (p>0.05 for all). There was a significant difference between the two groups in terms of the number of fetuses before fetal reduction (p=0.016). The number of patients with two fetuses before fetal reduction was five in the transabdominal KCl group and one in the transcranial KCl group. The number of patients with three fetuses before fetal reduction was three in the transabdominal KCl group and seven in the transcranial KCl group. The number of patients with four fetuses before fetal reduction was three in the transabdominal KCl group and none in the transcranial KCl group.

Table 2 shows the comparison between the two different treatment groups of pregnant women who underwent the feticide procedure. There was no significant difference between the two groups in terms of operative time per fetus, reduced number of fetuses, or finishing number of fetuses (p>0.05 for all). The operative time per fetus for transabdominal KCl and transcranial KCl patients was 31±4.0 and 30.2±3.2 minutes, respectively (p=0.831). The number of patients who underwent fetal reduction for a single fetus was seven in the transabdominal KCl group and six in the transcranial KCl group. The number of patients who underwent fetal reduction for two fetuses was two in both the transabdominal KCl and transcranial KCl groups. The number of patients who underwent fetal reduction for three fetuses was one in the transabdominal KCl group and none in the transcranial KCl group. The number of patients with one fetus after fetal reduction was seven in the transabdominal KCl group and three in the transcranial KCl group. The number of patients with two fetuses after fetal reduction was four in the transabdominal KCl group and five in the transcranial KCl group.

Table 3 shows the comparison of obstetric outcomes of the remaining fetuses after the feticide procedure between the two different treatment groups. There was no significant difference between the two groups in terms of preterm premature rupture of membranes, preterm labor, fetal growth restriction, gestational hypertension,

Table 2. Comparison of procedural features and complications

	Transabdominal KCL n (11)	Transcranial KCL n (8)	p
Operative time per fetus	31±4.0	30.2±3.2	0.831
Reduced number of fetuses			
1	7 (63.6%)	6 (75%)	0.662
2	2 (27.3%)	2 (25%)	
3	1 (9.1%)	0	
Finishing number of fetuses			
1	7 (63.6%)	3 (37.5%)	0.370
2	4 (36.4%)	5 (62.5%)	

Table 3. The obstetric outcomes of procedures

Neonatal outcomes	Remaining fetuses after transabdominal KCL n= 15	Remaining fetuses after transcranial KCL n= 13	p
PPROM	2 (13.3)	3 (23.1)	0.639
Preterm labor	5 (33.3)	7 (53.8)	0.477
Fetal growth restriction	3 (20)	2 (15.4)	1.000
Gestational hypertension	1 (6.7)	1 (7.7)	1.000
Mean GA at delivery (weeks)	37±4.7	38±1.7	0.526
GA at birth 24–31 6/7	1 (6.7)	0 (0)	0.824
32–36 6/7 weeks	4 (26.7)	5 (41.7)	
> 37 weeks	10 (66.7)	7 (58.3)	
Take-home-baby rate	14 (93.3)	12 (92.3)	0.722
Co-twin death ≤1 week	0	1	0.942
Co-twin death > 1 week	0	0	
Perinatal mortality	1	0	1.000

KCL: potassium chloride, PPROM: preterm premature rupture of membranes, GA: gestational age. Data are expressed as mean±SD or number (percentage) where appropriate. p<0.05 indicates significant difference.

mean gestational age at delivery, take-home baby rate, or perinatal mortality (p>0.05 for all).

DISCUSSION

Termination of pregnancy in the first trimester is a procedure that may be necessary due to various medical indications or serious risks to the mother's health. In this procedure, various methods are used to terminate fetal life. Intrathoracic (IT) and intracranial (IC) potassium injections are among the frequently used methods for fetal termination. These are invasive procedures in which a potassium solution is injected into the heart or brain of the fetus (9).

In IT potassium injection, a potassium solution is injected directly into the fetus's heart. This method acts quickly on the fetus and ensures the termination of fetal life. IC potassium injection, on the other hand, is carried out by injecting a potassium solution into the fetal brain. This method aims to quickly shut down the brain functions of the fetus (10).

In this study, we wanted to compare the results of IT and IC potassium injections for the termination of the fetus in the first trimester. We examined the impact of both the degree of invasiveness and effectiveness on maternal health, the risk of complications, and neonatal outcomes.

Our study included 19 patients who underwent fetocide in the first trimester at our clinic between October 2022 and July 2023. We performed fetocide by administering IT potassium to 11 of these patients and IC potassium to 8 of them. Five of these patients had fetal anomalies, and the indication for termination was a fetal anomaly. This procedure was performed on 14 patients for fetal reduction, to reduce pregnancies with triplets or more fetuses to twins or singleton pregnancies. In addition, 12 of our 19 patients became pregnant through assisted reproductive techniques. It is well known that the need for fetal reduction procedures has increased significantly due to the rise in multiple pregnancies caused by the increasing use of assisted reproductive techniques and the negative impact of the increasing number of fetuses on perinatal and neonatal outcomes (11). One of the most common indications among the patients in our study was the reduction of multiple pregnancies. Only seven of our patients became pregnant spontaneously. The indication for termination of pregnancy in five of these patients was a fetal anomaly. In one study in the literature, the average week of pregnancy in which the reduction was carried out was given as 12+6 weeks (1). In our study, the average gestational age at which we performed the IT fetocide was 13.6 weeks, and for the IC fetocide, it was 12.3 weeks (p=0.081). For this reason, the most ideal time, as in our study, is the end of the first trimester or the beginning of the second trimester (8).

In the reduction procedures that we perform for multiple pregnancies, six patients had twin pregnancies, ten had triplets, and three had quadruplets. In the fetal reduction we performed, we selected the fetuses with an increase in NT, according to the literature, or the fetuses on which we could more easily perform the procedure, after detailed information and consent from the patients and their relatives regarding the selection of patients, the number of fetuses to be reduced, and the selection of fetuses. When planning this procedure, we preferred another alternative method, intracranial potassium administration, in fetuses where we thought that intracardiac potassium administration might be difficult, especially due to the fetal position. In one twin pregnancy, we had to administer IC potassium to a patient, but in 87.5% of the triplet pregnancies, we performed fetocide using the IC method (p=0.016). This suggests that, as in previous studies, the administration of IC potassium is an option to further reduce the complication rate and technical difficulties during the procedure, taking into account the risks associated with fetal position and the number of fetuses (9).

There was no significant difference in the application times between the two methods we used (p=0.474). Our average procedure time was 31 seconds for patients for whom we performed fetocide using the IT method and 30.2 seconds for patients for whom we performed fetocide using the IC method. In a study presented in a series of 3 patients, KCl was injected for 15 seconds in one patient, in the second patient it was observed that the fetal heartbeat stopped after a 45-second injection, and in the third patient the result was obtained after a 30-second procedure (9). Although our transaction times are similar, we have had no unsuccessful transactions. In addition, the procedure times were similar in the cases in which IT fetocide was performed. Although we do not prolong the duration of the procedure and there is no difference in terms of complications, we believe that fetal reduction using the IC method is advantageous in appropriate cases in terms of the comfort and safety of the procedure.

In multiple pregnancies in which we performed a reduction, the number of patients we reduced to 1 fetus was 7 patients (63.6%) with the IT method and 3 patients (37.5%) with the IC method. With regard to the number of pregnant women who had twin pregnancies, there were 4 patients (36.4%) with the IT method and 5 patients (62.5%) with the IC method. We found no significant difference between the choice of procedure and the final number of fetuses between the two groups. There are many factors related to the selection of procedures. Each patient must be assessed individually, and the decision depends on the patient, the number of fetuses, the presence of a fetal abnormality, the patient's wishes, and the technical suitability of the procedure to be performed. In one study in the literature, they reduced all quintuplet and quadruplet pregnancies in the included patients to twin pregnancies, and in triplet pregnancies, they reduced 50 out of 63 patients to twin pregnancies and 13 to singleton pregnancies (1). In this study, however, the same method, IT potassium injection, was used for each pregnancy. In our study, premature rupture of membranes occurred in 2 of the 15 babies (13.3%) in whom we performed IT procedures and in 3 of the 13 babies (23.1%) in whom we performed IC procedures (PPROM). The number of babies who went into premature labor was 5 (33.3%) in the IT group and 7 (53.8%) in the IC group. The difference between these groups was not statistically significant (Table 3). This included 1 baby (6.7%) that was born between 24-32 weeks and belonged to the IT procedure group. The rate of babies born between 32 and 36+6 weeks was 26.7% in the IT procedure group and 5% in the IC procedure group. No statistical difference was found between the groups (Table 3). In a comprehensive literature review on this topic, the rate of births under 28 weeks was given as 2.9%, and the rate of births under 32 weeks as 8.9% (11). In this study, a comparison was made with patients who were not treated and were observed spontaneously, and it was shown that extreme premature births, i.e., births under 28 weeks, were significantly reduced in the groups in which a reduction was carried out. This underlines the importance of reducing the number of fetuses by reducing the rate of babies born under 28 weeks gestation who have the worst neonatal outcomes. In another study, the PPROM rate

in the reduction group was 11.1%, and the preterm birth rate was 10%, and these results are comparable to the rates in our study (12).

In our study, the number of fetuses with fetal growth retardation in ongoing pregnancies was 3 (20%) in the IT group and 3 babies (15.4%) in the IC group. In both groups, one patient developed gestational hypertension. The difference between the groups was insignificant, suggesting that the method of intervention does not influence maternal and neonatal outcomes. However, the processing technique was the same in these studies; KCl was administered using a transabdominal method, and the groups that underwent reduction were compared with those that did not (12).

There was only one patient in the IC group whose other twin died within one week of the procedure. In the IT group, we had no patients with complications within one week. The difference between these two groups was not statistically significant (p=0.942). Perinatal mortality was observed in 1 patient, who belonged to the IC intervention group. These results indicate that the complication rate is very low, akin to the literature (13). The number of babies taken home was 14 (93.3%) in the group with IT procedures and 12 (92.3%) in the IC group. No significant difference was found between the two groups (Table 3). In a study comparing reduction results in 148 triplet, quadruplet, and quintuplet pregnancies, the groups in which IT KCl was used were compared with an intravaginal method in which a needle was inserted into the fetal thorax and the amniotic fluid was aspirated. This study aimed to reduce the complication rate with an alternative and earlier method, finding that the rate of babies taken home was 69.7% in the KCl group and 86.1% in the non-KCl group (p=0.045) (7). Although these rates do not compare with our study, they are still lower than our results.

The number of patients with multiple pregnancies is increasing due to the growing use of assisted reproductive techniques for infertility, one of the most significant problems of our time. It is known that 30-50% of multiple pregnancies in developing countries result from infertility treatments (13). As is well known, in multiple pregnancies, maternal and neonatal outcomes deteriorate as the number of fetuses increases (14). For this reason, fetal reduction will likely be employed more frequently, especially in triplet pregnancies and beyond. It is known that the number of fetuses, the position of the fetus, and the chorionic status increase the technical difficulty of the fetus reduction procedure. Moreover, our results show no difference in terms of procedure duration and maternal complications, which favors using this method.

CONCLUSION

Very few studies similar to ours exist in the literature. We believe that the intracranial KCl application is technically simpler and more convenient than the IT application. This method may be preferred due to its technical ease, particularly in clinics where there is a need to improve the learning curve for selecting suitable patients. However, as a limitation of our study, we acknowledge that neonatal outcomes and complication rates should be evaluated with a larger number of patients.

Ethics Committee Approval: This study was conducted with the permission of the Ankara Etlik City Hospital Local Ethics Committee (decision no: AEŞH-EK1-2023-745 date: 06.12.2023).

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REVIEW ARTICLE

An Overview of Psychopathological Manifestations in DDX3X Syndrome: A Narrative Review

ABSTRACT

Typical behavioral traits play a crucial role in the recognition of neurodevelopmental features in rare disorders, such as DDX3X syndrome. DDX3X syndrome is an X-linked genetic neurodevelopmental disorder and often presents with complex symptoms in the neurological, psychiatric, cardiological, ophthalmologic, and gastrointestinal domains, as well as structural brain abnormalities and precocious puberty. This overview study aims to review the psychopathological traits that are concurrent with DDX3X mutations. Although there are nearly 300 studies recorded in academic databases related to psychiatric comorbidities in this syndrome, it has been observed that most of these reports are at the case-report level, the number of cohort studies is quite low and there is only one review. A wide range of psychopathological manifestations is presented in patients with DDX3X syndrome, which may consist of but not limited to cognitive impairments, developmental delay, intellectual disability, language difficulties/delays, autistic traits, attention deficit-hyperactivity disorder, and conduct disorders. The complexity of neurodevelopmental issues in DDX3X syndrome highlights the requirement for a broader-based psychiatric screening, particularly for autism spectrum disorders

Keywords: Autism spectrum disorders, behavioral problems, DDX3X syndrome, developmental delay, intellectual disability, psychiatric comorbidity, neurodevelopmental issues

Although rare diseases (RD) are recognized primarily due to their low prevalence levels (1), defining their clinical phenomenology based on their genetic basis is important for early diagnosis, treatment, and prognosis. DDX3X syndrome, the second most common genetic cause of developmental delays in the pediatric population (2), is also a rare X-linked neurodevelopmental disease. DDX3X is part of the DEAD-box helicase family, located on p11.3–11.23 on the X chromosome. The demonstrated variants are located throughout the DDX3X gene; however, they tend to cluster in the helicase ATP coding domain and C-terminal coding domain (3). It has widespread expression across human tissues and, based on its function in RNA metabolism, plays a pivotal role in the regulation of gene expression, cell cycle control, viral replication, and innate immunity (4-7). Several types of sequence variants in DDX3X are reported in the literature, including missense, nonsense, frameshift, splice site, stop-loss, and in-frame deletions (8). The majority of genetic defects in DDX3X syndrome are de novo variants in the DDX3X gene, particularly in females (8,9). Only a few de novo DDX3X gene mutations have been detected in males (10). Unlike many X-linked genes, DDX3X escapes X-inactivation in females. In this regard, variance in the clinical presentation of different cases is thought to vary according to X-inactivation patterns, even in twins and siblings (11). DDX3X syndrome is the consequence of a de novo mutation within a DDX3X gene at conception, which can be inherited but not frequently (6,9-12). According to recent findings from multiple cohorts, the DDX3X gene has the highest proportion of missense variants identified among other autosomal dominant de novo monogenic rare neurodevelopmental disorders (2).

The most common psychopathological expression of DDX3X de novo variants is developmental delay in both genders (6,9,10,13). To date, a total of 848 reported cases (809 females and 39 males) exist worldwide (14). However, there is no exact epidemiological data on the real prevalence of DDX3X syndrome. The gene-based prevalence of de novo mutations was estimated in a 2022 paper by extracting data from the number of neurodevelopmental disorders cohort cases, and the prevalence of DDX3X-related neurodevelopmental

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disorders with intellectual disability was estimated at 0.0036% (2). According to another research, DDX3X gene mutations were one of the common genetic etiologies of intellectual disability, considering the 1-3% prevalence of unexplained intellectual disability in females (9). Not only intellectual disability but also neurological manifestations, motor retardation, behavioral issues, cardiac dysfunctions, ophthalmic, and gastrointestinal problems may be presented in DDX3X syndrome (9,11,13,15,16). DDX3X variants were also associated with macro-anatomical abnormalities (gross MRI findings and brain tumor) in the central nervous system (4,17). Due to the complexity of phenomenology and findings in imaging techniques, DDX3X mutations are frequently misdiagnosed as cerebral palsy or autism spectrum disorders (18,19). Therefore, compared to other diagnostic methods, careful screening of cases combined with Whole Exome Sequencing prior to a final DDX3X syndrome diagnosis is crucial.

Identifying the indicative behavioral, cognitive, affective, or physiological manifestations is helpful for clinicians to provide early diagnosis and multidisciplinary management of rare disorders (20). Knowledge of the DDX3X-related psychopathological symptom range enables early diagnosis, multidisciplinary screening, and treatment, which improves the prognosis and quality of life (3). Although nearly 300 studies are recorded in academic databases related to behavioral manifestations in this syndrome, it has been observed that most of these reports are at the case-report level, the number of cohort studies is quite low, and there is only one review (3,9,17,21). In this regard, an up-to-date review of the prevalence distribution of psychopathological features in patients with DDX3X syndrome may be useful in determining the themes for further research on the subject. The questions are:

"What are the indicative psychopathological features presented in DDX3X syndrome?"

"How is the prevalence of psychopathological features distributed among patients with DDX3X syndrome?"

Psychopathological Frame in DDX3X Syndrome

The most common behavioral issues have been reported as intellectual disability or developmental delay, speech-communication dysfunctions, autism spectrum disorders or autistic-like traits, attention deficit-hyperactivity disorder, general anxiety disorder, self-injurious behaviors, sensorial hypersensitivities, and sleep disturbances (3,8,9,11-13,19,21,22). Among these psychiatric conditions associated with DDX3X mutations, intellectual disability/developmental delay and speech/communication problems were the most commonly reported ones. The recent cohort of Tang et al. (8), the first cohort of pediatric DDX3X syndrome (n=15, 3-16 years old) in a prospective study design, provides a comprehensive characterization of neurobehavioral symptoms in contrast to previous research: high rates of intellectual disability (80%), autism spectrum disorder (60%), and attention deficit-hyperactivity disorder (53%), as well as generalized anxiety disorder (7%), were demonstrated (8). A detailed description of each psychopathological feature is presented in Table 1 and subsections as follows:

Cognitive Impairment: Intellectual Disability & Developmental Delay
Intellectual disability/developmental delay is increasingly identified and appears to be a universal characteristic among patients

Table 1. Summary of the data regarding psychopathological features of DDX3X syn.

Frequently reported psychopathological features	Approximate Ratios from Studies*
Cognitive impairments: Intellectual disability/ Developmental delay	98%
Speech problems: Communication/Speech delay Developmental apraxia of speech	70%
Autism spectrum disorders	26%
Sensory symptoms: Sensorial hypo/hypersensitivity Sensory seeking	65%
Attention deficit-hyperactivity disorder	20%
Anxiety disorders: General anxiety disorders Specific phobias	40%
Self-injurious behaviors: Hair pulling Skin picking biting hands or knees Hitting their heads Throwing themselves onto the floor	56%
Sleep disturbances: Hypo/hypersomnia Early waking Long sleep latency Difficulty maintaining sleep Midnight awakenings	70%

*References: (3,8,9,11-14,19,21,22)

with DDX3X syndrome, both in pediatric and adult samples. The average prevalence of intellectual disability (Table 1), reported in most current cohorts, was nearly 98% (3,8,9,11-13,21,22), and the majority of reported patients met the criteria for intellectual disability ranging from mild to severe (9,12,13). Additionally, up to 3% of females with unexplained intellectual disability/developmental delay were associated with DDX3X mutations (9). However, intellectual disability was not reported in some case studies or cohorts with small sample sizes (11,19). Although the case (7 years old) reported by Stefaniak et al. (19) did not exhibit intellectual disability, severe difficulties were identified in social intelligence. In the cohort of Snijders et al. (9) of 38 females with DDX3X mutations (1-33 years old), de novo mutations in DDX3X were demonstrated as the most common genetic cause of intellectual disability in females. In the cohorts of Wang et al. (13) (1-47 years old; n=28) and Dai et al. (22) (1-6 years old; n=23), the ratio of patients with developmental delay or intellectual disability was 100%. Comparatively, the vast majority of participants with DDX3X mutations exhibited intellectual disability in the studies of Lennox et al. (12) (106:107, 1-24 years old), Tang et al. (8) (13:15, 3-16 years old), and Ng-Cordell et al. (21) (13:21, 3-22 years old). In the cohort of Levy et al. (3), intelligence levels ranged from average to severe, with the vast majority of cases demonstrating a global delay across all domains of adaptive functioning (according to Vineland III: communication, socialization, and daily living skills), with -3 standard deviations below the population mean (3). A subset of missense variants, likely with a dominant-negative functional consequence, are associated with more severe clinical manifestations, such as polymicrogyria and more severe intellectual disability (8,12). Furthermore, patients with protein-truncating variants, such as nonsense, frameshift, or splice site variants, tended to have a less severe phenotype than those with missense variants (8).

Speech / Communication Problems

A global delay in developmental milestones appears to be the most common neurodevelopmental issue in DDX3X syndrome, and language difficulties were almost universal across all available cohorts, with a report of approximately a 70% ratio (Table 1) (3,8,11,19,21,22). However, Snijders et al. (9) and Wang et al. (13) did not report communication or speech delay as a feature of DDX3X syndrome. Almost half of females with DDX3X syndrome were nonverbal after 5 years of age in the cohort of Lennox et al. (12), whereas 1/3 of those were reported as nonverbal in the cohort of Tang et al. (8). Furthermore, the verbal participants in the cohort of Tang et al. (8) also presented with delays in both receptive and expressive language skills. Patients with autism spectrum disorder scored higher on all language assessments compared to those without ASD (8). Beal et al. (11) described speech or motor delays in 4 out of 6 patients, one of whom exhibited severe speech and language deficits despite having a mild to moderate intellectual disability diagnosis. Almost 91% (21,23) of the patients in the cohort of Ng-Cordell et al. (21) exhibited speech/communication abnormality, with 17% of participants presenting with severe (non-verbal), 20% with moderate (expressing only with single words), and 48% with mild symptoms (expressing with both words and phrases). In the case report of Stefaniak et al. (19), the 7-year-old female case was non-verbal and had a strong desire for social interaction. In the Chinese cohort of Dai et al. (22), almost all of the participants with DDX3X syndrome were described as minimally verbal (expressing no more than four words). In the cohort of Levy et al. (3), language milestones were achieved with significant delays, such as expressing the first word at the 31st month and phrase speech at the 48th month. The use of augmentative and alternative communication was an auspicious form of support for some patients with DDX3X syndrome, though the statistic was not given in the cohort of Levy et al. (3). Given the example of monozygotic female twins with discordant phenotypes (one with autism, aggression, and non-verbal, the other with only minimal language problems) in the same cohort, specific variants may not predict the clinical presentation of DDX3X syndrome in contrast to the known paradigm in other genetic disorders (3).

Autism Spectrum Disorders (ASD)

DDX3X syndrome has recently emerged as the most prevalent genetic cause of ASD in females (9). According to recent reports from 'ddx3x.org' covering 50 countries, up to 769 DDX3X cases (38 males and 731 females) have also presented with ASD traits (14). Most available data on DDX3X syndrome reported ASD characteristics in patients with a ratio of approximately 26% (Table 1) (3,8,12,19,21,22), whereas few data did not describe ASD characteristics as separate traits but included them along with aggression and hyperactivity in the category of conduct problems (9,11,13). The heterogeneity in reports of ASD traits in patients with DDX3X syndrome may depend on the variety of assessment techniques used in previous studies. The highest prevalence of ASD traits (63%) was reported in the study of Levy et al. (3), which used gold standard assessment techniques, including The Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R). However, previous research using parent-proxy clinical tools for assessment of autistic traits demonstrated different prevalence of ASD-resembling characteristics, although they also reported moderately higher levels of autism traits compared to general population norms (19,21,22). A novel non-canonical splice-site variant of the DDX3X gene was recognized in recent research, which exhibited autistic-like symptoms such as stereotypic behaviors that improved with inclusive education and behavioral interventions, as well as some characteristics that did not meet the diagnostic criteria of ASD, such as spontaneous behaviors, curiosity, and good socialization ability despite being nonverbal (19). ASD-resembling symptoms appear to be prevalent psychopathological features of DDX3X syndrome that can manifest as a wide range of symptoms with varying severity (3,23,24).

Sensorial Hypo / Hypersensitivity

Sensorial hypersensitivity/hyposensitivity was considered a new criterion in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for the diagnosis of ASD but is also reported in other neurodevelopmental disorders (25,26). Sensorial symptoms, defined as behavioral reactions (hyporeactivity, hyperreactivity, or sensory seeking) associated with atypical responses or unusual interest in sensory stimuli (25), were particularly mentioned as important characteristics in DDX3X syndrome in the previous two cohorts and one case report (8,19,21). In the prospective study of Tang et al. (8), using the Short Sensory Profile and Sensory Assessment for Neurodevelopmental Disorders for assessment of sensory symptoms, definite sensorial changes were reported in all participants with DDX3X syndrome. As part of the research of Tang et al. (8), the participants with DDX3X syndrome were matched with typically developing controls (n=29), and the Z-score was calculated.

Sensory symptoms in all symptom domains and sensory modalities were more frequent in the DDX3X group (100%) compared to the control group. Findings indicated that sensory processing disorders such as sensory seeking and hyporeactivity were more frequent than hyperreactivity (8). Moreover, tactile hyporeactivity was more common than visual or auditory hyporeactivity, while visual hyperreactivity was more frequent than tactile and auditory hyperreactivity (8). In the cohort of Levy et al. (3), high levels of sensory hyporeactivity (80%) and high sensory seeking behaviors (87%) were demonstrated in the DDX3X patients.

Attention Deficit-Hyperactivity Disorder (ADHD)

ADHD was particularly mentioned in the cohorts of Lennox et al. (12) and Tang et al. (8). The ADHD ratio was identified as 15% in the cohort of Lennox et al. (12), while it was 40% in the cohort of Tang et al. (8). The disruptive and maladaptive behaviors exhibited by participants in other studies may be considered as belonging to other psychiatric or behavioral concerns (3,9,11,13,19,21,22). On the other hand, behavioral and psychotropic interventions for disruptive and maladaptive behaviors, and further assessment of these behavioral traits as ADHD diagnosis were recommended (3).

Internalizing Traits and Other Psychopathological Issues

General anxiety disorder was particularly mentioned in the two most recent cohorts (3,21), but it had not been addressed in papers before 2022 (8,9,11-13,19,22). The presentation ratio is approximately 40% for anxiety disorders in available studies (Table 1). Anxiety symptoms, including specific phobias related to sounds, animals, or objects, shyness, social withdrawal, and concerns about routines, were presented in 69% of DDX3X participants in the cohort of Ng-Cordell et al. (21). One case in the paper by Levy et al. (3) presented with separation anxiety and behavioral aggression triggered by fear of frustration. Anxiety and affective disorders require further investigation in DDX3X patients as newly described conditions in the literature.

Self-injurious behavior was mentioned only in the paper by Ng-Cordell et al. (21), where this behavioral pattern was first identified as a significant feature of DDX3X syndrome. In the cohort of Ng-Cordell et al. (21), almost 56% (13,23) of participants with DDX3X syndrome presented with self-injurious behaviors, including stress-triggered hair pulling, skin picking, biting hands or knees, hitting their heads, and throwing themselves onto the floor; the prevalence of self-injurious behaviors was higher than in the control group with autism (21). The authors of this study particularly highlighted the link between self-injurious behaviors and anxiety (21), suggesting that further research on the role of stress, anxiety, and affective traits in other frequently reported maladaptive behaviors in DDX3X syndrome is warranted. There is a need for more research on self-injurious behaviors among patients with DDX3X syndrome, particularly in the affected pediatric population, to establish appropriate management strategies.

Sleep disturbances have been recognized in some previous studies, with a prevalence of nearly 70% (3,11,19,21) (Table 1). Nearly one-third of participants in the study by Beal et al. (11) presented with sleep disturbances, while almost 56% of DDX3X patients in the study by Ng-Cordell et al. (21) presented with sleep problems such as hypo/hypersomnia, early waking, long sleep latency, and difficulty maintaining sleep. In the review by Levy et al. (3), the prevalence of sleep disturbances was summarized as high as 80% (20,25).

DISCUSSION

Early diagnosis of manifestations in different domains is crucial for the accurate management of rare disorders. DDX3X syndrome is a rare, complex genetic disorder associated with varied psychopathological phenotypes, particularly neurodevelopmental issues. However, the full spectrum of psychopathological issues in DDX3X syndrome is not well known or investigated. Therefore, more studies with diverse and larger samples are needed to broaden our understanding of this syndrome and its behavioral manifestations. Additionally, there is an important need for Whole Exome Sequencing screening in children with unexplained intellectual disability/developmental delay, developmental speech delays, and childhood apraxia of speech, as various DDX3X gene mutations are a highly plausible genetic etiology for these disorders (9,27).

The findings from this manuscript, aiming to present a narrative review of the limited literature on the psychopathological framework of DDX3X syndrome, demonstrate varied psychiatric manifestations, predominantly including neurodevelopmental issues like intellectual disability/developmental delay, speech/communication problems, autism spectrum disorders, and ADHD, as well as internalizing and behavioral traits such as general anxiety disorder, specific phobia, self-injurious behaviors, sleep disturbances, and sensory symptoms (Table 1). The wide range of externalizing and internalizing traits in pediatric patients with DDX3X syndrome also raises concerns about the high possibility of misdiagnosing early neurodevelopmental issues. Therefore, the clinical utility of exome sequencing in preventing misdiagnosis of ASD, cerebral palsy, Rett syndrome, Dandy-Walker syndrome, Toriello-Carey syndrome, or idiopathic intellectual disability is important (19,28). It should be noted that patients with DDX3X syndrome often demonstrate a strong desire to be cooperative, caring, and friendly in social situations, according to parent-proxy reports of social functioning (21), in contrast to autistic-like behaviors, self-injurious behaviors, and anxiety disorders. However, the positive social abilities of patients with DDX3X syndrome have not yet been described or explored in the literature, other than brief mentions in medical interviews with caregivers (19,21).

On the other hand, the alertness of psychiatrists regarding the association of the aforementioned developmental and behavioral traits with discordant DDX3X mutations is important to prevent overlooking the physical manifestations that accompany psychiatric problems. These include neurological issues (hypotonia, epilepsy, gait disturbance, and other movement disorders), cardiological conditions (ventricular septal defect, atrial septal defect, patent ductus arteriosus, patent foramen ovale, and long QT syndrome), gastrointestinal problems (chronic constipation, gastroesophageal reflux, and feeding issues), ophthalmological concerns (ocular and visual abnormalities such as strabismus, nystagmus, colobomas, myopia, hypermetropia, astigmatism, etc.), endocrinological disorders (precocious puberty, hypothyroidism), dermatological conditions (café-au-lait spots, eczema, congenital dermal melanocytosis, cutaneous mastocytosis, and other types of nevus), recurrent infections (recurrent otitis media, urinary tract, and upper respiratory infections), auditory problems, and scoliosis (3). Accurate and early diagnosis of each symptom domain in DDX3X syndrome can enable patients to benefit from appropriate therapy, early educational and physical rehabilitation programs, and primary care. Due to insufficient clinical data, formal diagnostic criteria for DDX3X syndrome

have not been established, nor have formal practice parameters for managing the care of patients with DDX3X syndrome (3,29).

With the help of 'Next Generation Sequencing' or 'Whole Exome Sequencing', a broader group of genes related to intellectual disability can be detected, enabling the differential diagnosis of DDX3X syndrome from other intellectual disability-related genetic disorders (3,30-32). Patients with RSRC1 gene mutations present with global intellectual disability/developmental delay, behavioral problems, and hypotonia (30), whereas ADGRL1 haploinsufficiency can lead to consistent developmental, neurological, and behavioral abnormalities (32), and variants in the RAC3 gene have been linked with structural brain abnormalities and facial dysmorphia (31). Therefore, 'Next Generation Sequencing' and 'Whole Exome Sequencing' are particularly crucial for patients who do not exhibit strictly marker features for well-known developmental disorders. Even if patients meet clinical features of such disorders as ASD, ADHD, intellectual disability, speech delay, articulation problems, general anxiety disorder, self-injurious behaviors, communication/speech delay, or sensory symptoms, psychiatric consultation and a thorough clinical investigation before a final diagnosis are essential. For patients with each specific diagnosis, a specialized educational program based on standardized adaptive and academic testing is necessary to support the individual's unique learning profile.

A developmental assessment (e.g., determination of expressive and receptive language and communication abilities, evaluation of verbal and nonverbal cognitive function, and evaluation of the achievement of fine and gross motor milestones and skills) is recommended at the time of DDX3X syndrome diagnosis. This should be followed by referrals for early intervention and special education, speech and language therapy, occupational therapy, and ABA therapy as clinically indicated. Recommendations include the possible use of pharmacological approaches, as indicated by the treating physician, behavior therapy, and caregiver training and guidance to support patient-based behavioral intervention strategies. Additionally, there is no reason to assume that individuals with DDX3X syndrome have any less risk for mood disorders; thus, mood and affect should be assessed, and developmentally appropriate engagement in pleasurable activities should be screened for and encouraged at routine pediatric visits, with referral for psychiatric assessments as indicated.

CONCLUSIONS

In this narrative review of the psychopathological features of DDX3X syndrome, the most up-to-date knowledge is presented, based on the recent increase in research on the issue over the last few years. Given the insufficiency of available data, especially regarding the small group of patients living in different locations around the world, more specific studies of these psychopathological traits are required, particularly in a wider context. This includes studies on speech and internalizing problems, as well as the correlation between anxiety and self-injurious behaviors, reflecting the increased demand for behavioral and psychotherapeutic support during childhood.

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ACADEMIC JOURNAL OF HEALTH

CASE REPORT

Adeloye – Odeku Disease in Turkish children: A Case Report and a Short Literature Review

ABSTRACT

Congenital dermoid inclusion cysts located in the anterior fontanelle were defined as Adeloye-Odeku Disease by Adeloye and Odeku in 1971. The epidemiological characteristics of this rare disease are still unclear. These cysts are subgaleal benign lesions, and the main treatment is surgical excision. Radiological imaging is important in diagnosis and surgical planning due to their location. Although adult cases have been reported in the literature, Adeloye-Odeku Disease is primarily a subject of pediatric neurosurgery. In this study, we present a 10-month-old case of an anterior fontanel dermoid cyst and conduct the first national review of the disease with 9 cases reported from our country.

Keywords: Anterior fontanelle, congenital, dermoid cyst, pediatric

Dermoid cysts arise from the cystic enlargement of ectodermal inclusions in the neural tube during the 3rd-5th weeks of fetal life (1). Craniospinal dermoid cysts were first described by Cruveilhier in 1892. Adeloye and Odeku introduced anterior fontanel dermoid cysts as Adeloye-Odeku Disease in 1971 by publishing a case series of 18 Nigerian patients (2). Although it was thought to be an African cyst for many years due to this case series, cases from different nations have been reported subsequently (3-5). Anterior fontanel dermoid inclusion cyst and bregmatic dermoid cyst are other names for this disease. Congenital anterior fontanel dermoid cysts, which constitute 0.1-0.5% of childhood brain and skull tumors, are very rare (5). Although it is a very rare disease, they are significant lesions from a surgical perspective because of features such as their midline location, being congenital cranial lesions, and their adjacency to the superior sagittal sinus and cerebrum (6,7). The curative treatment for Adeloye-Odeku Disease is always surgical excision. Adjuvant treatment is not required because they are benign lesions. No recurrence has been reported in the literature (8). In our literature review on Adeloye-Odeku Disease in Turkish children, we found that a total of 9 pediatric cases were reported in 5 different articles from our country (5,7,9-11). Since it is not possible to obtain large case series for a disease with such a low incidence, case reports are valuable for providing the necessary accumulation in the literature and understanding rare diseases. In this study, we aim to contribute to the literature by presenting a pediatric case of Adeloye-Odeku Disease that was successfully treated in our clinic. Additionally, this report is the first review of 9 case reports originating from Türkiye.

CASE

The parents brought a 10-month-old girl with no significant medical history to our clinic with a complaint of a palpable swelling in the frontal midline of the head. The patient's parents stated that they noticed the swelling when the patient was only 2 months old and that it increased in size over time. She had no neurological deficit, and growth and development were compatible with her age. On physical examination, we detected a mass of approximately 3x4x4 cm, located on the anterior fontanel, covered with normal skin and partially fluctuant (Figure 1a and 1b). The transillumination test was positive (Figure 2). Laboratory tests were normal. Computed tomography (CT) showed a cystic lesion on the anterior fontanel without bone erosion or depression (Figure 3a, 3b, and 3c). T1 and T2 weighted (T1W, T2W) magnetic resonance

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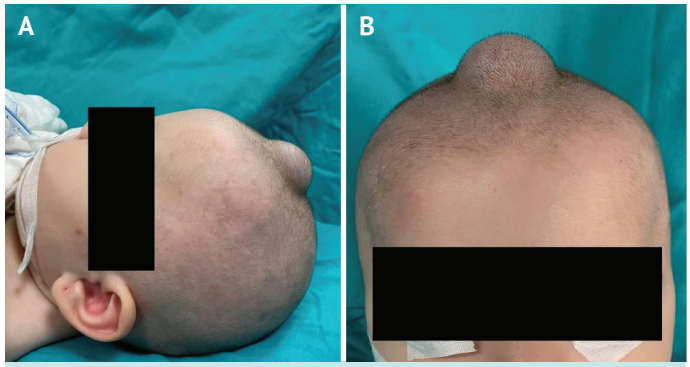

Figure 1a and 1b. Morphology of the cycst.

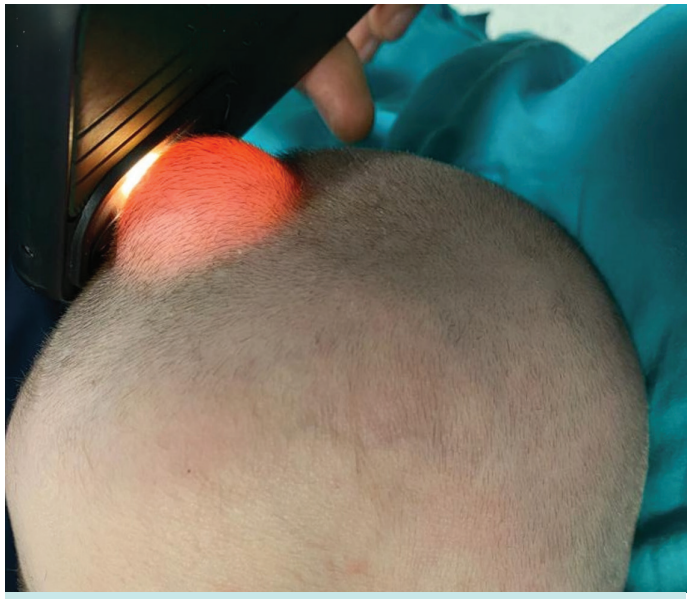

Figure 2. Transillumination test (positive).

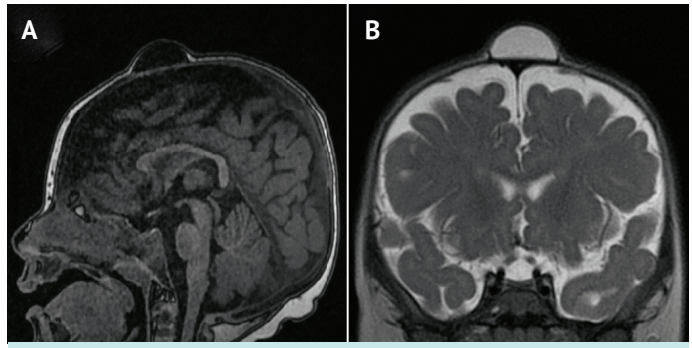

Figure 4. Magnetic resonance images of the cycst. (A) is sagittal view of T1W and (B) is coronal view of T2W images.

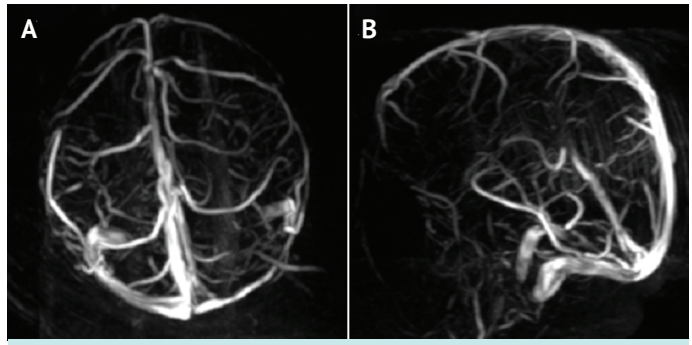

Figure 5. MR venography. Note that there is no irregularity or invasion of the superior sagittal sinus in neither axial (A) nor sagittal (B) view.

imaging (MRI) revealed a cystic lesion isointense with cerebrospinal fluid, located extracranially and without intracranial extension (Figure 4a and 4b). Magnetic resonance venography study was successful in demonstrating that the cyst was not associated with the superior sagittal sinus (Figure 5a and 5b).

Surgical technique

In the operating room, under general anesthesia, we made a coronal-oriented linear incision of approximately 5 cm, passing through

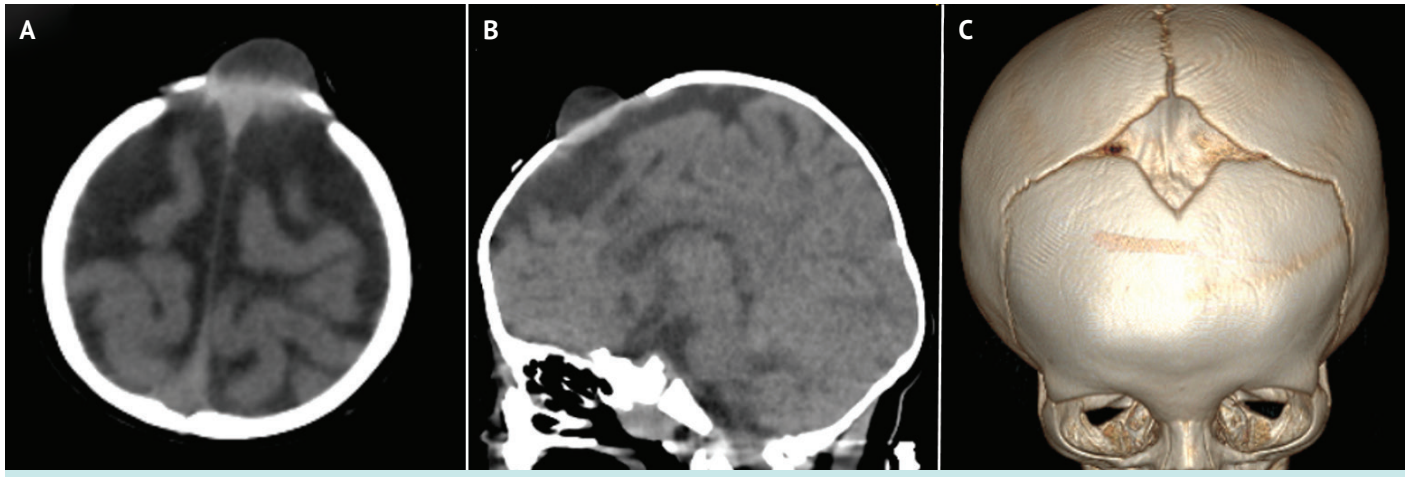

Figure 3. CT images of the anterior fontanelle dermoid cycsr. (A) is axial, (B) is coronal image. (C) ise 3D reconsruction of CT scan. Note that there is no bone flattening or erosion.

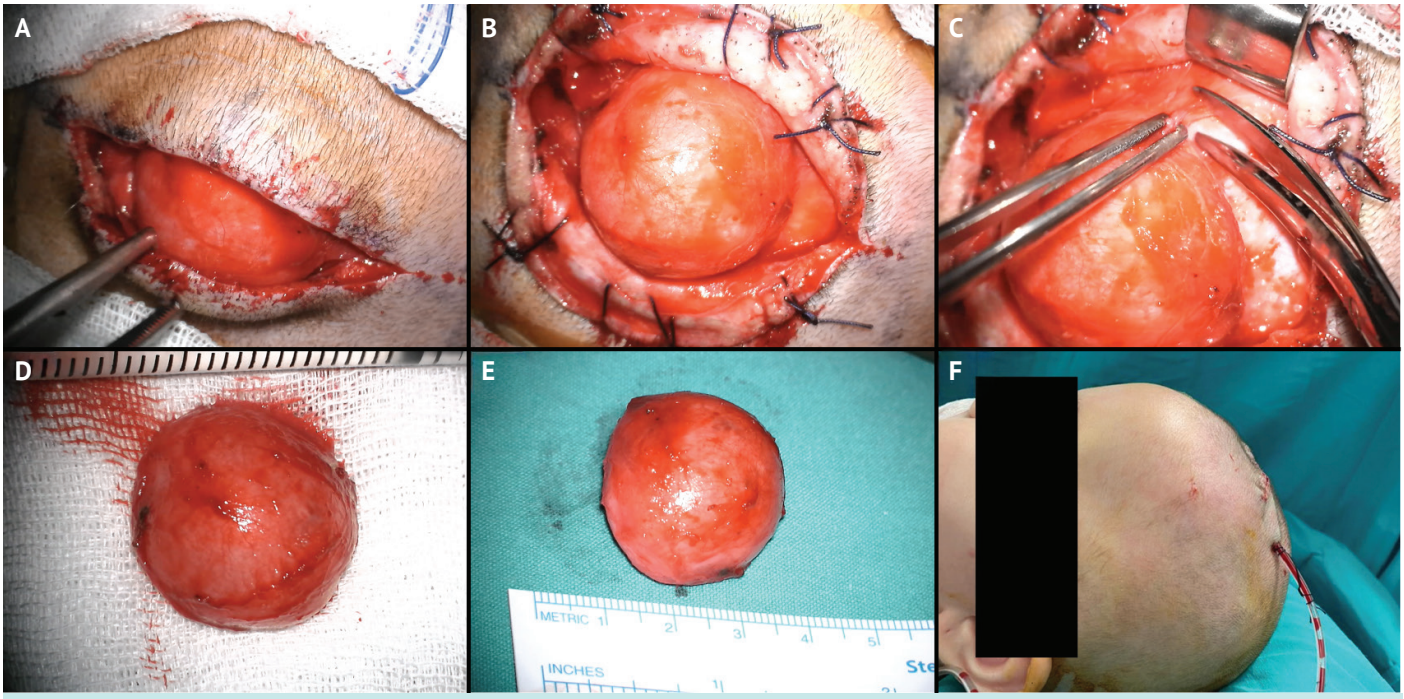

Figure 6. Intraoperative images. Note that the aponeurosis covering the cyst is thinned and adhered to the cyst wall in the Figure 6B. Figure 6C shows how we cut the dural aponeurosis from the neck of the cyst without dissecting it.

Table 1. This table summarizes the morphological and clinical features of cases reported from Turkey

Case	Age	Sex	Size	TI	Fibrous pedicle	Sinus invasion	Intracranial extension	Bone flattening	Bon erosion	Recurrence
İzgi et al.	16 years	Male	2x5x5 cm	-	-	-	-	-	+	-
Berkman et al. (1)	6 months	Male	2x2x2 cm	-	+	-	-	-	-	-
Berkman et al. (2)	8 months	Male	3x3x3 cm	-	+	-	-	-	-	-
Aslan et al. (1)	6 months	Male	3x3x3 cm	-	-	-	-	+	+	-
Aslan et al. (2)	5 years	Male	4x4x4 cm	-	-	-	-	+	+	-
Aslan et al. (3)	3 years	Male	3x3x3 cm	-	-	-	-	+	+	-
Aslan et al. (4)	5 years	Male	3x3x3 cm	-	-	-	-	+	+	-
Yılmaz et al.	11 years	Female	4x5x5 cm	-	+	-	-	+	+	-
Genç et al.	4 months	Female	4x5x5 cm	+	-	-	-	-	-	-
Emrahoğlu et al.	10 months	Female	3x3x3 cm	+	-	-	-	-	-	-

TI: Transillumition test

the apex of the cyst and including the skin and subcutaneous tissue, with the patient in a supine and head-neutral position (Figure 6a). The cyst was located subgaleally. The galeal aponeurosis covering the cyst was thinned and adhered to the cyst. To facilitate dissection and provide hemostasis, we preferred to traction the skin with silk sutures (Figure 6b). To avoid the risk of cyst rupture, we cut the aponeurosis overlying the cyst from the neck of the cyst without dissecting it using a surgical microscope (Figure 6c). Since the cyst was attached to the external dura layer on the ventral surface, sharp dissection was effective in preserving the superior sagittal sinus, and we were able to remove the cyst en bloc with this technique (Figure 6d and 6e). Finally, the excess skin was reconstructed and closed with 4.0 subdermal nylon (Figure 6f). The patient was taken to the ward in the early postoperative period. We did not detect any abnormalities in the physical examination, laboratory tests, and postoperative imaging. On the postoperative first day, 5 cc of serohemorrhagic fluid was present in the drain. We removed the drain and discharged the patient. The pathology examination results confirmed the dermoid cyst. In the postoperative 3-month follow-up of the patient, cosmetic improvement was excellent, and there was no recurrence.

DISCUSSION

Anterior fontanel dermoid cysts fall into the category of congenital inclusion cysts according to the new classification. They are theorized to form from the cystic dilatation of ectodermal remnants

in the neural tube and are situated under the galeal aponeurosis (12). This condition, first identified as Adeloye-Odeku Disease in the Nigerian population, seemed unusual in non-black races when considering early literature. However, subsequent publications have indicated that this rare disease is not exclusive to the black race (13). The literature includes 9 pediatric and 1 adult Turkish cases of Adeloye-Odeku Disease. İzgi et al. (10) reported the first of these in 1989. The characteristics of cases reported from our country are summarized in Table 1.

In international literature reviews, consensus on the disease's gender distribution is lacking, with inconsistent data (14). Nonetheless, a higher prevalence in females is often reported (8). Including the case we present, the female-to-male ratio among the 10 pediatric cases reported in our country is 3:7, contradicting the notion that the disease is more common in females.

Anterior fontanel dermoid cysts are present from birth, growing slowly due to content increase (13). They are typically noticed by parents as a swelling on the forehead in early infancy (5). These cysts are covered with normal skin and can be fluctuant or entirely solid, but not pulsatile. A negative transillumination test supports a dermoid cyst diagnosis (15). The cysts are painless, and manipulation does not trigger pain (4,7). In the case we presented, the patient's parents reported that the lesion enlarged over months. The swelling was fluctuant, immobile, non-pulsatile, and painless upon palpation. Other cases reported from our country similarly showed no pulsation or pain, with cyst fluctuation noted in 6 out of 9 cases. Contrary to general belief, our case had a positive transillumination test, aligning with a few rare instances in the literature (15). Among the 9 cases reported from Türkiye, only Genç et al. (9) noted a positive transillumination test in the 4-month-old patient they presented. The lesions in both our case (3x3x3 cm) and the other 9 cases reviewed (mean 3.1x3.7x3.7; min: 3 – max: 5 cm) vary in size from 1 to 7 cm, as documented in the literature (16). Literature suggests lesion size correlates with patient age, but our review's limited case number precludes testing this hypothesis (17).

Physical examination and radiological imaging are key diagnostic elements. X-ray imaging, ultrasonography (USG), CT, and MRI can aid in diagnosing Adeloye-Odeku Disease. Coronal and lateral radiographs can reveal whether the lesion is cystic and if any bone irregularities are present. USG can detail the cyst's morphology and, if the anterior fontanelle remains open, its intracranial extension and superior sagittal sinus invasion (18,19). CT scans effectively show the lesion's relationship with bone structures, with coronal and sagittal plane images almost perfectly displaying a hypodense extracranial cyst without calcifications. Some cases have reported external table erosion or flattening. Dermoid cysts typically appear hyperintense on T2W images and hypointense on T1W images in MRI scans. MRI excellently delineates the cyst's intracranial extension. Given the lesion's location, MR venography is invaluable for assessing its proximity to the superior sagittal sinus, a crucial surgical planning aspect (7,20,21). Differential diagnosis for Adeloye-Odeku Disease includes conditions like encephalocele, meningocele, sebaceous cyst, lipoma, cephalohematoma, hemangioma, lymphangioma, sinus pericranii, and meningioma, making radiological imaging techniques essential for accurate diagnosis (22,23). The case we present is our clinic's first operated case, utilizing both CT and MRI for diagnostic and surgical planning. The

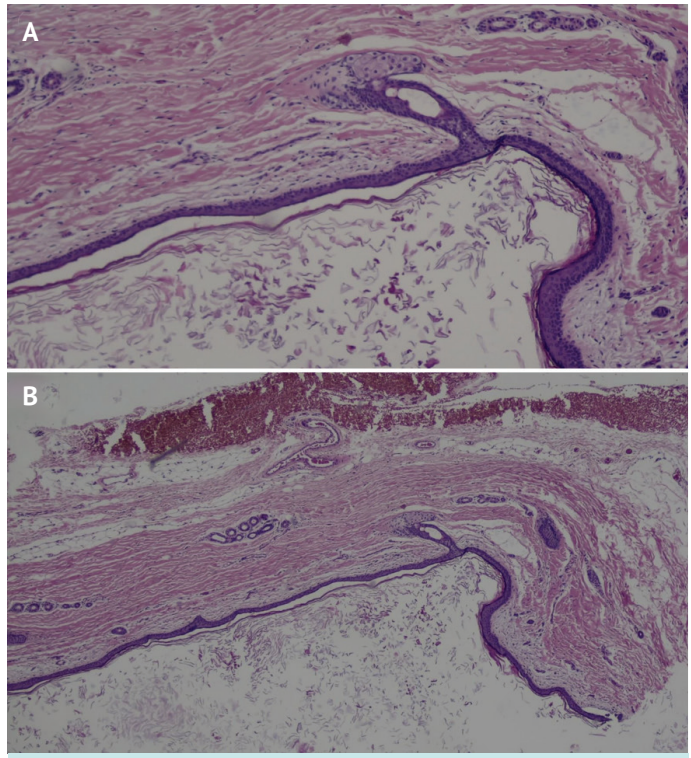

Figure 7. In the preparations stained with hematoxylin-eosin, a cystic lesion lined with stratified squamous epithelium and keratin lamellae are noted (7a x100, 7b x40).

lesion's radiological characteristics matched those in the literature, with no observed bone erosion or flattening. MR venography was particularly useful for surgical planning to assess the lesion's superior sagittal sinus invasion status. Bone structure erosion was noted in 6 of the 9 cases reported from our country, with 5 showing bone depression (5,7). None of the cases had superior sagittal sinus invasion. Despite CT's X-ray exposure drawback and MRI's limited resources, we recommend both for patients due to the surgical significance of the lesion's anatomical location and the prevalence of midline anomalies in the pediatric age group.

Anterior fontanel dermoid cysts are benign; the treatment is always surgical excision. Adjuvant therapy is not required after surgery (9). Surgical excision is performed for cosmetic reasons, to prevent infectious complications, and to confirm the diagnosis histopathologically. To avoid potential infectious spread and aseptic meningitis during surgery, it is crucial to maintain the cyst's integrity and protect the superior sagittal sinus (6). In the surgical management of the patient we presented, since the galeal aponeurosis covering the cyst was thinned and adhered to the cyst wall, we chose to remove the cyst along with the aponeurosis to prevent cyst rupture and shorten the procedure's duration. We believe this approach is safer and more straightforward when dissection of the aponeurosis and cyst is challenging. Additionally, while both elliptoid and linear coronal incisions have been suggested in the literature, we opted for a linear coronal incision. We reasoned that tissue loss from the first incision would be unsuitable for reconstructing the remaining skin after cyst removal. In reviewing cases from our country, we found that a linear incision was preferred in 7 of 9 cases and an elliptoid incision in 2, with no significant difference in outcomes.

Moreover, in 3 of the reviewed cases, the authors noted a fibrous pedicle connecting the cyst to the external dural layer (7,11). Our case did not have such a stalk. However, due to the adhesion between the external dural layer and the cyst, we deemed blunt dissection risky for superior sagittal sinus penetration and thus preferred sharp dissection.

The diagnosis of a dermoid cyst is confirmed by histopathological examination, identifying a cyst lined with stratified squamous epithelium and skin appendages such as keratin lamellae, sebaceous glands, and sweat glands (24). In our case's histopathology preparations, a cyst lined with stratified squamous epithelium and keratin lamellae was observed (Figure 7).

Adeloye-Odeku Disease is benign, with no additional treatment required post-surgery (1,4,5). No recurrence was reported in any case from Türkiye, including the case we presented, aligning with the global literature.

CONCLUSION

Adeloye-Odeku Disease denotes congenital dermoid inclusion cysts located in the anterior fontanelle. The condition is quite rare, leaving its epidemiological characteristics yet to be fully elucidated. In the case we presented, we highlighted the efficacy of a linear skin incision in surgical technique and the unnecessary dissection of the galeal aponeurosis and cyst due to the risk of rupture and procedure prolongation. Through this study, we aimed to add a case to the literature on Adeloye-Odeku Disease, a rare condition. Additionally, this study represents the first review discussing cases reported from Türkiye within the literature context.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.E.E., E.R.Y.; Design – H.D., M.E.E.; Supervision – E.R.Y.; Analysis and/or Interpretation – M.E.E., E.R.Y.; Literature Search – M.E.E., H.D.; Writing – M.E.E., E.R.Y.; Critical Review – E.R.Y., M.E.E., H.D.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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ACADEMIC JOURNAL OF HEALTH

CASE REPORT

Brachymetatarsia of The First Metatarsal

ABSTRACT

Brachymetatarsia, also known as hypoplastic metatarsal, is a rare skeletal anomaly characterized by the abnormal shortening of the metatarsal bones. This condition can be congenital, idiopathic, or secondary to surgery, trauma, or other underlying conditions. Radiographic findings typically reveal a shortened and underdeveloped metatarsal. The clinical manifestations of brachymetatarsia can vary significantly, influenced by various factors. The fourth metatarsal is most commonly affected, followed by the first metatarsal.

The current report presents a unique case of congenital unilateral brachymetatarsia with radiographic findings in the first metatarsal of a young adult male. Understanding the anatomical and clinical implications of brachymetatarsia is crucial for radiologists, orthopedic surgeons, and other medical professionals, as it informs diagnosis, management, and potential surgical interventions.

Keywords: Brachymetatarsia, short toe, deformity, metatarsal bones, skeletal anomaly

CASE REPORT

A 32-year-old male presented to the emergency department with a chief complaint of a recent inversion injury to his left foot. His medical history was unremarkable, with no documented chronic ailments or prior surgical interventions. On clinical examination, localized tenderness was identified over the fifth metatarsal region of the left foot. Notably, a distinct discrepancy in length was observed between the first digits of the bilateral feet, with the left appearing shorter. The patient reported this anatomical variation as congenital, emphasizing that it had neither posed any functional limitations nor elicited cosmetic concerns throughout his life.

Diagnostic imaging, comprising anteroposterior and lateral oblique radiographs of the left foot, corroborated the clinical observation, revealing a shortened first metatarsal. In contrast, the morphological attributes and numerical count of the remaining metatarsals, phalanges, and tarsal bones in both feet were consistent with standard anatomical presentations (Figure 1 a, b).

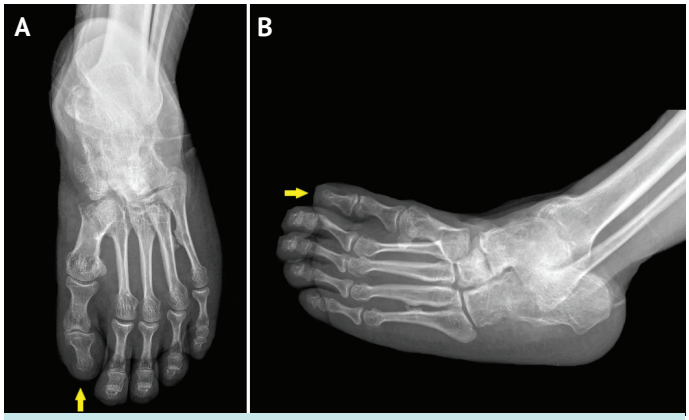

Figure 1. Anteroposterior (A) and lateral oblique (B) radiographs of the left foot, showing that the first metatarsal is shorter than others (yellow arrows).

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DISCUSSION

Brachymetatarsia is defined as the atypical shortening of one or more of the metatarsal bones, specifically when a metatarsal concludes more than 5mm proximally relative to the alignment of the metatarsal heads (1,2). This foot anomaly has a documented incidence ranging between 0.02% and 0.05%, exhibiting a pronounced gender predilection with a female-to-male ratio of approximately 10.53:1 (3). The etiology of brachymetatarsia is multifaceted. While some cases are congenital, others are acquired due to various reasons, including iatrogenic interventions. Furthermore, brachymetatarsia has been associated with a spectrum of medical conditions and syndromes, such as Apert syndrome, Down's syndrome, Albright's osteodystrophy, dystrophic dwarfism, sickle-cell anemia, poliomyelitis, pseudohyperparathyroidism, and certain malignancies (1,4).

Congenital brachymetatarsia originates during embryogenesis and persists as the child matures, leading to a retardation in the overall developmental trajectory of the affected metatarsal (5). The precise etiological factor prompting the premature cessation of the growth plate remains elusive, but current hypotheses suggest a potential association with specific genetic markers (1). While the anomaly can be discerned during early childhood when the growth plates (physes) are still patent, its manifestation typically becomes pronounced just prior to the definitive fusion of the metatarsal growth plate (5).

The clinical manifestations of brachymetatarsia can be diverse. In adults, common complaints include pain, skin irritation at the toe adjacent to the respective commissure due to footwear, and ambulatory challenges (6). A notable consequence of the shortened metatarsal not bearing weight is that the associated digit fails to contact the ground, leading to an unstable digit presentation, colloquially termed the "floating toe syndrome" (1). Particularly during adolescence, the condition can engender a skewed self-perception, occasionally culminating in psychological distress. This is particularly poignant given that the maturation of metatarsal growth plates typically transpires around the age of 14, coinciding with the adolescent phase (5).

The diagnosis of brachymetatarsia is primarily established through radiographic evaluations, which typically reveal a metatarsal that is not only shortened (terminating more than 5mm proximal to the alignment of the metatarsal heads) but also underdeveloped (2). It's imperative to note that brachymetatarsia, when concomitant with various conditions and syndromes, necessitates a comprehensive multidisciplinary assessment. Contemporary literature underscores the significance of gauging the emotional and psychological resilience of patients when considering diverse therapeutic interventions (6). Therapeutic strategies for brachymetatarsia can be bifurcated into conservative measures, such as the adoption of accommodative footwear, and more invasive surgical interventions (4).

CONCLUSION

In this report, we presented a rare case of congenital unilateral brachymetatarsia in a 32-year-old male, emphasizing the radiographic findings in the first metatarsal. While brachymetatarsia is a known entity, its occurrence in the first metatarsal, especially in males, is uncommon. This case underscores the importance of comprehensive radiographic evaluation in patients presenting with foot deformities. Furthermore, it highlights the need for individualized patient assessment, considering both physical and psychological aspects, to determine the most appropriate therapeutic approach.

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ACADEMIC JOURNAL OF HEALTH

LETTER TO THE EDITOR

The Relationship Between Microorganisms That Cause Pelvic Inflammatory Disease and Serum Cortisol Level

Pelvic inflammatory disease (PID) is a wide spectrum of inflammatory diseases including endometritis, salpingitis, oophoritis, tubo-ovarian abscess, and pelvic peritonitis. The causative microorganisms spread from the vagina or cervix to the upper genital structures via an ascending route (1). It may be asymptomatic or may present with mild or serious clinical symptoms. Based on stress intervals, there is a connection between normal flora, pro-inflammatory processes, and cytokines in cortisol levels (2). It is a cause of many morbidities and mortality such as infertility, subfertility, abscess formation, and the risk of sepsis.

Neisseria gonorrhoeae and C. trachomatis are the most common causes, and other cervical microorganisms, including Mycoplasma genitalium, are also thought to contribute to the disease. In addition, pathogens responsible for bacterial vaginosis (Peptostreptococcus species, Bacteroides species), respiratory pathogens (Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus), and enteric pathogens (Escherichia coli, Bacteroides fragilis, Streptococcus agalactiae) have been associated with acute PID (3).

The microorganisms that make up the vaginal flora vary from puberty to menopause, and there is a balance between these microorganisms and the vagina. While the vaginal environment controls the flora microorganisms, these microorganisms also regulate the vaginal environment. Many aerobic and anaerobic microorganisms, along with lactobacilli, are found in the vaginal flora without causing disease, and they are protective against sexually transmitted diseases, especially bacterial vaginosis, fungal infections, and urinary tract infections (4).

Rather than behavioral changes linked to stress, the impact of stress on the development of BV may be mediated by immune function dysregulation brought on by stress. The best possible immune response is necessary to stop the spread of anaerobes linked to BV. An inadequate reaction, possibly resulting from genetic variations, raises the danger of infection (5).

Stress enhances the progression of infection (including BV) and its pathophysiologic consequences (6).

Cortisol produced by stress binds to glucocorticoid receptors on a variety of immune cells and modifies NF-κB activities, which control the release of inflammatory mediators such as chemokines (IL-8, CCL5) and cytokines (IL-1β, IL-6, TNF-α, and IFNγ). Additionally, by preventing lymphocyte and leukocyte proliferation, migration, and cytotoxicity as well as the release of IL-2 and IFNγ, glucocorticoids aid in immunosuppression (7,8).

A stress-induced dysbiosis of the vaginal mucosa characterized by disturbed immune response-related and vaginal mucosal proteins (such as lactoferrin), decreased neutrophil bactericidal power, and decreased commensal abundance of Lactobacillus have been shown in a study using mice (9). There is a need for further studies.

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