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Temperament Characteristics, Anxiety and Depression in People with Familial Mediterranean Fever

Ailesel Akdeniz Ateşi Olan Kişilerde Mizaç Özellikleri, Anksiyete ve Depresyon

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Öz

Amaç: Ailesel Akdeniz Ateşi (AAA), tekrarlayan ateş, peritonit, plörit ve sinovit atakları ile karakterize, otozomal resesif geçişli, kendi kendini sınırlayan bir hastalıktır. Kronik hastalığa sahip olan bireyler depresyon veya anksiyete yaşama eğilimindedir. Ayrıca duygulanımla ilgili mizaçların duygudurum bozukluklarının temeli olduğu belirtilmiştir. Çalışmamızın amacı, AAA hastalarında anksiyete ve depresyon sıklığını belirlemek, baskın mizaç türünü belirlemek ve bulguları sağlıklı kontrol grubu ile karşılaştırmaktır.

Yöntem: Çalışmaya 73 AAA tanılı hastayla birlikte herhangi sistemik hastalığa sahip olmayan yaş ve cinsiyeti uyumlu 30 sağlıklı birey alındı. Hastane anksiyete ve depresyon ölçeği depresyon ve anksiyeteyi ölçmek için ve Temperament Evaluation of Memphis, Pisa, Paris and San Diego –Autoquestionnaire (TEMPS-A) mizaç ölçeği mizaç tipini belirleme amaçlı kullanıldı.

Bulgular: Hasta grubunda anksiyete skoru yüksek vaka sayısı 33 (%45,2), kontrol grubunda ise beş (%16,6); hasta grubunda depresyon skoru yüksek vaka sayısı 23 (%31,5), kontrol grubunda ise iki (%6,6) olup, her ikisi de istatistiksel olarak anlamlı derecede yüksekti (sırasıyla p=0.007 ve p=0.01). Cinsiyet, yaş, hastalık süresi, düzenli tedavi kullanımı, gen mutasyonu varlığı, atak tipi ile anksiyete ve depresyon skorları arasında istatistiksel olarak anlamlı bir bağlantı bulunmadı.

TEMPS-A mizaç ölçeğine göre hastalardan depresif mizaç tanısı alanların yüzdesi (%20,5) kontrol grubuna göre (%3,3) daha yüksekti ve aradaki fark istatistiksel olarak anlamlıydı (p=0,035).

Sonuç: AAA hastalarındaki klinik tablo anksiyete veya depresyon ile komplike hale geldiğinde veya bu durumlara yatkın mizaç varlığında hastaların tedaviye uyumunda ve tedaviye yanıtında çeşitli sorunlar olabilmektedir. AAA hastaları, takip sırasında eşlik eden anksiyete veya depresyon açısından izlenmelidir.

Anahtar kelimeler: Ailesel Akdeniz Ateşi, Anksiyete, Depresyon, Mizaç

Abstract

Objective: Familial Mediterranean Fever (FMF) is an autosomal recessive and self-limiting disease. FMF is characterized by recurrent episodes of fever, peritonitis, synovitis and pleuritis. Individuals with chronic illness tend to experience depression or anxiety. It has also been stated that affective temperaments are the basis of mood disorders. The aim of our study is to determine the frequency of anxiety and depression in FMF patients, to determine the dominant temperament type, and to compare the findings with the healthy control group.

Method: 73 patients with FMF and 30 age- and gender-matched healthy individuals without any systemic disease were included in the study. The hospital anxiety and depression scale were used to measure depression and

anxiety, and the Temperament Evaluation of Memphis, Pisa, Paris and San Diego –Autoquestionnaire temperament scale was used to determine the temperament type.
Results: The number of cases with high anxiety score was 33 (45.2%) in the patient group and five (16.6%) in the control group; The number of cases with high depression score was 23 (31.5%) in the patient group and two (6.6%) in the control group, and both were also found to be statistically significantly higher. (P values p=0.007 and p=0.01, respectively). Gender, age, disease duration, regular use of treatment, existence of gene mutation, attack type, and anxiety and depression scores had no statistically significant link. The percentage of patients identified with depressive temperament (20.5%) was higher than the control group (3.3%), according to the TEMPS-A temperament scale, and the difference was statistically significant (p=0.035).
Conclusion: When the clinical picture in FMF patients becomes complicated with anxiety or depression or in the presence of a temperament predisposed to these conditions, there may be various problems in patients' compliance and response to treatment. FMF patients should be monitored for accompanying anxiety or depression during follow-up.

Keywords: Anxiety, Depression, Familial Mediterranean Fever, Temperament

Introductions

Familial Mediterranean Fever (FMF) is a self-limiting, autosomal recessive disease primarily affecting Mediterranean-origin individuals, but can be reported globally due to human migrations. The MEFV gene mutation, discovered in 1992, causes defects in pyrin and its products, leading to inflammation, fever, and apoptosis, causing uncontrolled inflammation. This mutation has been crucial in understanding the disease's pathogenesis [1,2]. Symptoms of this condition begin before age 10 in 60% of patients, and by age 20 in 80-90%. Men are more likely to experience it. Attacks usually last 12-72 hours, with fever above 38°C, abdominal pain, and chest pain in 40% of cases. Constrictive pericarditis and cardiac tamponade are rare [1]. FMF is characterized by AA-type amyloidosis, a deposition of amyloid A protein, leading to nephrotic syndrome and end-stage renal disease [3]. Based on clinical observations, the Tel-Hashomer FMF criteria are used to diagnose FMF. A conclusive diagnosis is made if there are more than two major or one major + two minor criteria, whereas one major + one minor criterion is likely [4].

Colchicine took its place in the treatment of FMF as a result of the studies conducted by Goldfinger in 1972 and by Özkan et al. from Turkey at the same time [5]. Colchicine, an anti-inflammatory agent, is believed to prevent attacks and amyloidosis development by directly affecting microtubules [6, 7]. It was previously reported that some chronic rheumatological disorders (ankylosing spondylitis rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), etc.) may cause anxiety or depression in individuals with it [9-11]. FMF patients experience a range of effects on their social, family, and work lives, including pain, physical disability, and mood disorders. Inflammation is believed to contribute to the pathophysiology of anxiety and depression [12,13]. FMF-induced inflammation may lead to depression and anxiety, causing increased attacks and treatment resistance in patients despite regular colchicine treatment [14]. Akiskal et al. [15] suggested that temperament types may be the basis of mood disorders, as depression can lead to inadequate treatment response and serious complications like amyloidosis. A study on patients with ankylosing spondylitis found a significant correlation between temperament types, particularly depressive and anxiety types, and psychiatric symptoms [16].

The major goal of our study was to determine the incidence of anxiety and depression in people with FMF. Furthermore, we hoped to determine the predominant temperament type within this patient cohort and then compare our findings to those from a demographically matched healthy control group.

Materials and Methods

This study was planned as a cross-sectional survey study. Before the study, all patients and people in the control group were given an informed consent form containing the details of the study. Informed consent was obtained from all the participants. Study; It was approved by the Kahramanmaraş Sütçü Imam University Ethics Committee's decision dated 23.06.2014 and numbered 2014/09-03.

73 patients with FMF followed in the rheumatology outpatient clinic of a university medical faculty hospital and 30 age- and gender-matched healthy individuals without any systemic disease were included in the study. Patients between the ages of 17-65 who did not have any chronic disease or any psychiatric disease other than FMF were included in the study. In the control group, those without any systemic chronic disease or psychiatric disease were included in the study. Sociodemographic characteristics of the patients such as gender, age, duration of FMF disease, duration of treatment, mean treatment dose, history of regular use of treatment, and FMF attack type were recorded as clinical data form.

The hospital anxiety and depression (HAD) scale and Temperament Evaluation of Memphis, Pisa, Paris and San Diego– Autoquestionnaire (TEMPS-

A) temperament scale were given to the patients who came to the outpatient clinic and healthy control groups to determine the frequency of depression and anxiety and to reveal the temperament type and asked to fill it. TEMPS-A was used to evaluate dominant affective temperament and mean score of affective temperament subtypes. The original TEMPS-A scale, which was prepared by Akiskal et al. in 1997, has 109 items for men and 110 items for women. TEMPS-A scale, Vahip et al. It was adapted into Turkish by. The scale consists of 99 items. It is a five point Likert-type scale that should be filled in by itself as "true" and "false", taking into account the whole life of the individual, and consists of five subgroups that determine depressive, cyclothymic, hyperthymic, irritable, anxious temperaments. One or more dominant temperaments can be identified in an individual. On the other hand, no dominant temperament may be detected in the individual [17]. HAD scale was used to evaluate the anxiety and depression levels of individuals. The scale includes 14 questions in total. Seven of them measure anxiety (odd numbers), the other seven measure depression (even numbers). The validity and reliability study of the Turkish version was carried out by Aydemir et al. [18] and reported in 1997. The cut-off points for the Turkish version were determined as 10 points for the anxiety subscale and seven points for the depression subscale.

Our study's data were analyzed with the SPSS 16.0/Windows (SPSS for Windows, Chicago, IL, United States of America) application. The Shapiro-Wilk test was employed to determine normalcy. The normally distributed data was expressed as mean standard deviation, whereas the non-normally distributed data was expressed as median and first to third quartile. Numbers and percentages were used to express categorical variables. The independent samples t-test was used to compare continuous data having a normal distribution. The Mann-Whitney U test was used to compare continuous data with a non-normal distribution. The chi-square test or Fisher's exact test was used to compare percentage summaries of categorical variables. $p < 0.05$ was regarded as statistically significant.

The sample size was estimated with the G*Power program (v3.1.9.7), which revealed a total sample size of 42 participants to have 80% power (two-tailed, an alpha level of 0.05) to detect anxiety in FMF compared to the healthy control group [19].

Results

The study included 73 FMF patients (patient group; 51 females, 22 males) and 30 healthy volunteers (control group; 21 females, 9 males)). Age and gender distribution revealed comparable medians and percentages between FMF patients and controls ($p=0.371$, $p=0.989$, respectively). Notably, FMF patients had a statistically significant median disease duration of 4 years ($p<0.05$). There was no statistically significant difference between the two groups in terms of age or gender ($p>0.05$). Table 1 shows the demographic features of the patients.

Table 1. The demographic characteristics of the patients and control group

		FMF Patients (n: 73)	Control Group (n: 30)	p value
Age (Year)		31 (25-38)	32 (29-36	0,371
Gender n (%)	Male	22(% 30,1)	9 (% 30)	0,989
	Female	51(% 69,9)	21 (% 70)	
FMF disease duration (year)		4 (2-10,5)	–	–

FMF: Familial Mediterranean Fever, n: number, Continuous data was expressed as median (1^{st}-3^{rd} quartile). Categorical data was expressed as numbers (percentages)

Table 2 presents the clinical features of 73 patients with FMF. The overwhelming majority (98.6%) of FMF patients received colchicine as treatment, with only 1.4% undergoing Anakinra therapy. The median treatment duration was 4 years (2nd-10.5th quartile), and the mean colchicine dosage was 1.4±0.26 milligrams. Colchicine use was reported as regular in 80.8% and irregular in 19.2% of cases. Genetic analysis indicated that 38.4% of patients had a positive gene mutation, while 17.8% were negative, and the mutation status was unknown in 43.8% of cases. Regarding attack types, the majority experienced abdominal pain (89%), while arthritis and pleuritis were less common (2.8% and 8.2%, respectively). The clinical features of the patients are shown in Table 2.

Tablo 2. Clinical characteristics of FMF patients

		FMF patients (n:73)
Treatment	Colchicine	72 (% 98,6)
	Anakinra	1 (% 1,4)
Treatment duration (year)		7,28±7,41
Mean Colchicine dosage (mg)		1,4±0,26
Use of Colchicine	Regular	59 (% 80,8)
	Irregular	14 (% 19,2)
Gene mutation	Positive	28 (% 38,4)
	Negative	13 (% 17,8)
	Unknown	32 (% 43,8)
Attack type	Arthritis	2 (% 2,8)
	Abdominal pain	65 (% 89)
	Erysipelas like erythema	0 (% 0)
	Pleuritis	6 (% 8,2)
	Pericarditis	0 (% 0)

FMF: Familial Mediterranean Fever n: Number, mg: Milligrams, Continuous data was expressed as mean±standard deviation or median (1st-3rd quartile). Categorical data was expressed as numbers (percentages)

The number of cases with high anxiety score according to the cut-off score in the HAD scale; was 33 (45.2%) in the patient group and 5 (16.6%) in the control group. The number of cases with high depression score according to the cut-off score in the HAD scale was 23 (31.5%) in the patient group and two (6.6%) in the control group. The presence of both anxiety and depression was found to be statistically significantly higher in the patient group than in the control group (p=0.007 and p=0.01, respectively) (table 3).

Table 3. Comparative results of the patient and control groups in terms of presence of anxiety and depression

	FMF Patients n:73 (%)	Control Group n:30 (%)	p value
Anxiety	33 (% 45,2)	5 (% 16,6)	0,007
Depression	23 (%31,5)	2 (%6,7)	0,01

FMF: Familial Mediterranean Fever n: Number , Categorical data was expressed as numbers (percentages)

When the patients were evaluated with the TEMPS-A temperament scale, depressive temperament in 15 patients (20.5%), anxious temperament in 15 patients (20.5%), irritable temperament in three patients (4.1%), cyclothymic temperament in one patient (1.3%) was available. Hyperthymic temperament was not detected in any patient. More than one dominant temperament was found in ten patients. While eight of them had anxious temperament and depressive temperament, two of them had anxious temperament, depressive temperament and irritable temperament. In the control group; anxious temperament was found in two individuals (6.6%), depressive temperament in one person (3.3%), and irritable temperament in one person (3.3%). Among the FMF patients (n=73), 20% exhibited a depressive temperament, significantly higher than the control group (n=30) at 3% (p=0.035). Cyclothymic temperament showed no statistically significant difference between the groups (p>0.05). Irritable temperament was observed in 4% of FMF patients compared to 3% in the control group (p>0.05). Hyperthymic temperament was absent in both groups. Anxious temperament was present in 20% of FMF patients and 7% of the control group, with no significant difference (p>0.05) (Table 4).

Table 4. Comparative results of temperament characteristics of patient and control groups according to TEMPS-A temperament scale

		FMF Patients n:73 (%)	Control Group n:30 (%)	p value
Depressive Temperament	**Yes**	15 (%20)	1 (%3)	0,035
	No	58 (%80)	29 (%97)	
Cyclothymic Temperament	**Yes**	1 (%1,7)	0	>0.05
	No	72 (%98,3)	30	
Irritable Temperament	**Yes**	3 (%4)	1 (%3)	>0.05
	No	70 (%96)	29 (%97)	
Hyperthymic Temperament	**Yes**	0	0	–
	No	73	30	
Anxious Temperament	**Yes**	15 (%20)	2 (%7)	>0.05
	No	58 (%80)	28 (%93)	

FMF: Familial Mediterranean Fever n: Number Categorical data was expressed as numbers (percentages)

Discussion

Deterioration of general health in people with chronic diseases makes it difficult to comply with treatment and facilitates the emergence of psychological problems. Depression has been reported as a comorbidity in chronic diseases such as coronary artery disease, cancer, and neurological diseases. Similarly, anxiety is common in people with chronic diseases [19]. Depression and anxiety are also common in rheumatological diseases. Depression and anxiety are frequently encountered in chronic rheumatological diseases such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis [9-11].

In the study conducted by Değer et al. [20] with 90 FMF patients and a control group consisting of 67 people, the incidence of anxiety and depression was found to be higher in FMF patients than in the control group. Anxiety was found in 53% of FMF patients, 16% in the control group (p<0.001), while depression was found in 33% of FMF patients and 12% in the control group (p<0.01). In the study of Makay et al. [21] with 43 FMF patients in the pediatric age group and a control group of 53 people, they found the depression score to be significantly higher in the patient group compared to the control group, but no significant difference was found in terms of anxiety scores. In the study of Giese et al. [22], anxiety and depression were examined in FMF patients living in Germany and Turkey. Anxiety was found to be 52.5% in FMF patients living in Germany and 22.5% in the control group, and it was found to be statistically significant. When FMF

patients living in Germany and the control group were compared, no significant difference was found in terms of depression. No significant difference was found between FMF patients living in Germany and Turkey in terms of depression and anxiety. Lidor et al. (23) from Israel, consisting of 7670 FMF patients and a control group of 7670 people and using the depressive illness, anxiety disorders and FMF diagnosis codes in the patient registry system, the prevalence of depression was found to be higher than the control group. (6.22% vs 4.58%, $p<0.001$). Similarly, the prevalence of anxiety was higher than the control group (4.93% vs 3.14%, $p<0.001$). In our study, the frequency of both depression and anxiety was higher in FMF patients compared to healthy individuals, and it was found to be compatible with the literature.

FMF may lead to limitation of physical activity, although it is not expected. Restriction in physical activity facilitates the emergence of psychological problems. In addition, it should be kept in mind that some additional factors such as having a chronic disease at a young age and being under medical treatment for a lifetime may cause the development of anxiety and depression in FMF patients.

It has been shown that inflammation may play an important role in the pathophysiology of anxiety and depression. TNF-α levels and cytokine levels such as IL-2, IL-6, IL-12, and IL-18 were found to be high in depressive patients [12]. Similarly, it has been shown that TNF-α, IL-1 and IL-6 may be associated with anxiety [13]. Although FMF is a disease characterized by recurrent inflammatory attacks, it has been shown that subclinical inflammation persists in non-attack periods [24]. Thus, it can be thought that both the inflammation during the attack periods and the subclinical inflammation that continues during the non-attack periods play a role in the development of anxiety and depression in FMF patients. The fact that platelet and plasma serotonin levels show different patterns in attacks and attacks-free periods in patients with colchicine responsive and resistant to colchicine treatment, and the fact that the frequency of FMF attacks can be reduced by SSRI suggests that there may be a pathogenetic relationship between FMF and anxiety and depression [25,26].

Sönmez et al. [27] compared the quality of life, anxiety, and depression scores of children and adolescents with FMF to those of healthy controls. They reported that FMF patients' anxiety levels were higher and their disease duration was longer. Early detection of mood swings may help with FMF management. According to this study, children and adolescents with FMF benefit greatly from the close collaboration of pediatric rheumatologists and child and adolescent psychiatrists.

In recent years, the relationship between chronic diseases, autoimmune diseases and autoinflammatory diseases and temperament features has begun to attract the attention of researchers. There has been no study published in the literature on temperament characteristics in FMF patients. In a study of patients with ankylosing spondylitis, no difference was found in the distribution of temperament subtypes between patients with ankylosing spondylitis and the control group, but it was reported that there was a significant relationship between depressive, cyclothymic, irritable and anxious temperament types and psychiatric symptoms [16]. In another study, it was shown that irritable and depressive temperament types were the most common affective temperament types in patients with rheumatoid arthritis, but it was reported that dominant affective temperament did not affect the functional abilities of patients with RA [28]. In our study, depressive temperament was found to be significantly higher in the patient group than in the control group. Determining temperament subtypes may benefit the closer follow-up of patients in terms of psychiatric diseases during the follow-up of a chronic disease such as FMF. As stated in other studies, we think that temperament subtypes may be stimulating in terms of psychiatric symptoms.

Our study is valuable because it evaluates depression, anxiety and temperament characteristics in FMF patients and there are few studies on this subject, but it has some limitations. Our study was cross-sectional and the effects of temperament characteristics on treatment success in FMF patients were not examined. Furthermore, due to the small number of patients included in our study, bigger investigations to analyze anxiety, depression, and temperament traits in FMF patients are needed.

Conclusion

As a result, in FMF patients when the clinic becomes complicated with anxiety or depression or in the presence of a temperament predisposed to these conditions, there may be various problems in patients' compliance and response to treatment. In patients whose treatment response is not sufficient, complications such as amyloidosis with a high risk of morbidity and mortality may occur. FMF cases should be monitored for accompanying anxiety or depression during follow-up. Although the study did not have a one-to-one result, high doses of colchicine and interleukin-1 blocker treatments may not be required in case of treatment of existing psychiatric diseases of resistant FMF patients with anxiety and depression. It is thought that it would be beneficial to carry out more comprehensive studies on this subject.

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